Regulatory Perspective on Real World Evidence (RWE) in scientific advice

EMA Human Scientific Committees’ Working Parties with Patients’ and Consumers’ Organisations (PCWP) and Healthcare Professionals’ Organisations (HCPWP)

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Overview

RWE for regulators, guidance in context of pre and post licensing evidence generation

Examples in Scientific Advice (SA), Marketing Authorisation (MA)

Cooperation in the chain of decision making to market access

Conclusions

*Excluded specific focus on patient reported outcomes, digital or wearables*
Regulators’ expectations

Primary concern: benefit risk assessment throughout product lifecycle

For scientific question on safety/efficacy – right study - high quality timely data and methods (control of chance, bias and confounding)

- RWD - data on health interventions collected outside highly-controlled Randomised Controlled Trials
- Primary research data collected on how interventions are used in routine clinical practice
- Secondary research data derived from routinely collected data for other purposes
- Includes pragmatic randomised controlled trials
Role of RWE for regulators

Primarily to address important questions that we cannot answer in standard RCTs or to better understand single arm data when RCTs are not/less feasible.

Recognise that today that there are important questions that we do not answer prior to first approval and cannot be addressed through RCTs

To facilitate a strengthened life-cycle approach

Not about lowering regulatory standards at marketing authorisation

Not to replace RCT
Regulatory guidances

Scientific guidance on Post-Authorisation Efficacy Studies **PAES**

- Categories of uncertainties, roles for studies
- Distinguish data source (1º, 2º) from study design (RCT & NonRCT)
  - e.g. Registries can allow variety of observational study design options
- Data quality crucial. Measures include common terminologies, quality control and standards, Limitations acknowledged

Other guidance; PASS, pregnancy, ATMP
Potential for RWE contribution?

Purpose of studies

Pre-MAA studies
- Pre-authorisation safety
- Pre-authorisation efficacy/effectiveness
- Historical controls
- Natural history

Post-MAA studies
- Post-authorisation safety
- Post-authorisation efficacy/effectiveness

Infrequent RWE proposals in SA
Regulatory experience- scientific advice (SA) on RWE

Pre licensing evidence generation efficacy –

• Applicant propose use of external controls
  – SAWP strongly prefers underpowered RCT for very rare conditions;
  – Relevance and quality of the control data, analysis?

• Collection of natural history data
  – Endorsed, esp for endpoint and biomarker development

Supplementing Pre-authorisation safety with Non EU registry data
  – Considered as supportive data for the EU MAA

Regulatory experience- scientific advice (SA) on RWE

**Post authorisation evidence generation in effectiveness**

Various examples endorsed: pragmatic trial in an oncology setting, a randomised controlled trial supplemented with external controls, cohort studies.

Sources; comprised primary data collection, registries, claims database, access program

Challenges- bias, eligibility of participants, outcome definition, safety for participants, and extrapolation to the EU
Regulatory experience in SA

Post authorisation evidence generation in safety

• Several examples e.g Rare condition, imposed registry for Post Authorisation Safety Study (PASS) - Post MAA discussion including PRAC. HTA as observers

Overall RWE is part of evidence generation package, complementary in nature
Post-authorisation efficacy study (PAES): In order to evaluate the long term efficacy and safety of nusinersen in symptomatic patients with spinal muscular atrophy, the MAH should conduct and submit the results of the Phase 3, open-label extension study (SHINE, CS11).

Post-authorisation efficacy study (PAES): In order to evaluate the long term efficacy and safety of nusinersen in pre-symptomatic patients with spinal muscular atrophy, the MAH should conduct and submit the results of the Phase 2, open-label study (NURTURE (SM201)).

August 2023 submission of results
<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA US Neuromuscular Disease Registry</td>
<td>Prospective longitudinal study inc patient demographics, SMN copy numbers, motor milestones, vital status, surgical history, hospitalisations, medications, nutrition, respiratory function and devices, and cause of death</td>
</tr>
<tr>
<td>International SMA Consortium (ISMAC) natural history study</td>
<td>natural history - 3 regional centres (UK, IT, Nemours) inc baseline characteristics, longitudinal treatment patterns, motor function, respiratory function, hospitalisations, comorbidities</td>
</tr>
<tr>
<td>TREAT-NMD Alliance registries</td>
<td>natural history to expand current registries to include nusinersen treatment information</td>
</tr>
</tbody>
</table>

**Address safety profile in patients with low or higher SMN2 copy number and/or different disease severity from clinical trials**
Spectrum of Post-Authorisation Studies (PAS)

- **12 Specific Obligations:**
  - All Orphans except 1 pandemic
  - Usually ongoing interventional comparative efficacy studies, also PASS

- **6 PAES:**
  - All Delegated act all ongoing, 1 Biomarker

- **3 Annex II PASS**
  - All Registries,
  - 5 Category 3 PASS
    - 3 ongoing studies

- **3 Recommendations**
  - 2 Biomarkers, 1 interventional efficacy

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Volt-girolt 02 to 10/16 Advisory group on classification of post-authorisation studies (PASS)
Conditional Marketing Authorisation 10 year EMA report

**Figure 22.** Status of the imposed studies at the time of CHMP opinion (N=77)

- 16: New study
- 32: Ongoing
- 29: Ongoing (some results in MAA)

**Figure 26.** Study designs of imposed studies (N=77)

- Multiple arm
  - Randomisation not specified: 5
  - Randomised: 40
  - Not randomised: 4

- Single arm
  - Not randomised: 28

Spectrum of study objectives, study designs and status
Regulatory experience at Marketing Authorisation - Registries


• Issues: Delayed completion, Delayed start, Slow accrual, Low data quality or missing data, Disease registries preferred

Data on Annex II & required registries;

• 53% of 73 registries primary for safety issues, 10% safety outcome & real-world effectiveness; Products 2007 and 2010

Pharmacoepidemiol Drug Saf, doi: 10.1002/pds.4196

Gaps in workability of registries
Studies with safety and effectiveness
Review PASS protocol 2012 to 2015

189 PASS; involved primary data capture (58%).

Majority no comparator (65%)

• 35% assessed clinical effectiveness endpoints.
• Patient reported outcome (PRO) in 14%

• “Protocol content review . . . related to methodological issues and feasibility concerns should raise awareness among PASS stakeholders to design more thoughtful studies according to pharmacoepidemiological principles and existing guidelines”


See also F1000Research 2017, 6 :1447 (doi: 10.12688/f1000research.12198.2)
Toolbox for cooperation in planning evidence generation

Opportunities for parallel consultations involving other stakeholders in planning Evidence Generation

Parallel consultation—product specific

(Parallel) qualification advice / opinion—not product specific

• Qualification Advice (Confidential) on future protocols and methods for further method development towards qualification, Letter of support possible

Patient representatives are invited
Toolbox for collaboration

- Qualification Opinion (publicly available) acceptability of a specific method (e.g. use of a biomarker) in drug development based on assessment of submitted data; Public consultation
  - Registry - kinds of regulatory studies that could be conducted
  - Subsequent protocol interaction with regulators still preferred
- Public workshop - potentially wider face to face inputs, complementary to Committee assessment procedures as above
Toolbox for collaboration

Qualification of novel methodologies for medicine development in parallel with Health Technology Assessment Bodies:

• First parallel review completed for the European Cystic Fibrosis Society Patient Registry (ECFSPR).

• Public consultation closed 9 April 2018

Qualification opinion - The European Cystic Fibrosis Society Patient Registry (ECFSPR)
Other tools relevant to collaboration

Learning Healthcare systems, EMA registries initiative

Big data- mapping of, possible usability of, and future needs to use

- Recent workshops/meetings:
  - A Common Data Model for Europe? 11-12 December 2017
  - Observational Data in Benefits and Risks of Drugs 1st Dec 2017
  - Multiple strands
Regulatory use of RWE: Conclusions

- Real world evidence can form part of evidence lifecycle
- Existing regulatory guidance - strengths, limitations, current role RWE
- RWE complements Pivotal RCT data for licensing dossier - remaining uncertainties; greater role in post licensing
- Gap workability of RWE studies; scope - improvement quality /timeliness/methods
- To progress - need RWE discussions on specific proposals
- Encourage discussions including other decision makers and representatives
Thank you for your attention

Further information

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