External challenges for the acceptance of RWE

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Conflicts of Interest

I am a permanent employee of Merck KGaA

The views and opinions expressed in the following PowerPoint slides are my personal view and should not be attributed to my company.
RWE derived from RWD
Not a new concept, but more and more used!

Adapted from IMI Get-Real3

Evidence required

- Development
  - Trial design
  - Understanding standard of care
  - Unmet need / disease burden

- Growth phase
  - Post marketing commitments (safety etc.)
  - Adherence
  - Utilization / prescribing patterns
  - Effectiveness

- Mature phase
  - Head to head comparative effectiveness
  - Differentiation in sub-populations
  - Target populations
  - Usage
  - Difference
  - Effects of switching on outcomes
  - Differentiate with or vs. protected galenics

Past

Now
RWD & RWE
And more and more under the focus of decision-makers
Definition

External challenges for acceptance of RWE

Survey among 20 leading bio-pharmaceutical companies on receptivity to RWE generated by Pharma Industry, both internally and by healthcare stakeholders (Deloitte 2018)

- 60% lack access to necessary external data
- Lack of trust and collaboration between key stakeholders

Definition

External challenges for acceptance of RWE

Acceptance...
by regulators, HTA bodies, payers, any decision-makers...
including physicians and patients

Internal
Linked to study design
(Observational studies)

External
Data access and/or availability
Data quality
Generalisability of the study results
Inconsistent results
Transparency
Openness to RWE
Challenge 1

Data access and/or availability ... to industry

1. Access to RWD
   And clear lack of governance

2. Lack of sustainability
   Especially critical for long-term outcome studies
Challenge 1
Data access and/or availability ... to industry

3 Data infrastructure
• Significant challenges in sharing RWD across countries linked to differences in structure, setup and content of different data sources
• No or poor standards for collaboration, lack of incentives for data sharing

4 Patient consent, privacy and data security
Balancing public and privacy interests
• Advancing society’s understanding of medical treatments through evaluation and research thanks to rich patient-level data
• Protecting individuals’ privacy, which is necessary to safeguard against improper use of personal information
Feasibility of re-consent
• for primary data, opportunities for re-contact with the patient, but difficult and likely high drop-out
• for secondary data, even more challenging as no open lines of communication with the patient
=> Streamlining consent for use of patients data for future potential research that has been approved via appropriate processes (e.g., ethics board), with an opt out option at any point

May severely hamper access to data and can result in high costs for data protection in order to comply with relevant regulation (e.g., adherence with privacy laws, such as the EU General Data Protection Regulation)
Challenge 2
Data quality

**Data reliability** (data accuracy and data consistency)

- Data must be collected and maintained in a way that provides an appropriate level of reliability (e.g., diagnostic precision, lab results within the limits of biological plausibility...)
- Data must be suitable to address specific regulatory question of interest (relevant outcomes captured across populations, robust data on covariates)
- Data must be consistent for each patient within related data fields and over time
- Provenance of each datapoint must be clear, traceable, and auditable

Data quality should be systematically measured – validated within predetermined frameworks and against benchmarks (e.g., SEER)
Challenge 2

Data quality

Completeness requires predefined rules for abstraction of structured and unstructured data, data harmonisation, and quality monitoring... but are the data measured but not available or not captured during routine care?

& needs to be benchmarked to appropriate gold standards (e.g., National Death Index for date of death)

RWD reflects daily clinical decisions

Reliable RWE needs to be **recent and timely**

Details about the timepoint that the data analysis represents must be reported

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Data integrity refers to maintaining and assuring accuracy and consistency of collected data, especially after data processing and transformation. Includes data source and intention, fidelity (e.g. a female is coded as a female), completeness (i.e. absence of missing data), plausibility (i.e. the data is believable), and cohort construction and linkage.

=> Ensuring data point validity by validating algorithms that identify the study population accurately, validating the approaches to derive data points if not directly recorded in the data...
<table>
<thead>
<tr>
<th>Data Quality Component</th>
<th>Definition</th>
<th>Proposed indicators of quality</th>
<th>Quality Solutions to facilitate data quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consistency</strong></td>
<td>Uniformity of the data overtime (e.g. lab data routinely entered)</td>
<td>Number of fields changed over time</td>
<td>Manual checks at centres level, audits</td>
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<td></td>
<td></td>
<td>% of fields missing over time</td>
<td>Standard terminology, coding</td>
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<td></td>
<td>% of forms reported per scheduled follow-up</td>
<td>Standard operating procedures, user guides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Change in value of data filed by x% creates alerts</td>
<td>Campaigns, dashboards for clinicians</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>Uniformity of the data overtime (e.g. lab data routinely entered)</td>
<td>Variability across fields</td>
<td>Validate against source data (e.g., 10%), cross form validation</td>
</tr>
<tr>
<td></td>
<td>Accuracy of data entry: no errors, no contradictions or impossibilities in data, absence of duplicates</td>
<td></td>
<td>Staff training, software checks.</td>
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<td>Help screens/desks, training, newsletter</td>
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<td></td>
<td>Funding for data managers</td>
</tr>
<tr>
<td><strong>Completeness</strong></td>
<td>How much data is missing?</td>
<td>Agreed % of fields completed in audit procedures (e.g. &gt;90%)</td>
<td>Audits</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lost to follow up %</td>
<td>Mandatory fields</td>
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<tr>
<td></td>
<td></td>
<td>Minimum agreed core common data elements reported</td>
<td>Engagement with patients and/or health care providers (HCPs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All treated patients reported, not selected patients only</td>
<td>Agreed list of data elements and definitions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross check patient numbers with numbers of products used at treating centres during a defined period</td>
<td></td>
</tr>
</tbody>
</table>
Challenge 2
Data quality

Possibility to “qualify” the data sources to further assure quality of RWD

Thanks to one global & independent accreditation body?

This report provides a final agreed Context of Use describing where ECFSPR is deemed by CHMP as an appropriate data source for post-authorisation studies to support regulatory decision making on medicines for the treatment of cystic fibrosis, together with CHMP’s response to the questions posed by the Consortium.
Challenge 2
Data quality

Current draft version

• 8 “methodological” items related to the suitability of the registry for a specific purpose
  – Type of registries, objectives and research question, geographical and organisation setting, duration, data providers, size, inclusion and exclusion criteria, follow-up

• 13 “essential” standards relevant to any registry for regulatory and HTA purposes
  – Covering governance aspects, data and information, legal and ethical issues

• 3 additional requirements for specific purposes

Gimenez E, Valentic M, Espallargues M, Rodriguez J, m Varela L, Guzina I, Patrick H, Long J. The registry evaluation and quality standards tool (REQueST) for health technology assessment from an outcome assessment perspective. ISPOR Europe Annual Meeting 10-14 November Barcelona - Spain
Challenge 2
Data quality

Is the data set fit-for-purpose on these dimensions of data quality and relevancy for a potential decision within the context of a specific disease or therapeutic area?
Challenge 3
Generalisability of the study results

1. Broad range of patients which can translate into better generalisability

2. Representiveness
   Is the used data source representative of the wider patient population?

3. Transferability
   Can results of a study in one country be easily transferable to other countries?
Challenge 3
Generalisability of the study results

Representativeness may be essential for opinion polls, but is not a reasonable aim for a scientific study

When Doll and Hill studied the mortality of male British physicians in relation to their smoking habits, their findings about smoking and health were considered broadly applicable despite the fact that their study population was unrepresentative of the general population of tobacco users with regard to sex, race, ethnicity, social class, nationality and many other variables

“It is not representativeness of the study subjects that enhances the generalization, it is knowledge of specific conditions and an understanding of mechanism that makes for a proper generalisation”
Challenge 3

Generalisability of the study results

Differences in clinical practices between and within countries/regions, leading to wide heterogeneity in RWD and limitation in the interoperability between different datasets

Minimum requirements for data input and collection to ensure high-quality data and interoperability where possible using existing standards or guidance that are applied in clinical practice

From “Framework for FDA’s Real-World Evidence Program - Jacqueline Corrigan-Curay, J.D., M.D. Director, Office of Medical Policy / CDER FDA
Given the plethora of data sources and analytical approaches, differences in RWE study results are inevitable!

**Competing sources of RWD**
- Verifying the analyses by using different methods in the same datasets (sensitivity analysis) or the same method in different datasets

**With insufficient technical expertise** (or time or willingness?) to conduct a critical comparison of the methodological aspects of each study, no predictability of results interpretation for the Industry and the average decision maker is likely to ignore RWE*

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Challenge 5
Transparency

About study methodology data source selection analyses

Pre-specification of protocol and SAP
Avoid deviations from pre-specified study design **BUT** allow some flexibility linked to unexpected findings that require additional exploration (unanticipated changes clearly documented in study reports or in protocol or SAP amendments)

**Code lists, algorithms, associated logs, and analytical data files shared** to facilitate study reproducibility

Internal policies on RWD studies with clear **mandate for posting** study protocol on an appropriate forum and **commitment for publication** of study results regardless of the outcome
Challenge 6
Openness to RWE

Still limited expertise

- Need core capabilities to critically assess the method, the analysis and do the interpretation

Lack of agreement between different parties

- Regarding what data are needed, for what purpose, at which point in time, and when enough is enough to be persuasive

Lack of trust and collaboration between key stakeholders

- For all the above-cited external challenges & lack of randomization leading to potential uncertainty & bias in RWD studies, and resulting impact on the study’s findings
Important to engage with all stakeholders (regulators, HTA bodies, payers, caregivers, clinicians, clinical administrators, patients, industry) when designing, conducting, and disseminating RWD studies.