Federal Institute
for Drugs
and Medical Devices

The regulatory view:

Patient-, Observer- and Clinician-reported outcomes (PROs, ObsROs, ClinROs) – key elements of patient centred medicines development

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The views expressed in this presentation are primarily those of the author and do not represent those of the BfArM or EMA/CHMP

Content

1. Introduction:
   a) What is a PRO (and ObsRO, ClinRO)?

   b) What for do we need PROs?

   c) What is needed before a PRO (etc) can be „qualified“

2. Regulatory experience with the qualification of PROs (ObsROs, PhROs).
   – Evaluation of EMA regulatory output of QoNM procedures of PROs (etc) 2013-2018

3. Conclusions

Introduction – What is a PRO/ObsRO/PhRO?

Definitions

- PRO: A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.
    - can include signs and symptoms, as well as impacts and implications or combinations of these

- ObsRO: A measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health professional
    - Cannot include impact/implications (QoL assessement questionable)
    - Usually reported by parent, caregiver when patients are unable to report themselves

- PhysicianRO: A measurement based on a report of observable signs, events or behaviors related to a patient's health condition by the treating physician

- In the following (as will be seen later), the main focus will be on PROs/ObsROs

Why do we need PROs (etc)?

What for and when do we need PROs (ObsROs, PhROs)

- PRO(M)s (etc.) in the regulatory context:

  - The focus on PROs (etc.) in the regulatory context is different from other contexts:

  - PROs (etc) are meant to provide reliable information on the change of the overall condition(s) of patients by a pharmacological treatment in the context of a clinical trial and hence treatment benefit on individual and population level

  - The relevance and importance of PROs (etc.) for evaluation of treatment benefit is dependent on the underlying disease, and the obectives of a clinical trial:
    - Functional diseases vs. life-threatening diseases
    - Disease modification vs. symptomatic treatment

  - This relationship as well as the stringency of the validation relevantly determine the proposed context of use statement with regard to „positioning“ (= primary, secondary, or exploratory endpoint)

What do we need for the qualificationof PROs (ObsROs, PhROs)?

What is needed before a PRO/ObsRO can be „qualified“

- The process called „validation“
  - Validation is usually divided into at least 2 important steps:
    - Content validation:
      - Concept elicitation
        - Evaluation of literature
        - Input from experts
        - Patient centered interviews
      - Cognitive debriefing
        - Patient understanding, refinement, correction, „early psychometrics“
    - Psychometric validation
        - Use in oberservational and randomised treatment trials
        - Evaluation of consistency, test-re-test validity, construct validity discriminant validity, responsiveness, determination of MCID.

Evaluation of PRO (etc.) related regulatory output

PROs, ObsROs, PerfOs

Analysis of the regulatory output (Advice Letters or Opinions) of EMA Qualification Procedures finalised between January 2013 and December 2018

Silva M, Moseley J, Vetter T, Regnstrom J, Tome M, Aarum S, Cerreta F, Schabel E: Patient-reported, observer-reported and performance outcomes in qualification procedures at the European Medicines Agency (EMA) 2013-2018. Experience and learnings from qualification procedures Submitted for publication

Methodology:

- Analysis of the "regulatory output" (advice letters, letters of support, or qualification opinion)
- Identification of procedures via key word search from EMA's document repository (DREAM)
- Evaluation by data collection form:
  - Frequencies (procedure based, application based, and tool based datasets)
  - Characteristics
  - (type of) instruments
  - questions of applicants
  - level of agreement (full, partial and no agreement)
  - Acceptance of tools

The analysis has a slightly different focus with analysing „Performance Outcomes" (instead of „Physician Reported Outcomes") – Focus is therefore also on the PRO/ObsRO part!

Conclusions/Questions/Points for discussion:

- Since even for developments with high level agreement relevant refinements are considered necessary, qualification advice appears to be a useful tool, both for applicant as well as for regulators
- External communication in the form of LoS and Qualification opinions are useful tools for transparency and guidance to developpers (and regulators)
- The need for a(n) (overarching) regulatory guidance remains to be clarified
- The impact of qualification advice on the success and quality of PROs/ObsROs and PhROs (and PerfOs), their use in development of medicinal products, and on MAA remains unknown

Thank you very much for your attention!

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