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SCIENCE MEDICINES HEALTH

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)

Presented by Jane Moseley on 17 April 2018

Senior Scientific Officer – Scientific Advice Office

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

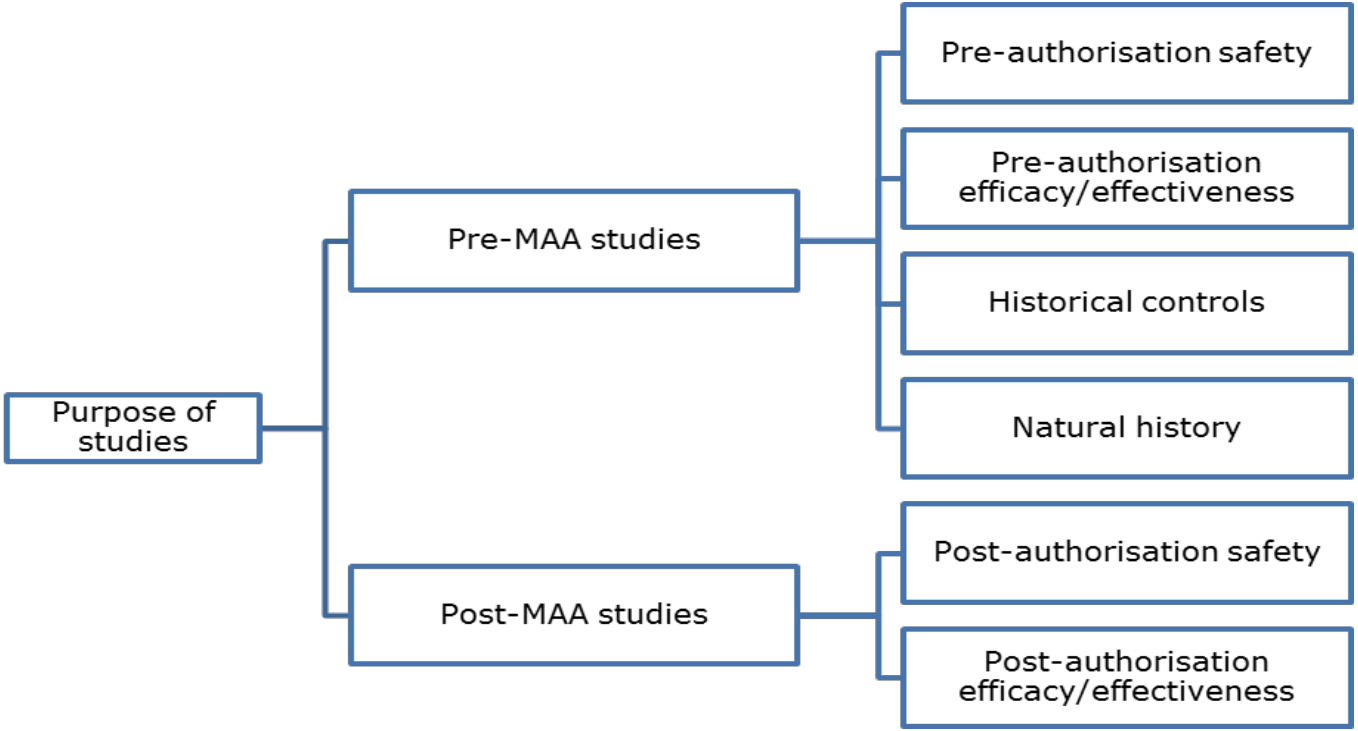
Regulatory guidances

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?



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 v 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

RWE at MAA eg Spinraza Imposed PAES

Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy

Description
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

MAA eg Spinraza required PASS

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Study	Objectives
MDA US Neuromuscular Disease Registry	Prospective longitudinal ..inc patient demographics, SMN copy numbers, motor milestones, vital status, surgical history, hospitalisations, medications other comorbidities, nutritional thera function and devices, and cause of d
International SMA Consortium (ISMAC) natural history study	natural history - 3 regional centres (baseline characteristics, longitudinal treatment patterns, motor function, respiratory function, hospitalisations, comorbidities
TREAT-NMD Alliance registries	natural history to expand current registries to include nusinersen treatment information

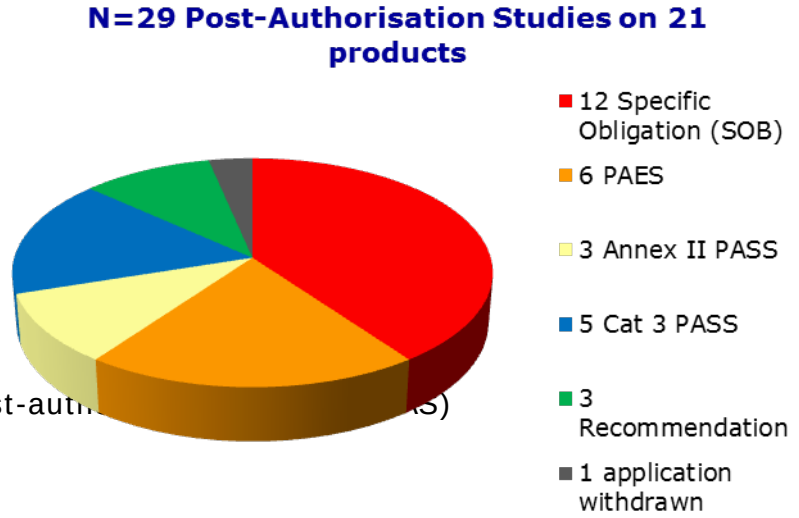
Example - happening but better collaboration needed

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

Volt-girolt 02 to 10/16 Advisory group on classification of post-auth [illegible] S)



Conditional Marketing Authorisation 10 year EMA report

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

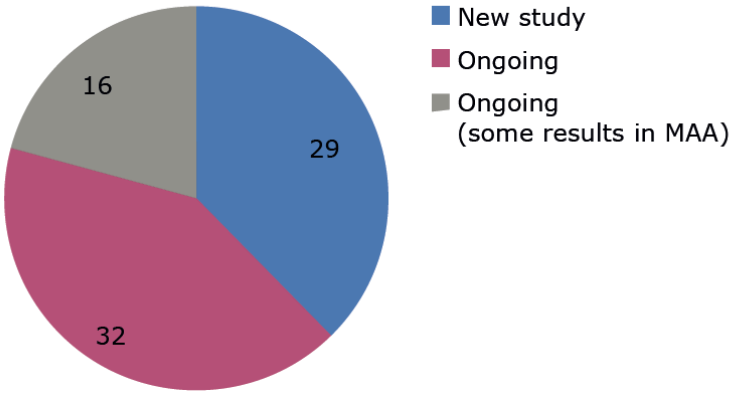
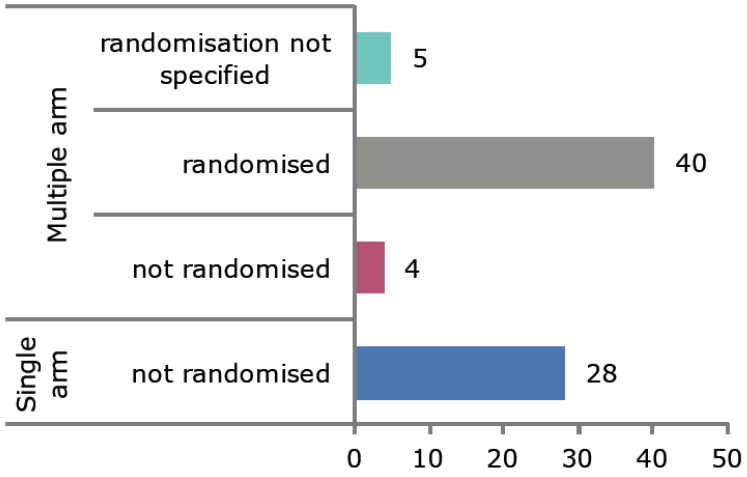


Figure 26. Study designs of imposed studies (N=77



Spectrum of study objectives, studiy designs and status

Regulatory experience at Marketing Authorisation - Registries

Registries as a condition of the EU marketing authorisation (Annex II), 2005–2013.

•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

Pharmacoepidemiol Drug Saf. 2017 Oct 6. doi: 10.1002/pds.4332.

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"

Br J Clin Pharmacol. 2017 Apr;83(4):884-893.

See also *F1000Research* 2017, **6** :1447 (doi: 10.12688/

Studies with safety and effectiveness
Methodology issues

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

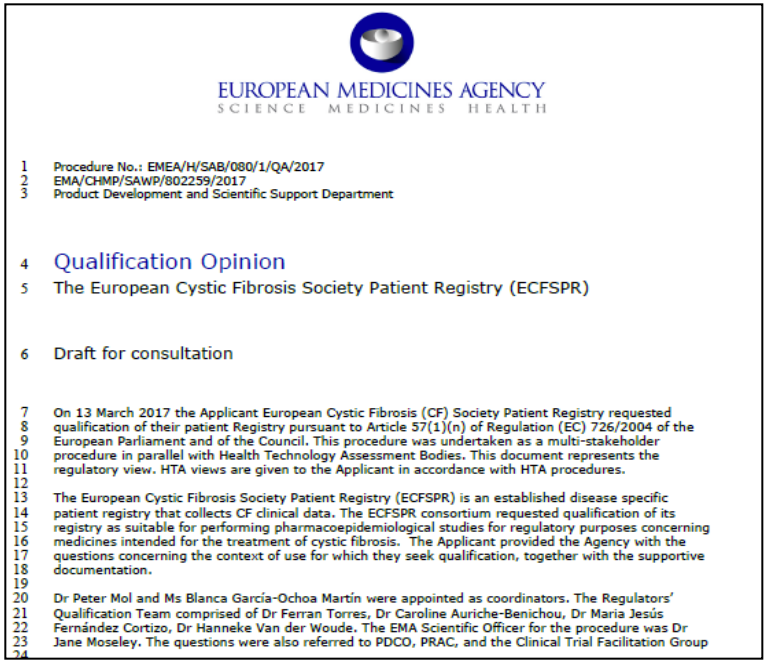
- Qualification Opinion (publicly available) acceptability of a specific method (e.g. use of a biomarker) in drug development based on assessment of submitted data; Public consultation
  - Registry - kinds of regulatory studies that could be conducted
  - Subsequent protocol interaction with regulators 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)]



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Procedure No.: EMEA/H/SAB/080/1/QA/2017
EMA/CHMP/SAWP/802259/2017
Product Development and Scientific Support Department

Qualification Opinion

The European Cystic Fibrosis Society Patient Registry (ECFSPR)

Draft for consultation

On 13 March 2017 the Applicant European Cystic Fibrosis (CF) Society Patient Registry requested qualification of their patient Registry pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council. This procedure was undertaken as a multi-stakeholder procedure in parallel with Health Technology Assessment Bodies. This document represents the regulatory view. HTA views are given to the Applicant in accordance with HTA procedures.

The European Cystic Fibrosis Society Patient Registry (ECFSPR) is an established disease specific patient registry that collects CF clinical data. The ECFSPR consortium requested qualification of its registry as suitable for performing pharmacoepidemiological studies for regulatory purposes concerning medicines intended for the treatment of cystic fibrosis. The Applicant provided the Agency with the questions concerning the context of use for which they seek qualification, together with the supportive documentation.

Dr Peter Mol and Ms Blanca García-Ochoa Martín were appointed as coordinators. The Regulators' Qualification Team comprised of Dr Ferran Torres, Dr Caroline Auriche-Benichou, Dr Maria Jesús Fernández Cortizo, Dr Hanneke Van der Woude. The EMA Scientific Officer for the procedure was Dr Jane Moseley. The questions were also referred to PDCO, PRAC, and the Clinical Trial Facilitation Group

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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