Opportunities at the Intersection of Pharmacometrics and Health Economics for Insightful Drug Development Decision Making: A Problem Based Learning Session with Interactive Scenario Evaluations

Moderators:

Marc R. Gastonguay, PhD - Metrum Research Group

Jing Liu, PhD - Pfizer
Overview

Session Introduction
Marc R. Gastonguay, PhD – Metrum Research Group

Introduction to Health Economics Concepts and Economic Models
Jean Lachaine, PhD – PeriPharm Inc.

Linking PMX and HE Models
Anna (Georgieva) Kondic, PhD, MBA – Nektar Therapeutics

Interactive Simulation Based on an Integrated Pharmacoeconomic-Pharmacometric Model
Daniel G. Polhamus, PhD – Metrum Research Group

Live Q&A
ISPOR 2020 Top 10 Trends in Health Economics

1. **Real-World Evidence**
   Real-world evidence in healthcare decision making has risen in this year's trends list due to a number of converging factors.

2. **Drug Pricing**
   Pressure is increasing on drug makers as to how they price their products.

3. **Novel Curative Therapies**
   Many of these medicines represent great strides forward in treatment; however, their pricing may put them out of the reach of many patients.

4. **Overall Healthcare Spending**
   WHO reports that the world spent $7.5 trillion on health, representing close to 10% of global GDP.

5. **Universal Health Coverage—Access and Equity**
   Universal healthcare will remain an important issue as many countries still seek to provide their citizens with healthcare.
ISPOR 2020 Top 10 Trends in Health Economics

6. **Value-Based Alternative Payment Models**
   Innovative, high-cost therapies drive the search for novel payment models.

7. **Price Transparency**
   Lack of clarity about information on pricing for healthcare products and services impacts healthcare budgets and patients.

8. **Digital Technologies**
   A new topic for 2020, digital healthcare is advancing rapidly with the potential to transform healthcare delivery and outcomes assessment.

9. **Aging Population**
   This global demographic trend will have a long-term impact on healthcare delivery and costs for some time to come.

10. **Precision Medicine**
    Precision, or personalized, medicine is a growing field that intersects with big data.
Opportunity at the Intersection

- Shared Learning, Resources, Science, Technology
- Better Inform Drug Development Decisions
- Better Inform Health Economic Decisions
Jean Lachaine Ph.D.
PeriPharm Inc

Introduction to Health Economics
Concepts and Economic Models
Role of The Economic Evaluation in Health Care

Health care resources are limited

Choices need to be made for an optimal allocation of resources

Economic evaluations can support the decision making process
Economic Evaluations in Health Care

• Compare different interventions on the basis of their costs and their outcomes.

• The objective of the economic evaluation is not to identify the less costly alternative, but the most efficient alternative.
Key Drivers of Drug Reimbursement Decisions

- Therapeutic value
  - According to the available clinical evidence

- Cost-effectiveness
  - Depends on the cost-effectiveness or cost-utility ratio (cost per QALY)
  - Closely linked to the magnitude of the clinical effect as well as the drug costs

- Budget impact
  - Supplemental costs (or savings) encountered following the addition of the new drug
Economic Evaluation of New Medications

• The most common type of economic evaluation is the « Cost-utility » analysis
• Results are estimated in terms of cost per QALY (Quality adjusted life year)
• Number of QALYs = Duration x Utility
• Incremental cost-effectiveness ratio (ICER):

Costs of new drug – Cost of comparator

\[ \frac{\text{QALYs with new drug} - \text{QALYs with comparator}}{\text{Costs of new drug} - \text{Cost of comparator}} \]
Cost-Effectiveness Analysis (Decision Rules)

<table>
<thead>
<tr>
<th>Cost</th>
<th>Effectiveness</th>
</tr>
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<tbody>
<tr>
<td>-</td>
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- Dominated (More costly and less effective)
- Decision based on ICER
- Decision based on ICER (Less costly and more effective)
- Dominant
Calculation of Incremental Cost-Utility Ratio (Example)

• Standard of care =
  • Cost = $20,000
  • Survival = 1.2 years / Utility = 0.7 \(\rightarrow\) 0.84 QALY

• New drug =
  • Cost = $40,000
  • Survival = 1.4 years / Utility = 0.8 \(\rightarrow\) 1.12 QALY

\[
\text{ICER} = \frac{\$40,000 - \$20,000}{1.12 \text{ QALY} - 0.84 \text{ QALY}} = \frac{\$20,000}{0.28 \text{ QALY}} = \$71,429 / \text{QALY}
\]
## Cost-Utility Analysis

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost</th>
<th>Incremental Cost</th>
<th>Effectiveness (QALYs)</th>
<th>Incremental Effectiveness</th>
<th>Average Cost-Effectiveness Ratio</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>SoC</td>
<td>$20,000</td>
<td></td>
<td>0.84</td>
<td></td>
<td>$2,500</td>
<td></td>
</tr>
<tr>
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<td>$40,000</td>
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<td>0.28</td>
<td>$4,000</td>
<td>$71,429 / QALY</td>
</tr>
</tbody>
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Health Economic Models

• Decision trees
• Markov Models
• Partitioned Survival Models
• Discrete event simulations
Health Economic Modelling: Decision Tree
Health Economic Modelling: Decision Trees
Health Economic Modelling: Markov Models
Health Economic Modelling: Markov Models
Health Economic Modelling: Markov Models

![Markov Model Diagram]

- Pre-progression
- Post-progression
- Death

The diagram illustrates a Markov model with transitions between pre-progression, post-progression, and death states.
Health Economic Modelling: Partitioned Survival Models

State membership determined using matrices of transition probabilities which determine the probability that an individual will transition in a given time period.

Partitioned Survival Models

State membership derived from non-mutually exclusive survival curves. Overall survival (OS) is portioned to estimate the proportion of patients in the progression-free and progressed disease health states.
Health Economic Modelling: Discrete Event simulations

Figure 1. Schematic representation of the possible pathways within the pertussis DES (Discrete Event Simulation) model. Red circles and red lines indicate events and pathways associated with vaccination, respectively; dashed circles indicate events where no time is actually involved; and shaded circles indicate events where resources are consumed and therefore costs are included.
The economic evaluation in healthcare, is now a key criterion in decision making

*Even if good health has no price, we cannot deny that diseases have a cost...*
Anna Georgieva Kondic, PhD, MBA

Linking Pharmacometrics and Health Economics: A Personal Perspective
Outline

• General concepts

• Challenges and opportunities

• Case studies

• Conclusions
Framing the opportunity: value proposition of a new therapy

• Traditional paradigm
  • Cost-effectiveness and budget impact
  • Separate regulatory process for approval and reimbursement with different tools

• Evolving paradigm: driving towards precision and personalized medicine
  • Matching the patient with the right treatment
  • Value based reimbursement
  • Number of joint regulatory-HTA advice meetings is increasing; new tools are emerging
Conceptual Framework of PMx-PE interaction (Srinivasan et al)

• Drug model
• Disease model
• Trial model

How to strengthen the value proposition?
A word (or two) of caution

- Goal is to decrease the uncertainty and guesswork in the decision making
- Fit for purpose models
- Internal vs external decisions
- Must-haves vs nice-to-have
  - Focus on cases studies where joint approach provides further clarity
- Speed and ease of use are of utmost importance
Early (prior to P2) economic evaluation
Questions/focus

• Given an assumed efficacy, what may be a good price?

• What is a needed efficacy in order to meet a prescribed threshold?

• Is there a need for enrichment of a particular sub-populations to facilitate registration?

• How important are quality of life and routes of administration?

• Include QoL and other tools (e.g. ease of use) as secondary endpoints in a clinical trial (if a key parameter)?

• Benchmark single arm studies
What does success look like

• General requirements:
  • Commercial and clinical interest in go/no go decisions
  • Multi-disciplinary team efforts, alignment needed on multiple levels

• Tool requirements
  • Visual in order to answer questions on the spot (GUI)
  • Be able to incorporate uncertainty and variability
  • Fast and powerful computational capabilities
  • Ability to incorporate new and dynamically changing information (e.g. competitive landscape) in a seamless fashion

• Ongoing and iterative process: knowledge database, rather than a tool
  • New data integration, including drugs, biomarkers and patient populations
  • Quality control
Application 1: Combinations in Oncology

• Evaluate a proposed design for a late phase clinical study of the combination in ovarian cancer
• Both drugs in combination approved and expensive
• The economic evaluation pointed out to a higher hurdle than expected for efficacy for both PFS and OS in order to achieve acceptable ICER
  • Identify responders and enrich patient population in clinical study
  • A conversation starter rather than a definitive Go-No go; value in cancer goes beyond cost-effectiveness
Application 2: Commercial potential of an asset

• Characterize commercial potential of a molecule in CV space using disease modeling and HE approaches
  • Price range
  • Sequential clinical approach evaluation

• Factors impacting project
  • Published models for several diseases
  • Multitude of patients with different responses
  • Clear reimbursement guidance determining the hurdle
  • Ability to integrate team point of view and assumptions in a single framework
Aspiring to understand the real world
Focus

• Problem statement: bridging efficacy-to-effectiveness gap
  • Characterize the impact of the differences between RCT and RW
  • Prepare for address in order to maximize “value” (including value-based reimbursement)

• Why?
  • Different patient populations
  • Different adherence and behavioral patterns
  • Country-specific pathways

• Multiple tools are being considered
Case study 3: Hodgkin’s Lymphoma

- Innovative Medicines Initiative (IMI) initiative
- HL was one of the case studies for different methodologies
  - Clear discrepancy between performance of approved treatments in RW as compared to RCT
  - Simplest scenario:
    - Age
    - Tolerability
    - Mixture of the two
- Conduct simulations for novel therapies to inform on clinical drug design and optimize on value
Conclusions

- Pharmacometrics and pharmacoeconomics are well-established quantitative disciplines.

- Joint efforts can strengthen the quality of decision making and impact bottom line.

- Several promising efforts exist yet this is an area of enormous growth potential.
Thank you!
Interactive Simulation Based on an Integrated Pharmacoeconomic-Pharmacometric Model
Pharmacoeconomic (PE) Model: Dupilumab in Atopic Dermatitis

Economic Evaluation of Dupilumab for Moderate-to-Severe Atopic Dermatitis: A Cost-Utility Analysis

Marita Zimmermann MPH PhD, David Rind MD MSc, Rick Chapman PhD, MS, Varun Kumar MBBS MPH MSc, Sonya Kahn MPH, Josh Carlson PhD MPH

6.3% yearly discontinuation used in article, but RWE suggests substantially higher rates (~83% persistence at 1 year)

WHO gender and age based mortality

In combined PD-PE model, this is determined by week 16 response rate from longitudinal model

Silverberg, et al 2021
Pharmacometric (PM) Model: Dupilumab Effects on EASI

Longitudinal EASI score is a fractional decrease of baseline EASI score (E0). For patient \(i\)'s \(j\)th observation at time \(t\):

\[
EASI(t_{ij} | \text{drug}_i) = \frac{E0_i}{1 + g_{\text{Pbo}}(t_{ij}) + g_{\text{TCS}}(t_{ij}) + g_{\text{Drug}}(t_{ij})}
\]

**Drug effects are hyperbolic Emax models:**

\[
g_{\text{Pbo}}(t_i) = \frac{E_{\text{max, Pbo}} \times t_i}{\text{ET50}_{\text{Pbo}} + t_i}
\]

\[
g_{\text{TCS}}(t_i) = \frac{E_{\text{max, TCS},i} \times t_i}{\text{ET50}_{\text{TCS}} + t_i} \times e^{-k_{\text{off,TCS}} (t_i - \mu_{\text{TCS}})^+}
\]

\[
g_{\text{Drug}}(t_i) = \frac{E_{\text{max, Drug},i} \times t_i}{\text{ET50}_{\text{Drug}} + t_i}
\]

**Primary data sources:**

- **SOLO 1&2**
  - 16 weeks, placebo controlled in moderate-to-severe AD where TCS provided inadequate control or was medically inadvisable. TCS as rescue.

- **LIBERTY AD-CHRONOS**
  - Long-term (1 yr) management of moderate-to-severe AD with concomitant TCS

- **Abrocitinib dose ranging**
  - Used to specify proportional residual error
Efficacy Benchmarking via PMPE Model

Observed dupilumab 52 week efficacy (EASI-75) – Blauvelt et al, 2017
Projected Quality Adjusted Life Years (QALYs)

- Superior clinical efficacy translates into marginal differences in QALYs
Incremental Cost-Effectiveness Ratio (ICER)
Cost-Utility Analysis
Access to the Interactive Simulator

If you would like to explore the prototypical PMPE simulation app demonstrated in this session, please indicate **PMPE App** in the subject line and send your **name** and **email address** to:

training@metrumrg.com