Centre for Innovation in Regulatory Science (CIRS)

2019 Annual Report

A historical perspective and overview of 2019

CIRS Centre for Innovation in Regulatory Science

Contents

Foreword

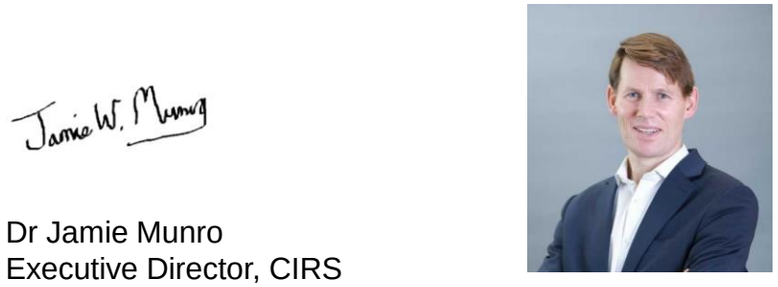
From the Executive Director

The last year, the first of my tenure, has witnessed significant change including the sad passing of Professor Sir Alasdair Breckenridge, the esteemed Chair of the CIRS Scientific Advisory Council (SAC) from June 2013 to December 2019. His support and guidance will be greatly missed.

CIRS has a rich history of helping to improve the regulatory and access landscape through its work in the areas of metrics, quality and alignment. As regulatory science continues to evolve, we will be looking to go beyond performance metrics and examine how agencies can improve their effectiveness.

As I write this, in the first half of 2020, we find ourselves in the midst of a global pandemic that is adversely impacting billions of people worldwide and creating economic turmoil unprecedented in modern times. There will inevitably be the impacts to consider as well as learnings but there will be other areas of interest to CIRS including the impact of ATMPs and the role of patient engagement within regulatory and reimbursement decision making.

I would like to take this opportunity to thank the significant number of members and wider stakeholders that have greatly contributed to CIRS outputs over the last year and am pleased to share the inaugural CIRS annual report with you.



Dr Jamie Munro
Executive Director, CIRS

Foreword

From the Chair of the Scientific Advisory Council

I write this in part honoured to have been endorsed by a committee of very eminent colleagues to serve as the new Chair of the CIRS Scientific Advisory Council. It is also in part with a heavy heart as I follow in this role after the passing of Professor Sir Alasdair Breckenridge.

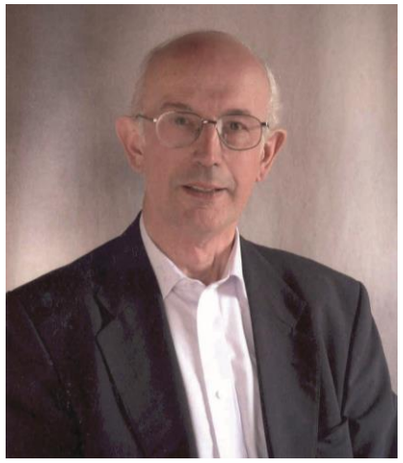
I first encountered Sir Alasdair's monumental contribution to the field of pharmacology when I was a final year undergraduate pharmacology student in 1979, where part of the course involved writing literature reviews on drug metabolism and clinical pharmacology topics. Some eight years ago, shortly after being appointed to head Australia's medicine regulator, the TGA, I was honoured to spend time with Sir Alasdair in person, and to maintain a close relationship with him until his passing.

CIRS is a unique organisation. Every organisation makes such a claim, but the ability of CIRS to connect and actively involve government (regulators, HTA and payers), academia and industry to identify major research priorities in the clinical development, regulatory evaluation and funding of medicines is genuinely unique. The Scientific Advisory Council plays a critical role in advising CIRS on the most pressing topics that are both suitable for research projects, surveys and workshops and feasible for the small team of CIRS staff and researchers to explore. Such research would often not be feasible for small or medium sized agencies or companies to conduct, and its conduct by CIRS also enables international comparisons and insights to be drawn out. CIRS also performs a unique role in its assembly and analysis of many of the key metrics that relate to regulator, HTA and company performance.

History tells us that epidemics and pandemics have been inflection points, transforming health care systems, economies and society rapidly and permanently. The COVID-19 pandemic is still evolving as I write this, but what is certain is that the medicines sector will face a number of "new normals". With the changed landscape we will all have to work in, CIRS metrics, research, workshops and partnerships will be more important than ever before.

Adj Professor John Skerritt
Chair, CIRS Scientific Advisory Council
Deputy Secretary, Australian Government Department of Health

Tribute to Professor Sir Alasdair Breckenridge



Professor Sir Alasdair Breckenridge, Chair of CIRS SAC 2013-2019

Professor Sir Alasdair Breckenridge died, aged 82, on the 12th of December 2019 after a short illness. I first got to know and work with Alasdair in 1969, while I was a lecturer in clinical pharmacology at the Cardiothoracic Institute, when he had just been appointed as Consultant and Senior Lecturer at the Royal Postgraduate Medical School in London at the young age of 32. So early on in his career he had already made a significant contribution to medicine where he established himself as an expert in the field of hypertension.

Just five years later in 1974 he moved to the University of Liverpool to become Head of the Department of Clinical Pharmacology, which he transformed into an internationally recognised research institution. Over a period of 50 years Alasdair's research contributions were extensive with many publications in prestigious journals, chairing and speaking at meetings around the world, during which time he received many awards too numerous to mention. He claimed that his work in Liverpool was his greatest achievement.

I may disagree with that, for in 1984 he joined the Committee on Safety of Medicines (CSM) and became its chairman in 1994. It was therefore appropriate that he should have been awarded the CBE in that same year, with a knighthood some 10 years later, for his outstanding contributions to medicine. In 2003 he was appointed as the inaugural chairman of the board of the Medicines and Healthcare Products Regulatory Agency (MHRA), where he combined his vision and expertise to the area of regulatory science.

I can say without any hesitation that he was a giant in his field, physician, academic, medicines regulator and clinical pharmacologist. It has been a privilege to have known and worked for him and his contribution to CIRS has had a major impact and significantly influenced what the organisation has achieved to date. Alasdair has left us a legacy on which I know we can build.

Professor Stuart Walker
Founder of CIRS

About CIRS

Mission

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 in developing and facilitating access to medicinal products

How we operate

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independently managed UK-based subsidiary of the Clarivate Analytics group. We operate as a not-for-profit organisation, deriving funding from membership dues, special projects and grants to cover our operating and research costs.

We are governed by our own dedicated advisory boards made up of external international experts from academia, industry, regulatory agencies and HTA bodies. Our Scientific Advisory Council (SAC) and HTA Steering Committee advise on workshop topics and content as well as our research programme.

What makes us unique

What sets us apart is our ability to bring **global** industry, regulators, HTA bodies, payers and academics together in a **neutral** setting to identify and address key issues in the development, licensing and reimbursement of new medicines. We have been doing this for over 35 years through **focused** meetings and collaborative research.

Our workshops have consistently received positive feedback ratings of over 90% and resulted in recommendations that inform strategic and policy level thinking. The strong support for our research as well as attendance in meetings demonstrates the trust and confidence our stakeholders have in us.

We are also **evidence-driven** and **transparent** in our work. The data we collect are used to support our workshops and we strive to make these publicly available though peer-reviewed journals or our R&D Briefings.

Our small but dedicated team of experienced scientists strive to ensure that the needs and priorities of our stakeholders are at the heart of CIRS activities. Our door is always open to new ideas and suggestions that fit with our mission.

Three pillars of CIRS activities

Metrics | Quality | Alignment

Metrics - evidence-driven insights into company and agency performance

CIRS provides unique insights and an independent viewpoint on the performance of companies, regulatory and HTA agencies through its metrics programmes. Data are collected and analysed to give a better understanding of regulatory and HTA assessment times and evidentiary requirements. This form of benchmarking details regulatory and HTA processes and practices, identifies where improvements can be made and informs company and agency strategies.

Quality– improving decision-making processes during the medical product lifecycle

CIRS works with companies and agencies to evaluate the quality of their processes, identify challenges, and implement best practices. Tools developed from these projects support decision making practices and their documentation in general or are specific to areas such as benefit-risk assessment. The aim is to foster learning and improve transparency, predictability and consistency of critical decisions during development, regulatory review and health technology assessment.

Alignment – converging stakeholder priorities and processes to accelerate patient access

Through collaborative research projects and multi-stakeholder workshops, CIRS promotes harmonisation and alignment across HTA and regulatory agencies, as well as between HTAs and regulators themselves. Not only does this facilitate capacity building but also helps to enable more efficient and effective development of medicines.

Our strategy

CIRS sets a rolling three-year strategy with input from the Scientific Advisory Council and HTA Steering Committee. Our 2018-2020 programme is grouped around four strategic areas:

- Enabling innovation and upstream partnering to enhance downstream innovation
- Pragmatic approaches to transparent decisions through reliance, recognition, reciprocity and regionalisation
- Patient engagement and ‘centricity’
- Disruptive technologies and the impact of digital and other technologies on development, regulation and value

2019 in numbers

22
Member pharmaceutical companies

43
Participating regulatory authorities

35
Participating HTA and coverage bodies

4.7
Out of 5 feedback score for multi-stakeholder workshops

29
Insight seminars and meetings with member companies

20+
Visits to regulatory and HTA agencies

10
Special research projects undertaken

6
R&D Briefings & reports, disseminating findings from CIRS research

CIRS **R&D Briefings** provide trusted benchmarks for companies and agencies. For example, R&D Briefing 73 looked at HTA outcomes and timelines in Australia, Canada and Europe between 2014-2018. This data was collected as part of our ongoing **metrics programmes monitoring regulatory and HTA performance**. As well as identifying differences between countries, other special analyses were carried out, including the impact of breakthrough designations on reimbursement outcomes.

6
Peer-reviewed journal publications

CIRS has published on a broad range of topics and has several publications in the pipeline. One recent paper in ***BMJ Open*** compared **FDA and EMA review outcomes** between 2014-2016. Although there was general alignment between the two agencies, there were some cases of different indications being approved, despite the same indication information being submitted. The FDA also approved more compounds and was more likely to expedite review and designate drugs as orphans than the EMA.

3
PhD students supported by CIRS

- *Ensuring equitable access to new medicines through the use of quality, company, regulatory and HTA decision making* - Tina Wang**,** Utrecht University and HTA Programme Manager at CIRS
- *The regulatory environment in South Africa: improving patients access to new medicines* - Andrea Keyter, University of Hertfordshire and SAHPRA, South Africa
- *Assessment of the regulatory review system in ZAZIBONA with a view to enhancing the evaluation process and patients' access to medicines* – Tariro Sithole, University of Hertfordshire and MCAZ, Zimbabwe

12
Conference presentations/posters

In addition to organising its own meetings, CIRS presents at many international scientific conferences. At **DIA 2019 in San Diego, USA,** CIRS representatives helped to organise and deliver a session called 'Informing development and authorisations using **real world evidence (RWE) and artificial intelligence (AI**)'. This session facilitated discussion around how AI and RWE can be used in conjunction with knowledge management to enable better development and regulatory decisions.

2019 publications and conference outputs are listed in full on p25-26.

Highlights of 2019

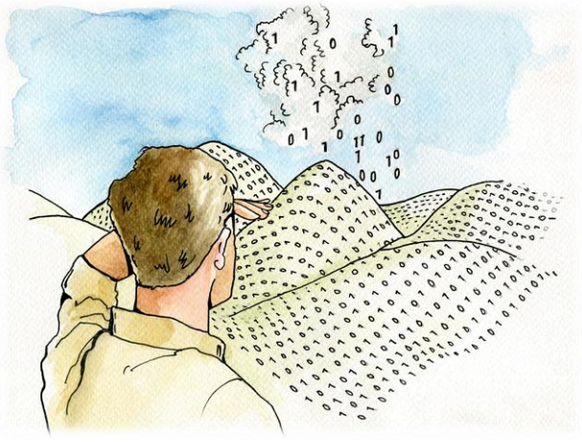
Meetings and workshops

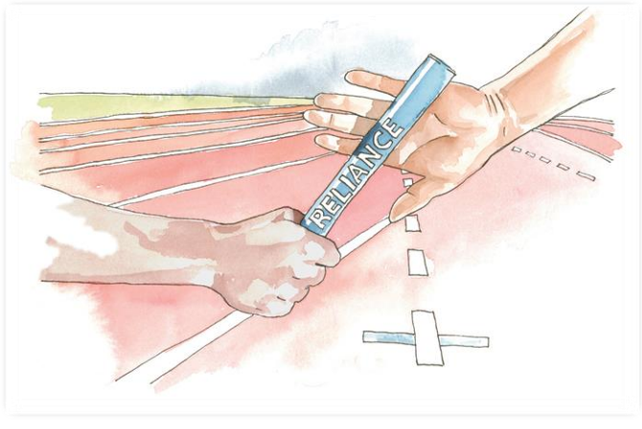
CIRS hosted a multi-stakeholder workshop '*Optimising the regulatory review process by evaluating performance and addressing* ***good reliance practices****'* in collaboration with the Centre for Regulatory Excellence (CoRE) in Singapore. This produced recommendations on embedding performance-based measurements in agencies, codifying trust between those involved in reliance and implementing and assessing the impact of good reliance practices.

FDA Center for Drug Evaluation and Research Director, Dr Janet Woodcock, gave the keynote presentation at CIRS' multi-stakeholder workshop *'Approaches to better decision making in companies and regulatory and HTA agencies through documentation,* ***quality decision making*** *practices and* ***knowledge management****'*. Key outcomes of the workshop were the validation of a draft template for documenting decision making processes and the endorsement of a standardised public assessment report for agencies.

CIRS hosted a multi-stakeholder workshop, '*Identifying and understanding* ***regulatory and reimbursement uncertainty*** *during development: How can this improve predictability of regulatory and HTA outcomes?'* , which featured presentations from G-BA and NICE. The workshop produced recommendations on a framework to facilitate the management of uncertainty during development.

CIRS hosted two company Technical Fora, the first of which examined the use of **digital technologies** to support the development of new medicines, with a focus on collaborative cloud-based solutions for submission and leveraging artificial intelligence for regulatory intelligence and decision making. The second Forum looked at strategies and actions that **build value into development** and enable sponsors to effectively articulate the value of new medicines during review and reimbursement





Committees

In recognition of the increasing role of the **payer** in drug development, the CIRS HTA Steering Committee gained representation from the German payer, AOK-Bundesverband.

The CIRS Scientific Advisory Council (SAC) was strengthened to include representatives from the Chinese regulatory agency, **NMPA**, and the Japanese agency, **PMDA**, as well as continuing to have representation from EMA's **CHMP** through the new CHMP Chair.

Research projects and interactions

Building on the results of a phase 1 study in 2017, CIRS was selected by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to conduct a phase 2 study to monitor the implementation and adherence to **ICH guidelines**. As well as facilitating trust and transparency, these results could be used to support decisions related to ICH membership applications.

In response to increasing awareness of the **Institute for Clinical and Economic Review (ICER)**, CIRS organised an interactive discussion over Webex where member companies shared their perceptions and experiences of ICER.

2019 marked the final year of our first grant from the Bill and Melinda Gates Foundation, which supported the **Optimising Efficiencies in Regulatory Agencies (OpERA) Programme** in emerging countries (see p20-21 for more information).

Building on previous work with the Turkish regulatory agency (TITCK) over the past five years, CIRS held a joint workshop with **TITCK** focusing on implementation of Good Review Practices, reliance approaches and international guidelines.

A historical perspective of CIRS

The advent of the thalidomide tragedy in the early 1960s resulted in medicines regulations being established in several countries underlining the importance of demonstrating the safety and the efficacy for new therapies. However, over the next two decades regulatory requirements increased significantly thereby challenging patients' access to new medicines. Consequently, there was a need for evidence-based initiatives to ensure that there was the right balance to the increasing cost of drug development in the light of the significant regulatory demands.

Therefore in 1981 the Association of the British Pharmaceutical industry (ABPI) had the foresight to establish the Centre for Medicines Research International (CMR) to provide the evidence, from a scientific and medical viewpoint, to challenge and where appropriate change regulations and public policies that were thought to be detrimental to efficient drug development. I was delighted to be appointed Director of this new innovative centre and throughout the 1980s, produced the evidence to support patent term restoration in Europe (from 15 to 20 years) as development time had increased to 10-12 years. In addition we initiated a database to monitor the increasing regulatory review times in Europe and the USA as well as challenging the design of long-term animal studies where the requirements ranged from 6-18 months between the United States, Europe and Canada.

This area then became part of CMR's role in contributing significantly to several working parties established by the International Conference on the Harmonisation of Medicinal Products (ICH) in the 1990s. In that decade, CMR also initiated benchmarking of both R&D and clinical studies with the top 20 pharmaceutical companies as it challenged their efficiency and performance while at the same time its remit expanded into Europe, United States and Japan. During this period of 20 years, CMR had the opportunity of working closely with key individuals such as Chairmen and Presidents of R & D within pharma, as well as the heads of agencies in all major jurisdictions.

In 2002, CMR, now funded by some 40 international pharmaceutical companies in all three geographical regions namely Europe, Japan and the United States, became independent of the ABPI. We established its business as a for-profit organisation whilst retaining the work of the Institute for Regulatory Science as a not-for-profit entity.

CMR team, 1990

Opening of Novellus Court, Epsom, UK, by Baroness Helen Hayman, Under Secretary, Ministry of Health, 1999

During the next decade we continued to work with the major established regulatory authorities but expanded its operation to include more than 25 regulatory agencies from the emerging economies of the Asia-pacific region, Latin America as well as Africa and the Middle East. Our key focus was to provide the tools for those agencies with limited resources to become more efficient and effective. This included the Universal Methodology for Benefit Risk Assessment (UMBRA) and a questionnaire to assess Quality Decision-Making Practices (QDMPs), which were recognised as key components in the regulatory review as well as the process by which a reliance strategy should be implemented to maximise its resources. These continue to be a key aspect of the Centre for Innovation in Regulatory Science (CIRS) today.

To aid continuity and support the long-term sustainability of CMR International, a suitable home was found and the centre became an independent autonomous subsidiary of Thomson Reuters in 2006, while the Institute of Regulatory Science was rebranded as CIRS. This independent autonomous structure was maintained within the Thompson Reuters Intellectual Property and Science Division and CIRS subsequently became part of Clarivate in 2016. During this period CIRS initiated its OpERA programme to optimise the efficiencies of regulatory authorities as well as extending its remit by establishing a database to evaluate and monitor Health Technology Assessment Agencies (HTAs) as well as pharma companies with a steering committee chaired by Dr Brian O'Rourke and vice-chair Professor Adrian Towse.

In recent years CIRS' strategy has been informed by the Scientific Advisory Council (SAC) chaired by the late Professor Sir Alasdair Breckenridge and vice chair Professor John Skerritt. In addition, because CIRS had a link with academia, I was able in my role with a chair at Cardiff University and now with the University of Hertfordshire, to integrate its work with the supervision of many doctoral students both in industry and regulatory authorities who were engaged in the development, review and reimbursement of medicines.

Today, CIRS continues to provide a thought leadership role to regulatory authorities, pharmaceutical companies as well as HTA agencies and maintains its strategy to provide the advice and support to ensure patients' access to safe and effective medicines worldwide.

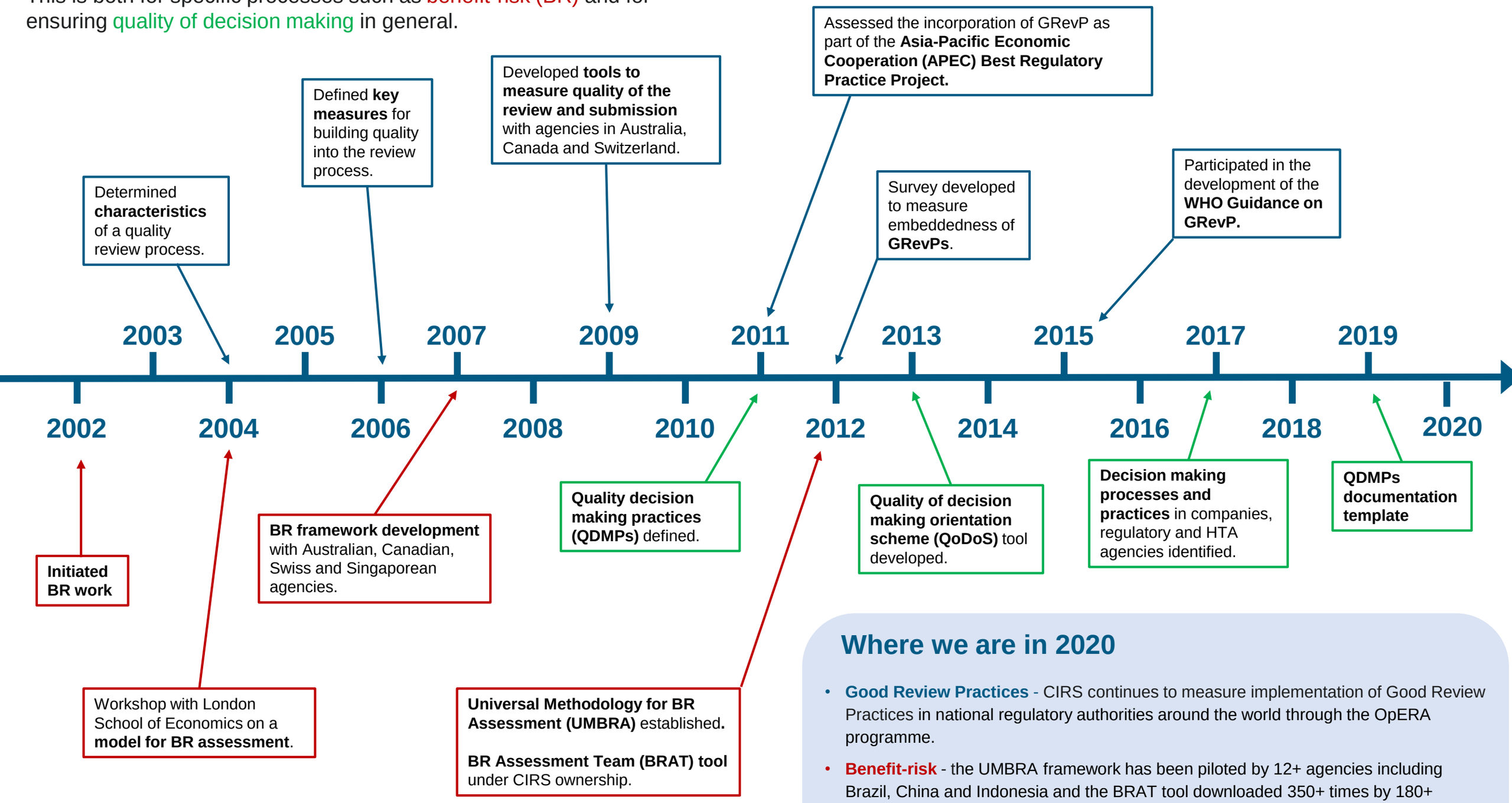
Professor Stuart Walker

Founder of CIRS, London, UK
Professor of Regulatory Science, University of Hertfordshire, Hatfield, UK
Academic Visiting Expert, Centre of Regulatory Excellence, Singapore

CIRS activities on quality

CIRS has laid the foundations for the development of practices for building quality into review and decision-making processes. This has helped to define Good Review Practices (GRevP) and increase the quality of processes by using structured frameworks and ensuring documentation. This is both for specific processes such as benefit-risk (BR) and for ensuring quality of decision making in general.

Key: Good Review Practices | Benefit-risk | Quality of decision making



Where we are in 2020

- **Good Review Practices** - CIRS continues to measure implementation of Good Review Practices in national regulatory authorities around the world through the OpERA programme.
- **Benefit-risk** - the UMBRA framework has been piloted by 12+ agencies including Brazil, China and Indonesia and the BRAT tool downloaded 350+ times by 180+ organisations.
- **Quality of decision making** – research is ongoing into the documentation of decision making and its communication in Public Assessment Reports. CIRS also continues to assess decision making in companies, regulators and HTA agencies.

Key references for this timeline are listed on p24.

CIRS metrics activities

CIRS provides unique insights into the performance of companies, regulatory and HTA agencies through its metrics programmes. Data are collected and analysed to give a better understanding of regulatory and HTA assessment times and evidentiary requirements. This form of benchmarking helps to improve agency processes and inform company strategies.

Key: Regulatory | HTA

1998

Identified **key milestones in the review process**.

2000

First full-scale benchmarking study with FDA, EMA, Health Canada, Swissmedic and TGA.

2002

Preliminary discussions with industry to initiate **Emerging markets (EM) Programme.**

2004

Presentation of agency benchmarking results highlighted **importance of quality of review, in addition to time**.

2006

EM Industry Benchmarking Programme initiated.

2008

Benchmarking study won award for most downloaded publication in *TIRS* journal.

2010

Approached by EM countries to initiate an **agency benchmarking programme**.

2012

HTA Industry Benchmarking Programme established.

Annual benchmarking of FDA, EMA and PMDA using information from the public domain.

2014

HTA Agency Benchmarking Programme developed with agencies.

OpERA programme initiated

2016

HTADock database established to curate information from the public domain on HTA performance.

Swissmedic, Health Canada and TGA added to annual benchmarking.

Facilitated Regulatory Pathways included in annual benchmarking

2018

Time to reimbursement and flexible regulatory pathways assessed in HTADock Briefing.

BMGF funding awarded to expand OpERA.

2020

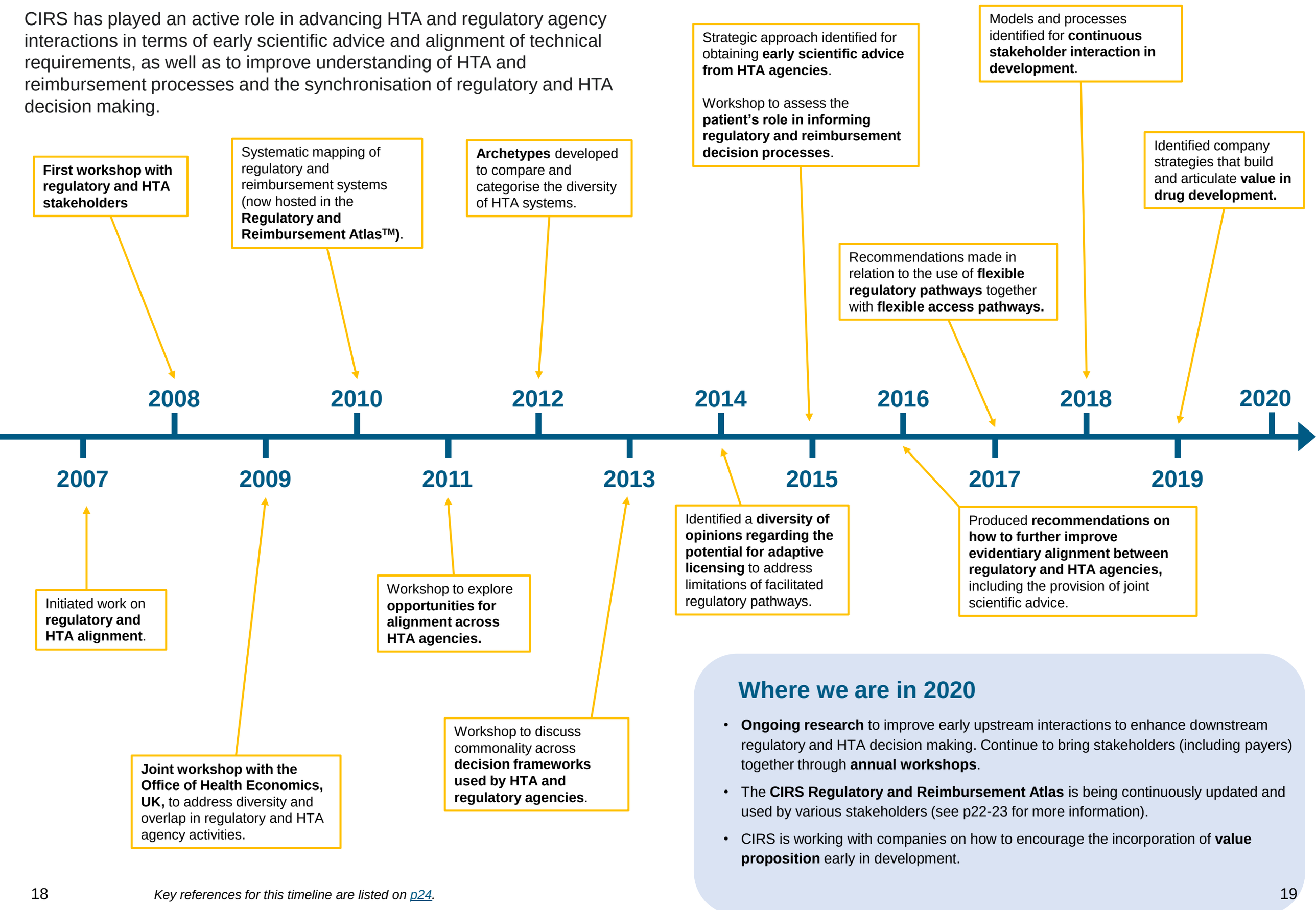
Where we are in 2020

- **Benchmarking regulatory and HTA agencies** on an annual basis, publishing the results in R&D Briefings.
- The **Optimising Efficiencies in Regulatory Agencies (OpERA) Programme** funding from the Bill and Melinda Gates Foundation (BMGF) has been renewed to continue with regulatory strengthening (see p20-21 for more information).
- **HTA and EM Industry Benchmarking Programmes** continue to provide insights to companies on the HTA and regulatory landscape.
- Ensuring effective and efficient review processes through research on **reliance-based models** and facilitated pathways.

Key references for this timeline are listed on p24.

CIRS activities on alignment

CIRS has played an active role in advancing HTA and regulatory agency interactions in terms of early scientific advice and alignment of technical requirements, as well as to improve understanding of HTA and reimbursement processes and the synchronisation of regulatory and HTA decision making.



Where we are in 2020

- **Ongoing research** to improve early upstream interactions to enhance downstream regulatory and HTA decision making. Continue to bring stakeholders (including payers) together through **annual workshops**.
- The **CIRS Regulatory and Reimbursement Atlas** is being continuously updated and used by various stakeholders (see p22-23 for more information).
- CIRS is working with companies on how to encourage the incorporation of **value proposition** early in development.

Key references for this timeline are listed on p24.

Case study: Regulatory system strengthening through the OpERA Programme

Strengthening regulatory systems is key to ensuring that regulatory agencies are providing effective and efficient services to their stakeholders. Over the past 20 years, CIRS has played an active role in this area by collecting performance metrics and building quality into the review process. Building on the success of its early benchmarking studies in ICH and ICH-observing countries, in 2013 CIRS initiated a unique metric collection programme called Optimising Efficiencies in Regulatory Agencies (OpERA) with agencies and regional alignment initiatives from Asia, Latin America, Africa and the Middle East. This was later expanded with the help of a grant from the Bill and Melinda Gates Foundation (BMGF).

What are the objectives of the OpERA Programme?

- Understand the regulatory processes that drive assessment and approval times
- Encourage systematic re-assessment of the medicine authorisation processes
- Provide a basis for comparison across processes used in the review of marketing authorisations
- Provide a simple process to collect benchmarking data specific to the regulatory review and assessment process
- Encourage the development of a systematic approach to self-monitoring and continuous improvement
- Help regulators integrate best practices that are fit-for-purpose for their remit, while ensuring the safety, efficacy and quality of their products.

What tools are used to promote regulatory system strengthening?

CIRS has a number of externally validated tools that can help to strengthen regulatory systems:

- OpERA tools - the **Country Report**, which consolidates details of the regulatory assessment process, including Good Regulatory and Decision Making Practices, and the **Metrics assessment tool** to collect specific product-related regulatory metrics.
- **Quality of Decision Orientation Scheme (QoDOS)** – a survey tool that has been designed to assess the implementation of ten quality decision-making practices (QDMPs) within agencies.
- **Good Review Practices Embeddedness Tool** – a survey tool that has been designed to confidentially collect regulatory staff's perceptions as to how well their department and agency follow Good Review Practices. The results provide a gap analysis that is used for training to build quality into the medicines assessment process and to strengthen regulatory activities overall.
- **Unified Methodology for Benefit Risk Assessment (UMBRA) template** – used to systemically document key factors that contributed to the benefit-risk assessment, how these were weighted and how the overall decision outcome was reached. This provides a platform for internal discussions within an agency, for agency to company interactions, agency to agency interactions and can serve as the basis for Public Assessment reporting.

What has the OpERA Programme achieved?

Over 30 countries and several regional initiatives have been taking part in the OpERA Programme since its inception in 2013. The programme has successfully built a culture of measurement and refinement within participating agencies, helping them to define their review performance goals and optimise their review processes.

For example, CIRS worked with the Saudi Food and Drug Authority (SFDA) to characterise its review processes and practices and make comparisons with regulatory systems in Canada, Singapore, and Australia. This study not only identified SFDA's key milestones and timelines, but also highlighted opportunities for improvement, including exploring a reliance model like that used in Singapore and publishing approval summaries that transparently communicate the rationale for agency decisions. The SFDA has since implemented a risk stratification model in its review process based on this study's recommendations.

A more recent study with the National Pharmaceutical Regulatory Agency (NPRA) in Malaysia has identified where time is spent in NPRA's process and provided the agency with a baseline for which performance improvements can be measured against. Participating in OpERA has not only helped NPRA to understand its regulatory performance but has also identified weaknesses and areas lacking capacity, which the agency is working to address. For example, NPRA has implemented a target start time for scientific assessment and limited the applicant response time to six months.

Annual OpERA Forums organised by CIRS have provided important opportunities for emerging national regulatory agencies to come together and share learnings. Attendees have identified new ways to improve their organisational efficiency and learned about tools and processes that will help build best regulatory assessment practices.

What are the next steps?

At the beginning of 2020, CIRS was awarded further funding from BMGF to continue promoting the OpERA Programme to target economy regulatory agencies and to refine the reporting outputs from data collection activities. A key goal will be to support the long-term sustainability of the OpERA Programme by developing a transition mechanism to a data monitoring system that can be used by participating agencies and allow for self-reporting.

Attendees at the 2019 Annual OpERA Regulatory Forum in Singapore

Case study: Promoting alignment by mapping regulatory and reimbursement processes

The ability to effectively navigate regulatory, HTA and payer pathways throughout the product lifecycle is key to successful medicine development. As the global development environment becomes more complex, the need to understand the confluence of these pathways has become a driver of the medicine development process.

What did we do?

Over the past 20 years, CIRS has collaborated with more than 75 regulatory, HTA and payer agencies to understand the nature of their activities. Using our proprietary methodology to map regulatory and reimbursement pathways and to illustrate the core functions of each agency involved, CIRS has developed a simple, globally recognised approach to understanding this diverse landscape. Thus, the CIRS Regulatory and Reimbursement Atlas™ was developed to illustrate the sequence of interactions with agencies in each jurisdiction, while understanding each agency's particular functions. More than 70 national and regional maps were created for the following regions: Asia, Europe, North America, Oceania and South America.

Such process mapping allows the planning of development strategy by identifying potentially rate-limiting steps. Benchmarking industry, regulatory and HTA performance against peers with similar mandates and processes can encourage good practices and promote timeliness, predictability, consistency, transparency, clarity, efficiency and quality. Tracking and measuring performance can convey achievements and needs to policy makers, promote continuous improvements and opportunities for work optimisation and build trust in each other's systems and approaches.

What has been the impact?

Supporting policy change across HTA agencies: The Atlas was presented at the 6th meeting of the HTA Network (Brussels, 20 May 2016) to demonstrate the comparative mapping method and identification of differences and similarities of HTA systems in Europe. It has also been shared with the EU Commission to support a mapping project that has informed the 2017 Impact Assessment.

Supporting research with HTA agencies: The Atlas outlines which agencies provide scientific advice to companies during drug development, which is currently a much-discussed area. CIRS were approached by the Swedish HTA agency, TLV, to undertake an assessment of HTA agencies' perceptions of the value of providing scientific advice. The results of the study have been presented at international workshops and shared learnings will be published soon.

Strategic tool for companies: The Atlas is available to the 20+ CIRS member companies to help meet the following goals:

- Plan market access strategy by identifying potentially rate-limiting process steps
- Compare processes between jurisdictions to facilitate simultaneous development programmes and to identify potential 'best practice' pathways
- Train staff on the diversity of regulatory and reimbursement systems to inform strategic planning for evidence generation and deliver value messages to different stakeholders.

Educational and training tool for patient groups: The Atlas has been used as an educational and training tool by patient groups. The maps show a clear picture of the regulatory and HTA processes in each country and provide insights into how HTA agencies reach their recommendations across jurisdictions as a comparative tool.

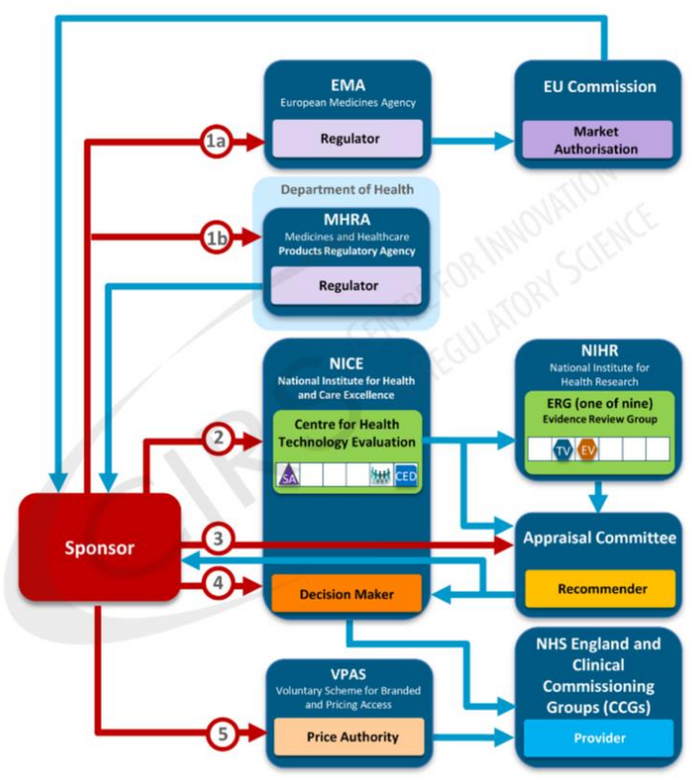
Supporting further research around the confluence of HTA: The Atlas tracks which agencies offer scientific advice and this information has been used to provide a baseline for further research on this topic. In addition, the archetype methodology has been utilised by other groups, for example, to develop system and process taxonomies for 12 countries in Latin America.

Future direction

Understanding the confluence of HTA in Asia: CIRS will apply the archetype methodology to HTA systems in Asia.

Regional level information: Currently the Atlas focuses on national level processes. However, for many countries, key steps in the process (or even the entire process), occur at a regional level. Regional level maps for 12 Canadian jurisdictions have been added to the Atlas but in future this will be expanded to include regional maps for more countries.

Assessing patient interactions with HTA agencies: Currently, the Atlas process maps illustrate whether HTA processes incorporate patient input. Moving forward, a detailed country profile of HTA-patient interaction could be created based on guidance published by Health Technology Assessment International (HTAi) and recommendations from the 2015 CIRS Workshop "What is the patient's role in informing the decision process for approval and reimbursement of new medicines"?



Process map for England. Updated September 2019

Key publications

Quality:

- Liu, L., McAuslane, N., Tzou, M. et al. (2013) Characterising Good Review Practices: A Survey Report Among Agencies of APEC Member Economies. *Ther Innov Regul Sci* **47,** 678–683.
- Salek, S., Mallia-Milanes, A., McAuslane, N., Walker, S. (2012) Development and Application of Scorecards to Assess the Quality of a Regulatory Submission and Its Review. *Drug Information Journal*, *46*(1), 73-83.
- Walker, S., McAuslane, N., Liberti, L. et al. (2015) A Universal Framework for the Benefit-Risk Assessment of Medicines: Is This the Way Forward?. *Ther Innov Regul Sci* **49,** 17–25.
- Walker S, McAuslane N, Bujar M, et al. (2017) Quality decision-making practices: Their application and impact in the development, review and reimbursement of medicines. ISBN: 978-94-6182-866-8. Available at: https://www.offpage.nl/ebooks/2018_swalker/

Metrics:

- Hirako, M., McAuslane, N., Salek, S. et al (2007). A Comparison of the Drug Review Process at Five International Regulatory Agencies. *Drug Information Journal*, *41*(3), 291–308.
- CIRS (2012) R&D Briefing 51 Characterising the influencers of submission lag time for medicines in the emerging markets: analysis of short and long lag time factors. Centre for Innovation in Regulatory Science, London, UK.
- CIRS (2020) R&D Briefing 74: The OpERA programme: Measuring process and performance in regulatory agencies. Centre for Innovation in Regulatory Science, London, UK.
- Wang T, McAuslane N, Liberti L, et al (2020). Benchmarking health technology assessment agencies – methodological challenges and recommendations. *International Journal Technology Assessment Health Care.* [In press]

Alignment:

- CIRS (2016) R&D Briefing 60 Early scientific advice from HTA agencies: how does the effective use of the various kinds of advice support a positive HTA recommendation? Centre for Innovation in Regulatory Science, London, UK.
- Allen N, Pichler F, Wang T, et al (2013) Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems. *Health Policy* 113(3):305-312.
- Wang, T., McAuslane, N., Liberti, L., et al. (2018). Building Synergy between Regulatory and HTA Agencies beyond Processes and Procedures-Can We Effectively Align the Evidentiary Requirements? A Survey of Stakeholder Perceptions. *Value in health,* 21 6, 707-714.
- McAuslane, N., Liberti, L., Connelly, P. (2019), The Confluence of Accelerated Regulatory and Health Technology Assessment Access Pathways. *Clin. Pharmacol. Ther.*, 105: 935-942.

2019 publications

6 R&D Briefings/reports:

- R&D Briefing 70 New drug approvals in six major authorities 2009-2018: Focus on facilitated regulatory pathways and orphan status
- R&D Briefing 71: Trends in the Regulatory Landscape for the Approval of New Medicines in Latin America
- R&D Briefing 72: Trends in the Regulatory Landscape for the Approval of New Medicines in Asia
- R&D Briefing 73: Review of HTA outcomes and timelines in Australia, Canada and Europe 2014-2018
- 2019 Project Report: Monitoring the Adequacy of Implementation and Adherence to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines. ICH, Geneva, Switzerland.
- 2019 CIRS Executive Colloquium Report “What is the value and return on investment for our company to maintain a regulatory policy function?” Rockville, MD, USA.

6 Peer-reviewed publications

- McAuslane N, Liberti L, Connelly P (2019) The confluence of accelerated regulatory and health technology assessment access pathways. *Clin Pharmacol Ther.* 105:935-942.
- Bujar M, McAuslane N, Walker S (2019) Quality decision making in health technology assessment: Issues facing companies and agencies. *Ther Innov Reg Sc*i. 2019 Mar 4:2168479019833660.
- Bujar M, McAuslane N, Walker S, Salek S (2019) The Reliability and Relevance of a Quality of Decision Making Instrument, Quality of Decision-Making Orientation Scheme (QoDoS), for Use During the Lifecycle of Medicines. *Front Pharmacol*. ;10:17.
- Kuhler T, Bujar M, McAuslane N, Liberti L (2019) Characterising regulatory outcomes for medicines submitted simultaneously to EMA and FDA and initially approved 2014-2016. *BMJ*;9:e028677.
- Keyter A, Banoo S, Salek S, Walker S (2019) The South African Medicines Control Council: Comparison of its Registration Process with Australia, Canada, Singapore and Switzerland. *Front. Pharmacol.* 10:228.
- Keyter A, Salek S, Gouws J, Banoo S, Walker S (2019) Evaluation of the performance of the South Africa regulatory agency: recommendations for improved patients’ access to medicines. *Ther Innov Reg Sci.*

10+ manuscripts in the pipeline

Publications listed here are available to download at cirsci.org/publications

2019 conference presentations

4 Poster presentations

- 2019 HTAi – Cologne 15th -19th June. Cai J: “Do Conditional Regulatory Pathways Affect HTA Recommendations”
- 2019 Annual DIA – San Diego. McAuslane N: “Regulatory Review Reliance Models: What are the Barriers and Enablers to the Successful use of These Models for Medicines?”
- 2019 Annual DIA – San Diego. Bujar M: “The Impact of US FDA Breakthrough Designation (BTD) on Global Access to Innovative Medicines”
- 2019 iSPOR. Cai J: “Does FDA Breakthrough Designation Affect HTA Recommendations in terms of Timing and Outcome?”

8 Oral conference presentations

- CADTH Symposium, 2019. Liberti L: “The Relationship of Conditional Regulatory Approvals to HTA Recommendation
- Annual DIA: CIRS-DIA joint session on AI-RWE – Liberti L as chair; Bujar M as presenter
- Annual DIA: Session Chair: Liberti L “Aligning Facilitated Regulatory and Access Pathways: Observations from the North American Experience”
- 2019 TOPRA meeting – Session Chair McAuslane N “Accelerating regulatory approvals globally”
- 2019 DIA North Africa Regulatory Conference, Cairo – McAuslane N: “Regulatory System Strengthening: A Global Perspective – Good reliance practices”
- AUDA- NEPAD: ScOMRA :4th Biennal scientific conference
  - Liberti L: “Maximising the regulatory efficiency and effectiveness of the AMA: learning from the experience of others “AUDA- NEPAD:ScOMRA :4th Biennal scientific conference
  - Patel P: “Optimising regulatory agencies process and performance thorugh standardised systematic measures”
  - Session Chair: Liberti L: “Harmonisation of regulation of medical products- innovative approaches to measuring regulatory outcomes, reliance and harmonisation”

Thank you to those we work with

2019 was a productive year for CIRS, but our achievements would not have been possible without the commitment and dedication of our advisory committees. We thank them for the invaluable support and direction they have provided. We would also like to thank our member companies and the Bill and Melinda Gates Foundation for its continued support.

Scientific Advisory Council (SAC)

Chair: Adjunct Prof John Skerritt, Deputy Secretary for Health Products Regulation, Department of Health, Canberra, Australia
Vice-Chair: Prof Hans-Georg Eichler, Senior Medical Officer, EMA

Deborah Autor, Global Head of Regulatory Excellence, AstraZeneca, USA
Dr Fabio Bisordi, Global Head International Regulatory Policy, F.Hoffmann-La Roche Ltd
Dr Claus Bolte, Head of Sector Marketing Authorisation, Swissmedic
Dr Harald Enzmann, Chair, CHMP/EMA
Dr Tim Garnett, CMO, SVP, Eli Lilly
Adrian Griffin, Vice President for HTA Policy, Johnson & Johnson
Dr Peter Honig, Senior Vice President and Head of Worldwide Safety and Regulatory, Pfizer
Mark Hope, Senior Vice President, Global Regulatory Head, UCB
Dr Ian Hudson, Senior Advisor, Integrated Development, Global Health, Bill and Melinda Gates Foundation, UK
Dr David Jefferys, SVP, Head of Global Regulatory, Eisai Europe Ltd
Prof John Lim, Professor of Practice, Executive Director of CoRE, Duke-NUS Medical School and Policy Lead, SingHealth Duke-NUS Global Health Institute
Dr Sabine Luik, Chief Regulatory Officer, SVP, Global Regulatory Affairs and Quality Assurance, GlaxoSmithKline
Dr Theresa Mullin, Director, Office of Strategic Programs, US FDA, CDER
Dr Brian O'Rourke, CEO and President, CADTH, Canada
Dr Junko Sato, Office Director, Office of International Program, Pharmaceuticals and Medical Devices Agency (PMDA), Japan
Dr Xie Songmei, Deputy Director of Clinical Department Center for Drug Evaluation, NMPA, China
Dr John Patrick Stewart, Director General, Therapeutic Products Directorate, Health Canada
Dr Roopal Thakkar, Vice President, Global Regulatory Affairs, Abbvie
Prof Stuart Walker, Founder, CIRS
Dr Max Wegner, Head Regulatory Affairs PH & CH, Bayer AG

Thank you to those we work with

Specialist Advisors to the Executive Director

Dr Thomas Lönngren, Former Executive Director, EMA
Dr Murray Lumpkin, Deputy Director, Integrated Development, and Lead for Global Regulatory Systems Initiatives, Bill and Melinda Gates Foundation
Prof Mamoru Narukawa, Associate Professor Pharmaceutical Medicine, Kitasato University Graduate School of Pharmaceutical Sciences, Tokyo, Japan
Dr Tomas Salmonson, Former Chair, CHMP/EMA
Dr Joseph Scheeren, President, CEO, Critical Path Institute

HTA Steering Committee

Chair: Dr Brian O'Rourke, CEO and President, CADTH, Canada
Vice-Chair: Prof Adrian Towse, Director Emeritus and Senior Research Fellow, OHE
Dr Nick Crabb, Programme Director, Scientific Affairs, NICE
Prof Hans-Georg Eichler, Senior Medical Officer, EMA
Dr Wim Goettsch, Associate Professor HTA, Utrecht University; Special Advisor HTA, ZIN
Adrian Griffin, Vice President for HTA Policy, Johnson & Johnson
Dr Michael Happich, Director, BioMed HTA, Eli Lilly and Co
Dr Adam Heathfield, Senior Director, Patient and Health Impact Innovation Centre, Pfizer
Niklas Hedberg, Chief Pharmacist, TLV
Evert Jan van Lente, Director EU-Affairs, AOK-Bundesverband
Prof Finn Børlum Kristensen, Former EUnetHTA Executive Committee Chairman and EUnetHTA Secretariat Director, Faculty of Health Sciences, University of Southern Denmark
Dr Maria Kubin, Head of MACS TA Cardiovascular, Bayer
Andrew Mitchell, Strategic Adviser, DoHA
Dr Vanessa Elisabeth Schaub, Global Access Senior Health Systems Strategy Leader HTA & Reimbursement, Roche
Dr Sean Tunis, Principal, Rubix Health and Senior Advisor, FDA

Keep in touch

Dr Magda Bujar, *Manager, Strategic Development*	mbujar@cirsci.org
Dr Jesmine Cai, *Senior Research Analyst*	jcai@cirsci.org
Gill Hepton, *Administrator*	ghepton@cirsci.org
Dr Lawrence Liberti, *Head, Regulatory Collaborations*	lliberti@cirsci.org
Dr Neil McAuslane, *Director*	nmcauslane@cirsci.org
Dr Jamie Munro, *Executive Director*	jmunro@cirsci.org
Prisha Patel, *Manager, Global Development Programme*	ppatel@cirsci.org
Dr Céline Rodier, *Senior Research Analyst*	crodier@cirsci.org
Dr Jenny Sharpe, *Senior Scientific Writer*	jsharpe@cirsci.org
Prof Stuart Walker, *Founder*	swalker@cirsci.org
Tina Wang, *Manager, HTA Programme*	twang@cirsci.org

Follow us on LinkedIn

www.linkedin.com/company/centre-for-innovation-in-regulatory-science-ltd

About CIRS

The Centre for Innovation in Regulatory Science (CIRS) is a neutral, independently managed UK-based subsidiary company, forming part of the Clarivate Analytics group. CIRS' mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and 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 and to facilitate access to medical products through these activities. This is CIRS' purpose. CIRS is operated solely for the promotion of its purpose. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, special projects and grants.

Centre for Innovation in Regulatory Science (CIRS)
Friars House, 160 Blackfriars Road
London SE1 8EZ, UK

Email: cirs@cirs.org
Website: www.cirsci.org
LinkedIn: www.linkedin.com/company/centre-for-innovation-in-regulatory-science-ltd

Published July 2020