

Controlled Human Infection Model Studies

Summary of a workshop held on 6
February 2018



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Contents

Executive summary	4
Introduction	6
Regulatory requirements for CHIM studies	9
The funding landscape for CHIM studies	14
Manufacturing standards for human challenge agents	18
The governance of CHIM studies.....	20
Guiding principles for CHIM studies	24
Conclusions and next steps.....	26
Annex I – Responsibilities and best practice for stakeholders	27
Annex II – Agenda	28
Annex III – Participant list	30
Annex IV – Glossary	32

Executive summary

Controlled Human Infection Model (CHIM) studies, trials that purposely infect human volunteers with infectious agents (known as challenge agents), are an essential component of pathology, immunology and vaccines research. There are unique ethical, safety and scientific challenges associated with CHIM studies that mean that robust governance and appropriate regulation is essential to their effective use and continued growth.

On 6 February 2018, the Academy of Medical Sciences, supported by HIC-Vac, the Medical Research Council and Wellcome, convened a workshop to discuss the current environment for CHIM studies in the UK and internationally and whether any of the matters identified in a previous 2005 Academy of Medical Sciences report, 'Microbial Challenge Studies of Human Volunteers', merited re-examination.¹ The issues originally identified in the 2005 report included the need for guidance and oversight of the scientific, ethical, safety, legal and societal issues imparted by conducting CHIM studies.

During the workshop, participants raised a number of points that they felt were pertinent to the current landscape for CHIM studies:

- **There continues to be significant investment in CHIM studies** as part of a wider goal of tackling endemic, pandemic and emergent infectious diseases. Such funding, driven by Wellcome, the Medical Research Council, the Bill & Melinda Gates Foundation and Horizon 2020, among others is targeted towards areas of ongoing unmet need, such as malaria and leishmaniasis, as well as pandemic outbreaks.
- There is a **need to build the capacity and capabilities of low- and middle-income countries** (LMICs) for conducting CHIM research locally. Research conducted within areas of unmet need will result in studies that are more relevant to the at risk populations as well as boost quality of research and provide economic benefits.
- There is a **need for an ethical framework that guides the use of CHIM studies**. Such a framework could be targeted at those designing, conducting, commissioning or funding studies, and should not only consider the risks, but also scientific justification and the impact on the study participants and wider population.
- CHIM studies are not without their risks, and **high quality standards of manufacturing challenge agents and conducting CHIM studies** should be adhered to as far as possible, with the Good Manufacturing Practice guidelines a useful tool in minimising risks of challenge agents.
- **Increasing numbers of collaborations between sectors**, both within the UK and internationally, are allowing an exchange of knowledge and expertise that can expand the use of CHIM studies and accelerate the benefits derived from them. These collaborations are especially important in helping LMICs build their expertise and capacity, and researchers in high- and middle-income countries should look for opportunities to conduct their CHIM studies in these countries where possible and of benefit.

¹ Academy of Medical Sciences (2005). *Microbial Challenge Studies of Human Volunteers*
www.acmedsci.ac.uk/policy/policy/microbial-challenge-studies

- Establishing an **archive of challenge agents** would be of great benefit to the research community. At the minimum this could consist of the characterisation of agents, but could be expanded to include a 'bank' of samples that could be accessed by other researchers wishing to use an existing challenge agent in a study.
- **Registration of CHIM studies is essential** to knowledge sharing and open innovation in this area of research. A universal requirement for registration could allow the multitude of methodologies, challenge agents and results to be shared and built upon more rapidly, whilst also preventing duplication of effort.
- **The research community should engage with regulators** to ensure that regulation remains proportionate and fit for purpose in light of any developments in CHIM studies.

Introduction

Controlled Human Infection Model (CHIM) studies are clinical studies that, as part of the protocol, deliberately expose trial participants to an infectious pathogen. These studies are often done in the context of vaccine development, with participants exposed to a pathogen after being immunised with an experimental vaccine. However, exposure to pathogens can also be part of studies examining the pathogenesis, immunology or natural history of an infectious disease. CHIM studies are a critical part of the development of new vaccines for infectious disease, and so contribute to tackling an area of high unmet need in healthcare globally. According to the World Health Organization, infectious diseases account for at least 1 in 8 deaths globally.²

The nomenclature for CHIM studies is diverse, and they are variously known as, among others, Microbial Challenge Studies (MCS), Human Infection Challenge (HIC) studies, Human Challenge Studies (HCS), Human Challenge Trials (HCT), Human Challenge Models (HCM) and Volunteer Infection Studies (VIS). In this report, Controlled Human Infection Model (CHIM) is used throughout for consistency, and widespread agreement by the community of the nomenclature will be important to avoid unnecessary confusion in the future.

In 2002, the Academy of Medical Sciences held a workshop to discuss the risks, benefits, and conduct of CHIM studies, where participants recognised the need for further examination of the key issues. Subsequently, the Academy convened a working group to make recommendations to key stakeholders. The report, 'Microbial Challenge Studies of Human Volunteers', published in 2005, recommended the creation of a National Expert Advisory Committee (NEAC) to identify mechanisms to ensure the safety and welfare of human subjects involved in these studies.³ The NEAC would have had the remit to oversee the scientific, ethical, safety, legal and societal issues of CHIM studies, to establish a central registry of studies and to provide guidance on the proper preparation and storage of CHIM materials.⁴

While the report has helped to inform consideration of CHIM studies in the 13 years since its publication (for example, through its checklist of ethical issues that researchers and ethics committees need to consider), regulators did not feel the creation of the NEAC was warranted and so did not implement the recommendation. The number of CHIM studies undertaken in the UK has since continued to increase, and there has been no concerted reconsideration of the level of oversight needed in the UK for this type of study since the Academy's report. However,

² www.who.int/mediacentre/factsheets/fs310/en/

³ Academy of Medical Sciences (2005). *Microbial Challenge Studies of Human Volunteers*
www.acmedsci.ac.uk/policy/policy/microbial-challenge-studies

⁴ *Ibid.*

the appropriate level of oversight for CHIM studies continues to be a source of debate amongst funders and academics involved in the conduct of this type of research. Therefore, on 6 February 2018, the Academy, supported by the Medical Research Council, Wellcome and HIC-Vac, convened representatives from a variety of stakeholders involved with CHIM studies, including representatives from research and funding bodies, experts in medical ethics and regulatory agencies, to discuss whether the landscape has significantly changed since the 2005 report, if the recommendations from the report are still relevant and to refresh the key challenges that CHIM studies face and possible ways to address these.

The workshop was co-Chaired by Professor Andrew Pollard FMedSci, Professor of Paediatric Infection and Immunity, University of Oxford; Director, Oxford Vaccine Group; Co-Director, HIC-Vac; and Professor Maria Zambon FMedSci, Deputy Director of National Infection Service, Public Health England. After a series of presentations from key stakeholders, participants examined the ethical and regulatory frameworks for conducting CHIM studies in the UK and internationally with the aim of generating draft guidelines that would be relevant to those conducting CHIM studies in the UK. Though the workshop did not aim to have significant international representation, the discussions may also be more broadly of interest to the international CHIM community, and future meetings on this topic would benefit from gaining the perspectives of representatives from low- and middle-income countries.

This report summarises the discussions held at the meeting. The views expressed in this document are the views of the delegates who attended the meeting and are not necessarily the positions of the Academy of Medical Sciences, HIC-Vac, the MRC, or Wellcome.

Review of the 2005 Academy report

Professor Richard Moxon FRS FMedSci, Emeritus Professor of Paediatrics, University of Oxford and Chair of the 2005 Working Group, gave an overview of the findings and recommendations of the 2005 Academy report.⁵ He explained that it originated in the realisation, following the 2002 workshop, that there was a need for specific guidance of the ethical, safety, legal and societal implications of CHIM studies. In 2004, the Medicines for Human Use Regulations that introduced the EU Clinical Trials Directive into UK law appeared to not specifically cater for studies that intentionally infect individuals and so would not cover many CHIM studies.⁶ Consequently, the Academy convened a working group of experts to examine whether there were fundamental differences between CHIM studies compared to other forms of clinical research that would require additional oversight or regulation. It was felt that the unique challenges that CHIM studies present, such as the risk of severe adverse effects, may merit a need for: a mechanism to ensure more responsible management of these risks; an accountability structure if an event occurs, and for registration and transparency of conducted studies.

The report concluded that although the core principles for determining whether or how a study should take place were not intrinsically different from other medical research involving human subjects, there was a gap in the guidelines and frameworks that should be filled to ensure that CHIM studies were subject to the same high standards as other forms of research. Therefore, the report recommended the formation of a National Expert Advisory Committee (NEAC) for CHIM studies. The aim of the NEAC would be to identify mechanisms to safeguard the safety and welfare of human subjects involved in CHIM studies. It would do this by providing expert, independent and representative advice on the relevant scientific, ethical, safety, legal and societal issues relating to CHIM studies. The NEAC would also provide a framework for ensuring adequate standards of manufacture and storage of challenge materials, the suitability and robustness of study protocols and to establish and maintain a registry of CHIM studies.

Ultimately, regulators were not persuaded to implement the recommendations to establish the NEAC, and so there is a lack of a centralised body for registering studies and providing oversight on safety issues. This means that the governance is left to the study sponsor and ethics committee.

⁵ *Ibid.*

⁶ Medicines and Healthcare products Regulatory Agency (2004) *The Medicines for Human Use (Clinical Trials) Regulations 2004* www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf

Regulatory requirements for CHIM studies

Overview of the UK, EU and US regulation of CHIM studies

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) oversees and regulates medicines and medical devices. However, under current UK law a CHIM study only requires MHRA approval if it is a clinical trial of an investigational medicinal product (IMP) as defined by the clinical trials Directive 2001/20 EC (e.g. a study involving administration of a vaccine prior to administering the pathogen to participants). If a vaccine is part of the protocol, the entire protocol, including the challenge agent, will be scrutinised.⁷ If no vaccine is involved in the study, MHRA approval is not necessary. Responsibility for ensuring that the challenge agent is manufactured and used appropriately lies solely with the sponsor of the study. In addition, while the MHRA guidance states that Good Manufacturing Practice (GMP) standards should be considered to ensure the safety of patients and quality of the challenge agent, it is not a formal requirement. However, all CHIM studies, regardless of protocol, must undergo ethical review and be approved by a Research Ethics Committee (REC) prior to the study.

In contrast, the Food and Drug Administration (FDA) in the US does require that studies are approved, through the Investigational New Drug application, and also that challenge agents are manufactured in compliance with GMP. In addition, ethical review by the US equivalent of a REC, an Investigational Review Board, is a requirement.⁸

In the case of genetically modified organism (GMO) challenge agents, the UK Department for Food & Rural Affairs' Advisory Committee on Releases to the Environment (ACRE) assesses the risk to non-participants and the environment and must give approval before the GMO challenge agent can be administered as part of a CHIM study.

Participants highlighted the important role that funding bodies have in facilitating and joining together standards for CHIM studies. Although funding bodies are not regulators themselves, it

⁷ European Commission (2011). *The Rules Governing Medicinal Products in the European Union Volume 10 - Guidance Documents applying to Clinical Trials Guidance on Investigational Medicinal Products (IMPs) and 'Non Investigational Medicinal Products' (NIMPs)*. (Rev. 1, March 2011)
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/imp_03-2011.pdf

⁸ www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm

was suggested that by having a unified approach with common goals and requirements from funded studies, the currently diverse landscape of CHIM studies could become more standardised, which would aid both researchers as well as the regulators using CHIM studies as evidence in evaluation.

In addition, it was suggested that the Health Research Authority could be the source of key ethical guidance for ethics committees. Equally, coordination of a potential universal registry for CHIM studies conducted either in the UK or worldwide could fall to a regulatory or advisory body such as the MHRA or HRA, or to the funding bodies that fund such research.

The World Health Organization's role in supporting National Regulatory Agencies

Dr Ivana Knezevic, Scientist, Technologies, Standards and Norms Team; Group Lead, Norms and Standards for Biologicals, World Health Organization (WHO) gave an overview of WHO's standards that facilitate regulatory oversight of vaccines and other biologicals.⁹ WHO has, as part of its mandate, a unique role to support regulatory authorities in its 193 member states. One of WHO's core functions is '*setting norms and standards and promoting and monitoring their implementation*'. WHO recommendations and guidelines are intended to ensure the availability of biological products of appropriate quality, safety and efficacy for use at a global level. Furthermore, these documents serve as a benchmark for global acceptability of these products and as a basis for defining national regulatory requirements for licensing as well as for post-licensure evaluation. WHO's Norms and Standards Programme for biologicals includes both measurement (physical standards) and written standards for vaccines, biotherapeutic products including biosimilars, blood products and in-vitro diagnostics. The development of measurement standards involves elaborate collaborative studies in numerous laboratories worldwide and the WHO written standards are based on scientific consensus achieved through a comprehensive international consultation. After adoption of documents by WHO's Expert Committee on Biological Standardization, WHO publishes a Technical Report Series that serves as recommendations that countries may adopt as their own requirements or adapt for their needs and use for their standard-setting.¹⁰ The work is supported by WHO Collaborating Centres, national regulatory authorities in many WHO member states, pharmacopoeias, manufacturers associations and academia. WHO also plays an important role in the implementation of new guidelines and recommendations.

Dr Knezevic emphasised that WHO's role is advisory, and that regulatory decisions remain with the National Regulatory Agencies (NRA). However, WHO's guidelines can support NRAs in setting their national requirements whilst allowing NRAs the space to formulate additional requirements that are appropriate to their locality.¹¹ She also explained that the guidelines are a '*living document*' that can develop to keep pace with scientific knowledge and experience. In addition to the guidelines, WHO conducts a range of workshops, training and advisory meetings to disseminate the guidelines and directly support stakeholders.

The WHO document 'Human Challenge Trials for Vaccine Development: Regulatory Considerations' provides some basic information about CHIM studies and data generated in that

⁹ www.who.int/biologicals/en/

¹⁰ www.who.int/biologicals/publications/trs/en

¹¹ www.who.int/biologicals/expert_committee/WHO_TRS_1004_web_Annex_9.pdf

context.¹² It was developed to raise awareness among regulators that reviewing clinical trial applications and/or data that came out of CHIM studies may be quite challenging. Therefore, regulatory expertise and preparedness for these reviews needs to be in place.

Dr Knezevic explained how WHO has successfully supported the introduction of regulation for vaccine trials in countries that previously did not have such regulation. It does this by helping NRAs to understand the key challenges of vaccine trials and CHIM studies which merit the need for bespoke regulation. For example, CHIM studies have multiple outcomes, such as understanding pathogenesis, assessing the efficacy of a vaccine pre-licensure or assessing protection longevity post-licensing.¹³ As a result, there is not a 'one size fits all' approach to regulating CHIM studies. In addition, there are a range of other factors, such as consideration of the necessity of GMP standards, a diverse range of protocols, operational challenges and safety and ethical considerations.

There are additional challenges when supporting NRAs in low- and middle-income countries (LMICs). A WHO survey of Developing Country Vaccine Regulators' Network representatives found that 11 countries reported having no experience of CHIM studies, and WHO are planning a follow-up survey to see if this is a common challenge across the globe. The survey also revealed several concerns amongst LMIC regulators, such as the safety of participants, the risks of challenge agents spreading to the environment, the availability of suitable care for participants, public perceptions and coercive payments for participation. As a result, WHO is organising implementation workshops for LMICs to allow their local NRAs to learn from case studies of other LMICs that have implemented regulation. As there is a drive to conduct more CHIM studies in LMICs, these concerns, and WHO's support for LMICs, are highly relevant to international researchers looking to carry out studies in new localities.

Finally, Dr Knezevic briefly described a WHO initiative for standardisation of priority pathogens such as Ebola that is part of a broader project, 'A research and development Blueprint for action to prevent epidemics'.¹⁴ The 'List of Blueprint priority diseases' seeks to identify diseases that pose an epidemic health risk, and that have no effective treatments, to allow R&D programs to focus on areas of urgent need.¹⁵ Part of this R&D program includes investigating the role that CHIM studies might have in rapid vaccine development for urgent health emergencies.

The role of the UK regulator

Dr Graham McNaughton, Pharmaceutical Assessor at the MHRA gave an overview of the MHRA's role in regulating CHIM studies. Currently, the MHRA does not regulate the studies used to develop CHIM agents and there are currently no plans for the MHRA to adopt this role. However, Dr McNaughton said that the MHRA is receptive to input from the CHIM research community as to its potential role in the future.

As part of the scientific and regulatory advice services offered by the MHRA, sponsors of clinical trials which involve a challenge agent can obtain advice from the regulator either as part of its use in an individual clinical trial or as part of an ongoing development program. However, this advice and guidance is supportive and responsibility for conducting the study appropriately remains with the sponsor.

Dr McNaughton also stated that challenge models, when used in the context of a vaccine trial,

¹² World Health Organization (2017). *Human Challenge Trials for Vaccine Development: Regulatory Considerations*. Who Expert Committee on Biological Standardization, Sixty-seventh Report; Who Technical Report Series, No. 1004, 2017, Annex 10 <http://apps.who.int/medicinedocs/en/d/Js23329en/>

¹³ www.who.int/biologicals/expert_committee/WHO_TRS_1004_web_Annex_10.pdf

¹⁴ www.who.int/blueprint/en/

¹⁵ www.who.int/blueprint/priority-diseases/en/

are subject to regulation under the Clinical Trials Directive.¹⁶ Once part of a vaccine trial, challenge agents would need to be assessed and the MHRA may ask questions as to the quality and appropriateness of the agent. The 2004 Clinical Trials Directive did not specify a formal review of the manufacture of challenge agents.¹⁷ However, guidance has since been introduced that recommends more formal assessment and specifies that appropriate GMP requirements foreseen for the safety of patients are applied and to ensure that Non-Investigational Medicinal Products (NIMPs) such as challenge agents are of an appropriate quality.¹⁸ This guidance does not formally require this assessment. Under the new Clinical Trials Regulation, which is scheduled to come into effect in 2019/20, challenge agents fall under a new classification as Auxiliary Medicinal Products – a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product.¹⁹

European regulation of CHIM studies

Dr Marco Cavaleri, Head of Anti-infectives and Vaccines, Scientific and Regulatory management Department, European Medicines Agency (EMA) explained that the EMA does not approve CHIM study protocols and it is up to NRAs, such as the MHRA in the UK, to decide whether they wish to regulate CHIM studies. However, the EMA would discuss CHIM studies with developers in the context of Scientific Advice procedures and other frameworks for interaction with sponsors of investigational vaccines.²⁰

Dr Cavaleri described the various roles that CHIM studies could play in streamlining vaccine development, for example in proof-of-concept studies and investigation of the correlation of immune markers with protection. It was not excluded that there may be well-defined opportunities for using CHIM studies as evidence for licensure in the future, but for such a study to support approval or provide reliable supportive evidence, several factors would need to be considered as part of the evaluation. The first of these is the level of attenuation of the strain used in the CHIM study. Greater attenuation of the challenge organism increases the safety profile of the trial but may also lead to results that do not sufficiently reflect the protective level against strains found in the natural environment (the 'wild-type' strains). As such, evidence to support licensure should attempt to define how protection achieved with the attenuated strain translates to protection from the wild-type strains. The second factor is whether the route of administration mimics the natural route of exposure, and whether the dosing of the challenge agent is comparable to natural exposure. In addition, extrapolation of findings from a CHIM study that uses a single strain of a pathogen to other strains might be problematic, especially in diseases known to have significant genetic variation, such as malaria. The length of protection conferred by the vaccine will also be considered; CHIM studies often administer the challenge pathogen soon after vaccination, when the humoral response of the immune system is likely to be at its peak. Finally, the impact of pre-existing immunity in the trial population on the effectiveness of the vaccine may be significant, limiting the possibility of extrapolation between different populations, for example for travellers versus local populations.

Dr Cavaleri noted that the FDA has approved a cholera vaccine for use in adult travellers based on evidence generated using a CHIM study.²¹ In case the vaccine was to be submitted for

¹⁶ The Medicines for Human Use (Clinical Trials) Regulations 2004, www.legislation.gov.uk/ukxi/2004/1031/pdfs/ukxi_20041031_en.pdf

¹⁷ *Ibid.*

¹⁸ European Commission (2011). *The Rules Governing Medicinal Products in the European Union Volume 10 - Guidance Documents applying to Clinical Trials Guidance on Investigational Medicinal Products (IMPs) and 'Non Investigational Medicinal Products' (NIMPs)*. (Rev. 1, March 2011) https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/imp_03-2011.pdf

¹⁹ European Commission (2017). *Auxiliary Medicinal Products in Clinical Trials*. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf

²⁰ www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=W00b01ac05800229b9

²¹ www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm505866.htm

approval in the EU, the EMA would be open to considering whether the evidence base for this vaccine could be sufficient for approval. He also noted that ethical considerations on whether a CHIM study should take place can be impacted by its expected role towards a regulatory decision. For example, a recent report from the National Institute of Allergy and Infectious Diseases examined the ethics of running CHIM studies for Zika virus, and concluded that such studies could only be justified if the findings would be used to support a regulatory decision on the vaccine, and not just to learn more about the pathogenesis and natural history of the virus.²² It was noted that further discussions about Zika CHIM studies are ongoing.

Finally, Dr Cavaleri stated that the EMA is eager to discuss proposals of how CHIM studies might be part of regulatory decisions, especially where they can help confirm the predicted effectiveness of rapidly developed new vaccines for preventing diseases for which conducting field efficacy studies is unlikely to be feasible.

Case study 1 – Developing a human challenge model for tuberculosis

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* bacteria (MTB) that most often affect the lungs. Professor Helen McShane, Professor of Vaccinology, University of Oxford described work on developing an attenuated, labelled genetically modified TB strain for use in studies. There is an urgent need for more effective tuberculosis vaccines, but efforts have been hampered by the poor predictive value of animal models and a lack of understanding of the correlation between the immune response and effective protection. As such, an attenuated strain is desirable to allow vaccines to be effectively tested without putting people at significant risk. She presented her research in taking the Bacillus Calmette-Guérin (BCG) vaccine, which provides variable protection against tuberculosis, and using it to develop an experimental model of mycobacterial infection through intradermal or aerosol challenge. The successful development of this model will be used to test new vaccines against TB. BCG, delivered either intradermally or by aerosol, does not need regulatory approval if the purpose of the study is to use BCG as a controlled human challenge model. Any recombinant attenuated strain of either MTB or BCG would also need GMO approval.²³

²² The National Institute of Allergy and Infectious Diseases (NIAID) and the Walter Reed Army Institute of Research (WRAIR) (2017). *Ethical Considerations for Zika Virus Human Challenge Trials*. www.niaid.nih.gov/sites/default/files/EthicsZikaHumanChallengeStudiesReport2017.pdf

²³ www.hse.gov.uk/pubns/priced/l29.pdf

The funding landscape for CHIM studies

Wellcome's initiatives to support CHIM studies

Dr Charlie Weller, Head of Vaccines Priority Area, Wellcome, gave an overview of Wellcome's Vaccines Priority Area that was established in early 2017. It aims to stimulate research, technology and policy to address unmet healthcare needs, initially over five years.

The Vaccines Priority Area has four pillars of activity, with an initial focus on:

- i. epidemic preparedness including investment in CEPI (Coalition for Epidemic Preparedness Innovations)²⁴, and
- ii. innovation in vaccine development through the expanded use of CHIM studies in disease endemic areas.

The additional pillars of activity will focus on:

- iii. generating evidence and maximising its use in vaccine policy and decision-making, and
- iv. strengthening global expertise in vaccinology.

The priority area will not function through a broad funding call. Instead, it will address specific outcomes through a variety of approaches that utilise the expertise and activities across Wellcome including targeted research, commissioned work, advocacy, policy development and through catalysing partnerships. The Vaccines Priority Area sits alongside investigator initiated funding in Wellcome's response mode schemes including fellowships, investigator and innovator awards and collaborative and seed awards, which will continue to accept applications in the vaccines field.

She described how the priority area is particularly focused on expanding the use of CHIM studies in endemic areas. This will ensure that these studies are more relevant to the populations where the vaccine will be used, given that the host-pathogen and host-vaccine interactions have been shown to vary across different populations, and the genetic and environmental factors governing the success of a vaccine can also vary geographically. The Vaccines Priority Area will take a holistic and coordinated approach to expanding CHIM to disease endemic areas including strengthening ethical and regulatory frameworks, supporting

²⁴ <http://cepi.net/>

community engagement, strengthening expertise and encouraging comparability and harmonisation of approaches where appropriate.

Finally, Dr Weller described how Wellcome has developed Funders Principles with the Bill and Melinda Gates Foundation and others to guide funders in supporting CHIM research. She stated that as a funder, Wellcome has a responsibility to support innovation that promotes and sustains the public good. Given the unique ethical concerns of CHIM studies, there is a high burden of responsibility when conducting these studies. The principles are designed to be complementary to those from other organisations, both internationally and locally, and to be implementable in research practice. The funders principles themselves are being developed around ethical acceptability, and provide a range of additional criteria that funders should consider, such as a strong scientific justification. They will also address issues of national importance and build local governance and capacity to foster acceptable quality and safety. This approach will encourage researchers and sponsors to build a community of best practices, and engage meaningfully with participants and their communities throughout the studies.

The Medical Research Council's initiatives to support CHIM studies

Dr Jonathan Pearce, Head of Infections and Immunity, Medical Research Council (MRC), introduced the MRC's vaccine strategy. Infectious disease continues to be a major challenge and is being exacerbated by climate change, urbanisation and globalisation. Recently outbreaks of Ebola, Zika and other diseases demonstrate the large-scale challenge that infectious diseases pose and the importance of being able to rapidly develop effective vaccines. He explained how worldwide, vaccines avert an estimated 2-3 million deaths from infectious disease each year. Dr Pearce also described how vaccines have generally avoided antimicrobial resistance, in stark contrast to antibiotics. This provides a huge opportunity for tackling infectious diseases where effective antibiotics may not be available in the future.

In 2014, the MRC Review of Vaccines Research recommended that the MRC funds basic science around transmission, pathogenesis and experimental medicine for vaccines, to stimulate the generation of novel tools and technologies and to facilitate networking and partnership building.²⁵ Following this, the MRC, Biotechnology and Biological Sciences Research Council (BBSRC) and Engineering and Physical Sciences Research Council (EPSRC) launched a Highlight Notice for novel veterinary and medical vaccines.²⁶ This resulted in the funding of five projects with a total of £3.7m. More recently, a joint MRC and BBSRC £8m fund to support Vaccine R&D Networks through the Global Challenges Research Fund was established to encourage interdisciplinary working, strengthen research capacity and capability and to catalyse support for short-term, innovative projects. As part of this network, the Global Challenges Research Fund has funded five collaborative projects including HIC-Vac, and the Developmental Pathway Funding Scheme supports the evaluation of new programmes and helps build networks to increase capability and capacity. Together, these networks will receive £9.4m of funding.

Other initiatives across the Research Councils include the establishment of one or two Vaccine Manufacturing Centres, funded by the EPSRC and the Department of Health and Social Care.²⁷ These centres will each receive between £5m and £10m of funding. Dr Pearce also described the UK Vaccine Development and Manufacturing network, funded by Innovate UK, and the UK Vaccines Network, established following the 2015 Ebola outbreak, which has received £120m of funding from the MRC, BBSRC and Department of Health and Social Care and aims to coordinate UK vaccine research by funding projects that develop vaccines on the UK Priority

²⁵ www.mrc.ac.uk/documents/doc/mrc-review-of-vaccines-research-2014/

²⁶ www.bbsrc.ac.uk/funding/filter/novel-tools-technologies-for-vaccinology/

²⁷ www.gov.uk/government/news/medicine-and-vaccine-manufacturing-centres-apply-for-funding

Pathogen List.²⁸

Finally, Dr Martin Broadstock, MRC Programme Manager for Immunology, emphasised that the MRC has a long history of supporting CHIM studies, with its origins in the Common Cold Unit in the 1940s. CHIM studies now make up 16% of the MRC's live vaccine portfolio, and recent work has included projects to increase capacity for tackling malaria in Kenya, a grant to build a research centre in The Gambia and funding for projects looking at the pathogenesis of genetically modified organisms.

International funding for CHIM studies

Through its Horizon 2020 funding programme, the European Union has supported a number of vaccine research programmes within its 'Societal Challenge: Health, Demographic Change and Wellbeing' funding stream.²⁹ Within this, a number of specific challenges have been incorporated as part of the work programme, including the development of a vaccine against malaria, tuberculosis and HIV.^{30,31} Some of these projects are coordinated through the Innovative Medicines Initiative, which coordinates the allocation of Horizon 2020 funding and is also funded by other associated partners such as the Wellcome and the Bill and Melinda Gates Foundation.^{32,33}

Participants noted that the Bill and Melinda Gates Foundation has emerged as a major international funder of vaccine and CHIM studies research. The Foundation has pledged to invest \$10bn over 10 years for vaccination programs across the world, and as part of this are investing \$100m per year for the Bill & Melinda Gates Medical Research Institute, which will develop novel vaccines alongside other research.³⁴ In addition, the Foundation funds a range of research aimed at tackling infectious diseases in LMICs through its Vaccine Development and Surveillance Program. For example, \$17m has been invested into the Malaria Clinical Trials Alliance, a program run by INDEPTH, an organisation that monitors health threats in 19 LMICs.³⁵ Researchers funded through the Program have access to the Global Health Vaccine Accelerator Platform, which acts as an infrastructure and data-sharing platform.³⁶

HIC-Vac: a new network for CHIM researchers

Professor Peter Openshaw FMedSci, Professor of Experimental Medicine, Imperial College London, described a new collaboration, the HIC-Vac collaborative network, founded in 2017, which is supported by the MRC and the BBSRC to support, develop and advocate the use of CHIM studies, both in the UK and internationally.³⁷ Professor Openshaw stated that HIC-Vac is a timely initiative to seize the opportunities of CHIM studies to tackle some of the major global health challenges. He described how CHIM studies provide a fast and cost-effective way to develop vaccines and that the UK is uniquely positioned to lead in this field, with world-leading expertise, extensive infrastructure and strong industry support. He also described that from a

²⁸ www.gov.uk/government/groups/uk-vaccines-network

²⁹ <http://ec.europa.eu/programmes/horizon2020/en/h2020-section/health-demographic-change-and-wellbeing>

³⁰ http://ec.europa.eu/research/participants/data/ref/h2020/wp/2016_2017/main/h2020-wp1617-health_en.pdf

³¹ http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/main/h2020-wp1415-health_en.pdf

³² www.imi.europa.eu/

³³ www.imi.europa.eu/get-involved/associated-partners

³⁴ [www.gatesfoundation.org/Media-Center/Press-Releases/2010/01/Bill-and-Melinda-Gates-Pledge-\\$10-Billion-in-Call-for-Decade-of-Vaccines](http://www.gatesfoundation.org/Media-Center/Press-Releases/2010/01/Bill-and-Melinda-Gates-Pledge-$10-Billion-in-Call-for-Decade-of-Vaccines)

³⁵ www.gatesfoundation.org/Media-Center/Press-Releases/2006/04/Malaria-Clinical-Trials-Alliance

³⁶ www.indepth-network.org/

³⁷ www.hic-vac.org/about-us

societal perspective there is a surprising willingness from the public to allow CHIM studies to take place, as the public recognise the benefits they produce and the pressing health issues they address.

Professor Openshaw went on to describe how HIC-Vac will create new collaborations via a £2.3m, 4-year MRC funded network that aims to support, develop and advocate the use of CHIM studies and to use them to better understand diseases and develop better vaccines and treatments. The HIC-Vac network is global, and includes collaborations in LMICs to help address some of the diseases of highest unmet need, such as malaria, typhoid and leishmaniasis, among others. In addition to forming these collaborations, the network aims to support regulatory and ethical structures governing CHIMs, support funding applications, enhance public understanding and stimulate the environment for conducting Phase III vaccine studies.

Professor Openshaw stated that HIC-Vac members range from across academic principal investigators, post-docs and affiliated researchers and is expected to grow further, both in the UK and internationally.

Finally, Professor Openshaw noted that the metrics for the success of HIC-Vac will be an increase in the number of successful grant applications, citations and, importantly, an increase in the number of CHIM studies.

Manufacturing standards for human challenge agents

The WHO GMP guidelines are a set of international standards designed to ensure that biological products, including human challenge agents, are manufactured to minimum standards.³⁸ In the US, the FDA requires that challenge agents are manufactured to a GMP standard. However, in the UK and the EU it is not currently a strict requirement to manufacture these to GMP standards. Manufacturing to GMP standards is, for practical reasons, more costly than not manufacturing to these minimum standards, but ensures that the agent meets minimum, internationally recognised standards. As a result, the decision of whether to manufacture challenge pathogens to GMP for use in CHIM studies is an important consideration when conducting a CHIM study.

Whilst the research community recognises the need for high quality in the manufacture of human challenge agents, it has been suggested that these standards could be at least '*GMP-like*', meaning that they would fulfil GMP requirements to as much as is practically possible without being GMP certified. Such a step would enable the manufacture of challenge agents outside of GMP certified settings, such as in academic labs or in countries where GMP facilities might not be as practical. This is especially relevant if the ambition is to manufacture challenge agents in the country where the CHIM study is to be conducted, such as LMICs. However, it is recognised that while GMP-like standards would allow this flexibility, it should not be an excuse for adopting low standards of manufacturing, as GMP standards provide reassurance about the safety of agents and the reproducibility of data generated, and '*GMP-like*' would need to be justified in each specific case. In addition, it was suggested that having variable standards for manufacture might reduce the ability to compare findings, especially if a study is conducted in multiple locations. As such, '*GMP-like*' needs to be clearly defined through guidelines to ensure quality and consistency.

The circumstances under which an agent should be GMP certified, rather than just GMP-like, was suggested as being when the CHIM study contributes directly to the licensing of a vaccine. However, it was recognised that, in some cases, it might not be technically feasible to manufacture an agent to GMP. An example was given of a challenge agent that had been successfully and safely used since the early 1990s, before the GMP guidelines were adopted (see case study 2). It was remarked that it would be impractical to now require this challenge agent to meet GMP for future studies. Currently, in circumstances where adhering to GMP might be too impractical to implement, or just impossible as a result of the requirements of production of the pathogen, the acceptability of the resulting agent and the evidence it generates to

³⁸ www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/

regulators would be in doubt. Regulators could have the flexibility to consider evidence about older agents on a case-by-case basis, however the process for doing this should be transparent and clearly articulated, and ensure that the manufacture of any agent meets clear quality standards that are agreed to be an acceptable alternative to GMP and offering sufficient protection to participants.

Case study 2 – use of well-established viral models

Professor Sebastian Johnston, Asthma UK Clinical Chair, National Heart and Lung Institute, Imperial College London conducts clinical studies using a rhinovirus strain to examine the clinical features of rhinovirus infections. These studies have used, and continue to use, a strain of rhinovirus, RV-16, that was originally inoculated into HeLa cells between 1992 and 1994. In the years since, RV-16 has been used in a number of studies as a model infectious agent for the common cold. As the rhinovirus was originally inoculated before GMP standards for biologicals existed, the agent pre-dates the WHO's GMP standards for biological products, which were first published in 1992 as well as the MHRA's 2004 Clinical Trial Directive.^{39,40} If legislation were to be updated to require live viral agents to be GMP-certified in line with other biological products, continued use of the rhinovirus, even within GMP certified manufacturing laboratories would not meet GMP requirements. This is despite the fact that the virus has been used safely for a significant number of years. This therefore raises the question of whether requiring challenge agents to meet GMP standards would be practical or proportionate given examples such as these.

³⁹ World Health Organization (1992). *Requirements for the collection, processing and quality control of blood, blood 34 components and plasma derivatives*. In: *WHO Expert Committee on Biological Standardization: Forty-third report*. Geneva: World Health Organization; 36 Annex 2 (WHO Technical Report Series, No. 840).

⁴⁰ Medicines and Healthcare products Regulatory Agency (2004). *The Medicines for Human Use (Clinical Trials) Regulations 2004*. www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf

The governance of CHIM studies

Ethical considerations for CHIM studies

Dr Claudia Emerson, Director, Institute on Ethics & Policy for Innovation, McMaster University introduced some of the ethical concepts that should govern the use of CHIM studies. Though they have played a pivotal role in the development of vaccines, CHIM studies, like most research involving human subjects, have the potential to cause harm. Therefore there needs to be a strong ethical justification to carry out these studies. CHIM studies have been conducted for many years without any major incidents that have caused great harm. However, the risk of such an incident remains, and it is important to identify the gaps in policy that can mitigate such risk. Dr Emerson explained that these gaps include the fact that there are very few guidelines for conducting CHIM studies beyond the need for REC approval. These committees also have little guidance to conduct aspects of evaluation of CHIM studies such as risk and benefits.

The risk-benefit considerations of a CHIM study vary depending on where the study is conducted. Most experimental vaccines are for infectious diseases that are endemic to LMICs, and so carrying out studies in those countries may make the findings more relevant to the real world, therefore increasing the benefit of the study. She also described how there continues to be gaps in the ethical guidance for CHIM studies. For example, a 2017 report presenting conclusions from an ethical review of Zika human challenge studies convened by the US National Institutes of Health, stated that *'the literature provides limited guidance on the ethics of conducting [CHIM] studies when the medical consequences are more uncertain.'*⁴¹ Dr Emerson also stated that a high risk does not necessarily make a trial unethical and the risk threshold for a particular study is highly contextual. However, ethics committees may not have the guidance or expertise in place to consider these contexts.

She described a situation where a CHIM study might be *'ethically required'* beyond just being *'ethically permissible.'* If it can be considered that *not* conducting a study would cause greater harm through untreated disease, then a CHIM study that may cause lesser harm may be ethically required.

An important consideration when assessing the ethics of conducting a CHIM study is informed consent of participants. In high- and middle-income countries, volunteers for trials are often

⁴¹ The National Institute of Allergy and Infectious Diseases and the Walter Reed Army Institute of Research (2017) *Ethical Considerations for Zika Virus Human Challenge Trials* www.niaid.nih.gov/sites/default/files/EthicsZikaHumanChallengeStudiesReport2017.pdf

young, healthy people with higher formal education, who would not naturally be exposed to the pathogen, and are participating in the trial due to the remuneration involved. However, if a study were to be conducted in an LMIC, the trial population might be very different, with a greater diversity of level of formal education, existing health conditions and age. While the latter provides benefits in terms of the relevance of the study to the real-world population, it makes ensuring informed consent more challenging, and may require cultural understanding and adjustments in the communication given to participants.

Dr Emerson highlighted that a large proportion of CHIM studies are run in the US and UK, with only 7% of studies run in LMICs according to her sampling of registered trials from clinicaltrials.gov.⁴² This may be because there are additional challenges, both practical and ethical, when conducting studies in LMICs. Practical challenges include a requirement for the essential infrastructure to allow production of the challenge agent, clinical facilities to conduct the trial, and to monitor and treat adverse events and issues with sanitation that may make environmental contamination more likely. Ethical challenges include ensuring fair recruitment and inclusion of volunteers, achieving an adequate level of informed consent and using an appropriate compensation scheme that does not exploit vulnerabilities.

Finally, Dr Emerson described an expanded framework for the ethical evaluation of CHIM studies. This framework, consisting of ten ethical issues and how they might be considered, incorporates new research to build upon the original seven ethical issues published by the National Institutes for Health in 2001.^{43,44} In addition, new research proposes extending this list to 14 ethical issues.⁴⁵ As such, the expanded framework for the ethical evaluation of CHIM studies consists of:

1. Rationale for the study – studies should have a clear scientific rationale and be designed to maximise the chances of answering the scientific question.
2. Risks of the study – the entire range of potential risks, including to participants and staff and also including environmental exposure, should be considered.
3. Discomforts that may be imparted – consideration of the acceptability of the direct discomfort expected to be imparted on participants.
4. The vulnerability of subjects – consideration of the trial participants and the circumstances under which they might be taking part in the study, including cultural context.
5. Informed consent – how participants can be effectively and adequately informed before participation.
6. Financial compensation – the most appropriate model for remuneration of participants that does not prey upon vulnerabilities.
7. The right to withdraw from research – ensuring participants can withdraw from a trial and that there is a mechanism to do so.
8. Independent review of models and methodologies – ensuring that the study protocols are independently reviewed and amended where required.
9. Publicly available rationale – protocols and rationale can be made publicly available.
10. Protection of the public – clear considerations of both potential environmental effects and societal implications of a study.
11. New models of compensation for harm – appropriate compensation for both the risk of harm and also harm actually caused.
12. Knowledge and data sharing – mechanisms for effectively sharing data or findings with the research community.
13. Community engagement – consideration of the interests and concerns of participant communities and how they might impact the appropriateness of a study.
14. Governance – oversight and clear assignment of responsibilities.

⁴² <https://clinicaltrials.gov/>

⁴³ Miller FG & Grady C (2001). *The ethical challenge of infection-inducing challenge experiments*. Clin Infect Dis. **33(7)**, 1028-1033

⁴⁴ Bamberg B *et al.* (2015). *Ethical Criteria for Human Challenge Studies in Infectious Diseases* Public Health Ethics. **9(1)**, 92-103

⁴⁵ Emerson C & Cullen K (2018). Unpublished manuscript.

Advisory oversight of UK CHIM studies

Professor Jonathan Montgomery, Chair, Health Research Authority (HRA) described the HRA's role in the governance of CHIM studies in the UK. He described how the HRA supports ethics committees and aims to identify '*smart regulation*' opportunities.

He described that the '*ethics of ethics*' is an area for consideration. More regulation does not necessarily ensure improvement in ethical standards or lead to ethically desirable outcomes. Regulators need to consider unintended outcomes. For example, children have often been excluded from studies for ethical reasons. However, many infectious diseases affect children the most, and as such there is an urgent unmet need for effective vaccines that can be given to children. He warned against creating a set of '*well-meaning anxieties*' that seem good intentioned but result in a poor evidence base. He suggested that this had occurred in the 1990s through establishing the principle that research involving children should only occur after data from adult research was available. Although the intention was to protect children, the unintended consequence had been that specific paediatric research was not undertaken, and medicines were commonly used in paediatric practice with a limited evidence base. It is important that regulation does not do harm, a familiar principle in medical ethics, and desirable that it actually does good. Regulation is not to be considered something that is automatically beneficial and it needs to be justified.

He went on to raise some concerns about the effectiveness of the informed consent model to address the challenges that CHIM studies bring. It needs to take into account all the different kinds of people who might be interested in taking part in CHIM studies. Following the reports of the adverse events in the Phase I study at Northwick Park,⁴⁶ interest from volunteers increased rather than dropped. He highlighted examples of 'citizen scientists' prepared to take risks for themselves that might be considered unreasonable in approved trials. The limitation of trials to those that fall below specified risk thresholds seems difficult to justify without becoming paternalistic: we are commonly permitted to decide for ourselves whether to take risks. However, within the informed consent model, it is appropriate for regulators to be concerned about the possibility that participants might be coerced or misled into participation. There is also the concern that participants might be wasting their time and effort as it is unfair to invite participants to take part in trials that are not deemed of sufficient benefit. This may therefore merit oversight of the invitation to participate rather than only the consent to do so.

The Nuffield Council for Bioethics highlighted the challenges around involving children in research in its 2015 report.⁴⁷ These included the principle that participants must be given a '*fair offer*' to participate in research and that certain requirements must be met for a study to be considered ethically sound. Firstly, the study must of sufficient scientific value to justify the anticipated risks, which should be mitigated as far as possible (otherwise participants are being treated merely as objects of study not be respected as co-contributors). Secondly, we should think about *who* should be invited. participant selection must be fair (for example, to avoid discrimination against excluded groups and selection bias), and appropriate (to ensure that the research will generate results that are applicable to the populations that might benefit from the knowledge to be produced). Thirdly, we should consider whether the researchers are the right people to be given a '*licence to ask*'. This includes not only the robustness of the protocols, but also the competency of the researchers including whether they are the best people to undertake the study and appropriately qualified and experienced to be permitted to invite participation. These questions do not displace other requirements for ethical approval but seem important aspects of our approach to oversight.

⁴⁶ Attarwala H (2010). *TGN1412: From Discovery to Disaster*. Journal of Young Pharmacists : JYP, 2(3), 332–336. <http://doi.org/10.4103/0975-1483.66810>

⁴⁷ Nuffield Council for Bioethics (2015). *Children and clinical research: ethical issues*. <http://nuffieldbioethics.org/project/children-research>

With regards to the infrastructure of regulation, he suggested that *'flagged ethics committees'*, who develop the particular experience and expertise to enable the decisions to be made most appropriately, might be a suitable way to better oversee CHIM study ethical approvals. He thought that this would be more helpful than a separate ethics committee. A separate committee would be appropriate if the trials raised radically different ethical problems from other trials and therefore needed dedicated ethical expertise. However, such an approach risked delays in the production of guidance and delays in approvals that might be avoided by enhancing expertise of existing RECs and using the administrative support that is already in place for efficient decision-making.

Professor Montgomery described a range of measures that could support CHIM studies. These include guidance on achieving informed consent and the appropriateness of model protocols, as well as potential incentives for publication, data sharing, reanalysis and sample sharing. These could be developed once for re-use in subsequent studies and in partnership by researchers, regulators and participants, to be brought together into published guidance. Such measures, which could also include transparency requirements and standardised good practices, could form part of a condition of funding for the main public sponsors. Subsequently, it might become possible, if the research community supported it, to make these measures conditions of regulatory approval. This would be worth considering if it enhanced the integrity of research and justified public trust in the outcomes.

He noted that the House of Commons Science & Technology Committee's current inquiry into research integrity provided the opportunity to raise such issues.⁴⁸

Finally, Professor Montgomery stated that the objective of all organisations and individuals involved in CHIM studies should be to maximise the *'returns on investment'* made by study participants, researchers and funders to ensure that the regulatory barriers are proportionate and do not prevent full realisation of the huge contribution that CHIM studies can make to our understanding and prevention of infectious disease.

⁴⁸ www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/inquiries/parliament-2017/research-integrity-17-19/

Guiding principles for CHIM studies

The ethics review environment for CHIM studies

Participants agreed that ethical guidelines would be useful for both researchers developing CHIM studies and the ethical committees tasked with reviewing them. The expanded ethical framework presented at the workshop could form the basis of these guidelines, however these need further development to ensure that they offer adequate protection for participants and proportionate governance for research within LMICs. Potential mechanisms could include a requirement for ethics review in the country of the funder as well as countries where the research is conducted and participants enrolled, clear guidelines on the involvement of local researchers and ensuring fair partnerships, and clarity about the different issues to be considered when implementing CHIMs in LMICs or high-income countries. It was also felt that these guidelines would be especially helpful for lay members on committees, who may not be familiar with some of the ethical issues of CHIM studies. The guidelines could also include case studies to help contextualise applications. Participants agreed that any framework must be accessible and transparent. It was suggested that they could be constructed by the CHIM research community, with others, and made freely available online.

While participants were broadly happy with the range of ethical guidelines that had been discussed, several important nuances were noted that should be considered in any potential guidelines. For example, participants were worried that guidelines for ethically selecting trial participants could be discriminatory towards certain groups, for example children, pregnant women or those unable to give fully informed consent. In an instance of an urgent health need, such as during an epidemic, this could mean that these groups are unable to access experimental vaccines that could otherwise benefit them. However, the group were of the view that CHIM studies which involved such vulnerable groups should be considered with extreme caution as there is both a high ethical risk and a risk of loss of confidence in research ethics if an approach was ill-advised.

Participants also felt that specialist expertise on ethics committees, in the form of 'flagged ethics committees' could be an effective way to ensuring that ethical reviews are conducted with consideration for a wide range of factors that are unique to CHIM studies. However, there was also concern that, as the number of CHIM studies increases, flagged committees might not have the capacity to review all applications, and as a result, other committees may need to bring in external experts.

Participants also discussed the necessary mechanisms for ensuring informed consent for

participants taking part in CHIM studies. There was concern that in some cases, the benefits and risks of a study were not clearly communicated to participants, and that lengthy information sheets were not an effective way of informing consent. In addition, long-term complications, such as the reactivation of an infection might not be routinely included in consent risk information. Typically, in clinical trials there is a cut-off time point beyond which risks are often not disclosed, and participants were unsure if CHIM studies should follow this same model.

The case for registration and sample banking

Participants agreed that the widespread and standardised registration of CHIM studies (using clinical trials registries such as isrctn.com and ClinicalTrials.gov) was an achievable and desirable ambition. It was noted that several funders, such as the MRC and Wellcome, require registration as part of the terms and conditions of the award. However, WHO have found that many CHIM studies are currently not being registered as there is no centralised, international system for doing so. It was suggested that registration must allow open access to the methodologies and results of studies, and if possible extend to open access to challenge agents to allow them to be used by other researchers.

There was widespread agreement that in principle, the characterisation and 'banking' of challenge agents for future use in research would be a worthwhile ambition. However, it was recognised that this was a significant challenge, and that previous attempts to do this have not been that successful. It was proposed that networks such as HIC-Vac could run such a storage facility. The characterisation of materials was also highlighted as an important facet of open and transparent research, especially if the physical banking of materials is likely to be an insurmountable challenge. However, it was also recognised that funding such a storage facility could be costly, and it is not clear how this would be funded. In addition, challenge agents can be physically and genetically unstable over time, which could reduce the utility of such a platform as well as make characterisation and standardisation of agents difficult. Furthermore, the insurance liability for institutions sharing challenge agents would need to be carefully considered. Finally, challenge agents used in small scale studies are often not manufactured in large quantities, which might preclude their future use in studies if there are not adequate stocks.

Guidance from regulatory authorities

Workshop participants felt that funders, regulatory agencies and ethics committees might be best placed to provide guiding principles on conducting CHIM studies. In addition to provide guidance on ethical considerations through the HRA, such guidance could also include recommendations for manufacturing processes, safety and data standards, transparency and openness, registration of studies and reporting adverse incidents. Participants felt that it was important that any such guidance was proportionate, and would be welcomed by the research community if it did not place a disproportionate burden on researchers.

Conclusions and next steps

The co-Chairs of the workshop, Professor Andrew Pollard FMedSci and Professor Maria Zambon FMedSci, closed the workshop by summarising the key messages that emerged from the day's discussions.

Participants felt strongly that CHIM studies were an increasingly important tool for developing vaccines. However, they also highlighted that the current lack of cohesive guidelines and direct regulation might dissuade researchers from having the confidence to undertake studies, impart unnecessary heterogeneity and risk into conducted studies, and undermine confidence in the results from studies. As such, it was suggested that the research community needs to come together with regulatory agencies and funding bodies to decide on the guiding principles and responsibility for maintaining and updating them. There are already established processes for clinical trials which could be adopted to provide appropriate support for CHIM studies. In addition, the research community could engage more with regulatory agencies such as the MHRA to determine if there is a need for the regulators to take an active role in overseeing the manufacture of challenge agents or to help develop further guidelines on the conduct of studies.

There was also a consensus that there is an ongoing need to explore the possibility of a universal registry for CHIM studies, as well as a possible material bank for challenge agent characterisation and storage. The role and use of GMP standard manufacturing, and the appropriateness and acceptability of 'GMP-like' standards was also a key source of debate.

Finally, participants felt that there was an ongoing need for improved data- and sample-sharing within the research community, and greater engagement outside of the community to improve transparency and public confidence in CHIM studies and the vaccine development they support.

Following the discussions held at the workshop, the co-Chairs suggest that:

- The CHIM research community develops a set of guiding principles for RECs to support them in their decision making when considering CHIM studies and to enhance their experience and expertise in assessing such studies. These guidelines could be independently reviewed by the HRA prior to recommending their adoption by RECs as Standard Operating Procedures.
- The CHIM research community and the MHRA engage in dialogue to discuss the need for, and appropriateness of, any further regulatory oversight. Any such regulation would aim to provide reassurances to stakeholders whilst being proportionate.
- The CHIM research community, in addition to funders and regulators, should come to a unified, international agreement on the roles and responsibilities of stakeholders in ensuring CHIM studies are conducted with best practice worldwide – which includes adhering to CONSORT-like guidelines to ensure appropriate reporting and transparency.
- Stakeholders should consider the potential for further deliberation on the key issues facing CHIM studies, particularly with an international focus and involving LMIC representatives.
- Funding bodies should consider the funding or creation of an archive for the banking of characterised challenge agents and their associated studies, methodologies and results, and develop the associated governance of this archive.

A further summary on the current responsibilities and steps for best practice for stakeholders suggested by participants during the workshop can be found in Annex I.

Annex I – Responsibilities and best practice for stakeholders

<p>Principal investigators</p> <ul style="list-style-type: none"> • Ensure Research Ethics Committee approval prior to undertaking human studies. • Ensure MHRA approval prior to undertaking human studies involving a vaccine. • Ensuring ACRE approval when conducting a study using GMO challenge agents, and approval by the appropriate local GMO committee. • Ensure NHS R&D approval when undertaking a study using NHS facilities. • Consider seeking MHRA regulatory expert scientific advice as guidance for conduct of studies. • Strive to manufacture challenge agents to GMP standards where practical and achievable. • Consider registering studies with the most relevant national or international trial registry • Consider making data from studies available and publish in academic literature where possible. • Consider the appropriate governance and due diligence to allow the sharing of challenge agents with third parties in a safe and accountable manner. 	<p>Regulatory bodies</p> <p>MHRA</p> <ul style="list-style-type: none"> • MHRA approval is necessary for UK studies involving vaccines. • MHRA can provide regulatory expert scientific advice to researchers and sponsors. <p>Ethics</p> <ul style="list-style-type: none"> • Research Ethics Committee approval is necessary for all human studies involving human challenge agents.
	<p>Funding bodies</p> <ul style="list-style-type: none"> • Encourage grant-holders to adhere to funders' research policies on publication and data-sharing. • Encourage grant-holders to adhere to requirements to register trials on databases. • Ensure that studies have undergone scientific review to ensure these are important and relevant.
	<p>Sponsors of studies</p> <ul style="list-style-type: none"> • Consider seeking MHRA regulatory expert scientific advice as guidance for sponsoring studies.

Annex II – Agenda

09.30 – 10.00	Registration
Introduction	
10.00 – 10.10	Welcome from the co-Chairs
10.10 – 10.15	Human challenge studies: the 2005 Academy of Medical Sciences report Professor Richard Moxon FRS FMedSci , Emeritus Professor of Paediatrics, University of Oxford.
Session 1: The UK environment for human challenge studies	
10.15 – 10.25	The HIC-Vac network: structure and aims Professor Peter Openshaw FMedSci , Director of the HIC-Vac Network and Professor of Experimental Medicine, Imperial College London
10.25 – 10.50	Funding human challenge studies in the UK Dr Charlie Weller , Head of Vaccines Programme, Wellcome; Dr Jonathan Pearce , Head of Infection and Immunity, Medical Research Council & Dr Martin Broadstock , Programme Manager for Immunology, Medical Research Council
10.50 – 11.10	Developing a human challenge model for TB Professor Helen McShane , Professor of Vaccinology and Wellcome Trust Senior Clinical Fellow, University of Oxford.
11.10 – 11.30	Refreshment break
Session 2: The ethics and regulation of human challenge studies	
11.30 – 11.50	Ethical considerations for human challenge studies Dr Claudia Emerson , Director of the Institute on Ethics & Policy for Innovation, McMaster University.
11.50 – 12.10	Oversight of UK human challenge studies Professor Jonathan Montgomery , Chair, Health Research Authority
12.10 – 12.30	Human Challenge Trials for vaccine development: WHO approach Dr Ivana Knezevic , Group Lead, Norms and Standards for Biologicals, World Health Organization.
12.30 – 13.00	Regulatory perspectives on human challenge studies Dr Marco Cavaleri , Head of Anti-infectives and Vaccines, Scientific and Regulatory management Department, European Medicines Agency. Dr Graham McNaughton , Pharmaceutical Assessor, Medicines and Healthcare products Regulatory Agency.
13.00 – 13.45	Lunch
Session 3: Developing a model of best practice to ensure safety	
13.45 – 13.55	Recap of the morning's discussion Chairs
13.55 – 14.35	Break-out session 1

	In this break-out session, attendees will be split into groups and asked to consider the key issues for: a) the manufacture of agents, b) the oversight of studies, and c) how to maximise the benefits of volunteer challenge studies.
14.35 – 15.00	Feedback and discussion
15.00 – 15.15	Refreshment break
15.15 – 15.55	Break-out session 2 In this break-out session, attendees will discuss practical steps that could be taken to improve current best practice and what should be included as guiding principles for ethics committees and investigators.
15.55 – 16.50	Feedback and discussion
16.50 – 17.00	Closing remarks Chairs
17.00 – 19.00	Drinks reception
19.00	Close

Annex III – Participant list

Co-Chairs

Professor Andrew Pollard FMedSci, Professor of Paediatric Infection and Immunity, University of Oxford; Director, Oxford Vaccine Group

Professor Maria Zambon FMedSci, Director of Reference Microbiology, Public Health England

Speakers and panellists

Dr Martin Broadstock, Programme Manager for Immunology, Medical Research Council

Dr Marco Cavaleri, Head of Anti-infectives and Vaccines, European Medicines Agency

Dr Claudia Emerson, Director, Institute on Ethics & Policy for Innovation, McMaster University

Dr Ivana Knezevic, Group lead, Norms and Standards/Biologicals, World Health Organization

Dr Graham McNaughton, Pharmaceutical Assessor, Medicines and Healthcare products Regulatory Agency

Professor Helen McShane, Professor of Vaccinology, Wellcome Senior Clinical Fellow at the Jenner Institute, University of Oxford

Professor Jonathan Montgomery, Chair, Health Research Authority

Professor Richard Moxon FRS FMedSci, Emeritus Professor of Paediatrics, University of Oxford

Professor Peter Openshaw FMedSci, Director of the HIC-Vac Network and Professor of Experimental Medicine, Imperial College London

Dr Jonathan Pearce, Head of Infection and Immunity, Medical Research Council

Dr Charlie Weller, Head of Vaccines Programme, Wellcome

Participants

Professor Richard Ashcroft, Professor of Bioethics, Queen Mary University of London

Ms Shobana Balasingam, Senior Project Officer, Wellcome

Dr Paul Bowyer, Principal Scientist, Division of Bacteriology, NIBSC

Professor Jeremy Brown, Professor of Respiratory Infection, University College London

Dr Bryan Charleston, Director, Pirbright Institute

Ms Jane Cheeseman, Member, South Central Research Ethics Committee (Oxford A)

Dr Christopher Chiu, Clinical Senior Lecturer, Imperial College London

Mr Thomas Darton, NIHR Academic Clinical Lecturer in Infectious Diseases, University of Sheffield

Dr Hugh Davies, Chair, South Central Research Ethics Committee (Oxford A)

Dr Jeanne-Marie Devaster, Director, Clinical and Epidemiology Lead Early and Discovery projects, GSK Vaccines

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Annex IV – Glossary

ACRE – Advisory Committee on Releases to the Environment
BBSRC - Biotechnology and Biological Sciences Research Council
BCG – Bacillus Calmette-Guérin
CEPI – Coalition for Epidemic Preparedness Innovations
CHIM – Controlled Human Infection Study
CONSORT – Consolidated Standards of Reporting Trials
CTD – Clinical Trials Directive
EMA – European Medicines Agency
EPSRC – Engineering and Physical Sciences Research Council
FDA – Food and Drug Administration
GCP – Good Clinical Practice
GMO – Genetically Modified Organism
GMP – Good Manufacturing Practice
HRA – Health Research Authority
IRB – Institutional Review Board
MHRA – Medicines and Healthcare products Research Agency
MRC – Medical Research Council
MTB – Mycobacterium tuberculosis bacteria
NEAC – National Ethics Advisory Committee
REC – Research Ethics Committee
RV-16 – a strain of rhinovirus
WHO – World Health Organization



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