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Policy Guidelines

The COVID-19 pandemic exposed critical gaps in Europe's clinical trial infrastructure and regulatory frameworks for responding to health emergencies. The COVend consortium, through its experience conducting the IXION and IXION2.0 trials, identified key areas where existing European regulatory guidance requires enhancement to enable more agile, effective responses to future pandemics while maintaining robust scientific standards.

These policy guidelines present specific recommendations aligned with existing European regulatory frameworks, addressing six critical areas: adaptive trial design, disease recognition standards, mechanism-based drug development, inter-pandemic infrastructure maintenance, cross-European data harmonisation, and artificial intelligence (AI)-driven clinical decision support. Each section maps COVend's operational insights to relevant European Medicines Agency (EMA) guidelines, European Health Emergency Response Authority (HERA) frameworks, and EU regulations, proposing concrete improvements based on real-world pandemic trial experience.

The recommendations support transitioning from disease-specific to mechanism-based therapeutic approaches, enabling treatments developed for one condition to be rapidly deployed against others with shared pathophysiology. Throughout these guidelines, we use the terms "mechanism-based" and "host-directed" therapies. Mechanism-based trials and therapies can target biological mechanisms in either the pathogen or the host, the prerequisite is understanding the underlying biological mechanisms. Host-directed therapies specifically target host biological responses which we may not necessarily fully understand. The COVend approach was host-directed from the beginning, targeting endothelial dysfunction and capillary leak - host responses common across multiple conditions. The strategic shift was from disease-specific application (COVID-19 only) to mechanism-based application (multiple conditions causing acute respiratory distress syndrome, ARDS), while maintaining the same host-directed therapeutic strategy. This evolution from COVID-19-specific IXION to the broader IXION2.0 trial based on mechanistic knowledge offers a sustainable model for maintaining clinical trial readiness between health emergencies while advancing routine patient care.

These guidelines aim to inform policymakers, regulatory authorities, and research organisations in establishing more resilient, adaptable frameworks for clinical research that can seamlessly scale from routine operations to emergency response.

Adaptive Trial Design Framework

Relevant Guideline: EMA Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design (CHMP/EWP/2459/02)

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Purpose: This document focuses on the opportunities for interim trial design modifications, and the prerequisites, problems and pitfalls that must be considered as soon as any kind of flexibility is introduced into a confirmatory clinical trial intended to provide evidence of efficacy. It provides regulatory guidance for planning, conducting, and reporting adaptive clinical trials while maintaining scientific validity and regulatory acceptability.

COVend Recommendations:

- Establish pre-approved protocols for pivoting from pathogen-specific to mechanism-based and/or host-directed approaches, enabling rapid response to evolving epidemiological conditions (as demonstrated in the transition from COVID-19-specific IXION to mechanism-based IXION 2.0)
- Create regulatory pathways for rapid protocol amendments when epidemiological conditions change, including streamlined approval processes for expanding patient populations from single-pathogen to multiple aetiologies
- Develop templates for transitioning trials from emergency response to routine clinical research, incorporating lessons learned from pandemic-to-endemic transitions
- Include provisions for maintaining trial integrity when adapting primary endpoints and patient populations mid-study
- Establish clear communication channels between sponsors and regulatory authorities (EMA/national competent authorities) for discussing mechanism-based adaptations during ongoing trials

ARDS Recognition Standards

Relevant Guideline: European Society of Intensive Care Medicine (ESICM) Guidelines on Acute Respiratory Distress Syndrome: Definition, Phenotyping and Respiratory Support Strategies (2023)

Purpose: The aim of these guidelines is to update the 2017 clinical practice guideline (CPG) of the ESICM. The scope of this CPG is limited to adult patients and to non-pharmacological respiratory support strategies across different aspects of ARDS, including ARDS due to COVID-19. These guidelines address definition, phenotyping, and management strategies to improve recognition and treatment of ARDS across European intensive care settings.

COVend Recommendations:

- Implement systematic screening protocols for mild/moderate ARDS on general wards, addressing the significant under-diagnosis identified during the IXION 2.0 trial where eligible patients were frequently missed outside intensive care unit (ICU) settings
- Standardise ARDS diagnostic criteria across European hospitals using Berlin criteria, with particular emphasis on recognizing mild ARDS (PaO2/FiO2 200-300 mmHg) which often goes undetected
- Create awareness programs for non-ICU healthcare professionals including training on early ARDS recognition, as many cases present initially on general medical and surgical wards
- Develop rapid assessment tools for ward staff to identify patients at risk of ARDS progression, incorporating simple clinical parameters and biomarkers
- Establish clear referral pathways between general wards and ICU teams for suspected ARDS cases, ensuring timely intervention opportunities and patient enrollment into clinical trials

Mechanism-Based Drug Development Pathway

Relevant Guideline: EMA Innovation Task Force (ITF) Framework and EU Innovation Network (EU-IN) Mandate

Purpose: The Innovation Task Force (ITF) briefing meetings offer developers early dialogue with the EMA on innovative medicines. They address regulatory, technical and scientific concerns arising from innovative medicines, technologies and methodologies. The EU Innovation Network's aim is to improve regulatory support for medicine developers at national and European level in order to make investment in innovative medicines more appealing.

COVend Recommendations:

- Establish regulatory framework for host-directed therapies targeting multiple conditions with shared pathophysiology (e.g., capillary leak/endothelial dysfunction across COVID-19 and other infectious diseases, sepsis, reperfusion injury)
- Define biomarkers for endothelial dysfunction that can guide treatment decisions across different aetiologies
- Create guidance for drugs addressing pathophysiological mechanisms rather than specific pathogens, enabling broader therapeutic applications
- Develop accelerated pathways for host-directed drugs that demonstrate efficacy across multiple conditions through common biological targets
- Support early ITF briefing meetings for mechanism-based approaches, facilitating regulatory dialogue on cross-indication development strategies

Inter-Pandemic Infrastructure Maintenance

Relevant Guideline: EU Health Emergency Preparedness and Response Authority (HERA) Framework and European Partnership for Pandemic Preparedness

Purpose: Via Horizon Europe and EU4Health funding, HERA is further investing in pandemic preparedness research and development, for instance by setting up sustainable networks, platforms and infrastructures that can be adapted quickly to emerging or previously unknown pathogens. The framework aims to maintain "ever-warm" production capacity and clinical trial networks that can smoothly transition to public health interventions during emergencies.

COVend Recommendations:

- Create protocols for studying mechanism-based therapies in endemic diseases (e.g., dengue, sepsis) during peacetime, maintaining active research that provides dual benefits for routine care and pandemic readiness
- Establish minimum readiness standards for clinical trial networks, including requirements for maintaining trained staff, validated eCRF systems, and regulatory compliance between emergencies
- Support "ever-warm" clinical trial sites through sustainable funding models that prevent the loss of expertise and infrastructure during inter-pandemic periods

- Implement expedited pathways within the Clinical Trials Information System (CTIS) for pandemic-related trials, ensuring rapid regulatory review and approval processes can be activated during health emergencies while maintaining scientific rigour

Cross-European Harmonisation

Relevant Guideline: European Health Data Space (EHDS) Regulation and GDPR Harmonisation Framework

Purpose: The provisional agreement establishes clear rules for the use of health data for better healthcare delivery, research, innovation, and policymaking. The EHDS creates a unified legal framework to address the fragmentation caused by divergent member state implementations of GDPR, enabling secure cross-border exchange of health data while establishing a harmonised legal and technical framework for electronic health record (EHR) systems, fostering interoperability, innovation, and the smooth functioning of the internal market.

COVend Recommendations:

- Standardise data sharing agreements for multi-center trials using EHDS framework, eliminating the need for bilateral agreements between each participating country, institution, and partner
- Harmonise biobanking protocols for -omics research across EU member states, establishing common standards for sample collection, storage, and transfer that comply with both GDPR and EHDS requirements
- Implement interoperable electronic health record systems that support both primary care and research use, facilitating seamless data flow for clinical trials across borders
- Establish common technical standards for pseudonymisation and data security in clinical trials, ensuring consistent protection levels while enabling legitimate research across member states

AI-Driven Clinical Decision Support Framework

Relevant Guideline: EU AI Act (Regulation EU 2024/1689) and EMA Guidelines on AI in Healthcare

Purpose: The EU AI Act is an important change for the providers and deployers of AI systems, also in the healthcare sector. The Act classifies many AI systems used in healthcare and clinical trials as high-risk, requiring strict compliance with transparency, data governance, and human oversight requirements to ensure safe and trustworthy AI deployment in medical contexts. To support the post-market surveillance of the AI system, the personnel need to record the true outcomes of the patients to the AI system logs so that its performance can be followed.

COVend Recommendations:

- Establish validation frameworks for AI models using synthetic data when real patient data is limited, as demonstrated in COVend's approach to developing decision support tools during recruitment challenges

- Avoid restrictive inclusion criteria in patient recruitment because diversity in model training is considered useful and the inclusion criteria can be refined in the model development cycles later if necessary
- Implement explainable AI requirements for clinical decision support systems, ensuring healthcare professionals understand the reasoning behind AI-generated treatment recommendations
- Develop continuous monitoring systems for AI performance in clinical settings, particularly for models predicting treatment response or disease progression
- Establish interdisciplinary review boards combining AI expertise with clinical knowledge to evaluate AI-driven decision support tools before deployment and consider the inclusion of patient representatives in such boards