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Use of Standard Methodology for Novel Outcomes in Clinical Trials: Advantages for New Therapeutics in Neurosciences

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Abstract

This invited commentary provides a summary of recently published recommendations on outcomes selection when designing clinical trials for new therapeutics in psychiatry and neurology. The authors, a recently convened independent and interdisciplinary group of experts, highlight the relevance of harmonizing research practices, either by private or public researchers, in order to increase the likelihood of successfully identifying effective and safe treatments in psychiatric or neurologic conditions. This represents the first attempt to provide guidance to the field that aims to improve the efficiency of clinical research and the likelihood of demonstrating efficacy and safety for new compounds.

Keywords: Therapeutics • Psychiatry • Neurology • Treatments

Introduction

Neurosciences-high percentage of negative trials

Advances in understanding the neurobiological factors associated with neurologic and psychiatric conditions have yet to be adequately translated into successful treatments. In the neurosciences field, a high percentage of clinical trials fail to support efficacy and safety claims for new drugs, resulting in a lower innovation index when compared to other disciplines. Development of new treatments or repositioning old compounds for new applications, requires being innovative in regard to outcomes and measurement tools. Eventually, health outcomes will serve as the cornerstone supporting the efficacy and safety of novel interventions [1].

The science of clinical outcomes is not only relevant to private drug industries and biotechs, but also to clinical researchers aiming to test their own therapeutic strategies, reposition compounds for new indications or highlight additional beneficial properties of a specific treatment in a condition.

The recent paper "Methods for neuroscience drug development: Guidance on standardization of the process for defining clinical outcome strategies in clinical trials" co-authored by 22 experts proposes and advocates for the adoption of a standard methodology for selecting outcomes when designing clinical trials. This collaborative work is developed through consensus and is useful to researchers striving to innovate in new therapies for psychiatric or neurologic conditions [2].

Description

Promoting good practices in outcomes research

Legacy instruments in current use for clinical trials are familiar to clinicians and accepted by regulatory bodies. However, it is now understood that they present limited utility for demonstrating efficacy in certain contexts of use and/or exhibit uncertain sensitivity to capture change in specific disease dimensions particularly when assessing innovative pharmacological mechanisms of action [3].

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Therefore, there is agreement that innovative drug study designs urgently require additional efforts and research on novel outcomes and endpoints to address existing gaps in legacy outcome measures. Additionally, there is a need to promote initiatives aimed at comprehensively identifying and defining core the Core Outcomes Sets (COSs), *i.e.*, a minimal set of outcomes to be included in clinical trials for specific conditions. This could serve as a benchmark for future research in the field.

This recent publication serves a dual purpose, firstly introduce to the readers the consensus-based guidance document for clinical outcomes research as detailed elsewhere and secondly, give special attention to the impacts on drug development and marketing either streamlining the process, or using by inertia specific default legacy instruments with recognized weaknesses [4].

The main goal of the COAs and ECNP COAs groups, is to provide methodological guidance that is currently lacking in the neuroscience research field, and which is in line with current FDA guidelines for Patient-Focused Drug Development (FDA-PFDD).

Based on expert opinions, there is agreement that increasing awareness about adhering good research practices may enhance the likelihood of successfully demonstrating efficacy and safety of new interventions, or at least this would help mitigate potential concerns regarding measurement methods in the event of negative results.

It is worth mentioning that the concept of success related to novel therapies is multiple *i.e.*, not only refers to demonstrating efficacy/ safety in clinical trials in agreement with regulatory agencies, but also having the capacity to obtain final approval and later on, get acceptance by payers as Health Technology Assessment agencies (HTAs) [5].

Investigator-sponsored trials (e.g., those initiated by researchers or clinicians) offer a unic context for innovation but can also carry significant risk, as typically there is just one opportunity to demonstrate to industrial partners the value of the new intervention, compelling them to continue investing in its development following a positive outcome. Thus, it is critical that good practices be followed.

Establishing good practices in outcomes research starts with a more accurate description of the disease, encompassing not only the clinician's perspective but also that of the patient and their environment. Based on qualitative research, one can reach an adequate disease definition and build a disease concept model including symptoms/signs and its impact in life. This process may unveil new facets of the disease and therefore require the inclusion of additional concepts to measure. The imperative now is to listen to patients within their own environments to learn more about the disorder and how patients feel, functions and survive. The same principle applies for technological endpoints based on sensors or digital health technologies when intended to be used in clinical trials; validity rationally starts from health concepts of interest to be measured. Some interesting examples of concept models can be found in the neurology field but rarely in psychiatric conditions (which opens opportunities for qualitative research) [6].

Despite the comments above, existing measurement instruments, known as legacy clinical outcomes measurement, predominately rely on clinical evaluations (ClinROs) by clinicians to assess patients to rate symptoms and their severity. It is also common practice in clinical trials, to transfer instruments already validated in one specific therapeutic field to clinical trials for other therapeutic indications. This practice, invites the problem of face or content validity, exemplifying one of the many issues stemming from current practices when designing clinical trials. During internal meetings held within the group, other pitfalls were also discussed [7].

To address these issues, the proposed standard process outlines 7 fundamental steps starting, as previously mentioned, from a thorough description of how the disease impacts the patient and the therapeutic background (Step 1), concluding with future research actions as a final summary of all necessary the processes required to progress in the therapeutic field (Step 7).

The seven steps proposed are outlined as follows, with potential the main issues when these steps are not implemented as summarized in the following way:

Describe the disease impact model and therapeutic background: Omission of this step entails the risk of "missing" relevant information about the disease, impact on patient and families.

Define the scope of use for the COS/outcomes: If not done, there is the risk of distorting the final application of the study results in several ways e.g., such as outcomes intended for clinical practice may not be appropiate for clinical trials.

Decide stakeholder involvement: If not comprehensive enough, the absence of key stakeholders (clinicians, patients, carers, practitioners, policy makers, payers, etc.), can significantly impact the final generalizability approval/authorization, reimbursement or even drug access to country markets.

Determine "What to measure" in terms of domains or concepts of interest for efficacy and safety: If this research is inaccurate, it can impact the specificity regarding the health domains ultimately measured. Therefore, relevant domains can be missed, including perhaps even the most important outcomes.

Determine "How to measure" the outcomes including validation principles: If the outcome measurement instruments are not adequately selected, there is a risk of using instruments that do not capture the outcome domains, are insufficiently sensitive to detect clinical response or using instruments that fail to meet all technical or regulatory requirements.

Make final generic recommendations for optimal COS measurement: This step aims to address the risk of repeating past errors. When previous lessons learned are not heeded there may be a lack of clarity regarding the rationale behind the selection process or eventually the progress in the field can be delayed.

Conclusion

If this step is skipped, there is a risk of producing insufficient evidence to support the use of the endpoints, missing information necessary to progress in terms of innovation regarding outcomes/endpoints and failing to translate its benefits for patients.

It is clear that this process requires effort and resources, and for that reason the guidance document sets also the minimal and key activities that can be conducted to achieve each step.

Within the group discussion, several programs were reviewed and put forth as examples of learned lessons, that can be found as supplementary information to the published paper.

Given the effort and time required in such activities, it is also advisable to start pre-competitive initiatives allowing researchers and private partners to start from step 1 and move up to the final validation of new tools to be used in the field in early-phase trials. Joint efforts of this type are currently ongoing, for instance the Cognitive Impairment in Schizophrenia (NIH-MATRICS) or a variety of examples from the critical path (C-Path), where the MCOA is an example of public-private collaborations that accelerate drug development, among other consortia.

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