Towards More Efficient Clinical Outcome Assessment (COA) Selection Methods to Accelerate New Innovative Drug Development in Epilepsy

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Methodological Question Being Addressed:

How can the current landscape for selecting clinical outcome assessments/measurements (COAs/COMs) be improved in epilepsy clinical trials (CTs)?

Introduction:

Challenges for new antiepileptic drug (AEDs) development include better efficacy-safety profiles, drug-resistant seizures, disease modifying treatments, comorbidities, among others. Selection of health outcomes measurement instruments in randomized AED CTs is an area of high interaction between several disciplines and different stakeholders. There are several initiatives to improve the efficiency of CTs for new AEDs, including optimization of COAs tools selection and COMs development. Efforts are needed to make existing and new initiatives easily accessible to drug developers.

Our goals are: (1) to identify the ***stakeholders*** dealing with COAs in AED CTs, (2) to describe existing sources available to support AED COAs selection, (3) to describe the most innovative currently used ***strategies*** for COAs/COMs selection, and (4) to propose new innovative COAs developments applicable to future study designs based on efficiencies rather than legacy.

Methods:

Published literature and public resources[1,2] were used to identify stakeholders dealing with COAs/COMs selection. Public CT databases were searched using keywords *epilepsy, seizures,* and *phase 2-3*. Core outcome set (COS) public databases were searched using the term *epilepsy*. All elements found were organized within a pre-defined framework[3]. Strategies for COAs/COMs selection were identified, and suggestions for future research were described.

Results:

Of the 400 CTs retrieved, 166 (42%) were in phase 2, and 266 (67%) included only children highlighting that this area includes a significantly vulnerable population.

Main drivers for *clinical endpoints* selection for CTs of new AEDs were provided by regulatory authorities' (FDA and EMA) guidance documents. Other guidance documents (e.g., League Against Epilepsy, NIH, NINDS) issued as complementary to clarify study samples and other features of

clinical research. CT designs included a variety of COAs (>52)/COMs (>27 PROs). Strategies to select COAs/COMs included clinician-researcher advisory groups conducting surveys or using full COS protocols. We identified 11 COS projects from different groups focusing on different epilepsy-related disorders and on a variety of patient populations - four projects addressing adults, three childhood epilepsy (e.g., CHOICE and CORE-KDT), two in pregnant women (e.g., E-CORE), and intervention types. Review papers also comment on unmet needs and innovative CT designs for future AED development.

Conclusion:

Existing stakeholders in the field are clearly identified and COS/COMs legacy is also well described. There is consistency with the innovation needs mentioned across review papers in this field. AED CTs constitute a big challenge with several new avenues for future development. In this way, review papers highlight several unmet needs and foresee innovative approaches by which CTs will be selected to address the needs in the field:

- COAs selection more focused on RDoC dimensions (i.e., based on drug molecular targets and its measurement in behavior, cognition and mood)
- Consensus-based decision making of COAs in which stakeholders seek to reach agreement on COAs based on efficiencies rather than opinions
- Use of comorbidities (e.g., cognitive/executive function COAs) to enrich study samples

Also, to develop and implement solutions to mitigate or close existing as well as expected gaps:

- Seizure underreporting requiring automatic seizure counting
- New endpoints focused on cognitive changes (PerfRO) and self-regulation (i.e. executive function as PRO/ProxyRO) for efficacy and safety
- Validation of remote assessments of different endpoints (patients functional, mood, cognitive monitoring)
- QoL instruments based on innovative methods and standardization of reporting of outcomes

References:

1. www.clinicaltrials.gov (30-12.19)
2. http://www.comet-initiative.org/
3. https://isctm.org/14th-annual-meeting-posters/ Zaragoza Domingo S and Bishop K.