LETTER TO THE EDITOR

Patient-prioritized primary endpoints in clinical trials

In the 1940s the randomized controlled trial (RCT) ushered a new era of clinical research and has been a cornerstone in the improvement of treatments [1]. Since then we have to a large extent only applied single or un-weighted composite endpoints as outcome measures. Increasing demands for involvement of patients in design of research – not least from funding institutions and regulatory authorities – may markedly change future designs of clinical trials. Currently less than 1% of trials engage patients actively and meaningfully [2]. We may approach new challenges demanding a more holistic assessment with patient-prioritized endpoints, e.g. quality of life, side effects, costs, follow-up burden etc. to be integrated in primary endpoints.

Current approach

Selection of a meaningful endpoint that adequately assesses the effect of the intervention is a key component of clinical trials. The primary endpoint determines the efficacy of the intervention – but has a number of pitfalls. First, design and interpretation of current clinical research mainly focus on hard endpoints. This may downplay side-effects in the safety section without any "endpoint weight", and soft endpoints may be published in papers with less impact on guidelines (Figure 1). This method may be prone to the streetlight effect; one should not make important what can be easily measured, but measure what is important. Ideally, the endpoint should include all important events induced by the treatment including endpoints that may be more important to patients, but perhaps more complicated to measure. Second, a composite endpoint is a common approach, however individual entities in the composite endpoint are generally analysed un-weighted without patient prioritization [3,4]. Major adverse cardiac events (MACE) are commonly used unweighted in cardiovascular research. But would a patient really compare a debilitating stroke with permanent aphasia with a transient ischemic attack as 1:1? [5] Third, the current approach for choice of primary endpoint may be considered paternalistic as the clinical researcher may assign the endpoint without the patient’s input. If the patient is the raison d’être of the clinical research the choice of endpoint should follow the question we are trying to address – for the patient.

Initiatives for patient involvement

To encompass what we believe are pitfalls requires a shift in research culture towards "research being carried out ‘with’ or

![Figure 1. Clinical trial primary endpoint in a common currently applied approach compared to a novel likely patient-prioritized endpoint approach. MACE: Major adverse cardiovascular events Death might count differently in a patient aged 38 years as compared to the 82 years old patient – i.e. an age-adjusted weight might be relevant.]
Development of patient-prioritized endpoints

One proposal to embed patient-prioritized endpoints might be to list all potential benefits, side effects, safety concerns, costs, difficulties of administration, necessary follow-up regimens etc. and let a group of “target” patients prioritize and weight the potential outcomes. This might yield a weighted composite endpoint with potentially positive and negative components that matter to the patients. Sufficient guidance in the process and presentation of options must be provided and challenges to address include logistical issues and tokenism [7]. Homogenizing endpoints to ease comparison of studies is important to acknowledge, although we believe that the concept of patient-prioritized endpoints can comprehend this over time through a common approach [8]. The goal is to integrate patient’s preferences in the trial design with the clinical trialist [7,9]. This proposal may be an initial step for patients, patient organizations, funding parties and politicians together with the medical societies to re-think how to compose endpoints that more accurately reflect what patients prioritizes and are willing “to pay” for.

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