Why COAs

(Clinical Outcome Assessments) are important criteria in the evaluation of dossiers by health authorities (EMA, FDA, HAS, EFSA)

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Dedicated to eCOA & Patient Engagement

Clinical Outcomes Assessment (COA) criteria include[1]:

1/ Patient-Reported Outcomes (PRO)

2/ Clinician-Reported Outcomes (ClinRO)

3/ Observer-Reported Outcomes (e.g. patients or non-clinical caregivers) (ObsRO)

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Diverse elements have combined in recent years to make Clinical Outcome Assessments (COAs), and particularly Patient Reported Outcomes (PROs), important criteria for various health authorities in the evaluation of new therapeutic strategies.

Why is this and what are the consequences for evaluation of new drugs in clinical development programs?
When should COA endpoints be considered for inclusion in a new drug development program?

1. Because in chronic pathologies, the expected therapeutic benefits can vary

Over recent years, in the context of comorbidities and an ageing population there has been an evolution in therapeutic objectives. Effective treatments are available for many pathologies, and so new therapeutic approaches focus more on improving symptoms, function, and health-related quality of life (HRQL) rather than the provision of cures per se or the prolongation of life-expectancy. A wide range of Phase III clinical studies are increasingly designed to demonstrate non-inferiority of efficacy compared to a pre-existing standard

of care rather than aiming to demonstrate a less likely conclusion of superiority based on an endpoint of mortality or morbidity. As well as demonstrating non-inferiority of efficacy to a standard of care, it is increasingly important to demonstrate improvements in other important criteria such as symptoms, tolerability, side-effects, compliance, acceptability, and quality of life.

2. Because for most pathologies COAs can have a role as clinical study endpoints

The following pathologies and situations can be considered separately:

- Symptomatic pathologies for which the main criteria can only be measured by the patient him- or herself (e.g. irritable bowel syndrome [IBS] or erectile dysfunction). In these situations, the main study criteria would be evaluated using a PRO questionnaire. Historically in clinical studies, symptoms (e.g. the intensity of pain) have been evaluated by the Investigator to avoid subjectivity associated with patient evaluation. However, Investigator subjectivity can be equally problematic.
- Pathologies for which there are no strict objectives/endpoints, or alternatively for which there are numerous markers such as symptoms or PROs (e.g. pain and functional disability [osteoarthiritis], pain [migraine], IBS, or vertigo).
- Pathologies for which the principal assessment criteria are Clinician-Reported Outcomes [ClinRO] (e.g. questionnaire used for the assessment of severity in psoriasis or the Rankin score for neurological assessments).
- Pathologies for which a COA criterion is part of a composite score (e.g. ACR in rheumatoid arthritis) or a co-primary endpoint (e.g. assessment of dyspnea in COPD which can be assessed in conjunction with lung function [FEV_1]).

- Situations in which it is necessary to demonstrate that improved survival (usually of a matter of weeks) associated with a new drug is not at the expense of quality of life (e.g. cancer, heart failure, diabetes). The comparison of the length of survival versus the quality of survival is a clear EMA request [2].
- All other pathologies for which, in the absence of an improved survival, there is an improvement in symptoms, functional state, or day-to-day life (e.g. rheumatoid arthritis, Parkinson's disease, Alzheimer's disease).

In summary, COA criteria are important in most chronic pathologies.

Why is PRO important in the development of a new drug?

(e.g. IBS, a multi-symptomatic functional bowel disorder with no "objective" marker)

- PRO (pain & bowel function scales) is the primary endpoint in IBS trials
- Secondary/tertiary PRO endpoints provide additional supportive evidence to the clinical benefits (e.g. other gastro-intestinal symptoms, HRQL)
- PRO is used to highlight an unmet medical need in IBS e.g. by using SF-36 at baseline
- PRO captures the disutility of IBS, e.g. by using EQ 5D
- PRO captures loss of work productivity induced by IBS

In a highly competitive market place, PRO endpoints may support product differentiation and ease market access.

3. Because COA endpoints provide information that is not captured by other endpoints

COA endpoints allow a wider understanding of patients' experience of a new therapy.

- Studies have repeatedly shown a poor correlation between so-called "objective" endpoints and PROs in various conditions. This prevents the assessment of an improvement in a symptom or quality of life from an objective endpoint alone (e.g. an assessment of day-to-day activity at home in angina pectoris based simply on a hospital exercise test [3]; an assessment of breathing problems using the Breathing Problems Questionnaire [BPQ] in COPD based simply on arterial oxygen saturation [4]; an assessment of the quality of life in adolescent diabetic patients using the Diabetes Quality of Life for Youths questionnaire [DQOLY] based simply on glycemic control [5]).
- Similarly, different COA approaches may measure different aspects and so the correlation between them may not be optimal. For example, clinicians (ClinRO) tend to underestimate the severity of pain in IBS compared to patient assessment (PRO) [6]. Additionally, clinicians do not necessarily correctly estimate their patients' quality of life, e.g. in COPD [7]. Although clinicians can generally evaluate their patients' physical capacities with reasonable accuracy, the clinician's assessment of patients' social and emotional state is less accurate. In pediatrics, there may be differences in assessments made by mothers and fathers of their dependants, i.e. a difference based on the perspective of the observer (ObsRO), e.g. mothers generally better estimate the physical functioning of a dependent adolescent with cystic fibrosis than fathers [8].
- As would be expected, there is often a correlation between endpoints that measure different aspects of the patient's experience, but not sufficiently to infer, e.g., the HRQL of IBS patients based on their pain severity score alone [6].

These examples demonstrate the importance of using COA questionnaires that measure specific aspects for evaluation in a particular clinical trial.

4. Because of the rigorous way in which COA criteria are developed

The methods for the development, validation, and local adaptation of COA questionnaires are rigorous (more so than for numerous more established criteria) and covered by FDA guidance [9] and by ISPOR [10,11]. This methodology combines qualitative and quantitative research techniques [12,13]. A large range of specific questionnaires that cover almost all pathologies are available and validated in numerous languages.

5. Because the quality of COA data in clinical studies has improved

Historically, quality of life data obtained in clinical studies have not been of good quality, which has led to a persistent lack of confidence in these data by health authorities, especially for licensing and reimbursement decisions. Today, the data obtained using COA questionnaires in clinical studies are more rigorous and allow health authorities to consider them with more confidence when evaluating new therapeutic products [14].

6. Because health authorities have integrated COA data in their evaluation of therapeutic products

- **Marketing authorization authorities.** FDA started to consider the role of PRO data in the evaluation of drugs in 1999, resulting in a guidance document that was published in 2009 [9]. In parallel, the EMA began the same process in 2003, resulting in the publication of a Reflection Paper on Health-Related Quality of Life in 2006 [15]. Additionally, several EMA guidelines for specific pathologies include COA as a primary or secondary evaluation criteria. The guideline for the development of psoriasis drugs clearly describes the benefit of measuring patient perception even for mild cases of psoriasis [16]: "Efficacy of a new drug evaluated by the patient is important when … even relatively limited extent of skin psoriasis may severely socially and psychologically disable the patient". More recently, the guideline for the clinical investigation of medicinal products in the treatment of COPD includes patient- and investigator-reported outcomes as efficacy endpoints (after lung function and disease exacerbation): "Disease-specific questionnaires, dyspnoea and symptom scales are considered relevant outcomes for the characterisation of response to treatment" [17].

- **Health Technology Assessment authorities.** More recently, the European network of Health Technology Assessment (HTA) agencies (EunetHTA) has published a series of guidelines [18] which state that there are 3 types of clinical endpoints that are important for the assessment of relative effectiveness, i.e. mortality, morbidity, and HRQL, thus acknowledging the importance of PRO in the context of the reimbursement of health products.

- **Finally, the European Food Safety Authority (EFSA)** has also clearly acknowledged the value of PRO for substantiating a health claim of gastrointestinal improvement, e.g. with probiotics: "reducing gastro-intestinal discomfort is considered an indicator of improved gastro-intestinal function" [19,20].

7. Because of patient empowerment

As patient empowerment increases, health authorities increasingly include patients and consumer organizations as committee members, e.g. the FDA Benefit-Risk Framework Patient Focused Drug Development (PFDD) initiative ("Patients are uniquely positioned to inform FDA's understanding of the disease impacts and current treatment options") [21] or the EMA pilot project to involve patients in assessing the benefit-risk of medicines during marketing authorization evaluation [22].

Increasingly, drugs are marketed and/or reimbursed based primarily or partially on COA data. Although positive COA data may allow improved claims and differentiation from competitors, sponsors must also be aware that regulators may also use these data (if negative) to refuse a marketing authorization, e.g. as was the case for erlotinib in pancreatic cancer: "The benefit on patients" survival seen in the study was very limited and it did not outweigh the risk associated with the combination of erlotinib and gemcitabine, given the side effects of the treatment. The study did not show any improvement in the quality of life of the patients treated [23]. Thus, ultimately the decision to integrate COA endpoints in a new drug development program needs strong justification, hypothesis, and rigor, with full consideration of the Target Drug Profile.

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