GLOBAL ALIGNMENT ON APPROACHES TO USE OF REAL WORLD EVIDENCE IN DECISION MAKING

Issues Panel
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GLOBAL ALIGNMENT ON APPROACHES TO USE OF REAL WORLD EVIDENCE IN DECISION MAKING

• Dr Nick Crabb, NICE
• Professor Shunichi Fukuhara, Kyoto University
• David Pearce, Takeda
• Rob Thwaites, Takeda (facilitator)

The opinions expressed in this session and on the following slides are solely those of the presenter and not necessarily those of the respective employer. The presenters do not guarantee the accuracy or reliability of the information provided herein.
REAL WORLD EVIDENCE IN EUROPE

NICK CRABB, NICE

• Cancer drugs fund (CDF) in England
• Key messages from the European Innovative Medicines Initiative (IMI) GetReal project
• European Network in HTA (EUnetHTA)
• Proposed European Commission regulation on HTA

EVIDENCE GENERATION (OFTEN RWE) IS A CORE FEATURE OF THE CANCER DRUGS FUND (CDF)

• NICE and NHS England introduced major reforms to the CDF operating model in April 2016
  • CDF has become a "managed access fund" to enable patient access to cancer medicines which appear promising but where NICE indicates that there is insufficient evidence to support a recommendation for routine use
  • All cancer drugs expected to receive a marketing authorisation (MA) are appraised by NICE
  • Draft guidance issued prior to MA and final guidance within 90 days of MA
• NICE recommendation options:
  • Recommended for routine use
  • Not recommended for routine use
  • Recommended for use within the Cancer Drugs Fund
CRITERIA FOR “RECOMMENDED FOR USE WITHIN THE CANCER DRUGS FUND”

- Insufficient evidence of clinical and cost effectiveness to be recommended for routine use
- Plausible potential for satisfying the criteria for routine use
  - Incremental cost effectiveness ratio in the normal £20,000 to £30,000 range (taking account of end of life criteria where appropriate)
- Evaluation within a pre-determined time period (normally up to 24 months) to address uncertainty in outcomes impacting clinical and cost effectiveness is feasible
- **Company agrees to fund the collection of a pre-determined data set**
- Commercial access arrangement (typically confidential) agreed between company and NHS England that is affordable within the Cancer Drugs Fund budget

PRACTICAL ARRANGEMENTS FOR PRODUCTS IN THE CANCER DRUGS FUND

- Arrangements for data collection exercise agreed between company, NHS England and NICE (often includes RWE from the Public Health England Systemic Anti-Cancer Therapy (SACT) data base)
- Duration product is to remain in the Fund determined (normally up to 24 months)
- Data collection monitored and interim review of data collected undertaken
- At end of data collection period NICE undertakes a review of its original recommendation through a short Technology Appraisal process with two decision options:
  - Recommended for routine use
  - Not recommended for routine use
CASE STUDY – BRENTUXIMAB VEDOTIN FOR CD30+ HODGKIN’S LYMPHOMA

- Recommended for use within the Cancer Drugs Fund in June 2017 (TA 446)
- Main uncertainty impacting clinical and cost effectiveness was the transplant rate after treatment (treatment is a bridge to transplant)

- **Retrospective analysis of patients treated via the CDF undertaken by Public Health England (treatment starting April 2013-April 2016) based on a survey**

- Public Health England report included in committee papers on NICE website https://www.nice.org.uk/guidance/ta524/documents/committee-papers
- NICE reappraisal completed in June 2018 and final guidance published (TA524)
IMI GET-REAL IS A MAJOR DRIVER OF RWE BEST PRACTICE IN EUROPE

• Policy recommendations from the GetReal project (2013-2016):

  1) **Integrity, quality, access** and **privacy** protection of RWD sources
  2) Guidance on RWE study **design**, evidence **synthesis** and **interpretation** in decision making
  4) RWE **training** and **education**
  5) Broader **involvement** of stakeholders in RWE generation and use of RWD
  6) Emphasis on **a joint scientific advice** process (regulatory/HTA/ payer)
  7) Construction of a RWE **forum** and **linking** with ongoing initiatives

The new IMI GetReal Initiative

- Research community
- Think tank
- Task forces
- Tools (NMA, pragmatic trials, methods, RWE Navigator)
- Education and training
- Dissemination (webinar, conferences, publications)

Continue to drive international consensus and use of RWE in decision making

A self-funding entity that will:

Continue to provide the tools that are required to deliver high quality RWE

Continue to provide the education and training required to generate and use RWE
EUNETHTA SUPPORTS SCIENTIFIC AND TECHNICAL COOPERATION IN HTA ACROSS EUROPE

• The European Network for Health technology Assessment (EUnetHTA) is a collaboration with 81 partners from 29 countries

• The current Joint Action 3 project includes work packages on:
  • Joint production of relative effectiveness reports
  • Life cycle approach to improve evidence generation
  • Quality management, scientific guidance and tools
  • National implementation and impact

• RWE activities include:
  • Multi-agency pilots for collaborative evidence generation post-launch
  • Quality Standards tool for registers used to inform HTA

THE PROPOSED EC REGULATION ON HTA, IF ADOPTED, WILL DRIVE CONVERGENCE IN HTA METHODS AND STANDARDS

• The European Commission has published a proposed regulation for HTA that if approved will support cooperation across Europe

• Proposals include:
  • Production of clinical assessments
  • Scientific Advice
  • Methods and Tools
  • Evidence generation to support HTA
REAL-WORLD EVIDENCE IN JAPAN

WHY IS EVIDENCE FROM OBSERVATIONAL STUDIES NOT ACCEPTED BY THE CLINICAL COMMUNITY?

SHUNICHI FUKUHARA, KYOTO UNIVERSITY

WHAT I WILL DISCUSS:

1. How RCT results can mislead clinical practice and harm patients
2. How RWE can improve medical care and policy in Japan
3. How to build confidence in the usefulness of evidence from observational studies (in the context of evolving value-generation efforts)
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<table>
<thead>
<tr>
<th>Setting</th>
<th>RCTs</th>
<th>Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Strict inclusion &amp; exclusion criteria</td>
<td>Some flexibility in inclusion &amp; exclusion May include “all” patients</td>
</tr>
<tr>
<td>Number of Exposures/Comparisons</td>
<td>One or two</td>
<td>Many can be studied. Comparisons are possible</td>
</tr>
<tr>
<td>Adherence</td>
<td>Usually measurable</td>
<td>Difficult to measure</td>
</tr>
<tr>
<td>Confounding</td>
<td>Can withstand both measured and unmeasured confounding</td>
<td>Can withstand confounding by measured confounders only</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Can be defined by the researcher Evaluations can be “blinded.”</td>
<td>Routinely collected data on endpoints Evaluations may not be “blinded.”</td>
</tr>
<tr>
<td>Rare outcomes</td>
<td>Very expensive</td>
<td>Feasible</td>
</tr>
</tbody>
</table>

Sorensen, Lash, & Rothman, 2006
From Division of Cardiology
University of Michigan, CVRF
Netherlands, France

PREScriptions FOR SPIRONOLACTONE

DEATH DUE TO?


**RCT** (RALES): 65 y.o. vs. Real world: 78 y.o.
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DIALYSIS OUTCOMES AND PRACTICE PATTERNS STUDY (DOPPS)

Randomly selected sites stratified by unit type and region

- Japan (63 facilities)
- Europe (140 facilities)
- Australia & New Zealand (20 facilities)
- Canada & US (120 facilities)
DOPPS CHANGED MODIFIABLE PRACTICE PATTERNS AND POLICY

1. Dialysate: endotoxin concentration
2. Diagnosis and treatment of depression
3. Pre-dialysis care by nephrologists
4. Vascular access - practice changing
5. Dialysis time - changed reimbursement

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Can the Learning Health Care System Be Educated With Observational Data?

Figure: Comparison of Propensity Score Analyses and RCT Results From 3 Recent Empirical Assessments

Scatter plots of results from empirical comparisons of propensity score analyses (y-axis) and corresponding randomized clinical trial (RCT) (x-axis). Markers denote comparisons between observational and randomized study estimates for the same research question. Similar populations, interventions, and outcomes; statistically significant differences (P < 0.05) are shown in orange. The dotted lines indicate lack of effect in RCTs (vertical lines) and observational studies (horizontal lines). Values lower than 1 indicate that the new treatment evaluated in the trial was more effective than the more established treatment; observational study results are expressed in the same way as the corresponding trial results. Markers in the top-right and bottom-left quadrants in each panel indicate agreement between randomized and observational results with respect to the direction of effects. Markers in the top-left and bottom-right quadrants indicate discordant direction of effects between designs. Black dashed diagonal lines indicate the line of identity (perfect agreement) between RCT and observational study results, gray dashed lines demarcate observational study relative risks that are between 0.67 and 1.5 times those produced by the corresponding RCT results. The term “relative risk” is used to denote risk, odds, or hazard ratio estimates, as reported in the 2 empirical analyses contributing data to this figure.

Why Most Published Research Findings Are False

Probability of results from observational studies being true

< .2 !
SKEPTICISM OF RESULTS FROM OBSERVATIONAL STUDIES

• Probability of study result being true depends on pre-test probability (Ioannidis)
• Testing multiple hypotheses

• Unmeasured confounding!
  • Confounding by indication = Confounding by treatment selection
  • Physicians’ and facilities’ preferences
  • Unmeasurable factors (e.g. gestalt)

OVERCOMING SKEPTICISM, BUILDING CONFIDENCE

• Pre-registering observational studies, and publishing each study’s protocol

• Design
  • complete enumeration: RWE

• Analysis
  • Propensity-score matching is not ideal.
  • Other quasi-experimental designs are better. (instrumental-variable methods, etc.)
Thank you for your attention!

Contact below for requesting my slides.

GLOBAL RWE FOR DECISIONS IN COUNTRIES IN ASIA PACIFIC

DAVE PEARCE, TAKEDA

- Generalisability
- Diversity of healthcare and payer systems
- Acceptance, capability to communicate and interpret RWE
- Some ideas to address; Takeda examples
GENERALISABILITY

- Availability of treatments
  - E.g. Current treatment of Multiple Myeloma in EU versus China

- Treatment paradigms
  - E.g. Use of autologous stem cell transplant (ASCT) in treatment of Hodgkin’s Lymphoma

- Cost structures
  - Delivery of care via primary/secondary care; funding via national/regional; unit costs in countries; funding flows and incentives

- HRQoL issues
  - EQ-5D reporting and tariffs

DIVERSITY OF HEALTHCARE AND PAYER SYSTEMS

- APAC countries represent huge diversity
  - GDP/capita
  - Cost
  - Mortality outcomes (e.g. Breast Cancer)

- Payers AND regulators may have interest in RWE

- Reimbursement evolution
  - Developing/out of pocket markets, mixed markets, reimbursed markets
ACCEPTANCE, CAPABILITY TO COMMUNICATE AND INTERPRET RWE

- Requires significant Infrastructure to collect data
  - Some good examples - Japan Medical Information Database Network, South Korea HiRA database

- Current requirements around evidence differ

- No formal requirements of APAC countries to consider RWE, however Singapore (ACE) mentions supplementary to RCTs

- Pharmaceutical companies’ capabilities to communicate need, appropriateness and results of RWE are limited

- Healthcare systems’ and payers’ ability to utilise RWE

- Custodial concerns over data, requires guidelines

- Mistrust between public and private sectors

SOME IDEAS TO ADDRESS; TAKEDA EXAMPLES

- EXPLORER study – IBD in Emerging markets
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