WORKSHOP REPORT

High public health impact medicines for chronic diseases – Do regulatory, HTA and payer paradigms need to change?

12-13th June 2025
Hyatt Regency Hotel,
Tysons Corner, Virginia, USA

CIRS Centre for Innovation in Regulatory Science

Executive summary

Background

In recent years, life expectancy has declined in several affluent countries, particularly the US. While one of the causes has been deaths from COVID-19 infections, deaths from non-infectious metabolic 'lifestyle' diseases and the impacts of dementia and mental health conditions have been major factors. A recommendation from the CIRS workshop on regulatory agilities in 2022 was that several innovations introduced during the pandemic could be considered beyond emergency use, for example, for treatments addressing highly prevalent serious illnesses. Developing an approach for identifying illnesses that would benefit from the same sense of urgency as applied during the pandemic, and a unified effort grounded in risk-based principles, could be of value.

Except for a few therapeutics (e.g. GLP-1 agonists for type 2 diabetes, anti-amyloid therapies for Alzheimer's disease) recent drug development for chronic disease has been limited. The success rate is often low – for example only 5-6% of small molecules in phase 1 clinical trials for cardiovascular or neurology indications proceed to regulatory approval, compared with about 8% overall (Thomas et al. 2021). More public research funding, venture capital investment and stock raising has gone into cancer, rare diseases and vaccines in recent years, than non-communicable metabolic diseases. Regulatory incentives such as orphan drug fee waivers and facilitated regulatory pathways have generally not been made available or are less widely used. The use of low-cost generic drugs for conditions such as diabetes, hypertension and depression as HTA comparators also make payers set the bar very high for reimbursement of new, more expensive therapies.

An active area of drug development for chronic diseases is for drugs that can modify (prevent or slow) disease progression, rather than simply treating the symptoms of disease. These medicines tend to be targeted at an earlier stage of disease progression. Early treatment with such disease-modifying therapies could have a great impact on public and individual health. However, there are significant regulatory and reimbursement barriers to overcome due to high uncertainty around small effect size, a lack of validated biomarkers and variable disease progression. Real world evidence and patient-reported outcomes are very important, but measures also need to be developed and agreed in guidance.

Addressing the alternative of behaviour and lifestyle change on certain chronic diseases also needs to be considered, as payers would argue that in some cases money could be better spent on encouraging behavioural changes to reduce the burden of disease.

To help address these issues, CIRS convened a multi-stakeholder workshop involving industry, regulators, HTA agencies, payers, academics and patient organisations. The aim was to identify key challenges and explore solutions for improving the drug development paradigm for common chronic diseases.

Workshop objectives

- Review and discuss high public health impact medicines for common chronic diseases to understand the challenges these medicines face from a regulatory, HTA, payer and patient perspective.
- Identify how to incentivise medicines targeting diseases of significant public health interest that drive life expectancy down.
- Propose options and make recommendations on how to address policy challenges in the development, regulatory review, HTA and funding of high public health impact medicines for common chronic diseases. This includes particular policy challenges for drugs that can modify or potentially reverse a disease, rather than simply treating the symptoms of disease.

GRAPHIC SUMMARY

Common chronic diseases: A global health challenge

Example conditions:


Respiratory


Metabolic


Diabetes


Cardiovascular


Neurological

Key challenges:

- High mortality rates
- Economic burden
- Limited treatment options

A CIRS workshop involving


Pharmaceutical companies


Regulators


HTA agencies


Payers


Patient organisations


Academics

Calls for new adaptive, collaborative, patient-centered approaches to chronic disease treatment development, review and reimbursement.

What needs to change?

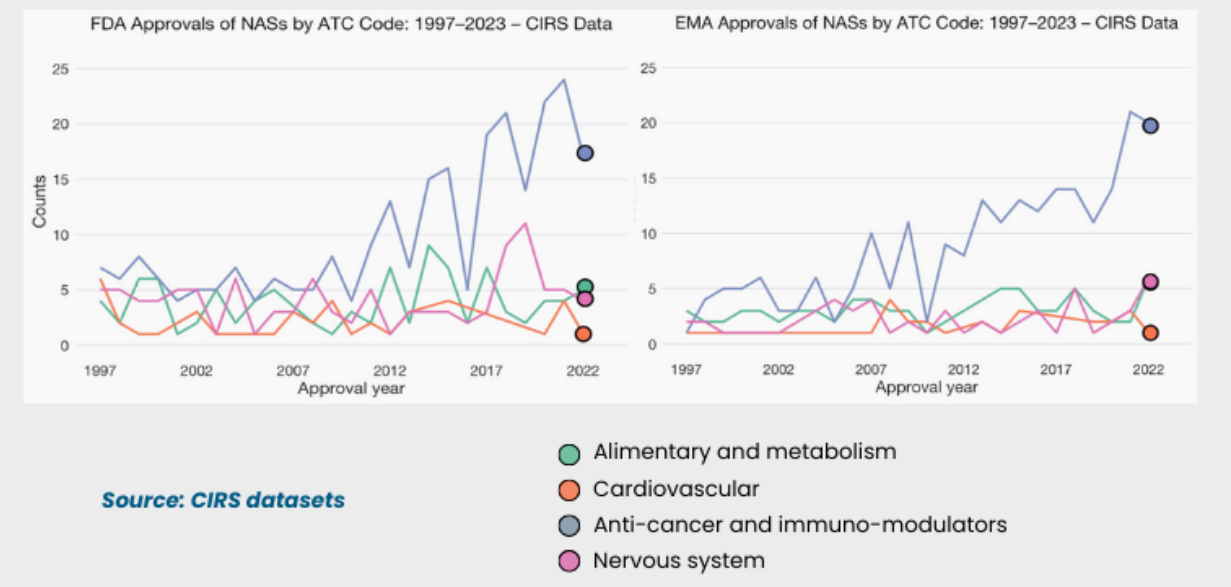
- Improve clinical trial efficiencies through novel trial designs and digitalisation.
- Promote company-regulator-HTA collaboration through early scientific advice and data sharing initiatives.
- Establish stakeholder expectations around the strength of the relationship between surrogate endpoints and clinical outcomes.
- Implement incentives for R&D in neglected chronic disease areas.
- Explore adaptive regulatory pathways and innovative pricing and payment models for common chronic diseases.

Key points from the plenary sessions

Evaluating the chronic disease landscape with CIRS metrics

CIRS routinely collects publicly available data from regulatory and HTA agencies to evaluate assessment timelines for new active substances (NASs). Since 2011, the number of FDA and EMA approvals for anti-cancer and immunomodulatory NASs has outpaced those for elementary metabolism, cardiovascular, and nervous system therapies (see below). This disparity may reflect the greater availability of incentives and facilitated regulatory pathways in oncology compared to other chronic disease areas. In addition, across various countries, the time taken from regulatory submission to first HTA recommendation tends to be shorter for anti-cancer and immunomodulatory NASs than for metabolic or cardiovascular NASs (though this is driven by faster regulatory rather than HTA timelines).

CIRS data also demonstrates the positive impact of collaborative regulatory models in accelerating the availability of innovative medicines. For example, oncology NASs approved via Project Orbis showed faster median rollout times – primarily due to reduced submission gaps - compared to those not included in Project Orbis. This prompts the question of whether regulatory collaborative models like Project Orbis could be adapted or expanded to accelerate registration of treatments targeting common chronic diseases.



Enabling flexibility in clinical development and evidence generation

Clinical trials for common chronic diseases face several challenges, including difficulties measuring subtle changes in disease progression, selecting appropriate endpoints and biomarkers, variable disease progression with frequent comorbidities, patient recruitment challenges and high costs due to large patient numbers and long trial durations. Investing in patient engagement and research to better understand disease natural history, molecular mechanisms and targets are key to establishing better endpoints that are meaningful to patients.

There is a need to embrace innovation in the form of novel trial designs, such as decentralised, hybrid and adaptive trials, and digital technologies that can reduce patient burden e.g. wearables and enhance data analysis such as AI. The platform approach could potentially improve efficiency in chronic disease development by allowing developers and regulators to leverage information across multiple products. Real-world evidence (RWE) is also important to supplement evidence from clinical trials.

Learnings from the chronic obstructive pulmonary disease (COPD) field highlight the need for multi-stakeholder collaboration to shift the focus towards earlier intervention to prevent disease progression. Progress in Alzheimer's disease illustrates how biomarkers can be used to support early therapeutic intervention, yet there are still challenges with demonstrating the relationship between surrogate endpoints and clinical outcomes.

Adapting regulatory processes and practices

Regulatory challenges for common chronic diseases include: the increased use of surrogate endpoints, which may not clearly demonstrate clinical outcomes and thus increase uncertainty in evidence; more personalised treatment approaches; and differences in benefit-risk expectations due to the typically slow progressive nature of these diseases.

While the regulatory system has evolved to expedite rare disease and oncology drugs, medicines for chronic diseases have been neglected: they lack the sort of incentives available for orphan drugs and rarely qualify for facilitated or expedited regulatory programmes. This creates a misalignment in public health policy, as drugs that could modify prevalent chronic diseases at early stages could potentially have greater societal and economic impact than some oncology and rare disease treatments.

Therefore, the current regulatory model for common chronic diseases needs to evolve and become more flexible. Potential improvements to consider are:

- Using adaptive approval pathways and rolling reviews.
- Being more open to surrogate endpoints and RWE.
- Reviewing existing pathway criteria to better reflect and address health system needs.
- Leveraging learnings from collaborative assessments, including Project Orbis and the Access Consortium.
- Engaging in early and iterative dialogue with other regulators, industry and HTA agencies.
- Increasing collaboration with HTA agencies on surrogate endpoints and patient engagement.
- Strengthening the integration of patient experience data and patient-reported outcomes in decision making.

Evolving HTA and payer frameworks

Early large-scale adoption of innovative treatments for common chronic diseases faces substantial technical and financial hurdles. Some innovations require changes to delivery models and infrastructure that are difficult to quantify in cost-effectiveness analyses. The interplay with supportive services e.g. for behavioural and lifestyle changes, is also difficult to determine. Horizon scanning may help to give HTA agencies and payers more sight of these issues before making coverage decisions.

While surrogate endpoints can be valuable for initial approval of treatments for common chronic diseases, HTA agencies and payers ultimately require evidence of direct effects on patient-centric outcomes. Increased reliance on surrogate endpoints and less mature evidence creates uncertainty around cost-effectiveness estimates. Outcomes-based agreements, such as managed access arrangements, can help mitigate this, but may necessitate investment in health data infrastructure to capture robust data. Establishing and communicating expectations around the strength of relationships between surrogate endpoints and clinical outcomes is crucial, requiring collaboration between regulators, HTA agencies and payers.

Cost-effectiveness comparisons can be skewed when generic drugs are used as benchmarks. For example, novel non-opioid analgesics may appear less viable when compared to morphine on a dollar-per-dose basis. A broader definition of value and agreement on appropriate comparators are needed.

Affordability is a key issue for HTA agencies and payers, given the large chronic disease patient populations that could be eligible for early-stage treatment. Exploring innovative pricing and payment models and identifying patient subgroups most likely to benefit from treatment may help to tackle affordability issues.

Broader elements of value, such as productivity, social care costs, and caregiver burden, should be incorporated into HTA and payer frameworks. However, robust data on these aspects is not always available at the time of assessment.

Finally, for payers, patients moving between insurance providers creates challenges for evaluating long-term outcomes, as the payer initially covering a treatment may not see its future health and cost benefits.

Keeping patients at the centre

For some chronic diseases like COPD, development approaches have remained largely unchanged for decades, and so approvable endpoints are not aligned with patients' primary concerns. Despite effective existing treatments, many patients remain unsatisfied and want new options. To successfully change this paradigm, patients should be involved earlier in development processes and all stakeholders must work together while considering patient perspectives.

While the value of patient involvement is broadly recognised, often less consideration is given to how patient input is integrated throughout development, regulatory, HTA and payer processes. It is important to distinguish between different types of patient input; for instance, patient perspectives on areas of unmet need and drug development can differ significantly from patient preferences or patient-reported outcomes.

When involving patients, clarity is essential. Stakeholders should be clear about the type of information they are seeking — whether it's about lived experience, day-to-day expenditures, barriers to receiving care or treatment, or treatment experiences.

There is often a perception issue of potential conflicts of interest when engaging with patients. However, when clear parameters are in place to protect all parties, meaningful discussions can take place.

In addition to individual patients and patient groups, valuable insights can be gained from collaborative partnerships with organisations representing multiple disease communities, such as the American Brain Coalition.

Advancing research in women

Women experience a higher prevalence than men of many chronic conditions, including hypertension, arthritis, and dementia. However, research to understand these differences is limited, contributing to poorer health outcomes for women and substantial costs to individuals and society. The National Academies Committee on a Framework for the Consideration of Chronic Debilitating Conditions in Women has recommended a research agenda focused on:

- **Better data, better biology -** Need for better data collection, surveillance, biological models that reflect women's bodies.
- **Improving care pathways -** Challenges in diagnosis, treatment, and managing multiple chronic conditions in women.
- **Understanding lived experience -** How trauma, identity, and inequities shape health; need for women-centered, inclusive research.

Is it time for a shift in the development paradigm?

There is no doubt that common chronic diseases have been underserved in recent years, despite posing a major global health challenge. These conditions are associated with high mortality rates, significant economic burden, and limited treatment options. Addressing this challenge requires more than incremental change — it demands a fundamental reimagining of how treatments are developed, evaluated, and brought to market. A more adaptive, collaborative, and patient-centered approach is urgently needed, with targeted incentives playing a central role.

Recommendations from the breakout discussions

Clinical trials – How should the thinking be reframed for undertaking clinical trials for high impact chronic diseases?

- Increase collaboration across stakeholders, including patients, regulators, payers, HTA agencies, sponsors, and clinicians, through early dialogue e.g. scientific advice, and pilots to move initiatives forward.
- Improve clinical trial efficiencies by:
    - Focusing on understanding the early trajectory of the disease and the patient's perspective, making use of technological enablers e.g. AI, wearables.
    - Identifying appropriate surrogate biomarkers and establishing their efficacy.
    - Embracing pragmatic and decentralised trial (DCT) designs.
    - Harmonising endpoints globally.
- Explore 'clinical research as a care option', where trials procedures can be regarded as usual care and reimbursable through health care provision. This could be facilitated by delivery networks or public-private set-ups.
- Explore adaptive approval and reimbursement models to allow early entry for initial indications, provided there is a clinically relevant effect size, while label extension/variations are being addressed in subsequent studies that involve DCT/pragmatic trial elements.
- Promote use of RWE, exploring regulators' requirements and acceptance of evidence from electronic health records.

How should regulatory and HTA frameworks evolve to incentivise and enable development for high impact chronic diseases?

- **Financial incentives** - Implement tax credits, grants, vouchers, subsidies and/or patent extensions to incentivise R&D in neglected chronic disease areas.
- **Adaptive regulatory pathways** – Introduce accelerated approval mechanisms that incorporate RWE and patient-reported outcomes (PROs).
- **Flexible trial design** – Encourage innovative trial designs, such as adaptive or pragmatic trials, to improve efficiency and cost-effectiveness.
- **Multi-stakeholder collaboration:** Promote company-regulator-HTA collaboration through early scientific advice and data sharing initiatives.
- **HTA/payer predictability:** Establish clear and consistent guidelines for the types of evidence needed to help streamline reimbursement and improve patient access.
- **Dynamic pricing:** Investigate dynamic pricing to incentivise development for chronic diseases.
- **Medical guidelines:** Update medical guidelines for chronic diseases more frequently to avoid delays in the adoption of new treatment approaches.
- **Priority setting:** Establish national health targets to provide clear signals of priorities and unmet needs, helping to inform investment decisions.

How to address the regulatory, HTA and payer challenges for therapeutics that slow or prevent disease rather than merely act on symptoms?

Development

- Use platform review and early consultation.
- Place a higher valuation of societal impact, PROs and healthcare resource utilisations in trial design.
- Increase emphasis on disease sub-populations and improve understanding of underlying pathophysiology.
- Consider running a natural history cohort/external control arm in addition to RCTs to help address potential evidence gaps.

Regulatory review

- Leverage existing RWE frameworks e.g. Data Analysis and Real World Interrogation Network (DARWIN EU), FDA RWE programmes.
- Elicit patient-centric value of 'delay/prevention'.
- Include clinical outcome assessments/PROs in the label.
- Consider the appropriateness of surrogate endpoints and the possibility of offering longer market exclusivity if product approval is delayed to accommodate longer-term data collection.
- Adapt existing frameworks to prioritise high impact chronic diseases.

HTA/reimbursement

- Review the appropriateness of current HTA methodologies for evaluating treatments delaying disease onset or progression.
- Consider using alternative reimbursement models e.g. subscription model, Per Member Per Month, Pay for Performance, including the potential for re-evaluation of access decisions based on longer-term data or RWE.

Recommendations for CIRS from across the breakout groups:

- Facilitate a multi-stakeholder study to investigate unmet medical needs for chronic diseases from the patient's and caregiver's perspective.
- Conduct a landscape analysis on the effectiveness of tax credits, funding models, and market exclusivity in stimulating R&D investment in chronic disease innovation.
- Review existing research on alternative payment models including managed entry agreements and survey CIRS members to assess whether these models work and how they could be improved.
- Analyse the current global landscape for joint scientific advice, including learnings, recommendations and potential for expansion into the US.
- Convene multiple stakeholders to develop policy solutions for the lack of progress in the consideration of patient-centred outcomes, PROs and societal benefits in regulatory, HTA and payer decision making.

Workshop programme

Please click on a section of interest to find that section in the report.

Day 1: 12th June 2025

Session 1: The impact of chronic disease on health systems and life expectancy - Current landscape and challenges	
09:00	**CIRS welcome and introduction**
09:15	**Chair's welcome and introduction – Prof Hans-Georg Eichler**, Consulting Physician, Association of Austrian Social Insurances
	Is it time for a shift in paradigm for development of medicines for highly prevalent serious illnesses to enable new therapies to be brought to the market sooner? Current landscape and challenges
09:20	**Company perspective – Jeffrey Francer,** Vice President, Head of Global Regulatory Policy and Strategy, Eli Lilly, USA
09:35	**HTA agency perspective - Dr Nick Crabb,** Chief Scientific Officer, National Institute for Health and Care Excellence (NICE), UK
09.50	**Panel discussion and comments from the floor** **Above speakers plus 5 minute reflections from:** **Patient perspective – Dr Bruce Miller,** Chief Scientific Officer, COPD Foundation, USA **Payer perspective – Vicky Brown,** Associate Vice President, Clinical Drug Safety Humana, USA **Regulator perspective – Prof Tony Lawler,** Deputy Secretary, Health Products Regulation Group, Australian Government Department of Health and Aged Care **Regulator perspective – Kelly Robinson,** Director General, Pharmaceutical Drugs Directorate, Health Canada
10:30	**Break**
Session 2: Enabling flexibility in clinical development and evidence generation for high impact chronic diseases	
11:00	**Treating the disease not just the symptoms: Modification or reversal of chronic disease progress - What are the regulatory and HTA challenges?** **Professor John Skerritt,** Enterprise Professor in Health Research, University of Melbourne, Australia
11.15	**Discussion**
	Accelerating clinical development for high impact chronic diseases – What needs to be considered?
11:20	**Company perspective – Alexis Miller, Head,** Global Regulatory Policy, Merck & Co, USA
11:35	**Regulator perspective – Prof Ton de Boer,** Chair, Medicines Evaluation Board, The Netherlands
11:50	**Health economics and outcomes research (HEOR) perspective - Dr Daniel Ollendorf,** Chief Scientific Officer and Director of HTA Methods and Engagement, Institute for Clinical and Economic Review (ICER), USA
12:05	**Discussion**

	Company case studies that highlight the need to adapt or reframe the paradigm for development review and reimbursement
12:15	**New approaches to chronic obstructive pulmonary disease (COPD) – Bisola Filchak,** Vice President, Immunology and Inflammation, Global Regulatory Affairs, Sanofi, USA
12:25	**Anti-amyloid drugs for Alzheimer's – Simon Bennett,** Director, Global Regulatory Policy Biogen, UK
12:35	**Discussion**
12:45	**Lunch**
Session 3: Adapting regulatory and HTA process and practices for high impact chronic diseases – what needs to be considered?	
13:45	**Chair's introduction – Dr Supriya Sharma**, Chief Medical Adviser, Health Canada
13:55	**Women's health and chronic disease – What changes are needed?** **Dr Melissa Laitner,** Director of Strategic Initiatives, National Academy of Science, USA
14:10	**Panel discussion – 8 mins viewpoints** **Regulatory considerations: Focus on the regulatory review framework** **Does the regulatory model for development and review of medicines for high impact chronic diseases need reframing? Is there a need for regulatory incentives beyond what is available?** **Company perspective – Ginny Beakes-Read,** Head, Global Regulatory Policy and Intelligence, Johnson & Johnson Innovative Medicine, USA **Regulator perspective – Dr Eveline Trachsel,** Head of Medicinal Products Approval and Vigilance, and Member of the Management Board, Swissmedic **Policy perspective – Dr June Cha,** Director, Policy, Milken Institute, USA
15:10	**Break**
15:40 ***15:55*** ***16:10***	**HTA/payer considerations - Focus on HTA/payer assessment framework for high impact chronic diseases and their effects on health systems** **Do HTA/payers need to be 'system shaping' by investing in innovations for health?** **Company perspective – Paul Villa,** Disease Area Head, Respiratory Global Pricing and Market Access, GlaxoSmithKline, USA **HTA perspective – Dr Sahar van Waalwijk van Doorn-Khosrovani,** Member of the National Funder's Committee for Evaluation of Specialised Medicines and Companion Diagnostics, CZ, The Netherlands **Payer perspective – Jessica Daw,** Vice President, Pharmacy, Sentara Health Plans, USA
16:25	**Discussion**
Session 4: Breakout discussions: Priority research areas and how to address policy challenges	
16:30	**Introduction to breakout discussions - delegates to go to breakout rooms**

16:45	**Breakout discussions – each group is asked to consider both qualitative and quantitative issues. Please review, debate and make recommendations for the following:** **A: Clinical trials – How should the thinking be reframed for undertaking clinical trials for high impact chronic diseases?** **Chair: Kelly Robinson,** Director General, Pharmaceutical Drugs Directorate, Health Canada **Rapporteur: Dr Odd Erik Johansen**, Principal Medical Director, Roche, Switzerland **B: How should regulatory and HTA frameworks evolve to incentivise and enable development for high impact chronic diseases?** **Chair: Em Prof dr Ton de Boer,** Chair, Medicines Evaluation Board, The Netherlands **Rapporteur: Michael Cunha,** Senior Director, Regulatory Policy & Science, Bayer, USA **C: How to address the regulatory, HTA and payer challenges for therapeutics that slow or prevent disease rather than merely act on symptoms?** **Chair: Prof Hans-Georg Eichler,** Consulting Physician, Association of Austrian Social Insurances **Rapporteur: Alix Arnaud,** Global Market Access Strategy and Operations Lead, Sanofi, USA
17:45	**End of day one**

Day 2: 13th June 2025

Session 4: Breakout discussions (continued)	
08:30	**Continuation of syndicate discussions**
10:15	**Break**
Session 5: Feedback from breakout discussions and panel discussion	
11:00	**Chair's introduction – Dr Brian O'Rourke,** Chair, CIRS HTA Steering Committee
11:05	**Feedback from breakout rapporteurs, with discussion**
12:00	**Panel discussion – Policy actions/considerations - 8 minute viewpoints followed by discussion with workshop participants** **Company perspective – Andrew Emmett,** Vice President, Global Regulatory Policy and Intelligence, Pfizer, USA **Regulatory perspective – Prof Anthony Lawler,** Deputy Secretary, Health Products Regulation Group Department of Health, Disability and Ageing, Australia **HEOR perspective - Dr Daniel Ollendorf,** Chief Scientific Officer and Director of HTA Methods and Engagement, Institute for Clinical and Economic Review, USA **Patient perspective – Leslie Ritter,** Vice President, Healthcare Access, National MS Society, USA, and Board Member & Advocacy Chair, American Brain Coalition
13:00	**Close of meeting**

Session summaries

Please note that the following summaries represent the views of the individual presenters and do not necessarily represent the position of the organisation they are affiliated with. Included slides are attributed to the individual presenters and have been reproduced with their permission.

Session 1: The impact of chronic disease on health systems and life expectancy – Current landscape and challenges

Is it time for a shift in paradigm for development of medicines for common chronic diseases to enable new therapies to be brought to market sooner?

Company perspective

Jeffrey Francer, Vice President, Head of Global Regulatory Policy and Strategy, Eli Lilly, USA

Prevalence and burden of chronic disease

According to the World Health Organization (WHO), non-communicable diseases (NCDs) killed at least 43 million people in 2021, accounting for 75% of non-pandemic related deaths globally. Many of these deaths were premature, and while some risk factors can be mitigated, others have genetic components. Cardiovascular diseases, cancers, chronic respiratory diseases and diabetes are the main types of NCDs, collectively responsible for 80% of all premature NCD deaths. In the US, Alzheimer's disease and other dementias are also a leading cause of death and a growing burden to the healthcare system.

Imbalance in drug development

Despite being the leading cause of death and disability in the US, novel cardiovascular disease drugs accounted for only 4% of new approvals in the last five years. This imbalance is evident when comparing the number of treatments developed for cardiovascular disease versus cancer, indicating a clear need for new treatments in areas with high societal burden. Disease prevention remains an important focus and should be viewed as a complementary strategy to treatment.

Strategies to accelerate development

Several strategies should be considered to accelerate drug development for chronic diseases:

- Learning from successful tools like Orbis and Access to promote collaborative approvals and reviews.
- Pursuing regulatory convergence and global clinical trials where regulators examine the same data simultaneously.
- Making clinical trials more accessible to patients through decentralised approaches.
- Reducing the burden on clinical trial participants.
- Leveraging technology for remote measurement of key health indicators (heart rate, respiratory rate, weight, blood sugar).

Conclusion

There is a clear need to incentivise and accelerate drug development for common chronic diseases, which cause significant mortality and healthcare system costs. The apparent imbalance between development efforts for conditions like cardiovascular disease compared to cancer suggests opportunities to apply successful regulatory approaches from oncology to underserved chronic diseases. Transforming regulatory frameworks and embracing technological innovation may help to enable streamline development for common chronic diseases and ensure public health based regulatory decisions.

Important Key Takeaways

- **Need for Chronic Illness Drug Development**
- **Expanding & Transforming Regulatory Frameworks**
- **Public Health-Based Regulatory Decisions**
- **Rapid adoption of technologies to speed and enable convergence of global regulatory reviews**

Is it time for a shift in paradigm for development of medicines for common chronic diseases to enable new therapies to be brought to market sooner?

HTA agency perspective

Dr Nick Crabb, Chief Scientific Officer, National Institute for Health and Care Excellence (NICE), UK

Focus on highly prevalent chronic illnesses has recently increased, with strong pipelines of innovative medicines, diagnostics, and medical devices emerging in disease areas such as obesity, metabolic dysfunction-associated steatotic liver disease, and dementia. While these developments are exciting for public health, there are significant technical and financial challenges in timely adoption and roll out at scale.

Technical challenges

Surrogate endpoints

Early adoption of medicines with potential to improve public health will likely require increased use of surrogate endpoints. Establishing and communicating expectations around the strength and validation of relationships between surrogate endpoints and clinical outcomes is crucial, requiring collaboration between regulators and HTA agencies. NICE collaborated internationally on a white paper outlining best practices for using surrogate endpoints in cost-effectiveness analysis for HTA and plans to embed these into in its methods.

Economic modelling consistency

In disease areas with high levels of innovation and product launches, inconsistent approaches to economic modelling can make it difficult to ensure consistent guidance across products. To address this, NICE is developing disease-specific extensions to its reference case, with obesity and obesity-related comorbidities as the first priority.

Delivery models for disruptive technologies

Some innovations in areas like dementia and obesity require new delivery models and infrastructure. Without clarity on these models, it is difficult to estimate costs in economic modelling and ensure timely implementation. The NICE HTA Innovation Laboratory (HTA Lab) is working on capturing infrastructure and service redesign costs in evaluations, though this work needs to occur before HTA assessment, requiring effective horizon scanning and planning.

Financial challenges

Managing Uncertainty

Increased reliance on surrogate endpoints and less mature evidence creates uncertainty around cost-effectiveness estimates. Managed access arrangements help manage this uncertainty, but healthcare systems will need to invest more in managed access and data infrastructure to capture evidence of clinical and cost-effectiveness, supporting a lifecycle approach to HTA.

Affordability

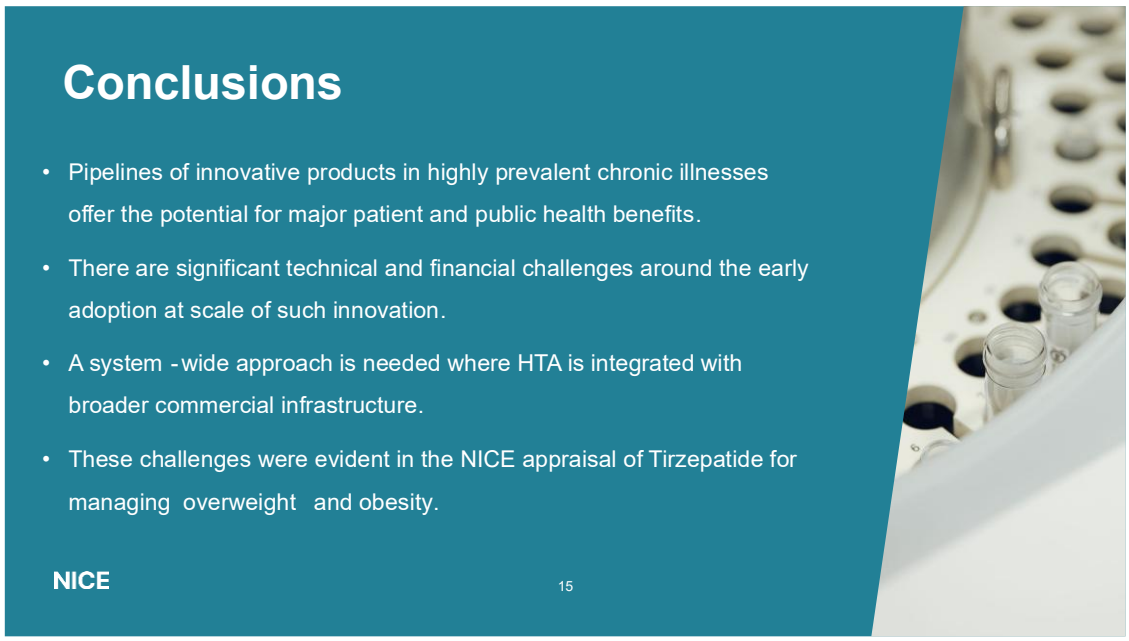
Large-scale adoption of interventions for highly prevalent conditions presents affordability challenges, especially when combined with high delivery infrastructure costs. These challenges cannot be solved through HTA alone and require a system level approach where HTA is integrated into broader commercial infrastructure. A potential approach could be to use current HTA frameworks as the initial arbiter of value to the healthcare system, leading to initial adoption in patients with the highest unmet need, followed by commercial arrangements like price-volume agreements to facilitate affordable large-scale implementation.

Case study: Tirzepatide for obesity

NICE issued a positive recommendation for tirzepatide for managing overweight and obese patients in December 2024. As the recommendation could apply to approximately 3.4 million patients, full implementation would have been highly disruptive for service delivery and finances. NHS England requested and received a funding variation allowing for full rollout over 12 years, with 220,000 patients with the highest potential benefit to be treated in the first three years, followed by a formal NICE review.

Conclusion

While there are promising pipelines of innovative products for highly prevalent chronic illnesses offering significant patient and public health benefits, substantial technical and financial challenges exist around early large-scale adoption. A system-wide approach is needed, integrating HTA with broader system preparedness and commercial infrastructure.



Is it time for a shift in paradigm for development of medicines for common chronic diseases to enable new therapies to be brought to market sooner?

Patient organisation perspective

Dr Bruce Miller, Chief Scientific Officer, COPD Foundation, USA

Chronic obstructive pulmonary disease (COPD) is one of the most highly prevalent diseases in both developed and undeveloped countries, with a global average prevalence of approximately 12%. Despite being the fourth leading cause of death worldwide and third leading cause of disability in the US, COPD is often overlooked in policy discussions. The total societal costs in the US range from $60-100 billion annually, yet it ranks very low (176th) in disease-specific research funding from the National Institutes of Health.

Challenges in drug development

New drug development for COPD is challenging, with approaches remaining largely unchanged for 30 years. The limited number of approvable endpoints (exacerbations, lung function, and mortality) are not aligned with patients' primary concerns, which include symptoms (particularly breathlessness), physical activity, and disease progression. Despite effective existing treatments, many patients remain unsatisfied and demand new options. For successful paradigm change, all stakeholders must work together, keeping patient perspectives at the centre.

Varying stakeholder priorities

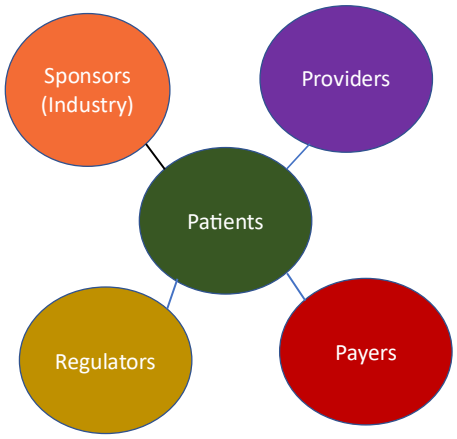
A key challenge with COPD and other chronic diseases is that different stakeholders have varying priorities:

- Patients want new medicines that address unmet needs and slow or halt disease progression, requiring early intervention.
- Companies need clear decision-making markers to manage investment risk, as well as clear paths to regulatory approval and commercialisation.
- Regulators require substantial evidence of effectiveness, understanding of benefit-risk trade-offs, and appropriate endpoints that are validated for specific contexts of use (though it is not always clear what evidence is needed to demonstrate that a new endpoint is ‘fit for purpose’).

Conclusion

For COPD and other chronic diseases, additional endpoints are needed to address unmet patient needs and impact disease progression. More effective interactions are needed between regulators and patients/patient organisations to ensure understanding of patient priorities and make patient-focused drug development a reality. There is an opportunity for innovation in clinical trial design and identifying novel endpoints if all stakeholders can work together, keeping patient perspectives at the centre.

Stakeholders in Drug Development – Patients at the Center



- 3 endpoints currently accepted for approval of COPD Tx: exacerbations, FEV1, mortality but …
- Top patient concerns: symptoms (particularly breathlessness), physical activity, disease progression – misalignment between patient priorities and regulators

The challenge & problem:
(Dr. Janet Woodcock, former CDER director, US FDA):
"It turns out that what is really bothering the patient and what is really bothering the doctor can be radically different things….patients are true experts in their disease".

"It's clear you have to start with an understanding of the impact of the disease on the people who have it, and what they value most in terms of alleviation before you set up a measurement and go forward with truly patient-focused drug development."

(PDUFA V Clinical Outcome Assessments Public Workshop, April 1, 2015)

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COPD FOUNDATION

Is it time for a shift in paradigm for development of medicines for common chronic diseases to enable new therapies to be brought to market sooner?

Regulator perspective

Prof Tony Lawler, Deputy Secretary, Health Products Regulation Group, Australian Government Department of Health and Aged Care

Regulatory challenges

Regulators often find themselves in a challenging position, being both reactive to downstream developments and responsive to upstream health policy. In Australia, where the state is predominantly the payer, decisions about payment involve long-term policy considerations about how to allocate a fixed budget. There can be challenges where clinical practice and payment policy diverge. For example, in Australia, as in many other countries, the profitability of antibiotics is based on volume of use, which can run counter to the principles of antimicrobial stewardship.

Clinical development is shifting from large, multi-centre trials involving hundreds of thousands of participants to more personalised approaches, including treatments for single patients (n=1). This requires a paradigm shift in regulatory approaches, to facilitate an approval at the patient level that still allows for further evidence to be gathered.

Best practice principles

Regulators should be governed by three best practice principles:

- **Continuous improvement and building trust** through effective horizon scanning and understanding key challenges.
- **Stakeholder engagement**, not only with industry and policymakers but also with patients, recognising that clinical endpoints regulators examine may not align with endpoints that matter most to patients.
- **Risk-based and data-driven approaches** that balance facilitating access while safeguarding safety and quality.

Conclusion

While regulators can adapt their approaches to facilitate access to treatments for chronic diseases, they cannot operate in isolation. Effective interaction with HTA bodies, industry, and patient groups is essential to addressing the challenges associated with prevalent chronic diseases.

Is it time for a shift in paradigm for development of medicines for common chronic diseases to enable new therapies to be brought to market sooner?

Regulator perspective

Kelly Robinson, Director General, Pharmaceutical Drugs Directorate, Health Canada

Reframing regulatory approaches

Rather than creating bespoke solutions, existing regulatory tools and processes could potentially be leveraged or adapted to enable new therapies for common chronic diseases. These include:

- **Priority review policies** could potentially be adapted to incorporate health system needs in their criteria
- **Conditional review processes**, typically not used for chronic diseases affecting large populations, might be appropriate when considering different endpoints or surrogate markers
- **Patient engagement** could be improved, for example, in Canada, there could be opportunities for Health Canada to learn from the HTA agency, Canada's Drug Agency, which has well-established patient engagement networks.

Regulator-HTA collaboration

There are opportunities for collaboration between regulators and HTA bodies, particularly in patient engagement. Given Canada's small population, regulators and HTA bodies often approach the same patient populations with similar questions. Better collaboration could enrich patient engagement while reducing burden on patients.

Conclusion

Regulators should consider how existing tools and processes might be adapted to address challenges for chronic disease treatments rather than creating entirely new approaches. Enhanced collaboration between regulators and HTA bodies, particularly in patient engagement, could improve efficiency and effectiveness.

Is it time for a shift in paradigm for development of medicines for common chronic diseases to enable new therapies to be brought to market sooner?

Payer perspective

Optimising pharmaceutical benefits and maximizing outcomes, while balancing competing demands

Vicky Brown, Associate Vice President, Clinical Drug Safety, Humana, USA

Humana is a leading US health and well-being company providing national coverage primarily for government programmes. Humana operates an integrated platform with care delivery assets (primary care, home health, and pharmacy) and an insurance portfolio encompassing approximately 5.8 million Medicare Advantage members, 2.4 million standalone prescription drug benefit programme members, and about 1.4 million Medicaid beneficiaries across nine states, as of June 30, 2025.

Health-first approach to formulary design

Humana puts patients at the centre. In alignment with that mission, Humana strives to develop a health-first formulary that is focused on affordably achieving the right outcome, for the right member, at the right time. During formulary design, Humana places a strong emphasis on clinical efficacy and medication safety by reviewing scientific literature and expert guidelines to ensure significant health benefits. Affordability and access to medications are also pivotal components of the decision-making process. Formularies are reviewed and approved by Humana's Pharmacy & Therapeutics Committee that includes internal and external pharmacists and physicians from various specialties. The goal is to balance clinical outcomes with affordability to deliver value to members.

Challenges in assessing medications for large populations

When assessing medications for large populations, payers face several challenges including:

- Balancing upfront investment against potential long-term medical cost savings.
- Uncertainty about real-world experience and limited evidence timeframes.
- Delays in professional societies incorporating new agents into guidelines, leaving payers to make decisions without up-to-date expert guidance.

Importance of wraparound services

Wraparound services and care delivery models are key to optimising medication benefits. Payers often must make coverage decisions without understanding how these supportive services will be implemented in real-world delivery models.

Conclusion

Making coverage decisions for new medications for chronic diseases involves balancing clinical evidence with affordability considerations, while managing significant uncertainty about real-world outcomes. The challenges are particularly pronounced for treatments targeting large populations, where long-term benefits may be difficult to quantify. Wraparound services and appropriate care delivery models are crucial for optimising medication benefits, but information about these elements is often lacking when coverage decisions must be made.

Session 2: Enabling flexibility in clinical development and evidence generation for high impact chronic diseases

Treating the disease not just the symptoms: Modification or reversal of chronic disease progress - What are the regulatory and HTA challenges?

Prof John Skerritt, Enterprise Professor in Health Research Impact, University of Melbourne, Australia

Chronic disease treatment landscape

Chronic diseases have recently received renewed focus as a major cause of death and disability. The chances of success in drug development vary significantly, however across different therapeutic areas, with endocrine, neurology, and several other chronic disease areas having lower success rates compared to areas like haematology. In recent years, more public research funding, venture capital investment and stock raising has gone into cancer, rare diseases and vaccines rather than for chronic disease drug development.

Only 8 out of 50 FDA drug approvals in 2024 were for chronic diseases, and many of these were for less common chronic conditions. Similarly, when examining Australian government drug funding in 2023/24, cardiovascular and many other chronic diseases were not among the top reimbursed medications despite their comparatively high prevalence.

Regulatory challenges

The regulatory system has evolved to expedite the review of rare disease and oncology drugs, but chronic diseases have been largely forgotten. They lack orphan drug incentives and only rarely qualify for facilitated or expedited regulatory programmes. This creates a misalignment between public health policy and investments in new medicines, as drugs that could modify prevalent chronic diseases at early stages would potentially have much greater societal and economic impact than some oncology and rare disease treatments.

CIRS data shows that orphan drug approvals are faster on average than non-orphan approvals, likely due to regulatory incentives. When examining the use of FDA's expedited pathways across different therapeutic areas, approvals in oncology and haematology tend to frequently receive expedited designations, while those in urology, dermatology and psychiatry rarely do.

Disease modification challenges

Constructing a development paradigm for drugs that slow or reverse disease progression is inherently complex. For many chronic diseases, it is challenging to show a significant effect size in clinical trials when looking at slowing deterioration or disease progression rates. For example, in COPD, FEV1 (a measure of respiratory function) typically drops by only about 50 ml per year, making it difficult to demonstrate a meaningful effect over a six-month clinical trial.

Understanding disease natural history and the underlying disease mechanisms is critical for developing early disease stage-modifying drugs for chronic diseases. This is complicated by the interconnection of risk factors and comorbidities. For many chronic diseases like chronic kidney disease, there often isn't a single causative factor but rather a combination of factors.

Clinical trial considerations

Clinical trials for disease-modifying therapies for chronic diseases face several challenges:

- High costs due to large patient numbers and long duration
- Difficulty identifying suitable biomarkers
- Variability in disease progression between trial participants
- Challenges targeting early-stage patients in trials, as they are still relatively well
- Issues with patient-reported endpoints and use of questionnaire scales
- Lack of disease-specific diagnostic tests for some conditions.

Seeking early scientific advice from regulators and health technology assessment (HTA) bodies on trial design and endpoints is key, especially when looking for subtle effect sizes in disease progression.

Affordability and comparator issues

Cost-effectiveness comparisons can be skewed when low-cost generic drugs are used as benchmarks or comparators in HTA assessments. For example, novel non-opioid analgesics may appear less viable when compared to morphine on a dollar-per-dose basis. A broader definition of value and agreement on appropriate comparators are needed.

The affordability of new therapeutics for common chronic diseases remains a significant issue, especially for therapeutics targeting early stages of the disease with even larger numbers of potential patients. HTA agencies and payers are likely to urge sponsors to narrow proposed indications to help reduce costs to the health system and obtain maximum effect sizes.

Conclusion

Despite some exciting recent results in certain chronic diseases, drug development for these diseases often remains neglected and the current regulatory incentives and HTA/payer frameworks are not sufficient to attract more investment. Learning from success stories is important—understanding disease natural history, molecular mechanisms, targets, and clinical trial design. Early interaction with regulators and HTA agencies, especially on trial design and agreed endpoints, is essential. There are still neglected areas, such as mental health, where policy advocacy for incentives for early-stage intervention may also be necessary.

Conclusions

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- Drug development for modification of chronic disease is a **challenging but potentially rewarding area**
- Still **neglected** compared with the burden of chronic disease
- We can learn from **recent success stories** – where natural history understood and molecular mechanisms/ specific targets identified
- Clinical trial design, endpoints and comparators, clinically relevant effect size, safety and differentiation of disease modification from impact on symptoms **all require close attention**
- **Early engagement** with regulators and HTAs is important
- **Is policy advocacy needed** – especially on neglected areas - as few current incentives for drug development for chronic disease ?

CIRS

Accelerating clinical development for high impact chronic diseases – What needs to be considered?

Company perspective

Alexis Reisin Miller, Head, Global Regulatory Policy, Merck, USA

Platform approach

A platform approach could help to compress drug development timelines for common chronic diseases, allowing structural features, cell-based assays, and early development data to be leveraged from one product to another. Historically, regulators have leveraged prior knowledge to expedite reviews when appropriate, particularly in small populations. For prevalent chronic diseases, there is a need to shift the mindset to recognise that impact on a greater number of people is worthwhile in the benefit-risk calculation. This approach could drive innovation, efficiency, and knowledge management while having clear public health benefits.

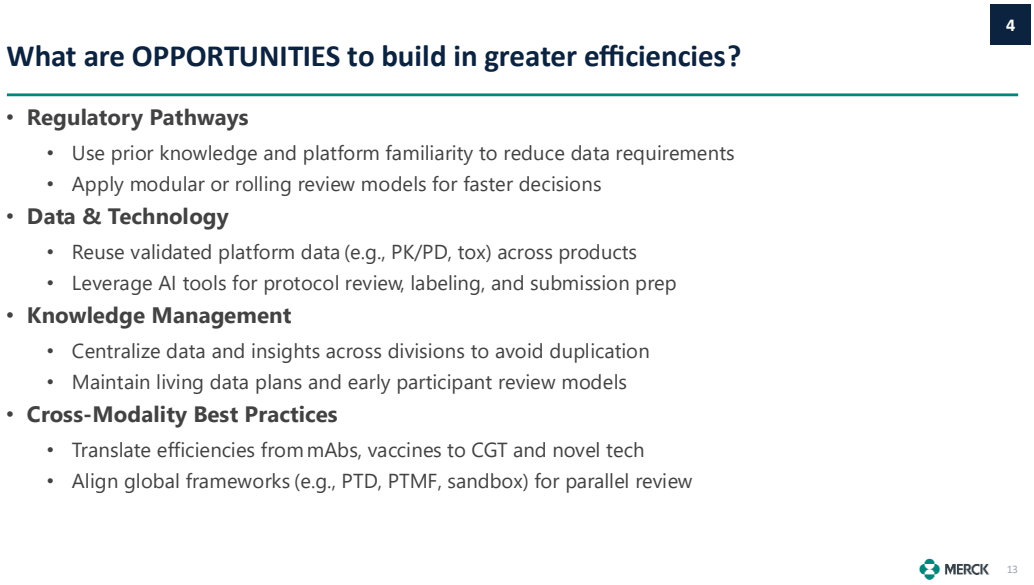
Various regulatory frameworks are emerging globally that incorporate platform approaches:

- Platform Technology Designation in the US
- Platform concepts in the updated EU General Pharmaceutical Legislation
- Health Canada's Regulatory Sandbox.

These frameworks aim to recognise established technologies and leverage information across multiple products without compromising quality or safety. The concept extends beyond manufacturing to include elements of product design.

Opportunities and challenges

Several opportunities exist to build greater efficiencies, including in regulatory pathways, data/technology, knowledge management and cross-discipline learning (see below).



Despite these opportunities, challenges remain:

- Regulatory complexity across different health authorities globally
- Data and technology limitations, including standardisation issues
- Lack of clear or consistent standards for data review across products
- Knowledge management gaps between different groups
- Legal frameworks and financial regulations that limit information sharing.

In addition, there are 'unknowns' to consider, such as whether a platform approach can support timeline compression across different modalities, the necessity for a formal platform designation, and implications for data protection and patent exclusivity.

Conclusion

The platform approach is a promising option for chronic disease therapy development as it allows developers and regulators to build upon existing knowledge rather than starting from scratch. While there are challenges and unknowns, the opportunities for improving efficiency in drug development are significant. This approach could help compress development timelines by leveraging structural features, cell-based assays, and early development data from one product to another, particularly for chronic disease therapies where large populations and protracted development timelines are expected.

Accelerating clinical development for high impact chronic diseases – What needs to be considered?

Regulatory agency perspective

Prof Ton de Boer, Chair, Medicines Evaluation Board (MEB), The Netherlands

Decentralised clinical trials – could they help stimulate drug development for high impact chronic diseases?

Decentralised clinical trials (DCTs) are an operational model where trial activities – such as recruitment, screening, drug administration, and monitoring – are designed to take place at or near participants' homes rather than at traditional clinical sites. This approach has gained traction, particularly during the COVID-19 pandemic when many trials continued with measurements taken at home.

Challenges with conventional trials

Conventional clinical trials face numerous challenges, such as limited generalisability due to strict inclusion/exclusion criteria, slow recruitment, low retention rates, and high costs. Factors affecting recruitment and retention (especially relevant for chronic diseases) include adverse reactions, additional visits, financial burden e.g. work interruptions, understanding of the trial, engagement during the study, and study location. These issues call for methodological and operational innovation, which DCTs can provide.

Potential benefits of DCTs

For participants, DCTs offer easier access to clinical trials, less burdensome participation, greater sense of ownership, and the potential for real-time feedback. For investigators, DCTs have several benefits including faster recruitment, better retention and engagement, real-time safety and monitoring, less manual data entry, and being more cost-effective. Other stakeholders also benefit from DCTs through faster access to trial outcomes, trial data being generated in real-world settings, increased diversity of trial populations, greater geographical reach and more agile and resilient trials.

Current landscape for DCTs

Currently, few full DCTs exist, and these mostly focus on already authorised medicinal products rather than developing new medicines. Analysis of EMA scientific advice shows that remote monitoring devices are frequently recommended for measurements like blood pressure, electrocardiogram and glucose monitoring. At-home blood sampling is also possible, as demonstrated by the development of Paxlovid, for instance.

An assessment of trial.gov data showed that only 1.6% of trials are fully at-home (fully decentralised), while 67% are hybrid approaches (combining conventional and at-home elements), and 31% are solely on-site. Most trials using digital health technologies are conducted by non-industry sponsors, rather than pharmaceutical and medical device sponsors.

Stakeholder perspectives

Several studies were carried out with different stakeholders across Europe to understand their perspectives of DCTs. Ethics committee representatives reviewing a mock DCT protocol were hesitant towards DCTs, tending to focus on the risks and burdens of DCT approaches, rather than prioritising potential benefits. Interviews with regulators and HTA representatives identified several opportunities for DCTs: data collection in daily practice, less

memory bias, greater generalisability and reduced burden for participants. However, challenges were also noted, including less controlled data collection, potential behaviour change when patients see their own outcomes, and potential selection bias towards 'technology-savvy' patients.

A review of recent literature suggests that patients appreciate not having to travel to research institutes and show greater willingness to participate in DCTs.

Representativeness study

A study compared the demographics and risk factors of diabetic participants from a conventional trial and a fully decentralised trial with a similar research question, to those of patients in daily practice. The DCT achieved better representativeness in terms of age, insulin use, smoking status, and body mass index, compared to the conventional trial. This supports the hypothesis that DCTs can improve the generalisability of trial results.

Ongoing research

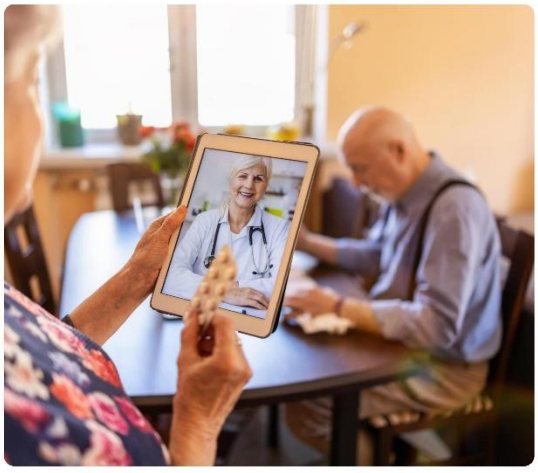
The Trials@Home consortium is currently conducting a study comparing conventional, hybrid, and fully decentralised approaches for a diabetes treatment (the RADIAL study). This study will provide insights into the acceptability of DCTs and explore their potential benefits in real-life settings across multiple countries.

Conclusion

DCTs offer a promising approach for conducting research, particularly for chronic diseases requiring long-term follow-up. While fully at-home trials may not be suitable for all situations, hybrid approaches combining conventional and at-home elements show significant potential. DCTs have demonstrated better representativeness of target populations and may help overcome many challenges associated with conventional trials. Further research will provide additional evidence to support the adoption of DCT approaches.

Take home messages

- The use of a single term, *decentralized clinical trial*, is proposed to describe those clinical trials conducted closer to participants' homes
- European regulators are open to decentralized clinical trial approaches, although they recognize (potential) challenges
- Decentralized clinical trial approaches are currently used to a limited extent and mostly to complement on-site clinical trial conduct
- Decentralized clinical trial approaches have the potential to increase the representativeness of the target population
- The uptake of decentralized clinical trial approaches in Europe should be facilitated through explorative research and circumventing overregulation



Acknowledgement: *Thanks to Dr Amos de Jong, Postdoctoral Researcher at University Medical Center Utrecht, The Netherlands, for his support in preparing this presentation, which draws on findings from his PhD thesis.*

Accelerating clinical development for high impact chronic diseases – What needs to be considered?

Health economics and outcomes research (HEOR) perspective

Dr Daniel Ollendorf, Chief Scientific Officer and Director of HTA Methods and Engagement, Institute for Clinical and Economic Review (ICER), USA

Surrogate endpoints and validation

Regulatory evidence typically comes from well-designed randomised controlled trials (RCTs) with standard measures, large populations, and reasonably long follow-up. However, patient-centric events of interest may be too far in the future to track in clinical trials, necessitating the use of surrogate endpoints.

For many chronic conditions, surrogate endpoints have been well-validated through natural history studies, epidemiologic studies, and clinical trials. Three key characteristics of a validated surrogate are:

- Plausibility of a link to meaningful clinical outcomes
- Precision of the surrogate measurement itself
- Correlation between the surrogate and the outcome of interest.

Low-density lipoprotein (LDL) cholesterol is a good example demonstrating how these characteristics are met. LDL levels have been linked to cardiovascular risk (plausibility), can be measured precisely, and show strong correlation with event rates in clinical trials.

PCSK9 inhibitors case study

PCSK9 inhibitors received initial regulatory approval based on LDL lowering, with the requirement for long-term cardiovascular event trials. ICER conducted reviews using the LDL data initially and then updated when cardiovascular event data became available.

The expected effects based on LDL reduction showed significant risk reductions. However, when clinical event data became available, the effect sizes were somewhat diminished for certain outcomes like myocardial infarction and angina. This presents a challenge for payers when expectations about a drug's effectiveness change as new evidence emerges.

An additional challenge in the US was the high initial price of these drugs—approximately $14,000 per year list price, with net prices around $10,000 after discounting. Compared to generic statins, this represented a significant budget impact. ICER's analysis suggested a 50% discount would be required for cost-effectiveness based on LDL data, with an even greater discount needed when cardiovascular event data became available.

Interestingly, over time, the price of these drugs has aligned with value considerations. The list price is now about $6,000 per year, with a net price around $3,400, which falls within the cost-effective range. This represents a rare case where evidence evolution has led to price adjustment.

Payer and HTA needs

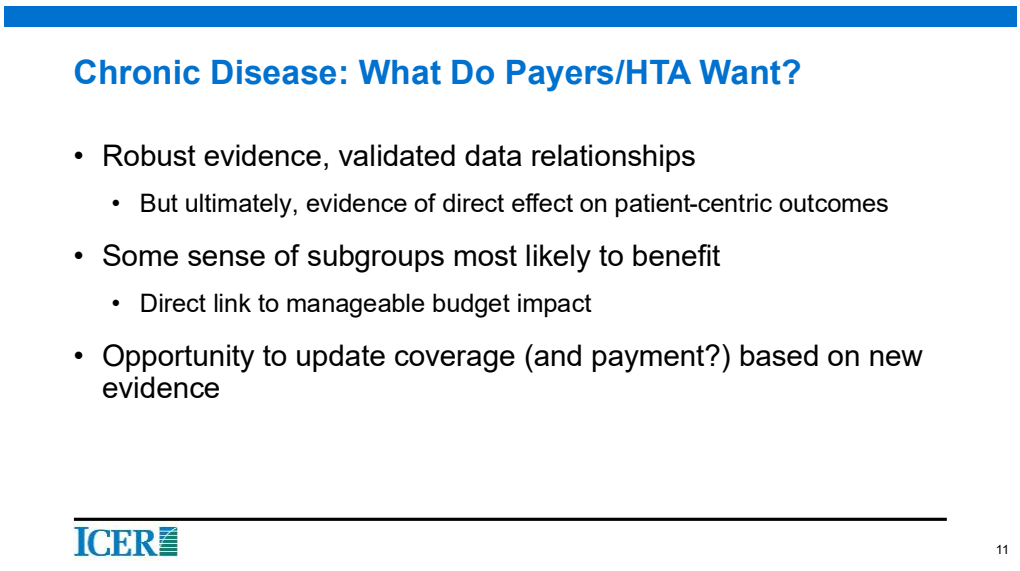
The payer and HTA community ultimately need evidence of direct effect on patient-centric outcomes. While surrogate endpoints are acceptable for initial approval, especially for underserved populations, direct outcomes data remains a key consideration.

Recommendations for developers

- Talk to patient groups and collect information on important outcomes affecting daily burden, even if exploratory.
- Identify subgroups most likely to benefit to prioritise treatment, especially with large budget impacts.
- Explore opportunities to update coverage decisions or payment levels based on new evidence.
- Consider outcomes-based agreements for chronic conditions with trackable outcomes in administrative datasets.

Conclusion

While surrogate endpoints can be valuable for initial approval of treatments for chronic diseases, the HTA and payer community ultimately seeks evidence of direct effects on patient-centric outcomes. The case of PCSK9 inhibitors demonstrates how evidence evolution can impact value assessment and pricing. Engaging with patients to understand what outcomes matter most to them and collecting data on these outcomes, even if exploratory, is crucial for developing treatments that address the true burden of chronic diseases. Outcomes-based agreements represent an underutilised approach for generating evidence and adjusting coverage and payment for chronic conditions affecting large populations.



Company case study: New approaches to COPD

Bisola Filchak, Vice President, Immunology and Inflammation, Global Regulatory Affairs, Sanofi, USA

Chronic obstructive pulmonary disease (COPD) affects an estimated 384 million people worldwide and is the third leading cause of mortality globally (excluding COVID-19). It is characterised by airway obstruction, chronic inflammation, comorbidities, such as cardiovascular issues, and breathing difficulties.

COPD treatment evolution

Twenty years ago, COPD treatment focused on bronchodilators, with a saturated portfolio of products targeting the same indication. Then there was an era of landmark studies using combination treatments (LABA/LAMA or ICS/LABA combinations), and later, triple therapies (ICS/LABA/LAMA). Phosphodiesterase (PDE) inhibitors were also investigated as add-on therapies. Most of these treatments were approved and integrated into clinical guidelines for COPD, with a stepwise approach moving from mono to dual to triple therapy as the disease advances.

Shift to biologics

After the failure of large mortality studies, investment in COPD programmes declined. There was a perception that with dual bronchodilators, the maximum improvement in FEV1 (measure of forced expiration) had been reached. However, the advent of biologics has brought a more targeted treatment approach.

Dupilumab, approved in September 2024, was the first novel approach in over 10 years. It targets a subset of the COPD population with an eosinophilic phenotype (increased levels of eosinophils, a type of white blood cell). The clinical studies showed significant reduction in rates of exacerbation on top of triple therapy, along with improvement in FEV1. Dupilumab received FDA Breakthrough Therapy Designation and was assessed under priority review.

Following dupilumab, mepolizumab was approved for a similar patient population with eosinophilic COPD. There are now many more biologics in development for COPD, including different targets such as anti-IL4, anti-IL33 and anti-TSLP.

Progress and remaining challenges

The greatest improvement in COPD treatment has been in reducing rates of exacerbation, with products like dupilumab showing up to 30% reduction on top of triple therapy. Quality of life measures are making it onto the label for some treatments, indicating better symptom control and daily functioning. While FEV1 improvement has been achieved, its clinical significance remains questionable, and it hasn't translated to a decline in the rate of lung function deterioration over years.

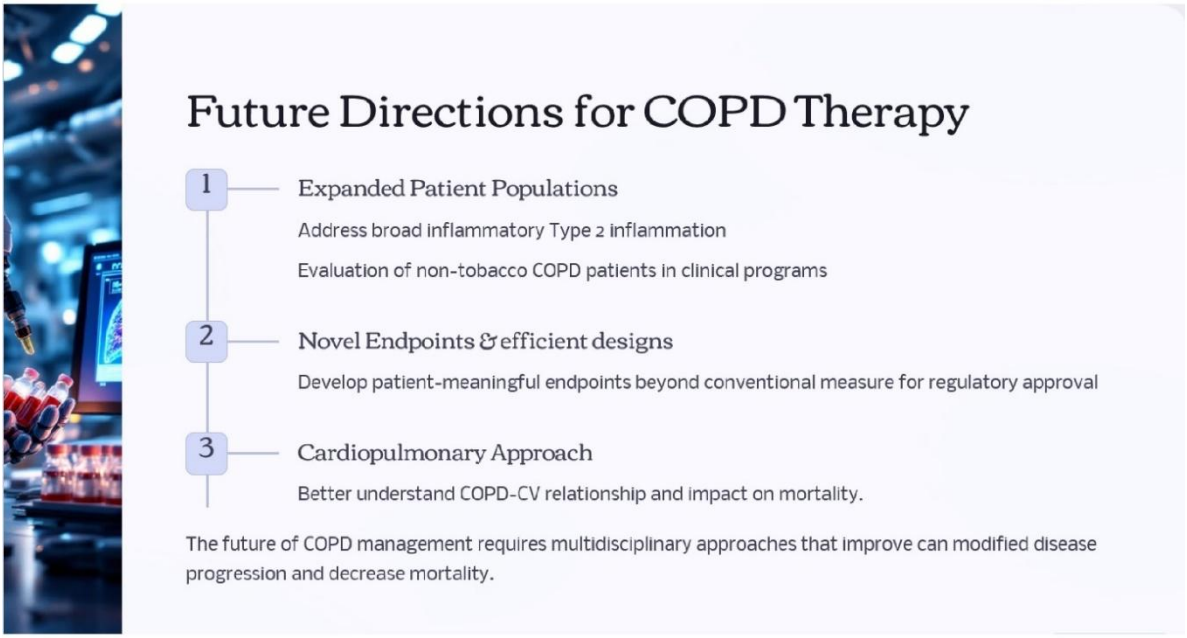
Despite all approved treatments, nothing has significantly impacted mortality. COPD remains a leading cause of death, yet mortality reduction is not even an area of focus in many development programmes, which centre primarily around exacerbation.

Patient preferences regarding route of administration and dosing frequency are important considerations. For biologics, the discussion has shifted from once vs. twice daily to every four vs. every eight weeks, aiming to enhance patient experience and adherence.

Unmet needs and future directions

There remains a huge unmet medical need in COPD. Early intervention is critical—rather than waiting until patients have significant decline in lung function and irreversible damage. This requires a shift in both developer and payer perspectives. Biomarker development is important but progress has been limited, with qualification of new endpoints being a lengthy process.

Focusing on modifying the disease by reversing or delaying lung function decline is key. Current biologics focus primarily on type 1 inflammation and don't address non-smokers, who represent a sizable portion of the COPD population. Better and novel endpoints are needed for more efficient development, particularly mortality endpoints to demonstrate survival benefits.



Conclusion

While progress has been made in COPD treatment, particularly with biologics showing promising results in reducing exacerbations, significant challenges remain. The focus needs to shift toward earlier intervention to prevent disease progression rather than treating advanced disease. This requires collaboration between industry, regulators, and payers to develop clear pathways for programme development and reimburse the right subset of patients earlier. Novel endpoints, biomarkers, and disease-modifying approaches are needed to truly impact the course of COPD and improve patient outcomes beyond symptom management.

Company case study: Anti-amyloid drugs for Alzheimer's

Simon Bennett, Director, Global Regulatory Policy, Biogen, UK

Alzheimer's disease has been well-characterised histologically by amyloid beta plaques and tau protein bundles that form neurofibrillary tangles. These have long been a hallmark of the disease, though their direct causative role has been debated within the amyloid hypothesis. Importantly, the pathology—the appearance of amyloid beta in the brain—precedes symptoms by decades.

Evolution of anti-amyloid treatments

Early generations of anti-amyloid beta agents showed no impact on clinical symptoms in large clinical studies. In retrospect, this may have been because they targeted different amyloid peptides (monomers, oligomers) rather than plaques themselves, and because the clinical trial populations included patients at later disease stages or even those without confirmed Alzheimer's disease.

Currently, three products have been approved by some regulators for treating Alzheimer's disease:

- Aducanumab: Received accelerated approval from the FDA in June 2021 as the first disease-modifying therapy for Alzheimer's disease.
- Lecanumab: Approved in the US in January 2023 via accelerated pathway, converted to full approval in July 2023; EU approval granted in April 2025.
- Donanemab: Approved in the US in July 2024 as a full approval.

Aducanumab case study

Aducanumab's phase 3 studies in the late 2010s examined patients over 18 months, with the Clinical Dementia Rating-Sum of Boxes (CDR-SB) as the primary endpoint. The clinical trial results were inconclusive—one study showed statistical significance on the clinical primary endpoint, while the second did not meet its primary endpoint. However, sub-studies examining biomarkers in positron emission tomography (PET) scans and cerebrospinal fluid (CSF) from over 1,000 patients showed that removal of amyloid beta plaques positively correlated with clinical outcomes. This biomarker data became crucial in the regulatory decision-making process.

The FDA granted accelerated approval of aducanumab based on data demonstrating a reduction in amyloid beta plaques, citing that this impact on biomarkers was reasonably likely to predict clinical benefit despite inconclusive clinical evidence. This decision was controversial, as the FDA's advisory committee did not support the approval.

The flexibility shown by the FDA wasn't matched by US payers. The Centers for Medicare and Medicaid Services (CMS) issued a national coverage decision requiring coverage with evidence development, meaning patients on aducanumab had to be part of a CMS-approved study to receive insurance coverage.

Biomarkers in neurological conditions

The EMA finalised a biomarker qualification opinion on the centiloid measurement of amyloid PET in 2024, supporting the enrichment of clinical trials using amyloid as a marker. This demonstrates ongoing work to validate biomarkers in Alzheimer's disease.

Amyotrophic lateral sclerosis (ALS) is another neurological condition (although a rare disease) where biomarkers are being used. A neurofilament biomarker associated with axonal degeneration can be detected in blood and CSF.

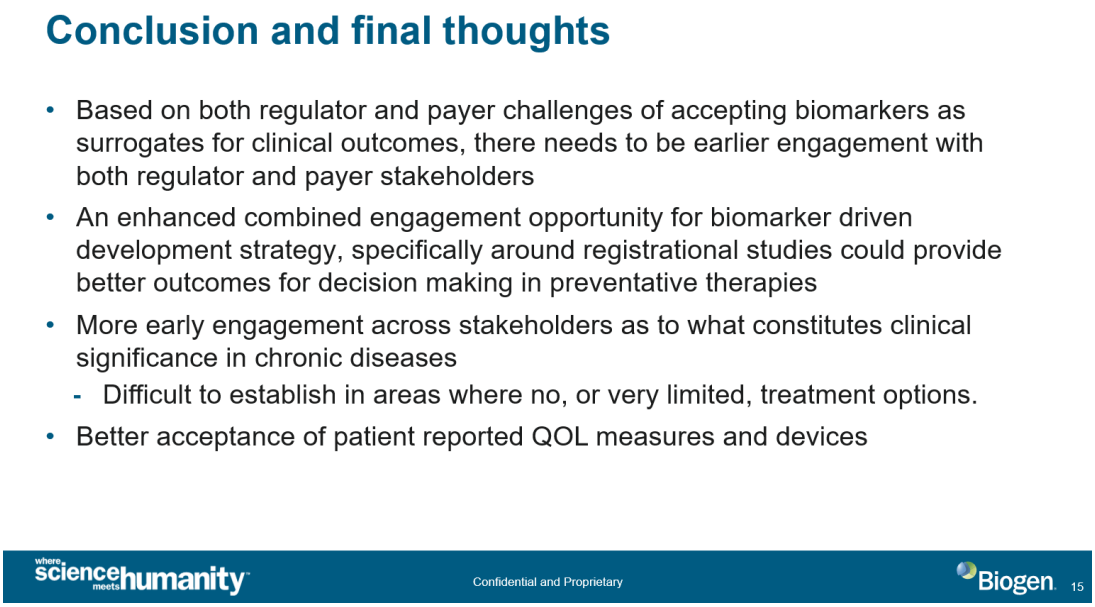
This biomarker is now being used to identify pre-symptomatic patients at risk for developing ALS, potentially allowing earlier treatment intervention.

Key considerations for biomarkers

For a biomarker to be considered a surrogate endpoint, strong data demonstrating a relationship between the biomarker and clinical outcome is essential. The FDA's decision to approve aducanumab under the accelerated pathway, using amyloid PET as a surrogate to reasonably likely predict clinical benefit, was controversial but may have helped advance the field more quickly. The subsequent approvals of lecanumab and donanemab have further substantiated the relationship between amyloid reduction and clinical benefit. An outstanding question is whether other Alzheimer's disease therapeutics not directly targeting amyloid, but targeting amyloid pathology, will benefit from the accelerated pathway.

Conclusion

Progress in Alzheimer's disease illustrates how biomarkers can be used to support early therapeutic intervention, yet there are still challenges with demonstrating the relationship between surrogate endpoints and clinical outcomes. For any biomarker to serve as a surrogate endpoint, strong data demonstrating its relationship to clinical outcomes remains critically important. This approach may help address the challenges of developing treatments for chronic diseases where clinical outcomes take years to manifest. Early engagement across stakeholders as to what constitutes clinical significance is key.



Session 3: Adapting regulatory and HTA process and practices for high impact chronic diseases – what needs to be considered?

Women's health and chronic disease – What changes are needed?

Findings from the National Academies Committee on a Framework for the Consideration of Chronic Debilitating Conditions in Women

Dr Melissa Laitner, Director of Strategic Initiatives, National Academy of Medicine, USA

With the aging of the US population and longer life expectancies of women compared to men, chronic conditions pose an increasingly significant burden on the health of women. Six chronic conditions defined by the Centers for Medicare & Medicaid Services (CMS) have higher prevalence in women: hypertension, arthritis, depression, dementia, asthma, and osteoporosis. In addition, 20% of women in adulthood have two or more chronic conditions.

Why sex and gender matter in chronic disease

Both biological sex and social gender constructs affect disease experiences. Biological factors include hormonal differences affecting vascular health and heart disease, immune system variations influencing autoimmune diseases, and differences in vaccine response and cancer treatment outcomes. Gender-related factors include exposure to stress and trauma, challenges accessing care, lower socioeconomic status increasing chronic disease risk, and women's symptoms being more likely dismissed in clinical settings, leading to delayed diagnoses. Understanding sex and gender is essential to improve diagnosis, treatment, and outcomes for women, including those with one or more chronic conditions.

Framework for chronic conditions in women

In 2023, the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) published a framework for categorising chronic debilitating conditions in women:

- Female-specific diseases (e.g., reproductive tract cancers, fibroids, endometriosis) where research remains limited
- Diseases more common or with greater morbidity in women (e.g., depression, migraines, autoimmune conditions) that receive disproportionately low funding
- Potentially understudied conditions (e.g., Alzheimer's, osteoarthritis) that affect women differently but aren't studied through sex/gender lenses
- Diseases of higher morbidity (e.g., heart disease, lower back pain) that go unrecognised as significant women's health issues.

Recommendations for advancing research on chronic conditions in women

In response to a request from NIH ORWH, the National Academies of Sciences, Engineering, and Medicine convened an ad hoc interdisciplinary committee to review the literature on chronic debilitating conditions specific to women. A report was published in 2024 that describes current knowledge, identifies gaps in evidence, and recommends a research agenda for the future.

Three key recommendations were made to NIH and other research funders:

- **Better data** collection, surveillance, and biological models reflecting women's bodies. This includes research on hormonal fluctuations, improving symptom management across reproductive stages, clarifying roles of hormones and sex chromosomes in disease and developing improved animal models reflecting female biology.
- **Improving care pathways** by addressing challenges in diagnosis, treatment, and management of multiple chronic conditions in women.
- **Understanding lived experiences**, including how trauma, identity, and inequities shape women's health experiences.

Conclusion

Women bear a greater burden of chronic conditions, often face delayed diagnosis, and frequently lack access to appropriate treatments. Research gaps remain in understanding female-specific conditions, symptom variability, and the impact of reproductive milestones. The National Academies Committee on a Framework for the Consideration of Chronic Debilitating Conditions in Women recommends a reimagined research agenda focusing on biology that includes lived experience, considers gender and sexual equity, acknowledges multiple comorbidities and social determinants, and views women's health through an equity lens across the life course.

Summary: Advancing Research on Chronic Conditions in Women

- Women bear a greater burden of chronic conditions, often facing delayed diagnosis, limited treatment options, and lower quality of life.
- Sex and gender intersect with social factors like trauma and structural inequities, influencing disease risk and care outcomes.
- Significant research gaps remain in understanding female-specific conditions, symptom variability, and the impact of reproductive milestones.
- Data systems are lacking, with poor representation of women and limited disaggregation by race, gender identity, and other factors.
- The committee calls for a research agenda focused on biology, lived experience, diagnostic equity, multiple conditions, and social determinants—viewed across the life course and through an equity lens.

Does the regulatory model for development and review of medicines for high impact chronic diseases need reframing?

Company perspective

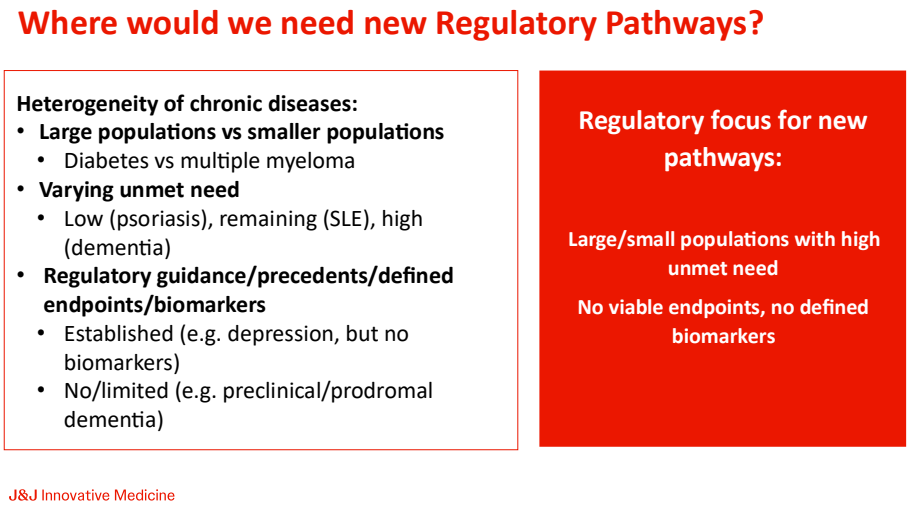
Ginny Beakes-Read, Head, Global Regulatory Policy and Intelligence, Johnson & Johnson Innovative Medicine, USA

Challenges in benefit-risk assessment

Demonstrating a positive benefit/risk balance for chronic disease therapies can be challenging as disease typically progresses slowly and there are often different therapies already available. For large populations these factors lead to the requirement for increased data packages with higher expectation for benefit, lower risk tolerance, and a desire for minimal uncertainty.

Improving the regulatory process

New regulatory pathways may be most needed for chronic diseases with high unmet medical need where appropriate endpoints are lacking (see below). Developers and regulators tend to be comfortable with known endpoints, especially those with established guidance, but this creates gaps for conditions without such established measures. More iterative and timely dialogue across stakeholders is key.



Conclusion

Risk-based, flexible approaches are needed to demonstrate benefit risk in chronic diseases with high unmet need:

- Expedited process/breakthrough designation for qualification of new endpoints, biomarkers, patient selection tools (liquid, digital, tissue).
- Acceptance of new study methodologies, e.g. using real-world data, external controls/digital twins and prediction models.
- New/adapted/phased early licensing tools with rigorous post-marketing surveillance using integrated/interoperable data and a mechanism for regulators to take actions.
- Stronger integration of regulatory deliverables in public-private partnerships for new endpoint or tool validation.

Does the regulatory model for development and review of medicines for high impact chronic diseases need reframing?

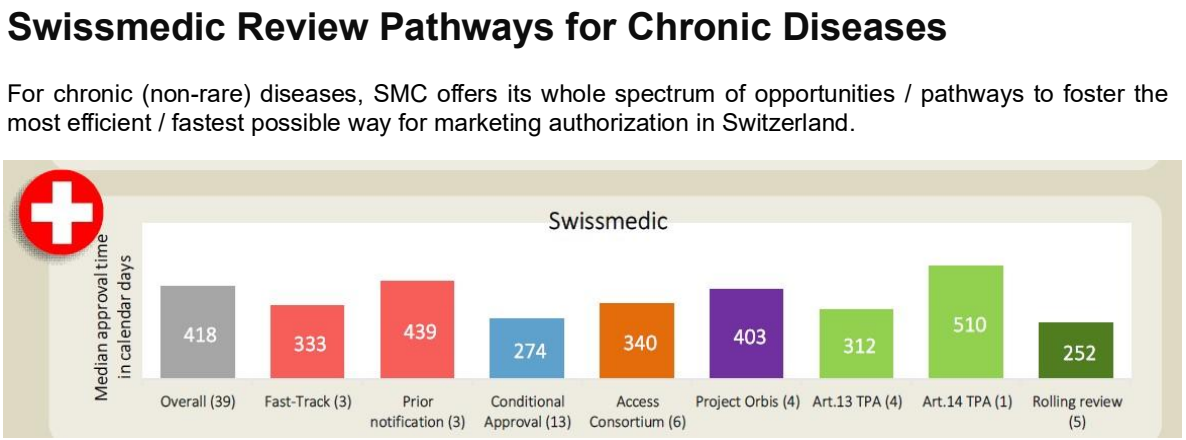
Regulatory agency perspective

Dr Eveline Trachsel, Head of Medicinal Products Authorisation and Vigilance, and Member of the Management Board, Swissmedic, Switzerland

Rather than identifying new regulatory models for chronic disease treatments, it may be possible to adjust existing models to make them more effective. It is also important to consider how interventions like lifestyle changes and surgery fit alongside medical products in chronic disease management.

Facilitated regulatory pathways

Swissmedic offers various facilitated regulatory pathways that can be used for medicines for chronic diseases (see below). The only facilitated pathway not available for most chronic diseases is Project Orbis, which is specific to oncology. The Access Consortium has been particularly valuable for reviewing compounds for chronic diseases in recent months and years.



Facilitated Review Pathways at Swissmedic (data from 2022, CIRS R&D Briefing 88).

Areas for improvement

While Swissmedic has implemented several new measures following the COVID-19 pandemic, such as virtual and more flexible meeting formats, there are still areas needing improvement:

- Some new endpoints are not yet represented in guidance documents e.g. delay of onset of disease doesn't qualify for fast-track procedures under current criteria.
- Real-world evidence needs greater acceptance as part of data packages.
- Patient involvement should be enhanced at certain stages of the regulatory process.
- Joint assessments, especially within the Access Consortium, should be strengthened.

Off-label challenges

Off-label use of medications is an important issue for chronic diseases with large patient populations. For example, midazolam is widely used off-label in palliative care home settings in Switzerland, but it is difficult to get it reimbursed without formal regulatory approval. This raises the question of whether regulators should/can identify ways to formally include routine off-label uses into product labels.

Conclusion

Addressing chronic disease regulatory challenges requires involvement from various stakeholders—pharmaceutical companies, academic researchers, patient groups, HTA agencies, and regulators. CIRS provides an ideal forum for addressing these complex issues collaboratively. While existing regulatory tools can be leveraged for chronic disease products, there are areas where regulatory frameworks need to evolve to better accommodate new endpoints, real-world evidence, patient involvement, and off-label use considerations.

Does the regulatory model for development and review of medicines for high impact chronic diseases need reframing? Policy perspective

Scientific and systemic integration of patient experience data and patient-reported outcomes for precision prevention

Dr June Cha, Director, Policy, FasterCures, Milken Institute, USA

The Milken Institute is a non-profit, non-partisan think tank focusing on accelerating measurable progress on the path to a meaningful life. FasterCures has been fulfilling its mission for over 20 years focusing on accelerating biomedical innovation and access, advocating for scientific and systemic patient engagement as a core of biomedical innovation.

The importance of prevention

Early detection is essential to preventing chronic disease but presents several challenges:

- Biomarkers and endpoints: Measuring subtle changes in pre-disease or early disease stages, linking them to long-term outcomes is difficult.
- Validated clinical outcomes: Disease progression during pre-disease or early disease states is not clearly defined or validated.
- Screening and clinical research: A systematic approach early in development is required.

When implementing the delivery of preventive services, it is important to consider the healthcare ecosystem as a whole. In the US, preventive services are accessed through primary care providers and informed by guidelines from the US Preventive Services Task Force, professional medical organisations and insurance coverage decisions. However, preventive services are often difficult to access; less than half of the US population receives recommended preventive services, with even lower rates among those with lower socioeconomic status and presents significant racial, ethnic, and geographic disparities.

Improving access to preventive services requires a collaborative, community focused approach, particularly through outreach by community-embedded non-physician providers. Real-world data that can inform post-marketing studies, determining the value of medical products and healthcare, and standards of care and practices must be collected from the settings where people receive care to ensure preventive interventions have meaningful impact.

The Milken Institute's Project Prevent brings together experts across health, government, finance and technology sectors to promote prevention-first policies, share best practices, and spotlight success stories. The aim is to create a scalable and sustainable blueprint for a prevention-first health system.

Integrating patient input across the innovation spectrum

Patient engagement should occur across the entire spectrum of biomedical innovation, from discovery and R&D through regulatory and reimbursement phases. Early patient engagement creates better innovation and improves patient uptake. Patient experience data (PED) and patient-reported outcomes (PROs) provide valuable context, especially when clinical outcomes are still being developed e.g. for early disease states.

Studies consistently find that the efforts of integrating PED and PROs is heterogeneous in R&D, particularly in cancer and neurodegenerative diseases. Transparency and communication on how PED and PROs inform regulatory decision making need to be improved. In addition, there are opportunities to integrate PED and PROs more quantitatively and qualitatively into benefit-risk frameworks.

Conclusion

In addition to R&D and regulatory cycles, patients and caregivers must be engaged in the access to medical products and healthcare. Community-based research infrastructure and scientific and systemic patient engagement across the life cycle of medical products will support the shift towards prevention-first healthcare, and accelerate biomedical innovation and access of transformative medicines, taming the burden of high-impact chronic disease.

Do HTA/payers need to be 'system shaping' by investing in innovations for health?

Company perspective

Paul Villa, Disease Area Head, Respiratory Global Pricing and Market Access, GSK, USA

Common terminology

A key challenge in the chronic disease area is that stakeholders use different terminology when discussing the same issues or similar concepts, making meaningful dialogue difficult. Establishing a common terminology is essential for productive conversations about chronic disease management.

Innovation in disease management

Diabetes care is a good example of a complex chronic disease that has gone through multiple eras of advancement over time, from basic treatments to progressive technologies such as continuous glucose monitors, closed hybrid loop systems connected to smartphones, insulin pumps, and even AI-powered 'bionic pancreas' systems. These innovations aim to make disease management less complex, more holistic, and reduce the care burden on patients. However, there is a potential risk that some technological solutions might inadvertently reduce patient accountability and responsibility for their own health behaviours, which remain a crucial component in managing chronic diseases.

Adherence issues and long-acting therapies

Medication adherence is a significant challenge in treating chronic diseases. A recent report has shown that for chronic disease medications, only 29% of patients maintain one-year persistence with their treatment. This means that despite significant investments in drug development and approval processes, many treatments are not being used effectively.

Technologies to address adherence issues in chronic diseases can take a variety of forms, including digital options, tracking technologies, and long-acting formulations. Gene therapies may even fall into this category, although their role in chronic diseases would be limited by the likelihood of significant budget impact concerns. The full value of such long-lasting technologies is not fully captured in current HTA and payer value frameworks; these should be expanded to incorporate broader value dimensions, fostering a comprehensive evaluation of the full value of long-acting therapies.

Conclusion

Addressing chronic diseases requires collaborative effort across stakeholders to develop a common nomenclature, reconsider evaluation frameworks, and explore innovative pricing and reimbursement models. Current value frameworks may not capture all relevant variables; therefore, stakeholders need to come together to develop approaches that balance innovation, risk, and value. The goal should be to improve patients' lives through mechanisms that recognise the complexity of chronic disease management while providing appropriate incentives for continued innovation.

Current value frameworks risk under recognizing broader value if focused on short term economics and/or not designed to look holistically

Do HTA and Payers need to be "system shaping" by investing in innovations for health?	Yes
What is the challenge of large patient populations for HTA/payers?	Right product, Right patient Right time
Should HTA/payer perspectives be to enable the focus to be on long term health, economic and societal return on investing in health vs short term budgetary costs?	Yes
Are there new approaches to HTA and payment that utilize RWE and reward development of therapeutics that prevent or slow disease progression, while addressing the major economy-wide costs of the burden of these major diseases?	Yes
Is there a need to articulate value for Chronic disease products as well as how to enable innovative pricing model?	Yes

Do HTA/payers need to be 'system shaping' by investing in innovations for health?

HTA perspective

Sahar van Waalwijk van Doorn-Khosrovani, Member of the National Funder's Committee for Evaluation of Specialised Medicines and Companion Diagnostics, CZ, The Netherlands

Addressing social determinants of health

Diseases with the highest disability-adjusted life years in the Netherlands include mental and neurological problems, chronic obstructive pulmonary disease, renal failure, arthritis, diabetes, and cardiovascular diseases. These conditions are linked to long-term productivity loss, early retirement, disability benefits, caregiver burden, and significant economic impact.

Addressing social determinants of health is a critical aspect of prevention. Factors such as housing, education, health literacy, working conditions, and financial stability significantly influence health outcomes. Financial problems, in particular, can be major risk factors for chronic diseases through mechanisms like chronic stress, mental health issues, postponed medical care, and unhealthy lifestyle choices.

Investing in prevention

The Netherlands has implemented several preventive measures for chronic diseases, including lifestyle interventions, weight loss programmes, and smoking cessation programmes. Investing in early detection is essential, but while population-based screening programmes exist for cancer, chronic diseases lack similar screening initiatives. This means detection often depends on patients visiting their primary care provider, potentially missing those with low health literacy or disadvantaged backgrounds.

Regulatory and HTA misalignment

Investing in innovative treatments for chronic diseases is complicated by a lack of alignment between regulatory and HTA approaches. Regulators focus on safety, quality, and efficacy, often approving products based on surrogate endpoints and early evidence. In contrast, HTA bodies require long-term data to ensure treatments work in real-world populations and provide value for money.

While most HTA bodies now look beyond traditional clinical effectiveness and cost-effectiveness to consider quality of life and patient-reported outcomes, these measures are not standardised, making comparison across trials difficult. Additionally, data on social and economic consequences like productivity, social care costs, and caregiver burden are usually not available at registration.

Innovative payment models

The current payment/reimbursement system rewards long-term maintenance treatment over one-time cures, creating misaligned incentives. For pharmaceutical companies, maintenance therapies offer faster development, lower risk, and steady revenue. For healthcare providers, they ensure steady patient visits. For payers, while one-time cures might theoretically be preferable, high upfront costs and the possibility of patients switching insurers create challenges.

The Netherlands has established a pilot scheme for orphan indications called Orphan Drug Access Protocol (ODAP), which uses milestone-based reimbursement. Drugs are assessed at different time points, with negotiated prices varying at each stage based on demonstrated efficacy. This approach could potentially be adapted for more common chronic diseases by focusing on specific patient groups based on disease biology or targeting high-risk patients who cannot be treated with current generics.

Academic involvement

While about half of clinical trials in Europe are independent academic trials, academia plays a limited role in developing new therapies that reach registration. Barriers include lack of funding for the complete development pathway, absence of a structured regulatory pathway for academic drug development, and unclear reimbursement pathways for off-label indications.

Conclusion

Addressing chronic diseases requires investment in prevention, including promotion of healthy lifestyles, screening and early intervention, and addressing social determinants of health, such as housing, education, working conditions, and financial stability. Reform of incentives is needed to facilitate funding for one-time curative therapies and focus on long-term patient outcomes.

Summary

Invest in prevention: promote healthy lifestyles, screening and early intervention

Address social determinants: improve housing, education, working conditions and financial stability

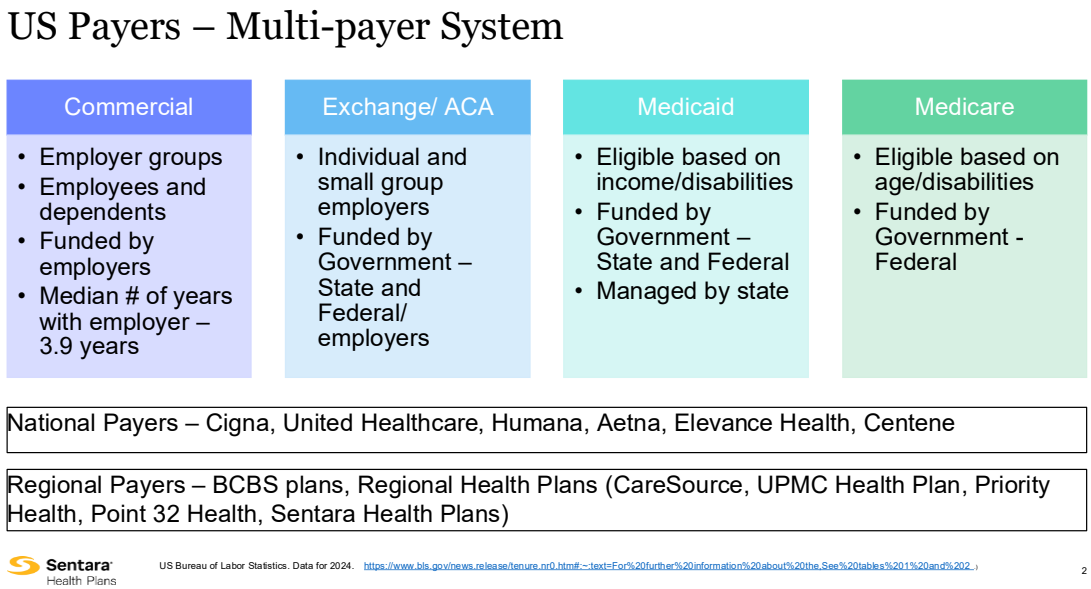
Reform incentives: focus on long-term outcomes for patients and reduce the burden on caregivers and society

Do HTA/payers need to be 'system shaping' by investing in innovations for health?

Payer perspective

Jessica Daw, Vice President, Pharmacy, Sentara Health Plans, USA

The US healthcare system is made up of multiple payers, including commercial employer groups, exchange plans, Medicaid, and Medicare, all with different funding sources (see below). This creates a complex landscape where patients frequently move between different coverage types, for instance, when they change employers or move into different eligibility categories.



Data and affordability challenges

There are several challenges relating to availability of data and evidence that US payers face when making coverage decisions for chronic disease treatments. While long-term data is preferred, this is usually unavailable at the time of drug approval. For example, pivotal trials for depression medications typically last only 12 weeks, which provides insufficient information for making formulary placement decisions for a condition that requires long-term management.

There are also concerns among payers about surrogate endpoints, particularly when some studies fail to clearly demonstrate how these endpoints correlate with long-term outcomes.

Real-world data and evidence (RWD/E) can provide valuable insight on treatment effectiveness, prescribing practices, and patient usage, adherence and quality of life. However, US payer interest in RWD/E varies significantly, with some smaller health plans showing little interest.

To help manage drug costs, some US payers are even considering implementing benefit exclusions for all accelerated approval drugs. This could be a 'slippery slope' given that many important treatments, particularly in oncology, come through the accelerated pathway.

Payer vs societal benefits

Patient movement between payers creates challenges for evaluating long-term outcomes, as the payer investing in a treatment may not be the one that benefits from improved outcomes years later. This disconnect between who pays for treatment and who benefits from outcomes makes it difficult to capture the societal impact of treatments within the US payer system. When conducting health technology assessments, it's important to consider how and when societal impacts should be incorporated into analyses.

Defining unmet need

Unmet needs vary across conditions, for example, for dementia, the focus might be on keeping patients at home and reducing caregiver burden, while for mental health, it may be addressing stigma and access issues. Collaboration between regulators, payers, and patients is essential to define unmet needs in different disease categories.

Potential solutions

Potential approaches to address payer-related challenges include:

- Innovative payment/contracting models, such as subscription models and outcome/value-based contracts.
- Engaging with regulators and patients earlier in the process to promote the study of most relevant outcomes.
- Focus on clinical outcomes instead of surrogate endpoints.

Conclusion

While there is no single solution to the challenges of managing chronic diseases in the US payer system, engaging stakeholders to understand outcomes and unmet needs is essential. There is a need to move beyond short-term studies and surrogate endpoints to more meaningful clinical endpoints. The complexity of the US system creates additional challenges for implementing innovative contracting approaches, but these difficulties should not prevent stakeholders from working toward better solutions for chronic disease management.

Session 4: Breakout discussions

Workshop participants were assigned to a breakout group and provided with a background document developed by CIRS, containing information and questions for discussion. The Chairs and Rapporteurs of each breakout were asked to facilitate and document the discussion, respectively. The Rapporteurs then fed back to all workshop participants in the main plenary session.

Breakout A: Clinical trials – How should the thinking be reframed for undertaking clinical trials for high impact chronic diseases?

Chair: Kelly Robinson, Director General, Pharmaceutical Drugs Directorate, Health Canada

Rapporteur: Dr Odd Erik Johansen, Principal Medical Director, Roche, Switzerland

Reframing the approach

The breakout group agreed that current clinical trial models are not well-suited to the complexities of chronic diseases. These conditions often have slow, variable progression and lack validated biomarkers, making it difficult to measure the impact of treatments. There was a strong call to better understand the **natural history of disease**, particularly for early disease stages and understudied conditions, using **AI and digital technologies** to analyse large datasets and uncover patterns that can inform trial design. Incorporating the **patient perspective** throughout drug development was seen as essential to ensure trials measure outcomes that matter to patients.

Adaptive approach

An adaptive approach was proposed, establishing surrogate marker efficacy initially and then expanding to more cost-effective larger trials using pragmatic or decentralised trial (DCT) designs. This data could then be used for label extension, which was identified as a key strategy. Dialogue with regulatory agencies and HTA/payers is key to evaluating the applicability of such an approach.

Changing mindsets

Several approaches to changing the mindset around chronic disease research were discussed:

- Early touch points for sponsors, regulators, HTA/payers and patient groups to come together, though this may be challenging in practice.
- Understanding patient experience using novel and established methods to assess acceptability and tolerability.
- Utilising wearables, AI, and other technology enablers.
- Implementing adaptive approval and reimbursement models that allow early entry for initial indications, provided there is a clinically relevant effect size, while label extension/variations are being addressed in subsequent studies that involve DCTs or pragmatic trial designs.
- Exploring ‘clinical research as a care option’, where trials procedures can be regarded as usual care and reimbursable through health care provision. This could be facilitated by delivery networks or public-private set-ups.

Enabling early and collaborative engagement

A recurring theme was the need for **early, multi-stakeholder dialogue** involving sponsors, regulators, HTA bodies, payers, and patients. This would help align expectations around evidence requirements and reduce uncertainty. Participants stressed the importance of:

- Joint scientific advice to support trial planning.
- Collaboration to explore adaptive approval and reimbursement pathways.
- Harmonisation of endpoints across regions to support global trials.

Incentivising innovation

To mitigate uncertainties and encourage investment, the group proposed:

- **Conditional approval mechanisms** linked to HTA acceptance.
- **Dynamic pricing models** and **patent extensions** for sponsors developing impactful chronic disease treatments.
- Broader use of **real-world data (RWD)** commonly used in clinical practice, even if not guideline-standard.
- Improved **biomarker development**, especially for early-stage disease and neglected conditions.

Recommendations for further work and research

- Increase collaboration across stakeholders, including patients, regulators, payers, HTA agencies, sponsors, and clinicians, through early dialogue e.g. scientific advice, and pilots to move initiatives forward.
- Improve clinical trial efficiencies by:
    - Focusing on understanding the early trajectory of the disease and the patient's perspective, making use of technological enablers e.g. AI, wearables.
    - Identifying appropriate surrogate biomarkers and establishing their efficacy.
    - Embracing pragmatic and DCT designs.
    - Harmonising endpoints globally.
- Explore 'clinical research as a care option', where trials procedures can be regarded as usual care and reimbursable through health care provision.
- Explore adaptive approval and reimbursement models to allow early entry for initial indications, provided there is a clinically relevant effect size, while label extension/variations are being addressed in subsequent studies that involve DCT/pragmatic trial elements.
- Promote use of RWD, exploring regulators' requirements and acceptance of evidence from electronic health records.

Breakout B: How should regulatory and HTA frameworks evolve to incentivise and enable development of high impact chronic diseases?

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

Rapporteur: Michael Cunha, Senior Director, Regulatory Policy & Science, Bayer, USA

Recognising the limitations of current frameworks

The breakout group identified several systemic limitations within current regulatory and HTA frameworks:

- Insufficient incentives for companies to invest in chronic disease R&D.
- Rigid regulatory pathways requiring large, costly trials.
- Limited collaboration between regulators, HTA bodies, and industry.
- Lack of multi-stakeholder alignment and predictability, particularly in relation to the definition of unmet medical need and HTA/payer evidence expectations.

These limitations contribute to underinvestment and slow progress in chronic disease innovation, despite the significant public health burden.

Recommendations to enable innovation

To address these challenges, the group proposed a series of practical and policy-level changes:

- **Financial incentives** - Implement tax credits, grants, vouchers, subsidies and/or patent extensions to incentivise R&D in neglected chronic disease areas.
- **Adaptive regulatory pathways** – Introduce accelerated approval mechanisms that incorporate real-world evidence (RWE) and patient-reported outcomes (PROs) to reduce trial burden and improve efficiency.
- **Flexible trial design** – Encourage innovative trial designs, such as adaptive or pragmatic trials, to improve efficiency and cost-effectiveness.
- **Multi-stakeholder collaboration:** Promote company-regulator-HTA collaboration through early scientific advice and data sharing initiatives.
- **HTA/payer predictability -** Establish clear and consistent guidelines for the types of evidence needed to help streamline reimbursement and improve patient access.
- **Priority setting -** Establish national health targets to provide clear signals of priorities and unmet needs, helping to inform investment decisions.
- **Dynamic pricing -** Investigate dynamic pricing to incentivise development for chronic diseases.
- **Medical guidelines -** Update medical guidelines for chronic diseases more frequently to avoid delays in the adoption of new treatment approaches.

Breakout C: How to address the regulatory, HTA and payer challenges for therapeutics that slow or prevent disease?

Chair: Prof Hans-Georg Eichler, Consulting Physician, Association of Austrian Social Insurances

Rapporteur: Alix Arnaud, Global Market Access Strategy and Operations Lead, Sanofi, USA

Unique challenges

Breakout C focused on the unique challenges faced by therapeutics that aim to delay or prevent disease progression, rather than simply treat symptoms. Participants highlighted several systemic barriers across development, regulatory review, HTA, and reimbursement:

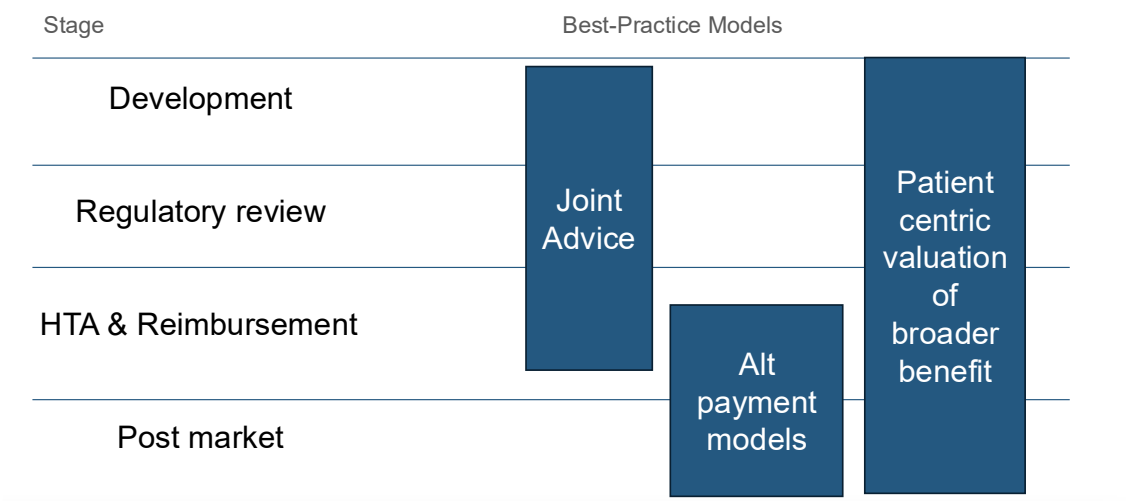
- **Uncertain clinical endpoints** and lack of validated surrogate markers.
- **High development costs** and extended timelines.
- **Regulatory and reimbursement uncertainty**, especially around accelerated approvals.
- **Limited payer recognition** of early-stage or conditionally approved therapies.
- **Insufficient valuation of societal benefit**, including productivity and caregiver impact.
- **Lack of joint scientific advice frameworks** in some regions (e.g. US).
- **Health system readiness** and infrastructure gaps for delivering preventive therapies.
- **Inconsistent definition of unmet medical needs** across stakeholders.

Adapting existing frameworks

The group also explored best-practice models and frameworks that could be adapted for disease-modifying drugs (see figure below). **Joint/parallel regulatory-HTA advice** was identified as an area for improvement, with the consensus that more offerings and uptake of joint advice could help resolve uncertainty around clinical endpoints early on.

Alternative HTA/payment models were extensively discussed as a solution to affordability challenges for disease-modifying drugs. These could be models where reimbursement is based on surrogate endpoints, with a commitment to review additional real-world evidence (RWE) after an agreed period. If pre-agreed clinical endpoints and thresholds are met, access would continue; if not, there would be a re-evaluation. For example, the Early Access Scheme in France conducts periodic reassessment of early-stage approvals based on evolving RWE. There was also a suggestion that regulatory agencies could act as an "honest broker" in the conditional reimbursement process by setting out clinical outcomes to be achieved.

Throughout the discussion, the importance of **patient-centric valuation** was emphasised. There was a sense that there is insufficient valuation of broader benefits in chronic diseases, particularly when delaying onset or progression. Sometimes clinical endpoints may not be patient-relevant, highlighting the need for more patient-centric valuation of broader benefits.



Recommendations for expansion of existing frameworks and further work/research

Development

- Use platform review and early consultation.
- Place a higher valuation of societal impact, PROs and healthcare resource utilisation in trial design.
- Increase emphasis on disease sub-populations and improve understanding of underlying pathophysiology.
- Consider running a natural history cohort/external control arm in addition to RCTs to help address potential evidence gaps.

Regulatory review

- Leverage existing RWE frameworks e.g. Data Analysis and Real World Interrogation Network (DARWIN EU), FDA RWE programmes.
- Elicit patient-centric value of delaying disease onset/progression.
- Include clinical outcome assessments/PROs in the label.
- Consider the appropriateness of surrogate endpoints and the possibility of offering longer market exclusivity if product approval is delayed to accommodate longer-term data collection.
- Adapt existing frameworks to prioritise high impact chronic diseases.

HTA/reimbursement

- Review the appropriateness of current HTA methodologies for evaluating treatments delaying disease onset or progression.
- Consider using alternative reimbursement models e.g. subscription model, Per Member Per Month, Pay for Performance, including the potential for re-evaluation of access decisions based on longer-term data or RWE.

Recommendations for CIRS from across the breakout groups:

- **Unmet medical needs -** Facilitate a multi-stakeholder study to investigate what constitutes unmet medical needs from the perspectives of patients and caregivers, not just from a clinical or economic standpoint.
- **Effectiveness of incentives -** Conduct a landscape analysis on the effectiveness of tax credits, funding models, and market exclusivity in stimulating R&D investment in chronic disease innovation. Comparisons could be made to incentives used in rare diseases and oncology.
- **Alternative payment models** - Review existing research on alternative payment models including managed entry agreements and survey CIRS members to assess whether these models work and how they could be improved.
- **Joint scientific advice** - Analyse the current global landscape for joint scientific advice, including learnings, recommendations and potential for expansion into the US.
- **Patient-centric decisions** - Convene multiple stakeholders to develop policy solutions for the lack of progress in the consideration of patient-centred outcomes, PROs and societal benefits in regulatory, HTA and payer decision making.

Session 5: Panel discussion - Policy actions/considerations for high public health impact medicines for chronic diseases

Company perspective

Andrew Emmett, Vice President, Global Regulatory Policy and Intelligence, Pfizer, USA

Despite being a significant societal burden, chronic diseases may not have the same level of unmet medical need as for oncology, rare diseases or infectious diseases, as chronic diseases are often 'lived conditions' for many people. This can lead to a degree of medical complacency that influences benefit-risk decisions across the lifecycle of development, from investment decisions to regulatory and payer considerations.

Research challenges

Chronic conditions present several research challenges, including:

- They are prevalent conditions requiring large, complex studies.
- Disease progression is lengthy and cumulative, requiring early diseases interception and longer studies.
- There is a need for more basic and translational research to give greater clarity on natural histories and validate more biomarkers and endpoints.
- Traditional research approaches create significant burdens on patients, leading to low trial participation.

Policy solutions

There are several policy solutions for could potentially help to address these challenges, including:

- Early and sustained mutual engagement to get patient input on meaningful study endpoints and surrogates.
- Regulatory capacity and coordination, leveraging the successful pandemic experience of early, frequent, and intensive engagement between sponsors and regulators.
- Digital health technologies to assess endpoints and understand patient function throughout their disease journey.
- Real-world evidence (RWE) and point-of-care trials to follow patients long-term and expand indications.
- Prescription drug use-related software to provide companion apps to help patients manage their conditions.
- Global convergence through greater use of reliance and work sharing, facilitated by cloud-based submissions platforms and globally harmonised development strategies.

Conclusion

Addressing the challenges of chronic disease drug development requires creative public policy approaches that consider the unique nature of these conditions. Early and sustained engagement with patients, enhanced regulatory coordination, digital technologies, RWE, and global convergence are key elements of potential solutions. The goal should be to create a more efficient and effective pathway for developing treatments that can intercept disease early and provide meaningful benefits to patients living with chronic conditions.

Regulator perspective

Prof Tony Lawler, Deputy Secretary, Health Products Regulation Group, Department of Health, Disability and Aging, Australia

Patient-centric approaches

Regulators need to improve at engaging and building trust with the community and patients in governance and assessment processes. Importantly, what regulators value (e.g., FEV1) may not align with what patients value (e.g., how many stairs they can climb). Using patient-reported outcome measures and experience measures in a sustainable and defensible manner is vital to addressing this challenge.

Global collaboration and cooperation

Global collaboration and cooperation are essential, with use of collaborative review models such as reliance and work sharing. When regulators work in ways that are acceptable, predictable, and reliable, they generate trust with industry, policymakers, and the community.

Effective communication

More effective communication is needed across the spectrum, including between regulators and with industry. In Australia, frequent horizon scanning meetings and pipeline meetings give regulators insight into upcoming products and trends, allowing them to prepare from both resourcing and legislative perspectives.

Regulatory-HTA interface

More effective scientific discussions between regulatory and HTA stakeholders are needed. Australia recently had an HTA review that included parallel processing and the use of information dossiers for specific disease groups, including chronic disease.

Policy challenges

There is a tendency for public policy and funding to focus on acute response rather than primary and preventative care. The challenge is shifting this needle both within the community and among policy decision makers. Chronic diseases present specific challenges due to differential evidentiary availability and burden, with a tendency towards scientific, objective demonstration that does not reward treatments that prevent rather than treat conditions.

Risk acceptance and valuation

The regulatory approach to chronic disease treatments uses the same risk acceptance profile as for other therapeutic areas, such as oncology, which may not be appropriate. There needs to be a shift in the ability of decision makers and funders to value what is difficult to demonstrate but introduces significant functional improvement for patients and productivity boosts for societies and communities.

Conclusion

The regulatory approach to chronic diseases should evolve to better incorporate patient perspectives and recognise the unique challenges these conditions present. This requires building trust, improving communication, enhancing global collaboration, and shifting the evaluation paradigm to recognise benefits that may be difficult to demonstrate but are significant for patients and society. Traditional regulatory and policy frameworks may need to be amended for treatments that slow or prevent rather than treat conditions, necessitating new approaches that better align with the realities of these conditions.

Health economics perspective

Dr Daniel Ollendorf, Chief Scientific Officer and Director of HTA Methods and Engagement, Institute for Clinical and Economic Review (ICER), USA

Collaborative conversations on evidence

HTA agencies wish to be included in early and collaborative conversations between stakeholders. There is a duty to share expectations around evidence requirements that study sponsors and clinical trial investigators should consider. The HTA community has lagged behind in defining areas where real-world evidence (RWE) could be used, including considerations around data repositories and standardisation of datasets. Clearer guidance is needed on what constitutes high-quality evidence and where it should be applied.

AI integration in HTA

The HTA community has taken a cautious approach to integrating AI into its methods and processes. However, there is potential to ease this caution, particularly around language models. For new interventions being developed for well-understood chronic diseases, AI could be used to interrogate existing repositories of information to develop clinical studies and validate outcome measures.

Resource constraints

Every HTA agency, even those offering early advice services, faces resource and capacity constraints. ICER is considering piloting early scientific advice, but with only 30 employees, creating a dedicated team is challenging. Funding commitments are necessary for these early collaborative conversations, even for government-supported HTA agencies.

Patient community engagement

If early collaborative conversations are to occur, the patient community must be the first repository of information. Discussions should begin with understanding the experience of living with a disease, what patients hope new interventions will address, and how the disease impacts families and caregivers. While this is often discussed, these conversations don't always happen at an early stage.

Payer involvement

In the US, early conversations often happen without payers, partly due to legal and regulatory barriers. However, opportunities exist to address these barriers, whether through sponsor consent models like in Canada, or other approaches. Having payers present helps them understand how new treatments fit into existing therapeutic pathways and potential challenges in widening use to broader populations.

Data requirements for broader value assessment

Industry often suggests that HTA should take a wider perspective and consider broader elements of value. However, this cannot be done without data, and the responsibility to collect that data primarily lies with industry. ICER has recently used a published algorithm that connects patient time use data and quality of life to estimate societal impacts when direct data are unavailable, but this is only used in scenario analyses to maintain incentives for sponsors to collect robust direct data.

Adaptive reimbursement

Adaptive reimbursement approaches are valuable, but all parties need to agree on the terms at the outset. If a drug performs better than in trials, the price might increase; if worse, the price should decrease.

Conclusion

To address HTA challenges for chronic disease treatments, there is a need for clearer guidance on RWE use, greater involvement in early collaborative conversations, and integration of new technologies like AI. However, these efforts require funding commitments and resources. Patient engagement should be the starting point for all discussions, and payers should be included in early collaborative conversations. For chronic diseases with broader societal impact, robust direct data is essential for comprehensive value assessment. Finally, all stakeholders must agree on the rules of engagement for adaptive reimbursement approaches to be successful.

Patient organisation perspective

Leslie Ritter, Vice President, Healthcare Access, National MS Society, USA, and Board Member and Advocacy Chair, American Brain Coalition

Patient involvement considerations

While the value of patient involvement is broadly recognised, often less consideration is given to how patient input is integrated throughout development, regulatory, HTA and payer processes. It is important to distinguish between different types of patient input; for instance, patient perspectives on areas of unmet need and drug development can differ significantly from patient preferences or patient-reported outcomes.

When involving patients, clarity is essential. Stakeholders should be clear about the type of information they are seeking — whether it's about lived experience, day-to-day expenditures, barriers to receiving care or treatment, or treatment experiences.

Resource and staffing constraints within government agencies and patient organisations can impact the ability for patients to engage and participate in regulatory and HTA processes.

Collaborative partners

In addition to individual patients and patient groups, valuable insights can be gained from collaborative partnerships with organisations representing multiple disease communities. For example, the American Brain Coalition represents both rare disease and chronic disease patients, and there has been significant discussion about translating incentives built for the rare disease community into the chronic disease community.

Supporting incentives

Patient advocacy groups are well-positioned to have conversations with policymakers about the patient experience. For example, the discussions between patient advocacy groups and the FDA during US user fee negotiations differed from those of industry but were equally important in figuring out how the patient advocacy community can support incentives.

Perception issues

There is often a perception issue of potential conflicts of interest when engaging with patients. However, when clear parameters are in place to protect all parties, meaningful discussions can occur about what constitutes an unmet need, whether it matters to the patient community, and how it impacts quality of life. Missing any element of this conversation can lead to misallocation of resources—investing in drugs that won't be used or failing to secure proper reimbursement for treatments coming to market.

Conclusion

From a patient advocacy perspective, it is essential to recognise the nuances in patient engagement and to clearly define what information is being sought from patients. Collaborative partnerships with organisations representing multiple disease communities can provide valuable insights. There is a need to address perception issues around conflicts of interest and to create protected spaces for meaningful discussions between all stakeholders. The ultimate goal should be to make novel treatments available for patients to use in shared decision-making with their providers, which requires collaboration and openness to new approaches.

Conclusion

Throughout the workshop, it became clear that common chronic diseases have been underserved in recent years, despite posing a major global health challenge. These conditions are associated with high mortality rates, significant economic burden, and limited treatment options. Addressing this challenge requires more than incremental change — it demands a fundamental reimagining of how treatments are developed, evaluated, and brought to market. A more **adaptive**, **collaborative**, and **patient-centered** approach is urgently needed, with **targeted incentives** playing a central role.

List of attendees

Affiliations are stated as they were at the time of the meeting.

Pharmaceutical companies		
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About CIRS

The Centre for Innovation in Regulatory Science is a neutral, independent UK-based subsidiary of Clarivate plc. Its 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 bodies and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy. 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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