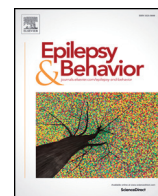


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Brief Communication

Which outcomes should we measure in adult epilepsy trials? The views of people with epilepsy and informal carers

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ABSTRACT

Objective: So that informed treatment decisions can be made, clinical trials need to evaluate treatments against domains that are important to people with epilepsy (PWE), their carers, and clinicians. Health professionals have identified domains of importance to them via the International League Against Epilepsy's Commission on Outcome Measurement (COME). However, patients and carers have not been systematically asked.

Methods: Via the membership of the British Epilepsy Association, we recruited and surveyed 352 PWE and 263 of their informal carers. They were presented with 10 outcome domains (including the 5 identified by COME) and asked to rate their importance using a 9-point Likert scale. They were also asked to identify any additional domains of importance.

Results: The patients' mean age was 49 years, the median number of years since diagnosis was 20, and 65% had experienced seizures in the prior 12 months. Most carers were the spouse or parent. Patients' and carers' mean ratings indicated that their outcome priorities were similar, as were those of patients who had and had not experienced recent seizures. There was consensus among patients that 6 domains were of critical importance. These included the 5 identified by COME (namely, and in order of importance, the effects of the treatment on "Seizure severity", "Seizure frequency", "Quality of life", "Cognitive function", and "Adverse events"), as well as one additional domain ("Independence/need for support"). There was consensus among carers that the 5 COME domains were also critically important. They, however, identified 3 further domains as critically important. These were the effects of the treatment on patient "Depression", "Anxiety", and "Independence/need for support".

Conclusions: Our study found some overlap between the priorities of PWE, carers, and health professionals. They, however, highlight additional areas of importance to patients and carers. Our results could inform a core outcome set for epilepsy that represents the domains that should be reported as a minimum by all trials. This could promote trials which produce meaningful results and consistency in measurement and reporting.

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1. Introduction

A variety of pharmacological and nonpharmacological treatments have been developed to help people with epilepsy (PWE) with the management of seizures and comorbidities. Choosing which treatment to receive can be complex, not least because all treatments have the potential for harm and benefits. The results of randomized controlled trials should be able to help treatment decisions. Unfortunately, interpreting the results of epilepsy trials can be challenging [1,2], and it is unclear whether the information they report is meaningful to patients. Why? This is because there is considerable variability in the aspects of

outcome that trial investigators measure and report and because there has been no systematic effort to ask patients and carers what outcomes are important to them [3–5].

In line with regulatory guidance [6], success within a placebo-controlled antiepileptic drug (AED) trial in people with refractory epilepsy is frequently judged by whether a person experiences a seizure frequency reduction of $\geq 50\%$. This criterion might, though, be arbitrary and not align with patients' preferences. Improving the design of epilepsy trials and increasing the applicability of their evidence to clinical practice have been identified as a priority [1,2,7–10]. Some recommendations have been made concerning which outcomes epilepsy trials should measure [11,12] – the most notable being those of the International League Against Epilepsy's (ILAE) Commission on Outcome Measurement in Epilepsy (COME) [11]. However, these were made on the basis of round table discussions between representatives from some health professions. It has not been established whether the priorities of patients and families regarding outcomes are the same.

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To allow them to make fully informed treatment choices, it is possible that patients and families may want information about a treatment's effect on aspects of outcome beyond seizure frequency. Gilliam [13], for instance, found patient-perceived quality of life was associated with the experience of adverse events and depression, not seizures, while Smith et al. [14] found that improvements in seizure severity helped explain why some patients continued to take lamotrigine, despite experiencing no reduction in seizure frequency. For reasons such as these, some trials have captured information about the effect of a treatment on outcomes beyond seizure frequency. However, many have not.

For other conditions, there have been efforts to form consensus on what aspects of outcome are most important to people affected by that condition and clinicians [15–21]. This is then used to form a 'core outcome set' (COS). Core outcome sets are not extensive lists of outcomes but rather a few particularly important ones that should be reported as a minimum by trials in that condition [22,23]. The existence of a COS does not preclude inclusion of additional relevant outcomes for a given trial.

No COS exists for epilepsy trials [24]. Having one could facilitate trials which produce evidence relevant to stakeholders. It could also help reduce reporting bias and make evidence synthesis easier [25–27]. All but 3 of the 20 most accessed and cited epilepsy Cochrane Reviews in 2014 described problems due to inconsistencies in the outcomes reported by trials [28–38]. It is for reasons such as these that COSs are becoming supported by journal editors and research funders [39,40].

To develop a COS for epilepsy and promote uptake, a momentum for change needs to be established, and research is required. A variety of approaches could be used to develop the COS [41]. These include expert panel meetings and Delphi surveys. Whichever is used, a key part of the exercise should be for evidence to be considered on which outcomes PWE and carers consider most important. There is published evidence on the subjective experience of epilepsy [42,43], but there is none on patients' and carers' priorities for outcomes in trials.

Therefore, to assist with the development of an epilepsy COS, we surveyed a large and diverse sample of PWE and informal carers about the importance they attached to outcome domains that have been recommended for use in trials. We asked patients and carers to also identify additional outcome domains of importance to them and sought to determine whether the priorities of patients and carers differed and whether any differences existed between patients who were continuing to experience seizures and those who were not.

2. Methods

2.1. Participants

Participants were PWE affiliated with the British Epilepsy Association (Epilepsy Action) and their informal carers. All participants were aged ≥ 16 years, and patients needed to report a diagnosis of epilepsy (of any type) for at least one year. People were excluded if they could not provide informed consent or independently complete questionnaires in English.

2.2. Procedure

Data were collected as part of a larger, longitudinal study. The purpose of that study was to examine how similar ratings of patient outcomes made by patients themselves were to those made by their informal carers. As part of that study, patients and carers completed a questionnaire pack that asked them to make ratings of outcomes on a number of measures upon recruitment and then again 12 months later. Of relevance to the current report, the questionnaire pack completed by patients and carers upon recruitment also asked them about the importance they ascribed to different outcome domains in the context of a trial.

With regard to recruitment, the British Epilepsy Association maintains a database of people, including patients, carers, and interested

parties, who are willing to be contacted by the Association. Three thousand eight hundred sixty-six people were randomly selected from this database in 2013, and invitations to participate in the larger study were posted. Attached to the invitation was a questionnaire pack for PWE, as well as a pack for them to pass on to a family member or friend.

The University of Liverpool's Institute of Psychology, Health and Society Research Ethics committee approved the study (1213-LB-093). Informed consent was obtained from all participants.

2.3. Measures

2.3.1. Characteristics

Participants were asked as part of the questionnaire pack to report their demographics and medical history. For patients, this included age at diagnosis, who they considered to be their main epilepsy doctor, and number of different antiepileptic drugs currently prescribed. Thapar et al.'s [43] scale was used to capture the number of seizures (of any type) the patient had experienced in the previous 12 months.

2.3.2. Importance of different outcome domains

Participants were presented with the following instructions which were adapted from COS studies in other fields [16,44]: "New treatments for epilepsy are tested to see how helpful they are. We want to know which things you feel should be looked at and reported on when testing a new treatment. Please tell us how important you feel each of the things below is". Patients and carers were then asked to rate the importance of different domains.

The 10 domains that they were asked to rate included the 5 domains which the ILAE COME suggested [11] – namely, the effects of the treatment on i) "Seizure frequency", ii) "Seizure severity", iii) "Adverse events", iv) "Cognitive function", and v) "Quality of life". On the basis of qualitative evidence concerning the impacts which epilepsy can have from the patient perspective [42], participants were asked to rate the importance of 5 additional domains. These were the effects of the treatment on vi) "Depression", vii) "Anxiety", viii) "Independence/need for support", ix) "Felt stigma", and x) "Economic cost" (in this case, to the health service provider since this study was conducted within the context of publicly funded health service which is free at the point of delivery). The headings given to the different domains within the questionnaire are shown in Table 2.

Respondents were asked to score the importance of each domain using the 9-point Likert scale proposed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) group (<http://www.gradeworkinggroup.org>), in which 1 to 3 signifies an outcome of "Little importance", 4 to 6 as "Important", and 7 to 9 as "Very important". This scoring system has been used in other COS studies to discriminate the importance of different domains [16,45,46]. In order to not overlook other domains of importance to patients and carers, participants were invited to record other aspects of outcome that were important to them.

The questionnaire was piloted to check face validity, understanding, and acceptability.

2.4. Statistics

The primary objective was to identify the importance of the different domains to patients and informal carers. There are no guidelines for the numbers of participants required to develop a COS [47]. However, given the heterogeneity of epilepsy, we followed other COS studies [16] and considered that approximately 300 PWE and 300 carers would be necessary to ensure all relevant groups were sampled adequately.

Descriptive statistics were used to examine participants' characteristics and the importance they ascribed to each outcome domain. For each domain, the mean importance rating given to it by participants is presented, and the domains have been ranked by the proportion of patients and carers that identified them as being "Very important" (score:

7 to 9). Patients' and carers' ratings of importance were analyzed separately to ensure that outcomes important to the two groups could be identified.

Interpreting what rating qualifies an outcome for inclusion in or exclusion from a COS remains debated. We followed Williamson et al.'s [41] suggestion that consensus on whether a domain should be included can be understood to be present when $\geq 70\%$ of participants rate the domain as being "Very important", and $< 15\%$ rated it as of "Little importance" (score: 1 to 3) [16,41,46].

Independent samples t-tests compared the mean importance scores provided by patients and those provided by carers for each domain, as well as the mean importance scores given to the domains by patients who had experienced a seizure in the prior year to those given by patients who had not. When comparing patients' and carers' scores, differences were calculated by subtracting the carers' mean ratings from those of the patients. When comparing the ratings of patients by seizure status, the scores of those with ongoing seizures were subtracted from the scores of those who had not experienced seizures. Mean differences, along with 95% confidence intervals (CIs), are reported.

Where free-text responses were provided by participants regarding additional domains, these were extracted by AN, grouped where possible, and reported using broad headings.

All analyses are based on actual response data; no responses were imputed. Analyses were performed using SPSS 22.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Participants

From the 3866 invitations sent, 352 PWE agreed to participate in the study and returned a completed questionnaire, as did 263 informal carers. Of the remaining invitations, 180 were returned as the person no longer resided at the address, 14 recipients responded to say that they were not eligible, 4 PWE actively declined to participate, and 36 resulted in incomplete questionnaires being returned. No responses were received for the remaining 3283 (84.9%) invitations.

The characteristics of the participants are shown in Table 1. With respect to patients, the mean age was 49.1 years (standard deviation [SD]: 15.7), and 63.6% were female. The median time since diagnosis was 20.0 years (interquartile range [IQR]: 8–37), most (65.2%) had experienced a seizure (of some type) within the prior 12 months, and 60% reported at least one comorbidity. In terms of the carers, their mean age was slightly older at 56.02 years (SD: 14.4), and most were female (60.8%). Most were either a spouse/partner to the patient (53.2%) or a parent (30.4%).

3.2. Importance of different outcome domains

Eight of the domains were given a mean importance rating of ≥ 7 by both patients and carers — indicating that these domains were typically rated as being "Very important" from their perspective (Table 2). The only two domains not to receive such a high average importance rating were "Felt stigma" and "Economic cost".

When applying Williamson et al.'s [41] criteria, consensus on the importance of a domain was present for 6 of the 10 domains from the patients' perspective and for 8 of the domains from the carers' perspective. For patients, these domains were "Seizure severity" (89.5%), "Seizure frequency" (87.5%), "Quality of life" (85.8%), "Cognitive function" (84.4%), "Adverse events" (84.1%), and "Independence/need for support" (73.9%). For carers, the domains were "Quality of life" (91.6%), "Adverse events" (89.0%), "Seizure frequency" (89.0%), "Seizure severity" (86.7%), "Cognitive function" (85.2%), "Depression" (80.2%), "Anxiety" (75.7%), and finally, "Independence/need for support" (75.3%).

Table 1
Participants' characteristics.

	Patients (N = 352)	Carers (N = 263)
Age		
Mean (SD)	49.1 (15.7)	56.02 (14.40)
Range	16–94	16–92
Sex (n/%)		
Female	224 (63.6)	160 (60.8)
Ethnicity (n/%)		
White British	342 (97.2)	255 (97.0)
Other	10 (2.8)	8 (3.0)
Highest educational attainment (n/%)		
Basic school certificate or lower	200 (56.8)	153 (58.2)
Advanced school certificate or higher	152 (43.2)	110 (41.8)
Employment (n/%)		
Employed (full/part-time)	127 (36.1)	137 (52.1)
Student	10 (2.8)	6 (2.3)
Retired because of age	57 (16.2)	71 (27.0)
Retired because of ill health	61 (17.3)	13 (4.9)
Homemaker	18 (5.1)	19 (7.2)
Unemployed	53 (15.1)	10 (3.8)
Other	26 (7.4)	7 (2.7)
Main epilepsy doctor (n/%)		
Primary care	110 (31.2)	–
Hospital specialist	242 (68.8)	–
Years diagnosed		
Median (IQR)	20.0 (8–37)	–
Antiepileptic medication (n/%)		
None	6 (1.7)	–
Monotherapy	153 (43.4)	–
Polytherapy	193 (54.9)	–
Seizures (any type) in the prior 12 months ^{ab} (n/%)		
Yes	229 (65.2)	–
No	122 (34.8)	–
Median (IQR)	4.0 (0–10)	–
Medical history (beyond epilepsy for patients) (n/%)		
None	142 (40.3)	162 (61.6)
Another medical diagnosis	159 (45.2)	88 (33.5)
Psychiatric diagnosis	17 (4.8)	4 (1.5)
Both medical and psychiatric diagnoses	34 (9.7)	9 (3.4)
Relationship to patient		
Spouse/partner	–	140 (53.2)
Parent	–	80 (30.4)
Friend	–	20 (7.6)
Child	–	12 (4.6)
Other	–	11 (4.2)

Notes: IQR = interquartile range, n = number, SD = standard deviation.

^a Thapar et al.'s [43] scale which asks "How many attacks have you had in the last 12 months?". The patient can choose from the following ordinal categories: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more.

^b Seizure frequency data missing for 1 patient participant.

3.3. Additional domains of importance

Only 48 (13.6%) of the patient participants and 31 (11.8%) of the carers identified additional domains of importance. Most of these patients (93.8%) and carers (87.1%) identified just one domain.

There was substantial overlap in the additional domains noted, which permitted their categorization. In descending order of how frequently they were noted, patients identified the following domains: "the effect of the treatment if taken when pregnant" (43.8%), "how the treatment interacts with other treatments I am receiving" (33.3%), "the complexity of taking and storing the treatment" (18.8%), "the ethics of the treatment's production, including the use of animals and carbon emissions" (6.3%), and "the effect of the treatment on comorbid conditions" (4.2%). The domains identified by carers were "how the treatment interacts with other treatments the patient is receiving" (41.9%), "the complexity of taking and storing the treatment" (35.5%), and "the effect of the treatment if taken when pregnant" (29.0%).

Table 2
Ratings of importance given to the outcome domains by patients and by carers.

Domain	Patients (N = 352)				Carers (N = 263)				Mean difference (95% CI)	P-value
	Rank	% rated as "Very important" (7–9)	% rated as "Little importance" (1–3)	Mean score (SD)	Rank	% rated as "Very important" (7–9)	% rated as "Little importance" (1–3)	Mean score (SD)		
Seizure severity "The treatment's effect on how many seizures you have"	1	89.5%	2.0%	8.22 (1.46)	4	86.7%	3.8%	8.15 (1.68)	0.07 (−0.18, 0.32)	0.595
Seizure frequency "The treatment's effect on how severe your seizures are"	2	87.5%	2.8%	8.24 (1.55)	2=	89.0%	2.3%	8.31 (1.48)	−.07 (−0.32, 0.17)	0.531
Quality of life "The treatment's effect on your quality of life"	3	85.8%	2.6%	7.97 (1.62)	1	91.6%	1.1%	8.35 (1.26)	−0.38 (−0.61, −0.15)	0.001
Cognitive function "The treatment's effect on your mental skills (such as, memory, concentration, and thinking)"	4	84.7%	3.4%	7.94 (1.69)	5	85.2%	2.7%	7.95 (1.65)	−0.01 (−0.27, 0.26)	0.962
Adverse events "The side effects that the treatment has on you"	5	84.1%	2.6%	8.01 (1.66)	2=	89.0%	1.1%	8.17 (1.40)	−0.17 (−0.41, 0.08)	0.192
Independence "The treatment's effect on how much support/care you need from your family and friends"	6	73.9%	8.2%	7.28 (2.19)	8	75.7%	6.8%	7.43 (2.13)	−0.15 (−0.50, 0.19)	0.381
Depression "The treatment's effect on mood/how depressed you feel"	7	69.3%	6.3%	7.32 (2.12)	6	80.2%	3.8%	7.76 (1.82)	−0.44 (−0.75, −0.12)	0.006
Anxiety "The treatment's effect on worry/your anxiety levels"	8	67.6%	8.0%	7.10 (2.21)	7	75.7%	5.3%	7.52 (1.93)	−0.41 (−0.74, −0.08)	0.014
Felt stigma "The treatment's effect on how stigmatized you feel by epilepsy"	9	52.6%	21.0%	6.17 (2.79)	9	58.6%	12.9%	6.62 (2.43)	−0.45 (−0.86, −0.03)	0.034
Economic cost "How much the treatment costs the health service"	10	33.9%	36.2%	4.86 (2.94)	10	25.9%	46.4%	4.30 (2.99)	0.56 (0.08, 1.03)	0.021

Notes: CI = confidence interval, SD = standard deviation. Ranking is based on the proportion of participants within the sample that rated the domains as being "Very important" (score: 7–9). For carers, domain labels were adjusted so as to be in reference to the patient, rather than themselves (e.g., "The treatment's effect on how severe the seizures are that the person with epilepsy that you know has" was used instead of "The treatment's effect on how severe your seizures are"). Entries in **bold** indicate statistically significant differences ($P < 0.05$). = indicates a tied position in ranking when based on the percentage of participants who rated the domain as being "Very important".

3.4. Comparison of importance ratings

3.4.1. Patients versus carers

For most of the domains (8/10), the mean ratings given by carers were slightly higher than those reported by patients, indicating that carers attributed more importance to the domains than patients (Table 2). For 5 domains, namely, "Quality of life", "Depression", "Anxiety", "Felt stigma", and "Economic cost", the difference between the patients' and carers' ratings was statistically significant. However, the magnitude of the differences was small, with all mean differences being < 1 point.

3.4.2. Patients with versus patients without seizure/s in the prior 12 months

There were no statistically significant differences in the mean scores of these two subgroups, and all mean differences were < 1 point (Supplementary Table 1). Moreover, when looking at which domains were rated as being "Very important" by $\geq 70\%$, the two subgroups identified the same 6 domains.

4. Discussion

4.1. Main findings

To help understand what the key outcome domains are to adults with epilepsy and their informal carers, we, for the first time, asked patients and carers to rate the importance they attributed to 10 outcome

domains and invited them to suggest additional ones. The views of over 600 people were obtained.

On the basis of roundtable discussions among health professionals, the ILAE COME [11] had suggested outcome domains which epilepsy drug trials should measure. As well as seizure frequency, they recommended measuring seizure severity, quality of life, cognitive function, and adverse events. We found that patients and carers also viewed each of these domains as being critical. This is an important finding in itself and confirms that the effect a treatment has on seizure frequency is only one of the pieces of information which service users want when evaluating the benefit of a treatment for health.

Our results, however, expand the work of the ILAE COME as we found that there was consensus among patients that an outcome measure relating to their independence/how much support they require from others should also be included in trials and reported, while the views of carers indicated that they would want the inclusion of three further measures – namely, measures relating to the effect of the treatment on patients' independence, depression, and anxiety levels.

We also asked participants to write down additional domains which they considered to be important. Most participants did not. This suggests that the domains they were presented with captured their main priorities. The additional domains that were most frequently noted related to the complexity of the treatment regime, as well as the effect of treatment on women who were pregnant. That these are priorities of service users concurs with the wider literature. Treatment adherence is related to dosing complexity [48], and we know that one-third of people treated for epilepsy are women of child-bearing age [49].

Finally, we compared the outcome priorities of patients to carers, as well as the views of patients who had experienced seizures in the 12 months preceding participation to those of patients who had not. We did not find any meaningful differences between these groups. This suggests that the importance of the domains is consistent across these groups. This is important when considering the scope and applicability of the provisional COS that our results indicate. Future studies should, however, evaluate the relevance of other characteristics, such as whether a patient has a new or established diagnosis of epilepsy.

4.2. Strengths and weaknesses

Strengths of our study include it being the first study to elicit the opinions of PWE and their carers on outcome priorities and that a large sample was surveyed. That our study was completed within the context of the UK health service is also advantageous. Like those in the majority of Western countries, healthcare in the UK is predominately publicly funded [50]. This could suggest that similar findings might be found in other Western countries.

Any COS should be feasible to collect within the context of a trial. Our results suggest that at least 8 domains should be included. Core outcome sets for other conditions have contained 6–11 different domains [16,19–21]. We were not able to ask participants to identify their “top outcome domains” for inclusion. This could be done by future studies to potentially reduce the number of domains that should be included. Indeed, while they are presented as independent, distinct outcome domains to participants, in reality there is likely to be overlap. Some of the more global outcomes could be seen to subsume other, more specific ones. Quality of life is one of these, with epilepsy quality-of-life measures often comprising a number of subscales, including emotional well-being and physical independence [51]. Some reduction might therefore be possible by including only global measures and excluding some of the more specific ones.

Like many COS studies [15,19,21], recruitment of patients was limited to those affiliated with a patient organization – in this case, the British Epilepsy Association. Since people with uncontrolled epilepsy are overrepresented within such groups [43,52], this permitted efficient targeting of those who are the focus of many trials. Nevertheless, it remains to be determined whether the views of those affiliated with such a group are comparable to those of patients who are not. Our participants' mean age and number of years since diagnosis were comparable to the wider population with epilepsy [53]. There were, however, more females than would be expected (~15%). Also, when compared to the UK population [54], there was an underrepresentation of people from minority ethnic groups.

A further potential source of bias within the recruited sample is the relatively low response rate. Our study was nested within a longitudinal study recruiting patient–carer dyads and achieved a response rate of approximately 10%. However, this rate is not unusual for COS studies [44] nor for epilepsy studies that use comparable recruitment approaches; e.g., cross-sectional studies, rather than longitudinal studies, achieved uptake rates of 17% [55,56].

Possible reasons for the low acceptance rate and high number of nonresponses to the invitations include the following. The information held by the British Epilepsy Association about individuals on their database is limited. It does not identify whether the individuals have epilepsy themselves or are persons without epilepsy who simply contacted the Association for information. Some invitations may therefore have been sent to noneligible persons for whom the study was not relevant. To comply with the terms of use of the database, invitations were also sent out on our behalf, and it was not possible to send reminders to individuals who did not respond. Finally, the contact details of people on the database can be outdated.

4.3. Conclusions

This work has for the first time, to our knowledge, elicited the views of PWE and their informal carers about their outcome priorities and generated a provisional list of outcomes for inclusion in a COS for epilepsy. As well as confirming the importance of domains previously suggested as being important by health professionals, our study has identified additional domains of importance. As a COS is not itself a measurement instrument, a next step will be to determine how and when these key outcomes should be measured.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.yebeh.2016.01.036>.

Conflict of interest

The authors state that they have no conflicts of interest to declare.

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