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13:10-14:00, 9 June 2025

Enhancing Cooperation Between Clinical Evidence Generation and Economic Modeling in HTA: How R Can Help

Discussion Panel at ‘R for HTA’

Queen’s University Belfast, UK

Today's Panel

Dominic Muston

Exec Dir, Health Economic & Decision Sciences, "BARDS", Womens' Cancers and Haem, Merck & Co., Inc., Rahway, NJ, USA

- Leads global health economics / modeling team for an oncology portfolio
- Global and local roles in Pharma and Consulting
- Engaged in R Cons HTA WG and 'R for HTA'
- Author of *psm3mkv* package
- BSc Applied Math, MSc Medical Statistics

Gregory Chen

Principal Scientist, HTA Statistics, "BARDS", MSD Zurich, Switzerland

- Statistician in pharma for 15 years, across manufacture, laboratory, quality control and assurance, clinical, and now 4 years in HTA/Market Access
- Active in internal and external research and software collaboration (e.g. openstatsware, R Consortium HTA WG, ASA-Biop Cov Adj SWG)
- Co-author of *maicplus* package
- BSc in Statistics and Econometrics, MSc in Mathematics, PhD in Statistics

Anders Gorst-Rasmussen

Head of HTA Data Science, Novo Nordisk, Copenhagen, Sweden

- Statistician for >20 years across various domains
- 10 years at Novo Nordisk in various roles across late phase developments
- Dedicated to HTA/Market Access for 4 years
- Author of *ahaz* package
- Actively engaged in cross-company collaborations including the PSI/EFSPI HTA SIG and importantly, the R Consortium HTA WG.

Robert Hettle

Director, Health Technology Assessment and Modelling Science, AstraZeneca, Cambridge, UK

- Responsible for HTA analysis and economic modelling for an oncology portfolio
- My role can include statistical analysis and economic modelling
- 17+ years of experience in health economics, including consultancy and global pharma
- R user for >10 years
- Mathematician, MMATH

Declaration:

Dominic Muston and Gregory Chen

We are employees of MSD.

The views expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or opinion of our employer(s), its subsidiaries, or affiliates.

Feature or a Bug? Specialist or Silo?

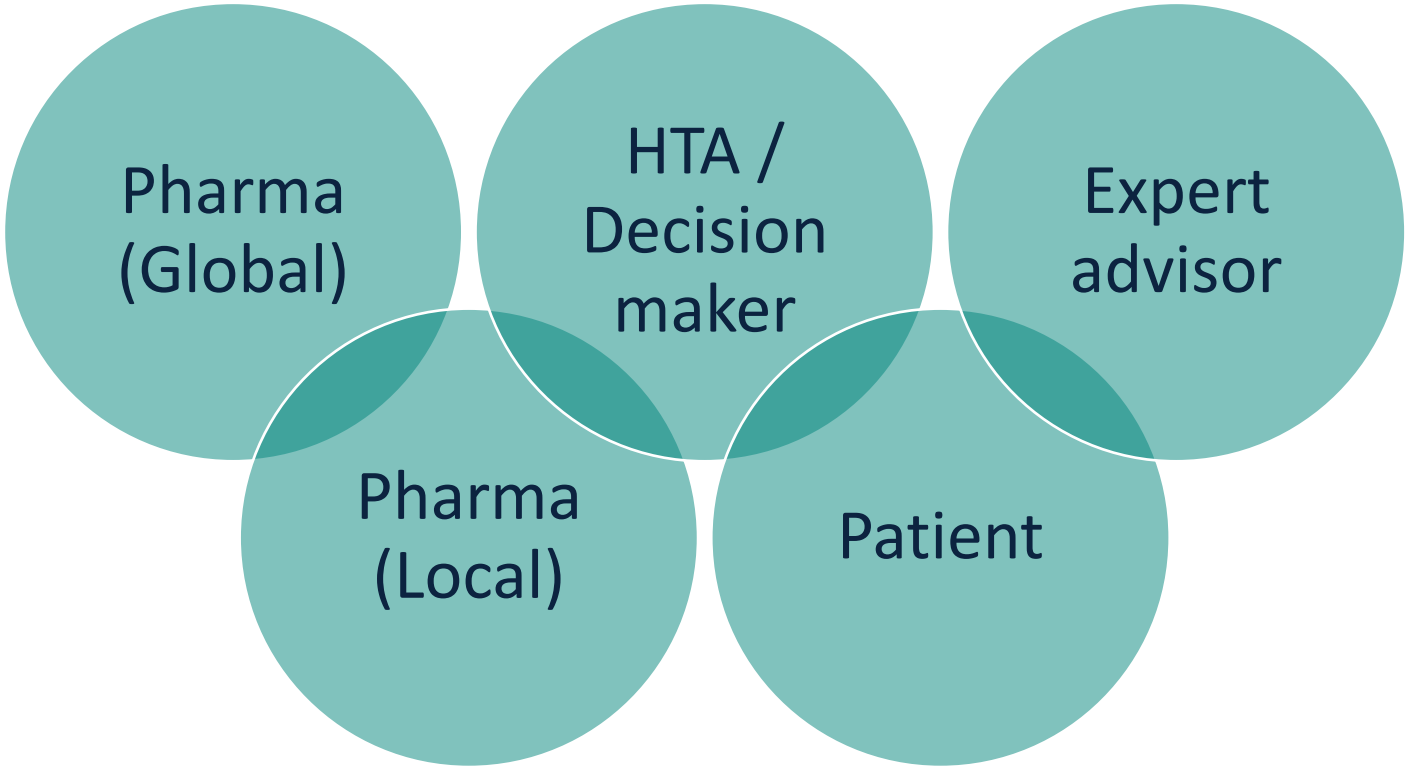
Many external pressures to specialize

- Drug development occurs in phases, examining principally safety and efficacy
- Clinical trials are carefully designed with pre-determined interim/final analysis points
- Regulators examine quality, safety and efficacy
- Health Technology Assessment bodies examine clinical effectiveness vs standard of care;
  - and then consider efficiency (cost-effectiveness) and affordability (budget impact)
- Reimbursement and access can occur once pricing and reimbursement are agreed
- Then comes new competition and re-appraisals
- The world is complex!

Each function in Pharma plays its own role in ensuring patients can access safe and effective medicines and vaccines

	Global	Regional	Local
Clinical			
Medical Affairs			
Statistics			
Health Economics			
Outcomes Research			
Market Access			
Commercial			
Epidemiology			
Regulatory			
Manufacturing			
And many more…			

Different stakeholders are likely to have very different needs from health economic modeling for HTA; ‘Division of Labor’ can be helpful



Research is needed to understand – and then address – barriers to adopting modern health economic modeling technologies, particularly scripted approaches

Gregory Chen, PhD

Principal Scientist, HTA Statistics

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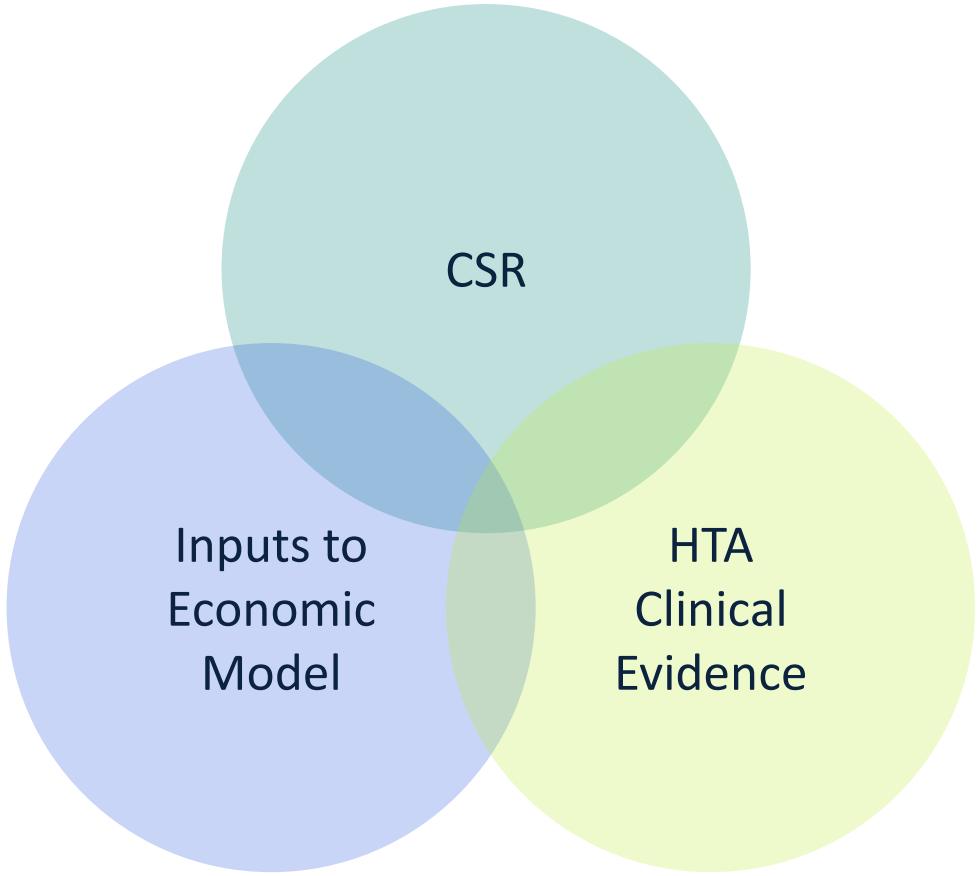
HTA Evidence Requirements Beyond CSRs

CSRs focus on regulatory purposes, it alone often do not provide sufficient data for HTA decisions



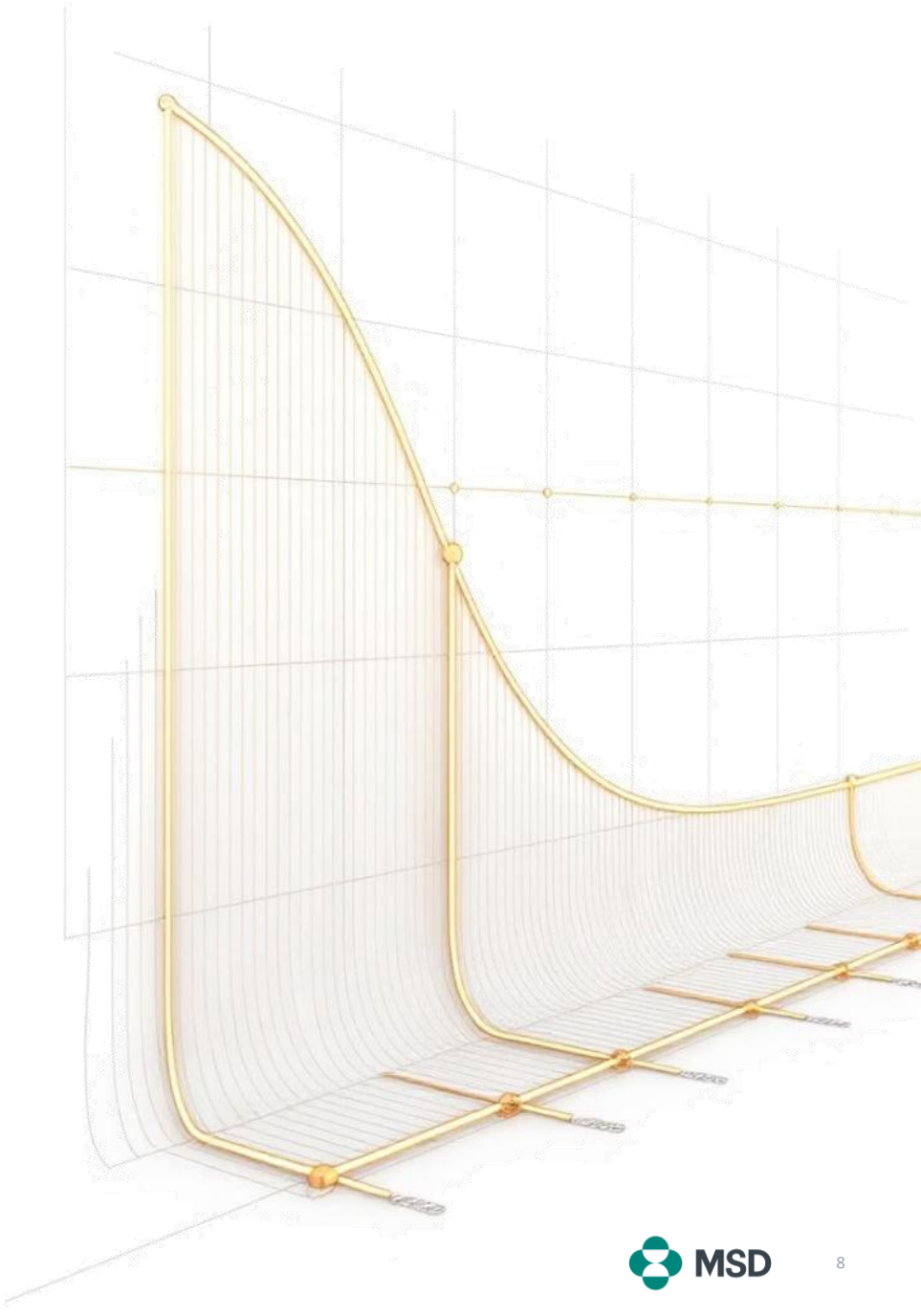
Ex 1: Long-term Survival extrapolation

Not a numerical exercise to find the best AIC or BIC!

Interdisciplinary Coordination is crucial: economic model, statistics, clinical, epidemiology

Beyond the obvious, example of important additional aspects for modeling choices

- **Assessment on the tail region**
  - Evaluate plausibility in the tail region, seek possible external validation
  - Check for conflicts among endpoints (e.g. tail of OS curve is above PFS).
- **Validity of PH Assumption:**
  - long-term appropriateness of the proportional hazards (PH) assumption (e.g. non-PH during trial period, or treatment effect wanning)
  - Identify clinically and data-supported breakpoints if needed.
- **Consistency Across Uses:**
  - Ensure extrapolation assumptions align with regulatory analyses.



Ex 2: Health Utility Analyses based on EQ5D

Mapping Algorithms for EQ5D

Convert PRO data to utility values using appropriate algorithm

Longitudinal Analysis

Utilizing all PRO records per patient and user proper statistical model to estimate average per health status and its estimation uncertainty

Impact Assessment

Evaluate missing patterns, existence of outliers, and their potential impact on the point and interval estimate

Ex 3: Treatment Switching

Adjust or not to Adjust?

It is the question!

Then, what to adjust?

Different approaches based on context

Assumptions & Feasibility

Validate key assumptions for methods

Scenarios to Explore:

- Adjust comparator arm for patients switching to the experimental arm.
- Adjust both arms for subsequent treatments:
  - Regulatory focus: eliminate confounding.
  - HTA focus: reflect realistic post-launch treatment paths.

What is also important, assumptions & feasibility assessment of desired methods (e.g., two-stage estimation, IPCW)**:**

- Incorporate clinical insights.
- Perform preliminary analysis to validate key assumptions for methods

Ex 4: Example Statistical Analyses for AMNOG

Subgroup analyses

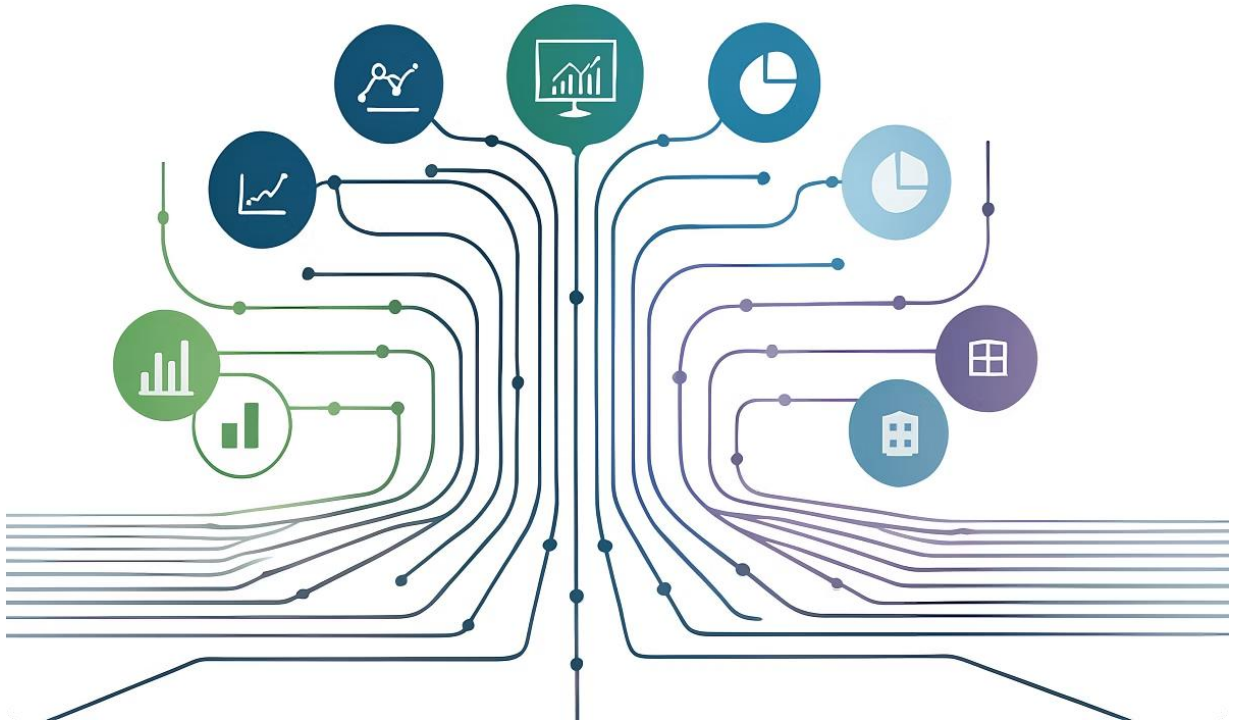
With interaction test

Extensive Safety Analyses

Risk Ratio as preferred effect measure

Multiplicity Control

To alleviate overinterpret chance finding



Why Use R for HTA Evidence Synthesis?

End-to-End Workflows

From data synthesis to reporting in one platform

Advanced Visualization

Even interactive ones, with ample example code

Efficiency & Automation

Using for example parameterized quarto and shiny app

Rich Package Ecosystem

a plethora of packages for HTA needs

Reproducibility

Easily compatible to version-controlled platform like Github

Transparency

Script-based and can print out sessionInfo()

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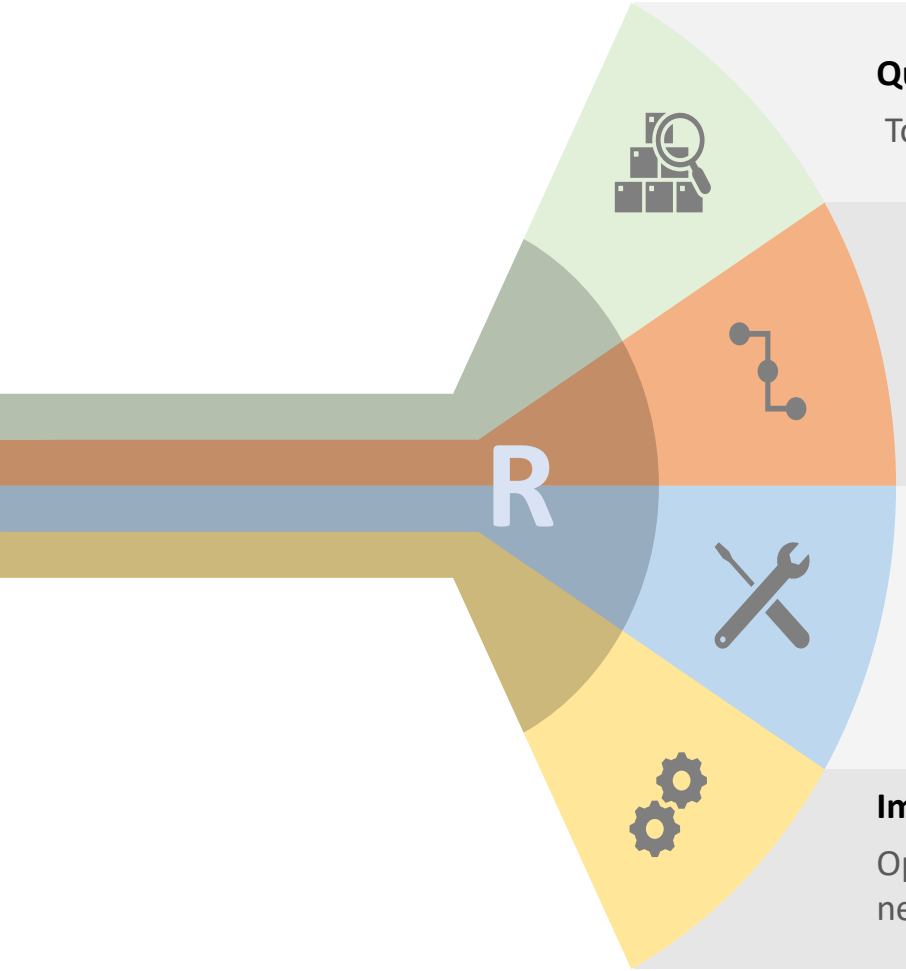
Using Open-Source Software can also come with challenges



Qualiy and Validation

Too many packages to choose from

Version Control for Reproducibility

Upversion rate is different from package to package, because they are developed and maintained by different individuals or teams. Each R package may have dependency on multiple other R packages.

Maintain and Support

Will the trusted R package be well maintained when base R version has an upgrade? Who to call when there is a bug?

Implementation and Deployment

Operating may lead to small difference based on the same code and data. In-house IT support might be needed

Open-source collaboration can help to address them, in particular

Quality and Validation

Some good initiatives are in place: R Validation hub, CAMIS.

The goal is to built up a pool of validated R packages that are suitable for regulatory submission via cross-industry collaboration

Maintain and Support

Many company and cross-industrial initiatives make open source now. A package has now an active team or community behind it, not relying on one or few individuals, stronger sustainability and continuity (e.g. pharmaverse, openpharma, openstatware)

Anders Gorst-Rasmussen, PhD

Head of HTA Data Science

Novo Nordisk

Declaration

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Enhancing Cooperation Between Clinical Evidence Generation and Economic Modeling in HTA

An HTA statistician perspective

Context

- Novo Nordisk HTA Data Science separate from both regulatory stats and health economics
- Increasingly lean clinical study reports vs. increasingly sophisticated HTA evidence needs
- Growing pressure for (cost-effectiveness models with) granular clinical inputs

Challenges and Opportunities

- **Subgroup/subpopulation analyses:** comprehensive subgroup/subpopulation exploration→ manual, time-intensive
- **Tool fragmentation:** Hand-overs regulatory stats → HTA stats → HEOR create potential failure points
- **Extensive analysis, minimal impact:** Complex clinical analyses (e.g. trial-based risk equations) with limited ICER impact
- **Sequential workflows:** Different functions building one after another, often with vendors → overhead and risk of misalignment

How can R help?

Enable harmonization

- Shared R infrastructure creates pathway toward integrated clinical → economic workflows

Scalable, maintainable automation

- R's strengths in building reproducible workflows
- e.g. Subgroup analyses

Agile development

- R as a natural backbone for sprint-based workflows with MVPs - test economic impact early before investing in complex statistical work

Robert Hettle, MMath

Director, Health Technology Assessment and Modelling Science; AstraZeneca

Disclaimer

- I am an employee of AstraZeneca (AZ), and I own stocks and shares in the company. The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or opinion of AZ PLC, its subsidiaries, or affiliates.

Enhancing Cooperation between Clinical Evidence Generation and economic modelling in HTA

A global health economics and HTA statistician perspective

- Context
  - At AstraZeneca, the oncology health economics and HTA science team sits within the market access group in our commercial function
  - Biometrics (statistics and programming) sits within R&D
  - Evolving science and pathways are driving **faster** development, regulatory and HTA timelines
- Growing **analytical demand** arising from
  - International growth of HTA
  - New EU joint clinical assessment
  - Methodological advancements
  - Dynamic and evolving treatment landscapes
- At launch, the main source of evidence for new medicines is clinical trials

Challenges and opportunities

- **Decision problem expansion:** increasingly complex PICOs and data demands (e.g., subgroups of subgroups)
- **Faster turnaround:** time from trial reporting to regulatory/HTA submissions are becoming shorter, with increasing overlap in global activities across countries
- **Growing complexity:** New methodologies allow us to better tackle ‘old problems’, however, they require new skill development, time to implement, and may require more ‘intensive’ stakeholder alignment
- **Multi-step analysis process:** regulatory analysis tends to be built in ‘commercial’ programs (e.g. SAS), while HTA analysis can be conducted in a mix of commercial (‘direct’ analyses for JCA/IQWiG submissions) and R (everything else)
- **Multi-step implementation process:** ‘Manual’ evidence exchanges typically relying on data/file sharing platforms (e.g., SharePoint); economic models are often built in Excel

What is the role of R?

- **Open-source, scalable, end-to-end solutions:** Ability to scale solutions and/or prepare analytics in advance of data access, to meet faster turnaround times.
- **Evidence tracking and retrieval:** Potential to handle the increasing volumes of HTA evidence through quarto books or similar frameworks, and to integrate these with other emerging digital solutions
- **Economic models:** A divisive topic.
  - **Global:** need to deliver for the needs of diverse markets
  - At present, a rule of ‘lowest common denominator’ applies. If Excel is accepted everywhere but R isn't – is it ‘inefficient’ to build two models?
  - Skill gaps and ‘uncertainty’ over how some local HTAs will accept R is an ongoing issue. Will it enable, hinder or have no ‘direct’ impact on patient access to medicines?
  - R is better suited to handling increasing analysis demands, and to automate information flow from analysis to model

Discussion