1. *Title, all authors, author affiliations*

Towards More Efficient Methods for Clinical Outcomes Assessment (COA) Instrument Selection in Clinical Trials

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1. *Methodological Question being addressed*

A large number of initiatives are being conducted under different approaches to improve efficiency of clinical trials in CNS disorders. A conceptual frame is needed to organize existing initiatives and to provide a global landscape.

2. *Abstract content should be formatted into sections as outlined in the Guidelines, with word count up to 500 exclusive of title, authors, affiliations.*

Objective To innovate on Clinical Outcomes Assessment (COAs) endpoint and instrument selection by introducing the concept of *efficacy-based selection*. With this objective, as a first step, a theoretical framework for existing initiatives is presented.

Rationale There is an urgent need in CNS to improve the efficiency of clinical trials. The selection of COAs endpoints and instruments for randomized clinical trials (RCTs) has been increasingly gaining the attention of many public and private institutions, i.e. companies, scientific organizations, and regulatory agencies (RAs) e.g., FDA and EMA). Health outcomes measurement in RCTs is an area of high interaction between several disciplines and different stakeholders. RAs are the main drivers for the final COAs endpoint and instrument selection, which guide the clinical endpoints required to claim a New Drug Application (NDA), followed by field experts on the therapeutic area. However, the definition of COAs provided by RAs is often not specific enough. Therefore, the disease-specific guidance issued is open to discussion, and consequently COA instrument selection requires a more interdisciplinary methodology.

Design We review and describe the **strategies** used by different **stakeholders** for COA selection. As for selection **strategies** we define the use of (a) RA guidance, (b) Results from Published Meta-Analysis, (c) Literature reviews, (d) Libraries of COAs, (e) Libraries of Instruments (f) Authors of the specific instruments (g) Key Opinion Leaders for specific diseases (h) New COAs validation set for specific drug development plans (i) Initiatives to systematize the selection as decision tools i.e. Checklists for COAs selection and for COAs instrument selection. The use of an *efficacy-based selection* approach within existing COA selection strategies is reviewed.

Results Different examples for each above specified strategies and stakeholders' categories were identified based on specific searches on public databases and authors' experience in the field. Examples of identified strategies are systematic reviews (e.g., COMET initiative), checklists for PRO selection (COSMIN, EMPRO) or even PRO dimensional approach (PROMIS, ICHOM). Furthermore, other strategies exist coming from alliances (pharma, academia, patients, public health bodies, etc.) promoting COA identification, selection and validation, as is the case of some

IMI Initiatives, NIMH – RDoC*, Specific Funding actions (Foundations, University Chairs, etc.), Working Groups within Scientific Societies (e.g., ECNP, ISCTM, etc.).

Conclusion The number of trial failures in the neurosciences makes COAs and COA instrument selection especially critical. A review of the state of the art regarding all initiatives to improve COA and COA selection process is presented. Overall innovative approaches on endpoint selection will require an approach focused on *efficacy based COA selection* requiring pre-competitive actions in order to: (i) Confirm the psychometric features of COAs completed in clinical trials (global and by country-language), (ii) Explore potential derived composite scores as clinical surrogates or endpoints, (iii) Confirm efficiency of COAs used in past trials at global and by country-language level, (iv) explore feasibility of Core Outcome Set (COS) specific for indications, based on qualitative and as well as quantitative methods.

Initiatives do exist in EU and USA but there is a need to describe the *state-of-the-art*, to set a framework for all this activity and to highlight the weaknesses and strengths of the existing ones, ideally available to drug developers, and end users i.e. clinical trial designers and scientists. Within the existing initiatives a more *efficacy-based approach* for COAs needs to be explored.

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