Bridging the Gap between Efficacy and Effectiveness: Methods to identify Drivers Of Effectiveness before launch

IMI GetReal, Work Package 2

Chris Chinn, MSc (Sanofi)

ISPOR 2016, Vienna

What is effectiveness?

- Effectiveness may be defined as the impact of drug efficacy (pharmacological effect) when all ‘interactions’ are at play
  - Interaction being used in the broad sense of ‘interaction’ / ‘effect modification’
- 3 levels of interaction may be considered
  - The real/actual use of drug
  - The patient/disease-related characteristics
  - The healthcare system-related characteristics
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DRIVERS OF EFFECTIVENESS are therefore the factors likely to influence the efficacy of the drug

- Build a theoretical model to understand relationship
- Study the distribution and magnitude of factors in the target population

GapAnalysis and New Solutions

Systematic approach to understand and address “drivers of effectiveness”

- Guidance on a range of methodologies useful to assess the drivers of effectiveness within a disease area
- Exploring statistical and analytical issues arising from designing trials to provide information on the impact of specific drivers of effectiveness

Yields insights into most appropriate trial designs and analytical approaches to better understand effectiveness
Today’s presentations

• Methods to identify drivers of effectiveness
  • Systematic/Focused Literature Reviews, experts interview
  • Aggregate/Patient-level Data Analyses
  – Examples
    • Antidiabetic drugs
    • Anticancer drugs in Hodgkin’s Lymphoma
    • Antipsychotic drugs in schizophrenia

Identifying Efficacy/Effectiveness Gaps and Drivers of Effectiveness: Literature Reviews

The Hodgkin's Lymphoma case study

Robert Olivares, MD, MSc (Sanofi)
ISPOR 2016, Vienna
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<table>
<thead>
<tr>
<th>Key differences between systematic and focused/targeted reviews</th>
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<tbody>
<tr>
<td><strong>Systematic Lit. Review (SLR)</strong></td>
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<tr>
<td><strong>Question formulation</strong></td>
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<tr>
<td><strong>Structured Search</strong></td>
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<tr>
<td>• Titles/Abstracts screening</td>
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<td>• Full text review</td>
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<tr>
<td>• Critical Appraisal</td>
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<tr>
<td>• Data extraction</td>
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</table>

Gold Standard

As a result review time is very different: ~2-3 months for FR vs. ~6-9 months (or more) for SLR!

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**The Hodgkin Lymphoma (HL) case study: A Systematic Literature Review**

**Objectives:**
- Is there an efficacy-effectiveness gap (EEG) in HL?
  - Differences in patient population, outcome results,…?
- What are the potential drivers of effectiveness (DoE)?

**Methods:**
- Search in Embase & Medline + reference cross checking
- Double data selection of 619 citations (titles & abstracts)
- Full papers review: double data selection (n=68) and double data extraction (n=47)

11 articles with data on HL
Efficacy/effectiveness gaps (EEG) and Drivers of Effectiveness (DoE)

<table>
<thead>
<tr>
<th></th>
<th>EEG</th>
<th>DoE</th>
</tr>
</thead>
<tbody>
<tr>
<td># of articles</td>
<td>5/11</td>
<td>9/11</td>
</tr>
<tr>
<td>Age (#1 factor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reported as EEG</td>
<td>Patients with age &gt; 60: 5-10% in clinical trials vs. 20-44% in observational studies</td>
<td>Older age associated with shorter PFS and OS: Hazard Ratios in multivariate models from 1.76 to 3.97 for PFS and from 2.24 to 3.90 for OS</td>
</tr>
<tr>
<td></td>
<td>8% of patients from a HL registry excluded of clinical trials for age &gt; 75, and 7% for an age &lt; 16 (Terschuren 2010)</td>
<td>Elderly were found not to be treated as aggressively as younger patients</td>
</tr>
<tr>
<td>Other factors</td>
<td>Patients from a HL registry excluded of clinical trials for (Terschuren 2010):</td>
<td>Advanced disease -&gt; shorter PFS and OS Comorbidities -&gt; shorter OS Treatment toxicity -&gt; lower remission rates</td>
</tr>
<tr>
<td></td>
<td>• Comorbidities: 6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• poor PS: 2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• poor compliance : 6%</td>
<td></td>
</tr>
</tbody>
</table>

Overall, 64% of patients from a HL registry deemed eligible for clinical trials (Terschuren 2010)

Examples of articles describing EEG

If a EEG is also a DoE then difference between efficacy & effectiveness of a drug is likely to be observed (e.g. age in HL)
Example of the impact of EEG & DoE
(Kasper et al. European Neuropsychopharmacology 2014: 24, 125-132)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline demographic and clinical characteristics of patient sample.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical practice study</td>
</tr>
<tr>
<td></td>
<td>Prepubertal 156 mg/day</td>
</tr>
<tr>
<td>Female</td>
<td>%</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>mean (SD)</td>
</tr>
<tr>
<td>Gender</td>
<td>%</td>
</tr>
<tr>
<td>ADHD-IV,</td>
<td>mean (SD)</td>
</tr>
<tr>
<td>VAS-Anxiety</td>
<td>%</td>
</tr>
<tr>
<td>Depression</td>
<td>%</td>
</tr>
</tbody>
</table>

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• Advantages:
  – Retrieves existing information (avoids re-inventing the wheel)
  – Uses scientifically recognized (SLR) or robust (FLR) methodology
  – Always a good starting point to evaluate the data gaps, before generating further information

• Limitations:
  – Relies on available evidence (and its quality)
  – Depends on the objectives and data presented by the authors: you cannot study interactions, correlations etc. between factors if not included in the publication
  – Beware of publication bias!

Literature reviews to identify Efficacy-Effectiveness gaps (EEG) and Drivers of Effectiveness (DoE)
Questions from the audience?

Linking clinical and registry data

Lifang Liu, MD, PhD (EORTC)
ISPOR 2016, Vienna
Outline

• Why?
• How?
• Results?
• Reproducibility?

Why?

An observation

A Literature Review

How?

Procedure: EORTC ID data -> Cancer Registry -> EORTC

EORTC trial participants

Cancer Registry

Results?

>50% of the survival gap is explained by age differences

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Reproducibility?

- No misclassification on trial participation preconditioned by
  a. full coverage of trial participants at EORTC of HL cases;
  b. full coverage of total HL patients in registry;
- How reproducible is this approach?
- Suggestions?

Questions from the audience?
Identifying Efficacy/Effectiveness Gaps and Drivers of Effectiveness: Data Analyses

The Schizophrenia case study

Clementine Nordon, MD, PhD (LASER Analytica)
ISPOR 2016, Vienna

Study outline

• Objectives
  – To identify drivers of effectiveness (DOE), defined as effect-modifiers of antipsychotic drugs in schizophrenia (SCZ)
  – To explore the impact of using these characteristics as eligibility criteria in RCTs

• SOHO dataset
  – A European observational cohort\(^1\) including > 10,000 schizophrenia outpatients
  – 3-month follow-up

\(^1\)Haro et al, Acta Psychiatrica Scand, 2005
Measures

• Which potential drivers of effectiveness to “test”?  
  – Before any data analysis  
    • Focused Literature Review  
    • Experts interviews

Potential drivers of effectiveness
- Nicotine use
- Substance use disorder (cannabis, LSD, etc.)
- Adherence to medication
- Illness duration (chronicity)
- Severity at onset
- Severity of “negative” symptoms

– Which ones are typically used as exclusion criteria in RCTs?

Potential drivers of effectiveness
- Substance use disorder (cannabis, LSD, etc.)
- Adherence to medication
- Illness duration (chronicity)

Measures

• Measure of effectiveness
  – Exposure: initiating/switching antipsychotic drugs (no comparison: absolute effectiveness)
  – Outcome: level of improvement in schizophrenia symptoms (standardized measurement scales), in the short-term (3 months)
  – Effectiveness ≈ association between exposure and outcome

EXPOSURE = Initiation of antipsychotic drugs

OUTCOME = Improvement of schizophrenia symptoms 3 months later

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• Measure of effect-modification
  – Effect-modification occurs when the magnitude of the effect of the primary exposure on an outcome (i.e., the association) differs depending on the level of a third variable
  – Effect-modification ≈ effectiveness is different in patients with or without each DOE (substance use disorder, etc.)

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Data analyses 1
• To identify drivers of effectiveness of antipsychotic drugs in SCZ
  – Level of symptoms improvement, in patients with or without each “DOE” characteristic (Substance abuse or not, Good/poor adherence, Short/long duration of SCZ)

<table>
<thead>
<tr>
<th>N</th>
<th>Mean ΔCGI-S (SD)</th>
<th>n</th>
<th>Mean ΔCGI-S (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>-0.78 (1.0)</td>
<td>8250</td>
<td>-0.78 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Poor adherence</td>
<td>-0.78 (1.0)</td>
<td>7930</td>
<td>-0.78 (1.0)</td>
<td>0.055</td>
</tr>
<tr>
<td>Duration of illness ≤ 3 years</td>
<td>-0.73 (0.97)</td>
<td>5814</td>
<td>-0.89 (1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>-0.78 (0.99)</td>
<td>7855</td>
<td>-0.80 (1.1)</td>
<td>0.679</td>
</tr>
</tbody>
</table>

The level of symptoms improvement is higher in patients with a short illness duration.
Data analyses 2

- To explore the impact of using these characteristics as eligibility criteria in RCTs

Exclusion of patients with:
- Poor adherence
- Shorter duration of illness
- Substance use disorder

SOHO cohort (N=8250)

RCT (n=5348)

Effectiveness of drugs AE, AD and R
ΔCGI-S=−0.78 (SD=1.0)

Effectiveness drugs AE, AD and R in the “RCT sub-group”
ΔCGI-S=−0.73 (SD=0.96)

“GAP”

Data analyses 2

- To explore the impact of using these characteristics as eligibility criteria in RCTs

Conclusion

- Data analyses required multiple methodological questions to be addressed ahead of data analyses
- Key results
  - Drivers of effectiveness in antipsychotic drug treatment of SCZ are few
  - Illness duration was evidenced as a driver of effectiveness consistently
  - That excluding patients with a short duration of illness from an RCTs might underestimate drug’s effect estimate
Questions from the audience?