Health technology assessments and the role of statisticians

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Health technology assessment (HTA)

What is **health technology assessment**?

- A **health technology** is an intervention used to promote health, e.g., a pharmaceutical product or a medical device
- An **assessment** is required to inform policy decision-making
- The assessment is **multidisciplinary**, involving social, economic, organizational and ethical aspects

HTA in the drug development plan

HTA forms part of the "**fourth hurdle**" of drug development:

1. Safety
2. Clinical efficacy
3. Quality
4. **Clinical effectiveness and cost-effectiveness**

- **Clinical efficacy**: Capacity to produce an effect under ideal and controlled circumstances
- **Clinical effectiveness**: Capacity to produce an effect in real-world conditions
- **Cost-effectiveness**: Clinical effectiveness versus economic cost in clinical practice

Novo Nordisk submits HTA evidence to payers to demonstrate the **value** of new treatments and overcome the fourth hurdle

HTA: fast and lean

1. Multiple stakeholders (HTA agencies) with different requirements
2. Cross-functional effort: market access, health economics, statistics, programming, clinical sciences, decision sciences, epidemiology, medical writing
3. Quickly changing environment: study designs, data sources, evidence base, methodologies, recommendations/guidelines, HTA agencies, HTA processes (e.g. EU harmonization)
4. Domain-specific knowledge needed; for instance, in health economics concepts
5. Departure from traditional clinical development (regulatory) biostatistics

HTA: multiplicity of stakeholders

There are many different HTA agencies with different requirements

Regulatory versus HTA statistics

REGULATORY

- Focus on safety, clinical efficacy, quality, benefit-risk
- Focus on confirmatory hypothesis testing
- Estimands
- Time-horizon is the trial follow-up; does not typically require extrapolation
- Relies mostly on data of a “pivotal” Phase III clinical trial as the primary source of evidence
- Comparator is usually placebo or standard of care in a head-to-head study
- Strict multiplicity strategy; strategy for subgroups and multiple endpoints is well-defined in protocols
- SAS programming

HTA

- Focus on clinical effectiveness and cost-effectiveness
- Focus on estimation
- PICOs
- Long-term or “lifetime” horizon; may require extrapolation beyond the trial follow-up
- Typically requires secondary data sources beyond the “pivotal” clinical trial (yet still relies on the pivotal trial)
- Comparators are all competing treatment options; direct comparisons may be unavailable
- Less strict multiplicity strategy; decision-making process may require post-hoc analyses
- R programming; spreadsheet software

Skills to be successful as a HTA statistician

Statistical leadership and negotiation: to drive and advocate for informed and statistically sensible decision-making; pursue alignment and manage conflicts within teams

Strategic thinking: to foresee operational and statistical challenges

Methodology: to incorporate, understand and challenge HTA guidelines/recommendations

Learning/flexibility: to navigate and adapt within an ever-changing HTA environment

Teamwork: to build trust and collaborate within cross-functional teams; understand the needs of other functions

Communication: to communicate clearly and persuasively; ability to express complex concepts in a language appropriate to the target audience

Technical skills: knowledge of relevant software tools and programming languages

Adapted from "HTA – A changing landscape and how data scientists can upskill to adapt to EU HTA" by Cornelia Schepers, Daniel Saure and Tabea Petelkau

HTA-specific statistical methodologies

The complexity of statistical methodology and methodological gaps in HTA is increasing

- **Evidence synthesis**
  - Meta-analysis and meta-regression
  - Advanced indirect comparison methods
- **Patient-reported outcomes**
  - EQ-5D analysis
  - Health state utility estimation
- **Observational data analysis**
  - Causal inference
  - Real-world data, real-world evidence generation
- **Decision-analytical modelling**
  - Health economic (cost-effectiveness) evaluation
  - Patient-level simulation
- **Survival analysis**
  - Parametric survival modelling
  - Adjustment for treatment switching
  - More flexible approaches (e.g., splines, cure models, landmark analysis)

There is a high unmet need for statisticians with expertise in these areas…in the pharmaceutical industry, contract research organizations, consultancy firms and the public sector

Role of a HTA statistician in a pharmaceutical company

Key responsibilities:

- Alignment of clinical development and HTA statistical analyses to meet HTA and reimbursement needs
- In-house development of statistical analysis plans for Phase III clinical trials as a strong basis for defining HTA requirements and planning resource allocation
- Oversight of external vendors to avoid transmission errors and time delays; facilitation of knowledge transfer; quality control of HTA submissions and other outsourced activities
- Supporting “Market Access” or “HEOR” functions in exchanges with HTA agencies, post-hoc analyses, parallel submissions in different countries, country-specific follow-up requests
- Implementing HTA-specific statistical methodologies; helping build competencies and capacities in statistical programming and analysis, libraries, standards
- Leadership of cross-functional teams involving clinicians, health economists, medical leads, medical writers, clinical statisticians, programmers…

Resources

Suggested resources to learn ”HTA statistics”

- NICE Decision Support Unit Technical Support Documents: https://www.sheffield.ac.uk/nice-dsu/tsds
- ISPOR Good Practices Reports (“Methodological and Statistical Research” in particular): https://www.ispor.org/heor-resources/good-practices
- A Newcomer's Guide to HTA: A collection of resources for early career professionals, HTAi (2023)
- Relevant journals: Value in Health, Medical Decision Making, Research Synthesis Methods, Statistics in Medicine, Statistical Methods for Medical Research, Pharmaceutical Statistics, Statistics in Biopharmaceutical Research

Concluding remarks

- Working in HTA as a statistician requires a very particular skillset
- HTA presents an ever-evolving landscape
- HTA statistical work differs from statistical work in traditional clinical development
- HTA business needs are fast-growing and there is a high unmet need for statisticians with expertise in HTA
- Upcoming changes in HTA processes will lead to major changes, which will affect current workflow and further increase demand for statisticians

Thank you!

Any questions?

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