CIRS Workshop:
Reimagining medicine regulatory models

Outputs from multi-stakeholder discussions

This R&D Briefing summarises the outputs of breakout group discussions held during a CIRS multi-stakeholder workshop entitled 'Reimagining medicine regulatory models: implementing fit-for-purpose sustainable activities for patient access'. Each breakout focused on one of the above areas and discussed activities that evolved as a result of the COVID-19 pandemic as well as lessons learned that could inform future regulatory models.

R&D BRIEFING 80

CIRS Centre for Innovation in Regulatory Science

Background

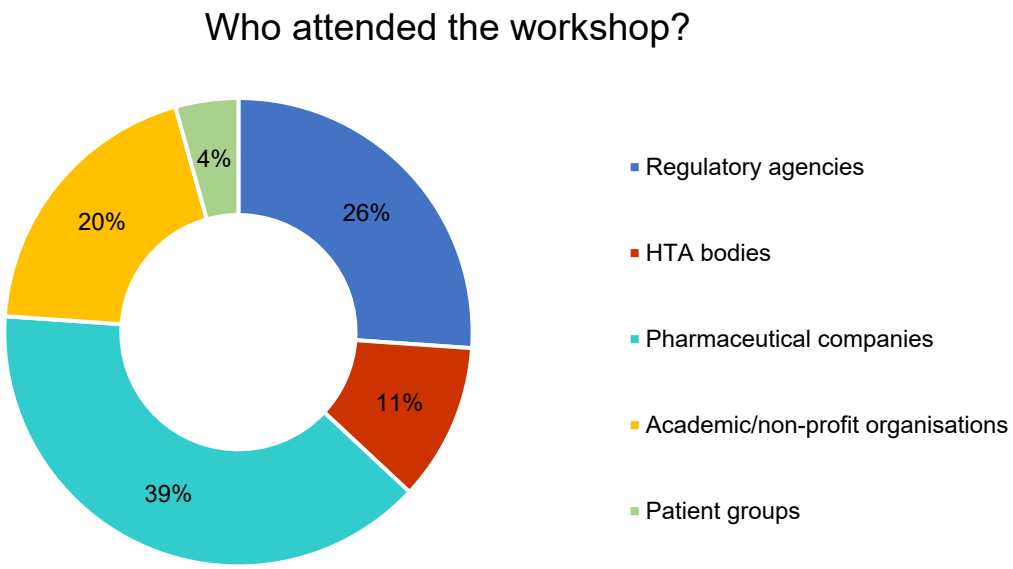
As the regulatory landscape changes to meet new challenges, such as increasingly sophisticated medical innovations, fundamental questions are being raised: What is the role of a 'modern' regulator today? Does the regulatory paradigm need to be reconstructed to meet future demands? These questions need to be addressed if regulators are to remain relevant as well as being part of the solution for the sustainable development and review of innovative medicines.

This issue has been confronted from a practical standpoint by the COVID-19 pandemic, as regulatory and Health Technology Assessment (HTA) systems globally have been (and continue to be) challenged to support the pandemic response. There has been increased stakeholder dialogue to identify where flexibilities are possible and can be enacted within an agency's legal framework. These have covered areas such as supply chain; conduct and reporting of clinical trials; manufacturing, inspection and quality audits; authorisation review processes; and post-authorisation activities.

As well as challenges, the pandemic has also created opportunities for developing and evaluating new medicines, such as in the areas of clinical trials, digital technologies, patient engagement, collaborative working and knowledge sharing. It will be important to carry these learnings forward into future regulatory models, for both emergency and non-emergency situations.

To evaluate whether current regulatory models are meeting evolving needs for medicines, CIRS held a virtual multi-stakeholder workshop on 8-9th December 2020. The workshop was held in memory of world-leading regulatory expert, Professor Sir Alasdair Breckenridge, who had challenged CIRS to consider this topic prior to his death in December 2019. Representatives from 13 regulatory agencies and related organisations, five HTA bodies, 18 international pharmaceutical companies, eight academic/non-profit organisations and two patient groups attended the workshop, with geographical representation stretching across Europe, Australia, Asia and the Americas.

A key objective of the workshop was to make recommendations on activities that should be considered to evolve a sustainable, fit-for-purpose regulatory model(s) for the development, review and access of new medicines. This was facilitated through breakout groups during which workshop participants discussed lessons learned from four areas that had to fundamentally change because of the pandemic: clinical trials, digital technologies, patient engagement and collaboration. The outputs of these breakouts are summarised in this Briefing to help inform future work and thinking in the studied areas as well as more sustainable regulatory models for the development and review of new medicines.

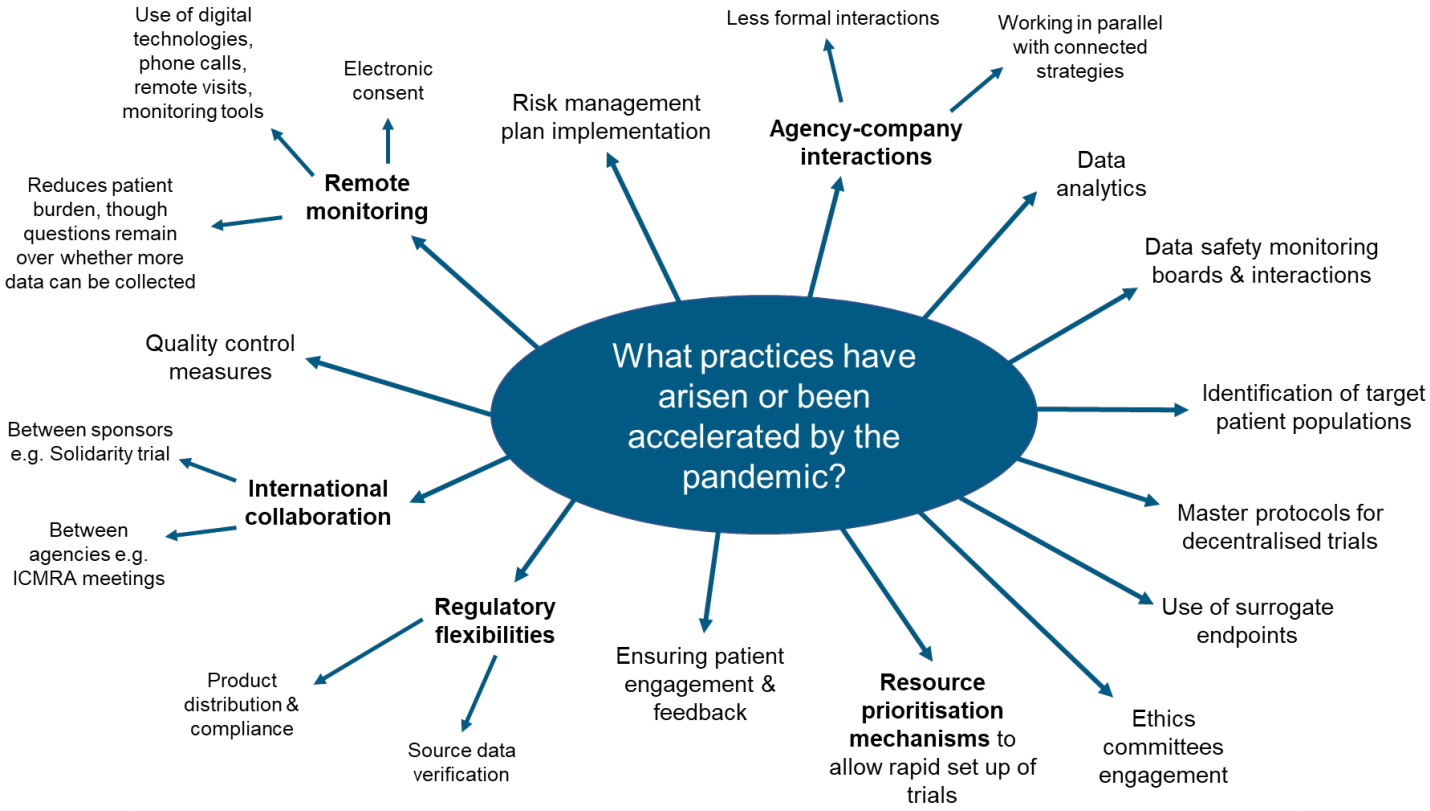


Clinical trials

Breakout Chair: Prof Ton de Boer, Medicines Evaluation Board, Netherlands

Rapporteurs: Prof Sam Salek, University of Hertfordshire, UK
Amelie Sylven, Abbvie, Switzerland

The breakout group focusing on clinical trials discussed practices that arose or were accelerated by the pandemic and were then challenged to identify up to five areas that it believed were critical and should continue post-pandemic (see below).



What should continue or be evolved post pandemic?

Stronger interactions

Between sponsors-agencies as well as stakeholders within each country e.g. ethics committees, health institutions

Remote monitoring

Important to ensure data quality

Regulatory flexibility

e.g. using a risk-based approach for source data verification

International collaboration

e.g. ICMRA meetings, multi-sponsor trials

Resource prioritisation

e.g. mechanisms within each country to enable rapid set up of trials

Topics to further explore

- Optimal use of facilitated regulatory pathways and how to enhance them
- Optimal use of digital tools/wearables e.g. 24-hour monitoring
- How co-development (multiple sponsors) and co-creation (agency-sponsor) can continue to drive innovation to address unmet needs
- Need for in-depth cases studies on COVID-19 trials – how can learnings be translated to non-COVID trials?
- Use of social media/technology for trial recruitment - currently no clear guidance

Digital technologies

Breakout Chair: Dr Alison Bond, Janssen, UK

Rapporteur: Megan Klopchin, Eli Lilly & Co.

One issue that was raised during the breakout but could not be discussed in the time available was around **access to digital technologies** e.g. there may be limited participation by some groups as a result of age, geography, social-economic factors.

The breakout group on digital technologies discussed the impact of several digital tools and activities during the pandemic and was challenged to identify up to three critical areas that should be retained post-pandemic (see below). The group was also asked to identify up to four key challenges and their potential solutions or policy changes needed to leverage the technologies' potential (next page).

Many of the digital technologies discussed were essential in enabling decentralised clinical trials and remote inspections during the pandemic but also have value outside of a pandemic setting.

How have digital technologies changed the regulatory model?		
Digital technologies (activities/areas)	**Impact on medicines development, review or post approval**	**Retain post-pandemic?** (Pick up to three)
Enablers of virtual or decentralised clinical trials and associated tools, including **electronic Patient Reported Outcomes, telehealth, apps and site monitoring**	• Provides additional clarity on endpoints, conduct, and what can be remotely captured • Continuous patient monitoring to enable insights • Reducing barriers to participation in research can facilitate faster and more diverse patient recruitment • Considerations – important that data privacy is still protected in a virtual setting and aspects related to data integrity must also be considered	✓
Use of **apps** (especially for the collection of safety data), **digital tools, wearables, devices with digital software** for pre/post authorisation utilisation	• Additional clinical aspects that can be collected and examined, including new novel endpoints • Increased ability to monitor compliance and patient engagement e.g. reminders	✓
Clarity of e-consent	• Ease of consenting and ensuring the right version gets to the patient at the right time • Ability to provide information in a more easily understood way • Increased control and security around consent • Better understanding of expectations which could also help with compliance	
Algorithms for signal detection (use of machine learning/artificial intelligence) and the potential for moving data to the Cloud	• Ability to better and more quickly detect issues and signals	
Common digital infrastructure and platforms for collaboration and work-sharing during the review, including Cloud submissions	• Ease of submission and review • Opportunities for parallel review • Facilitation of regulatory processes • Reduction of duplication • Improved review efficiency • Potential for increased harmonisation and alignment • Accelerated regulatory approval and patient access	✓

What are the main regulatory challenges and potential solutions for sustaining these digital technologies post-pandemic?

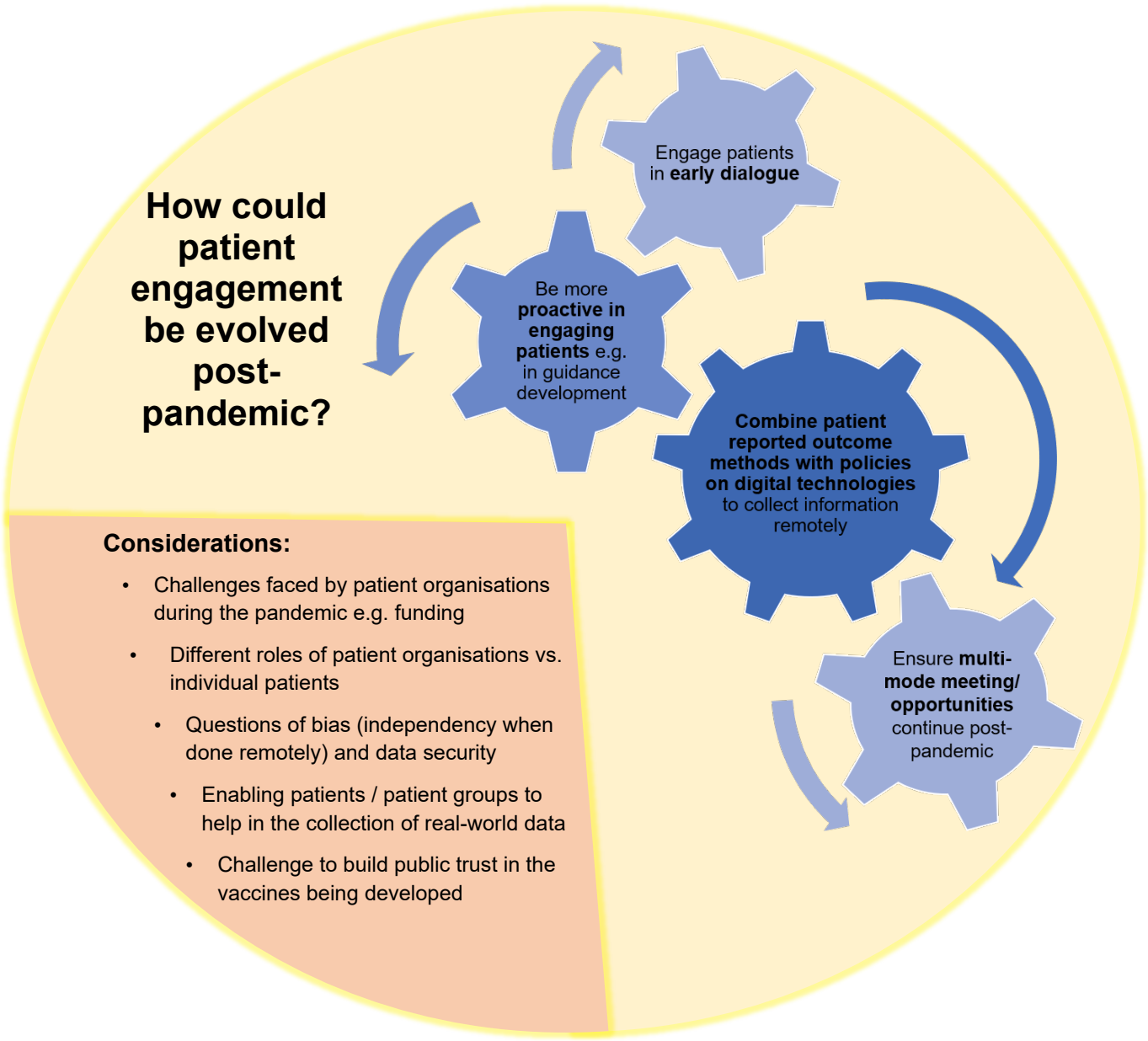
Challenges	Solutions/topics to further explore
Inconsistency in digital practices	• Deep dive into some areas e.g. confidence in security, trust in digital tools • Expanded guidance and use cases for new ways of working in digital space • ICH E6 (Good Clinical Practice) and other harmonisation or collaboration efforts • Need for perception survey of industry and regulators
Qualification, guidance and expertise to accommodate rate of change to technological innovation	• Should we regulate the process of validation vs regulating the product? • How is uncertainty in this area considered and handled? • Need for good practices outlined across the life cycle
Ability of trial sites and investigators to utilise digital tools	• Not just an issue of tool availability but also around their implementation • Training and ongoing support needed • Consider challenges and impact on all stakeholders

Patient engagement

Breakout Chair: Dr Mathieu Boudes, European Patients' Forum

Rapporteur: Dr Bettina Doepner, CSL Behring, Germany

What activities have arisen or been accelerated by the pandemic? The breakout group examining patient engagement highlighted a major opportunity in the use of virtual/remote technology as an engagement tool. The use of virtual meeting platforms increased significantly during the pandemic, making it easier to accommodate multi-stakeholder meetings including patients. These meetings were organised more quickly, more frequently and included more people, potentially reaching patients who had not engaged before. However, **it was noted that virtual meetings cannot easily facilitate the networking and personal interactions that occur in face-to-face meetings, which can offer important opportunities for drug developers and regulators to learn from patients (and vice-versa) in a less formal manner**. It will be important to build on the learnings from virtual meetings and expand the patient engagement toolbox after the pandemic.



Topics to further explore

- Significant progress has been made in relation to patient engagement in development and regulatory assessment over the last decade and policy continues to move in the right direction.
- However, the pandemic has highlighted the challenge of adapting patient engagement strategies and the collection of patient-reported data to expedited procedures and timelines – do new strategies need to be considered?

Collaboration

Breakout Chair:
Dr Thomas Lonngren, PharmaExec Consulting Filial SE, Sweden

Rapporteur: Stephen Fawbert, MSD, UK

The breakout group examining collaboration and knowledge sharing highlighted the roles of key organisations during the pandemic and how these may have changed. ICMRA played a more prominent role in bringing global regulatory agencies together to align on policy approaches and regulatory flexibility during the pandemic. However, it was noted that ICMRA could do more to increase its transparency, for example by improving its website to include information on its decision-making processes and criteria for membership.

The development of guidelines during the pandemic was also discussed; the length of time required to approve new guidelines through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) made it difficult to use this mechanism during the pandemic, however, ICH clearly plays a vital role in this area.

Key players & collaborations during the COVID-19 pandemic:

- World Health Organisation (WHO)
- Access to COVID-19 Tools (ACT) accelerator
- International Coalition of Medicines Regulatory Authorities (ICMRA)
- Africa Vaccine Regulatory Forum (AVAREF)

What activities have arisen or been accelerated by the pandemic?

Digital technologies

e.g. virtual meeting platforms, e-Patient Information Leaflets, virtual inspections, remote trial monitoring

These technologies maintained regulatory functions and patient access during the pandemic.

Co-creation

Agencies and sponsors worked together to pull products through development.

Use of rolling reviews helped to accelerate patient access.

Information sharing

The rate and degree of information sharing between regulatory agencies increased during the pandemic, leading to greater reliance.

Scientific advice & assessment

New types of rapid advice and assessment were introduced during the pandemic, which accelerated clinical development. However international competition in terms of who could advise/assess fastest/best, made it challenging for industry to keep up with.

How could these be further evolved to ensure sustainability?

Use of these digital technologies has worked well and should continue.

Rolling review is unlikely to be sustainable unless more resource is provided to regulators.

Information sharing should continue and be further increased to improve reliance. Greater transparency would also be beneficial so that the public and media understand what regulators do and how emergency use and conditional approval fit together.

There is a need for greater harmonisation in the agilities offered by regulators.

What gaps in current interactions were highlighted by the pandemic?			
Gap in current interactions	**Key stakeholders involved**	**Barriers to addressing gap**	**Solutions and next steps**
Connectivity gap in information sharing between all the international bodies	Companies, WHO, Low- and Middle-Income Countries (LMICs)	Confidentiality agreements for LMICs to obtain information from stringent authorities	**Global cloud** so that information can be uploaded to one place with access permissions.
Ensuring that LMIC receives same product	LMIC regulators, Marketing Authorisation Holders	Which version of products are coming to the LMIC?	**Need transparency on version** e.g. follow model where the manufacturer has to certify which version they are sending.
Greater use of reliance models for post-marketing commitments	ICMRA pharmacovigilance vaccines subgroup, Companies, ICH	Length of time to agree new guideline	Ensure global alignment on how to react to adverse reactions to vaccines. **Greater reliance** in the post approval space. ICH Q12 (Technical and regulatory considerations for pharmaceutical product lifecycle management) should help leading authorities in this space – how can LMICs have the confidence to rely on their decisions?

Topics/projects to further explore

- An independent review to determine the most appropriate use of rolling reviews e.g. for public health emergencies, when linked to a classification of unmet need.
- An independent benchmarking study to determine appropriate use of new scientific advice and assessment pathways and which worked best.
- Investigate the impact of confidentiality laws on reliance
- Alignment of politicians with scientific bodies to balance access demands with understanding of good regulatory practices
- Maintain the evolving role of ICMRA as well as other international/regional collaborations such as the International Pharmaceutical Regulators Programme (IPRP) and Pan-American Health Organisation (PAHO)

Workshop programme

Session 1: Current regulatory models: do they meet the evolving needs for 21st century medicines?

"While it may not be time to reframe the regulatory model, a more complex, multifaceted world needs a new degree of flexibility"
Agency viewpoint

Chair: Adj Prof John Skerritt, Deputy Secretary for Health, Products Regulation, Department of Health, Australia

Speakers:
Prof Dr Hans-Georg Eichler, Senior Medical Officer, EMA
Dr Khair ElZarrad, Deputy Director, Office of Medical Policy, CDER, FDA
Meindert Boysen, Deputy Chief Executive and Director of the Centre for Health Technology Evaluation**,** NICE, UK
Dr David Jefferys, Senior Vice President, Eisai, UK

Session 2: Accelerating change and enabling flexibility for early access – what will become a new way of working?

"In future, greater productivity gains may be unlocked through digital breakthroughs and may even help to predict and prevent the next pandemic"
Company viewpoint

Chair: Dr Joseph Scheeren, President and CEO, Critical Path Initiative, USA

Speakers:
Dr Max Wegner, Senior VP, Head of Regulatory Affairs, Bayer, Germany
Dr Martin O'Kane, Unit Manager, Clinical Trials Unit, Licensing Division, MHRA, UK
Dr Nikolai Brun, Director of Division, Medical Evaluation and Biostatistics, Danish Medicines Agency
Dr Virginia Acha, Associate VP, Global Regulatory Policy, MSD, UK

Session 3: Accelerating change and enabling flexibility for early access – what will become a new way of working? Continued

"The COVID-19 regulatory response has been a sandbox for experimentation"
Agency viewpoint

Chair: Dr J Patrick Stewart, Director General, Therapeutic Products Directorate, Health Canada

Speakers:
Dr Peter Arlett, Head of Data Analytics and Methods Taskforce, EMA
Andrew Emmett, FDA Liaison & Head of U.S. Regulatory Policy, Pfizer, USA
Dr Jillian Fuhs, Advisor, Global Regulatory Affairs North America, Eli Lilly, USA
Pat Furlong, Founding President and CEO, Parent Project Muscular Dystrophy (PPMD), USA

Session 4: Reimagining international partnerships - collaborations and convergence supporting global needs

"Not using the outputs and outcomes from other regulatory authorities would only mean lost opportunity"
Agency viewpoint

Chair: Dr Lorraine Nolan, Chief Executive, Health Products Regulatory Authority, Ireland

Speakers:
Dr Theresa Mullin, Associate Director for Strategic Initiatives, Center for Drug Evaluation and Research, FDA, USA
Dr Samvel Azatyan, Team Lead, Regulatory Convergence and Networks, WHO
Maria Cristina Mota Pina, Regulatory Policy Director for the Emerging Markets, Abbvie, USA
Dr Claus Bolte, Head of Sector Marketing Authorisation, Swissmedic
Dr Murray Lumpkin, Deputy Director, Integrated Development and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation, USA

While the breakout discussions presented in this Briefing help to identify lessons learned from the pandemic for four key areas, there is still a need for detailed case studies to give the 'full picture' and communicate tangible learnings and recommendations for the future.

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About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independent UK-based subsidiary of Clarivate plc. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and Health Technology Assessment (HTA) policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

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