Development of outcome criteria to measure effectiveness of antiepileptic therapy in children

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ABSTRACT

Purpose: Clinical trials of antiepileptic drugs frequently measure outcomes of seizure control, which demonstrate efficacy. Yet, functional status, quality of life, and long-term treatment effects reflecting effectiveness are scarcely assessed. We sought to use a consensus method to help identify which outcome criteria key stakeholders consider should be used to measure effectiveness in trials of antiepileptic treatments for children.
Method: A two-round Delphi survey was used; parents of children with epilepsy and local, international experts comprising academics and clinicians participated in the survey. In the first round, 32 experts, 50 parents, and 15 children with epilepsy aged >13 years suggested outcomes that they considered important in determining effectiveness of antiepileptic therapy in children, separately for preschool and school age.
In the second round, 29 experts and 42 parents scored the importance of outcomes from the list suggested by at least 10% of round 1 respondents and also proposed five most important outcomes.
Results: Complete seizure freedom (67%), seizure frequency (48%), ability to perform normal day-to-day activities (45%), and quality of life (40%) were identified as the most important outcomes of antiepileptic therapy in children of both age groups. Additionally, effect on developmental milestones (47%) and child's compliance to treatment regimen (39%) were identified as most important in preschool age group and school performance (49%); adverse effects (39%) were identified as most important in school age group.
Conclusion: For the first time, this study has identified outcome priorities regarding antiepileptic treatment in children based on the key stakeholders' perspectives. It could be used as a provisional list of outcomes for inclusion in a core outcome set for children with epilepsy.

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1. Introduction

Rational approach to drug therapy is based on a comparative assessment of the effect of individual pharmacological treatments on overall clinical outcome. Such an assessment can be made meaningfully, only when adequate clinical trials have been conducted using not only rigorous study design, but also clinically relevant outcomes. Currently, there is no general consensus on which outcomes should be reported in clinical trials for most clinical areas including epilepsy [1]. This results in difficulty to evaluate clinical trials in systematic reviews [2–6].

Antiepileptic drugs (AEDs) are a group of drugs with variable efficacy and effectiveness. Interpreting the results of AED trials is challenging [7–9] when there is variability in the outcome domains that are reported in each trial. Seizure activity (seizure frequency, severity, time to n[th] seizure, total seizure days), remission (seizure-free days, seizure freedom rate, time to 6-month remission), compliance (time to exit, retention rate, discontinuation rate, retention time), and quality of life are some of the outcome domains that have been reported in AED trials [7–11]. Clinical trials of AEDs seemingly differ not only in the outcome domains, but also on how these domains are operationalized. International League Against Epilepsy's (ILAE) Commission on Outcome Measurement in Epilepsy (COME) based mainly on expert opinions have published recommendations regarding the outcomes that should be measured in epilepsy trials [12,13]. A recent study based on the perceptions of adult patients with epilepsy and their caregivers had found similar outcome domains as in COME recommendations along with few new outcome domains [14].

Further, it is not known whether the outcome domains measured by different trials align with what a parent, a child with epilepsy, or the clinician would want to know about when making decisions about the treatment [14]. The variability in outcomes measured between trials

also means that it is hard to compare the strengths and weaknesses of different treatments. Initiatives are taken to develop core outcome sets, which are an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials, in a specific area of healthcare [15]. Core outcome sets have been developed for various clinical conditions such as rheumatoid arthritis, childhood asthma, palliative care, ulcerative colitis, traumatic brain injury, etc. [16–20]. However, there are no core outcome sets available for epilepsy in children [21].

Without a core set of measures, outcome reporting bias is possible, and the yield from scientific investment is restricted as it is hard to synthesize results and complete meta-analysis. Therefore, development of a set of outcome criteria is important for trials. The aim of this study was to develop outcome criteria to measure effectiveness of antiepileptic therapy in children.

2. Methodology

We adopted the methodology described by Sinha et al. [16], with relevant modifications. A two-round Delphi technique was used. Round 1 was to identify a list of potential outcomes that measure the effectiveness of AEDs, and round 2 was to identify which of these outcomes were most important. Outcomes for preschool (<6 years) and school-age (6–18 years) children were considered separately, because different outcomes may have varying relevance at different ages.

Ethical approval for this study was obtained from the ethics review committee of Faculty of Medicine, University of Colombo, Sri Lanka.

2.1. Round 1

Participants for round 1 were parents of children with epilepsy, children with epilepsy aged >13 years, and a group of experts. The group of experts comprised clinicians with experience in treating children with epilepsy (such as pediatricians, pediatric neurologists, neurologists, physicians), clinicians with experience of conducting clinical trials locally (identified from the clinical trials registry of Sri Lanka) and

internationally (identified from International Clinical Trials Registry of World Health Organization), and academics (pharmacologists and clinical pharmacist) attached to the state universities in Sri Lanka and internationally (pediatric clinical pharmacologists/clinical pharmacologists). The study flowchart is shown in Fig. 1.

Children with epilepsy aged 13–18 years seen consecutively at the pediatric or neurology clinics in Batticaloa and Ampara districts were recruited. Clinic record books of these children were checked for presence of any comorbid illnesses (such as cerebral palsy, neurological deficits, etc.). Children with comorbid illnesses were excluded in this study because their parents may have different treatment goals considering the extent and nature of the child's comorbid condition. Children with epilepsy and their parents identified their preferences of outcomes separately. Researcher explained what was meant by the terms "clinical trials" and "outcomes", as these are not commonly used terms among the local population. Informed written consent was obtained before data collection. Pretested questionnaire with open-ended questions was used to identify a list of potential outcomes of effectiveness of AEDs.

The group of experts was invited by e-mail to participate in this study. For those who consented to participate, the questionnaire was sent via e-mail. Further, as recommended by Sinha et al. [2], to minimize attrition, all participants were emphasized verbally and/or in writing about the importance of completing the whole Delphi process.

Each response from experts, parents, and children were interpreted and categorized individually by two reviewers as to which outcome of treatment was being described. The broad framework for categorizing responses as outcomes was based on the following categories: outcomes related to control of epilepsy, long-term functional outcomes, adverse effects, quality of life, long-term physical outcome, disease indices, and compliance to drug therapy. Any disagreements arising from categorization were discussed among four reviewers. Reviewers also discussed about whether the responses that did not fit into the broader categories should constitute a new outcome. Further review of the responses was not considered necessary since interpretation of responses was easier, and agreement became greater as the study progressed. Regardless of the group size, to have equal opportunity to suggest
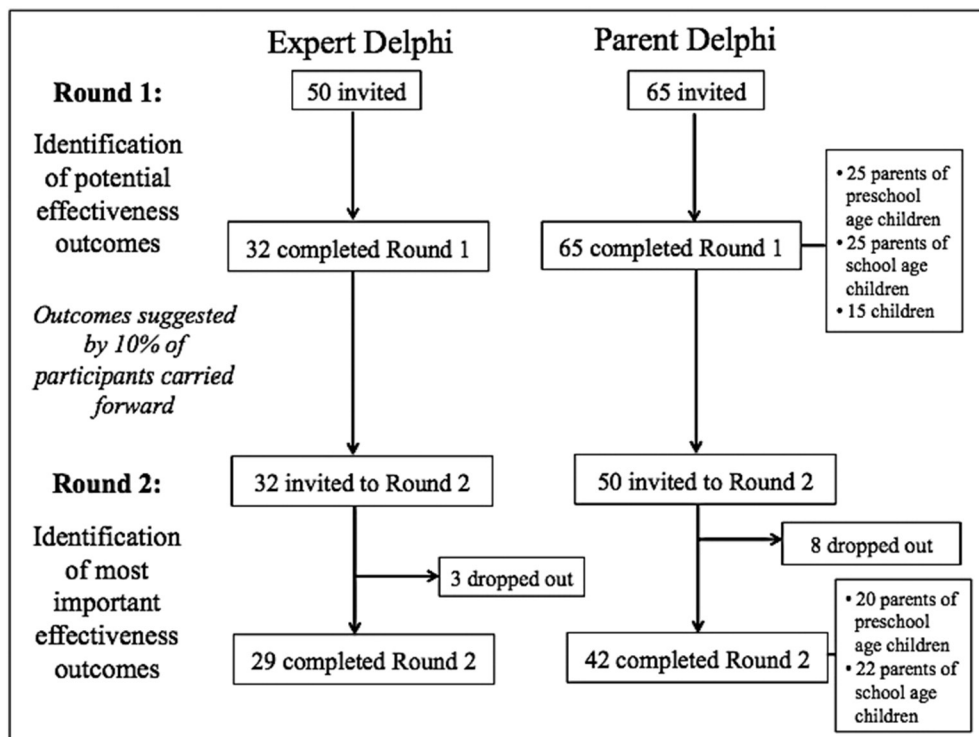

Fig. 1. Study flowchart showing participants in each round of the study.