



Inno4Vac ST2 Final Stakeholder Meeting – 28-29 September 2026

Stakeholder meetings organized to date: gaps identified and solutions

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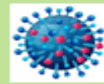
Inno4Vac ST2 – Novel CHIMs

- Optimized pipelines for identification, characterization & GMP manufacture of new challenge pathogen strains
- Clinically evaluate the challenge agents

ST2 Novel controlled human infection models:



C. difficile



Influenza



RSV

- Development of new and improved CHIMs
 - Positioning new developed CHIMs in regulatory framework
- Develop a strategy for integration of CHIMs into pharmaceutical development.
 - Position newly developed CHIMs in the regulatory framework by addressing hurdles to regulatory acceptance

Inno4Vac CHIM Stakeholder Workshops (2021-2025)

Influenza & RSV CHIM
strain selection and
immune assays

Regulatory Workshop on
Challenge strain
development and GMP
manufacture

C. difficile CHIM
development / strain-
selection workshop

CHIMs in endemic
countries + regulatory
issues

Ethical Approval for
CHIM Clinical Trial
Protocols

Design of CHIMs,
including clinical
procedures, endpoints,
data integrity and
ethical considerations

Refining the Regulatory
and Ethics Context of
CHIMs

→ Development of an Inno4Vac CHIM Roadmap based on Stakeholder Engagements

What informed the Roadmap?

Active stakeholder engagement, rather than a conventional literature review.

7 stakeholder meetings

Conducted between 2021 and 2025 across scientific, regulatory, ethics and implementation topics.

9 workshop manuscripts

Qualitatively reviewed and synthesised to extract gaps, challenges and recommendations.

D11.6 on NGS for QC

Added evidence on the optimal use of next-generation sequencing for quality control of human challenge agents.

Scope spans challenge agent selection and manufacture, clinical trial design and endpoints, data sharing, third-party risks, stakeholder engagement and ethics.

Inno4Vac CHIM Roadmap

Development and standardization of Controlled Human Infection Models for Influenza A(H3N2), RSV-B and toxigenic *C. difficile*

Influenza A(H3N2)

RSV-B

C. difficile

PURPOSE

From evidence gaps to coordinated action

- Provide a structured overview of key challenges, evidence gaps and priority actions.
- Support coordinated future CHIM research and model standardization.
- Inform policy and regulatory decision-making.

Topic for today: Novel CHIMs to be prioritized

The Roadmap at a glance



- 1 **Challenge agent selection & manufacturing**
- 2 **Scientific integration (design, endpoints, assays, data)**
- 3 **Third-party risks**
- 4 **Stakeholder engagement**
- 5 **Ethics**

These pillars are interconnected. Ethics, regulatory dialogue and stakeholder engagement run across the full lifecycle.

Pillar 1: Challenge agent selection & manufacturing

- Challenge strain selection:
 - ❑ Carries scientific, regulatory, legal and ethical implications.
 - ❑ Requires balancing clinical representativeness, virulence, transmissibility and shedding, genetic stability, treatment susceptibility, host immunity and route of administration.
- Wild-type isolates can create donor-liability, material-transfer, access/benefit-sharing and import challenges.
- Reverse-genetics approaches may ease sourcing but can trigger GMO classification and regulatory requirements.
- A central gap is how to manage production when conventional GMP requirements cannot reasonably be met.

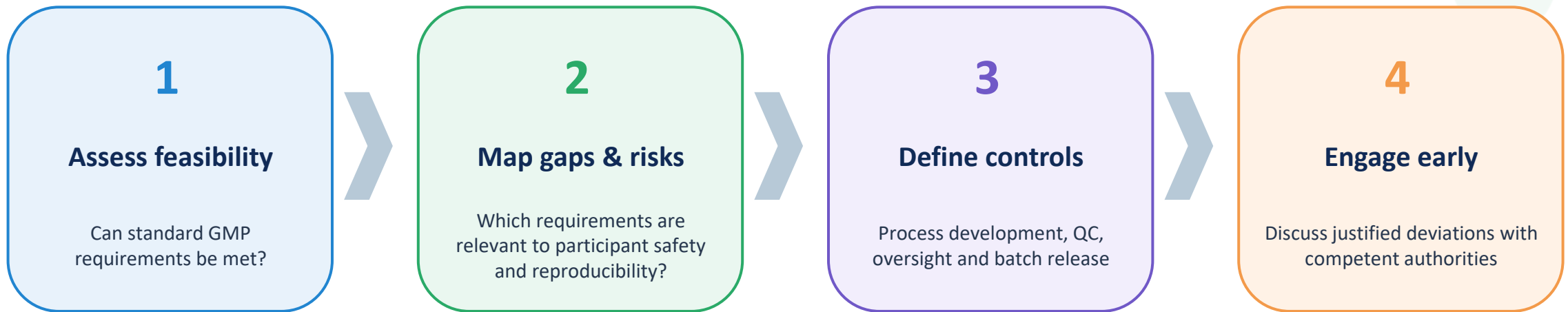
Topic for today: GMO regulation in the EU



From strain selection to quality-controlled challenge agent

Manufacturing: a proportionate, risk-based approach

The roadmap highlights the challenge of aligning conventional GMP expectations with the specific requirements of live challenge agents



CDMOs can provide mature quality systems, but availability, cost and limited experience with specific organisms may constrain feasibility.

Experienced research laboratories may sometimes be an alternative when operating to appropriate GMP principles and in close regulatory consultation.

Quality control and the evolving role of NGS

- NGS can strengthen:
 - ☐ identity confirmation, genetic-stability assessment, detection of variability in challenge agents and
 - ☐ safety if used for detection of adventitious agents.
- Potential use spans strain selection and manufacturing stages, including seed and cell-bank characterisation.
- NGS was not formally established as a pharmacopeial method at the time of the workshops.
 - ☐ NGS is currently established as a pharmacopeial method (Ph. Eur. 2.6.41) to detect viral extraneous and adventitious agents in biological products.

Topic for today: NGS in challenge agents QCs



Analytical characterisation as part of the manufacturing pathway

Pillar 2: Scientific integration

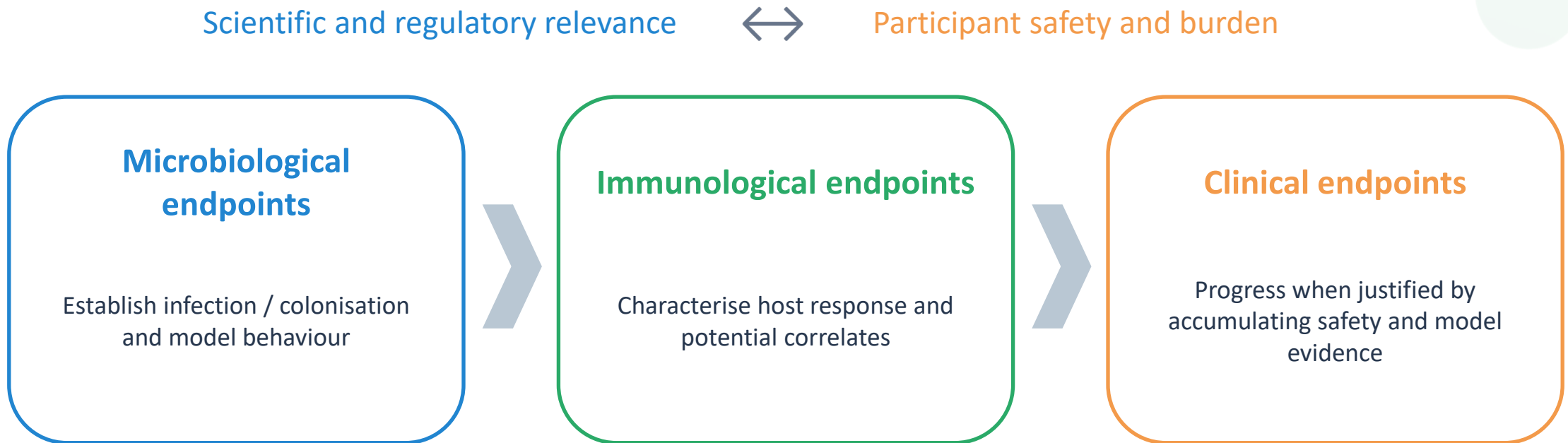
- Harmonise study protocols where appropriate.
- Standardise immunological, microbiological and clinical endpoints and assays to improve comparability.
- Balance clinically meaningful endpoints against participant risk.
- Ensure timely trial registration, reporting and data sharing.
- Develop data-sharing frameworks that ensure compliance with applicable privacy regulations while maximizing ethically appropriate data reuse.



Harmonising procedures, endpoints, assays and data

Endpoint strategy: build evidence stepwise

A pragmatic model-development sequence can increase scientific value while containing uncertainty and risk.



What evidence should trigger progression to more clinically meaningful endpoints?

Data sharing: make CHIM data reusable



- Clinical CHIM datasets are not consistently accessible or reusable for broader evidence synthesis.
- GDPR, international exchange, pseudonymisation/anonymisation and genetic data create practical constraints.
- Use standard data formats and robust governance to support cross-study comparability and secondary use.
- Strengthen prospective trial registration and adherence to FAIR principles: Findable, Accessible, Interoperable and Reusable.

Opportunity: connect to existing health-data infrastructures rather than creating parallel systems.

Pillar 3: Third-party risks

- Secondary transmission risk requires explicit attention, particularly where participants live with vulnerable contacts.
- Community-based risk communication and education can support prevention of onward transmission.
- GMO-based pathogens may trigger environmental-permit processes that explicitly consider bystander risk; equivalent processes may be less clear for wild-type agents.
- Risk assessment should be data-driven and linked to ethically acceptable thresholds.

**Topic for today: Third-Party Risk Mitigation:
Practical and Ethical Boundaries**



Safeguards extend beyond the enrolled participant

Outpatient CHIMs: benefits and safeguards

Outpatient designs can reduce burden and cost and may better reflect real-life settings, but they change the risk-management model.

Potential benefits

- Less confinement burden
- Lower operational cost
- More real-life context

Key risks

- Loss to follow-up
- Potential secondary transmission
- Reduced direct monitoring

Proportionate safeguards

- Facilitation and reminders
- Scheduled follow-up
- Clear escalation pathways
- Avoid coercion or undue influence

Pillar 4: Stakeholder engagement



- Engage stakeholders early and continuously
 - ❑ Engagement should begin during needs assessment and study design, not immediately before submission and/or recruitment.
- Different groups need different engagement approaches: communities, potential participants, clinicians, scientists, policymakers and regulators.
- Patient and Public Involvement and Engagement (PPIE) can be difficult where disease-specific patient organisations are limited or absent.
- Feedback loops and debriefing can improve future study design and engagement.
- Continuous regulator and stakeholder engagement is a roadmap priority.

Topic for today: Community Expectations and Acceptability: Beyond the Investigator View

Pillar 5: Ethics

The challenge is not to remove all risks. It is to ensure that risks are justified, understood, proportionate and managed.

Expertise

Improve knowledge sharing and access to CHIM-expertise.

Early dialogue

Strengthen interaction between sponsors/researchers and ethics committees.

Review criteria

Clarify how novelty, uncertainty, social value and third-party risks should be assessed during review.

Consent

Provide multiple opportunities to participants to understand study implications and assess comprehension.

Remuneration

Use transparent, contextually appropriate and ethically justified approaches.

Ethics review: focus on the quality of the whole design

- A strong ethics submission must justify why a CHIM approach is scientifically and ethically justified.
- Protocol, informed-consent materials and participant information should be consistent and create transparency.
- Risk reduction is embedded in design: inclusion/exclusion criteria, stepwise development, confinement when needed, strain selection and manufacturing controls.
- Safety oversight, including appropriate independent data safety monitoring, supports the balance between participant protection and scientific value.

Does the study create irreplaceable scientific or social value that justifies the residual risk after proportionate safeguards are applied?

Topic for today: Regulatory gaps to be filled



Standards & Compliance



Responsible conduct & Trust

1 Challenge agent selection & manufacturing

Define donor liability, legal restrictions and material transfer obligations for selecting and sharing pathogen isolates

Refine regulatory strategies for challenge agents based on RG strains & GMOs (EU)

Evaluate feasibility to manufacture challenge strains under GMP

Address risks associated with use of challenge agents manufactured under non-GMP conditions

Define the role of CDMOs in the production of challenge agents

Implement regulations governing challenge agents GMP production and process development (including QC)

Define the role for next-generation sequencing (NGS) into quality control processes

2 Scientific integration

Harmonise study protocols

Standardise immunological, microbiological & clinical endpoints assays

Facilitate data sharing while ensuring GDPR compliance

Adopt FAIR data principles across all study data

Ensure timely trial registration, reporting & dataset sharing

3 Third-party risks

Develop community-based risk communication & education strategies

Implement measures to prevent loss to follow-up in outpatient studies and third-party risk

Ensure equity in participant remuneration

4 Stakeholder engagement

Promote community and public engagement

Continuous engagement with Regulators

5 Ethics

Establish early & ongoing dialogue to improve communication between EC and institutions sponsoring CHIM studies

Implement defined review criteria to guide evaluations

Balance potential benefits and harms to participants

Ensure payments and remuneration are ethically justified

Perform risk assessments to evaluate social value & participant safety.

Assess risks to third parties during ethical review

Provide participants with multiple opportunities to understand the informed consent process



Topics for this Workshop

Looking ahead: challenges, gaps and CHIMs to be developed

- CHIMs to be prioritized
- NGS in challenge agents QCs
- GMO regulation in the EU
- Regulatory gaps to be filled

Protecting Third Parties from the perspective of CHIM Trial Organisers

- Third-Party Risk Mitigation: Practical and Ethical Boundaries

Community Perspective on CHIM studies

- Community Expectations and Acceptability: Beyond the Investigator View



Generative AI tools, including Microsoft Copilot, were used to support language refinement, content structuring, and the creation of selected visual materials. All scientific content and AI-generated outputs were reviewed and validated by the author.



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