Seizure First Aid Training For people with Epilepsy (SAFE) and significant others attending emergency departments: intervention development and pilot RCT

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Abstract

Seizure First Aid Training For Epilepsy (SAFE) for people with epilepsy and significant others attending emergency departments: intervention development and RCT

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Background: No seizure first-aid training intervention exists for people with established epilepsy (PWE) who regularly attend emergency departments (ED) and their significant others (SO), despite the potential to reduce clinically unnecessary and costly visits.

Objectives: (1) Develop Seizure First Aid Training For Epilepsy (SAFE) by adapting a broader intervention; (2) Determine feasibility and optimal design of a definitive randomised controlled trial (RCT) to test SAFE's efficacy.

Design: (1) Intervention informed by co-design approach with qualitative feedback; (2) Pilot RCT with 3-, 6- and 12-month follow-ups, assessments of treatment fidelity and cost of SAFE's delivery.

Setting: (1) Stakeholders recruited from user groups and professional organisations; (2) Recruitment via 3 English NHS EDs.

Participants: (1) PWE who had visited ED in the prior 2 years, their SOs and ED, paramedic, general practice, commissioning, neurology and nursing representatives; (2) PWE aged ≥16, diagnosed for ≥1 year, who had made ≥2 ED visits in the prior 12-months and one of their SOs. EDs identified ostensibly eligible PWE from attendance records and patients their confirmed eligibility.

Interventions: (1) None; (2) Randomly allocated 1:1 to SAFE + Treatment as Usual (TAU) or TAU alone.

Main outcome measures: (1) None; (2) Consent rate and availability of routine data on ED use at 12-months were main measures. Others of interest included: eligibility rate; ease with which PWE could

be identified and routine data secured; availability of self-report ED data; its comparability to routine data; SAFE's effect on ED use; ED use in the TAU arm to permit sample size calculations.

Results: (1) Nine health professionals and 23 service users provided feedback which generated an intervention considered NHS feasible and well-positioned to achieve its purpose; (2) Consent rate was 12.5%, with 53 PWE and 38 SOs recruited. The eligibility rate was 10.6%. Identifying PWE from attendance records was resource intensive for ED staff. Those recruited were more stigmatised than the wider epilepsy population. Routine data on ED use at 12-months was secured for 94.1%, but the application process took 8.5 months. Self-report ED data was available for 66.7%; PWE reported more visits compared to routine data. Most (76.9%) randomised to SAFE received it. SAFE was delivered with high-fidelity. No related serious adverse events occurred. ED use at 12 months was lower in the SAFE+TAU arm compared to TAU alone, but not significantly. Calculations indicated a definitive trial would need ~674 PWE and ~39 ED sites.

Limitations: Contrary to patient statements upon recruitment, routine data secured at the trial's end indicated ~40% may not have satisfied the inclusion of criteria of ≥2 ED visits.

Conclusions: An intervention was successfully developed, a pilot RCT conducted and outcome data secured for most. The consent rate did not satisfy a predetermined 'stop/go' level of ≥20%. The time ED staff needed to identify eligible PWE is unlikely to be replicable. A definitive trial is currently not feasible.

Future work: Research to more easily identify and recruit persons from the target population is required.

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List of abbreviations

APEASE.....	Affordability, Practicality, Effectiveness and cost-effectiveness, Acceptability, Side-effects/safety, and Equity
CONSORT.....	Consolidated Standards of Reporting Trials
CRF.....	Clinical Research Form
CTU.....	Clinical Trials Unit
ED.....	Emergency Department
ES.....	Epilepsy Society
FG.....	Focus group
HADS.....	Hospital Anxiety and Depression Scale
HES.....	Hospital Episode Statistics
IDP.....	Intervention Development Panel
NASH.....	National Audits of Seizure Management in Hospitals
NBR.....	Negative binomial regression
NHS.....	National Health Service
NIHR.....	National Institute of Health Research
PWE.....	Person(s) with Epilepsy
QOL.....	Quality of Life
RCT.....	Randomised Control Trial
SAE.....	Serious Adverse Event

SAFE.....	Seizure First Aid Training For Epilepsy
SMILE.....	Self-Management education for adults with poorly controlled epILEpsy
SNOMED	Systematized Nomenclature of Medicine
SO.....	Significant Other
TAU.....	Treatment as Usual
TIDieR.....	Template for Intervention Description and Replication
TSC.....	Trial Steering Committee
UK.....	United Kingdom

Plain English summary

Low knowledge of how to manage seizures leads some individuals with epilepsy to visit emergency departments following seizures, despite them not needing medical attention. Such visits are expensive and can be inconvenient for patients.

Part A of this project aimed to develop a self-management course for patients frequently visiting emergency departments for epilepsy and their significant others significant others, like family and friends. Having developed it, a large trial was needed to find out if it is beneficial. Before doing that we needed to answer the question, 'can such a trial be done?' Part B of this project aimed to answer this by conducting a 'pilot randomised controlled trial'. A pilot is like a practice-run.

In Part A, 9 health professionals and 23 service users helped us develop the course, called 'Seizure first Aid training For Epilepsy'. They considered it acceptable and National Health Service feasible.

In Part B, 53 patients diagnosed with epilepsy (and 38 significant others) were recruited from 3 emergency departments. Patients were randomly assigned to either an invitation to attend 'Seizure first Aid training For Epilepsy' (with or without their significant other) or usual treatment alone. Both took medication as usual. Participants were asked to complete questionnaires on use of emergency departments and confidence managing seizures 3, 6 and 12 months later.

The pilot found emergency departments could not easily identify people to invite and fewer people agreed to take part than expected (12.5% rather than at least 20%). Those who did though tended to stick with it, with information on their use of emergency departments 12 months later being obtained for over 90%. Nearly all participants said they would take part in such a trial again.

Even though Parts A and B were carried out successfully, because fewer patients agreed to participate and because of the difficulties identifying them, a large trial, as currently designed, is not feasible.

Word count: 313

Scientific summary

Background

Epilepsy is one of the United Kingdom's (UK) most common serious brain disorders. Up to 20% of people with epilepsy (PWE) visit hospital emergency departments (ED) each year; ~60% multiple times. These are expensive; half result in hospital admission.

PWE visiting ED report more seizures, anxiety, stigma and are more likely to live in a socially deprived area than those in the wider epilepsy population. Identifying them can be challenging. Most are unknown to specialist epilepsy services and are not referred on to them following ED visits. General practitioners are also not always informed of the contact these PWE have with the emergency services.

National Audits of Seizure Management in Hospitals and related works indicate many ED visits by PWE are clinically unnecessary. This is because most have known, rather than new epilepsy and have experienced uncomplicated seizures. Whilst frightening, guidelines state such seizures can be managed by PWE and their family and friends, without medical attention.

Emerging evidence indicates low confidence in seizure management on behalf of PWE and their significant others (SOs), to whom care decisions can be delegated, may explain why some PWE make clinically unnecessary visits. Offering PWE who frequently attend ED and their SOs a self-management intervention that improves their confidence and ability to manage seizures may lead to fewer visits.

We report a project seeking to develop the first such intervention, called 'Seizure first Aid training For Epilepsy' (SAFE). To develop the intervention, an existing group-based seizure management course offered by the Epilepsy Society (ES) within the voluntary sector to a broader audience was adapted. A pilot RCT of SAFE was then conducted. A pilot was appropriate given the feasibility and optimal design of a definitive trial was unclear.

Aim and objectives

Part A: Intervention development

1) Optimise content, delivery and behaviour change potential of the ES' course for PWE attending ED, and their SOs.

Part B: Pilot RCT

2) Conduct an external pilot randomised controlled trial (RCT) of SAFE + Treatment As Usual (TAU) vs. TAU alone to estimate likely recruitment, consent and follow-up rates in a definitive trial.

3) Calculate estimates of annual rate of ED visits in TAU group and likely dispersion parameter to inform the sample size calculation of a definitive RCT.

4) Test acceptability of randomisation to participants.

5) Evaluate SAFE's implementation fidelity within the pilot RCT.

6) Analyse cost of implementing the SAFE programme.

Methods and analysis

Part A: Intervention development

Design:

An experience-based co-design approach, comprising of 3 iterative stages, identified the changes required to the ES' intervention: Stage 1 – Leading representatives from the professional groups supporting PWE reviewed the course materials and were interviewed about changes needed; Stage 2 – The ES' original intervention was not underpinned by a clear behaviour change mode, thus during Stage 2 the intervention's behaviour change was optimized; Stage 3 – Focus group discussions with service user representatives who received an initial adaption of the intervention. Data from the different stages was captured using audio-recordings, thematically analysed and considered by a multidisciplinary intervention panel.

Recruitment:

A purposive sample of representatives from neurology, emergency medicine, the ambulance service, specialist nursing, general practice, user groups and health care commissioning was recruited with the help of professional organisations. Epilepsy user groups helped recruit service user representatives.

To be eligible they needed to be aged ≥16, be able to provide informed consent and the PWE needed to have visited an ED in the past 2 years for epilepsy.

Part B: Pilot RCT

Design:

External pilot RCT. Recruited PWE were randomised (with their SO if they took part with one) to receive SAFE+TAU or TAU alone. SAFE was delivered by an epilepsy nurse within a hospital's educational centre. TAU alone participants received SAFE once the trial finished.

The proposed primary outcome measure for a definitive trial of SAFE is ED use in the 12 months following randomisation measured using routine hospital data. In the pilot this was captured by Hospital Episode Statistics. Participants provided consent for the release of this data. Proposed secondary outcomes included self-reported ED use, fear of seizures, knowledge and confidence managing seizures, quality of life, distress, seizures, stigma, carer burden, service use and adverse events. These were measured by a researcher, blind to treatment allocation, completing questionnaires with participants 3, 6 and 12-months post randomisation. At the 12-month assessment, participants also provided feedback on trial participation.

Rates of recruitment and retention were calculated, as was the ED event rate in the control group. ED visits measured using routine hospital data for the 12 months prior to and 12 months following randomisation were also compared to self-reported ED visits for these periods. The estimates from the pilot trial were evaluated against two predetermined 'Stop/Go' progression criteria for a full trial – namely, that ≥20% of eligible PWE needed to agree to take part and primary outcome data at 12 months need to be secured for ≥75% of PWE. Whilst the trial was not designed to detect a clinically important difference in ED use, an estimate of SAFE's effect on this measure was also calculated to help inform the possible design of a future trial.

It was anticipated that 12 months of attendances at 3 National Health Service (NHS) Type 1 EDs would be sufficient to secure a sample of 80 PWE for the pilot, with 40 PWE in each treatment arm permitting the study to estimate a drop-out rate of 25% to within a 95% confidence interval of +/- 10% and a consent rate of 20% to within a 95% confidence interval (CI) of +/-4%. Assuming data on ED use at 12 months was not available for 25% of PWE, outcome data from 60 would still allow for robust estimation of the ED rate and dispersion parameter.

Measures of implementation fidelity (adherence and competence) for SAFE were developed and their interrater reliability assessed. Adherence was assessed by a checklist of the items comprising the intervention. Competence was measured by calculating facilitator speech during the intervention (didacticism). The measures were then used by independent raters who listened to audio-recordings of all trial SAFE sessions.

A micro costing exercise calculated the fixed and variable costs of delivering SAFE. The process involved a health economics researcher meeting with intervention staff and mapping out the work and resources required for each of the courses run. The cost of developing SAFE was also determined.

Recruitment:

Using electronic attendance records and triage cards, local principal investigators at 3 NHS Type 1 EDs in North-West England retrospectively identified PWE who had visited their EDs within the prior 12 months for epilepsy and posted an invitation letter. Inclusion criteria were: people aged ≥ 16 years, who had an established diagnosis of epilepsy (≥1 year) and were prescribed antiepileptic medication, who reported having visited an ED on ≥2 occasions in the prior 12 months, and who were able to provide informed consent, participate in SAFE and complete questionnaires in English. Those receiving the invitation letters were instructed that if they were not interested in taking part in the trial or not eligible that they should opt out of further contact within 3 weeks. A research worker telephoned those not opting out to explain the study further and verify patient eligibility and willingness to participate. The research worker met with those wishing to take part and their SO and secured informed consent and completed baseline questionnaire assessments.

Results

Part A: Intervention development

Over a period of 8 months, feedback from 9 representatives from different professional groups, 13 PWE and 10 SOs was secured and the finalised SAFE intervention developed.

At Stage 1, health professionals considered the ES' course to provide a good foundation but requested changes to its language and presentation style to make it less didactic and to emphasise the benefits to service users. They recommended the inclusion of new content to elicit and address service users' fears relating to seizures. To promote consistency and make the intervention suitable for delivery within the health service, a trainer's manual was also developed. In Stage 2, the behaviour change

potential of the intervention was optimised. Specifically, the intervention development panel considered Self-Affirmation Theory pertinent since the course would highlight to some participants that their past behaviour conflicted with medical guidance. To mitigate against the defensive processing of information which can result according to the theory, the brief 'Kindness Questionnaire' was inserted at the intervention's start. During Stage 3 service users reported a positive view of the intervention, its videos and the associated educational materials. Their feedback resulted in the order of content changing, the addition of information relating to post-ictal states and the generation of a website that held the content of the course so as to mitigate the effect of memory difficulties and to allow the information to be shared with other SOs.

The finalised SAFE intervention was for delivery to groups of up to 10 patient-carer dyads by a single facilitator with knowledge of epilepsy and lasted ~4 hours, including breaks. It contained 6 modules centred around basic epilepsy and first aid knowledge, the recovery position, informing others about epilepsy and how to help if seizures occur, medical identifications, seizure triggers and home safety. Materials included presentation slides and professionally produced videos. The total cost of developing SAFE was £9,947.

Part B: Pilot RCT

Fifty-three PWE and 38 of their SOs were recruited over ~7.5 months. The consent (12.5%, 95% CI 9.3 to 15.6) and eligibility (10.6%, 95% CI 9.6 to 11.5) rates were low. Despite an amendment to extend the period within which PWE could be identified from the EDs (i.e., from the prior 18, rather than 12 months of attendances), the intended sample size could not be recruited.

A lack of granularity by which attendances were coded within the EDs' record systems meant identifying PWE was resource intensive – requiring ~3 days of a local investigators' time at each site. Contacting patients by telephone was also challenging. The researcher made successful contact with only 47.8% of eligible patients.

Mean age of the PWE recruited was 39.9 years, 29 (56.9%) were female and most lived within areas high in social deprivation. Median time since diagnosis was 21 years. Those recruited were similar in age and social deprivation to those declining participation. The recruited sample might not though have been representative of the target population in sex. Moreover, 74.5% reported seeing an epilepsy specialist in the prior 12 months which is higher than expected.

Of those recruited, 51 PWE (and 37 SOs) were randomised; 26 PWE (and 18 SOs) to SAFE+TAU and 25 PWE (and 19 SOs) to TAU alone. The treatment groups' demographics, disease characteristics, and scores on the assessment tools at baseline were similar. There was some imbalance in their prior ED use. Most PWE (76.9%) randomised to SAFE received it and it was found to have been delivered with high fidelity. No TAU participants attended a SAFE course by mistake. Delivering SAFE was estimated to cost £333 per patient (with or without an SO) - and it is plausible it could be delivered for as low as £261 per patient.

Routine data on ED use at 12-months was secured for 94.1% of PWE, but obtaining it took 8.5 months, was resource intensive and at one point the application for it was rejected by NHS Digital on the basis of, what proved to be, incorrect reasoning. Self-report ED data at 12 months was secured for only 66.7% of PWE. It was found participants reported more ED visits to have occurred than routine data. For the 12 months prior to randomisation they reported 3.8 more ED visits on average than routine data.

Negative binomial regression estimated ED use at 12 months, according to routine data, to be ~47% lower in the SAFE+TAU arm compared to TAU alone, but not significantly so. It reduced from 2.1 visits over a 12-month period to 1.8 compared to an increase in the TAU group from 3 to 3.4 visits.
No serious adverse events related to participation occurred and all but one of the 32 (68.1%) PWE and 20 (62.5%) SOs providing feedback on trial participation said they would participate again, with SAFE participants valuing the intervention.

The estimated effect of SAFE on ED use and the dispersion parameter in the control group (k=0.69, range 0.17 to 1.21) indicated a definitive trial of SAFE's efficacy requires a sample of ~674 PWE. The consent rate within the pilot indicates it would need ~39 ED recruitment sites.

Conclusions

The co-design approach allowed for a brief, manualised intervention which was supported by stakeholders and based on an NHS feasible delivery method to be rapidly developed.

A successful pilot RCT was conducted. Persons from the target population could be identified, recruited, randomised, and treated as intended. Outcome data for the proposed primary outcome measure could also be secured for most participants and meant the trial satisfied the predetermined 'Stop/Go' criterion of ≥75%.

However, the consent rate for the pilot trial was low and meant the second 'Stop/Go' criterion of ≥20% was not met. Low consent raises concerns about the representativeness of the sample that would be recruited into a definitive trial and its external validity. The low consent rate means a definitive trial would also require a larger number of recruitment sites than most definitive trials and be expensive. It may even not be possible to secure the required EDs to act as recruitment sites since the resources required from them to identify participants may be prohibitive.

Implications for NHS service commissioning, policy and practice

1. The trial was not designed to determine SAFE's efficacy. There remains limited evidence to justify the commissioning of such a service.
2. Some PWE are unknown to ambulatory care services and cannot be readily identified. Increasing the granularity with which attendances at EDs are coded could enable them to be readily identified, supported and involved in research.
3. Using routine data on ED use in trials could make them less vulnerable to losses to follow-up and mean they are not exposed to apparent recall bias. However, stakeholders need to be given more assurances from those holding the data that it is likely to be provided and done so in a timely manner.
4. A case can be made for converting SAFE it into an free online resource that people could be directed to in the short term to go some way to address the otherwise unmet seizure first aid training needs of PWE who visit ED and their significant others.

Recommendations for further research

1. A full definitive trial of SAFE, with the current design, is not feasible.
2. Research to determine how people from the target population can be better recruited is required.
3. Converting SAFE into a free online resource could provide an opportunity for an alternative method of evaluating its effect. Via a pre-post design, persons accessing the online resource could complete brief measures to assess change in seizure first aid confidence and skills and provide consent to access routine data on their use of ED data before and after viewing the resource.

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Chapter 1: Introduction

This project sought to develop and pilot seizure first aid training for adults with established epilepsy who frequently visit hospital emergency departments (EDs) and their significant others (SOs). It had two-parts and used mixed-methods. In Part A, we developed the intervention, named Seizure First Aid Training For Epilepsy (SAFE). This was done by adapting a broader course being offered by the charity, the Epilepsy Society (ES). Part B was a pilot randomised controlled trial (RCT) of the SAFE intervention with people with epilepsy (PWE) from the target population and their SOs with the aim of assessing the feasibility and optimum design of a definitive randomised controlled trial (RCT) to test SAFE's efficacy.

The primary and secondary objectives for the project were:

Primary objectives

PART A: Intervention development

1) Optimise content, delivery and behaviour change potential of the ES's course for PWE attending ED, and their SOs.

PART B: Pilot RCT

2) Conduct a pilot RCT of SAFE + Treatment As Usual (TAU) vs. TAU alone to estimate likely recruitment, consent and follow-up rates in a definitive trial.

Secondary objectives

PART B: Pilot RCT

3) Calculate estimates of annual rate of ED visits in TAU group and likely dispersion parameter to inform the sample size calculation of a definitive RCT.

4) Test acceptability of randomisation to participants.

5) Evaluate SAFE's implementation fidelity within the pilot RCT.

6) Analyse cost of implementing the SAFE programme.

In this chapter, the rationale for providing seizure first aid training is provided. We then describe how the existing intervention was adapted. Finally, we outline why a pilot RCT, rather than proceeding straight to a definitive trial was appropriate.

Background

Epilepsy and its epidemiology

With a prevalence of ≥1%,[1-3] epilepsy is the United Kingdom's (UK's) second most common serious neurological condition.[4]

The International League Against Epilepsy [5] defines a person as having epilepsy if they experience ≥2 unprovoked (or reflex) seizures more than 24 hours apart; or if they have experienced one such seizure, but the probability of them experiencing another over the next 10 years is akin to that of a person who has experienced two (i.e., ≥60%).

Epilepsy's aetiology is variable. It can, for example, arise as a consequence of cerebrovascular disease, head trauma, congenital abnormalities and neurodegenerative disease, or be idiopathic.[6] Mortality risk varies for PWE, but with a standardised mortality ratio of ~2.2, it is higher than the general populations'.[7-8]

Trial data indicates most PWE (~70%) can theoretically become 'seizure free' via treatment, typically using antiepileptic drugs. However, up to 48% of PWE in the UK continue to experience seizures.[9] Epilepsy is though more than 'just' seizures. This is reflected in the International League Against Epilepsy's definition of epilepsy as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition" (p. 471).[10] The diagnosis itself can be associated with significant psychological and social costs for the individual. Being labelled negatively as "epileptic" can be accompanied by discrimination,[11-12] with potential detrimental effects on education, unemployment and driving. Around 30% of PWE also meet diagnostic criteria for an anxiety and/or depressive disorder. All undermine wellbeing.[9,13-14]

Use of emergency hospital services for epilepsy and societal implications

Epilepsy also has societal impacts. One is the cost of providing healthcare. In the European Union, the total cost of epilepsy was €15.5B in 2004,[15] with the cost per case that year being €2,000-11,500. One

costly element is the provision of emergency care which international evidence shows PWE frequently utilise.

In the UK, ≤20% of PWE visit a hospital ED for epilepsy each year.[16-18] Most (~90%) are transported there by an emergency ambulance.[19-21] The 2015/16 cost of providing emergency care to PWE in England was estimated to be at least £70 million[22](not including indirect costs).

Costs are high in part because half of ED attendances by PWE result in hospital admission.[16,19,23] Indeed, 85% of all admissions for epilepsy occur on such an unplanned basis.[24] Amongst chronic ambulatory care sensitive conditions, epilepsy is the second most common cause of unplanned admissions (17%).[25-27]

Reattendance also drives costs up. The exact distribution of ED use for epilepsy is unclear, but it is apparent reattendance rates are high. The 2014 UK-wide National Audit of Seizure Management in Hospitals (NASH)[28] examined data from approximately 4,000 seizure-related ED attendances from 85% of acute hospitals. Amongst those with established epilepsy, 60% had attended the same ED as a result of a seizure within the previous 12 months.[20] Whitson et al.[29] in their study found epilepsy to be the most frequent neurological reason for emergency readmission into UK hospitals. Dickson et al.'s[30] findings are also instructive. They examined data on unplanned admissions within English hospital's for suspected seizures of any cause (not just epilepsy) by adults between 2007 and 2013. They found 22.4% of patients had more than one admission a year and that there was a 34% chance of readmission within 6 years.

The most detailed evidence on ED use amongst PWE comes from a previous National Institute of Health Research (NIHR) funded study (reference: 08/1808/247) by Ridsdale et al. It prospectively recruited 85 people with established epilepsy from 3 London EDs and asked them to self-report on ED use within the prior 12 months; 60% reported multiple ED attendances;[27] 25% said they had made 2 visits and 36% at least 3 . The median number of visits for those who had made multiple visits was 2 (interquartile range= 2-5). This pattern contrasts with that seen in the general ED population. Moore et al.[31] found only 24% of persons from the general ED population reattend London EDs within 12 months.

ED use for epilepsy often clinically unnecessary but attendees often require more support

Seeking emergency care for epilepsy can be important, even life-saving. Reasons include a first seizure and status epilepticus. Some ED visits by PWE are for these reasons; most though are not. NASH,[20-21,28] for example, found most people attending ED for a suspected seizure had diagnosed, rather than new epilepsy. Moreover, most appear to have experienced an uncomplicated seizure. Dickson et al[32] reviewed records for 178 seizure incidents presenting to one regional ambulance service over one month in 2012. Medical emergencies were uncommon and seizures had self-terminated before the emergency vehicle arrived in >90% of cases. In only 8% of incidents, were emergency drugs required to terminate the seizure. Uncomplicated seizures in someone with established epilepsy, whilst potentially frightening and distressing to experience and observe, do not typically require the full facilities of ED and can be managed within the community by the PWE and their SO's. Indeed, going to ED in these circumstances may have iatrogenic harms due to unnecessary investigations and interventions (e.g., unused intravenous cannulations, unnecessary head computerised tomography scans).[33-35]

Although a high proportion of epilepsy-related ED visits do result in hospital admission, most appear unnecessary[36] with factors beyond the patient's clinical need appearing to play a role in why the admission occurred (e.g., lack of access to senior medical review, need to avoid breaches of ED waiting time targets).[37]

Whilst the acute episodes leading PWE to visit ED do not typically require the facilities of ED, PWE attending ED *do* often have poorer health than those in the wider epilepsy population. They report more seizures, poorer quality of life, lower epilepsy knowledge, more anxiety and feel more stigmatised by epilepsy.[27,38-43] Despite this, most (~65%) have not seen an epilepsy specialist in the prior 12 months.[28]

There is also inequality in use of ED, with attendees being more likely to reside in areas where social deprivation is high and seizure control worse.[39,44-45] Indeed, ED admissions for seizures vary >5-fold between geographical regions in England,[40,42] being most frequent in more socially deprived areas. [45-46]

The National Institute for Health and Care Excellence (NICE)[47] recommend when seizures are not controlled, a patient should be referred to specialist services. Going to ED due to an epileptic seizure does not though typically lead to this increase in support. NASH[20,28] found most (80%) PWE are not seen by a specialist during their attendance, usual care providers were often not informed of the attendance and most (60%) PWE are not referred to a specialist for follow-up. Of PWE attending ED, those living in the most deprived areas are amongst those least likely to be referred.[48]

Epilepsy identified as one area where opportunities exist to reduce demands

The NHS has been operating within a context of rising demand, slow funding growth and increasing operating costs. In 2015/16, this culminated in an aggregate funding deficit of £1.85 billion.[49-50] The NHS Plan,[51] Five Year Forward View[52-53] and related publications challenge the NHS to make substantial savings, whilst at the same time, work with patients and SOs to improve care experience, outcomes, and reduce health inequalities. Epilepsy has been identified as one condition where opportunities exist to improve patient outcome and experience, reduce demands and generate savings.[54]

Whilst there is a drive to reduce emergency visits for epilepsy and enhance patient outcomes, it has been challenging to know how to achieve this[25,55] not least because the reason(s) for the visits within publically funded health care systems has been unclear. The association between seizure frequency and ED use is, for example, only modest in size and seizure type has not proved a robust predictor.[17,27,38,56]

Emerging evidence now highlights the potential importance of a person's self-management skills in their use of ED. More specifically, the confidence and skills that they and those around them have to manage seizures, with this potentially moderating the relationship between an uncomplicated seizure and the help sought at the time.

The importance of seizure management skills and confidence in emergency health service use

'Self-management' is a broad term. It refers to an "individual's ability to manage their symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition"[57](p 178). In the context of epilepsy, self-management of adult epilepsy has been defined as "activities that an individual can perform alone that are known to either control frequency of seizures or promote well-being of the person with seizures".[58]

Much of the evidence regarding the potential importance of self-management skills in ED use comes from Ridsdale et al.'s aforementioned NIHR project. [27,56,59] It followed-up its sample of 85 PWE for 12 months. A subgroup was interviewed about the reasons for their visits. Analyses indicated that patients fell into two groups. In the first, there were patients who reported high levels of confidence in managing their epilepsy. Their views closely aligned with seizure first aid guidelines. Explanations offered by these patients for their visits included reasons such as having experienced an unusually long seizure or having sustained a significant injury. These persons had typically visited an ED only once in the previous 12 months.

By way of contrast, patients in the second group reported not feeling confident managing seizures. They expressed a need for immediate access to urgent care when they had a seizure and had typically made ≥2 ED visits in the prior year. They explained how they and their family (to whom care decisions were often delegated when the patient was unconscious or lacked capacity) were fearful of seizures, including the possibility of death and brain damage, and were unsure about how to manage them and could not tell others about how to help should they have a seizure. [56,59] This, they said, could lead them to call for an ambulance when they were about to have, or had had, a seizure. Despite having been diagnosed with epilepsy for ~10 years, they said they had not received sufficient information about epilepsy. Telling quotes from those interviewed included:[56,59]

> *"Cancer, you're awake. I know you can die, but you're awake. I'd prefer something like that…Having epilepsy, you're going into a fit. You don't know if you're going to wake up or die. That's why I call ['999']!" (Patient, number 23)*

> *"[I was] just worried because I don't know anything about epilepsy…I only know the bad things…I know you can die… I am so worried I decided just to ring an ambulance…better safe than sorry." (SO, number 60)*

Quantitative results from the project reinforced what patients said at interview. There was, for example, evidence of lower first aid knowledge. One third of the ED sample incorrectly stated that it was always necessary to call a doctor or ambulance if a PWE has a seizure, even if it occurs without complications.[27] Only 11% of the wider epilepsy population believe this.

Also important were the results of regression analyses to determine what baseline information predicted how many ED visits patients reported 12 months later. A range of variables were examined for their association, including seizure frequency, seizure severity and medication management skills. It was patients' level of confidence managing epilepsy (as measured by the Mastery scale[61]) and the

extent to which they felt stigmatised by epilepsy (as measured by Jacoby's Stigma Scale[62]) that were found to best predict ED use. These factors held similarly sized associations with ED use, with lower confidence (incidence rate ratio= 0.86) and increased feelings of stigma (incidence rate ratio= 1.32) being associated with more ED use.

'Mastery' refers to a state of confidence in which a person feels able to independently overcome the challenges with which they are faced.[63] The Mastery measure used captured the degree to which the patients perceived internal vs. external locus of control, with example items from the scale including 'I often feel helpless in dealing with my seizures' and 'Sometimes I feel that my epilepsy controls my life'.[61] Evidence suggests that when a person feels more confident in their ability to cope and manage their illness effectively; they are more likely to put self-management behaviours into practice.[64]

Epilepsy self-management and support currently offered to PWE and SOs

The findings from Ridsdale et al.'s project are in keeping with prior evidence since coping with life in the context of epilepsy requires an individual to accept their diagnosis and for them to learn and adopt specific self-management behaviours to prevent seizures and manage consequences. These tasks together comprise what Corbin and Strauss[65] (p. 358) labelled the "work" of living with a chronic condition.

It is for these reasons that NICE[47] recommend self-management support for PWE. Epilepsy specialist nurses form an important part of the way this support is delivered. It is known, however, that current care models in the UK and beyond continue to fail some PWE and mean they have less than optimal levels of self-management confidence. Unlike for some other chronic conditions, there remains no routine course PWE can go on to learn about their condition once diagnosed and there is limited time within routine care appointments.[66-68] Patients have previously summarised the lack of information and support they were given following diagnosis as *"I was left high and dry"*.[69-70] It is PWE who have lower levels of formal education who have been found to have the least epilepsy knowledge.[71-72]

The role which Ridsdale et al.'s project found a patient's family and friends to have when a seizure occurs also accords with wider evidence in that, despite greater social isolation, up to 90% of PWE can still identify a SO who acts as an informal carer [73] These people are though not always trained in how to manage seizures, including in the use of emergency medications.

One reason SOs may not have largely featured in discussions about why ED visits for epilepsy occur, is that it had widely been thought such visits primarily occur because the patient was alone in a public place, had a seizure and that an ambulance was called by a bystander and that a lack of information about the person's medical history (such as from an epilepsy identification card) meant paramedics transported the person to ED out of precaution (*see* for example: https://www.epilepsysociety.org.uk/not-always-a%26e-07-02-2014#.Ww_aOCAh02w [accessed 27th August, 2019] and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1960454/ [accessed 27th August, 2019]). Consequently, the focus has often been on how the public, rather than SOs, can be supported and educated (*see* for example: http://news.bbc.co.uk/1/hi/health/339872.stm [accessed 27th August, 2019]). ED visits for epilepsy do certainly occur via this mechanism [74-75] It does seem to be the minority though.

Reuber et al. [23] found that in their area of the UK only 15% of ED visits by PWE occurred because the person was alone and had a seizure in a public place. Most seizures leading to an ED visit instead occur within the patient's home[23] and most (70%) '999' calls for seizures are made by relatives or friends, rather than members of the public.[32]

Given indications that seizure management skills and confidence might have an important role in emergency service use, an idea that has emerged of promise is to offer PWE who frequently attend ED and their SOs a self-management intervention to improve their confidence and competence to manage seizures.[43,76] The objectives of self-management interventions are to facilitate patients taking an active role in their own healthcare by encouraging autonomy and providing accurate information on symptom management.[77] They are different to traditional educational approaches since as well as educating, they seek to empower those living with chronic healthcare conditions.[78] It is asserted that when people are supported to become more activated, they benefit from better health outcomes, improved care experiences and make fewer unplanned care admissions.[77]

What is the evidence self-management skills, including for seizure management, can be modified?

Evidence from adult and paediatric literature at the time of project design

Evidence from studies in the wider literature on self-management interventions for people living with other chronic conditions such as diabetes,[79-81] arthritis,[82-84] and asthma[85-87] indicate it is possible to elicit improvements in self-management. Consequently, in these fields, self-management support has become well-established.[88-94] In the UK, self-management courses have become freely accessible to

people with diabetes.[95-96] The evidence base on improving self-management skills in PWE is more limited.

A Cochrane review by Bradley et al[97] examined care delivery and self-management strategies for adults with epilepsy. It found 4 self-management studies focusing on adults with epilepsy.[98-101] None of the trialled programmes focused exclusively on seizure management, on those attending ED, systematically involved SOs, and none had been trialled in the UK. However, the review did conclude there was tentative evidence that such interventions can improve epilepsy self-care skills.

Helegeson et al's[98] small US RCT is worthy of note since it evaluated an intervention that included some discussion of seizure first aid. The intervention, the Sepulveda Epilepsy Education programme, is a psychosocial 2-day group course.[98] At 4-month follow-up, participants receiving Sepulveda Epilepsy Education demonstrated a statistically significant increase in understanding of epilepsy, a decrease in seizure fear, and a decrease in hazardous medical self-management practices compared to wait-list controls. Health service utilisation was not though measured and no significant changes were found in relation to anxiety or confidence managing epilepsy.

As the number of trials conducted with adults with epilepsy is small, Lindsay and Bradley's[102] Cochrane review of self-management interventions for children with epilepsy and their parents is instructive. It identified two RCTs of interventions which contained modules on seizure first aid.

The first, conducted by Tieffenberg and colleagues,[85] evaluated a Spanish group-based programme called 'ACINDES'. It is for children aged 6-15 years and is delivered by teachers and educates children and parents about epilepsy. It consists of 5 weekly 2-hour sessions, followed by a reinforcement session 2 to 6 months later. At 12-month follow-up, children in the intervention group showed statistically significant improvements in epilepsy knowledge compared with controls. There was also a significant reduction in ED visits. The mean number of ED visits made by children in the intervention group in the prior 12 months to randomisation was 0.90. It reduced to 0.22 for the 12 months of follow-up. For the TAU group it went from 0.83 to 0.46.

The second RCT was by Lewis and colleagues.[103-104] It examined the effect of another Spanish intervention called the 'Children's Epilepsy Programme'. It taught children and parents about seizures, living with epilepsy and communication. Children and parents separately attended 4 1.5 hour group sessions and met together at the end of each session to share learning. At 5-month follow-up, children

in the 'Children's Epilepsy Programme' arm had significantly improved epilepsy first aid knowledge compared to controls.[103] Their parents also showed significantly greater reductions in anxiety than controls.[104]

That training in self-care is associated with reduced service utilisation in the paediatric epilepsy population, without compromising patient outcome concords with the larger, higher quality evidence-base on interventions to reduce ED use by children with asthma – another chronic, relapsing condition.[86-87,105] Boyd et al,[87] for example, completed a Cochrane review of 17 RCTs of educational interventions for children (and their parents) at risk of asthma-related ED attendances. Data from >3000 children who presented to the ED for acute exacerbations and were then followed on average for 10 months was included. Educative interventions led to a 37% reduction in the relative risk of re-attendance at ED in the treatment group compared with the control group and a 21% reduction in the relative risk of subsequent hospital admission.

Conclusions from trials regarding the ability of self-management interventions to elicit behaviour change in PWE do however need to be tempered as most trials have been found to be of low methodological quality.[106-108] Such trials are at a higher risk of bias and potentially overestimate effects (*see* for example: Savovic et al.[109]). In Helgeson's[98] trial of SEE, for instance, no information was provided with regards random sequence generation or allocation concealment, only 38% of those randomised to the intervention completed it and outcome assessments were not blinded.[108]

Development of the SAFE intervention

On the basis of the evidence so far presented, we hypothesised that PWE, who frequently visit ED for epilepsy (here operationalised as 2 or more visits in the prior year) might benefit from an intervention that improves their own and their SOs' confidence and ability in managing seizures and empowers them to be able to tell others from their wider support networks about how to help if a seizure occurs. In the absence of an existing intervention it was necessary to develop one. This was done by adapting a broader intervention that was in existence and used by the Epilepsy Society (ES) for different purposes.

Offering such a programme to the target population is supported by the NHS policy of empowering and supporting people with long-term conditions to understand their own needs and self-manage them.[110-112] Indeed, the Keogh Urgent and Emergency Care Review [113] identified that better supporting people to self-care for their condition is one way EDs could become sustainable.

Background to the existing seizure management course and its development

The ES is an English charity (ref. 206186) with a 120-year history that has assumed an important role within the voluntary sector in producing information materials for PWE and in offering epilepsy training for different audiences https://www.epilepsysociety.org.uk/training-courses-epilepsy#.XSR5AutKj3g [accessed 27th August, 2019]. In 2012/13, >2,000 people attended their training courses (J. Fox, April, Learning and Development Manager Epilepsy Society, 2014 personal correspondence). Of relevance here is their training course titled 'Epilepsy awareness and seizure management' which they had been offering since 1998 to a fee-paying audience. Recipients included teachers, care staff, patients and SOs. The course was developed iteratively, with the involvement of neurologists, psychologists and social workers.

The course was delivered by a single educational facilitator. To deliver a course, a facilitator needed to follow a training programme developed by the ES and a quality assurance component of ongoing internal assessment promoted consistency in delivery. The professional background of the facilitator was not fixed; they did though require experience of working with PWE. Facilitators were typically persons with a nursing or social care background.

Although not formally evaluated, the course was considered of interest since one of its aims was to increase recipients' confidence in seizure management, emphasising how most seizures are self-limiting, and providing a practical understanding of when seizures do, and do not require emergency treatment.

Michie et al.'s[114] Acceptability, Practicability, Effectiveness/cost-effectiveness, Affordability, Safety/side-effects, Equity (APEASE) framework – which is intended to help guide choices about intervention development and selection for evaluation – emphasises the importance of considering, from the outset, issues such as the affordability and practicability of an intervention so as to ensure it is positioned to achieve its intended outcome once rolled-out. With this in mind, what was also considered advantageous about the ES' course was that its delivery did not depend solely on those with specialist training in epilepsy. The UK has fewer neurologists per head than other developed nations [115-116] and only ~55% of its acute trusts have access to an epilepsy nurse specialist.[117-118] Therefore, a care model that depends solely on such persons may not be sustainable and generalisable.

The course in its original form

The ES' course was delivered to groups of 10-20 people. It lasted ~3 hours, with breaks included. Educational aims for course recipients from the course are specified and outlined in Table 1. Materials for the course included slides, professionally produced video clips of seizure types and first aid and additional information booklets, such as on risk management and emergency medication. An information pack provided participants with a permanent record of the material and included space for notes to promote active processing of material, as well as participation

Table 1 Epilepsy training materials

SCOPE	CONTENT
• To provide practical understanding of seizure management • Audience: broad-based to include teachers, patients, care home staff • Timeframe: single, 3 hour session • Delivery: 1 x educational facilitator with knowledge of epilepsy • Format: group, n=10-20 • Style: interactive • Materials: standardised slides, videos, information booklet	• What is epilepsy? • Causes and triggers • Diagnosis • Seizure types • Potential post-seizure symptoms • Management • When to call an ambulance • Recovery position • Status epilepticus • Treatment, medication, side affects • Risk management • Accessing support and information

The intention was that learning be elicited rather than taught, with the behaviour of the educational facilitator seeking to promote a non-didactic approach. Course participants are encouraged to share experiences and ask questions. To some extent there is therefore meant to be tailoring of the information that is presented so it aligns with the needs of the group being taught (i.e., patient-centred). This, and that the course consists of a number of interacting components which may act both independently and interdependently, means it is what the Medical Research Council refer to as a "complex intervention".[119-120]

Justification for developing seizure management training: a policy and service user response

The ES course is not informed by detailed theoretical modelling or a clear behaviour change model. Having reviewed and observed the intervention, our multidisciplinary research team nevertheless identified several ways by which receipt of the intervention (or a suitable adaption) could plausibly support PWE to make fewer ED attendances and improve patient SO outcomes. These are detailed in full in Appendix 1. In brief, it was considered it might increase patient and SOs practical understanding of seizure management, increase their knowledge of how to make appropriate care and life-style decisions (including the need for ED attendance), and reduce fears about risk, increasing self-confidence and empowerment.

Importantly, the aims of the programme also broadly aligned with what PWE in general and their SOs had said they wanted and how they wanted to receive it. Studies, for example, consistently show PWE and their SOs want more information about living with epilepsy.[27,56, 126-132]

Adapting SAFE

To maximise acceptability, benefit and behaviour change potential, it was recognised that the ES' course would likely require adaptation for the target audience. To this end, the ES agreed for their course to form the basis of a new, adapted course called Seizure First Aid Training For Epilepsy (SAFE) for PWE who frequently attend EDs and their SOs. To identify the changes required we utilised a collaborative framework, underpinned by a philosophy of Experience-Based Co-Design.[133] This is an approach to improving healthcare services that combines participatory and user experience design and processes to bring about quality improvements in healthcare.[133]

The need for a pilot RCT of the seizure first aid training intervention

Having adapted SAFE, it would be necessary to evaluate its efficacy to help decide whether its use within routine practice was appropriate. A definitive RCT is the most reliable methodology for determining efficacy, including of complex interventions. RCTs can be costly and time-consuming – especially when the trial is evaluating change in health service contact and when the follow-up period needs to be reasonably long. Recruitment of participants for RCTs is also often slower or more difficult than expected, thus jeopardising the ability of the trial to answer its intended research question. For example, only 56% of the trials funded between 2004 and 2016 by the NIHR (*Health Technology Assessment programme*) met their final recruitment target.[134] Before proceeding to a definitive RCT the expenditure needs to therefore be justified, the trial deemed feasible and its design optimised.[135]

Because the adapted intervention was new and the target population not studied to a great extent, important process, management, resource and scientific uncertainties existed concerning the feasibility and optimal design of a full RCT of SAFE. The uncertainties were:

- No estimates of likely recruitment, consent and follow-up rates for a definitive trial were available;
- Acceptability of randomisation to participants was unknown;
- Annual rate of ED visits in the TAU group and the likely dispersion parameter were unknown;
- It was unclear whether SAFE could be delivered as intended within a trial context (fidelity);
- Resources/ costs required to deliver SAFE within the trial context were unclear;
- Estimates of the effect of SAFE on primary and secondary outcome measures and their precision were lacking.

For these reasons, and informed by Lancaster et al.'s[136] guidance, an external pilot RCT was considered appropriate. Resembling a full RCT in many respects, such a pilot would allow us to resolve the above uncertainties and permit an informed decision to be made about whether and how to proceed to a definitive trial. In advance of the pilot we specified two criteria against which we would primarily judge the pilot to help evaluate the feasibility of a definitive trial:

1. At least 20% of eligible patients need to agree to participate in the pilot RCT. This was based on results from previous evaluations of self-management interventions, including the diabetes programmes which have since been commissioned by the NHS. A participant uptake rate of less than 20% was deemed to raise significant concerns regarding external validity and could have implications for trial duration, recruitment centres required and feasibility.

2. 12-month primary outcome data needs to be secured for at least 75% of participants in the pilot RCT. This figure was based on results from previous evaluations of self-management interventions which reported rates of 70–80%.[107-108,137]

Depending on the results from the pilot, one of the following judgements, based on Thabane et al.'s[135] decision framework, would be made regarding the feasibility of a definitive trial:

a) Stop – the main study is not feasible
b) Continue, but modify the protocol (feasible with modifications)

c) Continue without modifications, but monitor closely (feasible with close monitoring)

d) Continue without modification (feasible as it is)

Chapter 2: Part A – Intervention development

Introduction

Part A sought to develop SAFE for PWE who frequently visit hospital EDs and their SOs. To do this, the existing ES' 'Epilepsy awareness and seizure management' course was adapted and its behaviour change potential optimised.

Many self-management interventions to date have been derived from limited expert opinion and not involved PWE and other stakeholders in the planning process.[132] To help ensure maximum benefit and acceptability to users, we in contrast used an experience-based co-design approach.[133] Such an approach allows researchers to work collaboratively with persons from the target population to identify their specific learning needs, clarify their delivery preferences and adapt the intervention to match these.

We were also mindful of the need for SAFE to be viable for delivery within the UK health service. [110-112] Examples abound, including from epilepsy,[138] showing the importance of ensuring any new intervention is supported by those who will be asked to ultimately refer their patients to it, deliver it, or allocate resources to it. Therefore, representatives from different key professional bodies involved in the support of PWE were also consulted as part of our co-design approach.

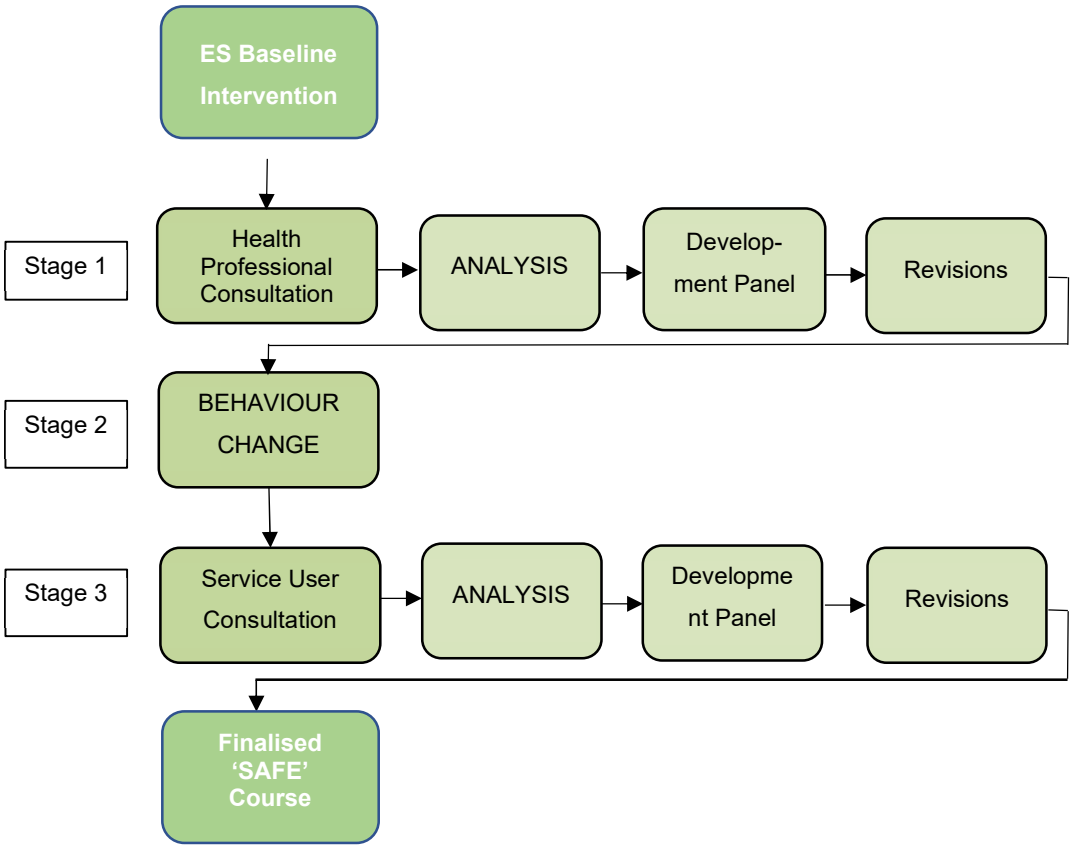
Methods

The co-design process used comprised of three iterative stages – namely, (i) qualitative interviews with health professionals about the existing intervention; (ii) optimisation of its behaviour change potential; and, (iii) focus group discussions with service users. The process is outlined in Figure 1.

Part A participant settings and samples

Stage 1 Recruitment of health professional representatives

Different health disciplines can be involved in the care of PWE. Some patients will identify a general practitioner as the main provider of their ambulatory care, others will identify a specialist, such as a neurologist or epilepsy nurse. The voluntary sector is also an important support structure for many PWE. When someone seeks emergency care for a seizure, other parts of the health system



and selecting individuals that were especially knowledgeable about or experienced with the phenomenon of interest.[140] In addition to knowledge and experience, participant availability and willingness to participate were key considerations.[141-142]

Seven professional organisations (Table 2) identified a representative potentially interested in participating. Each representative was sent a Participant Information Sheet (*see* Appendix 2), with those taking part signing a consent form . Interviews were conducted by a qualitative researcher (A.H.M.) and took place at a time and in a format convenient for the representative; be it via telephone, Skype, or face-to-face at the representative's office. Each representative was offered a consultancy fee of £200.

Table 2 Health professional consultation - groups supporting people with epilepsy

Groups

- The International League Against Epilepsy-UK Chapter
- College of Emergency Medicine
- General practitioners with Specialist Interest in Epilepsy
- Epilepsy Specialist Nurses Association
- North West Ambulance Service NHS Trust
- Cheshire Merseyside Strategic Clinical Networks - Commissioning representative
- Epilepsy Bereaved/SUDEP Action user group

Ultimately, a consultative group comprising of 9 health professionals from 7 different disciplines was established to provide feedback on the content of the ES course. It included two consultant neurologists (one with a specialist interest in epilepsy), two consultants in emergency medicine, a consultant paramedic, an epilepsy nurse specialist, a general practitioner with a specialist interest in epilepsy, a service commissioner with a healthcare background and an educational representative from an epilepsy charity, other than the ES.

Stage 3 Recruitment of service user representatives

Feedback on the intervention was obtained from a purposive sample of service user representatives. PWE were eligible to participate in SAFE training if they met the following inclusion criteria:

- An established diagnosis of epilepsy (1+ year)
- Currently prescribed antiepileptic drug
- Aged 16 years or older (no upper age limit)
- Have visited ED at least once in the past 2 years for epilepsy (as reported by the patient)
- Lives in the North-West area of England
- Able to provide informed consent and participate in SAFE course in English

PWE were excluded from participating in SAFE training if they reported:

- Acute symptomatic seizures, as were those with severe current psychiatric disorders
- Life-threatening medical illness

Patient participants could take part with or without a SO. SOs with the following characteristics were eligible to participate in SAFE training:

- A SO to the patient (e.g., family member, friend) who the patient identifies as providing informal support
- Age 16 years or older (no upper age limit)
- Live in the North-West area of England
- Able to provide informed consent and participate in SAFE course in English

SOs were excluded from participating in SAFE training if they reported:

- Severe current psychiatric disorders (e.g. acute psychosis)
- Life-threatening medical illness

The service user representatives were identified via adverts being circulated (by newsletters, websites and at meetings) to the affiliates of user-groups groups, including the Mersey Region Epilepsy Association, the Brain and Spine Foundation, NeuroSupport and the ES. This approach enabled the recruitment of 'Experts'; defined as a group of informed individuals with knowledge or experience of a specific subject.[143-144] Eligible patients and SOs, interested in taking part, were sent a Participant Information Sheet (*see* Appendix 3) with those taking part signed a consent form.

A total of 23 service user representatives were ultimately recruited. This comprised of 13 PWE (7 male/ 6 female) and 10 SOs (4 male/ 6 female). Each received a £10 shopping voucher.

Intervention Development Panel members

The process was overseen by an intervention development panel. The panel considered and discussed the findings from the interviews and focus groups and made required adaptations to the intervention. The panel included patient and SO representatives (M.P; L.P), a psychologist (A.N), a neurologist (L.R), a medical sociologist (M.M), a research nurse with specialist qualitative research training (D.S), and a representative from the ES' training division. Patient and SO representatives were active in all aspects of the decision-making and reimbursed in line with guidance.[145]

Developing the intervention

Stage 1 Consultation with health professional representatives

Consensus exists regarding what constitutes appropriate seizure first aid.[146-148] Thus, the purpose of this stage was to interview representatives from the main professional bodies caring for PWE to ascertain whether the medical information presented by the programme was correct and whether SAFE could be an intervention they could, in the future, support. It was considered important to seek

feedback from professionals in the first instance in order to prevent PWE (and SOs) being exposed to possibly incorrect information. Moreover, it would allow us to identify from the start what sort of seizure first aid intervention was considered feasible for delivery within the context of the NHS. To this end, the health professional representatives each conducted a baseline document and audio-visual review of the course materials for the ES' existing intervention.

In advance of their interviews, each representative was provided with the course materials. Approximately 2 weeks later, data from each of the 9 representatives was collected via audio-recorded semi-structured interviews. A topic guide was developed to reflect the intended purpose of the stage and on the basis of the literature (*see* Appendix 4). It was refined through the iterative process of conducting the interviews.[149-150] The exact questions varied depending on the representative's area of expertise, but all health professional interviews included key discussions on:

- Identifying inaccuracies in the content of the existing ES programme
- Likes/dislikes and appropriateness of the current content and delivery
- Suggestions of how to make the programme more helpful
- How SAFE might be best rolled out within the NHS, if a future trial found it to be effective

Stage 2 Optimisation of intervention's behaviour change potential

A significant component of the ES' intervention consisted of health-related information provision. It was anticipated that the provision of such information could reassure service users and increase seizure management confidence and competence. However, for some PWE, the information might actually highlight that their prior use of ED conflicted with medical guidance. From a psychological perspective, this could be construed as a threat to self-integrity. As a consequence, these persons might be at risk of rejecting or denigrating the information provided by the SAFE intervention, which may compromise its ability to elicit behaviour change. According to Self-Affirmation Theory,[151] people are fundamentally motivated to preserve a positive, moral, and adaptive self-image and to maintain self-integrity. Consequently, health messages which threaten one's sense of self-image can be subject to defensive processing (e.g., motivated scepticism, unrealistic optimism).[152]

To mitigate against this and maximise the behaviour change potential of SAFE, the intervention development panel decided to introduce a Self-Affirmation exercise – namely, Reed and Aspinwall's[153] 'Kindness Questionnaire' - that individuals would complete at the start of SAFE training. The rationale was evidence indicates having a person complete an exercise, such as recalling one's acts of previous

kindness, prior to receipt of health risk messages reduces resistance to threatening or dissonant health-risk information. It appears people defend a global sense of self-worth[154]– thus a person's self-image can be maintained by affirming in one domain whilst they are being threatened in another domain.

The 'Kindness Questionnaire' was considered ideal as it is a brief (~5 mins), effective[155-156] and does not need to be delivered by specialists. It consists of 10 questions that participants work through by themselves. For example, "Have you ever been concerned with the happiness of another person? Yes/No" and "Have you ever forgiven another person when they have hurt you? Yes/No?" The intention was PWE and SOs would each complete it at the start of SAFE. Their questionnaires were not to be collected by any member of the intervention team and the participant would not be asked how they answered.

Stage 3 Consultation with service user representatives

To allow service user representatives to critically feedback on SAFE, 2 practice courses were run in November 2015 using the adapted intervention that resulted from the first two stages. These were followed by focus group discussions.

The courses took place within a local hospital's education centre and were delivered on weekdays to groups of ~10 patient /SO dyads. A facilitator from the ES (J.B) who was an epilepsy nurse specialist with experience of delivering the ES' course, delivered the courses. She underwent a period of familiarisation with the adapted intervention by reviewing the new materials, a trainers' manual (*see* Supplementary material 1), and meeting the intervention development panel.

The focus groups, of around 60 minutes each, were conducted by a trained qualitative researcher (D.S) to explore participant views. The researcher also observed each course and recorded impressions of participants' engagement with the materials, the group and the facilitator. A topic guide (*see* Appendix 5) reflecting the discrete sections of the course, facilitated the focus groups. Participants were asked about issues related to the course content and delivery, as well as for views around perceived strengths and barriers to its successful implementation.

Analytic process

Interviews, practice course events and the focus groups were recorded (with participants' consent) and transcribed verbatim. Transcripts were checked for accuracy by the researcher (DS) who

conducted the data collection. A comprehensive inductive and deductive approach was used, with 'QSR International's' *NVivo* 10[157] being used to provide a transparent account of the work. Nodes (codes) were created to mark relevant concepts and topics in the text documents. Lower level nodes were then grouped into themes. An account of the process of analysis was logged in the memos attached to categories, interview and focus group documents, including the questions used to interrogate the data, and thoughts and decisions about what themes to focus on. These capabilities and associated process fit with the iterative goals of the development stages of the training intervention. Direct quotations are provided in the text as a means to verify interpretation and illustrate themes.

Results

Health professionals

Analysis of health professionals' responses highlighted three key themes namely; initial impressions, areas of intervention in need of revision to promote effective participation, and, course delivery.

Initial impressions

There was consensus on the need for such an intervention and its potential for cost-effectiveness. As one representative noted:

> *"[I]t will be a powerful tool to upskill and reassure(…)The clearer they are about what constitutes that person's normal epileptic fit and what maybe a bit unusual, the more(…) appropriate the response the better their...overall experience, privacy, dignity and everything to follow (…) [I]t's a fairly easy case to make for the commissioners (…)Resources directed by commissioners to pay for this really unnecessary attendance could be re-directed… win-win."* (ED Consultant)

The existing intervention was seen to provide a useful starting point for adaption and professionals' liked the videos and associated information booklets:

> *"There's a solid foundation in there which you can build on to then create the course to make sure it reaches the kind of outcomes that you are after* (…) *It's just making sure that it hits all those objectives along the way."* (User group representative)

The practical challenges of hosting a group-based course were highlighted by many; it was thought, *"Getting people together may be a difficulty"* that required careful consideration, especially in relation to *"distance and timing"*. It was important therefore to *"(...) think about local delivery and minimising travel time"* (Epilepsy Nurse Specialist).

It was also felt substantial changes were needed to make the intervention appropriate for its new audience and to achieve the aim of attenuating unnecessary/ avoidable ED use.

Areas of intervention in need of revision

It was deemed important to better emphasise the benefits of the course to the patient and SOs with a more focused and *"clear message"* at the start on the need or not for ED attendance after a seizure. Language level was highlighted as an area that required revision in line with the average UK reading age . There were also suggestions, as exampled below, to revise the style of presentation so that it was less for people who might be involved in epilepsy due to their profession:

> *"(...) it's written in quite a wordy way and probably a few more pictures and a few less words...would be better. This is probably a very good presentation to new health care professionals…but probably not great for people that...have no training whatsoever."* (Consultant Paramedic)

It was considered that a *"behavioural change focus"* (Emergency Medicine Consultant; 1) should be brought to the fore and that the benefits to the patient and SO of avoiding unnecessary ED visits should be emphasised. As explained by the general practitioner representative:

> *"It's about helping people manage their epilepsy better. What will the course do for you? What can you get out of the course? (…)The course should focus on behavioural change, but the impression should not be given that the focus is about reducing A&E admissions – that would be counter-productive. Rather, it is about highlighting the benefits, such as better management will reduce inconvenience in having to go to A&E."* (General practitioner)

A recurring theme was the need to better elicit and address patient concerns and that patient and SO participation should be promoted through more interactive exercises, the inviting of questions and the discussing of fears as this was when "*true education happens".* This was summarised by one representative:

> *"(...)seizure management, what you should do and what you wouldn't do...I'd make that part interactive (...) get them to tell you, get their opinion and their views before and then you show them what they probably should do afterwards but find out. Because you'll probably (...) challenge them (...) that's the point where you really get them I think."* (Consultant Neurologist)

It was highlighted by a number of participants that when seizures happen in public places the decision to seek emergency care was not necessarily the patients or SOs. As such, it was recommended that the intervention should support patients to develop and carry with them personalised care plans on paper or on their 'smart phones', which could be used inform decision making by paramedics:

> *"[I]f we [*the ambulance service*] tip up and we don't know anything about you we are taking you to hospital (…) we're tipping up to what we consider to be a first time fit until proven otherwise (..) have a care plan written or something on you that says I'm an epileptic and this is what happens to me normally."* (Consultant Paramedic)

Course delivery

Participants observed that to make the course suitable for delivery within the health service and to promote quality and consistency across trainers, the intervention should become fully standardised and a trainer's manual, including recommended times for each topic/ activity, developed.

With respect to attributes and skills of an ideal course facilitator to deliver the course, some identified epilepsy nurse specialists. However, others felt the epilepsy voluntary sector was well-developed and as such, commissioning organisations from it could help avoid shortfalls where specialist staff were not available. In any circumstance it was considered that:

> *"The facilitator is someone who should have knowledge of epilepsy and be good at leading groups. They need the ability to keep the course on track and to time especially when participants may want to talk a lot!"* (Epilepsy Nurse Specialist)

Changes made by Intervention Development Panel to create Version 1.1

The intervention development panel agreed the intervention's content needed to be revised to be better directed towards the goal of attenuating unnecessary ED use. They therefore specified the following aims for the new intervention:

- To help participants feel more confident to manage their seizures/ the seizures of someone they know
- Know how to tell others how to help
- Know some things that may reduce the chances of a seizure
- Know some things that may reduce the chances of injury from a seizure

The panel also agreed more interactive activities were needed. Interactivity was considered important since it permits participants to share and learn from each other, can foster a sense of empowerment, and means they ask questions and seek clarification to ensure the intervention is tailored to their needs. As part of their discussion, evidence from the diabetes self-management literature was reflected upon by the panel which suggests interaction between participants and the facilitator can be important in promoting behaviour change. Skinner et al.[158] in their study calculated the proportion of facilitator to participant talk during a group-based education intervention for diabetes and found

lower facilitator talk ratios predicted greater improvements in participants' metabolic control and beliefs about diabetes .

In line with these requirements, A.N and D.S revised the intervention generating new presentation materials, introduced new content and generated a training manual for facilitators. In doing this, attention was given to presenting information in an easy-to-understand style, with feedback from the 'plain English' section of the ES' information department being obtained. Table 3 details the changes made to the ES' intervention at this stage.

To promote more interaction, four new activities were introduced. One involved practicing the recovery position; another required subgroups to find answers to different questions concerning seizure first aid from amongst a group of acetates and to present these. This was designed to help identify participant beliefs, fears and for these to be discussed. The final two activities centred on case studies. These involved participants being read illustrated stories of patients and asked to consider what things the patient in the story might have done to have achieved a better outcome. The carrying of epilepsy identification was one way in which the outcome of one of the stories could have been changed.

Within the revised intervention, it was estimated that 114 minutes (47.5%) now comprised interactional/networking elements; 114 minutes (47.5%) taught slides; and, 12 minutes (5%) video

Service users

Having received version 1.1 of the adapted course, 3 key themes emerged from the analysis of service users' responses. These included; 'the need to know', 'barriers and drivers to effective participation in training', and, 'course delivery'.

The need to know

All patient and SO participants identified the need for such a course with lack of prior support in self-management as a recurring topic of debate. For example, participants explained:

> *"It can be quite overwhelming I think for... partners. It's...'all on their shoulders' what happens. I think your SO needs a lot of support to"* (Patient 3, M, Focus Group [FG] 1).

> *"The consultants they just presume that you know* [about epilepsy]*...but for all the years he got put on tablet or tablets...you didn't see or hear any of this* [information presented by course]*. So it's suddenly all of an 'eye-opener' and talking here you realise we are not on our own"* (SO 1, F, FG1).

Similarly, another SO noted:

> *"I always think of epilepsy as the poor relation (...) not much on TV or adverts about epilepsy support (…). A course like this helps to develop that sense of support as well as improve knowledge."* (SO 2, M, FGD).

SO concerns centred on the "*need to know I'm doing the right thing"* (SO 4, F, FG1). PWE expressed concerns in relation to disclosure and how best to tell others around them how they should help if a seizure happened; they wanted information and advice on how best to manage this. Overall, service user participants described three areas of perceived need, namely; knowledge acquisition around epilepsy, emotional and/ or practical support, and, dealing with isolation and stigma.

Table 3 Content of original course and revisions that were made to it in light of feedback

Original course – Version 1.0				**Post stage 1 – Version 1.1 (Post professional consultation and discussion by intervention development panel . This pilot version then was subsequently presented to users)**				**Post stage 2 – Version 1.2. (Post pilot training sessions, user FGs and discussion by interventon development panel. This final version was delivered as the training intervention in study phase B – pilot RCT**			
Title: "Epilepsy awareness and seizure management"				**Title:** "Epilepsy Seizure First Aid Training"				**Title:** "Managing seizures: epilepsy first aid training, information and support"			
Duration: 3 hours				**Duration:** 3 hours				**Duration:** 4 hours			
Materials: Slide projector, flip-chart, video, information packs, including, wallet sized first aid instructions cards, Paper Epilepsy ID Cards, the contact details of further information, Certificates of attendance.				**Materials:** Slide projector, flip-chart, video, information packs, including, wallet sized first aid instructions cards, Paper Epilepsy ID Cards and instructions for IDs on phone, the contact details of further information, Certificates of attendance.				**Materials:** Slide projector, flip-chart, video, information packs, including, wallet sized first aid instructions cards, Paper Epilepsy ID Cards and instructions for IDs on phone, the contact details of further information, the web address for copies of the course materials, Certificates of attendance.			
Order	**Learning topic**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**
1	Aim of this session:	Slide	-	1	Welcome	Slide	5	1	Welcome	Slide	5
2	Objectives	Slide	-	2	Taking on information (Kindness Questionnaire)	Interactive	10	2	Goals of this course	Slide	2
3	Session outline	Slide	-	3	Goals of this course	Slide	2	3	What would you like from today?	Interactive	20
4	Myth or truth?	Interactive	-	4	What would you like from today?	Interactive	5	4	True or false?	Interactive	12
5	What is epilepsy?	Slide	-	5	True or false?	Interactive	8	5	Taking on information (Kindness Questionnaire)	Interactive	10
6	The brain...	Slide	-	6	Epilepsy, seizures & how the brain works	Video	10	6	Epilepsy, seizures & how the brain works	Video	10
7	Lobes of the brain	Slide	-	7	First aid for convulsive seizures	Interactive	10	7	First aid for convulsive seizures	Interactive	10
8	How the brain works...	Slide	-	8	What can you do to help someone during a seizure?	Slide	5	8	What can you do to help someone during a seizure?	Slide	5
9	Seizures happen when...	Slide	-	9	What not to do during a seizure	Slide	5	9	What not to do during a seizure	Slide	5

Table 3 *continuation*: Content of original course and revisions that were made to it in light of feedback

Original course – Version 1.0				**Post stage 1 – Version 1.1 (Post professional consultation and discussion with IDP. This pilot version then was subsequently presented to users)**				**Post stage 2 – Version 1.2. (Post pilot training sessions, user FGs and discussion with IDP. This final version was delivered as the training intervention in study phase B – pilot RCT**			
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Order	**Learning topic**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**
10	Seizures are...	Slide	-	10	What to do after the seizure has stopped	Slide	5	10	What to do after the seizure has stopped	Slide	5
11	Possible causes of epilepsy	Slide	-	11	When to call an ambulance?	Slide	10	11	Questions or comments?	Interactive	10
12	Diagnosis	Slide	-	12	Questions or comments?	Interactive	5	12	Post-seizure states	Slide	15
13	Triggers	Slide	-	13	Refreshment break	Networking	10	13	Injuries	Slide	2
14	Seizure types & first aid	Video	15	14	Recovery position	Slide	2	14	When to call an ambulance?	Slide	10
15	Seizure management	Interactive	-	15	Recovery position	Video	2	15	Questions or comments?	Slide	10
16	Recovery position	Slide	-	16	Let's practice the recovery position	Interactive	8	16	Refreshment break	Networking	10
17	Maintain airway	Slide	-	17	Questions or comments?	Interactive	5	17	Recovery position	Slide	2
18	When to call an ambulance?	Slide	-	18	Who needs to know how to help?	Interactive	3	18	Recovery position	Video	2
19	Most seizures are...	Slide	-	19	What they need to know & why	Slide	5	19	Let's practice the recovery position	Interactive	15

Table 3 *continuation*: Content of original course and revisions that were made to it in light of feedback

Original course – Version 1.0				**Post stage 1 – Version 1.1 (Post professional consultation and discussion with IDP. This pilot version then was subsequently presented to users)**				**Post stage 2 – Version 1.2. (Post pilot training sessions, user FGs and discussion with IDP. This final version was delivered as the training intervention in study phase B – pilot RCT**			
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Order	**Learning topic**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**
20	Status epilepticus	Slide	-	20	How to get this information to them. Family, friends & work colleagues:	Slide	5	20	Questions or comments?	Interactive	5
21	Sudden Unexpected Death in Epilepsy	Slide	-	21	How to get this information to them. Members of the public and health workers:	Slide	5	21	Who needs to know how to help?	Interactive	5
22	Treatment with drugs	Slide	-	22	Questions or comments?	Interactive	5	22	What they need to know & why	Slide	5
23	Medications	Slide	-	23	Refreshment break	Networking	10	23	How to get this information to them. Family, friends & work	Slide	5
24	Medication	Slide	-	24	Personal stories - introduction	Slide	2	24	How to get this information to them. Members of the public and health workers	Slide	5
25	Possible side effects of medications	Slide	-	25	Ben's story	Slide	5	25	Questions or comments?	Interactive	5

Table 3 *continuation*: Content of original course and revisions that were made to it in light of feedback

Original course – Version 1.0				**Post stage 1 – Version 1.1 (Post professional consultation and discussion with IDP. This pilot version then was subsequently presented to users)**				**Post stage 2 – Version 1.2. (Post pilot training sessions, user FGs and discussion with IDP. This final version was delivered as the training intervention in study phase B – pilot RCT**			
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Order	**Learning topic**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**
26	Other possible treatments	Slide	-	26	How to change what happened to Ben? (Carrying medical ID; triggers)	Interactive	5	26	Refreshment break	Networking	5
27	Minimising risk	Slide	-	27	Triggers	Slide	5	27	Personal stories - introduction	Slide	2
28	Keeping safe	Slide	-	28	Knowing your triggers	Slide	5	28	Ben's story	Slide	6
29	Supporting the 'whole person'	Slide	-	29	Some ways of dealing with triggers	Slide	10	29	How to change what happened to Ben? (Carrying medical ID; triggers)	Interactive	5
30	To the future...	Slide	-	30	Questions or comments?	Interactive	5	30	Triggers	Slide	5
31	Further sources of information	Slide	-	31	Sandra's story	Slide	6	31	Knowing your triggers	Slide	4
32	Any questions?	Interactive	-	32	How to change what happened to Sandra (Warning signs; home safety)	Interactive	5	32	Some ways of dealing with triggers	Slide	4

Table 3 *continuation*: Content of original course and revisions that were made to it in light of feedback

Original course – Version 1.0				**Post stage 1 – Version 1.1 (Post professional consultation and discussion with IDP. This pilot version then was subsequently presented to users)**				**Post stage 2 – Version 1.2. (Post pilot training sessions, user FGs and discussion with IDP. This final version was delivered as the training intervention in study phase B – pilot RCT**			
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Order	**Learning topic**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**	**Order**	**Topics**	**Learning activity**	**Minutes allotted**
33	Certificates of attendance	Slide	-	33	Main points to remember, If you have epilepsy...	Slide	5	33	Sandra's story	Slide	6
34					Main points to remember; If you know someone with epilepsy...	Slide	5	34	How to change what happened to Sandra (Warning signs; home safety)	Interactive	2

Notes:

ID = Identification. FG= focus group

Taken as a whole, the content of the revised course (Table 3: Post stage 1 – Version 1.1), was felt to be *"excellent"* (Patient 3, FG 2) and appropriate. Of particular importance to the users' was the straightforward guidance that an ambulance was required when seizures lasted for 5 or more minutes. This information alone was found to be helpful and reassuring and some said they would no longer always call straightaway for an ambulance: *"I think I will wait longer* [to call an ambulance] *than I did before picking up the phone."* (SO 3, F, FG 2) *"(...) I will wait* [to call an ambulance], *rather than when he has a seizure going for the phone straightaway."* (SO 7, F, FG2)

Concerns with regard to how to tell others about epilepsy and how to help if a seizure happens were expressed:

> *"Like when you go somewhere you need to remember to like tell people that you have seizures"* (Patient 1, M, FG1)

> *"I need to know how best to share with others* [family/friends/workplace] *the implications of having epilepsy"* (Patient 2, F, FG1)

To this end there was consensus, for the most part, that the need to feel informed and reassured on what to do when seizures occurred had been met. Participants expressed how they had *"learned a lot"* (SO 5, F, FG1) from the session.

The balance between taught and interactive components was felt appropriate. The provision of information was viewed as reassuring and the opportunity to practice the recovery position was valued. As one patient asserted:

> *"Watching a video would just go straight over me head, but actually putting* [patient name] *on the floor and putting him in the right position will help. For me that's very useful (...) something like that I won't forget"* (Patient 5, F, FG1)

The training session was considered to cover more than implied by its title. Participants said the "*wider remit"* (Patient 10, F, FG2) was desirable, but that a more accurate title was needed to engage future service users - 'Managing seizures: epilepsy first aid training, information and support' was identified as more suitable for the purposes of advertising it.

Barriers and drivers to effective participation in training

Service users' perceptions of barriers and drivers to successful training were explored. One was the self-affirmation 'Kindness Questionnaire'.[152] It's positioning and purpose to the session was not understood by most participants, *"(...) just coming into the session the questionnaire seemed*

inappropriate" (SO 3, F, FG1). It was also found by some to be threatening, *"(...) it felt like a test and a bit off putting"* (SO 4, F, FG1).

Another barrier was some service users reported *"There's a lot of information to take in"* (Patient 4, M, FG1) and issues relating to memory difficulties were highlighted. Participants therefore supported the use of handouts and requested an online copy of the materials that they could access and share with others.

With respect to content, important feedback from service users was that they appreciated that attention was given to what the different types of seizures are, how to manage them and that the focus was not simply on "*grand mal seizures*" (SO 5 F, FG1). However, they suggested that more time be given to exploring triggers and auras and to explain that not everyone has triggers, which in itself, is a potential risk. It was also suggested that new sections should be included to discuss the risks associated with post-ictal states and how best to deal with them. Finally, some suggested that "*dealing with an injury as well as dealing with the seizure can be difficult*" (SO 7, F, FG2). As such, information and advice was needed on how to deal with common seizure injuries.

Course delivery

The size of the group (up to ~20) was considered appropriate and encouraged discussion. Indeed, peer support and a sense of feeling "*less isolated"* was highlighted as a key training experience. Many patients had not previously discussed their epilepsy with people other than their immediate family members and/ or healthcare professionals. They valued the group format, and described how they appreciated being able to meet others "*in the same boat*" and "*realising you are not on your with it*" (Patient 6, M, FG1). One SO noted:

> *"[R]eally glad I came. I think it's just being around people who know exactly, exactly how you feel and that's why this should have been put on a long, long time ago."* (SO 1, F, FG1)

In terms of who would be best to facilitate the course, many felt it should be a health professional as they believed this would make the course *"credible"* (Patient 8, F, FG2) and promote uptake. Others however, argued it could be facilitated by a representative from a user group as what was most important was that the trainer was knowledgeable, empathetic, and had the skills to facilitate discussions. Either way, it was argued that standardised training for the facilitators was important.

Changes made by Intervention Development Panel to create Version 1.2

The users' feedback led to a refashioning of a number of details in the way SAFE was to be delivered (Table 3: Post stage 2 – Version 1.2.). To increase the acceptability to users of the self-affirmation 'Kindness Questionnaire', it was agreed that this would not be introduced to participants until approximately ~30 minutes into the session and would follow the 'icebreaker', rather than immediately at the start.

Given the main aim of SAFE was to help patients and SOs manage uncomplicated seizures, the panel revised SAFE so information on managing common post-ictal states was also included. However, for the same reason, training patients and SOs in dealing with seizure injuries as requested was deemed to be beyond SAFE's scope. As such, SAFE was modified to simply acknowledge the possibility of injuries and direct participants to external resources on this.

The length of Version 1.2 of SAFE was extended from 3 to approximately 4 hours. The additional time meant more time could be allocated to the interactive elements of SAFE. Finally, a password-protected website (http://www.seizurefirstaid.org.uk/Intervention/) providing a copy of SAFE's content was developed in an effort to mitigate against potential memory difficulties within the target population. It also provided a means by which participants could share SAFE's content with others in their social network.

Discussion

The focus of part A was to develop an epilepsy first aid training intervention that met the needs and preferences of PWE who frequently visit hospital EDs and their SOs. To promote adequate development and piloting,[159] we worked collaboratively with service users and other key stakeholders. This activity was underpinned by the Medical Research Council's complex intervention guidance.[159] The process enabled us to access the unique perspectives of service users and health professionals. Clear, tangible changes to the ES' course were made in response to the feedback received and the developed SAFE intervention is substantially different in content and form. By doing this, the acceptability of SAFE within the target population has been increased. Stakeholder collaboration has maximised the SAFE's potential benefit and, positioned it well for sustained use within the health service, should this ultimately prove warranted. We described the process we followed and detailed the content of the finalised intervention that will be used within the pilot trial. Such an account is rare, with outcome papers frequently being criticized for not providing readers with sufficient information to interpret trial results.[160]

Chapter 3: Part B: Pilot RCT - Methods

Introduction

Part B of this project was an external pilot randomised controlled trial (RCT) of Seizure First Aid Training For Epilepsy (SAFE) + Treatment As Usual (TAU) vs. TAU alone. It sought to generate the following:

- Estimates of eligibility rate
- Consent rate
- Recruitment rate
- Retention rate
- Acceptability of randomisation to participants
- Speed of recruitment
- Estimates of completion rates of study assessment tools
- Rates of unblinding
- Annual rate of emergency department (ED) visits in the TAU group and the likely dispersion parameter
- Summary statistics to measure the effect of SAFE on the proposed primary and secondary outcome measures for a future definitive trial and the precision of such estimates at the post-treatment time points
- Determine the feasibility of measuring the primary outcome measure, ED use, by means of routine data.

Part B – design

The trial was as a multicentre, parallel arm pilot RCT. Participants were people with epilepsy (PWE) with or without a significant other (SO). PWE (and their SO if they participated with one) were randomised in a 1:1 intervention-to-control ratio and followed up for 12 months. The SAFE group received TAU and was offered the SAFE course, while the control group received TAU. To maximise recruitment, the TAU group were offered the intervention once all scheduled 12-month follow-up assessments had been completed. The study also contained an evaluation of the fidelity with which SAFE was delivered (Chapter 5) and an economic evaluation of the cost of delivering it (Chapter 7). The trial's design and the intended flow of participants are shown in Figure 2.

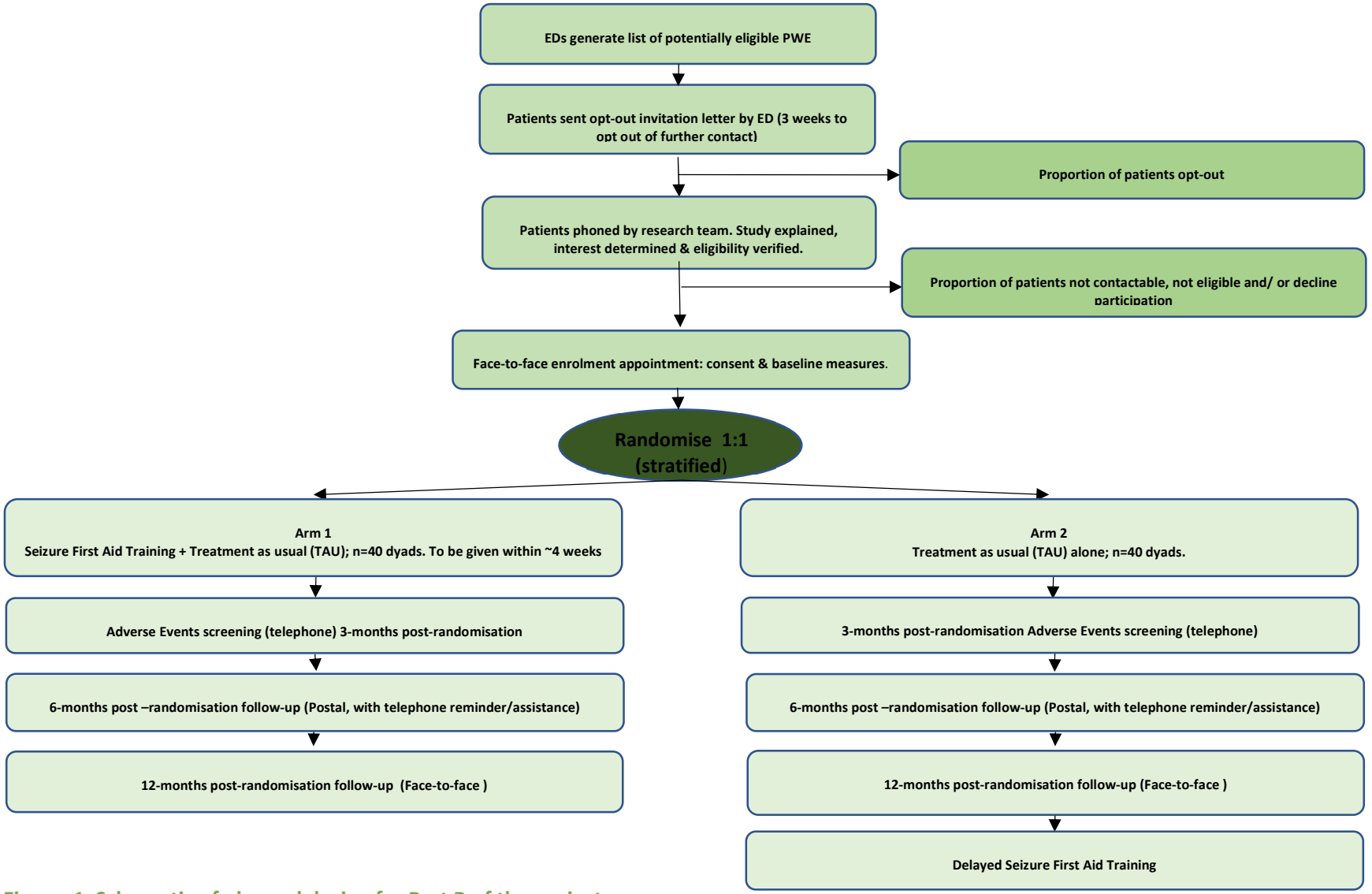


Figure 1 Schematic of planned design for Part B of the project

Trial approval and monitoring

The trial protocol received the favourable opinion of the National Research Ethics Service Committee North West—Liverpool East (15/NW/0225) and Health Research Authority (166241). Its Sponsor was the University of Liverpool (UoL001108). The trial was registered on an open access system (ISRCTN13 871 327).

Trial progress and conduct was monitored by an independent Trial Steering Committee composed in line with NIHR guidelines (see Acknowledgements). In line with these oversight guidelines, a Data Monitoring and Ethics Committee was not required.

Study setting and population

Centres

Participants were retrospectively identified from the EDs of 3 National Health Service (NHS) Merseyside hospitals – namely, Aintree University Hospital, Arrowe Park Hospital and the Royal Liverpool University Hospital. Together, these EDs served a local population of ~827,000 people, within which the prevalence of adult epilepsy was 0.98%.[26] At each site, an ED consultant acted as a local principal investigator.

The EDs were selected as research sites since they would likely be similar to those sites that would be most appropriate for a definitive trial. Specifically, they serve a population featuring high levels of social deprivation,[161-162] a level of epilepsy control that has been documented to be worse than the national average, and rates of emergency admissions for epilepsy that are amongst the highest in England (Liverpool 9th highest; Wirral 12th highest).[163] Epilepsy control is here defined – on the basis of the 2012/13 Quality and Outcome Domains Framework – as the percentage of PWE prescribed antiepileptic drug/s in the local population who have been seizure-free in the previous 12 months. When the trial was being designed, 70.9% of PWE from the Clinical Commissioning Group areas served by the hospitals were seizure free. The national average at the time was 75.4%.[163]

Participant inclusion criteria

Patients with the following characteristics were eligible for recruitment:

- Established diagnosis of epilepsy (≥1 year)
- All epilepsy syndromes and all types of focal and generalised seizures

- Currently being prescribed an antiepileptic drug/s
- Aged 16 years or older (no upper age limit)
- Visited an ED for epilepsy on 2 or more occasions within the previous 12 months (as reported by patient)
- Lives within 25 miles of any of the 3 ED recruitment sites
- Able to provide informed consent, participate in SAFE and independently complete questionnaires in English.

SOs with the following characteristics were eligible:

- A SO to the patient (e.g., family member, friend) who the patient identifies as providing informal support
- Aged 16 years or older (no upper age limit)
- Lives in the North-West area of England
- Able to provide informed consent, participate in SAFE and independently complete questionnaires in English.

Participant exclusion criteria

Patients with the following characteristics were excluded:

- Actual or suspected psychogenic non-epileptic seizures alone or in combination with epilepsy
- Acute symptomatic seizures related to acute neurological illness or substance misuse (e.g., alcohol or drug-induced)
- Severe current psychiatric disorders (e.g. acute psychosis) or life-threatening medical illness
- Enrolled in other epilepsy-related non-pharmacological treatment studies.

SOs with the following characteristics were excluded:

- Severe current psychiatric disorders (e.g. acute psychosis) or life-threatening medical illness
- Enrolled in other epilepsy-related non-pharmacological treatment studies.

Screening

Stage 1

There is no central, 'live' system that can be accessed and searched to identify PWE who have made visits to NHS EDs in England. Well-documented challenges to information sharing between NHS

services also meant specialist services and GPs are not necessarily aware of ED attendances made by PWE for whom they care.[20-21] Hospitals in the United Kingdom do though maintain local electronic records of attendances at their EDs. For each attendance, a local record contains the patient's contact details and a number of searchable fields, including date of attendance, patient age, home postcode, presenting complaint and, if provided, a discharge diagnosis. These attendance systems of the EDs were used to identify PWE who had attended the EDs within the last 12 months for invitation into the trial.

Searches of the local systems for PWE were completed by the Business Intelligence Units of the respective hospitals. We had envisioned that an independent expert panel of neurologists and ED clinicians would determine the search criteria to be used (e.g., presentation and diagnosis codes). During study set-up it became apparent that the architecture of the systems and the coding processes at each of the sites were sufficiently different that local knowledge of the system was required to have confidence that the criteria used would allow for a sufficiently sensitive and specific search to occur. Therefore, we instead worked with the local principal investigators at each site to identify the optimal search strategy for it. The terms used are detailed in Appendix 6.

Stage 2

The 'triage cards' of the patients captured by the searches during Stage 1 were reviewed by the local principal investigator team to identify persons who were and were not eligible to invite. This level of detailed screening was necessary since: i) no symptom presentation is pathognomonic with epilepsy (e.g., a presentation coded as 'blackout/faint' or 'fit/ seizure' could be attributable to syncope, diabetes, head-injury or stroke, rather than epilepsy); and, because ii) the discharge diagnosis field was often empty. In 2016/17, ~35% of ED attendances in England were not allocated a valid primary diagnosis code https://files.digital.nhs.uk/8B/94BB9E/AE1718_supporting_information.pdf [accessed 27th August, 2019].

Those patients who, following review of their 'triage card, were considered ostensibly eligible by the local investigator were sent a prepared invitation pack. It included a covering letter from the ED consultant and a patient Participant Information Sheet (*see* Appendix 7). The letter informed the patient that unless they opted out of further contact within 3 weeks or sent notification that they were ineligible, they would be telephoned by the research team with more information about the study. Patients could opt-out by email, telephone or by returning a FREEPOST slip. Those opting out

were encouraged to detail any reasons. Those interested in taking part were asked to await contact by the research team and consider whether they might like to take part with a SO.

Stage 3

Interested patients were telephoned to answer questions the patient had, confirm whether or not the patient wanted to participate and verify their eligibility (including that they had made 2 or more ED visits within the last 12 months for epilepsy). If a person was confirmed as eligible and wanted to participate, then consent in principle was taken over the telephone and the research worker arranged a baseline/ enrolment appointment at which informed signed consent was to be obtained from them and their SO if they were taking part with one.

Multiple calls were attempted with patients who had not opted-out. Attempts to call participants were made on different days of the week and at different times. Three phone calls were attempted – typically one morning, one afternoon and one in the evening. It was important to do this to minimise the influence of work status on ability to consider participation in the study. If a person could not be contacted (e.g., a correct number was unavailable or they did not answer), then they were posted a letter asking them to contact the team if they were interested in participating. The sending of a letter was not in the original protocol. It was a substantial amendment, and with funder and governance approval, incorporated into Protocol 1.2, 9.6.2016.

Randomisation

Computer-generated randomisation was conducted remotely by the Liverpool Clinical Trials Centre (CTU, Registration Number 12). Following consent and completion of the baseline measures the research worker entered the participant's information onto an online system and sent a request for randomisation to the CTU. This ensured randomisation was performed independent of the trial's research and statistical teams.

Patient participants were randomised to either the SAFE+TAU or TAU alone arm. If they were taking part with an SO, the patient-SO were randomised as a dyad. The unit of randomisation was the individual patient. Randomisation was 1:1 intervention to control and used a web-based minimisation program with a built-in random element utilising stratification factors that were not made known to the researcher (D.S) involved in data collection to minimise any potential for predicting allocation.

Like most trials using stratification,[164] we limited stratification to two factors. We selected factors based on evidence of their potential importance in influencing ED use and also pragmatic considerations. The factors chosen were recruitment site from which a patient participant was identified and whether or not the patient reported, at baseline, feeling stigmatised by epilepsy.

The reason for stratifying by recruitment site was that people who reside within more socially deprived areas are found to be more likely to use ED[44-45] and because the catchment areas of the 3 ED recruitment sites were not completely equal in deprivation. The reason for stratifying by felt stigma was because, as reported in Chapter 1, Ridsdale et al. found it to be a possible predictor of ED use and that it held a similarly sized relationship with subsequent ED use as mastery/ confidence managing epilepsy[27,131] It was not considered ideal to stratify by mastery/ confidence in epilepsy since it is typically measured on a quasi-continuous scale, rather than categorical and so stratifying patients by it would require transformation of scores prior to randomisation by the research worker (D.S) who we sought to keep blind to stratification factors.

Blinding and protection from bias

This was a single-blind (outcome assessors blinded) pilot trial. All participants were aware of their treatment allocation. The trial statistician (S.N), senior trial statistician (C.T.S) and the research worker (D.S) responsible for consent, data collection and the conducting of outcome assessments were not. Participants were asked not to inform the research worker of their treatment allocation and were reminded of this at the start of each data collection point.

Allocation concealment was maintained by email confirmations being automatically generated each time a participant randomisation was requested by the research worker and these being sent to relevant staff with or without details of the treatment allocation included, depending on their role in the study. The research worker submitting the request received only a confirmation of successful randomisation, whilst an administrator was notified of persons randomisation to SAFE. The administrator liaised with patients (and their SOs) to arrange attendance at a SAFE course. Participants usual care providers were informed of their patients' involvement in the trial, but not of treatment allocation.

To evaluate how the blinding process worked, the research worker completed a 'Research Worker Treatment Guess' form after the 12-month follow-up assessment or withdrawal of each participant and reported the circumstances of any unblinding.

PWE attending SAFE courses did so outside of their routine clinic appointments and so we did not expect transfer of SAFE-related knowledge (and therefore contamination of the TAU group) between those in the SAFE+TAU and TAU alone arms at a single site.

Intervention delivery

The SAFE intervention has been fully described in Chapter 2. Materials for the course included PowerPoint presentation slides, videos illustrating seizure types, the recovery position and appropriate first aid. Patients took copies of the slides and additional information booklets (such as on risk management and emergency medication) away with them and could access and share a website of the course's content.

For the purposes of the pilot RCT a single facilitator (J.B; *see* Acknowledgements), recommended by the ES, was trained to deliver SAFE. They were a registered nurse with 30 years of experience (18 months as an epilepsy nurse) and had delivered the ES' original course. Their training in the delivery of the revised intervention consisted of them, familiarising themselves with the trainer manual, delivering 2 practice courses with participants outside of the trial, and receiving feedback from the intervention development panel.

The SAFE courses were delivered within the education centre of a local teaching hospital. It was chosen as it was accessible and limited the distance participants needed to travel (i.e., it was near a major transport hub and centrally located), familiar to the patients and it had access to emergency care services, if required.

To facilitate group interaction, chairs were arranged in a semicircle. A flip chart was set up for writing notes and discussion points. Workbooks, pens and name badges were ready for participants on arrival.

An administrator was present at each course to support its running. This included audio recording the sessions and noting participant attendance. If a participant was present at the start and end of the course, it was considered they had received the intervention in full. If a participant was unable to attend their scheduled course, the administrator attempted to contact them to identify the reason/s and offer an alternative course date if appropriate and available.

All data on attendance and the communications between the administrator and participants to arrange attendance was inputted by them into a secure electronic database. This data was not accessible to the researcher responsible for participant recruitment and follow-up.

Data collection tools and follow-up visits

Primary

The proposed primary outcome measure for a definitive trial of SAFE would be subsequent ED use. This would require data on the number of ED visits each participant made over the 12-months following recruitment. Within the pilot trial this data was sought from the NHS's Hospital Episode Statistics (HES) system. This system is theoretically able to identify, amongst other things, the number of attendances a patient has made at all English EDs. It is primarily an administrative system, but with explicit patient consent, governance approvals and payment of a fee, it is possible to apply to NHS Digital for this HES system to be interrogated for research purposes. For the pilot RCT a request was thus submitted for the HES system to be searched for ED attendances within specified time periods by the patient participants (using their unique NHS numbers). As evidence was available at the time to indicate that for ~30% of ED visits no diagnosis is recorded https://files.digital.nhs.uk/8B/94BB9E/AE1718_supporting_information.pdf [accessed 27th August, 2019], we simply requested data on the total number of ED visits made for any reason by individual patient participants during specified periods. Information on the number of visits each person had made over the 12 months prior to randomisation was also sought for the purpose of adjustment within the analyses and to allow comparison of self-reported ED use to routine data.

Secondary

The secondary outcome measures (Table 4) were based on participant self-report and collected using clinical research forms (CRFs). Baseline (T0) and 12-month (T3) follow-up measures were completed during face-to-face sessions with research worker DS. During these appointments (and in line with completion guidelines) patient or SO participants completed their questionnaire by themselves, with the research worker only offering assistance if requested. An abbreviated questionnaire assessment occurred at 6 months follow-up (T2) for which participants were posted a set of questionnaires for completion and instructed to return them in a pre-paid envelope.

The use of routine outcome data within clinical trials is advocated by the National Institute for Health Research. However, limited evidence on its utility exists (*see* for example, Powel et al.[165]). The pilot

Table 4 Self-reported outcome measures by assessment and participant type

Outcome	Participants	Measure and derivation of outcome	Baseline (T0)	3-month (T1)	6-month (T2)	12-month (T3)
ED visits	PWE	At T0: *How many times have you used the following hospital and day care services over the past 12 months for epilepsy? Casualty / Accident & Emergency (A&E)* At T2: *You last saw our researcher for a face-to-face appointment about 6 months ago. Since then, have you visited a hospital Accident and Emergency (casualty) department for epilepsy? (No, not at all or yes).* *If Yes, how many times in total have you visited since your last face-to-face appointment with us?* At T3: *During the past 12 months have you visited a hospital Accident and Emergency (casualty) Department for epilepsy? (No or Yes).* *If yes, how many times in total have you visited during this time?*	✓	-	✓	✓
Fear of seizures	PWE; SOs	*Epilepsy Knowledge and Management Questionnaire – Fears subscale (5 items)* (Epton et al.[152]). Total fear score was calculated as the sum of the scores on the scale's 5 items, ranging from 5 to 30. Higher scores correspond to greater levels of fear.	✓	-	-	✓
Knowledge of what to do when faced with a seizure	PWE; SOs	*Items from Thinking About Epilepsy Questionnaire (13 questions*) (Martiniuk et al.[166]) Knowledge score was calculated as the number of questions answered correctly (out of a total of 13). Only correctly answered questions were recorded. No down weighting was be applied for incorrectly answered questions or questions not answered.	✓	-	-	✓

Table 4 *continuation*: Self-reported outcome measures by assessment and participant type

Outcome	Participants	Measure and derivation of outcome	Baseline (T0)	3-month (T1)	6-month (T2)	12-month (T3)
Confidence managing seizures/ epilepsy	PWE; SOs	*Epilepsy Mastery Scale (*Wagner et al.[61]) (PWE; 6 items). Total score was calculated as the sum of the scores on the scale's 6 items (with reverse weighting for two of the items), ranging between 6 and 24. Higher scores correspond to higher levels of mastery. *Parents Response to Child Illness Scale- Condition Management subscale* (SOs; 6 items) (Shore et al. [167]*).* Total score was be calculated as the average of the scores to scale's 6 items, ranging between 1 and 5. A higher score corresponds to a higher level of confidence.	✓	-	✓	✓
Quality of life	PWE	*Quality of Life in Epilepsy Scale-31-P (31 items)* (QOLIE-31-P) (Cramer et al.[168]) Total QOLIE-31-P score was calculated, ranging from 0 and 100. Higher scores correspond to a better quality of life.	✓	-	✓	✓
Distress	PWE; SOs	*Hospital Anxiety and Depression Scale (14 items)* (HADS) (Zigmond et al.;[169] Snaith[170]). Total anxiety score and total depression scores were calculated, ranging between 0 and 21. Higher scores correspond to higher levels of anxiety or depression respectively. Anxiety and depression categories were defined based on the total anxiety or depression score as: • 0 to 7, 'Normal range' • 8 to 10, 'Suggestive of anxiety / depression' • 11 to 21, 'Probable anxiety / depression.' (Measure used with permission from GL Assessment. Date permission granted 17/07/2015)	✓	-	-	✓

Table 4 *continuation*: Self-reported outcome measures by assessment and participant type

Outcome	Participants	Measure and derivation of outcome	Baseline (T0)	3-month (T1)	6-month (T2)	12-month (T3)
Seizure control	PWE	At T0, *Thapar's Seizure Frequency Scale* for the prior 12 months. (Thapar et al. [171]) At T2 and T3, patients asked for number of seizures (any type) since last assessment and dates of the first and most recent. To assist patients were offered a seizure diary at T0.	✓	-	✓	✓
Felt Stigma	PWE; SOs	*Stigma of Epilepsy Scale (9 items)* (Jacoby;[62]). Total stigma score calculated as sum scores on 3 items of scale, ranging from 0 to 9. Higher scores correspond to higher levels of stigma. Stigma categories were defined as: • 0, 'No stigma' • 1 to 6, 'Mildly to moderately stigmatized' • 7 to 9, 'Highly stigmatized'	✓	-	-	✓
Burden	SOs	*Zarit Caregiver Burden Inventory* (Zarit et al.[172]). Total burden score calculated as sum of scores on the measure's 22 items, ranging from 0 to 88. Higher scores correspond to a greater burden. Burden categories were defined as: • 0 to 20, 'Little or no burden' • 21 to 40, 'Mild to moderate burden' • 41 to 60, 'Moderate to severe burden.' • 61 to 88, 'Severe burden.'	✓	-	✓	✓
Health economics	PWE	*Client Service Receipt Inventory* (Beecham et al.[173] 1992) and *Euroqol-5D* (13 items) (Williams[174])	✓	-	-	✓
Feedback on trial participation	PWE; SOs	Adapted from Magpie Trial (3 items) (Smyth et al.[175]) (1) "If time suddenly went backward, and you had to do it all over again, would you agree to participate in the Seizure First Aid Training trial?"; (2) "Please tell us if there was anything about the Seizure First Aid Training Trial that you think could have been done better"; (3) "Please tell us if there was anything about the Seizure First Aid Training Trial, or your experience of joining the trial, that you think was particularly good"	-	-	-	✓

Notes: **PWE**= Person with epilepsy; **SOs**= Significant others

provided an opportunity to explore the ease and costs of obtaining routine data, the time it took for it to be secured, the proportion of participants it covered and, finally, how routinely collected administrative data on ED use compared to self-reported use.

Adverse events

As part of the trial, patient participants did not receive additional medical reviews. Therefore, the experience of adverse events was monitored by asking them to complete a standardised checklist as part of the CRF at 3- (T1, by telephone), 6- (T2, by telephone) and 12-months (T3, during a face-to-face appointment) post-randomisation.

Defining the outcomes

Primary

The proposed primary outcome measure for a future definitive trial is the number of epilepsy-related ED visits patient participants made over the 12 months following randomisation.

Secondary

There is currently no core outcome set for epilepsy.[176] A number of measures described in Table 4 were used to assess secondary outcomes considered to potentially be important to capture in a definitive trial.

Participants within the pilot trial were assessed using the secondary outcome measures to permit the sample to be fully described according to them at baseline, to accurately model potential burden of participation in a definitive trial, and to allow us to describe completeness of data on these measures. A full description on these measures is provided in Appendix 8.

Adverse events

What comprised a serious adverse event and how judgements regarding their relatedness to participation were made is described in Appendix 9.

Sample size

As this was a pilot RCT, a formal power calculation to permit it to be able to detect a clinically meaningful difference in the primary outcome between SAFE+TAU and TAU groups was not appropriate. Rather, the aim was to provide robust estimates of the likely rates of recruitment, consent and follow-up, and to yield estimates of the ED event rate and dispersion parameter to accurately inform power calculations for a future definitive trial. To be able to do this, it was considered 40 patients in each trial arm would provide these estimates with adequate precision.

We estimated that ≥20% of those who have visited ED on ≥2 occasions in the prior 12 months would agree to participate. It was anticipated that ~400 eligible PWE would have visited the 3 ED recruitment sites over the 12 months preceding our recruitment phase. This was informed by Health and Social Care Information Centre data on the number of attendances at the sites in 2012/13,[186] and audit data which shows ~1% of all ED visits are for epilepsy and that ~80% are by those with an established diagnosis[23,187] We also factored in evidence on the proportion of ED visits within a year that have been made by the same individual[20] and estimated, using data from Ridsdale et al.' study, the number of PWE that would satisfy the inclusion/exclusion criteria.[188]

With a sample size of 80, a participation rate of 20% could be estimated to within a 95% confidence interval (CI) of +/-4% and a drop-out rate of 25% to within a 95% CI of +/- 10%. Assuming that data on the proposed primary outcome measure of ED visits at 12 months was not available for 25% of patients, outcome data from 60 patients would still allow robust estimation of the ED rate and dispersion parameter. We considered 1 full-time researcher would be able to recruit the required sample within 8 months.

Completion of follow-ups

A range of evidence-based strategies were used to maximise retention of participants in the trial.[189] This included patient and SO participants receiving a £10 shopping voucher after each follow-up assessment they completed and delayed access to SAFE for the TAU arm.

Unless a participant formally withdrew consent to participate in the trial, HES data on them was requested and up to 3 attempts were made to contact patients or SO participant each time a follow-up assessment was due. The research worker also contacted participants by telephone approximately 2 weeks after the T2 questionnaires were posted.

When a patient participant did not complete a follow-up assessment, an attempt to monitor SAEs was made by sending their general practitioner a letter asking them to inform us if the patient was no longer alive and the circumstances of death.

Data management

With the exception of the routine outcome data on ED use from NHS Digital, all data were collected on paper-based CRFs by the research worker. The CRFs were kept in locked filing cabinets in a central research office with restricted access at the University of Liverpool. The paper CRFs were sent to the CTU for entry into Elsevier Macro 4.0 by a Data Manager. At the point of data entry, queries were raised. Participant contact information was kept on a secure central network server with access only granted to study staff.

Data Analysis

All statistical analyses were performed with *SAS* statistical software (version 9.4) by S.N and overseen by C.T.S. A full statistical analysis plan was developed and approved prior to conducting the final analysis.

Rates of eligibility, consent, recruitment, retention and unblinding

Derivation and statistical analysis

The eligibility rate is defined as the percentage of patients screened that satisfy eligibility criteria (*see* Chapter 3), the consent rate is defined as the percentage of eligible patients who provided informed, written consent for randomisation. The recruitment rate is defined as the number of participants recruited per calendar month.

Eligibility and consent rates are presented as percentages with 95% CIs. Recruitment rates are presented as the actual number of participants recruited per calendar month presented alongside the expected number of participants recruited per calendar month on recruitment graphs.

The age, sex and social deprivation profiles (available from the ED records) of eligible individuals who did and did not consent to take part in the trial are presented within side-by-side table columns for visual comparison to evaluate representativeness of the trial sample.

Retention rate is defined as the percentage of randomised patient and SO participants completing 3, 6 and 12 months of the study without withdrawing (i.e. formally withdrawing from any further data collection). Reasons for withdrawal, where known, are presented.

The completion rate of study assessment tools, i.e. the percentage of patient and SO participants completing each measure outlined in Table 4 is presented as an indicator of retention and participation within the trial.

The unblinding rate is defined as the proportion of correct treatment allocation guesses made by the research worker at the end of the trial (12 months) or at withdrawal of participant from the trial. The unblinding rate is presented with 95% CI. A Cohen's Kappa statistic for agreement (i.e. the correct guess of allocation) and 95% CI is also presented.

Demographic and baseline characteristics

Baseline characteristics are presented for PWE overall and by treatment group with comparisons presented for a subset of characteristics for those individuals identified as eligible and invited to participate in the trial who did not agree to participate in the trial.

Relevant baseline characteristics are presented descriptively for SO participants.

Categorical data are summarised by numbers and percentages. Continuous data are summarised by mean, median, standard deviation (SD) and range (minimum and maximum values). Tests of statistical significance are not undertaken for baseline characteristics; rather the potential clinical importance of any imbalance is noted.

Primary outcome: Epilepsy related ED visits

Derivation of outcome

The proposed primary outcome of a future trial is defined as the number of epilepsy-related ED visits made by patient participants over the 12 months following randomisation measured by HES data. As a secondary outcome, the number of patient self-reported epilepsy-related ED visits made by patient participants over the 12 months following randomisation is also presented.

Statistical analysis

Epilepsy related ED visits are presented at baseline (T0), at 12 months (T3) and the change in the number of ED visits made by the end of the 12 months compared to the number of ED visits made in the 12 months prior to baseline. Results are presented for all patient participants and by treatment group as mean and standard deviations, in addition to the median, the minimum and the maximum number of epilepsy related ED visits. Completeness of data for self-reported epilepsy-related ED visits is presented and no imputation of missing data was performed.

The difference between the SAFE+TAU group and TAU alone group is compared at the end of the 12 months with and without adjustment for baseline ED visits via negative binomial regression models for count data. Over-dispersion (i.e. variance is larger than the mean) and an excess number of zeros for individuals who did not visit the ED in the last 12 months was anticipated, therefore zero-inflated negative binomial regression models were also applied. The preferred model (negative binomial or zero-inflated negative binomial) was determined by Vuong's test.[190]

Between-group differences are presented as rate ratios with 95% CIs and statistically tested according to a 5% level of significance. In addition, as per guidance for pilot trials, 90% and 80% CIs are also presented to aid interpretation of between-group differences.[191]

Epilepsy related ED visits measured by HES data were compared to self-reported epilepsy related ED visits and Bland-Altman plots and limits of agreement statistics[192] calculated to determine the agreement of the two measurement methods. A Bland-Altman plot shows the mean of number of ED visits self-reported and recorded by HES data for each patient participant (x-axis) and the difference in the number of ED visits self-reported and recorded by HES data for each patient participant (y-axis). Bland-Altman limits of agreement (mean ± 2 standard deviations [SD]) of the difference in the number of ED visits are also shown on the plot. These limits can be interpreted as the level of agreement which is 'acceptable' between the two measurements of recording ED visits

Estimation of sample size of a future definitive trial

The average annual rate of ED visits in the SAFE+TAU and TAU groups and the likely dispersion parameter estimated from the preferred negative binomial regression model are used to estimate the sample size of a future definitive trial according to the methods outlined by Keene et al.[193] for a negative binomial regression. The number of patient participants required per group in a definitive trial to detect the size of the effect shown in the pilot study is:

$$n = \left\{ \frac{z_{1-\beta} + z_{1-\alpha/2}}{\log(\mu_1/\mu_2)} \right\}^2 \times \left\{ \frac{\mu_1 + \mu_2}{\mu_1 \mu_2} + 2k \right\}$$

Where $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ are critical values of the Normal distribution for specific values of α and β (typically α=0.05 for a 5% significance level and β=0.2 or 0.1 for 80% or 90% power). μ_1 and μ_2 are the estimated ED rates from the two treatment groups and k the negative binomial shape parameter from the associated gamma distribution which explicitly represents variability between subjects.

Secondary outcome measures

Derivation of outcomes

Details of the secondary outcome measures are described in Table 4.

Total scores for QOLIE-31-P (PWE participants only), burden (SO participants only), confidence in managing seizures / epilepsy (SO participants only), mastery (PWE participants only) and fear of seizures (PWE and SO participants) are presented at baseline (T0), 6 months (T2) and 12 months (T3). The change in total scores at 6 months (T2) and at 12 months (T3) compared to baseline (T0) are presented. Burden categories ('Little or no burden', 'Mild to moderate burden', 'Moderate to severe burden', and 'Severe burden') are presented.

Total scores for Stigma (PWE participants only) and Distress (Anxiety and Depression scores; PWE and SO participants) are presented at baseline (T0) and at 12 months (T3). The change in total scores at 12 months (T3) compared to baseline (T0) are also presented and stigma categories ('No stigma', 'Mildly to moderately stigmatised', and 'Highly stigmatised'), and anxiety and depression categories ('Normal range', 'Suggestive of anxiety / depression', 'Probable anxiety / depression) are presented.

'Knowledge of what to do where faced with a seizure' score is presented as the number of questions answered correctly (out of 13) at baseline (T0) and at 12 months (T3), in addition to the change in knowledge score at 12 months (T3) compared to baseline (T0).

Self-reported seizure frequency is presented at baseline (T0), at 6 months (T2) and at 12 months (T3) according to Thapar's seizure frequency scale.[171] The total number of seizures between baseline (T0) and 6 months (T2) and between baseline (T0) and 12 months (T3) are also presented.

Statistical Analysis

Total scores and the change from baseline scores of all measures, plus the total number of seizures are presented as mean and SD in addition to the median, the minimum and the maximum scores for each scale. Burden, stigma, anxiety and depression categories are also presented as the number and percentage of participants within each category. Results are presented for all participants and by treatment group and separately for PWE and SO participants where applicable.

Completeness of data for all self-reported scales is presented. Individual missing values within given scales of the QOLIE-31-P[177] and the HADS scale were imputed according to recommended rules.[194] No imputation was performed for other scales. Total scores are presented separately for all individuals (including those with missing data) and for individuals with complete data for the scale.

Visual comparison of differences between treatment groups only are made for secondary outcome measures; no formal statistical testing is performed.

Chapter 4: Part B: Pilot RCT - Recruitment, retention, intervention delivery and participants' baseline characteristics

Introduction

This chapter presents findings from the pilot trial relating to participant recruitment, their retention and attendance at Seizure First Aid Training For Epilepsy (SAFE) intervention sessions.

Participant flow through study

Search period

The Stage 1 searches were originally set-up to identify people with epilepsy (PWE) who had made an emergency department (ED) visit between 1st January and 31st December 2015. Recruitment though proved more challenging than anticipated and so, with funder and governance approval, the period within which people could be identified as having attended the EDs was extended by 7 months to 31st July 2016 (minor amendment, incorporated into Protocol version 1.2, 9.6.2016). A total of 417,381 attendances for any reason were recorded at the EDs between 1st January 2015 and 31st July 2016.

Eligibility

The Stage 1 searches indicated 6,359 (1.5%) of the ED attendances were attributable to epilepsy or a suspected epileptic seizure. These visits had been made by 4,016 individuals (Figure 3 CONSORT eligibility). Following Stage 2 review of the triage card associated with these visits, 1,220 individuals were considered to have visited for established epilepsy, with 555 of them being considered eligible for participation in the trial and sent an invitation.

Having received the letter, no patient opted out, but 122 patients did send notification that they were ineligible (Table 5). For 9 patients the postal address was incorrect or the letter was not sent in error. The remaining 424 patients were telephoned to determine their interest in the study and verify eligibility (Stage 3). Based upon these figures, the eligibility rate (424 eligible participants out of 4016 unique individuals screened) was 10.6% (95% confidence interval [CI] 9.6% to 11.5%).

It took the principal investigator at each site ~3 full days to complete the Stage 2 screening.

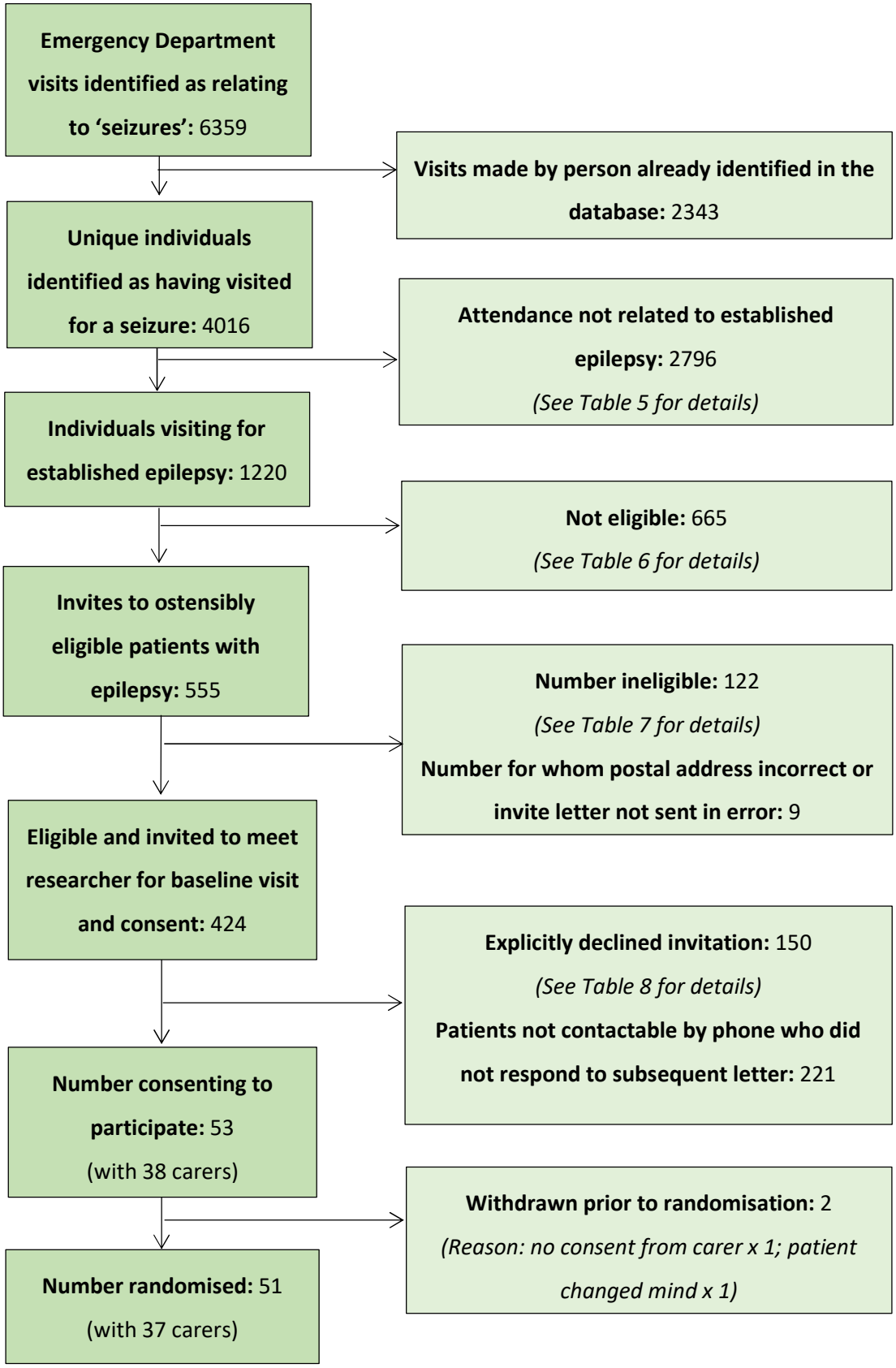


Figure 2 CONSORT diagram of eligibility screening for the trial

Table 5 Attendance at emergency department not related to epilepsy

Reason	Number of participants			
	Site 1 Aintree	Site 2 Arrowe Park	Site 3 Royal Liverpool	Total
No confirmed diagnosis of epilepsy/not attending because of epilepsy	737	483	715	1935
Acute symptomatic seizures related to neurological illness or substance abuse	238	240	191	669
Psychogenic non-epileptic seizures	19	55	29	103
Medical record missing	54	5	27	86
Ineligible, but no reason given	2	1	0	3
Total	1050	784	962	2796

Table 6 Other reasons for non-eligibility (individuals visiting for established epilepsy)

Reason	Number of participants			
	Site 1 Aintree	Site 2 Arrowe Park	Site 3 Royal Liverpool	Total
Postcode outside catchment area	148	94	60	302
Learning disability likely to impede individuals' capacity to provided signed, informed consent	45	51	52	148
Inability to converse in English and provide signed informed consent	10	24	46	80
Life threatening medical illness	35	26	10	71
Severe psychiatric disorder	11	3	18	32
No fixed abode	10	6	13	29
Participating in another trial	3	0	0	3
Total	262	204	199	665

Recruitment rates and speed of recruitment

The process of enrolment (i.e. participant consent and baseline assessment, rather than the period within which the participants' ED visits must have occurred within) began in May 2016 and concluded at the end of December 2016. Of the 424 patients telephoned, 53 agreed to participate and provided informed consent, thus giving a consent rate of 12.5% (95% CI 9.3% to 15.6%). The reasons participants offered for not taking part are provided in Table 8.

With regards consent, successful telephone contact could only be made with 203 of the 424 (47.8%) eligible patients. When the consent rate is restricted to just those who could be contacted, the rate is 26.1% (95% CI 20.0% to 32.2%).

Table 7 Reasons for non-eligibility (ostensibly eligible individuals)

Reason	Number of participants			
	Site 1 Aintree	Site 2 Arrowe Park	Site 3 Royal Liverpool	Total
Has not visited an ED for epilepsy on ≥2 occasions within previous 12 months (as reported by patient)	9	15	24	48
Not able to provide informed consent, participate in SAFE course if randomised or to independently complete questionnaires in English	9	7	7	23
Ineligible, but no reason given[a]	4	7	4	15
Not established diagnosis of epilepsy (<1 year)	3	2	5	10
Moved out of area; postcode no longer within 25 mile catchment area	4	1	3	8
Actual or suspected psychogenic non-epileptic seizures alone or in combination with epilepsy	2	1	4	7
Severe current psychiatric disorders or life-threatening medical illness	1	5	1	7
Not currently being prescribed antiepileptic drug	1	0	1	2
Acute symptomatic seizures related to acute neurological illness or substance misuse	0	1	0	1
Participating in another trial	1	0	0	1
Total	34	39	49	122

Notes:

a. Lack of reason due to patients returning participation slips and not stating actual reason for ineligibility

Table 8 Reasons for declining participation (eligible individuals)

Reason	Number of participants			
	Site 1 Aintree	Site 2 Arrowe Park	Site 3 Royal Liverpool	Total
Not interested	30	11	23	64
Too busy	11	12	11	34
No reason given	9	10	8	27
Too ill	5	5	9	19
Too well	3	1	2	6
Total	58	39	53	150

The process of enrolment lasted 226 days (equivalent to 7.43 months), with an average rate of 6.9 patients being randomised per month (ranging from 4 to 11 patients per month). Actual rates and expected rates of recruitment each month are presented in Appendix 10. As the target sample size of 80 patients was not reached, the speed of recruitment could not be calculated.

Randomisation

Of the 53 consenting patients, 51 were randomised (along with 37 SO participants with whom they took part with). The first was randomised on 19th May 2016, the last on 31st December 2016. The reason for two patient participants not being randomised was they withdrew prior to randomisation.

Of the 51 patient participants randomised, 26 (with 18 SOs) were allocated to SAFE+ Treatment as Usual (TAU) and 25 (with 19 SOs) to TAU alone. Participant flow through the SAFE trial is outlined in Figure 4.

Receipt of intervention

Seven SAFE intervention courses were run for the SAFE+TAU arm between June 2016 and February 2017. No seizures were recorded as having occurred during the courses and there were no instances of participants in the TAU arm attending a SAFE session by mistake.

We anticipated SAFE would be delivered to groups of 8-10 persons within the pilot trial. In practice, the average group size was 5, with 20 (76.9%) of the 26 patient participants and 13 (72.2%) of the 18 SOs randomized to the intervention attending a course. No patients or SOs completed only part of a course.

A total of 33 course bookings were made for the 26 patient participants randomized to SAFE. Most (n=18, 90%) patient participants attended the first course that they were booked on. The minority of patients who did not ultimately attend a course were associated with substantial administrative activity. Specifically, 6 patient participants who did not attend a course received between them 45 telephone calls from the study administrator and booked onto 11 course slots. This contrasts with the 34 telephone calls in total that were made to the 20 patient participants who attended a course. Reasons for non-attendance included poor health on the patients' behalf and work commitments on behalf of the SO.

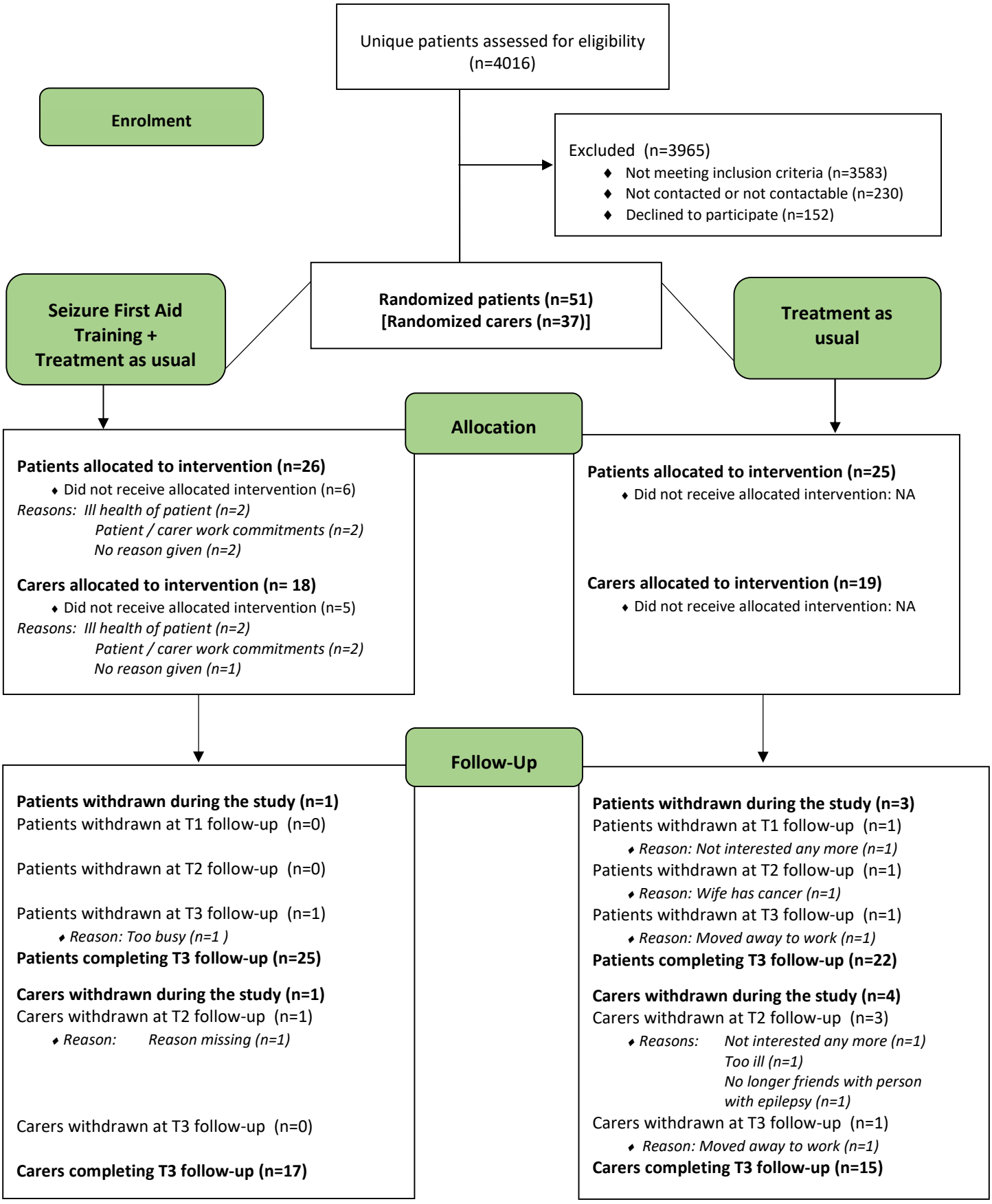


Figure 3 CONSORT diagram of flow through the SAFE trial

Withdrawals and completion of follow-ups

Formal withdrawals from trial

Of the 51 randomised patient participants, only 3 (5.8%) withdrew consent to participate and for routine data to be collected on them over the course of their 12 months in the trial; 2 withdrew from the TAU condition and 1 from the SAFE arm. This meant consent remained in place for securing routine outcome ED data for 48 (94.1%) patient participants. The reasons for participant withdrawal are described in Appendix 11. No withdrawals were initiated on the patient's behalf by a health care provider or a member of the research team. Of the 37 randomised SO participants, 5 (13.5%) withdrew.

Participation in questionnaire-based follow-up assessments

Thirty-seven (72.5%) of the patient participants and 21 (56.8%) SOs attended their scheduled 12-months post-randomisation primary outcome assessment (T3). The 37 patient participants attended their 12-month post-randomisation follow-up visit at a median of 286 days (range 252-365 days) post randomisation. Appointments often took place before 12 months because slower recruitment meant time for follow-up within the life of the project was reduced.

With respect to the interim questionnaire assessments, 43 (84.3%) patients returned the 3-month (T1) follow-up questionnaire and 39 (76.5%) patients and 26 (70.3%) SOs returned their 6-month (T2) follow-up questionnaire.

Securing outcome data and its completeness

Primary outcome: ED data from Hospital Episode Statistics system

Completeness of data:

Hospital Episode Statistics (HES) data on ED use was secured by the research team from NHS Digital for each of the 48 (94.1%) randomised patient participants for whom consent to participate and secure ED outcome data on them remained.

Process of securing the data:

After delays in being granted permission to access NHS Digital's application form, the research team submitted the application for the data on 16th February 2018. To minimise cost, a single application, rather than one relating to the baseline period and one for follow-up, was submitted. The data was

ultimately received by the research team on 31st October 2018 at a direct cost of £6,960.00 (inclusive of Value Added Tax).

Prior to starting the trial and submitting the application, the research team communicated with NHS Digital and ensured the Participant Information Sheet and consent form was consistent with their requirements. Despite this, it still took 7 months for the application to be reviewed and approved by NHS Digital and an additional 1.5 months for the data file to be produced and transferred.

During these periods, substantial effort was required by the research team to respond to queries raised by NHS Digital and to chase them once responses had been submitted. A log of all correspondence was kept by the research team. The team typically responded to queries raised by NHS Digital within 1 day; key milestones are outlined in Appendix 12. In one instance, the research team needed to successfully appeal against a decision by NHS Digital – 5 months into the application process – to reject it due to, amongst others, apprehensions regarding the project's scientific merit. The team was notified it was being rejected because of "concerns [over]... whether this pilot would yield findings that were statistically valuable to achieve the stated aims given the small numbers involved".

Secondary outcome data

The extent to which the secondary outcome measures were fully completed by the participants who participated in the follow-up assessments varied by assessment point, measure and by participant type (Table 9 and Table 10). Self-reported ED use 12-months post-randomisation (T3) by patient participants was the secondary means by which ED use was captured and so arguably the most important of the secondary outcome measures. Self-reported ED use data at T3 was available for 34 (66.7%) of the 51 randomised patient participants.

Baseline characteristics

Patient participants

Demographics

The mean age of the 51 randomised patient participants was 39.9 years (standard deviation [SD] 15.6, range 16-71); 29 (56.9%) were female and 94.1% identified themselves as being of 'white' ethnicity (Table 11). The Index of Multiple Depression score, measuring levels of deprivation according to participants' home postcode, https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 [accessed 27th August, 2019] indicated most (74.4%) lived in areas of high

deprivation; 49% (n=25) lived in areas in the top 10 percent most socially deprived in the country. Most (53%) patient participants had attained a basic level of formal education only (i.e., O' levels/ GCSEs/ Level 1 or 2 NVQ).

Table 9 Number of patient participants fully completing study assessment tools at each time point

Study assessment tool and timepoint	SAFE + TAU	TAU	Total
Patient Participants: Baseline (T0)	(n=26)	(n=25)	(n=51)
ED self-report	24 (92.3%)	21 (84.0%)	45 (88.2%)
Seizure control: Thapar[171] scale	26 (100%)	25 (100%)	51 (100%)
Quality of Life in Epilepsy Scale-31P (Cramer et al [177])	23 (88.5%)	16 (64.0%)	39 (76.5%)
Hospital Anxiety and Depression Scale (Zigmond et al.;[169] Snaith[170]).[a]	23 (88.5%)	24 (96.0%)	47 (92.2%)
Jacoby[62] Stigma of Epilepsy Scale	24 (92.3%)	24 (96.0%)	48 (94.1%)
Client Service Receipt Inventory (Beecham et al.[173])[b]	19 (73.1%)	17 (68.0%)	36 (70.6%)
EuroQol-5D (Williams[174])	21 (80.8%)	25 (100.0%)	46 (90.2%)
Wagner[61] 6-item Mastery Scale	26 (100.0%)	21 (84.0%)	47 (92.2%)
Fear of seizures: Thinking about Epilepsy Questionnaire (EP&MQ Fears subscale) (Mittan [181]).	16 (61.5%)	9 (36.0%)	25 (49.2%)
Patient Participants: 6 months (T2)	(n=26)	(n=23)[c]	(n=49)[c]
Quality of Life in Epilepsy Scale-31P (Cramer et al [177])	16 (61.5%)	12 (52.2%)	28 (57.1%)
Wagner[61] 6-item Mastery Scale	21 (80.8%)	15 (65.2%)	36 (73.5%)
Seizure control: Thapar[171] scale	16 (61.5%)	15 (65.2%)	28 (57.1%)
Patient Participants: 12 months (T3)	(n=25)[d]	(n=22)[d]	(n=47)[d]
ED self-report	17 (68.0%)	17 (77.3%)	34 (72.3%)
Seizure control: Thapar[171] scale	20 (80.0%)	14 (60.9%)	34 (72.3%)
Quality of Life in Epilepsy Scale-31P (Cramer et al [177])	10 (40.0%)	8 (36.4%)	18 (38.3%)
Hospital Anxiety and Depression Scale (Zigmond et al.;[169] Snaith[170])[a]	18 (72.0%)	17 (77.3%)	35 (74.4%)
Jacoby[62] Stigma of Epilepsy Scale	18 (72.0%)	17 (77.3%)	35 (74.4%)
Client Service Receipt Inventory (Beecham et al.[173])[b]	13 (52.0%)	10 (45.5%)	23 (48.9%)
EuroQol-5D (Williams[174])	18 (72.0%)	17 (77.3%)	35 (74.4%)
Wagner[61] 6-item Mastery Scale	18 (72.0%)	16 (72.7%)	34 (72.3%)
Fear of seizures: Thinking about Epilepsy Questionnaire (EP&MQ Fears subscale) (Mittan [181]).	8 (32.0%)	5 (22.7%)	13 (27.7%)
Feedback on participation	17 (68.0%)	15 (68.2%)	32 (68.1%)

Notes:

a. Completeness of the whole HADS scale (both anxiety and depression subscales)
b. Only six mandatory questions counted. Conditional questions (e.g. if yes, then…) not counted towards total completion
c. Two patient participants from the TAU group had withdrawn by the T2 visit
d. Four patient participants (three from the TAU group and one from the SAFE + TAU group) had withdrawn by the T3 visit
e. Note that whilst some participants did not fully complete all items within a questionnaire, this does not automatically mean their data would need to be excluded from analysis of a change in that domain since for some measures test developers permit imputation when the extent of missing items is low and follows a specific pattern. Information on the number of items completed for the specific assessment tools is presented in Appendix 13

Table 10 Number of significant other participants fully completing study assessment tools at each time point

Study assessment tool and time point	SAFE + TAU	TAU	Total
Significant other Participants: Baseline (T0)	(n=18)	(n=19)	(n=37)
Zarit[172] Caregiver Burden	17 (94.4%)	17 (89.5%)	34 (91.9%)
Hospital Anxiety and Depression Scale (Zigmond et al.;[169] Snaith[170])[a]	17 (94.4%)	18 (94.7%)	35 (94.6%)
Austin's[184] Parent Response to Child Illness Scale	18 (100.0%)	19 (100.0%)	37 (100.0%)
Fear of seizures: Thinking about Epilepsy (Mittan [281]). Questionnaire (EP&MQ Fears subscale)	6 (33.3%)	4 (21.1%)	10 (27.0%)
Significant other Participants: 6 months (T2)	(n=17)[b]	(n=16)[b]	(n=33)[b]
Zarit[172] Caregiver Burden	15 (88.2%)	8 (50.0%)	23 (69.7%)
Austin's[184] Parent Response to Child Illness Scale	16 (94.1%)	9 (56.3%)	25 (75.8%)
Significant other Participants: 12 months (T3)	(n=17)[c]	(n=15)[c]	(n=32)[c]
Zarit[172] Caregiver Burden	11 (64.7%)	10 (66.7%)	21 (65.6%)
Hospital Anxiety and Depression Scale (Zigmond et al.;[169] Snaith[170]). [a]	11 (64.7%)	10 (66.7%)	21 (65.6%)
Austin's[184] Parent Response to Child Illness Scale	11 (64.7%)	10 (66.7%)	21 (65.6%)
Fear of seizures: Thinking about Epilepsy Questionnaire (EP&MQ Fears subscale) (Mittan [281]).	6 (35.3%)	2 (13.3%)	8 (25.0%)
Feedback on participation	11 (64.7%)	9 (60.0%)	20 (62.5%)

Notes:

a. Completeness of the whole HADS scale (both anxiety and depression subscales),
b. Four SO participants (one in the SAFE group and three in the TAU group) had withdrawn by the T2 visit
c. Five SO participants (one in the SAFE group and four in the TAU group) had withdrawn by the T3 visit
d. Note that whilst some participants did not fully complete all items within a questionnaire, this does not automatically mean their data would need to be excluded from analysis of a change in that domain since for some measures test developers permit imputation when the extent of missing items is low and follows a specific pattern. Information on the number of items completed for the specific assessment tools is presented in Appendix 13

Epilepsy characteristics

Patient participants had been diagnosed with epilepsy for a median of 21 years. Most (62.8%) reported having had ≥10 seizures in the previous year. Most (54.9%) reported having another health condition. Median days since their last seizure was 14. Most (38; 74.5%) participants reported having seen a neurologist in the prior 12 months to their assessment (Table 12).

Emergency department use in 12 months prior to enrolment

HES ED data:

HES ED data for the 48 patients for whom consent was maintained over the trial showed they together made 122 ED visits in the 12 months before randomisation. Frequency of ED use amongst them was positively skewed (Figure 5). The median number of visits was 2 (range 0 to 12 visits) (Table 12).

Table 11 Demographic characteristics of patient participants

Demographic characteristic		SAFE + TAU	TAU	Total
Sex: n (%)		(n=26)	(n=25)	(n=51)
Male		10 (38.5%)	12 (48.0%)	22 (43.1%)
Female		16 (61.5%)	13 (52.0%)	29 (56.9%)
Missing		0 (0.0%)	0 (0.0%)	0 (0.0%)
Age at presentation to the emergency department (years)[a]				
N		26 (100.0%)	25 (100.0%)	51 (100.0%)
Mean		39.2	40.7	39.9
Standard deviation		13.96	17.52	15.66
Minimum		18.9	16.5	16.4
Median		37.1	41.4	38.8
Maximum		69.9	71.3	71.3
Missing		0 (0.0%)	0 (0.0%)	0 (0.0%)
Index of Multiple Deprivation (IMD)[b]		(n=26)	(n=25)	(n=51)
IMD Decile: 1	n (%)	11 (42.3%)	14 (56.0%)	25 (49.0%)
IMD Rank	Minimum	44	48	44
	Median	574.0	1231.5	673.0
	Maximum	3202	2166	3202
IMD Decile: 2 to 3	n (%)	7 (26.9%)	6 (24.0)	13 (25.4%)
IMD Rank	Minimum	4649	3989	3989
	Median	6785	6665	6785
	Maximum	8281	7816	8281
IMD Decile: 4 to 6	n (%)	2 (7.7%)	4 (16.0%)	6 (11.8%)
IMD Rank	Minimum	9881	11480	9881
	Median	12836	11924	11924
	Maximum	15791	16004	16004
IMD Decile: 7 to 10	n (%)	5 (19.2%)	1 (4.0%)	6 (11.8%)
IMD Rank	Minimum	24971	32724	24971
	Median	27642	32724	28876
	Maximum	31002	32724	32724
IMD Decile missing [c]	n (%)	1 (3.8%)	0 (0.0%)	1 (2.0%)
Ethnicity: n (%) [c]		(n=26)	(n=25)	(n=51)
White		25 (96.2%)	23 (92.0%)	48 (94.1%)
Asian / Asian British		0 (0.0%)	0 (0.0%)	0 (0.0%)
Black / African / Caribbean / Black British		1 (3.8%)	1 (4.0%)	2 (3.9%)
Mixed / multiple ethnic groups		0 (0.0%)	0 (0.0%)	0 (0.0%)
Other ethnic group		0 (0.0%)	1 (4.0%)	1 (2.0%)
Missing		0 (0.0%)	0 (0.0%)	0 (0.0%)
Other significant medical history: n (%)		(n=26)	(n=25)	(n=51)
No, none		13 (50.0%)	10 (40.0%)	23 (45.1%)
Yes, another medical condition/s		10 (38.5%)	13 (52.0%)	23 (45.1%)
Yes, a psychiatric condition		1 (3.8%)	0 (0.0%)	1 (2.0%)
Yes, both medical and psychiatric conditions		2 (7.7%)	2 (8.0%)	4 (7.8%)
Missing		0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 11 *continuation*: Demographic characteristics of patient participants

Demographic characteristic	SAFE + TAU	TAU	Total
Education: n (%)	(n=26)	(n=25)	(n=51)
O' levels/ GCSEs/ Level 1 or 2 NVQ	13 (50.0%)	14 (56.0%)	27 (53.0%)
A' Levels/ Level 3 NVQ	5 (19.2%)	3 (12.0%)	8 (15.7%)
University degree/ Graduate Certificate or Diploma	5 (19.2%)	5 (20.0%)	10 (19.6%)
Postgraduate university degree (e.g., PGCE, MSc, MA, PhD)	2 (7.7%)	0 (0.0%)	2 (3.9%)
Missing	1 (3.9%)	3 (12.0%)	4 (7.8%)

Notes:

a. Four participants (7.8%) had missing ages recorded from CRF data, therefore date of birth and date of presentation recorded in the bespoke screening database was used to calculate age at presentation to the emergency department

b. The Index of Multiple Deprivation (IMD) ranks every small area in England from 1 (most deprived area) to 32,844 (least deprived area).IMD rank and decile missing for one recruited participant as they resided in Wales

As described in Chapter 3, patient identification centred on the use of NHS ED attendance records and only patients who, when telephoned, said they had made ≥2 ED visits for epilepsy in the prior 12 months were recruited. Despite this process, data from the HES system indicated 4 (8.3%) patient participants had not made any ED visits during the 12 months prior to recruitment and a further 19 (39.6%) were noted to have made only one ED visit.

Self-report ED data:

Self-report data was available for 45 (88.2%) patient participants. The median number of visits was 4 (range 0 to 107 visits) (Table 12). Again, despite evidence the screening processes followed, 4 (8.9%) patients on the questionnaire completed subsequent to telephone screening said they had not made any visits during the prior 12 months and 3 (6.7%) reported having made only one visit.

Relationship between HES and self-report:

There were 42 patient participants who had self-report ED data at T0 and for whom consent remained in place for obtaining their HES ED data. Bland-Altman plots of the agreement between self-reported ED visits and HES data were produced.

Primary focus is given to the plot shown in Figure 6. This is based on data from 41, rather than 42 patient participants. This is because the distribution of self-reported ED use was particularly influenced by one patient participant who self-reported 107 visits in the prior 12 months. We can confirm that that report of 107 visits was checked against the participant's answer on the

questionnaire and did not reflect a data-entry error. Given that only one ED visit in the 12 months was recorded for this patient participant within the HES data, we considered the self-report of 107 ED visits to be an outlier and excluded them the plot shown in Figure 6 (Appendix 14 presents a Bland Altman plot without any exclusions).

Table 12 Baseline disease characteristics and key health service use of patient participants

Disease characteristic		SAFE + TAU	TAU	Total
Time since epilepsy diagnosis (years)				
	N	26 (100.0%)	25 (100.0%)	51 (100%)
	Mean	19.9	22.6	21.2
	Standard deviation	14.85	18.38	16.57
	Minimum	1.8	1.7	1.7
	Median	16.8	19.3	17.3
	Maximum	53.9	64.9	64.9
	Missing	0 (0.0%)	0 (0.0%)	0 (0%)
Time since last epileptic seizure (days)				
	N	23 (88.5%)	22 (88.0%)	45 (88.2%)
	Mean	53.6	40.1	47.0
	Standard deviation	101.10	61.21	83.34
	Minimum	1	0	0
	Median	14.0	10.5	14.0
	Maximum	340	235	340
	Missing	3 (11.5%)	3 (12.0%)	6 (11.8%)
Number of epileptic seizures in the last 12 months				
N		26 (100%)	25 (100%)	51 (100%)
	None	1 (3.8%)	0 (0.0%)	1 (2.0%)
	One	1 (3.8%)	0 (0.0%)	1 (2.0%)
	Two	0 (0.0%)	2 (8.0%)	2 (3.9%)
	Three	2 (7.7%)	1 (4.0%)	3 (5.9%)
	Four	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Five	0 (0.0%)	2 (8.0%)	2 (3.9%)
	Six	1 (3.8%)	3 (12.0%)	4 (7.8%)
	Seven	1 (3.8%)	1 (4.0%)	2 (3.9%)
	Eight	2 (7.7%)	2 (8.0%)	4 (7.8%)
	Nine	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Ten or more	18 (69.2%)	14 (56.0%)	32 (62.8%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0%)
Hospital Episode Statistics recorded health care use in the last 12 months:				
Emergency Department (ED)	N	25 (96.2)	23 (92.0)	48 (94.1)
	At least one attendance: n (%)[a]	23 (88.5)	18 (72.0)	41 (80.4)
	Mean	2.1	3	2.5
	Standard deviation	2.22	2.76	2.51
	Minimum	0	1	0
	Median	1	2	2
	Maximum	10	12	12
	Missing: n (%)	1 (3.8)	2 (8.0)	3 (5.9)

Table 12 *continuation*: Baseline disease characteristics and key health service use of patient participants

Self-reported healthcare use in the last 12 months for epilepsy: number of attendances at:				
Emergency Department (ED)	N	24 (92.2)	21 (84.0%)	45 (88.2)
	At least one attendance: n (%)[a]	23 (88.5%)	18 (72.0%)	41 (80.4%)
	Mean	*4.3*	*9.8*	*6.7*
	Standard deviation	*2.83*	*24.38*	*16.27*
	Minimum	*1*	*1*	*1*
	Median	*4*	*4*	*4*
	Maximum	*12*	*107*	*107*
	Missing: n (%)	2 (7.8%)	4 (16.0%)	6 (11.8%)
Neurology outpatient appointment	N	25 (96.2)	22 (88.0)	47 (92.1%)
	At least one attendance: n (%)[a]	21 (80.8%)	16 (68.0%)	38 (74.5%)
	Mean	*2.6*	*3.1*	*2.8*
	Standard deviation	*1.78*	*2.26*	*2.00*
	Minimum	*1*	*1*	*1*
	Median	*2*	*2*	*2*
	Maximum	*8*	*10*	*10*
	Missing: n (%)	1 (3.8%)	3 (12.0%)	4 (7.8%)
Number of times an emergency ambulance had been called (whether the ambulance took the patient to the emergency department or not)	N	21 (80.8)	21 (84.0)	42 (82.4)
	At least one attendance: n (%)[a]	18 (69.2%)	18 (72.0%)	36 (70.6%)
	Mean	*3.2*	*4.1*	*3.6*
	Standard deviation	*2.87*	*2.86*	*2.86*
	Minimum	*1*	*1*	*1*
	Median	*2*	*3*	*3*
	Maximum	*12*	*12*	*12*
	Missing: n (%)	5 (19.2%)	4 (16.0%)	9 (17.7%)
General practitioner	N	23 (88.5)	23 (92.0)	46 (90.2)
	At least one contact: n (%)	16 (61.6%)	13 (52.0%)	29 (56.9%)
	Missing: n (%)	3 (11.5%)	2 (8.0%)	5 (9.8%)
Number of contacts (if used)[c]	Mean	3.7	4.3	4.0
	Standard deviation	2.02	3.03	2.50
	Minimum	1	1	1
	Median	3.5	4.0	4.0
	Maximum	6	12	12
Epilepsy Nurse	N	22 (84.6)	23 (92.0)	45 (88.2)
	At least one contact: n (%)	12 (46.2%)	12 (48.0%)	24 (47.0%)
	Missing: n (%)	4 (15.4%)	2 (8.0%)	6 (11.8%)
Number of contacts (if used)[c]	Mean	2.4	2.1	2.3
	Standard deviation	1.37	1.56	1.45
	Minimum	1	1	1
	Median	2.0	1.5	2.0
	Maximum	6	6	6

Notes:

a. Mean, standard deviation, minimum, median and maximum number of attendances calculated for those with at least one attendance; NA for no attendance

b. Mean, standard deviation, minimum, median and maximum number of contacts and duration of contact calculated for those with at least one contact, NA for no contact

c. Denominator of the percentage is the number of participants with at least one contact

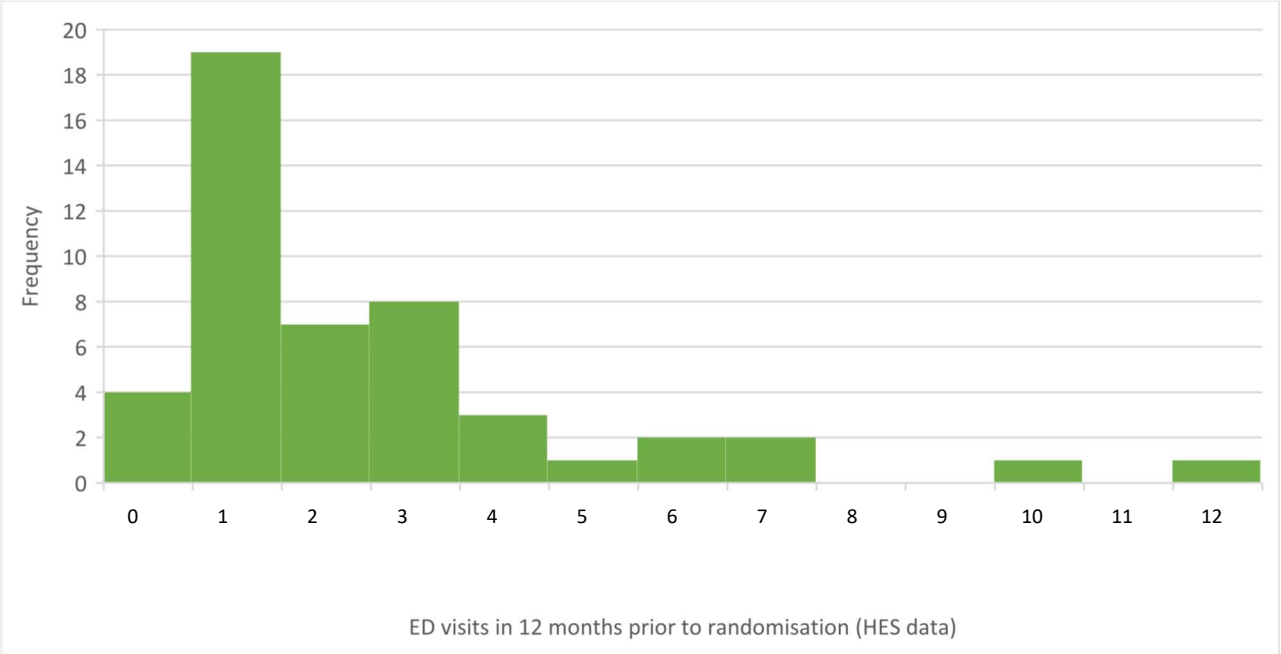
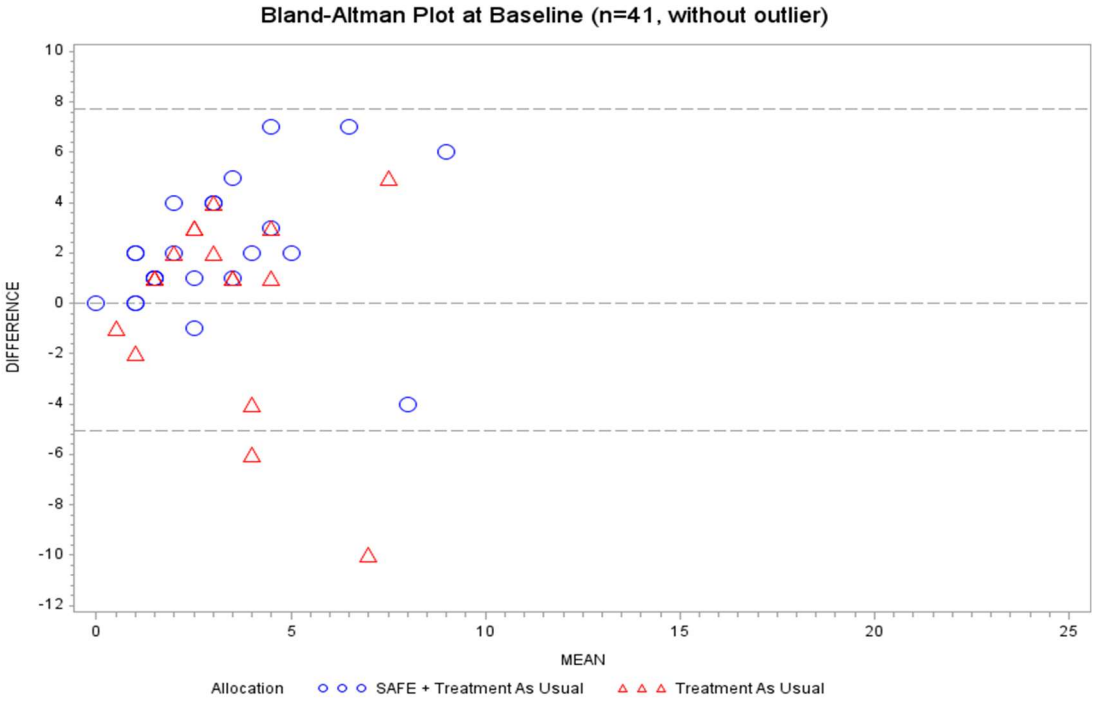


Figure 4 Histogram of number of emergency department attendances in previous 12 months by patients according to HES system



Note: A clear outlier was present – namely, one participant allocated to the TAU group reported 107 ED visits in the 12 months prior to baseline but 1 visit was reported in the HES data. This outlier is removed.

Figure 5 Bland Altman plot of agreement between self-reported ED visits and hospital episode statistics (HES data) at baseline

Figure 6 shows disagreement existed between self-report and HES data for most patient participants. Most (76.2%) participants self-reported more ED visits than indicated by the HES system. Only three (7.1%) participants reported the same number of ED visits as recorded by HES. Figure 6 shows the limits of agreement was -5.0 visits (i.e. 5 less visits recorded by self-report than in HES data) to 7.7 visits (i.e. 7.7 visits more recorded by self-report than in HES data).

Psychosocial measures:

Compared to a maximum possible score of 100, the mean score on the QOLIE-31-P quality of life questionnaire was 48.3 (SD 17.3), with a wide range from 17.1 to 79.5. Twenty-six (50.9%) participants had 'probable' anxiety and 11 (21.6%) had 'probable' depression. Assessment of self-stigma revealed most (n=42, 82.3%) felt at least some stigma because of epilepsy; 15 (29.4%) felt highly stigmatised.

Comparability of treatment groups, including in ED use

Considering the small sample size, the process of randomisation was largely successful in generating two treatment groups broadly similar in demographics and scores on the baseline assessment tools (Table 11, Table 12). Some differences were though apparent in their ED use prior to randomisation (as measured by HES and self-report). It was slightly higher for the TAU group than for the SAFE group (Table 12).

Representativeness

The age, sex and social deprivation profile of the randomised patient participant sample was compared to that of the patients who were eligible to participate, but who declined to participate or were not contactable. This showed the two groups were comparable in age and social deprivation profile, but that females were slightly overrepresented in the recruited sample (Table 13).

SO participants

Most (72.5%) patient participants took part in the trial with a SO. These were typically a partner or spouse (43.2%), a parent (21.6%) or a son or daughter (16.2%). Most (75.5%) SOs lived in the same household as the patient and had contact with them every day of the week (89.2%). Their mean age was 43.2 years (SD 17, range 17-79 years) and most (59.5%) were female. Of the SOs, 32.4% reported having a medical condition themselves.

Anxiety levels amongst SOs were high, with 15 (40.5%) of the SOs having a score indicating 'probable' clinical anxiety. Only 3 (8.1%) had a score indicating 'probable' clinical depression. The mean Zarit

Table 13 Demographic characteristics of eligible participants by agreement to participate in the trial

Demographic characteristic		Agreed to participate	Did not agree to participate
Sex: n (%)		(n=51)	(n=379)[a]
Male		22 (43.1%)	192 (50.7%)
Female		29 (56.9%)	187 (49.3%)
Missing		0 (0.0%)	0 (0%)
Age at presentation to the emergency department (years)			
N		51 (100.0%)	379 (100%)
Mean		39.9	40.6
Standard deviation		15.66	16.83
Minimum		16.4	16.2
Median		38.8	37.5
Maximum		71.3	84.4
Missing		0 (0.0%)	0 (0%)
Index of Multiple Deprivation (IMD)[b]		(n=51)	(n=379)
IMD Decile: 1	n (%)	25 (49.0%)	188 (49.6%)
IMD Rank	Minimum	44	28
	Median	673.0	924.5
	Maximum	3202	3107
IMD Decile: 2 to 3	n (%)	13 (25.4%)	82 (21.6%)
IMD Rank	Minimum	3989	3291
	Median	6785	5309
	Maximum	8281	9835
IMD Decile: 4 to 6	n (%)	6 (11.8%)	59 (15.6%)
IMD Rank	Minimum	9881	10277
	Median	11924	14459
	Maximum	16004	19659
IMD Decile: 7 to 10	n (%)	6 (11.8%)	50 (13.2%)
IMD Rank	Minimum	24971	19826
	Median	28876	22673
	Maximum	32724	32396
IMD Decile missing[a]	n (%)	1 (2.0%)[b]	0 (0%)

Notes:

a. Includes seven patients who could not be contacted due to an incorrect postal address and two patients who were not sent an invite letter in error.

b. The Index of Multiple Deprivation (IMD) ranks every small area in England from 1 (most deprived area) to 32,844 (least deprived area).

c. IMD rank & decile missing for one recruited participant as they resided in Wales.

caregiver burden score was 18.9 (SD=12.51), with most being categorised as reporting either little or no burden (n=23; 62.2%) or mild to moderate burden (n= 11; 29.7%). Further characteristics of the SOs, including by treatment group are provided in Appendix 15.

Researcher unblinding

The researcher correctly stated the treatment allocation of 35 of the 51 patient participants – giving a rate of unblinding of 68.6% (95% CI 54.1% to 80.9%). The chance-corrected kappa statistic for this level of agreement is 0.37 (95% CI 0.12 to 0.63) – indicating "fair" agreement. For SO participants, the researcher correctly stated the treatment allocation of 24 of the 36 SOs (guess was missing for one SO) – giving a rate of unblinding 66.7% (95% CI 49.0% to 81.4%) and a Cohen's Kappa statistic for agreement of 0.33 (95% CI 0.02 to 0.64). For only 3 (5.8%) patient participants and 3 (8.3%) SO participants did the researcher report that they strongly thought they knew the patient participants treatment allocation because of comments participants had made. Summary

A successful pilot trial was completed in terms of a largely representative sample being recruited, randomized and most patients randomized to SAFE receiving it. There were no protocol deviations and the research worker completing the outcome assessments remained blind to treatment allocation. However, only one of the two predetermined 'Stop/Go' criteria for a definitive trial was met. Specifically, the criterion of securing primary outcome data for ≥75% of participants was satisfied (in that it was secured for 94%), but the criterion regarding the percentage of eligible patients agreeing to participate was not. Only 12.5% agreed to take part, rather than ≥20%. The low consent rate, as well as fewer patients being found to be eligible to take part and contactable than anticipated, meant the target sample size for the pilot RCT was not achieved. The pilot trial also revealed how identifying patients from local ED records could be resource intensive and that securing routine outcome data on ED use via the HES system requires substantial time.

Chapter 5 Intervention fidelity

Introduction

Seizure First Aid Training For Epilepsy (SAFE) is a group-based intervention, is comprised of multiple interacting components and requires a number of behaviours on behalf of those delivering and receiving SAFE. These features create opportunity for variation in its delivery. To permit accurate interpretation of the estimates of its effect generated by the pilot randomised controlled trial (RCT), as well as help to determine whether SAFE can be delivered as intended within a trial context, information on its implementation fidelity within the pilot RCT is required. Implementation fidelity refers to the extent to which the core content of SAFE was delivered (adherence) as intended and with what sort of skill (competency). Such monitoring is recommended by the Template for Intervention Description and Replication (TIDieR) extension to the Consolidated Standards of Reporting Trials (CONSORT) statement.[195]

Assessing for both adherence and competence is important since the two are not necessarily equivalent (e.g., a facilitator can be highly adherent to treatment manual procedures, but not be competent in deploying them). An aspect of competence which appears important when delivering group-based complex interventions[158] is interactivity between facilitator and recipients – namely, the degree of "didacticism".[158,196] Whilst some didacticism is needed to ensure certain information is provided and participants remain oriented to the goals of the intervention, interaction means participants are asking questions, obtaining clarification and so ensuring the intervention is tailored to their needs. It also permits participants to share and learn from one another.

In view of the above information, we therefore report how we 1) developed a measure of adherence for SAFE and evaluated its reproducibility; 2) used an existing method for assessing didacticism and evaluated its reproducibility when applied to SAFE; and 3), using audio-recordings of intervention sessions, determined the extent of adherence and didacticism demonstrated in the delivery of SAFE within the pilot RCT.

Methods

All 7 courses run for the SAFE + Treatment as Usual arm of the pilot RCT were audio-recorded and assessed for implementation fidelity. Since SAFE is brief and because it is not known which

components comprise its key active, behaviour changing ingredients, all parts of SAFE were evaluated for their fidelity. The facilitator was aware course recordings were to be rated.

Developing the intervention fidelity measurement instruments

Adherence

A checklist of SAFE's intended content was developed on the basis of the facilitator's manual (*see* Supplementary material 1). It listed the 37 items that were meant to be delivered across SAFE's 6 modules. The checklist asked a rater to report the extent to which each item was delivered (0= item not delivered, 1= partially delivered, 2= fully delivered).

The number of items within the modules differed (range= 4-10). To allow adherence within the different course modules to be compared, average adherence ratings were thus calculated.

Competence

The intention was that learning be elicited rather than taught via SAFE, with the behaviour of the educational facilitator seeking to promote a non-didactic approach. It was not known what level of didacticism represented the optimum and might be associated with the greatest improvement in patient outcomes. It was important nevertheless to gauge what balance between adherence and didacticism was being achieved when SAFE was being delivered within the pilot.

Therefore, using a method previously developed by our team,[197] didacticism was assessed using the Eudico Linguistic Annotator 5.1 software.[198] It permitted a rater to listen to the audio recording of a SAFE course and simultaneously code when the facilitator was speaking. The total amount of facilitator speech, as a proxy measure of how "didactic" the course was, was then calculated. This was divided by the duration of the course to generate the percentage of course time during which the facilitator was speaking. Filler words (e.g. "oh"; "okay"; "yeah") were not considered instances of facilitator speech.

Testing the measures

To assess reliability of the implementation fidelity measures, 2 independent raters individually evaluated each course using the fidelity measures. The raters were final year students completing a

Bachelor of Science psychology degree. Their training consisted of them completing practice adherence and didacticism ratings on 2 courses not delivered as part of the trial.

Data Analysis

Testing the measures

Interrater agreement was calculated using *MedCalc* 18.2.1. The intraclass correlation coefficient[199] evaluated agreement between the two raters' didacticism ratings. For the adherence measure, the ratings from the two raters were tabulated and simple percentage agreement first calculated. Inter-rater reliability was then assessed using the chance-corrected weighted kappa statistic.

Since paradoxical values of kappa can occur because of bias or skewed prevalence,[200] the influence of these factors was considered by calculating a prevalence index and a bias index and by comparing the change in kappa when the prevalence-adjusted bias-adjusted kappa (PABAK-OS) was calculated using the PABAK-OS calculator http://www.singlecaseresearch.org/calculators/pabak-os [accessed 27th August, 2019]. The prevalence index can range from −1 to +1 (0 indicates equal probability), whilst the bias index ranges from 0 to 1 (0 indicates equal marginal proportions and so no bias)[201].

Course fidelity

The raters' adherence and didacticism scores for each course were averaged and described using descriptive statistics.

Results

Testing the fidelity instruments

Adherence scale – interrater reliability

For 96% of adherence items, the raters made the same judgement about the extent to which the item was delivered, but the weighted kappa statistic was only 0.66 (95% CI 0.50 to 0.83). This was a consequence of prevalence bias (–0.83; bias index=0.06), with 94.6% of the raters' ratings using the category "fully delivered". Given this, the PABAK-OS statistic of 0.91 (95% confidence interval [CI] 0.85, 0.97) (which equates to "substantial agreement") provided a more accurate reflection of rater concordance.

Didacticism measure - interrater reliability

With a coefficient of 0.96 (95% CI 0.78, 0.99), the intraclass correlation coefficient indicated the two raters judgement with regards didacticism were highly correlated.

Course fidelity

Adherence

Adherence was high. Of the 259 items meant to be delivered across the 7 courses; 228 (88.0%) were "fully delivered". Only 8 (3.1%) were "not delivered" (Table 14). The average adherence rating (the maximum being 2) given to the items across the SAFE courses was 1.88 (standard deviation [SD] 0.11, range 1.65 to 1.97) (*see* Appendix 16).

Table 14 Characteristics of the courses

Course number	Adherence rating		Didacticism rating: percentage of time facilitator speaking
	No. of items fully delivered (%)	M rating across 37 items (SD)	
1	35 (94.6%)	1.97 (0.11)	54.45%
2	33 (89.2%)	1.91 (0.35)	57.57%
3	33 (89.2%)	1.92 (0.25)	63.94%
4	35 (94.6%)	1.95 (0.22)	54.48%
5	32 (86.5%)	1.86 (0.40)	49.59%
6	27 (73.0%)	1.65 (0.69)	48.87%
7	33 (89.2%)	1.88 (0.39)	59.42%
Across 7 courses	228 (88.0%)	1.88 (0.11)	55.47% (SD=5.35)

Notes:
Each course consisted of 6 modules. Together these contained 37 items that were to be delivered. The extent of each of these items delivered was rated using the following scale: 0 = item not delivered, 1 = item partially delivered, 2 = item fully delivered.

The mean and range of adherence scores given to the individual intervention items showed no item proved too challenging to be fully delivered at least once. The mean score of only one intervention item – namely, that requiring the facilitator to inform the participants about when the demonstrated recovery position should and should not be delivered – fell below 1 (i.e., 0.79).

Didacticism

The mean percentage of facilitator speech across the courses was 55% (SD= 5.4), with a range of 49 to 64% (Table 14).

Summary

The SAFE intervention was found to have been delivered as intended across the pilot RCT. The adherence measure indicated the facilitator delivered almost all of the items prescribed by the treatment manual. Moreover, they were able to do this whilst maintaining a high degree of interactivity. These findings indicate that we do not anticipate that estimate of intervention effect found within the pilot RCT to be influenced by poor implementation fidelity.

Chapter 6 Outcomes of the pilot RCT and implications for a definitive trial

Introduction

Primary and secondary outcome measures were captured/ completed to varying degrees at baseline, 3-, 6- and 12-month follow-ups. This chapter outlines the findings from these assessments.

Outcome measures

Proposed primary outcome: ED use measured by HES system

Routinely collected data on emergency department (ED) use from the Hospital Episode Statistics (HES) system was secured for 48 (94.1%) of the randomised patient participants. The mean number of visits recorded over the 12 months following randomisation for the Seizure First Aid Training For Epilepsy (SAFE) group was 1.8 (standard deviation [SD]=3.14,) and the median was 1 (range 0 to 12). For the Treatment as Usual (TAU) group, the mean was 3.4 (SD=4.78) and the median 2 (range 0 to 20). Compared to the 12-months prior to randomisation, mean ED use over follow-up, reduced for the SAFE group by 0.3 (28%) visits. For the TAU group, it increased by 0.4 (11%) visits (Table 15).

ED use was over dispersed. There was not though an excess of zeros (Vuong's[190] test z=-0.17, P=0.87). For this reason, negative binomial regression (NBR) compared the effect of treatment group on ED use. It showed the estimated rate of ED visits following randomisation was around 46% lower in the SAFE+TAU group than for the TAU group (Rate Ratio= 0.54). This difference was not statistically significant at the 5% alpha level (95% confidence interval [CI] 0.24 to 1.18), nor at 10% (90% CI 0.28 to 1.04). It was at 20% (80% CI 0.32 to 0.90, P=0.12) (Table 16).

Due to a slight imbalance between groups in participants' ED use during the 12 months prior to randomisation (i.e. ED visits at baseline), we also applied an adjusted NBR including SAFE+TAU group and baseline ED visits. Results showed that an increased number of ED visits pre-randomisation was associated with an increased number of post-randomisation ED attendances (Rate Ratio=1.33, 95% CI 1.18 to 1.52). With the adjustment, the estimated effect size for treatment group reduced with the rate of ED visits for the SAFE group being around 38% lower than for the TAU group (Rate Ratio= 0.62). In this adjusted analysis, treatment group was not significantly associated with ED use at the 5% (95%

CI 0.33 to 1.17) or the 10% level (90% CI 0.36 to 1.06). It was significant at 20% (80% CI 0.41 to 0.94, P=0.14).

Table 15 Number of ED visits patient participants made according to HES data system

Outcome: Number of ED visits		SAFE+TAU	TAU	Total
In the 12 months to baseline	N	25 (96.2%)	23 (92.0%)	48 (94.1%)
	Mean	2.1	3	2.5
	Standard deviation	2.22	2.76	2.51
	Minimum	0	1	0
	Median	1	2	2
	Maximum	10	12	12
	Missing	1 (3.8%)	2 (8.0%)	3 (5.9%)
In the 12 months following randomisation according to Hospital Episode Statistics (HES) data.	N	25 (96.2%)	23 (92.0%)	48 (94.1%)
	Mean	1.8	3.4	2.6
	Standard deviation	3.14	4.78	4.05
	Minimum	0	0	0
	Median	1	2	1
	Maximum	12	20	20
	Missing	1 (3.8%)	2 (8.0%)	3 (5.9%)
Change from baseline over 12 months following randomisation according to HES data.	N	25 (96.2%)	23 (92.0%)	48 (94.1%)
	Mean	-0.3	0.4	0.1
	Standard deviation	1.99	3.81	2.99
	Minimum	-4	-5	-5
	Median	0	0	0
	Maximum	5	16	16
	Missing	1 (3.8%)	2 (8.0%)	3 (5.9%)

Table 16 Between intervention group differences in number of HES identified ED visits

Model and parameter	Parameter	Confidence Interval (CI)			P-value
		95%	90%	80%	
12 months following randomisation according to Hospital Episode Statistics (HES) data[a]					
Negative binomial: SAFE + TAU (Rate Ratio)	0.54	0.24 to 1.18	0.28 to 1.04	0.32 to 0.90	0.12
Negative binomial: Dispersion parameter	1.53	0.67 to 2.39	0.80 to 2.25	0.96 to 2.09	NA
Vuong's Test[b]	-0.17	NA	NA	NA	0.87
12 months following randomisation according to Hospital Episode Statistics (HES) data with adjustment for baseline ED visits					
Negative binomial: SAFE + TAU (Rate Ratio)	0.62	0.33 to 1.17	0.36 to 1.06	0.41 to 0.94	0.14
Negative binomial: Baseline ED visits (Rate Ratio)	1.33	1.18 to 1.52	1.20 to 1.49	1.23 to 1.45	<0.001
Negative binomial: Dispersion parameter	0.69	0.17 to 1.21	0.26 to 1.13	0.35 to 1.03	NA
Vuong's Test[b]	-0.13	NA	NA	NA	0.90

Notes:
ED=Emergency Department; SAFE=Seizure First Aid Training; TAU=Treatment as Usual,
a. Analysis based on 48 patient participants
b. Vuong's [190]test p-value interpretation, a significantly negative parameter value favours the Negative Binomial model and significantly positive favours the Zero-inflated Negative Binomial model. A non-significant value indicates no significant difference between the models therefore the simpler Negative Binomial model is preferred.

Secondary outcome data

ED use: Self-reported:

Self-report data on ED use over the 12 months prior to *and* following randomisation was available for 34 (66.6%) of the randomised patient participants. The mean number of ED visits reported by patient participants in the SAFE+TAU group was 1.2 and the median 0. The mean for the TAU group was 2.9 and median 1. Compared to the 12 months prior to randomisation, mean ED use over follow-up reduced by 2.6 visits for participants in the SAFE+TAU arm. For the TAU group, it reduced by 0.3 visits (*see* Appendix 17).

NBR with (Rate Ratio=0.34, 95% CI 0.11 to 1.07, P=0.10) and without (Rate Ratio=0.42, 95% CI 0.15 to 1.20, P=0.06) adjustment for ED use over the 12 months prior to randomisation indicated the estimated rate of ED visits following randomisation was around 66% and 58% lower in the SAFE+TAU group than for the TAU group respectively (Table 17).

Table 17 Between intervention group differences in number of self-reported ED visits

Model and parameter	**Parameter**	Confidence Interval (CI)			P-value
		95%	**90%**	**80%**	
12 months following randomisation according to participant self report					
Negative binomial: SAFE + TAU (Rate Ratio)	0.42	0.15 to 1.20	0.17 to 1.01	0.21 to 0.83	0.10
Negative binomial: Dispersion parameter	1.85	0.50 to 3.20	0.72 to 2.98	0.97 to 2.73	NA
Vuong's Test[a]	0.49	NA	NA	NA	0.62
12 months following randomisation according to participant self report with adjustment for baseline ED visits					
Negative binomial: SAFE + TAU (Rate Ratio)	0.34	0.11 to 1.07	0.13 to 0.88	0.16 to 0.72	0.06
Negative binomial: Baseline ED visits (Rate Ratio)	1.15	0.83 to 1.60	0.88 to 1.52	0.93 to 1.43	0.39
Negative binomial: Dispersion parameter	1.87	0.38 to 3.36	0.62 to 3.12	0.89 to 2.84	NA
Vuong's Test[b]	-0.13	NA	NA	NA	0.90

Notes:
ED= Emergency Department; SAFE=Seizure First Aid Training; TAU=Treatment as Usual.
[a] Vuong's[190] test p-value interpretation, a significantly negative parameter value favours the Negative Binomial model and significantly positive favours the Zero-inflated Negative Binomial model. A non-significant value indicates no significant difference between the models therefore the simpler Negative Binomial model is preferred.

Relationship between HES and self-report:

Out of the 34 patient participants who had self-report ED data at T3 (12 months) and for whom consent remained in place and HES data secured, eleven participants (32.4%) had the same number of ED visits recorded by HES data and by self-report; seven participants (41.2%) from the TAU group and four participants (23.5%) from the SAFE+TAU group. Thirteen patient participants (38.27%) had more ED visits recorded by HES data than by self-report and ten patient participants (29.4%) self-

reported more ED visits than were recorded by HES data; proportions were similar across the two treatment groups (Table 18).

Table 18 Comparison of HES identified ED visits and self-reported ED visits during the 12 months post-randomisation

Number of ED visits in the 12 months prior to baseline	SAFE+TAU	TAU	Total
More on HES than self report	7 (41.2%)	6 (35.3%)	13 (38.2%)
Self report and HES the same	4 (23.5%)	7 (41.2%)	11 (32.4%)
More self reported than on HES	6 (35.3%)	4 (23.5%)	10 (29.4%)

Figure 7 shows a Bland-Altman plot of the agreement between the mean of number of ED visits self-reported and recorded by HES data for the 34 patient participants; the limits of agreement being -5.3 visits (i.e. 5.3 less visits recorded by self-report than in HES data) to 4.4 visits (i.e. 4.4 visits more recorded by self-report than in HES data). Compared to baseline (Figure 6), this Bland-Altman plot demonstrates a relatively even spread of patient participants self-reporting more and less ED visits compared to HES data.

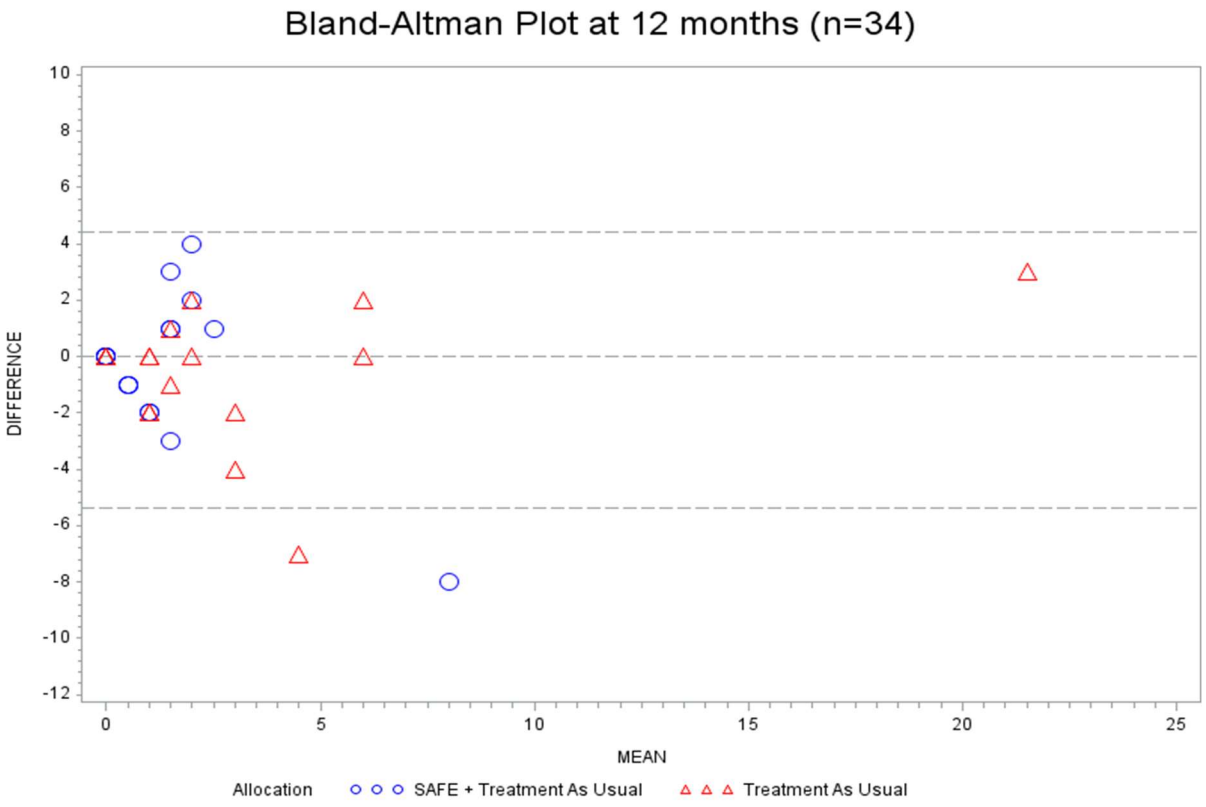


Figure 6 Bland Altman plot of agreement between self-reported ED visits and hospital episode statistics (HES data) at 12 months

Other secondary outcome measures:

As per the statistical analysis plan, differences between the two treatment groups on the remaining secondary outcome measures were not formally statistically tested. For completeness, summary statistics for the groups on these measures at T2 and T3 follow-up are reported in Appendix 18.

Safety and adverse events

Eighteen (35.3%) patient participants reported adverse events (AE) over the course of their follow-up (*see* Appendix 19). In the SAFE+TAU group, 6 AEs were reported by 6 participants, while 13 AEs were reported by 12 participants from the TAU group. Only one SAE occurred during the study – namely, a diagnosis of previous status epilepticus. This was reported by one SAFE+TAU group participant. Upon medical review, it was considered unlikely to be related to the SAFE or participation in the trial as it arose from investigations the participant had been having before they began participating in the trial.

Participant feedback

Thirty-two (68.1%) patient participants and 20 (62.5%) significant others (SOs) completed the participant feedback questionnaire at T3. All but one said they would participate in the trial again (Table 19 and 20).

Table 19 Feedback on participation in the SAFE trial (patient participants)

Outcome: Feedback on participation in the SAFE trial	**SAFE + TAU**	**TAU**	**Total**
If time suddenly went backward, and you had to do it all over again, would you agree to participate in the trial?	(n=26)	(n=25)	(n=51)
Definitely yes	15 (57.7%)	10 (40.0%)	25 (49.0%)
Probably yes	2 (7.7%)	4 (16.0%)	6 (11.8%)
Probably no	0 (0.0%)	1 (4.0%)	1 (2.0%)
Definitely no	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not sure	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	9 (34.6%)	10 (40.0%)	19 (37.2%)

Table 20 Feedback on participation in the SAFE trial (significant other participants)

Outcome: Feedback on participation in the SAFE trial	SAFE + TAU	TAU	Total
If time suddenly went backward, and you had to do it all over again, would you agree to participate in the trial?	(n=18)	(n=19)	(n=37)
Definitely yes	11 (61.1%)	9 (47.4%)	20 (54.1%)
Probably yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
Probably no	0 (0.0%)	0 (0.0%)	0 (0.0%)
Definitely no	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not sure	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	7 (38.9%)	10 (52.6%)	17 (45.9%)

When asked to explain why, the limited burden associated with participating was mentioned, as was a sense of duty to help improve things for others. Some SAFE+TAU arm participants mentioned the benefit they perceived themselves to have derived from SAFE. Illustrative quotes included:

> *"I found that the study was not an issue or an inconvenience and I was happy to participate and would happily take part in any future studies"* (PWE participant).
>
> *"I'm more than happy to help in a study that helps towards epilepsy"* (PWE participant)
>
> *"Before we done it* [participated in the research] *we didn't have a clue...sometimes we would have gone to the hospital if we needed...but now we don't need to go"* (SO)

Some participants provided comments relating to recruitment. No concerns were raised regarding randomisation, indicating that the process was acceptable. A point made by a number of participants was that whilst they valued the intervention, they felt the offer seemed somewhat reactive and that a more preventative approach to self-management support might be valuable. They said that taking part in SAFE had been their primary source of education since being diagnosed, with healthcare encounters having previously focused on *"medication and never about education or management"* (SO participant) and that there was a need to offer such an intervention to those who are also recently diagnosed with epilepsy.

In terms of continued participation in the trial, a number of participants reported they had experienced challenges in completing the questionnaires during the course of the study due to instances of being unwell. Several participants from the TAU group also noted that memory problems and the gap between data collection episodes meant they had forgotten about their participation in the study and so their motivation to take part when contacted had reduced.

Sample size calculation for future trial

The proposed primary outcome measure for a definitive trial is ED use as measured by HES. The pilot RCT found a reduction of around 47% in ED use in the SAFE+TAU group in the 12 months following randomisation compared to TAU.

Table 21 shows the number of patient participants that would be required *per* group for a definitive trial. Depending on the estimate of the dispersion parameter from the pilot trial that is used and the statistical power required, the number of patient participants needed per group in a definitive trial ranges from 123 to 451.

Table 21 Required sample size for a definitive trial to detect estimated effect of SAFE+TAU on ED use (measured using HES data)

Dispersion parameter (*k*)	**~47% reduction (from 3.4 to 1.8 visits) in 12 months compared to TAU**	
	n per group (α= 0.05; 80% power, β=0.2)	**n per group** (α= 0.05; 90% power, β=0.1)
0.17	123	164
0.5	191	255
0.69	230	308
1	293	393
1.21	337	451

Notes:

Dispersion parameter taken from the adjusted NBR model in the pilot RCT (i.e., k=0.69; 95% CI: 0.17 to 1.21); *see* Table 16

If the central value of the estimate range for the dispersion parameter k of 0.69 is used, 90% power stipulated and 9.4% of recruited patients would eventually withdraw consent to access their HES data (as observed in the pilot) then a sample of 674 patients ([308*2]+58) would need to be recruited for a definitive trial of SAFE. Using the estimates for eligibility and consent from the pilot trial, it would be anticipated that the triage cards of >51,000 patients would need to be screened and >7,000 patients invited to secure a sample of 674 patients.

For the pilot RCT, 3 Type 1 EDs acted as recruitment sites. These EDs generated, on average, 17.6 patient accruals each from 19 months of attendances – so about 1 per month. The EDs were similar in size to EDs in England, with the mean number of attendances (for any reason) at them being in line with the average for English EDs https://www.england.nhs.uk/statistics/statistical-work-areas/ae-

waiting-times-and-activity/statistical-work-areasae-waiting-times-and-activityae-attendances-and-emergency-admissions-2015-16-monthly-3/ [accessed 27th August, 2019]. It can therefore be estimated that a definitive trial would require around 39 average size ED sites to recruit the necessary sample. This would equate to about half of England's Type 1 EDs.

Summary

Using data from the 94% of patient participants on whom primary outcome data was secured, estimates for the effect of SAFE+TAU on ED use were generated. Feedback from participants on trial participation was also secured. Participation in the trial was not associated with adverse effects and participants for the most part welcomed taking part and receiving the intervention. Using the estimate of effect and evidence from the pilot RCT on eligibility and uptake, it was calculated that a large definitive trial, in terms of recruitment sites and starting sample, would be needed to definitively judge the efficacy of the SAFE intervention.

Chapter 7: Economic evaluation

Introduction

When the feasibility of a definitive trial is being considered, an important part of the decision calculus is the cost of delivering the intervention to be trialled. Cost is important since it will affect the ease with which 'excess treatment costs' can be secured and would be fundamental to future cost-effectiveness analysis. It is also important since stakeholders will want to consider the budget impact and scalability of the intervention to be tested should it be found to be cost-effective. In contrast to health technologies, the costs of complex interventions such as Seizure First Aid Training For Epilepsy (SAFE) are often less well characterised and may be variable depending on the context of use. Microcosting is a method that provides detailed, bottom-up cost data based on each component of the delivery of an intervention.[202]

We performed a microcosting to calculate the fixed and variable costs of delivering SAFE within the context of the pilot randomised controlled trial (RCT). The cost of developing the SAFE intervention via the processes described in Chapter 2 was also determined. Such information is rarely provided, but can be helpful for those planning similar endeavours and for research funders.

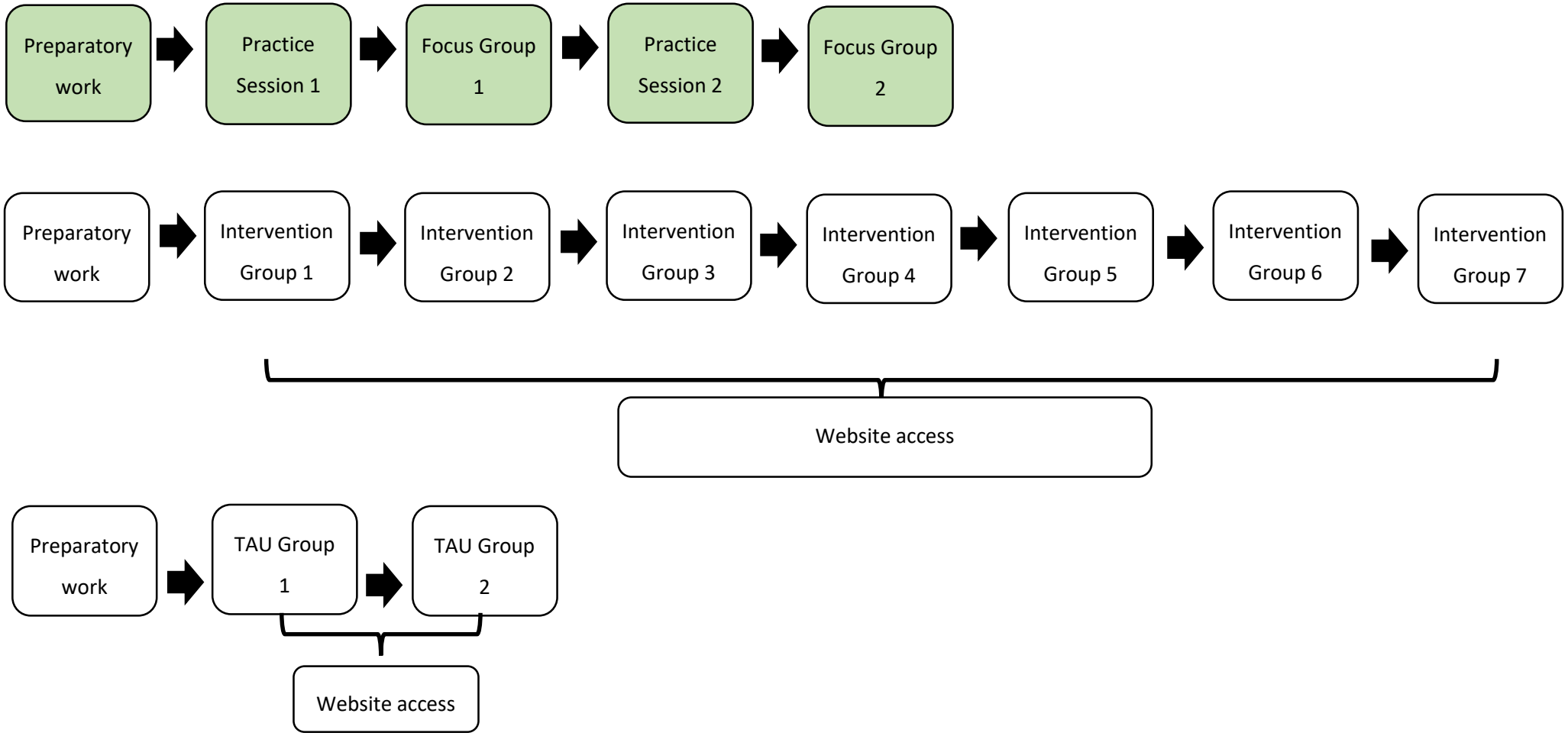
Methods

The microcosting adopted the perspective of an academic non-profit making institution and was conducted in three stages: (1) identification of resources; (2) measurement; and (3) valuation. [203]

Step 1: Identification of resources

An health economics researcher (E.H) met with staff central to the development of the SAFE intervention (academic staff A.N and D.S) and delivery (epilepsy nurse specialist SAFE facilitator J.B, project administrator G.M) to map out the courses run for the project. The work and resources required for each was attributed to one of three categories according to the primary purpose of the course: inform intervention design, for participants in SAFE + Treatment as Usual (TAU) arm, or for TAU alone arm participants (Figure 8).

Figure 7 Workflow (shaded boxes = research and development)



The resources and items required to deliver SAFE were also differentiated as being fixed or variable. Fixed resources were constant regardless of the number of people attending the course (e.g. room hire, facilitator). Variable resources were those that changed depending on the number of attendees (e.g. patient/significant other [SO] takeaway information packs, travel expenses etc.). Participant involvement was costed from the point at which they were invited to attend a SAFE session to more accurately reflect routine practice.

Step 2: Measurement

The quantity of use of the resources, identified in Stage 1, was measured. To capture this information we used the 'time and motion method'.[204] This involved A.N, D.S, J.B and G.M completing electronic data collection forms on which they self-reported the time they dedicated to different activities. The research team (A.N, D.S) also recorded details of the number of participants invited and attending each SAFE sessions and non-staff resources.

Staff time and costs

Time was split into preparatory work (time in meetings, designing the SAFE intervention, administration of SAFE's content, planning and organising practice sessions, attending practice sessions, reviewing and editing SAFE's content) and programme delivery (time spent inviting participants, organising and attending the SAFE sessions, packing-up, and administration of participant expenses and the website). Staff recorded their time against each task for each SAFE session.

Travel time and costs

Staff involved in SAFE's delivery recorded estimates of time travelling to sessions and any travel costs. Travel costs were recorded for participants and taken from the study finance records as the total claimed per group.

Other costs

The two academic staff central to adapting the intervention (A.N, D.S) recorded all the resources and items required to complete the activities identified in Stage 1. These included office space for staff involved in course preparation and administration, telephone calls, stationery, printing and postage, leaflets for patient-SOs, advertising, participant remuneration (practice sessions only), venue hire, refreshments, equipment, and website domain and administration costs.

Step 3: Valuation

A monetary value was attached to the quantities of resources used that were measured in Step 2. Unit costs and details of suppliers were obtained using local data from the finance office of the University of Liverpool, or national sources, as applicable (e.g. Royal Mail) (Table 22). Costs were calculated using price year 2017/18 and in Sterling (£). Value-added Tax was applied to equipment and consumables at a rate of 20%.

Details of staff job titles, employer and salary bands were obtained. Academic staff costs were based on University of Liverpool salary scales 2017/18 (hourly rate August 2017). Salary costs for the epilepsy nurse specialist delivering the training and the administrative assistant were calculated using hourly rates for casual workers and included 12.07% holiday pay. The epilepsy nurse specialist completed her role on the SAFE pilot study on an Honorary contract with University of Liverpool at an hourly rate equivalent to Band 6 in National Health Service (NHS) England or Wales (Royal College of Nursing, 2018). All salary costs were converted into cost per minute for the purpose of valuing time on activities. The staff costs per minute were multiplied by the time spent on each activity, then summed to obtain total staff costs.

Analysis

Resource use and costs were analysed to calculate the cost of developing the intervention, the fixed and variable costs of delivering the training sessions (SAFE+TAU or TAU), and the mean cost per participant or patient (which includes the cost of attending with or without an SO). The cost of developing SAFE was calculated as the sunk cost of designing the intervention (incurred and were independent of future training courses) plus the total fixed annual set-up cost. Calculations were based on an assumption of 11 groups per year and equipment life of one-year.

The epilepsy nurse specialist who facilitated the SAFE courses was not locally based, but rather located within the region of the offices of the Epilepsy Society. This meant she travelled to Liverpool to deliver the course. For this reason, a scenario analysis which excluded the travel time and travel expenses of the epilepsy nurse specialist facilitating the groups was conducted to explore a more realistic scenario of employing a local nurse.

The mean and standard deviation (SD) of observed data were calculated. The 95% central range (CR) for costs and differences was generated using 10,000 bootstrap replications. All data were managed and analysed in *Microsoft Excel*.

Table 22 Unit costs

Category	Unit cost (£)	Source
Staff (per minute)		
Lecturer (Grade 8)	0.46	University of Liverpool https://www.liverpool.ac.uk/media/livacuk/hr/working/Salary,Scales,and,Hourly,Rates,2017-18.pdf [accessed 30th April, 2018]
Administrative Assistant	0.23	
Research Fellow (Grade 8)	0.40	
Epilepsy Specialist Nurse*	0.25	
IT Technician (Grade 8)	0.47	
Delegate expenses (per group)		
Practice group (travel)	55.00	Research study financial statement. Practice group remuneration = £10 shopping voucher per focus group participant. Disaggregated travel expense data not available.
Practice group (remuneration)	135.00	
SAFE+TAU group (travel)	40.00	
TAU group (travel)	46.40	
Telephone (per min, including VAT)		
Office line to UK mobile	0.06	BT Business Phone Call Charges cited at: https://business.bt.com/content/dam/bt/business/PDFs/phonelines/BT-Business-Call-Charges.pdf [accessed 30th April, 2018]
Office line to UK land line	0.05	
Advertising (per advert)		
Practice group recruitment	45.00	Liverpool Daily Echo
Venue costs		
Room Hire (per course) 1/2 day, room capacity=20 delegates, includes PC and projector	80.00	Royal Liverpool Academy http://www.royalliverpoolacademy.nhs.uk/media/2777/room-charges-0417-pdf.pdf [accessed 30th April, 2018]
Refreshments (per head) Tea and coffee	1.50	Royal Liverpool Academy http://www.royalliverpoolacademy.nhs.uk/media/2777/room-charges-0417-pdf.pdf [accessed 30th April, 2018]
Equipment (including VAT)		
Dictaphone ('Olympus DM-650) and boundary microphone ('Olympus ME33)	355.98	Research study financial statement
Study laptop	592.87	The DTP Group (purchased via University of Liverpool) www.dtpgroup.co.uk [accessed 30th April, 2018]
Annual fees (including VAT)		
Website domain	20.94	Fasthosts Internet Ltd

Table 22 *continuation*: Unit costs

Category	Unit cost (£)	Source
Freepost licence fee	116.40	Royal mail https://www.royalmail.com/business/system/files/Response-Services-rate-card-March-2018-138.pdf [accessed 30th April, 2018]
Delegate packs (including VAT)		
Invite pack 1 x A4 black & white single side + envelope + 2nd class post + freepost reply envelope (n)	1.12	Lyreco stationery suppliers University of Liverpool printing rates Royal mail postage
Reminder pack 1 x A4 black & white single side + envelope + 2nd class post + freepost reply envelope (n)	1.12	
Focus group consent form 1 x A4 black & white single side (n)	0.04	
Delegate booking confirmation 1 x A4 colour double side + 1st class + envelope	0.80	
Delegate course pack (SAFE+TAU) Slide handouts: 10 x A4 colour single side + certificate + folder	0.89	
Delegate course pack (TAU) Slide handouts: 20 x A4 black & white single side + certificate + folder	0.89	
Name badge	0.60	
Leaflets (per leaflet)	1.00	Epilepsy Society
Convenor pack Acetate x4 + answer cards x 4 + pens x10 + flip chart + [trainer manual + clipboard + white board markers x2 + coloured marker pens x 12]**	4.96	Lyreco stationery suppliers

Notes:
*Epilepsy Specialist Nurse: Honorary contract with University of Liverpool ~ Band 6 in NHS England or Wales (Royal College of Nursing, 2018)
**Items in parenthesis single purchase, reused throughout 11 groups, convenor pack calculation uses mean cost per group

Results

Over the course of the project, 11 SAFE intervention courses were run. Two were run to inform intervention design, seven were run for participants in SAFE+TAU intervention arm, and two were run

after the trial was completed for the TAU group. Data were collected from the four noted members of staff with all data collection forms being complete, and with no missing data.

The total cost of developing the training was £9,947, which included two practice SAFE courses, attended by 27 people (Table 23); 88.72% of the development cost was a sunk cost independent of future training courses.

To deliver SAFE within the pilot RCT the fixed cost (SAFE+TAU or TAU group) was £263 per group, which represented the cost of course facilitation and venue hire. Mean variable cost per group (n=9) was £922 (SD: 131; 95% CR: £887 to £1,085). There were no statistically significant differences in the mean cost per group between SAFE+TAU and TAU (SAFE+TAU group mean=£903, SD 134; 95% CR: £760 to £1,087; TAU group mean £986, SD 140; 95% CR £887 to £1,085; difference in CR -£324 to £119).

On average, the TAU groups involved six more participants than the SAFE+TAU groups. The mean cost per participant was £119 (95% CR: £110 to £128) in the TAU arm; this was significantly lower than the cost per participant in the SAFE+TAU arm (£240, 95% CR: £211 to £278; difference in CR - £1,137 to -£872); both estimates exclude fixed annual set-up costs of £1,122.

The ratio of patients to SOs in the groups was 3:2 on average. The mean cost per patient (with or without SO) was £208 (95% CR: £192 to £225) in the TAU arm; this was significantly lower than the cost per patient in the SAFE+TAU arm which was £408 (95% CR: £358 to £472).

When including the cost of developing SAFE (£181 per person), the mean cost per participant, based on all 55 participants in SAFE+TAU or TAU arm was £375 per delegate (95%CR: £348 to £402). This reduced to £214 (95%CR: £188 to £241) when excluding sunk costs that would not be incurred again in the future.

Staff time account for 50.01% of the cost of the delivering SAFE, and almost 70.21% of the development cost. Staff travel expenses accounted for an additional 21.10%. Travel expenses were high as a consequence of the specialist nurse delivering SAFE not being locally-based.

Office costs, stationery, printing, postage and venue hire are relatively low. A scenario analysis of facilitator costs without travel expenses (time and cost), reduced the mean cost by 21.08% from £194 (95%CR: £167 to £221) to £152 (95%CR: £124 to £179) per delegate or from: £333 (95% CR: 288 to 380) to £261 per patient.

Table 23 Total observed costs and cost per delegate to deliver the SAFE intervention within a research trial with two academic researchers, one Epilepsy Specialist Nurse delivering the training, and administrative support

Description	Design & set-up	Practice Session 1	Practice Session 2	SAFE+TAU Group 1	SAFE+TAU Group 2	SAFE+TAU Group 3	SAFE+TAU Group 4	SAFE+TAU Group 5	SAFE+TAU Group 6	SAFE+TAU Group 7	TAU Group 1	TAU Group 2
Fixed costs (£)												
Equipment	928.85	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Website	77.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Freepost licence	116.40	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Venue	0.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00
Facilitator (staff cost)		192.79	192.79	177.96	177.96	177.96	177.96	177.96	177.96	177.96	177.96	177.96
Facilitation resources		4.96	4.96	4.96	4.96	4.96	4.96	4.96	4.96	4.96	4.96	4.96
Total (fixed)	1122.37	277.75	277.75	262.92	262.92	262.92	262.92	262.92	262.92	262.92	262.92	262.92
Variable costs (£)												
Staff costs	4243.41	612.88	1158.56	591.19	521.84	429.37	429.37	318.41	318.41	318.41	299.96	416.03
Staff travel expenses	44.10	279.87	279.87	274.67	274.67	265.43	265.43	265.43	265.43	265.43	233.63	265.41
Participant expenses	0.00	180.00	200.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00	92.80	0.00
Office costs (inc. telephone)	589.33	33.00	105.50	81.63	85.23	92.60	88.70	89.00	86.60	89.00	57.17	70.13
Stationery, print, post	0.00	156.35	196.96	57.44	93.68	68.93	68.93	34.46	22.98	45.95	182.73	298.44

Table 23 *continuation*: Total observed costs and cost per delegate to deliver the SAFE intervention within a research trial with two academic researchers, one Epilepsy Specialist Nurse delivering the training, and administrative support

Description	Design & set-up	Practice Session 1	Practice Session 2	SAFE+TAU Group 1	SAFE+TAU Group 2	SAFE+TAU Group 3	SAFE+TAU Group 4	SAFE+TAU Group 5	SAFE+TAU Group 6	SAFE+TAU Group 7	TAU Group 1	TAU Group 2
Refreshments	0.00	72.25	72.25	41.80	41.80	32.81	32.00	41.00	26.60	18.50	21.00	34.50
Advertising	45.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total (variable)	4921.84	1334.34	2013.13	1086.73	1057.22	929.13	924.42	788.30	760.01	777.29	887.28	1084.51
TOTAL COST (£)	6044.21	1612.09	2290.88	1349.65	1320.14	1192.05	1187.34	1051.22	1022.93	1040.21	1150.20	1347.43
Delegates (n) [patient:SO]		12	15	2:3	4:4	3:3	4:2	3:0	1:1	2:2	4:4	8:5
Mean cost/delegate (£)		134.34	152.73	269.93	165.02	198.68	197.89	350.41	511.47	260.05	143.78	103.65
Mean cost per group (sd) 95% central range [a]				£1,166 (134.22) £1,023-£1,350							£1,249 (139.46) £1,150-£1,347	
Mean cost per delegate 95% central range [a]				£240 £211-£278							£119 £110-£128	
Mean cost per patient (with or without SO) 95% Central range [a]				£408 £358-£472							£208 £192-£225	

Notes:

[a] Central ranges generated from 10,000 bootstrap replications

Discussion

Delivering SAFE was estimated to cost £333 per patient (with or without a SO) - and it is plausible that this could be delivered for as low as £261 per patient or £152 per delegate. The main cost contributors are staff costs and associated travel expenses and office costs. The annual fixed cost of setting-up and running SAFE is £1,122 (+35.07 per patient, based on 32 patients/ year attending with or without a SO).

Chapter 8: Discussion

Principal findings

PART A - Intervention development

A novel co-production approach enabled us to achieve our objectives of: a) optimising the content, delivery and behaviour change potential of the Epilepsy Society's (ES) existing course for people with epilepsy (PWE) attending emergency departments (ED), and their significant others (SO); and b) developing a seizure management intervention which had support from representatives from the target service user population and from professional groups involved in their care.

The finalised intervention – Seizure First Aid Training For Epilepsy (SAFE) – was brief, manualised, supported by the inclusion of a theory of behaviour change and based on a delivery method considered by stakeholders to be sustainable for the National Health Service (NHS). Feedback from service users who received the test version of the intervention was positive. This is despite it focusing on sensitive areas, such as potentially unnecessary hospital service by them and their own beliefs about epilepsy. Participants valued the straightforward guidance offered by SAFE and liked its group format. This concurs with previous observations, with PWE having previously been found to say the format helps them "feel less alone" and able to share and learn from others.[230] Our participants did identify potential barriers to intervention effect (e.g., memory difficulties) and we sought to ameliorate these (e.g., by providing participants with access to hard and online copies of the course materials).

Trialists have often been criticised for not describing complex interventions sufficiently for replication.[205] This is not the case for SAFE. Its content and the origin of each of its elements are clearly documented. A Template for Intervention Description and Replication (TIDieR) checklist [195] is also provided in (*see* Supplementary material 2).

The microcosting of intervention development activity is rare. At just under £10,000, the cost of developing SAFE is arguably low. This was, in part, because SAFE was adapted from an existing intervention and because the owners of the original course (the ES) did not charge for access to it or its materials. Our findings are important to disseminate as they could help those considering similar

endeavours to accurately forecast activity, timelines and costs. They also provide funders with a benchmark against which to judge applications.

PART B – Pilot randomised controlled trial

A pilot randomised controlled trial (RCT) comparing SAFE + Treatment as Usual (TAU) to TAU alone was successfully completed. As planned, it provided estimates of key parameters, including recruitment and retention, and allows an informed decision regarding the feasibility and optimal design of a definitive trial of SAFE to be made. Below we discuss the estimates, their relation to the 2 progression criteria established at project outset and the implications.

Positives for feasibility of a definitive trial:

The pilot demonstrated it is possible to identify, consent, randomise and largely retain persons from the target population and their SOs in a RCT. This was not a given at the outset since no trial had focused recruitment on it and because the population is potentially vulnerable.

No safety concerns arose from the trial's conduct and no protocol deviations occurred. Strategies within the trial to conceal treatment allocation worked. It was possible to get most (76.9%) patient participants randomised to the SAFE+TAU arm to a SAFE session and for it to be delivered as intended (i.e., with high fidelity). This is in line with that seen in previous RCTs of complex interventions with the epilepsy population.[71-72,206-208]

Feedback from participants indicated they valued SAFE and perceived benefits from receiving it. The SAFE intervention was perceived as being outside current epilepsy service provision. Most said they would participate in such a trial again if invited.

Importantly, by using routine outcome data on ED use as the basis for the proposed primary outcome measure, it was possible to secure 12-month outcome data for 94% of the randomised patient participants. This means the second progression criterion – namely, that 12-month follow-up data could be obtained for at least 75% of patient participants – was satisfied. The direct cost for this data was ~£10k. The progression criterion would not have been met had the trial relied on patients self-reporting on ED use since only 67.7% of participants were available and/or able to provide this information. Routine data would thus make a definitive trial less vulnerable to the effect of attrition. By way of context, the proportion of randomised patient participants with primary outcome data within recent NIHR (*Health*

Technology Assessment programme) trials (conducted 2005 to 2017) was 89% (interquartile range 79–97%), but these typically had shorter follow-up (median 6 months post-randomisation).[134]

Our pilot also revealed that relying on self-report would expose a definitive trial to what appears to be recall bias by patients relating to their use of ED. At baseline, 76.2% of patients reported more ED visits during the 12 months prior to recruitment than indicated by routine data for them (on average by 3.8 visits). It has often been believed that recall bias is not such an issue for ''big ticket'' items such as hospitalizations than for more routine lower cost service items e.g., ambulatory outpatient clinic visits.[209-210] Our findings indicate that caution should be exercised in using self-reported data on ED use.

The proportion of patients who self-reported a different number of ED visits to that recorded by the HES system was slightly smaller at 12-month follow-up (i.e., 29.4% reported more visits and 38.2% fewer). The reason for the greater congruence between the two data sources at this assessment point is not clear. The provision to patient participants upon their recruitment of seizure diaries by the trial team in which they were encouraged to record seizures and associated events might have attenuated bias.

The apparent bias and the smaller proportion of patients with self-reported ED outcome data meant that the effect size estimate for SAFE differed substantially depending on whether the calculation used self-report or HES data. When looking at the unadjusted NBR models, the self-report data indicated that the estimated rate of ED use in the SAFE+TAU group was 58% lower than for the TAU group. HES data indicated it was around 46% lower.

A microcosting exercise indicated that the cost per attendee (when excluding facilitator travel costs) of attending a SAFE course was ~£152. Accurately identifying the cost of an intervention's delivery allows excess treatment costs for a definitive trial to be forecast and helps with assessments regarding the potential for an intervention to be offered within clinical practice. The figure also allows for a simple and preliminary evaluation to be made of the potential for savings to be generated by comparing the cost of the intervention to the direct cost of the health service contact that the intervention seeks to reduce. The average cost of an ED attendance for a suspected seizure in 2007-2013 was £123, with an additional £1651 being incurred if the visit resulted in hospital admission[32] (which it does in around half of cases).

Microcosting of complex interventions remains rare. However, it is helpful to note that the NIHR funded Self-Management education for adults with poorly controlled epILEpsy ('SMILE [UK]') trial did include a microcosting of a self-management education for adults with poorly controlled epilepsy,[211] where the 2014-15 price was estimated to be £56.05 per session. The SMILE intervention however, required multiple sessions bringing the mean cost associated with the intervention to £180 (inflated to 2017-18 prices). The SAFE intervention, by contrast, requires a single session, at a comparable cost to the SMILE intervention (between £152 and £194 per delegate). The SAFE cost could be reduced if course attendance could be maximised to the intended level of ~10 patient /SO dyads per course.

Negatives for feasibility of a definitive trial:

The pilot revealed that only a small proportion of patients attending ED for a suspected seizure were eligible (10.6%) and willing (12.5%) to participate in a trial. A key reason for ineligibility was intellectual impairment. The leading reason for not wanting to take part was PWE saying they were not interested. The low rate of uptake means the other progression criterion stated at the project's outset – namely, that at least 20% of eligible patients agree to participate – was not satisfied.

Low participant uptake does not preclude a definitive trial from happening. It also may not reflect the acceptability of the intervention outside of the trial context. In the RCT of the self-management intervention Dose Adjustment for Normal Eating for Type 1 diabetes, now commissioned by the NHS, only 17% of those eligible participated.[95] If the low recruitment rate seen within our pilot trial did reflect patient support or interest in the intervention outside of a trial context, this would pose challenges to the intervention's delivery and commission within the NHS since, on average, a single ED was generating only 1 eligible patient who was willing to take part for every month of attendances.

One reason we set the consent rate criterion is that with such low participation, there is an increased likelihood that those who do and do not agree to take part may differ in important ways, thus limiting the generalisability of the trial's findings. We compared eligible patients who did and did not agree to take part in the pilot RCT by age, gender and deprivation status. We found no obvious differences in age and deprivation. Females were slightly overrepresented. The reason for this is not known (trials generally tend to underrepresent females). When telephoning patients about participation in the pilot trial we intentionally attempted telephone calls at different times of the day to minimise the influence of work status on participation.

We also do not know whether differences existed between participants and non-participants on other indices since access to the wider medical records of non-participants was not ethically permissible. One indication that the pilot trial might not have been recruiting a representative sample was that a high proportion (75.5%) of the recruited patient participants reported having seen an epilepsy specialist within the 12 months prior to the ED attendance that led to their identification. National audit data[28] indicates most (~65%) PWE attending ED have *not* done this.

The low uptake seen within the pilot also has implication for the likely cost of a definitive trial. In Chapter 6 we calculated that the sample size required for a definitive trial could be ~680 PWE. This was informed by the pilot trial estimate that SAFE may have only a modest effect on participants' subsequent ED use – reducing it on average by 0.3 visits over 12 months compared to an increase of 0.4 ED visits for the TAU alone group. Based on the participant uptake rate seen in the pilot, 39 recruitment sites could be needed to secure the required sample. The mean cost of NIHR (*Health Technology Assessment programme*) funded RCT trials is ~£1.3 million.[212] The median number of recruitment sites in them was only 15.[134] In requiring 2.5 times more sites, a definitive trial of SAFE would be more expensive. This and the potential unrepresentativeness of the sample likely to take part could mean a definitive trial of SAFE would not represent value for money from a funder's perspective.

It might not even be possible for a definitive trial to secure 39 EDs to be recruitment sites. The requirement for them to release clinical personnel to the extent required within the pilot trial to complete the screening work would not seem realistic considering how stretched most EDs already are in meeting their clinical priorities (e.g., Hassan et al.[213]). Thirty-nine EDs equates to about half of England's Type 1 EDs. A recent survey highlighted[213] that 62% of ED consultants in the United Kingdom (UK) viewed their current job as unsustainable and 94% regularly worked in excess of their planned activities.

A final negative to emerge from the pilot trial was that securing the routine outcome data on ED use was not straightforward. For data applications such as ours that involve identifiable data and require linkage across a series of datasets, NHS Digital's Service Level Agreements state these should be processed within ~2 months https://mrc.ukri.org/documents/pdf/obtaining-data-from-nhs-digital-v101016/ [accessed 27th August, 2019]. In practice, for our pilot it was not until 9 months after the last 12-month participant follow-up assessment had been completed that the raw outcome data was secured. This is despite our research team having communicated with the data provider before and during the pilot trial to ensure recruitment

and consent approaches were consistent with their requirements. Substantial time from the research team was also required following application submission to respond to queries from the data provider. Also, despite the current project being funded on the basis of external scientific reviews and its potential significance, the research team in one instance needed to appeal against a decision by the data provider midway through the application process to reject our data request, primarily because of unfounded concerns regarding the project's scientific merit.

Possible modifications to address negatives for progression to definitive trial:

Participant uptake:

Recruitment of people with uncontrolled epilepsy into evaluative studies has previously been reported to be challenging. In the 'SMILE (UK)' trial,[211] PWE living in the London area who had experienced at least 2 seizures in the prior year were invited in to a trial of self-management that had a 12-month follow-up;[214] 37% of those invited took part. In a non-randomised trial of self-management for PWE who had attended ED on one or more occasions in the prior 12 months, the uptake rate was 26%.[131] Challenges can arise due to the nature of the condition itself (e.g., unpredictable but frequent seizures) and its consequences (e.g., anxiety about travelling alone, inability to drive, memory impairment). A range of evidenced-based strategies were therefore used within the pilot RCT to try to maximise recruitment. These included, participant vouchers, first class postage for invitations, flexibility regarding when and where research appointments took place, the use of an "opt-out" approach to contacting patients about the study, multiple contact attempts and all patient facing documents being developed collaboratively with a patient and public involvement group. Despite this, a low recruitment rate was experienced.

The characteristics of the recruited patients offers one potential suggestion for the particularly low participant rate seen in the pilot RCT. Specifically, 82% of participants felt stigmatised by their epilepsy; 21.6% highly. This is more than found in those with epilepsy generally, including those with uncontrolled seizures (i.e., 63%).[214] Epilepsy, for reasons rooted deep in its history, has been called a "stigmatizing condition par excellence"[215] (p.353) and negative beliefs and lack of knowledge about the condition continue to be present. Consequently, PWE can feel ashamed of their diagnosis, guilty and reluctant to talk about it.[216] Those attending ED appear to be particularly at risk of this. This could be a barrier to participating in research. It is currently unclear how recruitment could be altered to mitigate against it.

It is also worth considering what changes might be possible to who approaches patients regarding participation. Local ED clinicians invited PWE to participate in the pilot RCT. Within trials it is usually preferable for a usual care provider, with whom a patient has an established relationship, to do the inviting. This was not considered ideal for the pilot RCT since national data indicated that most from the target population do not have a specialist usual care provider for their epilepsy (at least not one they have seen recently). Moreover, it was apparent that general practitioners were often not informed of ED visits made by PWE on their practice registers. As such neither specialists nor general practitioners are positioned to reliably identify PWE for invite. Given the low participant uptake rate, a modification that a definitive trial could consider making would be for the EDs to identify ostensibly eligible patients from their records and then request the identified patients' general practitioner to do the inviting. What impact this would have on uptake is not clear. It would require additional NHS Support Costs and additional approvals to permit EDs to communicate with general practices on what would be a research matter.

One of the leading reasons patients gave for not wanting to take part was lack of interest. Some of this lack of interest might have arisen because of the time that had elapsed between the ED visit that led to their identification and them receiving the study invite (the median was 9 months). This could be addressed by shortening the time period between identification and invite, or, even more drastically, recruiting patients prospectively instead. The latter would have significant implications for the resources required by a definitive trial. Also, the pragmatics of recruiting PWE directly from the ED requires clarification. For example, patients may often be in a postictal state and, also, a stay in the ED is typically far shorter than a stay on a hospital ward.

We would note that it is possible that the serial assessment of participants and the need for them to complete multiple secondary outcome questionnaires at the assessments might have been seen as overly burdensome by persons considering the invitation to participate in the trial. It might also have negatively impacted on retention of the participants who were recruited. If a definitive trial committed itself to using routine ED data as the source of data for the primary outcome measure, then that trial could theoretically reduce or even totally drop the use of the secondary assessment measures. This might increase uptake and improve retention. In considering how dramatic the improvements might be it is perhaps worth noting that none of the participants who did take part in the trial and who completed the trial participation feedback questionnaire identified the questionnaire packs as being burdensome or as an area of the trial that required improvement.

Identifying eligible patients:

Identifying eligible patients for the pilot RCT from the EDs attendance systems required substantial time and effort on behalf of the local investigators at the EDs. This was due to the nature of the condition, because the EDs' administrative systems did not code visits in a sufficiently granular way, and because much of the data on patients needed to determine eligibility (i.e., presence of certain comorbidities) was recorded in an unstandardized way within non-searchable, free-text fields. Consequently, searches of the attendances systems were limited to simply identifying persons who had attended for a 'suspected seizure'. The triage cards of these identified persons then needed to be accessed and screened by local clinicians to find persons suitable for invitation. This activity could not have been delegated to research staff, including 'research nurses', since it is not ethically permissible for a person outside of the patient's care team to access information on their medical history for the purposes of research, without prior consent https://www.gov.uk/government/publications/the-nhs-constitution-for-england/the-nhs-constitution-for-england [accessed 27th August, 2019].

Since our pilot RCT took place, a new coding system for EDs - the Emergency Care Data Set – has been phased in. From the perspective of a definitive trial, it brings some advantages since it seeks to standardise and increase the granularity with which presentations and comorbidities are recorded. For example, a specific presentation code for seizure caused by a neurologic condition now exists (https://www.england.nhs.uk/wp-content/uploads/2015/08/em-care-data-set.pdf [accessed 27th August, 2019]) The system also asks for diagnosis to be recorded using detailed Systematized Nomenclature of Medicine (SNOMED) Clinical Terms. The fields 'discharge diagnosis' and 'comorbidity' within the Emergency Care Data Set are not though mandatory.[217-218] It therefore remains to be seen how well completed these fields are before it is possible to conclude that the presence of the new system means PWE for a definitive trial can be more readily identified and demands on local sites reduced to a reasonable level.

Securing routine outcome data on ED use:

For a definitive trial of SAFE to be well positioned to be funded and for it to be designed optimally, stakeholders would want to be confident that primary outcome data could be secured and a fairly precise estimate would be needed as to when the data would be available. Our pilot demonstrated that the provision of such data is not a given and that the timeline is hard to estimate. Bodies, such as the NIHR,

have endorsed the use of routine data sources within clinical research. It is possible that as routine data becomes requested more and more for trials that NHS Digital's application processes will be revised and become more suitable for the research environment. It is notable that our experience is not unique. The challenges in securing routine outcome data from NHS Digital were described in detail by Powell et al.[165] in 2017 and recommendations for improvements with the system made.

Effect of the SAFE intervention:

Efficacy was not the primary focus of our pilot trial. No power calculation was completed and with such a small sample imbalance in pre-randomization covariates between the treatment arms is possible. The estimated modest effect of SAFE on subsequent ED use – namely, reducing it from 2.1 visits over a 12-month period to 1.8 compared to a slight increase in the TAU alone group from 3 to 3.4 visits – was though used to inform the sample size calculations for a definitive trial. It important therefore to consider how realistic this estimate is since a larger effect would likely make a definitive trial cheaper (i.e., because fewer patient participants and thus recruitment sites, would be required).

When the pilot RCT was being designed the empirical evidence on the ability of self-management interventions to change behaviour in PWE was positive, but inconclusive. An updated systematic review by Luedke et al[219] has since been published. It considered evidence from 13 randomised trials and 2 non-randomised trials of self-management interventions for epilepsy published up until April 2018. The review concluded that interventions showed clinically important benefit on only a limited number of outcome measures. Interventions that primarily sought to increase knowledge changed self-management behaviours moderately, whilst interventions that included techniques such as cognitive behavioural therapy or problem-solving treatment improved quality of life only modestly. Overall, self-management interventions were also not found to decrease seizure rates.

One RCT from the United States identified by Luedke et al.'s review[219] is particularly instructive since it is the only one to have also considered change in ED use. It focused on what its authors, Sajatovic et al.,[220] labelled an 'at-risk' population – defined as adults with established epilepsy who had had at least one negative health event within the past 6 months, be it a seizure, an accident, self-harm attempt, or an ED visit. The RCT compared the effects of an educational intervention, called 'Self-management for people with epilepsy and a history of negative health events', to a wait list control. It comprised of 8 sessions and

addressed myths surrounding epilepsy and introduced participants to key self-management tasks. One hundred-twenty patients were recruited and followed for 6 months. The trial found no statistically significant differences between groups in terms of subsequent ED/ hospitalization use. For the intervention group it reduced from 1.22 visits by -.44. For the wait-list control group it reduced from 2.4 by -1.26 visits.

The findings of the updated review suggest the relatively small estimated effect of SAFE is within the region of what might be expected of a self-management intervention and thus the estimate from our pilot trial constitutes a reasonable basis for the sample size calculations for a definitive trial. That a self-management intervention only reduces ED visits by a small amount also makes sense from a clinical perspective since we now know that factors beyond low seizure confidence can influence whether an ED visit occurs. One is that studies with the ambulance service show peripheral issues, such as performance targets and difficulties accessing information on the patients' medical history to determine normality or otherwise of the seizure presentation, can influence whether a person is conveyed to ED or not following an emergency call.[74-75]

Progression, feasibility and optimal design of a definitive trial:

Thabane et al.[135] provide a framework for judging whether or not to proceed to a definitive trial following a pilot. They describe the options as: a) "Continue without modification" (feasible as it is); b) "Continue without modifications, but monitor closely" (feasible with close monitoring); c) "Continue, but modify the protocol" (feasible with modifications); and d) "Stop" (main study is not feasible). In satisfying only one of the pre-specified progression criteria, a definitive trial based on our pilot trial's design is not feasible. On the basis of the discussion above we also do not consider that any options are currently available to modify to the protocol in such a way for it to become feasible. We therefore recommend not proceeding to complete a definitive trial.

Alternative steps to the diffusion of the SAFE intervention

A definitive trial of SAFE is needed to determine its efficacy. This information would help commissioners understand with confidence whether SAFE should be scaled up and rolled out. As noted, our pilot indicates such a trial is not currently feasible, although it might be in the future. In the meantime, the needs of many PWE who visit ED with respect to seizure first aid will continue to be unmet, with all the

consequences this has. As it is not known when any other intervention will become available, an argument could be made for making SAFE available in some form to the epilepsy population now.

In support of this approach is that SAFE was rigorously produced, including the key information that health professional representatives said the target population needs to routinely receive (but for various reasons, often do not). It received positive support from service users, with most who received it, welcoming it. There were also no indications that SAFE had any serious adverse effects and it might reduce some ED use.

One way of making SAFE available now would be to convert its materials into a free online resource that health professionals – such as epilepsy nurses and neurologists – and charities could direct interested persons to. The conversion could be in the form of a professionally produced video of a SAFE course that could be run with agreeable service users. To engage those viewing the online resource, interactive questions could be integrated into recordings.

The conversion would be a relatively straightforward process and allow the investment already made via this project to be capitalised on. To enable the conversion, only modest funding would be required to produce the website and maintain and update it over time. For the pilot trial, a more basic website was developed for trial participants to allow them to download (rather than interact with) the course slides and videos of the recovery position. The costs of the former activity provide some guidance as to the sort of costs envisioned. In 2017-18 the website domain cost the project £20.94 for 5 years and the hourly rate for an IT technician to maintain the site was only £28.09.

It is likely that a full conversion of SAFE would be welcomed by many health care professionals as specialist services are currently being asked to innovate, identify and care for those currently underserved, such as PWE who visit ED. The workforce is though, small and can already struggle to achieve waiting-time targets and respond to requests for help.

Sharing SAFE in the way described would also present new opportunities to evaluate SAFE's effect with a potentially large sample over time, albeit in a less rigorous way than by a full RCT. For instance, by using a pre-post design, those viewing the materials could be asked to fill in a brief online questionnaire immediately before and after the intervention to provide a measure of the intervention's effect on seizure

first aid knowledge and confidence could. The same persons could also be asked for consent for access to be given to routine data from NHS Digital on their use of ED during the 12 months before and after completion of the course.

Strengths and limitations

Intervention development

The intervention was co-produced. The process enabled us to access the unique perspectives of health professionals and service users in a non-tokenistic way. Clear, tangible changes to the intervention were made in response to their views. The Acceptability, Practicability, Effectiveness/cost-effectiveness, Affordability, Safety/side-effects, Equity (APEASE) framework[114] provides criteria that need to be considered when considering the utility and potential of interventions. Our project has provided positive evidence for the SAFE intervention on a number of these criteria – namely, Acceptability, Practicability, Affordability and Safety. SAFE is well positioned to be implemented within the UK's health service should this ultimately prove appropriate.

We anticipate that the description provided of the co-production process we adopted could also provide a useful template for the development of interventions by other groups. A concern of some researchers is the process of engaging service users and other stakeholders will be unwieldy and stakeholders will be challenging to engage[221] To this point, we would note that this process is not one that should be entered into lightly as it required careful planning, expertise, resources, and ethical approval. It took 9 months to complete, with a team including four experienced academics, two at the professorial level. We would argue though that the length of the feedback sessions and the quality of consideration given by the stakeholders goes someway to demonstrating how willing stakeholders can be to contribute to such processes. In terms of recruitment, we note that those with epilepsy can often have low self-esteem and confidence[184,215] This meant we needed to be mindful from the start of the need, when bringing people into this process, to clearly emphasize to participants what we were doing, why we wanted them involved and that it was their views, however critical, that we needed to hear.

Pilot trial

The pilot trial was completed in a rigorous manner according to best practice guidelines and reported according to the Consolidated Standards of Reporting Trials (CONSORT) extension for randomised pilot

and feasibility trial[222] (*see* Supplementary material 3). Randomisation was done remotely by computer and stratification factors and allocations concealed from those collecting baseline and follow-up data and analysing it. Patients were also recruited from NHS sites. Some RCTs, including Sajatovic et al.'s trial,[220] have focused recruitment on user group participants. Persons within such groups might differ in important ways from those who are not. We also used an opt-out method to recruitment whereby we contacted patients about the study unless they told us otherwise. The opt-in method, where the onus is on the patient to contact the research team to express their interest, was not considered ideal for a patient population that frequently reports memory problems and whose lives can be disrupted by episodic relapses of their condition. Another strength is that recruitment sites were in areas where social deprivation was high and epilepsy control poor and so similar to those where a definitive trial would likely need to focus recruitment.

We completed one of the few microcostings of a self-management intervention for epilepsy. We also described the content of the SAFE intervention in detail and independently monitored its fidelity and reported the results. A recent review of trials of psychosocial interventions for epilepsy found that only ~5% of trials did this for "adherence" and ~2% for "competence".[223] Indeed, we have also provided a rare worked example of how to conduct a fidelity assessment and the resources required. Medical Research Council publications[224] note the importance of evaluating fidelity. Minimal guidance is, however, provided regarding how to do it. Intervention developers say this is one reason why they fail to assess fidelity.[225]

The pilot trial is not without potential weaknesses. Firstly, despite the trial team identifying PWE for inclusion on the basis of them having at least one attendance at ED for epilepsy recorded and the patient, when questioned, reporting at least 2 visits in the 12 month prior to recruitment, ~40% of these patients might not have met the inclusion criteria (according to the routine health data subsequently obtained). The inclusion of these people could impact on the external validity of the trial and attenuate the estimated effect of SAFE since they had less opportunity for a reduction in ED use.

Also, whilst 18 (69%) of the 26 patient participants randomised to SAFE took part with an informal carer, 5 (28%) of these did not ultimately attend an intervention session. This is comparable to experience in the 'SMILE (UK)' trial. [211]Their non-attendance may have limited the effect of SAFE since carers can be key to decision-making when a seizure occurs.

Because a diagnostic code is often not recorded for ED visits we requested NHS Digital to simply tell us how many ED visits, regardless of diagnosis, each patient had made during specific periods of time. It is possible that not all of the visits therefore reported for the participants were associated with epilepsy. UK data on how many ED visits a person with epilepsy has made for reasons other than epilepsy in a set period is not known. PWE are certainly more likely to have a comorbidity than the general population and so it is possible they attend for other reasons.

When calculating the size of sample likely required for a definitive trial of SAFE, the pilot trial's estimate of SAFE's effect on ED use was used. We used the estimate since there is no consensus about what constitutes a minimally important clinical reduction in ED visits. We acknowledge that the estimate from the pilot might be lacking in precision[136] and that basing the sample size calculations on a smaller or larger effect size would substantially change the required sample size for a definitive trial.

Implications for NHS service commissioning, policy and practice

1. The trial was not designed to determine SAFE's efficacy. There remains limited evidence to justify for the commissioning of such a service.

2. Some PWE are unknown to ambulatory care services and cannot be readily identified. Increasing the granularity with which attendances at EDs are coded could enable them to be readily identified, supported and involved in research.

3. Using routine data on ED use in trials could make them less vulnerable to losses to follow-up and mean they are not exposed to apparent recall bias. Stakeholders need to be given more assurances from those holding the data that it is likely to be provided and done so in a timely manner.

4. Given SAFE is liked by service users, that it might reduce ED use in a small way and that it does not appear to have serious adverse effects, there is a case for converting it into an free online resource that people could be directed to in the short term to go some way to address the otherwise unmet seizure first aid training needs of PWE who visit ED and their significant others.

Recommendations for research

1. A definitive SAFE trial, with its current design, should not be conducted as it is not feasible, for the reasons given above. We cannot envision any immediate changes to trial design that could make it feasible.

2. Research is required to understand how people from the target population can be better recruited. It is possible that the high feelings of stigma apparent in the target population might be an important barrier to recruitment. If this is the case, it is important that recruitment methods are identified or developed to ensure that participants' feelings of stigma do not compound the difficulties they may already be facing by preventing high-quality research into their condition from being conducted.

3. Converting SAFE into a free online resource that people could be directed to could provide an opportunity for an alternative method of evaluating its effect on some of the primary and secondary outcome measures used in the pilot RCT. Via a pre-post design, persons accessing the online resource could complete brief measures to assess change in seizure first aid confidence and skills. They could also be asked for consent to access routine data on their use of ED data in the 12 months before and after their viewing of the resource.

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Department of Health Disclaimer

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Ethical Standards

The report does not contain clinical studies or patient data. The National Research Ethics Committee North West—Liverpool East approved the study (15/NW/0225) and informed consent was obtained from all participants.

Data sharing and accessibility position

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Contributions of authors

Adam Noble [A.N] (Senior Lecturer in Health Services Research) was Chief Investigator and led in the conception and design of the study, the supervision and co-ordination of the study, the interpretation of the data and, with Dee Snape and Sarah Nevitt, the writing of the final report.

Sarah Nevitt [S.N) (Research Associate, Biostatistics) contributed to conducting the study, developed and conducted the statistical analysis of the quantitative data, and helped write the final report.

Emily Holmes [E.H] (Research Fellow, Pharmacoeconomics) contributed to the design of the study, developed and conducted the statistical analysis of the health economic data and wrote-up the health economics results for the final report.

Leone Ridsdale [L.R] (Professor of Neurology and General Practice) supported AN in the conception and design of the study, contributed to its conduct and reviewed the final report.

Myfawny Morgan [M.M] (Professor of Medical Sociology) contributed to the design of study, its conduct, oversaw its qualitative aspects and reviewed the final report.

Catrin Tudur-Smith [C.T.S] (Professor in Medical Statistics) contributed to the design of study, supervised the statistical analysis of the quantitative data and reviewed the report.

Dyfrig Hughes [D.H] (Professor in Pharmacoeconomics) contributed to the design of study, supervised the collection of health economic data and its analysis and reviewed the final report.

Steve Goodacre [S.G] (Professor of Emergency Medicine) contributed to the design of the research, its conduct and reviewed the final report.

Tony Marson [T.M] (Professor of Neurology) contributed to the design of the research, its conduct and reviewed the final report.

Dee Snape [D.S] (Research Fellow, Health Services Research) was responsible for setting up the study, for participant recruitment and assessment, for analysis and interpretation of the qualitative findings and helped write the final report.

Publications

Noble AJ, Marson AG, Tudur-Smith C, Morgan M, Hughes DA, Goodacre S, et al. 'Seizure First Aid Training' for people with epilepsy who attend emergency departments, and their family and friends: study protocol for intervention development and a pilot randomised controlled trial. *BMJ Open,* 2015; http://dx.doi:10.1136/bmjopen-2015-009040 [accessed 27th August, 2018]

Snape DA, Morgan M, Ridsdale L, Goodacre S, Marson AG, Noble AJ, Developing and assessing the acceptability of an epilepsy first aid training intervention for patients who visit UK emergency departments: A multi-method study of patients and professionals, *Epilepsy & Behavior*, 2017; http://eprints.whiterose.ac.uk/112848/15/1-s2.0-S1525505016305649-main.pdf [accessed 27th August, 2018]

Noble A, Snape D, Morgan M, Goodacre S, Marson A; Ridsdale L. PO051 Seizure first aid training for people with epilepsy attending emergency departments, and SOs *Journal of Neurology, Neurosurgery, & Psychiatry,* 2017; 88: Supplement 1 pA25-A25, 1p., Database: Supplemental Index

Snape D, Nevitt S, Tudur-Smith C, Goodacre S, Hughes DA, Morgan M, et al. P300 Seizure First Aid Training for People with Epilepsy who Attend Emergency Departments and Their Family and Friends: Results from a Pilot Randomised Controlled Trial. *Epilepsia,* 2018; **59**:S3, pS140.

Noble A, Snape D, Ridsdale L, Morgan M, Nevitt SJ, Goodacre S, Marson A. Assessing treatment fidelity within an epilepsy randomized controlled trial – Seizure first aid training for people with epilepsy who visit emergency departments. B*ehav Neurol,* 2019; Feb 3;2019:5048794. eCollection 2019. https://doi.org/10.1155/2019/5048794 [accessed 27th August, 2019]

Noble, AJ, Snape D, Nevitt S, Holmes EAF, Morgan M, Tudur Smith C, Hughes DA, Buchanan M, McVicar J, MacCallum E, Goodacre S, Ridsdale L, Marson AG. Seizure First Aid Training For people with Epilepsy (SAFE) frequently attending emergency departments and their significant others: results of a UK multi-centre randomised controlled pilot trial. *BMJ Open* 2020;10:e035516. doi:10.1136/ bmjopen-2019-035516

Presentations

Snape D, Morgan M, Ridsdale L, Goodacre S, Marson AG, Noble AJ. *Developing and assessing acceptability of seizure first-aid training for emergency department users with epilepsy.* Assoc. British Neurologists Conference, The AAC Liverpool, United Kingdom. 3-5 May, 2017.

Snape D, Nevitt S, Tudur-Smith C, Goodacre S, Hughes DA, Morgan M, et al. *Seizure First Aid Training for People with Epilepsy who Attend Emergency Departments and Their Family and Friends: Results from a Pilot Randomised Controlled Trial.* 13th European Conference on Epileptology, Vienna, Austria. 26th-30th August, 2018.

References

1 Longmore M, Wilkinson I, Baldwin A, Wallin E. *Oxford handbook of clinical Medicine*. 9th edn. Oxford: Oxford University Press; 2014.

2 Smithson WH, Walker MC, editors. *ABC of epilepsy*. 1st edn. Chichester: Wiley-Blackwell; 2012.

3 Ridsdale L, Charlton J, Ashworth M, Richardson MP, Gulliford MC. Epilepsy mortality and risk factors for death in epilepsy: a population-based study. *Br J Gen Pract* 2011; **61**:e271–8.

4 MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000; **123**:665–676.

5 Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia* 2014; **55**:475-482.

6 Forsgren L, Beghi E, Õun A, Sillanpää M. The epidemiology of epilepsy in Europe – a systematic review. *Eur J Neurol* 2005; **12**:245-253.

7 Aidan NGS, Bell GS, Johnson AL, Goodridge DM, Shorvon SD, Sander JW. The long-term risk of premature mortality in people with epilepsy. *Brain* 2011; **134**:388–395.

8 Ridsdale L. Avoiding premature death in epilepsy. BMJ 2015;**350**:h718 doi: 10.1136/bmj.h718. (Accessed 29th August, 2019).

9 Moran NF, Poole K, Bell G, Solomon J, Kendall S, McCarthy M, et al. Epilepsy in the United Kingdom: seizure frequency and severity, anti-epileptic drug utilization and impact on life in 1652 people with epilepsy. *Seizure* 2004; **13**:425‑433.

10 Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005; **46**:470–472.

11 Räty LKA, Wilde-Larsson BM. Patients' perceptions of living with epilepsy: a phenomenographic study. *Journal of Clinical Nursing* 2011; **20**:1993-2002.

12 Jacoby A, Snape D, Baker GA. Epilepsy and social identity: the stigma of a chronic neurological disorder. *The Lancet Neurology*. 2005; **4**:171-178.

13 McLaughlin DP, Pachana NA, McFarland K. Stigma, seizure frequency and quality of life: The impact of epilepsy in late adulthood. *Seizure* 2008; **17**:281-287.

14 Taylor J, Baker GA, Jacoby A. Levels of epilepsy stigma in an incident population and associated factors. *Epil Behav* 2011; **21:**255-260.

15 Pugliatti M, Beghi E, Forsgren L, Ekman M, Sobocki P. Estimating the cost of epilepsy in Europe: a review with economic modeling. *Epilepsia.* 2007; **48**:2224–2233. doi.org/10.1111/j.1528-1167.2007.01251.x (Accessed 12th June, 2018).

16 Kitson A, Shorvon S. Clinical Standards Advisory Group. *Services for patients with epilepsy: a report of a CSAG Committee*. London: Department of Health; 2000. https://www.nice.org.uk/guidance/qs26/documents/epilepsy-in-adults-scope2 (Accessed 29th June 2019).

17 Jacoby A, Buck D, Baker G, McNamee P, Graham-Jones S, Chadwick D. Uptake and costs of care for epilepsy: findings from a U.K. regional study. *Epilepsia* 1998; **39**:776-786.

18 Hart YM, Shorvon SD. The nature of epilepsy in the general population. II. Medical care. *Epilepsy Res* 1995; **21**:51-58.

19 Ryan J, Nash S, Lyndon J. Epilepsy in the accident and emergency department--developing a code of safe practice for adult patients. South East and South West Thames Accident and Emergency Specialty Sub- committees. *J Accid Emerg Med* 1998; **15**:237-243.

20 Pearson M, Marson T, Dixon P, Scott K. *National Audit of Seizure Management in Hospitals: St Elsewhere's Clinical Report*. 2014. http://www.nashstudy.org.uk/Newsletters/St%20Elsewhere%27s%20Clinical%20Report%20NASH%202.pdf (Accessed 24th April, 2018).

21 Pearson M, Marson T, Dixon P, Billington K. *National Audit of Seizure Management in Hospitals: St Elsewhere's Clinical Report*. 2012. http://www.nashstudy.org.uk/Newsletters/St.%20Elsewhere's%20Hospital%20NASH%20Organisational%20Report.pdf (Accessed 24th April, 2018).

22 House of Commons Committee of Public Accounts. *Services to people with neurological conditions* (HC 502). 2016. https://publications.parliament.uk/pa/cm201516/cmselect/cmpubacc/502/502.pdf (Accessed 24th April, 2018).

23 Reuber M, Hattingh L, Goulding PJ. Epileptological emergencies in accident and emergency: a survey at St James's University Hospital, Leeds. *Seizure* 2000; **9**:216-220.

24 Bruce M, Griffiths C, Brock A, Majeed A. Trends in mortality and hospital admissions associated with epilepsy in England and Wales during the 1990s. *Health Stat Q* 2004; **21**:23-29.

25 Bardsley M, Blunt I, Davies S, Dixon J. Is secondary preventive care improving? Observational study of 10- year trends in emergency admissions for conditions amenable to ambulatory care. *BMJ Open* 2013; **3**:e002007. http://dx.doi:10.1136/bmjopen-2012-002007 (Accessed 24th June, 2019).

26 Health and Social Care Information Centre (HSCIC). Clinical Indicators team. *CCG Outcomes Indicator Set: Emergency Admissions*. 2013. http://www.hscic.gov.uk/catalogue/PUB10584/ccg-ind-toi-mar-13-v4.pdf. (Accessed 4th August, 2017).

27 Noble AJ, Goldstein LH, Seed P, Glucksman E, Ridsdale L. Characteristics of people with epilepsy who attend emergency departments: prospective study of metropolitan hospital attendees. *Epilepsia* 2012; **53**:1820- 1828.

28 Dixon PA, Kirkham JJ, Marson AG, Pearson MG. National Audit of Seizure management in Hospitals (NASH): results of the national audit of adult epilepsy in the UK. *BMJ Open* 2015; **5**:e007325. doi:10.1136/bmjopen- 2014-007325 (Accessed 23rd June, 2019).

29 Whiston S, Coyle B, Chappel D. *Health needs assessment for long term neurological conditions in North East England.* Stockton on Tees: North East Public Health Observatory, 2009.

30 Dickson JM, Jacques R, Reuber M, Hick J, Campbell MJ, Morley R, et al. Emergency hospital care for adults with suspected seizures in the NHS in England 2007-2013: a cross-sectional study. *BMJ Open* 2018; **8**:e023352. doi.org/10.1136/bmjopen-2018-023352 (Accessed 15th August, 2019).

31 Moore, L, Deehan, A, Seed, P, Jones, R. Characteristics of frequent attenders in an emergency department: analysis of 1-year attendance data. *Emerg Med J* 2009; **26**:263–267.

32 Dickson JM, Taylor LH, Shewan J, Baldwin T, Grünewald RA, Reuber M. Cross-sectional study of the prehospital management of adult patients with a suspected seizure (EPIC1).*BMJ Open* 2016; **6**:e010573. doi:10.1136/bmjopen-2015- (Accessed 23rd June, 2019).

33 Allen L, Jones CT. Emergency department use of computed tomography in children with epilepsy and breakthrough seizure activity. *Child Neurol* 2007; **22**:1099-1101.

34 Limm EI, Fang X, Dendle C, Stuart RL, Egerton Warburton D. Half of all peripheral intravenous lines in an Australian tertiary emergency department are unused: pain with no gain? *Ann Emerg Med.* 2013; 62:521–5.

35 Peterson CL, Walker C, Coleman H. 'I hate wasting the hospital's time': Experiences of emergency department admissions of Australian people with epilepsy. *Epil Behav*. 2019; **90**:228-232. doi:10.1016/j.yebeh.2018.11.018 (Accessed 20th July, 2019).

36 Craig J, Patterson V, Rocke L, Jamison J. Accident and emergency neurology: time for a reappraisal? *Health Trends* 1997; **29**:89-91.

37 O'Cathain A, Knowles E, Turner J, Maheswaran R, Goodacre S, Hirst E, et al. *Explaining variation in emergency admissions: a mixed-methods study of emergency and urgent care systems*. Southampton (UK): NIHR Journals Library, 2014 Dec. (Health Services and Delivery Research, No. 2.48). https://www.ncbi.nlm.nih.gov/books/NBK263724/ (Accessed 11th April, 2018).

38 Bautista RE, Glen ET, Wludyka PS, Shetty NK. Factors associated with utilization of healthcare resources among epilepsy patients. *Epilepsy Res* 2008; **79**:120–129.

39 QIPP/Right Care, *The NHS atlas of variation in healthcare*. 2010. www.fingertips.phe.org.uk/documents/Atlas_2010%20Compendium.pdf (Accessed 25th April, 2018).

40 NHS Right Care. *The NHS Atlas of Variation in Healthcare: Reducing unwarranted variation to increase value and improve quality*. 2011.

https://fingertips.phe.org.uk › documents › Atlas_2011 Compendium (Accessed 25th April, 2018).

41 Sajatovic M, Welter E, Tatsuoka C, Perzynski AT, Einstadter D. Electronic medical record analysis of emergency room visits and hospitalizations in individuals with epilepsy and mental illness comorbidity. *Epil Behav* 2015; **50**:55-60. https://www.ncbi.nlm.nih.gov/pubmed/26119621 (Accessed 29th August, 2019).

42 Public Health England. *The NHS Atlas of Variation in Healthcare: Reducing unwarranted variation to increase value and improve quality*. 2016 www.fingertips.phe.org.uk/documents/Atlas_2015%20Compendium.pdf (Accessed 25th April, 2018).

43 Allard J, Shanka R, Henley W, Brown A, McLean B, Jadav M, et al. Frequency and factors associated with emergency department attendance for people with epilepsy in a rural UK population. *Epil Behav* 2017; **68**:192–195.

44 Ashworth M, Seed P, Armstrong D, Durbaba S, Jones R. The relationship between social deprivation and the quality of primary care: A national survey using indicators from the UK Quality and Outcomes Framework. *Br J Gen Pract* 2007; **57**:441-448.

45 Shohet C, Yelloly J, Bingham P, Lyratzopoulos G.The association between the quality of epilepsy management in primary care, general practice population deprivation status and epilepsy-related emergency hospitalisations. *Seizure* 2007; **16**:351–355.

46 Morgan CL, Ahmed Z, Kerr MP. Social deprivation and prevalence of epilepsy and associated health usage. *Journal of Neurology, Neurosurgery and Psychiatry*. 2000; **69**:13-17.

47 National Institute for Health and Care Excellence. *The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE clinical guideline 137:NICE;* 2012. https://www.nice.org.uk/guidance/cg137 (Accessed 21st August 2019).

48 Grainger R, Pearson M, Dixon P, Devonport E, Timoney M, Bodger K et al. Referral patterns after a seizure admission in an English region: an opportunity for effective intervention? An observational study of routine hospital data. *BMJ Open* 2016; **6**: e010100. doi:10.1136/bmjopen-2015-010100 (Accessed 22nd August, 2019).

49 House of Commons Committee of Public Accounts. *Financial sustainability of the NHS: 43 2016–17* (HC 887). 2017. http://publications.parliament.uk/pa/cm201617/cmselect/cmpubacc/887/887.pdf. (Accessed 24th April, 2018).

50 King's Fund. 2017. Nine things we learnt about provider finances in 2016/17 www.kingsfund.org.uk/publications/nine-things-NHS-provider-finances-2016-17 (Accessed 24th April, 2018).

51 Department of Health. The NHS Plan: a plan for investment, a plan for *reform*. London, Department of Health; 2000.

52 NHS England. *Five year forward view*. 2014. www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf (Accessed 8th August, 2017).

53 NHS England. *Next step on the NHS Five Year Foward View*. 2017. https://www.england.nhs.uk/wp- content/uploads/2017/03/NEXT-STEPS-ON-THE-NHS-FIVE-YEAR-FORWARD-VIEW.pdf (Accessed 8th August, 2017).

54 NHS England. *NHS Outcomes Framework indicators - Feb 2017 release*. 2017. https://digital.nhs.uk/data-and-information/publications/clinical-indicators/nhs-outcomes-framework/archive/nhs-outcomes-framework-indicators---february-2017-release (Accessed 8th August, 2017).

55 National Institute for Health Research. *NIHR Evaluation, Trials and Studies Coordination Centre: glossary.* 2012. https://www.nihr.ac.uk/glossary?letter=F&postcategory=-1 (Accessed 21st August, 2017).

56 Ridsdale L, Virdi C, Noble A, Morgan M. Explanations given by people with epilepsy for using emergency medical services: a qualitative study. *Epil Behav* 2012; **25**:529–533.

57 Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. *Patient Education and Counseling* 2002; **48**:177-187.

58 Dilorio C, Faherty B, Manteuffel B. The development and testing of an instrument to measure self-efficacy in individuals with epilepsy. *J Neurosci Nurs* 1992; **24**:9-13.

59 Noble AJ, Morgan M, Virdi C, Ridsdale L. A nurse-led self-management intervention for people who attend emergency departments with epilepsy: the patients' view. *J Neurol* 2013; **260**:1022–1030.

60 Jarvie S. *Self perception and psychosocial functioning in people with intractable epilepsy (PhD thesis, Unpublished data)*, in Psychological Medicine. 1993, University of Glasgow.

61 Wagner AK, Keller SD, Kosinski M, Baker GA, Jacoby AM. Hsu A et al. Advances in methods for assessing the impact of epilepsy and antiepileptic drug therapy on patients' health-related quality of life. *Qual Life Res* 1995; **4**:115-134.

62 Jacoby, A. Felt versus enacted stigma: a concept revisited: evidence from a study of people with epilepsy in remission. *Soc Sci Med* 1994; **38**:269-274.

63 Morgan GA, Harmon RJ, Maslin-Cole CA. Mastery Motivation: Definition and Measurement. *Early Education and Development*. 1990; **1**:318-339.

64 Au A, Chan F, Li K, Leung P, Li P, Chan J. Cognitive-behavioral group treatment program for adults with epilepsy in Hong Kong. *Epil Behav* 2003; **4**:441-446.

65 Corbin JM, Strauss A. *Unending work and care: Managing chronic illness at home*. San Francisco, CA, US; Jossey-Bass: 1988. xviii, p.358.

66 Deveugele M, Derese A, van den Brink-Muinen A, Bensing J, De Maeseneer J. Consultation length in general practice: cross sectional study in six European countries. *BMJ* 2002; **31**:472.

67 Llewelyn JG. *Neurology*. 2 Specialties Neurology 2013; http://www.rcplondon.ac.uk/sites/default/files/neurology_0.pdf (Accessed 29th August, 2018).

68 Gilliam F, Penovich PE, Eagan CA, Sternd JM, Labinere DM, Onofreyc M, et al. Conversations between community-based neurologists and patients with epilepsy: Results of an observational linguistic study. *Epil Behav* 2009; **16**:315-320.

69 Ridsdale L, Morgan M, O'Connor C. Promoting self-care in epilepsy: the views of patients on the advice they had received from specialists, family doctors and an epilepsy nurse. *Patient Education and Counseling* 1999; **37**:43-47.

70 Long L, Reeves AL, Moore JL, Roach J, Pickering CT. An assessment of epilepsy patients' knowledge of their disorder. *Epilepsia* 2000; **41**:727-31.

71 Ridsdale L, Kwan I, Cryer C. The effect of a special nurse on patients' knowledge of epilepsy and their emotional state. Epilepsy Evaluation Care Group. *British Journal of General Practice* 1999; **49**:285-289.

72 Ridsdale L, Kwan I, Cryer C. Newly diagnosed epilepsy: can nurse specialists help? A randomized controlled trial. Epilepsy Care Evaluation Group. *Epilepsia* 2000; **41**:1014-1019.

73 Walker ER, Bamps Y, Burdett A, Rothkopf J, Diiorio C. Social support for self- management behaviors among people with epilepsy: a content analysis of the WebEase program. *Epil Behav* 2012; **23**:285-90.

74 Noble AJ, Snape D, Goodacre S, Jackson M, Sherratt F, Pearson M, Marson AG. Qualitative study of paramedics' experiences of managing seizures: a national perspective from England. *BMJ Open* 2016; **6**:e014022. doi.org/10.1136/bmjopen-2016-014022 (Accessed 30th August, 2019).

75 Burrell L, Noble A, Ridsdale L. Decision-making by ambulance clinicians in London when managing patients with epilepsy: a qualitative study. *Emergency Medicine Journal* 2012; **30**:236-240.

76 Ridsdale L. The social causes of inequality in epilepsy and developing a rehabilitation strategy: A U.K.-based analysis. *Epilepsia*. 2009; **50**:2175-2179.

77 NHS England. *Patient Activation: People's ability to manage their own health and wellbeing.* 2018. https://www.england.nhs.uk/personalisedcare/self-care/patient-activation/ (Accessed 4th May, 2018)

78 Foster G, Taylor SJ, Eldridge SE, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database Syst Rev* 2007. **4**:CD005108. doi.org/10.1002/14651858.CD005108.pub2 (Accessed 29th August, 2019)

79 Davies MJ, Heller S, Skinner TC, Campbell MJ, Carey ME, Cradock S, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *BMJ* 2008; **336**(7642):491-495. doi:10.1136/bmj.39474.922025 (Accessed 23rd June, 2019).

80 Davies MJ, Heller S, Skinner TC, Campbell MJ, Carey ME, Cradock S, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *BMJ* 2008; **336**:491-495.

81 Deakin TA, Cade JE, Williams R, Greenwood DC. StruCTRCred patient education: the diabetes X-PERT Programme makes a difference*. Diabetic Medicine* 2006; **23**: 944-954.

82 Barlow JH, Turner AP, Wright CC. A randomized controlled study of the Arthritis Self-Management Programme in the UK. *Health Education Research* 2000; **15**:665-680.

83 Buszewicz M, Rait G, Griffin M, Nazareth I, Patel A, Atkinson A, et al. Self-management of arthritis in primary care: randomised controlled trial. *BMJ* 2006; **333**:879.

84 Willis E. The making of expert patients: the role of online health communities in arthritis self-management. *J Health Psychol* 2014; **19**:1613–25.

85 Tieffenberg JA, Wood EI, Alonso A, Tossutti MS, Vicente MF. A randomized field trial of ACINDES: a child- centered training model for children with chronic illnesses (Asthma and Epilepsy). *Journal of Urban Health* 2000; **77**:280–297.

86 Tapp S, Lasserson TJ, Rowe B, Education interventions for adults who attend the emergency room for acute asthma. *Cochrane Database Syst Rev.* 2007, **3**: CD003000. 10.1002/14651858.CD003000.pub2 (Accessed 29th August, 2019).

87 Boyd M, Lasserson TJ, McKean MC, Gibson PG, Ducharme FM, Haby M. Interventions for educating children who are at risk of asthma-related emergency department attendance*. Cochrane Database Syst Rev* 2009;**15**:CD001290. doi: 10.1002/14651858.CD001290.pub2 (Accessed 27th August, 2019).

88 Institute of Medicine. Priority areas for national action: transforming health care quality. Washington DC: National Academies Press; 2003.

89 Brady TJ, Murphy L, O'Colmain B, Beauchesne D, Daniels B, Greenberg M, et al. A meta-analysis of health status, health behaviors, and health care utilization outcomes of the chronic disease self-management program. *Prev Chronic Dis* 2013; **10**:E07. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547675/ (Accessed 29th June 2019).

90 CDC Asthma Control Program. 2013 austinpureair.com/uploadimage/139828838266969.pdf. (Accessed 29th June 2019).

91 National Association of County and City Health Officials. Diabetes Self-Management Education and Training. Fact Sheet. 2013 http://archived.naccho.org/topics/HPDP/diabetes/resources/upload/factsheet_diabetes_aug2013_v2.pdf (Accessed 29th June, 2019).

92 Brady TJ, Anderson LA, Kobau R. Chronic disease self-management support: public health perspectives. *Front Public Health* 2015; **2**:1–5.

93 National Diabetes Education Program 2016. https://www.niddk.nih.gov/health-information/health-statistics/diabetes-statistics/ndep-national-diabetes- survey (Accessed 29th June, 2019).

94 CDC Arthritis Program. Self-management education. 2019 http://www.cdc.gov/arthritis/interventions/self_manage.htm. (Accessed 29th June, 2019).

95 DAFNE Study Group, Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* 2002; **325**:746.

96 Harris SM, Shah P, Mulnier H, Healey A, Thomas SM, Amiel SA, et al. Factors influencing attendance at structured education for Type 1 diabetes in south London. *Diabet Med* 2017; **34**:828–33.

97 Bradley PM, Lindsay B, Fleeman N. Care delivery and self-management strategies for adults with epilepsy. *Cochrane Database Syst Rev* 2016; **2**:CD006244. doi:10.1002/14651858.CD006244.pub3. (Accessed 29th August, 2019).

98 Helgeson DC, Mittan R, Tan SY, Chayasirisobhon S. Sepulveda epilepsy education: the efficacy of a psychoeducational treatment program in treating medical and psychosocial aspects of epilepsy. *Epilepsia* 1990; **31**:75‐82.

99 May TW, Pfafflin M. The efficacy of an educational treatment program for patients with epilepsy (MOSES): Results of a controlled, randomized study. *Epilepsia* 2002; **43**:539-549.

100 DiIorio C, Bamps Y, Walker ER, Escoffery C. Results of a research study evaluating WebEase, an online epilepsy self-management program. *Epil Behav* 2011; **22:**469-474.

101 Aliasgharpour M, Dehgahn Nayeri N, Yadegary MA, Haghani H. Effects of an educational program on self- management in patients with epilepsy. *Seizure* 2013; **22**:48-52.

102 Lindsay B, Bradley PM. Care delivery and self-management strategies for children with epilepsy. *Cochrane Database Syst Rev* 2010; **12**:CD006245. doi.org/10.1002/14651858.CD006245.pub2 (Accessed 29th August, 2019).

103 Lewis MA, Salas I, de al Sota A, Chiofalo N, Leake, B. Randomized trial of a program to enhance the competencies of children with epilepsy. *Epilepsia* 1990; **31**:101-109.

104 Lewis MA, Leake B, Hatton CL, Salas I, Chiofalo N.Impact of the Children's Epilepsy Program on parents. *Epilepsia.* 1991; **32**:365-374.

105 Gibson PG, Powell H, Wilson A, Hensley MJ, Abramson MJ, Bauman A, et al. Limited (information only) patient education programs for adults with asthma. *Cochrane Database Syst Rev* 2002. **1**:CD001005. doi:10.1002/14651858.CD001005 (Accessed 29th August, 2019).

106 Michaelis R, Tang V, Wagner JL, Modi William LaFrance C Jr., Goldstein LH, Lundgren T, Reuber M. Psychological treatments for people with epilepsy**.** *Cochrane Database Syst Rev 2017;* **10**:CD012081. doi:10.1002/14651858.CD012081.pub2 (Accessed 29th August, 2019).

107 Ramaratnam S, Baker GA, Goldstein LH. Psychological treatments for epilepsy. *Cochrane Database Syst Rev* 2008. **3**:CD002029. doi.org/10.1002/14651858.**CD002029**.pub3 (Accessed 29th August, 2019).

108 Bradley PM, Lindsay B. Care delivery and self-management strategies for adults with epilepsy. *Cochrane Database Syst Rev* 2008; **1**:CD006244. doi: 10.1002/14651858.CD006244.pub2 (Accessed 29th August, 2019).

109 Savovic J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JPT, et al. Association between Risk-of-Bias Assessments and Results of Randomized Trials in Cochrane Reviews: The ROBES Meta-Epidemiologic Study. *Am J Epidemiol* 2018; **187**:1113-1122.

110 Department of Health. *The expert patient: a new approach to chronic disease management for the 21st century.* London, Department of Health; 2001.

111 National Clinical Guideline Centre. *The Epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care.* London: National Clinical Guideline Centre; 2011.

112 Service NH. *Living with epilepsy.* 2014. http://www.nhs.uk/conditions/epilepsy/pages/living-with.aspx. (Accessed 14th September, 2017).

113 NHS England. *High quality care for all, now and for future generations: Transforming urgent and emergency care services in England - Urgent and Emergency Care Review End of Phase 1 Report* 2013. https://www.nhs.uk/NHSEngland/keogh-review/Documents/UECR.Ph1Report.FV.pdf (Accessed 23rd August, 2019).

114 Michie S, West R, Campbell R. Brown J, Gainforth H. *ABC of Behaviour Change Theories*: *an essential resource for researchers, policy makers and practitioners.* UK: Silverback Publishing; 2014.

115 Morrish PK. Inadequate neurology services undermine patient care in the UK. B*MJ.*2015;**350** https://doi.org/10.1136/bmj.h3284 (Accessed 29th June, 2019).

116 Royal College of Physicians. *Local adult neurology services for the next decade. Report of a working party.* London: RCP, 2011. https://www.mstrust.org.uk/sites/default/files/files/Local%20adult%20neurology%20services%20for%20the%20next%20decade.pdf (Accessed 29th June, 2019).

117 Epilepsy Action. *Best care: The value of epilepsy specialist nurses.* Leeds. British Epilepsy Association: 2010.

118 Epilepsy Action. *A Critical Time for epilepsy in England. A study of epilepsy service provision in England*. Leeds. British Epilepsy Association: 2013.

119 Medical Research Council. *A framework for the development and evaluation of RCTs for complex interventions to improve health*. London: Medical Research Council; 2000:18.

120 Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for the design and evaluation of complex interventions to improve health. *BMJ* 2000; **321**:694-696.

121 Kobau R, Price P. Knowledge of epilepsy and familiarity with this disorder in the U.S. population: Results from the 2002 HealthStyles Survey. *Epilepsia* 2003; **44**:1449-1454.

122 Faught E, Duh MS, Weiner JR, Guerin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. *Neurology* 2008; **71**:1572- 1578.

123 Tan JH, Wilder-Smith E, Lim EC, Ong BK. Frequency of provocative factors in epileptic patients admitted for seizures: A prospective study in Singapore. *Seizure* 2005; **14**: 464-469.

124 Mitchell WG, Conry JA, Crumrine PK, Conry JA, Crumrine PK, Kriel RL, etal. An open-label study of repeated use of diazepam rectal gel (Diastat) for episodes of acute breakthrough seizures and clusters: safety, efficacy, and tolerance. North American Diastat Group. *Epilepsia* 1999; **40**:1610-1617.

125 O'Dell C, Shinnar S, Ballaban-Gil KR, Hornick M, Sigalova M, Kang H,et al., Rectal diazepam gel in the home management of seizures in children. *Pediatric Neurology* 2005; **33**: 166-172

126 Jain P, Patterson V, Morrow J. What people with epilepsy want from a hospital clinic. *Seizure* 1993; **12**:75– 78.

127 Davis KL, Candrilli SD, Edin HM. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. *Epilepsia* 2008; **49**:446–454.

128 Moran N, Poole K, Bell G, Solomon J, Kendall S, McCarthy M, et al. NHS services for epilepsy from the patient's perspective: a survey of primary, secondary and tertiary care access throughout the UK. *Seizure* 2000; **9**:559-665.

129 Fraser RT, Johnson EJ, Lashley S, Barber J, Chaytor N, Miller JW, et al. PACES in epilepsy: Results of a self- management randomized controlled trial. *Epilepsia 2015;* **56**:1264-1274 doi.org/10.1111/epi.13052 (Accessed 8th October, 2017).

130 Laybourne AH, Morgan M, Watkins SH, Goldstein LH. Self-management for people with poorly control-led epilepsy: participants' views of the UK Self-Management in epilepsy (SMILE) program. *Epil Behav* 2015; **52**:159–64.

131 Noble AJ, McCrone P, Seed PT, Goldstein LH, Ridsdale L. Clinical- and cost-effectiveness of a nurse led self- management intervention to reduce emergency visits by people with epilepsy. *PLoS ON.* 2014; **9**:e90789.

132 Fraser RT, Johnson EK, Miller JW, Temkin N, Barber J, Caylor L, et al. Managing epilepsy well: self- management needs assessment. *Epil Behav* 2011; **20**:291–298. doi.org/10.1016/j.yebeh.2010.10.010 (Accessed 29th August, 2019).

133 Donetto S, Pierri P, Tsianakas V, Robert G. Experience-based Co-design and healthcare improvement: realising participatory design in the public sector. *The Design Journal. An International Journal for All Aspects of Design* 2015; **18:**227-248.

134 Walters SJ, Bonacho dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. *BMJ Open* 2017;**7**:e015276. doi:10.1136/bmjopen-2016- 015276 (Accessed 30th August, 2019).

135 Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol.* 2010; **10**:1. doi: 10.1186/1471-2288-10-1 (Accessed 3oth August, 2019).

136 Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 2004; **10**:307–312. Epub 2004/06/11. PMID:15189396 (Accessed 29th August, 2019).

137 Kralj-Hans I, Goldstein LH, Noble AJ, Landau S, Magill N, McCrone P, et al. Self-Management education for adults with poorly controlled epILEpsy (SMILE (UK)): a randomised controlled trial protocol. *BMC Neurology.* 2014; **14**:69.

138 Williams B1, Skinner J, Dowell J, Roberts R, Crombie I, Davis J. General practitioners' reasons for the failure of a randomized controlled trial (The TIGER Trial) to implement epilepsy guidelines in primary care. *Epilepsia* 2007; **48**:1275-82.

139 Patton MQ*. Qualitative research and evaluation methods*. CA: 3rd Sage Publications, Thousand Oaks, 2002.

140 Cresswell JW, Plano Clark VL. *Designing and conducting mixed method research*. CA, 2nd SAGE Publications; Thousand Oaks: 2011.

141 Bernard HR. *Research methods in anthropology: Qualitative and quantitative approaches*. Walnut Creek, CA, 3rd Alta Mira Press; 2002.

142 Spradley JP. *The ethnographic interview*. New York, NY: Holt, Rinehart & Winston; 1979.

143 Duffield C. The Delphi technique: a comparison of results obtained using two expert panels. *Int J Nurs Stud* 1993; **30**:227–237.

144 Lemmer B. Successive surveys of an expert panel: research in decision making with health visitors *J Adv Nurs* 1998*;* **27**:538–545.

145 INVOLVE. *Briefing notes for researchers: involving the public in NHS, public health and social care research.* Eastleigh, INVOLVE; 2012.

146 NHS Choices. *What to do if someone has a seizure (fit)*. 2014. http://www.nhs.uk/Livewell/Epilepsy/Pages/Ifyouseeaseizure.aspx (Accessed 19th September, 2017).

147 British Epilepsy Association. *What to do when someone has a seizure. Secondary What to do when someone has a seizure.* 2013. https://www.epilepsy.org.uk/info/firstaid (Accessed 7th August, 2016).

148 National Society for Epilepsy. *When to dial 999. Secondary When to dial 999*. 2012 http://www.epilepsysociety.org.uk/AboutEpilepsy/Firstaid/Whentodial999 (Accessed 8th January, 2016).

149 Britten N. Qualitative Research: Qualitative Interviews in Medical Research. *BMJ* 1995; **311**:251-253.

150 Mishler EG. *Research Interviewing Context and Narrative*. London: Harvard University Press; 1986.

151 Steele CM. The psychology of self-affirmation: Sustaining the integrity of the self. In L. Berkowitz, editor. *Advances in experimental social psychology*, New York, NY: Academic Press; 1988. pp. 261–302.

152 Epton T, Harris PR. Self-Affirmation Promotes Health Behavior Change. *Health Psychology* 2008; **27**:746–752.

153 Armitage CJ, Rowe R. Testing multiple means of self-affirmation. *Br Journ Psychol* 2011; **102**:535-545.

154 Schüz N, Schüz B, Eid M. When risk communication backfires: randomized controlled trial on self-affirmation and reactance to personalized risk feedback in high-risk individuals. *Health Psychol* 2013; **32**:561–570.

155 Reed MB, Aspinwall MG. Self-affirmation reduces biased processing of health-risk information. *Motivation and Emotion* 1998; **22**:99–132.

156 Cohen GL, Sherman DK. The psychology of change: self-affirmation and social psychological intervention. *Annual Review of Psychology* 2014; **65**:333-371.

157 Bazeley P, Richards L, editors. *The NVivo qualitative project book*. London; SAGE Publications Limited; 2000.

158 Skinner TC, Carey ME, Cradock S, Dallosso HM, Daly H, Davies MJ, Doherty Y, 'Educator talk' and patient change: Some insights from the DESMOND (Diabetes Education and Self Management for Ongoing and Newly Diagnosed) randomized controlled trial. *Diabetic Medicine* 2008; **25**:1117–1120.

159 Medical Research Council. *Developing and evaluating complex interventions: new guidance*. https://mrc.ukri.org/documents/pdf/complex-interventions-guidance/ (Accessed 6th January, 2016).

160 Möhler R, Köpke S, Meyer G. Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline (CReDECI 2). *Trials* 2015; **16**:204 https://www.ncbi.nlm.nih.gov/pubmed/25935741 (Accessed 29th August, 2019).

161 Department of Health. 2012. *Health Profile 2012. Liverpool*. http://fingertipsreports.phe.org.uk/health-profiles/2012/e08000012.pdf (Accessed 11th April, 2018)

162 Department of Health. 2012. *Health Profile 2012. Wirral*. http://fingertipsreports.phe.org.uk/health-profiles/2012/e08000015.pdf (Accessed 11th April, 2018)

163 NHS Right Care. *The NHS atlas of variation in healthcare.* 2010. https://www.england.nhs.uk/rightcare/products/atlas/ (Accessed 8th August, 2019).

164 Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. *BMJ* 2012; **345**:e5840. doi: 10.1136/bmj.e5840. (Accessed 29th August, 2019).

165 Powell GA, Bonnett LJ, Tudur-Smith C, Hughes DA, Williamson PR, Marson AG. Using routinely recorded data in the UK to assess outcomes in a randomised controlled trial: The Trials of Access. *Trials* 2017; **18**:389. doi: 10.1186/s13063-017-2135-9 (Accessed 29th August,2019).

166 Martiniuk ALC, Campbell MK. Development and psychometric properties of the Thinking about Epilepsy questionnaire assessing children's knowledge and attitudes about epilepsy. *Epil Behav* 2007; **10**:595-603.

167 Shore CP, Austin JK, Dunn DW. Maternal adaptation to a child's epilepsy. *Epil Behav* 2004; **5**:557-568.

168 Cramer J, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. *Epilepsia* 1998; **39**:81-88. doi.org/10.1111/j.1528-1157.1998.tb01278.x (Accessed 20th July, 2019).

169 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983; **67**:361-70.

170 Snaith RP. What do depression scales measure? *Brit J Psychiatr* 1993;**163**:293–298.

171 Thapar A, Kerr M, Harold G. Stress, anxiety, depression, and epilepsy: Investigating the relationship between psychological factors and seizures. *Epil Behav* 2009; **14**:134-140.

172 Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist* 1980; **20**: 649-655.

173 Beecham J, Knapp M. Costing psychiatric interventions. In G. Thornicroft, C. Brewin, J. Wing, editors. *Measuring Mental Health Needs.* London, Gaskell; 1992. pp. 163-183.

174 Williams, A. *The role of the EUROQOL instrument in QALY calculations*. Centre for Health Economics, University of York: York. 1995.

175 Smyth RM, Duley L, Jacoby A, Elbourne D. Women's experiences of participating in the Magpie Trial: a postal survey in the United Kingdom. *Birth* 2009; **36:**220-229.

716 Noble AJ, Marson AG. Which outcomes should we measure in adult epilepsy trials? The views of people with epilepsy and informal carers. *Epil Behav* 2016; **59**:105-10. doi: 10.1016/j.yebeh.2016.01.036. (Accessed 30th August, 2019).

177 Cramer JA, Van Hammee G, Group NS. Maintenance of improvement in health-related quality of life during long-term treatment with levetiracetam. *Epil Behav* 2003; **4**:118–123.

178 Stavem K, Bjornaes H, Lossius MI. Properties of the 15D and EQ-5D utility measures in a community sample of people with epilepsy. *Epilepsy Research* 2001; **44**:179-189.

179 Bjelland, I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52**:69-77.

180 Taylor SJC, Pinnock H, Epiphaniou E, Pearce G, Parke HL, Schwappach A, et al. *A rapid synthesis of the evidence on interventions supporting self-management for people with long-term conditions: PRISMS – Practical systematic Review of Self-Management Support for long-term conditions*: NIHR Journals Library, Southampton (UK); 2014.

181 Mittan, R. *Fear of seizures, in Psychopathology in epilepsy: social dimensions* In S. Whitman, B. Hermann, editors. New York, NY: Oxford University Press; 1986; pp. 90–121.1

182 Shore CP, Perkins SM, Austin JK. The Seizures and Epilepsy Education (SEE) program for families of children with epilepsy: a preliminary study. *Epil Behav* 2008; **12**:157-164.

183 Baumeister RF. Self-regulation and ego-threat: Motivated cognition, self-deception, and destruction in goal setting. In PM Gollwitzer, JA Bargh, editors. *The psychology of action: Linking cognition and motivation to behavior*. New York, NY: Guilford Press; 1996. pp. 27–47.

184 Austin JK, Dunn DW, Johnson CS, Perkins SM. Behavioral issues involving children and adolescents with epilepsy and the impact of their families: recent research data. *Epil Behav* 2004**; 5**(Suppl. 3):33–41. doi:10.1016/j.yebeh.2004.06.014 2004 (Accessed 24th June, 2019).

185 Morgan SR, Chang AM, Alqatari M, Pines JM. Non-emergency department interventions to reduce ED utilization: A systematic review. *Academic Emergency Medicine.* 2013; **20**:969-985.

186 Health & Social Care Information Centre (HSCIC). *Accident and Emergency Attendances in England 2012-13.* 2014. https://digital.nhs.uk/data-and-information/publications/statistical/hospital-accident--emergency- activity/accident-and-emergency-attendances-in-england-2012-13 (Accessed 4th August 2019).

187 Bhatt H, Matharu MS, Henderson K, Greenwood R. An audit of first seizures presenting to an Accident and Emergency Department. *Seizure* 2005; **14**: 58-61.

188 Ridsdale L, McCrone P, Morgan M, Goldstein L, Seed P, Noble A. Can an epilepsy nurse specialist-led self- management intervention reduce attendance at emergency departments and promote well-being for people with severe epilepsy? A non-randomised trial with a nested qualitative phase. *Health Services and Delivery Research.* 2013; 1.

189 Brueton VC, Tierney JF, Stenning S, Meredith S,Harding S, Nazarethet I, et al. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. *BMJ Open* 2014; **4**:e003821. doi:10.1136/bmjopen-2013- 003821 (Accessed 7th August, 2016).

190 Vuong, Q. Likelihood ratio tests for model selection and non-nested hypotheses. *Econometrica* 1989; **B**:307- 333.

191 Lee EC, Whitehead AL, Jacques RM, Julious SA. The statistical interpretation of pilot trials: should significance thresholds be reconsidered?. *BMC medical research methodology* 2014; **14**:41.

192 Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *The Lancet* 1986; **327**:307-310.

193 Keene ON, Jones MR, Lane PW, Anderson J. Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. *Pharmaceutical Statistics: The Journal of Applied Statistics in the Pharmaceutical Industry*. 2007; **6**:89-97.

194 Bell ML, Fairclough DL, Fiero MH, Butow PN. Handling missing items in the Hospital Anxiety and Depression Scale (HADS): a simulation study. *BMC research notes* 2016; **9**:479.

195 Hoffmann T, Glasziou P, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014; **348**:g1687.

196 Coffman JM, Cabana MD, Halpin H, Yelin E. Effects of asthma education on emergency department visits and hospitalizations for children with asthma: a meta analysis. *Pediatrics* 2008; **121:**575-86.

197 Wojewodka G, Hurley S, Noble AJ, et al. Implementation fidelity of a self-management course for epilepsy: method and assessment. *BMC Medical Research Methodology.* 2017; **17**:100.

198 Lausberg H, Sloetjes H. Coding gestural behavior with the NEUROGES–ELAN system. *BehavRes Methods* 2009; **41**:841–849.

199 Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *Journal of Chiropractic Medicine*. 2016; **15**: 155–163.

200 Feinstein AR, Cicchetti DV. High agreement but low kappa: I. The problems of two paradoxes. *J Clin Epidemiol* 1990; **43**:543-549.

201 Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. *Journal of Clinical Epidemiology* 1993; **46**:423-429.

202 Glick HA, Doshi JA, Sonnad SS, Polsky D. *Economic evaluation in clinical trials*. Oxford, OUP: 2014.

203 Sach, T H, Dsborough J, Houghton J, Holland R; CAREMED study team. Applying micro-costing methods to estimate the costs of pharmacy interventions: an illustration using multi-professional clinical medication reviews in care homes for older people. *International Journal of Pharmacy Practice* 2015; **23:**237-247.

204 Lopetegui M, Yen PY, Lai A, Jeffries J, Embi P, Payne, P. Time motion studies in healthcare: what are we talking about? *Journal of Biomedical Informatics* 2014; **49**: 292-299.

205 Loannidis JPA. How to Make More Published Research True. *PLoS Med* 2014; **11**: e1001747. https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001747 (Accessed 26th August, 2019).

206 Ridsdale L, Robins D, Cryer C, Williams H. Feasibility and effects of nurse run clinics for patients with epilepsy in general practice: randomised controlled trial. Epilepsy Care Evaluation Group. *BMJ* 1997; **314**:120–122.

207 Warren E, Baker GA, Campion P, Chadwick DR, Jacoby A, Luker K. *An evaluation of a nurse specialist/case manager intervention in the management of epilepsy*. Report for the North West Regional Health Authority, R&D Directorate; 1998.

208 Helde G, Bovim G, Bråthen G, Brodtkorb E. A structured, nurse-led intervention program improves quality of life in patients with epilepsy: a randomized, controlled trial. *Epil Behav* 2005; **7**:451–457.

209 Monfared AA, Lelorier J. Accuracy and validity of using medical claims data to identify episodes of hospitalizations in patients with COPD. *Pharmacoepidemiol Drug Saf*. 2006; **15**: 19-29.

210 Roberts RO, Bergstralh EJ, Schmidt L, Jacobsen SJ. Comparison of self-reported and medical record health care utilization measures. *J Clin Epidemiol* 1996; **49**: 989-995.

211 Ridsdale L, Wojewodka G , Robinson J, Noble AJ, Morgan M, Taylor SJC, et al. The effectiveness of a group self-management education course for adults with poorly controlled epilepsy, SMILE (UK): A randomized controlled trial. *Epilepsia*. 2018; **59:**1048-1061.

212 Raftery J, Young A, Stanton L, Milne R, Cook A, Turner D, Davidson P. Clinical trial metadata: defining and extracting metadata on the design, conduct, results and costs of 125 randomised clinical trials funded by the National Institute for Health Research Health Technology Assessment programme. *Health Technol Assess* 2015; **19**: 1-138. doi: 10.3310/hta19110. (Accessed 29th August, 2019).

213 Hassan TB, Walker B, Harrison M, Rae F. Stretched to the limit. A survey of Emergency Medicine consultants in the UK. *The College of Emergency Medicine*. 2013. www.rcem.ac.uk/docs/Policy/CEM7461-Stretched-to- the-limit-October_2013.pdf (Accessed 29th June, 2019).

214 Ridsdale L, McKinlay A, Wojewodka G, Robinson EJ, Mosweu I, Feehan SJ, et al. Self-Management education for adults with poorly controlled epILEpsy [SMILE (UK)]: a randomised controlled trial. *Health Technol Assess* 2018; **22**: 1-142.

215 Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of Life of People with Epilepsy: A European Study Dominique. *Epilepsia.* 1997*;* **38**:353-362. http://dx.doi:10.1111/j.1528-1157.1997.tb011287 (Accessed 24th June, 2019).

216 Scambler G, Hopkins A. Becoming epileptic: coming to terms with stigma. *Social Health and Illness* 1986; **8**:22-43.

217 NHS England *CDS Type 011 – Emergency Care Data Set (ECDS) User Guidance.* 2017. https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-sets/emergency-care-data- set-ecds (Accessed 15th July, 2019).

218 NHS England; ECDS FAQ – May 2017 Emergency Care Data Set Frequently Asked Questions. 2017 https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-sets/emergency-care-data- set-ecds/ecds-guidance (Accessed 15th July, 2019).

219 Luedke MW, Blalock DV, Lewinski AA, Shapiro A, Drake C, Lewis JD, et al. *Self-management of Epilepsy.* VA ESP Project #09-009; 2019.

220 Sajatovic M, Colon-Zimmermann K, Kahriman M, Fuentes-Casiano E, Liu H, Tatsuoka C, et al. A 6-month prospective randomized controlled trial of remotely delivered group format epilepsy

self-management versus waitlist control for high-risk people with epilepsy. *Epilepsia* 2018; **59**: 1686-1695. doi.org/10.1111/epi.14527 (Accessed 29th August, 2019).

221 Snape D, Kirkham J, Britten N, Froggatt K, Gradinger F, Lobban F et al. Exploring perceived barriers, drivers, impacts and the need for evaluation of public involvement in health and social care research: a modified Delphi study. *BMJ Open* 2014. doi:10.1136/bmjopen-2014-004943. (Accessed 15th July, 2019).

222 Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ* 2016; **355**:i5239. PMID: 27777223 (Accessed 29th August, 2019).

223 Noble, AJ, Marson, A., Blower S. Psychological interventions for epilepsy: How good are trialists at assessing their implementation fidelity, what are the barriers and what are journals doing to encourage it? A mixed methods study. *Epil Behav* 2019; **97:**174-181.

224 Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ 2015; 350* https://www.bmj.com/content/350/bmj.h1258 (Accessed 29th August, 2015).

225 Perepletchikova F, Hilt LM, Chereji E, Kazdin AE. Barriers to implementing treatment integrity procedures: survey of treatment outcome researchers. *Journal of Consulting and Clinical Psychology* 2009; **77**:212-218.

Appendix 1 Possible ways SAFE course might reduce unnecessary/avoidable ED use

Primary putative mechanisms	
Low seizure management confidence and skills	**How might course address & reduce ED use?**
PWE can have low knowledge of epilepsy and seizures, have incorrect beliefs concerning first aid, lack confidence managing seizures and be disproportionately fearful (e.g., Long et al.[70]). Consequently, some patients can routinely call for emergency medical assistance when they are about to have or have had a seizure, regardless of whether it is medically required or not.	Topics covered in the ES training course could increase patients' knowledge of what seizures are, their effects and help patients to know when it is and is not necessary to seek emergency assistance. This could serve to increase patients' confidence in managing seizures, including post-ictal states, and help them delineate the circumstances that require emergency services. The course could also help allay disproportionate fears.
Responsibility for managing epileptic seizures is often delegated to SOs (Walker et al.[73]). Some have low epilepsy knowledge, have incorrect beliefs concerning seizure first aid, lack of confidence in managing them and can be fearful of them and their threat to the patients' life (Kobau et al.[121]). Consequently, some SOs call for emergency medical attention when the patient has or has had a seizure, regardless of whether it is medically required.	The ES's course could help increase SOs' knowledge of what seizures are, what their effects are and help them to know when it is and is not necessary to seek emergency medical attention and identify alternative pathways of support. It could also help allay disproportionate fears held by the SO. The topics covered in the ES's course could also help PWE feel more informed and comfortable with their diagnosis. This could empower them to have a discussion with others in their caring network about epilepsy, relay correct information about how they can be helped if they have a seizure and what their preferences regarding transportation to ED are. To help PWE do this, the ES has a variety of resources which participants' are given or have their attention drawn to. For example, in participants' take-away information pack, there are a number of free wallet sized 'Seizure First Aid Cards' which can be given to friends and family members.

Secondary putative mechanisms	
Suboptimal medication or risk management	**How might course address & reduce ED use?**
Evidence that in some cases ED attendance by PWE may have been precipitated by the person having experienced a seizure or seizure-related injury because they have not managed their medication (e.g., have skipped doses) or epilepsy in an optimum manner or managed risk (e.g., not taken precaution to avoid a seizure trigger) (Faught et al.[122];Tan et al.[123]).	ES' course describes what antiepileptic medications do, explains why adhering to prescribed regimes is important and outlines potential seizure triggers. This could promote better medication and risk management by PWE and so reduce avoidable seizures and associated complications. Imparting this information to SOs could also be helpful and allow them to become powerful supporters of the development of self-management responsibility in the PWE that they know. (e.g., helping PWE with reminders) and risk management (e.g., helping the PWE to identify and avoid triggers, such as sleep deprivation, stress). The ES's course also briefly covers issues to do with the commonality of epilepsy, who it affects, its emotional impact, provides participants with the contact details of support agencies and helps dispel some misconceptions and myths about epilepsy (e.g., about its causes). This, along with meeting other people with epilepsy, may help reduce feelings of stigma and shame about the diagnosis. Stigma can be associated with willingness to accept one's diagnosis and antiepileptic treatments.
Lack of emergency seizure medication	**How might course address and reduce ED use?**
Portable emergency seizure medications are suitable for some PWE (e.g., buccal midazolam). They can be prescribed to PWE who have had a previous episode of prolonged or serial convulsive seizures (NICE[47]). They can empower patients and families to manage some seizures, without the need for medical assistance [Mitchell et al.[124]; O'Dell et al.[125]). However, patients and SOs might not be aware of them or their utility. They may also have incorrect beliefs about them, which could act as a barrier to their use (e.g., that all need to be rectally administered).	ES' course covers emergency medication. Sources of further information on this topic are also provided. The information could enable them to start a discussion with usual care providers about whether such treatment is suitable for them.

Lack of epilepsy ID at time of seizure	How might course address & reduce ED use?
In a minority of cases (~15%, (Reuber et al[23])), ED visits by PWE occur because the person is alone, has an uncomplicated seizure in a public place and a bystander calls for an ambulance. Evidence indicates that it can be challenging for ambulance staff to know whether it is safe to discharge the patient at the scene because they do not know the patient's medical history. The patient may also be 'post-ictal'; whilst it is not necessary to transport them to hospital, they do not have an alternative way of ensuring patient safety. Some evidence indicates that low confidence in managing seizures, results in some ambulance staff being insistent about transporting the patient to ED (Burrell et al.[75]).	ES's course does not currently cover this topic. However, with the help of experts and users consulted during the development phase, it might be feasible to introduce this as a new topic. This could involve briefly discussing with PWE and SOs the challenges that face ambulance crews when managing seizures, the benefits of patients carrying easily accessible epilepsy identification cards and of them carrying the contact details of a significant other who could be contacted to look after the patient and also help explain the patient's medical history. Patients could also be advised on the rules and regulations concerning transportation to ED by paramedics.

Appendix 2 Participant Information Sheet for health care professional representatives (project Part A)

PARTICIPANT INFORMATION SHEET

Study title: Research to design a course on seizure first aid for people with epilepsy and their family and friends

(REC reference no: 15/NW/0225)

1. Invitation paragraph

You are being asked to take part in a research study. Here is information to help you decide if you want to take part.

Please read it carefully. Ask us if there is anything you do not understand or if you want more information. You can take time to decide whether or not you want to take part.

2. The background to the study

Currently, 6 out of 7 hospital admissions for epilepsy are made on an emergency, rather than planned basis. Many of these visits have little long term benefit for patients as the seizures leading to them were uncomplicated and occurred in those in whom the diagnosis was already established. Moreover, these emergency visits do not typically lead to people with epilepsy receiving any additional ongoing support from the NHS.

One reason why people with epilepsy visit emergency departments for uncomplicated seizures is that they and their informal carers can lack confidence managing seizures. They can be unsure as to what the effects of seizures are, not know when medical attention is required, and can be fearful of death. As you will know, the NHS has not yet implemented routine education for people diagnosed with epilepsy and there is limited time within usual care appointments for this information to be provided.

Therefore, in partnership with the Epilepsy Society, our project aims to develop a short, group-based course on seizure first aid. It will be specifically designed for adults with established epilepsy who frequently make emergency visits and their family and friends. Once developed, we shall complete a pilot trial of the course.

3. How do you want people like me to be involved?

Rather than starting from scratch, the course that we will develop shall be based on a successful ½-day group course offered by the Epilepsy Society. Their course is titled 'Epilepsy awareness and seizure management'. People from a variety of backgrounds, including patients, carers, teachers and care home staff, pay to attend their course. It is delivered by an educational facilitator who has experience of working with people with epilepsy, such as a nurse.

The Society's course was not specifically developed to meet the needs of people with epilepsy who visit emergency departments. This group can be particularly challenged by epilepsy and may have lower educational levels. We therefore need to adapt the course, refining its content and format for the target population.

To help us do this, we are seeking advice on what changes are needed to the current course from representatives from the main groups and sectors supporting people with epilepsy. We shall also consult with patients and carers.

4. Why am I being invited to take part?

The groups we shall seek feedback from includes the ambulance service, neurologists, nurses, general practitioners, and emergency medicine doctors. We shall also speak with representatives from user groups and the commissioning sector. We believe your expertise makes you well placed to provide us with feedback on the course.

5. If I agreed to take part what would I have to do?

You would be sent the content and materials for the Epilepsy Society's current package and their guidelines on what constitutes appropriate first aid for seizures. Then ~2 weeks later you will be asked to provide feedback by means of an interview with our research worker. The interview would last about 60 minutes.

Depending on your preference, the interview will be conducted face-to-face, by telephone or by Skype. The things that we would like your feedback on will vary depending on your area of expertise. If you are medically trained, questions might include:

- "What did and didn't you like about the course's current content and delivery?"
- "What inaccuracies are there in the content of the current course?"
- "How do you suggest the programme could be more helpful?"
- "How do you think the intervention might be best rolled out within the NHS, if a future trial found it to be effective?"

6. Do I have to take part?

No. It is up to you. If you want to take part, you will be given this information sheet to keep, given the opportunity to have any questions answered and asked to sign a consent form.

If you decide to take part, you are free to change your mind at any time and you will not need to give a reason. No new information would be collected from you. However, any information that had already been collected would typically be kept by the study team.

7. Are there any benefits in taking part?

The information we get from the study may help us better support people with epilepsy in the future.

To recognise the time and effort involved in reviewing the course materials and in providing feedback you will receive a consultancy fee of £200.

8. Are there any risks in taking part?

There are no known disadvantages or risks of taking part.

9. Will my taking part be kept confidential?

Yes. Only the research team will be able to see the information. This includes the audio recording from your interview. Anything that we publish or pass on will have your name and address and any personal information removed so that you cannot be identified. All information will be stored on password protected computers at the University of Liverpool.

10. What if something goes wrong?

The University of Liverpool provides insurance cover just in case you experience a problem from taking part in the study. If you are worried about anything to do with the study, you should contact the research team. Their details are at the end of this sheet.

11. What will happen to the results of the study?

The results from this study will be used to identify what changes are needed to the Epilepsy Society's current course. They might also be published. You will not be identified in any report. If you would like to have a copy of any published results, you can ask for one by contacting the study team.

All information generated by this study, including the transcriptions from the interviews, will be held on password secured computers at the University of Liverpool offices. In line with the university's policy, data will be archived at the University of Liverpool for of at least 10 years, longer if judged to be of historical significance. After this period the data will be destroyed.

12. Who is funding and organising the study?

The study is funded by the National Institute for Health Research. The study is being done by the Institute of Psychology, Health and Society, The Whelan Building, University of Liverpool, L69 3GL. The lead researcher is Dr Adam Noble.

13. Who has reviewed the study?

This study has been reviewed and approved by National Research Ethics Service Committee North West - Liverpool East (Reference: 15/NW/0225).

14. Contact for further information:

Should you need further information about the study you can contact the research team at any time:

XXXXXXXXXX

You will be given a copy of this information sheet and a signed copy of your consent form to keep.

Appendix 3 Participant Information Sheet for service user representatives (project Part A)

PARTICIPANT INFORMATION SHEET

Study title: Research to design a course on seizure first aid for people with epilepsy and their family and friends

(REC reference no: 15/NW/0225)

1. Invitation paragraph

You are being asked to take part in a research study. Before you decide whether you want to take part, it is important for you to know why the research is being done and what it will involve.

Please read this information sheet carefully. If you wish to, you can talk about it with your friends and relatives. Ask us if there is anything you do not understand or if you want more information. You can take time to decide whether you want to take part.

2. What is the reason for the study?

People with epilepsy need to know what to do when a seizure happens. They also need to be able to tell others what to do. This is also true for the friends and family of people with epilepsy.

To feel confident to do these things, some people with epilepsy and family members have said they need more information about epilepsy and seizure first aid. They said they want to know more about the effects of seizures, how to deal with different types of seizures and know when they do and do not need emergency medical help.

Therefore, together with the *Epilepsy Society*, we have made a short course on seizure first aid that people with epilepsy and their family and friends can go on. The course is called Seizure First Aid Training.

Ambulance staff, neurologists, nurses and emergency medicine doctors helped us decide what information the course should give.

We now need to run some practice courses to find out what people with epilepsy and their family and friends think of the course. This will help us know if any parts of the course need changing to make sure it is as good as it can be.

3. Why am I being invited to take part?

We are looking for people with epilepsy to come to one of our practice courses in Liverpool with a family member or friend.

To take part in our study, people with epilepsy need to be aged 16 or over. They must have been diagnosed with epilepsy for 1 or more years and be prescribed anti-epileptic medication. They also need to have visited a hospital emergency department for epilepsy at some point during the last few years. The person can have any type of epilepsy and their seizures can be of any severity. As the Seizure First Aid Training course is given in English people only take part if they can speak, read and understand English well.

You are being invited to take part because we believe you fit this description. You, or a person that you know, contacted us after seeing our advert for participants.

4. Do I have to take part?

No. It is up to you. If you want to take part, you will be given this information sheet to keep, given the opportunity to have any questions answered and asked to sign a consent form.

If you decide to take part, you are free to change your mind at any time and you will not need to give a reason. A decision to stop taking part will not affect the standard of medical care you receive. No new information would be collected on you. However, any information that had already been collected would be kept by the study team.

5. What will happen to me if I take part?

If you agree to take part, a researcher will contact you to get you to sign a consent form. They will arrange for you and one of your family members or friends to come to one of the practice courses.

The course will happen in [INSERT MONTH] of this year. They last about 3 hours and will be held at the [INSERT NAME] centre. This is a specially designed centre for those with conditions like epilepsy. It is [INSERT SUMMARY OF LOCATION].

Each course will be given by a specially trained health professional from the charity, the *Epilepsy Society*. These people are typically nurses and will be able to help should a seizure happen.

The course will be run on a weekday. For the course you will need to go to the centre just once. The courses will typically start at [INSERT TIME] and finish at [INSERT TIME], with breaks included.

The research team will speak with you to find a course that is convenient for you to come to.

About 10 people with epilepsy and their family and friends will be at each of the courses.

During the course, the health professional will give lots of information about epilepsy and show some video clips. The things that the course will cover include:

- How common epilepsy is
- Its causes and some myths about epilepsy
- The tests doctors use to diagnose it
- The different types of seizures and their effects
- How to deal with different seizures, including when to call an ambulance and how to help paramedics help you
- How to improve your confidence and tell others what to do if a person with epilepsy has a seizure.

At the course, you can ask questions. If you want to, you can also share your experiences with the other people.

Everyone taking the course is given an information pack to keep. It includes all the things talked about on the course. It also gives the details of support organisations.

As we have said, the main reason for this study is to see if any part of the Seizure First Aid Training course needs changing to make it better. To help us do this, we want to hear participants' views of the course. Therefore, straight after the course, our researcher will spend about an hour with you and the rest of the group to hear your thoughts. This group talk will be audio-recorded to give an accurate record of the conversation.

6. Expenses

We do not expect that you will have any expenses from taking part in our study. If needed, we can pay for a taxi to take you and your family member or friend to and from the course. We will also provide refreshments for you. Each participant will also receive a £10 shopping voucher to thank them for their time and effort.

If you decide to take time off work to go on the course, we will not be able to pay you or your employer.

7. Are there any benefits in taking part?

We hope you and your family member or friend will get helpful information on epilepsy and learn some things that may increase your confidence to deal with seizures. However, this cannot be guaranteed. The information we get from the study may help us better support people with epilepsy in the future.

8. Are there any risks in taking part?

There are no known risks of taking part.

Taking part in the study will not change the care you get for epilepsy. Your medicines will stay the same and you will see your usual doctors and nurses as normal.

The Seizure First Aid Training course and the group chat afterwards will involve thinking about epilepsy and feelings. For some people, this may be upsetting. You can stop taking part in the course or the group chat at any time. This would not affect your medical care.

If taking part in the study makes you worried about your feelings, you could talk to your GP. You can also ask the health professional giving your course for advice. However, they would not be able to refer you to any NHS service themselves.

9. Will my taking part in this study be kept confidential?

Yes. Anything that we publish or pass on will have your name and address and any personal information removed so that you cannot be identified. All information will be stored on password protected computers at the University of Liverpool. Your participation will not affect your medical care.

Only the research team will be able to see the information will collect on you. This includes the audio recordings.

With your permission, we would want to tell your GP about your taking part. We would also need to tell your GP if the health professional giving your course or our researcher becomes worried about your health. However, we would talk about this with you first.

The Seizure First Aid Training course is given to groups of about 10 people with epilepsy and their family and friends. Because of this, we cannot promise that other participants will not share information about one another outside of the group. To lower the chances of this happening, we will get all participants to sign a form. This will say that they agree that anything they hear about other participants should not be talked about outside of the group. The health professional giving the course will remind participants of this at the start.

10. What if something goes wrong?

The University of Liverpool has insurance cover just in case you experience a problem from taking part. If you are worried about anything to do with the study, you should contact the research team. Their details are at the end of this sheet.

11. What will happen to the results of the study?

The results from this study will be used to see if any changes to the Seizure First Aid Training course are needed. They might also be published. You will not be identified in any publication. If you would like to have a copy of the published results, you can ask for one by contacting the study team.

All information generated by this study, including the transcriptions from the focus groups, will be held on password secured computers at the University of Liverpool offices. In line with the university's policy, data will be archived at the University of Liverpool for of at least 10 years, longer if judged to be of historical significance. After this period the data will be destroyed.

12. Who is funding and organising the study?

The study is funded by the National Institute for Health Research. The study is being done by the Institute of Psychology, Health and Society, The Whelan Building, University of Liverpool, L69 3GL. The lead researcher is Dr Adam Noble.

13. Who has reviewed the study?

This study has been reviewed and approved by National Research Ethics Service Committee North West - Liverpool East (Reference: 15/NW/0225).

14. Contact for further information:

Should you need further information about the study you can contact the research team at any time:

XXXXXXXX

You will be given a copy of this information sheet and a signed copy of your consent form to keep.

Appendix 4 Topic guide for interviews with health care professional representatives (project Part A)

***Reminder of context of study for interviewer*:**

Many visits to hospital emergency departments for epilepsy are clinically unnecessary. This is because they are by people with known, rather than new epilepsy, who have experienced an uncomplicated seizure. Research by our group indicates people with established epilepsy often attend hospital emergency departments for these seizures because they and their significant others (SOs) can lack confidence managing seizures. They say they want more information, are unsure as to what the effects of seizures are, do not know when medical attention is required, and some fear death. To better support these people, we are developing a seizure first aid training course for patients who frequently visit emergency departments, and their family and friends. The course will be adapted from an existing seizure management training course that has been delivered on a small scale by the Epilepsy Society.

Tools:

To help the interview process, take a copy of the course materials that were sent to the interviewee. The table of 8 topics covered may be a useful aide memoire for interviewees. The interviewee is also encouraged to bring any notes with them to the interview.

Areas to be covered by the interview with health professional/ user group stakeholders:

- Briefly, what is their area/ work/ career background?
- How are they involved in supporting people with epilepsy?
- What were their thoughts on the idea of the course?
- How successful/ unsuccessful do they think the course will be in improving patients and SOs seizure management skills and confidence? Any particular groups for which is likely to be most or least useful?
- What did they think from the course was most likely/ least likely to help patients make fewer clinically unnecessary ED visits?
- Are there any new things that they think the course needs to cover so that it is as helpful as possible? If so, what and how?

Specific areas to be explored here if not covered spontaneously:

- Some patients may hold disproportionate fears concerning the effects of seizures on the brain and the possibility of death. Does the interviewee think some course time should be given to the topic of what the effects of seizures are and the risks of events, such as status epilepticus and SUDEP? If so, what information do they think the course should provide and how?

- Does the interviewee think evidence on the high proportion of unnecessary ED visits for epilepsy should be explicitly presented to participants?

- Does the interviewee think some course time should be given to allow participants to discuss fears of unconsciousness/death in themselves and SOs; and seizure management?

- Participants might not be aware of emergency seizure medication and may also have incorrect beliefs about them. Does the interviewee think some course time should be given to the topic of emergency medication? If so, what information should be relayed and how?

- Some ED visits occur because the person is alone, has an uncomplicated seizure in a public place, and a bystander calls for an ambulance. Does the interviewee think some course time be given to the topic of how patients and families can help ambulance crews manage seizures in the community when appropriate, rather than having to transport the patient to ED? If so, what information or strategies do you think the course should provide patients with and how?

- Are there any things that they think should be removed from the course? If so, what and why?

- To accommodate that additional aspect/s, whilst keep the course length roughly the same, what you do they think could be removed and why?

- Are there any things currently covered by the course that they think should be changed? If so, what and how?

- What did they think about the way the course is delivered? (Group sizes, setting, educational facilitator background, capacity etc.)

- Do they have any thoughts on how the course will be received by PWE who frequently visit ED?

- Are there any barriers to participating and/or using information and training that they identify?

- Do they have any thoughts on how the course will be received by the family members and friends who attend the course?

One specific area to be explored here if not covered spontaneously - Does the interviewee think some course time should be given to how patients can best discuss their epilepsy and first-aid with friends and colleagues not on the course? If so, what information or strategies do you think the course should provide patients with and how?

- Did they identify any inaccuracies in the medical information that was presented? If so, what/ where?

- If the course were ultimately found to be effective, how do they think it could be best rolled out within the NHS? (e.g., identifying who needs it; how often courses should be provided; who pays for it) What would be the barriers and facilitators be?

Close:

- Any other questions or comments participant wishes to make
- Thank you for your time

Appendix 5 Topic guide for focus groups with service user representatives (project Part A)

Introduction:

- Introduce self and project role
- Well once again I would like to thank you all for taking the time to be here with us today.
- As I mentioned previously we are now interested in finding out about your views about today's training. Your comments and suggestions for change are important to us as we want to use those ideas to help us improve the content and presentation of this training.
- Before we start this discussion I just want to mention a couple of important points:
    - The discussion will work best if everyone feels comfortable to share their opinion and sometimes personal experiences. It is important that we agree from the start that any personal details people speak about during this session are respected by us all and kept confidential by not sharing any personal information about anybody else outside of this room. Does this sound okay to everyone? ...Thank you
    - Please note this FG is being audio recorded for the purpose of data collection. The recording will be transcribed and I will use the findings from this discussion to inform the further development of this training package
    - Can I just confirm that everyone has signed a consent form? … you will receive a copy of this form to keep
    - Please feel free to speak openly – there are no right or wrong answers. However it would be useful if when making a comment you could say whether you are speaking as a PWE / SO. This will help me to understand which perspective your response is coming from.
    - Any questions before we begin?

Ice-breaker - General Overview:

Right, so let's get started

- **As you may already know there are lots of different types of epilepsy and everyone is individual. This probably meant that some of things we talked about today may have been important to some of you, while some things may not. Thinking about your impressions overall then:**

    - How well was today's session organised overall?

EXPLORE,

    - What did you particularly appreciate and/or enjoy about the session? *(prompts)*
        - Content
        - Presentation
        - Timeframe *(including start time and duration)*
        - Venue *(including access and facilities*)

EXPLORE,

- What changes could we introduce to improve the session? *(prompts)*
  - Content
  - Presentation
  - Timeframe *(including start time and duration)*
  - Venue *(including access and facilities*)

Use previous discussion as the platform to explore follow-on questions:

- **Today's course was designed to give you information about epilepsy first aid:**
  - In your opinion how well did the taught aspects of the session meet:
    - This aim / What could we have done differently
    - Your own expectations / What would you like to see changed
    - We also tried to provide people with epilepsy and those who support them with a practical view of how to manage seizures, including what to do and what not to when seizures occur:
    - In your opinion how good were the explanation of topics provided in the session
    - Was enough time given to these explanations
    - Was enough time given to the practical demonstrations (recovery position)
    - What could we have done differently

- **In the future, we want everyone who takes part in these sessions to contribute as much as possible as we believe this will make what is being said more meaningful for the participants. With this in mind:**

  - How comfortable did you feel to:
    - Ask questions about the topics covered
    - To participate in the practical tasks in the session

(prompts to explore in turn/ in depth)

- Kindness Questionnaire
- Quiz
- What to do/ what not to do task
- Recovery demonstration/ practice

- In your opinion Does group size / mix, promote / hinder interaction
  - Was the group size / mix of PWE/ SOs appropriate:
    - Yes – why? / No – why?

- **This training session, its format and resources were informed by broader seizure management training that is currently offered by the Epilepsy Society. In your opinion:**

- How well *(or not)* do you think the session title reflects the:
    - The session aims
    - The session content

- **Thinking specifically about the content of the session, in your opinion:**
    - Where the key message(s) from today's session easy to identify?
    - Was the amount of material covered was about right?
    - Was there anything that was unclear or could have been better explained?
    - Was there anything you wanted to be included that wasn't?
        - If so what was it and why was this important?

- **If you have had an opportunity to look at the additional information provided today:**
    - How relevant to the session do you consider them to be?
    - What additional information, not provided would you have liked to have been included?

- **I would now like to hear your opinions about how the session was delivered today:**
    - Was the session leader considered to be knowledgeable / provide quality instruction?
    - How well did the session leader develop a good rapport with those taking part?
    - Was class participation and interaction encouraged sufficiently / too much
    - Where the teaching and learning methods used stimulating / interesting?
    - How good was the balance between the session leader talking, the group work and the discussion?
    - Was adequate provided for questions and discussion?
    - Overall, how well organised was the session?

CLOSE

- Are there any other comments anyone would like to make about any aspect of today's session?

- THANKYOU

Appendix 6 Search criteria employed at the different recruitment sites to identify potentially suitable persons attending ED for epilepsy

ED SITE		
Site 1 **Aintree University Hospital NHS Foundation Trust**	**Site 2** **Arrowe Park Hospital**	**Site 3** **Royal Liverpool University Hospital**
Identify those persons who within the free text box 'presenting complaint' are recorded as having visited the ED for a: • "fit" • "epilepsy" • "convulsion" • "seizure" And those patients admitted as an emergency from ED to a ward with any of the following primary or secondary ICD-10 diagnoses: • "G40 Epilepsy" • "G41 Status epilepticus" • "G83.8 Other specified paralytic syndromes" • "R56.8 Other and unspecified convulsions"	Identify those persons who within the free text box 'reason for visit' or 'presenting complaint' are recorded as having visited the ED for: • "fit" • "epilep" • "convuls" • "seiz" And those patients admitted as an emergency from ED to a ward with any of the following primary or secondary ICD-10 diagnoses: • "G40 Epilepsy" • "G41 Status epilepticus" • "G83.8 Other specified paralytic syndromes" • "R56.8 Other and unspecified convulsions"	Identify those persons who attended the ED and were given any of the following presenting complaint-discharge diagnosis profiles: • Presenting complaint "AE20 AEPRC Fit" AND ED discharge diagnosis "02 AEDIG Contusion/ abrasion"; • "AE20 AEPRC Fit" AND "04 AEDIG Head injury"; • "AE20 AEPRC Fit" AND "05 AEDIG Dislocation"; • "AE20 AEPRC Fit" AND "06 AEDIG Sprain/ ligament injury"; • "AE20 AEPRC Fit" AND "07 AEDIG Muscle/ tendon injury"; • "AE20 AEPRC Fit" AND "10 AEDIG Burns and scalds"; • "AE20 AEPRC Fit" AND "15 AEDIG Near Drowning"; • "AE20 AEPRC Fit" AND "33 AEDIG Facio-maxillary conditions"; • "AE20 AEPRC Fit" AND "38 AEDIG Diagnosis not classifiable". • "241 AEDIG Epilepsy". And those patients admitted as an emergency from ED to a ward with any of the following primary or secondary ICD-10 diagnoses: • "G40 Epilepsy" • "G41 Status epilepticus" • "G83.8 Other specified paralytic syndromes" • "R56.8 Other and unspecified convulsions"

Appendix 7 Participant Information Sheet for patients for pilot RCT (project Part B)

[INSERT TRUST LOGO]

PATIENT PARTICPANT INFORMATION SHEET

Study title: Research offering Seizure First Aid Training to people with epilepsy and their family and friends: A pilot trial (REC reference no: 5/NW/0225)

1. Invitation paragraph

You are being asked to take part in a research study. Before you decide whether you want to take part, it is important for you to know why the research is being done and what it will involve. Please read this information sheet carefully. If you wish to you can talk about it with your friends and relatives. Ask us if there is anything you do not understand or if you want more information. You can take time to decide whether you want to take part.

2. What is the reason for the study?

People with epilepsy need to know what to do when a seizure happens. They also need to be able to tell others what to do. This is also true for the friends and family of people with epilepsy. To feel confident to do these things, some people with epilepsy and family members have said they need more information about epilepsy and seizure first aid. They said they want to know more about the effects of seizures, how to deal with different types and know when they do and do not need emergency medical help. Therefore, together with the Epilepsy Society, we have made a short course on seizure first aid that people with epilepsy and their family and friends can go on. The course is called Seizure First Aid Training.

Ambulance staff, neurologists, nurses and emergency medicine doctors have helped us decide what information the course should give. The course takes 3 hours to do and people with epilepsy take it together with a family member or friend. It is a group based course so there are other people with epilepsy and their family and friends at the course. Our study is looking to see how helpful the Seizure First Aid Training course is. We want to know whether it helps people with epilepsy and their family and friends get the information they want and whether it makes them more confident managing seizures. We need to know this so the NHS can decide whether it should offer the course.

3. What type of study is it that you are doing?

The type of study we are doing is called a pilot randomised trial. In this sort of study, people taking part are put into one of two groups at random by a computer. The first group is called Group A and the second Group B. People who are put in Group A get the Seizure First Aid Training course straightaway and people in Group B continue to receive their normal medical care. The health of the people in the two groups is then compared to see if the Seizure First Aid Training was helpful or not.

After the two groups' health has been compared, people in Group B then get to go on a Seizure First Aid Training course if they want it. At the moment we do not know if the Seizure First Aid Training course is any more helpful than the normal care people already receive from the NHS. This means a randomised trial is the most exact and fair way to see how helpful the course is. Each year thousands of people take part in randomised trials.

4. Why am I being asked to take part?

We are looking for people with epilepsy to take part in our study with a family member or friend. To take part in our study, people with epilepsy need to be aged 16 or over. They must have been diagnosed with epilepsy for 1 or more years and be prescribed anti-epileptic medication. They also need to have visited a hospital emergency department for epilepsy two or more times in the last 12 months. The person can have any type of epilepsy and their seizures can be of any severity. However, people cannot take part in the study if they experience non-epileptic seizures. The Seizure First Aid Training course is given in English. This means people can also only take part if they can speak, read and understand English well. You are being invited to take part because we believe you fit the above description.

5. Do I have to take part?

No. It is up to you. Even if you decide to take part, you are still free to change your mind at any time. You would not need to give a reason. A decision to not take part will not affect your medical care. No new information would be collected on you. However, any information that had already been collected would be kept.

6. What will happen to me if I take part?

If you want to take part, our researcher will arrange to see you at a time and place that is convenient for you. They could meet you at your home or our university offices. You will also be asked to choose a family member or friend to take part in the study with you. At the appointment, the researcher will explain the study to you and your family member or friend and answer any questions you have. You will be given this information sheet to keep and each asked to sign a consent form. You will then be asked to each fill in a questionnaire. It will ask your health, quality of life and how you manage seizures. The researcher will be on hand to help you if needed. The appointment will last about one hour. After the appointment, the researcher will use a computer programme to put you into either Group A or Group B. The group you are put in will decide when you and your family member or friend gets to go on the Seizure First Aid Training. You will not be able to choose which group you are put in and we will not make the decision ourselves. We will let you know which group you have been put in.

7. What will happen to me if I am put into Group A?

If you are put into Group A you will be asked to go on a Seizure First Aid Training course about a month after you signed the consent form. You will still continue to take your medications and see your doctors and nurses as normal.

After going on the course you will be asked to fill in a short questionnaire about your health three times. The first time will be three months after you joined the study. The researcher will telephone you and ask you the

questions. It should take about 10 minutes. The second time will be six months after you joined the study. On this occasion you will be sent the questionnaire in the post and asked to post it back to us when you have finished it. It should take you about 30 minutes to do.

The final time you will be asked to fill in the questionnaire will be about twelve months after you joined the study. You will do it during a face-to-face appointment with our researcher. This appointment will last about one hour and happen at a time and place that is convenient for you.

8. What will happen to me if I am put into Group B?

If you are put into Group B you will not get to go on the Seizure First Aid Training course straightway. Instead, you will continue to receive you normal medical care for the next 12 months and be asked to fill in a questionnaire on your health three times. The first time will be three months after you first filled it in. The researcher will telephone you and ask you the questions. It should take about 10 minutes. The second time will be six months after you first filled it in. On this occasion you will be sent the questionnaire in the post and asked to post it back to us when you have finished it. It should take you about 30 minutes to do.

The final time you will be asked to fill in the questionnaire will be about twelve months after you first filled it in. You will do it during a face-to-face appointment with our researcher. This appointment will last about one hour and happen at a time and place that is convenient for you. You will be able to go on a Seizure First Aid Training course after everyone in the study has completed their final questionnaire. This should mean your course will typically take place about six months after you filled in your final questionnaire.

9. Where and how will the Seizure First Aid Training courses be run?

The courses will be run on weekdays at a hospital near to your home. For the course, you will need to go to the hospital just once. The courses will typically run from [INSERT TIME] until [INSERT TIME], with breaks included. The research team will speak with you to find a course that is convenient for you to go to.

Each course will be given by a specially trained health professional from the charity, the Epilepsy Society. These people are typically nurses and will be able to help should a seizure happen. About 10 people with epilepsy and their family and friends will be at each of the courses. During the course, the health professional will give lots of information about epilepsy and show some video clips. They will talk about things people with epilepsy and their family and friends have said they want to know more about. This includes giving information on:

- How common epilepsy is.
- Its causes and some myths about epilepsy.
- The tests doctors use to diagnose it.
- The different types of seizures and their effects.
- How to deal with different seizures, including when to call an ambulance and how to help paramedics help you.

- How to improve your confidence and tell others what to do to if a person with epilepsy has a seizure.

At the course, you can ask questions. If you want to, you can share your experiences with the other people taking the course. Everyone taking the course is given an information pack to keep. It includes all the things talked about on the course. It also gives the details of support organisations. If you agree, we will audio-record the Seizure First Aid Training course sessions. We want to do this to have a record how well the course was run by the health professional. If illness means you can only go to part of the course, we can arrange for you to finish the course on another day.

10. How long would I be involved in the study?

If you are put into Group A you will be in the study for about one year. If you are in Group B you will typically be involved with the study for about 18 months.

11. Expenses

We do not expect you will have any expenses from taking part in our study. If needed, we can pay for a taxi to take you and your family member or friend to and from the course. We will also provide refreshments for you. All participants will receive a £10 shopping voucher for each of the questionnaires they do by post or in person. This is to thank them for their time and effort. Therefore, each person who takes part in our study can get up to £30. If you decide to take time off work to go on the course, we will not be able to pay you or your employer.

12. Are there any benefits in taking part?

We hope you and your family member or friend will get helpful information on epilepsy and learn some things that may increase your confidence to deal with seizures. However, this cannot be guaranteed. The information we get from the study may help us better support people with epilepsy in the future.

13. Are there any risks in taking part?

There are no known disadvantages or risks of taking part. Taking part in the study will not change the care you get for epilepsy. Your medicines will stay the same and you will see your usual doctors and nurses as normal. The Seizure First Aid Training course and some of the questionnaires that we will ask you will involve thinking about your epilepsy and feelings. For some people, this may be upsetting. You can stop taking part in the course or doing the questionnaire at any time. This would not affect your medical care in any way.

If taking part in the course or answering the questionnaires makes you worried about your feelings, you can talk to your GP. You can also ask the health professional giving your course for advice. However, they would not be able to refer you to any NHS service themselves.

14. Will my taking part in this study be kept confidential?

Yes. All the information we collect on you during the study will be kept confidential. Only the research team will be able to see the information. This includes the audio recordings. Anything that we publish or pass on will have your name and address and any personal information removed so that you cannot be identified. All information will be stored on password protected computers at the University of Liverpool. Your participation will not affect your medical care.

With your permission, we would want to tell your GP/ hospital specialist about your taking part. We would also need to speak with them and possibly access your medical records if the health professional giving your course or our researcher becomes worried about your wellbeing. However, we would talk about this with you first.

The Seizure First Aid Training course is given to groups of about 10 people with epilepsy and their family and friends. Because of this, we cannot promise that other participants will not share information about one another outside of the group. To lower the chances of this happening, we will get all participants to sign a form. This will say that they agree that anything they hear about other participants should not be talked about outside of the group. The health professional giving the course will remind participants of this.

As part of the project we would like to see if being in the study helps you become more confident to deal with seizures. One way we would like to find this out is by seeing if your use of hospital emergency departments changes. Information on when you have visited hospital emergency departments is already stored by the Health and Social Care Information Centre. They are a public body, sponsored by the Department of Health. With your agreement, we would like to see information held by the Health and Social Care Information Centre on your visits to hospital emergency departments. To do this, we would send the Health and Social Care Information Centre your NHS number and ask them for information on how many times you used hospital emergency departments in the 12 months before coming into our study and then how many times you went whilst you are in the study. All information that will be sent between the Health and Social Care Information Centre and us would be done using secure methods.

15. What happens when the study stops?

You continue to receive your normal medical care.

16. What if something goes wrong?

The University of Liverpool has insurance cover just in case you experience a problem from taking part in the study. If you are worried about anything to do with the study, you should contact the research team. Their details are at the end of this sheet.

17. What will happen to the results of the study?

The results from this study will be published in scientific journals. You will not be identified in any publication. If you want a copy of the published results, you can ask for one by contacting the study team. All information generated by this study will be held on password secured computers at the University of Liverpool offices. In

line with the university's policy, data will be archived at the University of Liverpool for of at least 10 years, longer if judged to be of historical significance. After this period the data will be destroyed.

18. Who is funding and organising the study?

The study is funded by the National Institute for Health Research. The study is being done by the Institute of Psychology, Health and Society, The Whelan Building, University of Liverpool, L69 3GL. The lead researcher is Dr Adam Noble.

19. Who has reviewed the study?

This study has been reviewed and approved by National Research Ethics Service Committee North West - Liverpool East (Reference: 15/NW/0225).

20. Contact for further information:

Should you need further information about the study you can contact the research team at any time:

XXXXXXXX

Email: Seizure_First_Aid_project@liv.ac.uk

You will be given a copy of this information sheet and a signed copy of your consent form to keep.

Thank you!

Appendix 8 Full details of secondary outcome measures

Quality of life (QoL) (Patients only; T0, T2, T3) - This was measured using the epilepsy specific quality of life measure the Quality of Life in Epilepsy Scale-31-P (QOLIE31-P) (Cramer et al.[177]). It asks participants to reflect on how they felt over the past 4 weeks. It has 7 subscales that reflect the aspects of living that can be affected by epilepsy (emotional wellbeing, energy-fatigue, cognitive functioning, seizure worry, medication effects, social functioning, overall QoL). Scored according to guidelines, a participant's total score ranges from 0 to 100, with higher scores indicating better overall perceived quality of life. The QOLIE-31-P varies from the original QOLIE-31 (Cramer et al.[168]) in that at the end of each subscale there is one additional item which asks the participant to rate the degree of 'distress' caused by that particular topic.

Burden (SOs only; T0, T2, T3) - No epilepsy-specific measure is available to measure so-called 'caregiver burden' in the target population. Therefore, the Zarit Caregiver Burden Inventory (Zarit et al [172]) was used to capture the impact of informal caring on the patient participants designated SO. Its 22 items evaluate the effect of a condition on QOL, difficulty in social and family relationships, psychological suffering, shame, guilt and financial difficulty. It is the most widely used, standardized, validated scale and has previously been used in epilepsy (Stavem et al.[178]).

Psychological distress (Patients and SOs; T0, T3) - The 14-item Hospital Anxiety and Depression Scale (Zigmond et al.;[169] Snaith[170]) was used to measure self-reported distress in patients and SOs. It is a reliable, valid scale widely-used in UK epilepsy research. Anxiety and depression scores are grouped into symptom categories: 0–7 normal, 8–10 'suggestive of anxiety/depression' and 11–21 'probable anxiety/depression' (Bjelland et al.[179]).

Felt Stigma (Patients only; T0, T3) - Jacoby's (Jacoby[17]; Taylor et al.[180]) 3-item Stigma of Epilepsy Scale, with revised 4-point scoring, measured the extent to which patient participants felt they are stigmatised by their epilepsy. Response options include a four-point Likert scale: (0) 'not at all', (1) 'yes, maybe', (2) 'yes, probably' and (3) 'yes, definitely'. Total scores range from 0 (does not feel stigmatised) to 1–6 (mildly to moderately stigmatised) to 7–9 (highly stigmatised). The scale's internal consistency (Cronbach's α=.85) is good (Taylor et al.[14]).

Fear of seizures (Patients and SOs; T0, T3) - Both patients and SOs completed 5-items from the Fears subscale from the 60-item Epilepsy Knowledge and Management Questionnaire (Mittan [181]). They focus on knowledge about seizures and on fears of death or brain damage. The 5-items have previously been used in isolation (Shore et al.[182]).

Confidence managing seizures/ epilepsy (Patients and SOs; T0, T2, T3) - Wagner et al.'s [61] 6-item epilepsy-specific scale was used to measure patient participants' perception of epilepsy and its treatment and the extent to which they felt able to control these. This measure is able to distinguish between groups of PWE with differing

levels of severity. It has adequate internal consistency (Cronbach's α = .7) and test-retest reliability (Baumeister[183]). SOs completed the 6-item Condition Management subscale from Austin's[184] Parents Response to Child Illness Scale. It has been shown to have good internal consistency (Shore et al.[167]). SOs respond to each item using a 5-point scale.

Knowledge of what to do when faced with a seizure (Patient and SOs; T0, T3). Both patients and SOs completed a measure assessing their knowledge of what to do when faced with a seizure. The standardised questions come from Martiniuk et al.'s[166] 'Thinking About Epilepsy Questionnaire'.

Seizure control (Patients only; T0, T2, T3) - Patients only: At baseline (T0), patients were asked to complete Thapar et al.'s[171] seizure frequency scale for the prior 12 months. At 6- (T2) and 12-months (T3) follow-up, patient participants were asked for the number of seizures (of any type) that they had experienced since the last assessment and the date of the first and most recent seizure (if applicable) since last assessment. To assist patients to be able to provide this information they were offered a seizure diary at T0 and instructed on how to complete it.

Health economics (Patients only; T0, T3) - The Client Service Receipt Inventory (Beecham et al.[173]) enabled measurement of patient participants health service use (including use of ambulance services, regardless of whether transfer to ED happened), informal care (including work time lost by SOs), benefits received and employment status during the 12 months prior to baseline and 12 months following randomisation. The 5-item EQ-5D (Williams[174]), already shown to be valid in PWE (Cohen et al.[156]) was also used.

Feedback on participation (Patients and SOs, T3) - To capture patient and SOs feedback on their experience of taking part in the trial, including randomisation, we asked both parties to complete 3 questions at their final assessment. These were: (1) "If time suddenly went backward, and you had to do it all over again, would you agree to participate in the Seizure First Aid Training trial?" (definitely yes, probably yes, probably no, definitely no, and not sure; and free text to explain the response); (2) "Please tell us if there was anything about the Seizure First Aid Training Trial that you think could have been done better" (Free text response); and (3) "Please tell us if there was anything about the Seizure First Aid Training Trial, or your experience of joining the trial, that you think was particularly good" (Free text response). The questions are based on those used to explore participants' experience of participating in the Magpie Trial (Morgan et al.[185]).

Appendix 9 Serious Adverse Event Protocol

Event

Adapted from the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf [accessed 29th August, 2019] a serious adverse event (SAE) was defined as an adverse event which resulted in any of the following:

- Death
- Was life-threatening (subject at immediate risk of death, e.g., status epilepticus)
- Seizure resulting in hospital admission for ≥24 hours
- Emergency attendance or hospital admission for reason other than seizure
- Results in persistent or significant disability or incapacity, or
- Was otherwise considered medically significant.

'Life-threatening' in the definition of 'serious' referred to an event in which the patient was at risk of death at the time of the event; it did not refer to an event which hypothetically might have caused death if it were more severe. Hospitalisations for a pre-existing condition, including elective procedures that had not worsened, did not constitute an SAE. Prolongation of hospital stay due to social factors, for example, geographical location of the participant's home which prevented discharge was also not considered a SAE.

Given the characteristics of the subject population being studied, the following events were expected in this study population and were not recorded as part of the SAE monitoring process:

- Epileptic seizures with or without injury;
- Emergency or urgent medical attention. This includes visiting a hospital emergency department with the duration of the stay lasting <24 hours, attending an NHS out of hours primary care service (NHS Urgent Care 24), telephoning for an ambulance, telephoning NHS 111, seeking/ having an urgent/ fast-tracked appointment with a usual care provider (GP or specialist) or other registered health professional (e.g., a pharmacist);
- Side-effects of antiepileptic drug;
- Diagnosis of a comorbid psychiatric condition.

A delegated medically qualified person within the team (AM; LR) assessed each unexpected SAE. This person considered information on the temporal and physical relationship between the event and possible causes and assessed whether the event was related or unrelated to the patient's participation in the study. Further details on the process followed detailed below.

Monitoring

As part of this trial patient participants will not receive additional medical reviews. There is also no 'live' system which can be used to track SAEs such as emergency admissions and usual care providers are not systematically informed of them. Therefore, to monitor SAEs the research team will liaise with patients themselves. A standardised form will be completed as part of the CRF at 3- (T1, by telephone), 6- (T2, by telephone) and 12-months (T3, during a face-to-face appointment) post-randomisation to collect information on patient participants' experience of unexpected, SAEs.

In each instance, a maximum of 3 attempts will be made to contact the patient participant by telephone (including trying to contact them via their informal carer if they are taking part with one). Should the patient not be contactable a letter will be sent the patient's GP asking them to inform the research team if the patient is no longer alive and the circumstances of their death.

Given the characteristics of the subject population being studied the potential adverse events expected in this study population are as follows:

- Epileptic seizures with or without injury
- Emergency or urgent medical attention. This includes visiting a hospital emergency department with the duration of the stay lasting <24 hours, attending an NHS out of hours primary care service (NHS Urgent Care 24), telephoning for an ambulance, telephoning NHS 111, seeking/ having an urgent/ fast-tracked appointment with a usual care provider (GP or specialist) or other registered health professional (e.g., a pharmacist)
- Side-effects of anti-epileptic medication
- Diagnosis of a comorbid psychiatric condition

Whilst they will be captured as outcomes of the trial, they will not be recorded as part of the SAE monitoring process:

Causality

A delegated medically qualified person within the team will assess each unexpected SAE. This person will consider information on the temporal and physical relationship between the event and possible causes and assess whether the event was related or unrelated to the patient's participation in the study. In doing this, they will use the definitions in the Table below.

To complete their assessment, the research team may need to obtain medical records, such as contacting a hospital where a patient was admitted as emergency. For the following reasons a window of 10 days will be allowed for a SAE to be reviewed within by the medic: information on adverse events will have been collected by research workers during concentrated follow-up periods; there will only be one delegated medical assessor; and assessment may depend on the timeliness of response from hospitals for historically distant admissions.

Definitions of causality for serious adverse event

	Description
Unrelated	There is no evidence of any causal relationship. There is an alternative cause for the SAE.
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after receipt of the intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after receipt of the intervention). However, the influence of other factors may have contributed to the event (e.g. the participants clinical condition, other concomitant treatment).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Reporting

As per National Research Ethics Service (2015) guidelines for non-CTIMPs, the main REC approving the study and the Sponsor will be informed within 15 days of the team becoming aware of any SAE that in the opinion of the medical reviewers is both unexpected (that is, the type of event is not listed in the protocol as an expected occurrence) and judged to be "possibly", "probably" or "almost certainly" related to participation in the study (that is, it resulted from administration of any of the research procedures, including the intervention)

Notifications will include the following details: date of the SAE, location, a description of the circumstances of the event, and an assessment of the causal relationship to the SAFE intervention and the implications, if any, for the safety of study participants and how will these be addressed. Notifications made to the main REC shall be made using the NRES SAE Reporting Form for non-CTIMPs. A flowchart is given below to aid in determining reporting requirements.

A log of all SAE that are unexpected and which were judged to be related to participation in the study will also be reviewed by the Independent Trial Steering Committee and the implications for the study considered. This

information will also be sent to the funder as part of the progress reports and the Chief Investigator will include details of the event in the annual progress report to the REC and a copy sent to the Sponsor.

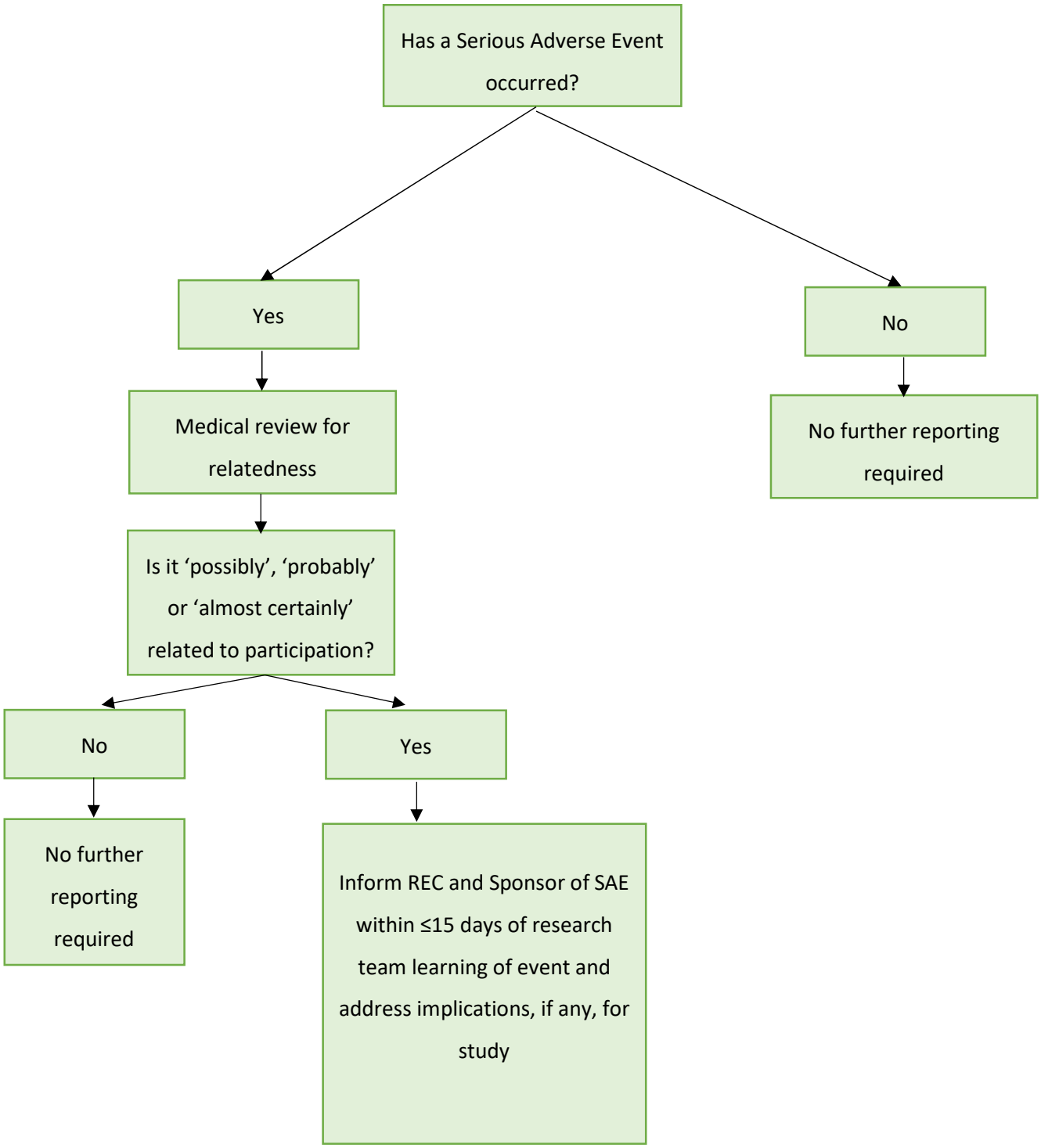
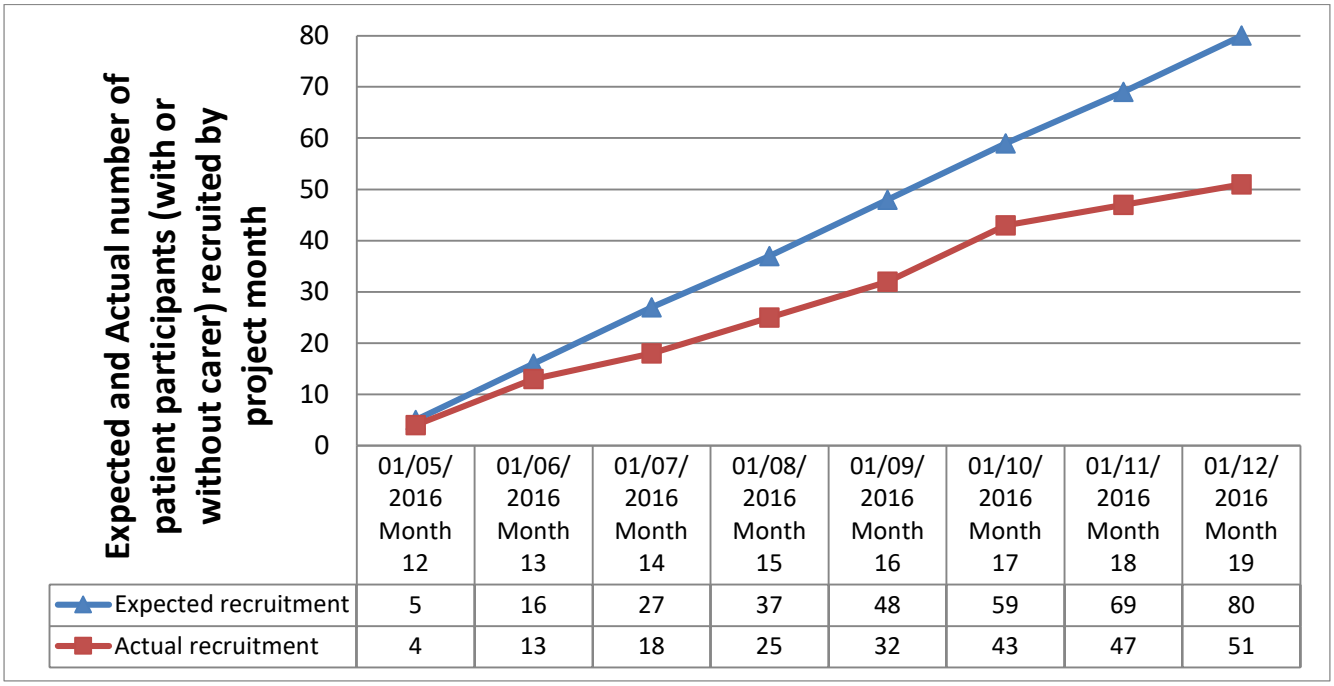


Figure: Flowchart for determining of reporting requirements for serious adverse events

Appendix 10 Cumulative, actual and expected recruitment (consented and randomised) in SAFE trial



	01/05/2016 Month 12	01/06/2016 Month 13	01/07/2016 Month 14	01/08/2016 Month 15	01/09/2016 Month 16	01/10/2016 Month 17	01/11/2016 Month 18	01/12/2016 Month 19
Expected recruitment	5	16	27	37	48	59	69	80
Actual recruitment	4	13	18	25	32	43	47	51

Appendix 11 Reasons for withdrawal from pilot RCT

Reasons for withdrawal	SAFE + TAU	TAU	Total
Patient participants withdrawing from the study	(n=1)	(n=3)	(n=4)
Too busy	1 (100.0%)	0 (0.0%)	1 (25.0%)
Not interested any more	0 (0.0%)	1 (33.3%)	1 (25.0%)
Other: Moved away to work	0 (0.0%)	1 (33.3%)	1 (25.0%)
Other: Wife has cancer	0 (0.0%)	1 (33.3%)	1 (25.0%)
SO participants withdrawing from the study	(n=1)	(n=4)	(n=5)
Too ill	0 (0.0%)	1 (25.0%)	1 (20.0%)
Not interested any more	0 (0.0%)	1 (25.0%)	1 (20.0%)
Other: Moved away to work	0 (0.0%)	1 (25.0%)	1 (20.0%)
Other: No longer friends with person with epilepsy	0 (0.0%)	1 (25.0%)	1 (20.0%)
Reason missing	1 (100.0%)	0 (0.0%)	1 (20.0%)

Appendix 12 Milestones in securing data from NHS Digital

Period	Project milestone		Milestone in obtaining data from NHS Digital	
	Date	*Note*	*Date*	*Note*
Pre-trial	**01 Jul 2015**	Project officially starts		
	01 Aug 2015	Intervention development starts		
			28 Sep 2015	Received feedback on draft Participant Information Sheets and Consent form for trial to ensure compliance.
Trial period	**19 May 2016**	First trial participant randomised		
			11 Oct 2017	Participated in NHS Digital training.
			18 Oct 2017	Registered as new user of application system.
			07 Nov 2017	Delays experienced. Access to application form granted after chasing.
	Dec 2017	Final 12-month follow-up completed		
Post -trial			**16 Feb 2018**	Application submitted to NHS Digital
			28 Feb 2018	Teleconference with NHS Digital. Provisional opinion given that only minor changes required and likely timeframe to receipt of data 1.5 months.
			07 Mar 2018	Received written feedback from NHS Digital after chasing on minor changes required.
			22 Mar 2018	Revised application submitted.
			03 Apr 2018	NHS Digital submit new query (1) to applicants requesting additional information. (Applicants respond 03 Apr 2018)
			26 Apr 2018	NHS Digital submit new query (2) to applicants requesting additional information. (Applicants respond 26 Apr 2018)
			30 Apr 2018	NHS Digital submit new query (3) to applicants requesting additional information. (Applicants respond 30 Apr 2018)
			05 May 2018	NHS Digital submit new query (4) to applicants requesting additional information. (Applicants respond 05 May 2018).
			10 May 2018	NHS Digital submit new query (5) to applicants requesting additional information (in light of new General Data Protection Regulation introduced on May 2018). (Applicants respond 11 May 2018)
			30 May 2018	NHS Digital submit new query (6) to applicants requesting additional information (in light of new General Data Protection Regulation introduced on May 2018). (Applicants respond 30 May 2018)
			30 May 2018	NHS Digital submit new query (7) to applicants requesting additional information. (Applicants respond 30 May 2018)

Period	Project milestone		Milestone in obtaining data from NHS Digital	
	Date	*Note*	*Date*	*Note*
post-trial			**15 Jun 2018**	NHS Digital confirm Data Approvals Owner will review revised application.
			27 Jun 2018	NHS Digital submit new query (8) to applicants requesting additional information and request revisions to trial website in light of new General Data Protection Regulation introduced on May 2018). (Applicants respond 28 Jun 2018)
			02 Jul 2018	NHS Digital submit new query (9) to applicants requesting additional information. (Applicants 02 Jul 2018)
			06 Jul 2018	NHS Digital notify applicants that Data Approval Owner has rejected application, primarily because: "concerns [over] whether this pilot would yield findings that were statistically valuable to achieve the stated aims given the small numbers".
			10 Jul 2018	Secured confirmation of right to appeal and process.
			20 Jul 2018	Applicants submit letter of appeal.
			25 Jul 2018	Appeal accepted by NHS Digital.
			15 Aug 2018	NHS Digital submit new query (10) to applicants following Independent Group Advising on the Release of Data (IGARD) committee's review of application. (Applicants respond 16 Aug 2018)
			16 Aug 2018	Teleconference with NHS Digital data production team.
			04 Sep 2018	NHS Digital send Data Sharing Agreement to applicants.
			10 Sep 2018	NHS Digital confirm receipt of completed Data Sharing Agreement.
			25 Sep 2018	Applicants securely transfer patient participants' details to NHS Digital.
			31 Sep 2018	NHS Digital release data to applicants.

Appendix 13 Completeness of secondary outcome measures by assessment point, tool and participant type

Number of questions of study assessment tool completed by patient participants at each time point

Outcome: Number of questions of study assessment tool completed at each time point		SAFE + TAU	TAU	Total
Quality of Life in Epilepsy Scale (QOLIE-31) (Cramer et al.[177]): baseline (T0)		(n=26)	(n=25)	(n=51)
	33	0 (0.0%)	1 (4.0%)	1 (2.0%)
	35	2 (7.7%)	2 (8.0%)	4 (7.8%)
	36	1 (3.8%)	6 (24.0%)	7 (13.7%)
	37 (maximum)	23 (88.5%)	16 (64.0%)	39 (76.5%)
Hospital Anxiety and Depression Scale[a](.[171]) : baseline (T0)		(n=26)	(n=25)	(n=51)
	7	1 (3.8%)	0 (0.0%)	1 (2.0%)
	13	2 (7.7%)	1 (4.0%)	3 (5.9%)
	14 (maximum)	23 (88.5%)	24 (96.0%)	47 (92.2%)
Jacoby[17] Stigma of Epilepsy Scale : baseline (T0)		(n=26)	(n=25)	(n=51)
	0	1 (3.8%)	1 (4.0%)	2 (3.9%)
	2	1 (3.8%)	0 (0.0%)	1 (2.0%)
	3 (maximum)	24 (92.4%)	24 (96.0%)	48 (94.1%)
Client Service Receipt Inventory[b] (Beecham et al.[173]): baseline (T0)		(n=26)	(n=25)	(n=51)
	2	1 (3.8%)	0 (0.0%)	1 (2.0%)
	4	1 (3.8%)	0 (0.0%)	1 (2.0%)
	5	5 (19.2%)	8 (32.0%)	13 (25.5%)
	6 (maximum)	19 (73.2%)	17 (68.0%)	36 (70.5%)
EQ-5D (Williams[174]): baseline (T0)		(n=26)	(n=25)	(n=51)
	5	5 (19.2%)	0 (0.0%)	5 (9.8%)
	6 (maximum)	21 (80.8%)	25 (100.0%)	46 (90.2%)
Wagner [61] 6-item Mastery Scale: baseline (T0)		(n=26)	(n=25)	(n=51)
	1	0 (0.0%)	1 (4.0%)	1 (2.0%)
	3	0 (0.0%)	1 (4.0.%)	1 (2.0%)
	5	0 (0.0%)	2 (8.0%)	2 (3.9%)
	6 (maximum)	26 (100.0%)	21 (84.0%)	47 (92.1%)
Thinking about Epilepsy Questionnaire (Martiniuk et al.[166]): baseline (T0)		(n=26)	(n=25)	(n=51)
	0	3 (11.6%)	2 (8.0%)	5 (9.8%)
	1	1 (3.8%)	1 (4.0%)	2 (3.9%)
	2	1 (3.8%)	5 (20.0%)	6 (11.8%)
	3	1 (3.8%)	4 (16.0%)	5 (9.8%)
	4	4 (15.4%)	4 (16.0%)	8 (15.7%)
	5 (maximum)	16 (61.6%)	9 (36.0%)	25 (49.0%)
Quality of Life in Epilepsy Scale (QOLIE-31) (Cramer et al.[177]).: 6 months (T2)		(n=26)	(n=25)	(n=51)
	0	4 (15.4%)	8 (32.0%)[c]	12 (23.5%)[c]
	16	1 (3.8%)	0 (0.0%)	1 (2.0%)
	34	0 (0.0%)	1 (4.0%)	1 (2.0%)
	35	0 (0.0%)	2 (8.0%)	2 (3.9%)
	36	5 (19.2%)	2 (8.0%)	7 (13.7%)
	37 (maximum)	16 (61.6%)	12 (48.0%)	28 (54.9%)

Number of questions of study assessment tool completed by patient participants at each time point

Outcome: Number of questions of study assessment tool completed at each time point		SAFE + TAU	TAU	Total
Wagner[61] 6-item Mastery Scale: 6 months (T2)		(n=26)	(n=25)	(n=51)
	0	4 (15.4%)	8 (32.0%)[c]	12 (23.5%)[c]
	2	1 (3.8%)	0 (0.0%)	1 (2.0%)
	5	0 (0.0%)	2 (4.0%)	2 (3.9%)
	6 (maximum)	21 (80.8%)	15 (60.0%)	36 (70.6%)
Quality of Life in Epilepsy Scale (QOLIE-31) (Cramer et al.[177]).: 12 months (T3)		(n=26)	(n=25)	(n=51)
	0	7 (26.9%)[d]	8 (32.0%)[d]	15 (29.4%)[d]
	1	1 (3.8%)	0 (0.0%)	1 (2.0%)
	31	0 (0.0%)	1 (4.0%)	1 (2.0%)
	35	1 (3.8%)	4 (16.0%)	5 (9.8%)
	36	7 (26.9%)	4 (16.0%)	11 (21.6%)
	37 (maximum)	10 (38.5%)	8 (32.0%)	18 (35.3%)
Hospital Anxiety and Depression Scale[a] (Zigmond et al.[169]): 12 months (T3)		(n=26)	(n=25)	(n=51)
	0	8 (30.8%)[d]	8 (32.0%)[d]	16 (31.4%)[d]
	14 (maximum)	18 (69.2%)	17 (68.0%)	35 (68.6%)
Jacoby[17] Stigma of Epilepsy Scale : 12 months (T3)		(n=26)	(n=25)	(n=51)
	0	8 (30.8%)[d]	8 (32.0%)[d]	16 (31.4%)[d]
	3 (maximum)	18 (69.2%)	17 (68.0%)	35 (68.6%)
Client Service Receipt Inventory[b] (Beecham et al.[173]): 12 months (T3)		(n=26)	(n=25)	(n=51)
	0	8 (30.8%)[d]	8 (32.0%)[d]	16 (31.4)[d]
	3	0 (0.0%)	1 (4.0%)	1 (2.0%)
	4	1 (3.8%)	1 (4.0%)	2 (3.9%)
	5	4 (15.4%)	5 (20.0%)	9 (17.7%)
	6 (maximum)	13 (50.0%)	10 (40.0%)	23 (45.0%)
EQ-5D (Williams[174]): 12 months (T3)		(n=26)	(n=25)	(n=51)
	0	8 (30.8%)[d]	8 (32.0%)[d]	16 (31.4%)[d]
	6	18 (69.2%)	17 (68.0%)	35 (68.6%)
Wagner[61] 6-item Mastery Scale: 12 months (T3)		(n=26)	(n=25)	(n=51)
	0	8 (30.8%)[d]	8 (32.0%)[d]	16 (31.4%)[d]
	5	0 (0.0%)	1 (4.0%)	1 (2.0%)
	6	18 (69.2%)	16 (64.0%)	34 (66.6%)
Thinking about Epilepsy Questionnaire (Martiniuk et al.[166]): 12 months (T3)		(n=26)	(n=25)	(n=51)
	0	10 (38.5%)[d]	8 (32.0%)[d]	18 (35.3%)[d]
	1	1 (3.8%)	0 (0.0%)	1 (2.0%)
	2	1 (3.8%)	0 (0.0%)	1 (2.0%)
	3	1 (3.8%)	7 (28.0%)	8 (15.7%)
	4	5 (19.2%)	5 (20.0%)	10 (19.6%)

	5 (maximum)	8 (30.9%)	5 (20.0%)	13 (25.5%)

Notes:

a. Completeness of the whole HADS scale (both anxiety and depression subscales)

b. Only six mandatory questions counted. Conditional questions (e.g. if yes, then…) not counted towards total completion

c. Including two patient participants from TAU group who had withdrawn by T2 visit

d. Including four patient participants (three from TAU group and one from SAFE + TAU group) who had withdrawn by T3 visit

Number of questions of study assessment tool completed by SO participants at each time point

Outcome measure	Number of questions of study assessment tool completed at each time point	SAFE + TAU	TAU	Total
Zarit[172] Caregiver Burden: baseline (T0)		(n=18)	(n=19)	(n=37)
	16	0 (0.0%)	1 (5.3%)	1 (2.7%)
	21	1 (5.6%)	1 (5.3%)	2 (5.4%)
	22 (maximum)	17 (94.4%)	17 (89.5%)	34 (91.9%)
Hospital Anxiety and Depression Scale[a] (Zigmond et al.[169]) baseline (T0)		(n=18)	(n=19)	(n=37)
	13	1 (5.6%)	1 (5.3%)	2 (5.4%)
	14 (maximum)	17 (94.4%)	18 (94.7%)	35 (94.6%)
Austin's[184] Parent Response to Child Illness Scale: baseline (T0)		(n=18)	(n=19)	(n=37)
	6 (maximum)	18 (100.0%)	19 (100.0%)	37 (100.0%)
Thinking about Epilepsy Questionnaire (Martiniuk et al.[166]): baseline (T0)		(n=18)	(n=19)	(n=37)
	0	2 (11.1%)	2 (10.5%)	4 (10.8%)
	1	2 (11.1%)	2 (10.5%)	4 (10.8%)
	2	1 (5.6%)	3 (15.8%)	4 (10.8%)
	3	1 (5.6%)	2 (10.5%)	3 (8.1%)
	4	6 (33.3%)	6 (31.6%)	12 (32.4%)
	5 (maximum)	6 (33.3%)	4 (21.1%)	10 (27.0%)
Zarit[172] Caregiver Burden 6 months (T2)		(n=18)	(n=19)	(n=37)
	0	2 (11.1%)[b]	9 (47.4)[b]	11 (29.7%)[b]
	10	0 (0.0%)	1 (5.3%)	1 (2.7%)
	21	1 (5.6%)	1 (5.3%)	2 (5.4%)
	22 (maximum)	15 (83.4%)	8 (42.0%)	23 (62.2%)
Austin's[184] Parent Response to Child Illness Scale: 6 months (T2)		(n=18)	(n=19)	(n=37)
	0	2 (11.1%)[b]	10 (52.6%)[b]	12 (32.4%)[b]
	6 (maximum)	16 (88.9%)	9 (47.4%)	25 (67.6%)
Zarit[172] Caregiver Burden 12 months (T3)		(n=18)	(n=19)	(n=37)
	0	7 (38.9%)[c]	9 (47.4%)[c]	16 (43.2%)[c]
	22 (maximum)	11 (61.1%)	10 (52.6%)	21 (56.8%)
Hospital Anxiety and Depression Scale[a] (Zigmond et al.[169]) : 12 months (T3)		(n=18)	(n=19)	(n=37)
	0	7 (38.9%)[c]	9 (47.4%)[c]	16 (43.2%)[c]
	14 (maximum)	11 (61.1%)	10 (52.6%)	21 (56.8%)

Number of questions of study assessment tool completed by SO participants at each time point

Outcome measure	Number of questions of study assessment tool completed at each time point	SAFE + TAU	TAU	Total
Austin's[184] Parent Response to Child Illness Scale: 12 months (T3)		(n=18)	(n=19)	(n=37)
	0	7 (38.9%)[c]	9 (47.4%)[c]	16 (43.2%)[c]
	6 (maximum)	11 (61.1%)	10 (52.6%)	21 (56.8%)
Thinking about Epilepsy Questionnaire (Martiniuk et al.[166]): 12 months (T3)		(n=18)	(n=19)	(n=37)
	0	7 (38.9%)[c]	10 (52.7%)[c]	17 (46.0%)[c]
	1	1 (5.6%)	0 (0.0%)	1 (2.7%)
	2	2 (11.1%)	2 (10.5%)	4 (10.8%)
	3	2 (11.1%)	3 (15.8%)	5 (13.5%)
	4	0 (0.0%)	2 (10.5%)	2 (5.4%)
	5 (maximum)	6 (33.3%)	2 (10.5%)	8 (21.6%)

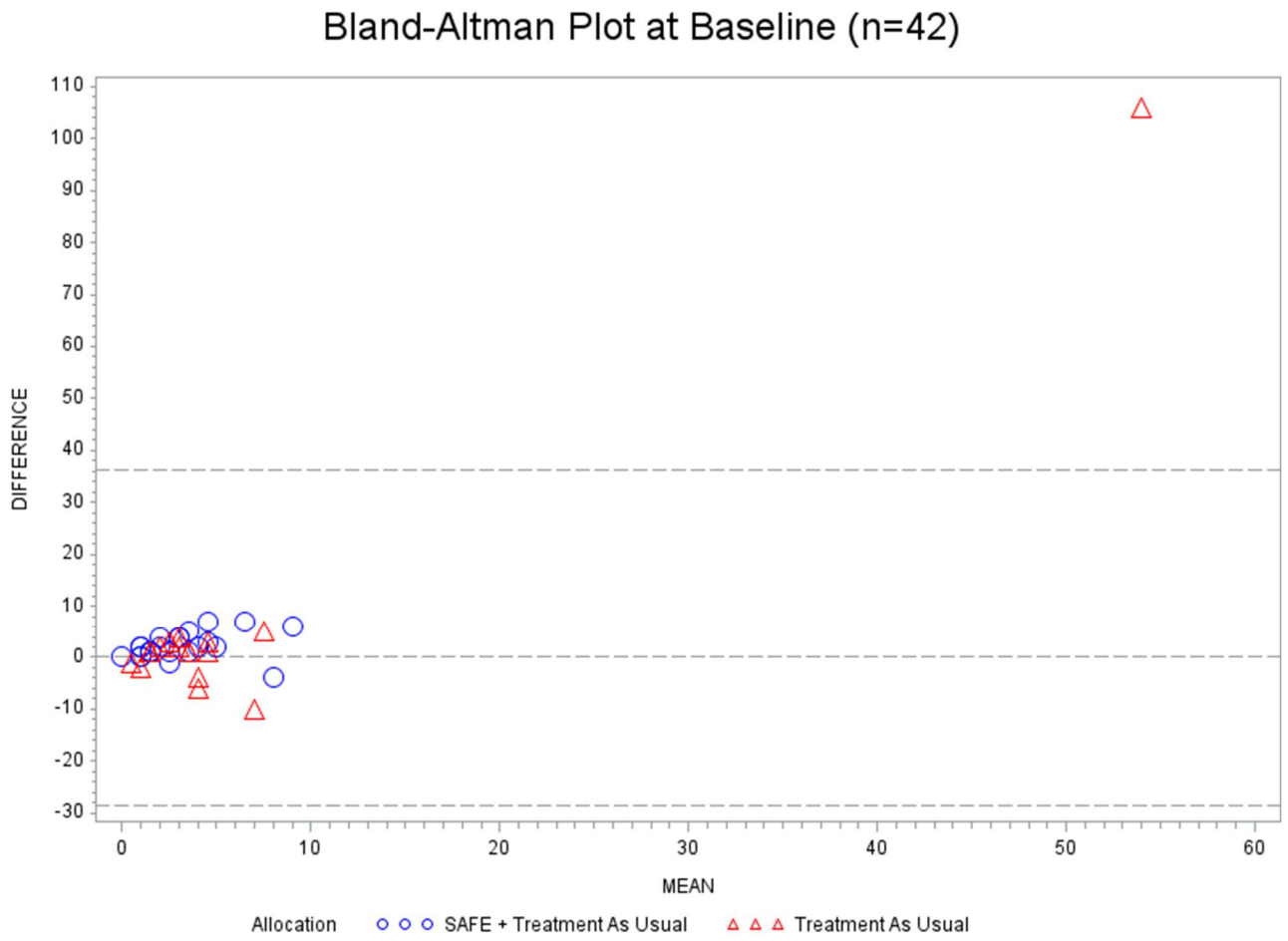
Notes:

a. Completeness of the whole HADS scale (both anxiety and depression subscales)

b. Including four SO participants (one in the SAFE group and three in the TAU group) who had withdrawn by the T2 visit

c. Including four SO participants (one in the SAFE group and four in the TAU group) who had withdrawn by the T3 visit

Appendix 14 Bland Altman plot of agreement between self reported ED visits and hospital episode statistics (HES) data at baseline, without any exclusions



Appendix 15 Demographic characteristics of SO participants

Demographic characteristic	SAFE + TAU	TAU	Total
Relationship with patient participant	(n=18)	(n=19)	(n=37)
Parent	4 (22.2%)	4 (21.1%)	8 (21.6%)
Son / daughter	2 (11.1%)	4 (21.1%)	6 (16.2%)
Grandparent	0 (0.0%)	0 (0.0%)	0 (0.0%)
Spouse / partner	9 (50.0%)	7 (36.8%)	16 (43.2%)
Sibling	1 (5.6%)	0 (0.0%)	1 (2.7%)
Cousin, aunt / uncle	0 (0.0%)	0 (0.0%)	0 (0.0%)
Niece / nephew	0 (0.0%)	1 (5.3%)	1 (2.7%)
Friend	2 (11.1%)	3 (15.8%)	5 (13.5%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Co-habitation with patient participant	(n=18)	(n=19)	(n=37)
Yes	14 (77.8%)	14 (73.4%)	28 (75.7%)
No	4 (22.2%)	5 (26.3%)	9 (24.3%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Contact with patient participant (number of days per week)	(n=18)	(n=19)	(n=37)
None	0 (0.0%)	0 (0.0%)	0 (0.0%)
One	1 (5.6%)	0 (0.0%)	1 (2.7%)
Two	0 (0.0%)	1 (5.3%)	1 (2.7%)
Three	0 (0.0%)	2 (10.5%)	2 (5.4%)
Four	0 (0.0%)	0 (0.0%)	0 (0.0%)
Five	0 (0.0%)	0 (0.0%)	0 (0.0%)
Six	0 (0.0%)	0 (0.0%)	0 (0.0%)
Seven (every day)	17 (94.4%)	16 (84.2%)	33 (89.2%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sex: n (%)	(n=18)	(n=19)	(n=37)
Male	6 (33.3%)	9 (47.4%)	15 (40.5%)
Female	12 (67.7%)	10 (52.6%)	22 (59.5%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age at consent into the trial (years)			
N	17 (94.4%)	19 (100.0%)	36 (94.6%)
Mean	41.3	44.9	43.2
Standard deviation	18.66	15.69	17.01
Minimum	17.8	18.1	17.8
Median	43.5	49.7	48.0
Maximum	79.7	71.5	79.7
Missing	1 (5.6%)	0 (0.0%)	1 (2.7%)
Ethnicity: n (%)	(n=18)	(n=19)	(n=37)
White	18 (100.0%)	18 (94.5%)	36 (97.3%)
Asian / Asian British	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black / African / Carribean / Black British	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mixed / multiple ethnic groups	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other ethnic group	0 (0.0%)	1 (5.3%)	1 (2.7%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Significant medical history: n (%)	(n=18)	(n=19)	(n=37)
No, none	13 (72.2%)	12 (63.2%)	25 (67.6%)
Yes, a medical condition	5 (27.8%)	6 (31.6%)	11 (29.7%)
Yes, a psychiatric condition	0 (0.0%)	0 (0.0%)	0 (0.0%)

Yes, both medical and psychiatric conditions	0 (0.0%)	1 (5.3%)	1 (2.7%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Education: n (%)	(n=18)	(n=19)	(n=37)
O' levels/ GCSEs/ Level 1 or 2 NVQ	9 (50.0%)	14 (73.7%)	23 (62.2%)
A' Levels/ Level 3 NVQ	4 (22.2%)	2 (10.5%)	6 (16.2%)
University degree/ Graduate Certificate or Diploma	5 (27.8%)	3 (15.8%)	8 (21.6%)
Postgraduate university degree (e.g., PGCE, MSc, MA, PhD)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)

Appendix 16 Adherence ratings for each checklist item and module

Module	Mean adherence rating for module across courses *(SD, range)*	Item	Mean adherence rating for item across courses *(range)*
Orientation & behaviour change optimisation	1.98 (*SD*=0.08, 1.50-2.00)	1. Welcome	1.92 (1.50-2.00)
		2. Goals of this course	2.00 (2.00-2.00)
		3. What would you like from today?	2.00 (2.00-2.00)
		4. True or false?	2.00 (2.00-2.00)
		5. Taking on information (Kindness Questionnaire)	2.00 (2.00-2.00)
Basic epilepsy & first aid knowledge	1.86 (*SD*=0.37, 0.00-2.00	6. Epilepsy, seizures & how the brain works	2.00 (2.00-2.00)
		7. First aid for convulsive seizures exercise	2.00 (2.00-2.00)
		8. What can you do to help someone during a seizure?	2.00 (2.00-2.00)
		9. What not to do during a seizure	2.00 (2.00-2.00)
		10. What to do after the seizure has stopped	2.00 (2.00-2.00)
		11. Questions or comments?	2.00 (2.00-2.00)
		12. Post-seizure states	1.64 (1.00-2.00)
		13. Injuries	1.07 (0.00-2.00)
		14. When to call an ambulance?	1.92 (1.50-2.00)
		15. Questions or comments?	2.00 (2.00-2.00)
Recovery position	1.55 (*SD*=0.78, 0.00-2.00)	16. Recovery position I	0.79 (0.00-2.00)
		17. Recovery position II	2.00 (2.00-2.00)
		18. Let's practice the recovery position	1.71 (0.00-2.00)
		19. Questions or comments?	1.71 (0.00-2.00)

Module	Mean adherence rating for module across courses *(SD, range)*	Item	Mean adherence rating for item across courses *(range)*
Informing others about epilepsy & how to help if seizures occur	1.95 (*SD*=0.14, 1.50-2.00)	1. Who needs to know how to help?	1.93 (1.50-2.00)
		2. What they need to know & why	2.00 (2.00-2.00)
		3. How to get this information to them. Family, friends & work colleagues.	2.00 (2.00-2.00)
		4. How to get this information to them. Members of the public and health workers.	2.00 (2.00-2.00)
		5. Questions or comments?	1.86 (1.50-2.00)
Medical ID, seizure triggers & home safety	2.00 (*SD*=0.00, 2.00-2.00)	6. Personal stories - introduction	2.00 (2.00-2.00)
		7. Ben's story	2.00 (2.00-2.00)
		8. How to change what happened to Ben?	2.00 (2.00-2.00)
		9. Triggers	2.00 (2.00-2.00)
		10. Knowing your triggers	2.00 (2.00-2.00)
		11. Some ways of dealing with triggers	2.00 (2.00-2.00)
		12. Sandra's story	2.00 (2.00-2.00)
		13. How to change what happened to Sandra (Warning signs; home safety)	2.00 (2.00-2.00)
Summary & consolidating learning	1.77 (*SD*=0.50, 0.00-2.00)	14. Main points to remember, if you have epilepsy:	1.93 (1.50-2.00)
		15. Main points to remember, if you know someone with epilepsy:	2.00 (2.00-2.00)
		16. Sources of further information	1.57 (0.00-2.00)
		17. What's on the back table and accessing the study website	1.50 (0.00-2.00)
		18. Questions or comments?	1.86 (1.00-2.00)

Appendix 17 Number of Self-reported Epilepsy related ED visits

Outcome: Number of Epilepsy ED related visits		SAFE + TAU	TAU	Total
In the 12 months prior to baseline (T0)	N	24 (92.3%)	21 (84.0%)	45 (88.2%)
	Mean	4.2	8.4	6.2
	Standard deviation	2.91	22.75	15.63
	Minimum[b]	0	0	0
	Median	3.5	4.0	4.0
	Maximum	12	107	107
	Missing	2 (7.7%)	4 (16.0%)	6 (11.8%)
In the 12 months following randomisation according to participant self report	N	17 (65.4%)	17 (68.0%)	34 (67.7%)
	Mean	1.2	2.9	2.1
	Standard deviation	1.60	5.55	4.11
	Minimum	0	0	0
	Median	0	1	1
	Maximum	4	23	23
	Missing	9 (34.6%)	8 (32.0%)	17 (33.3%)
Change from baseline over 12 months following randomisation according to participant self report[a]	N	16 (61.5%)	14 (56.0%)	30 (58.8%)
	Mean	-2.6	-0.3	-1.5
	Standard deviation	2.83	6.17	4.75
	Minimum	-10	-10	-10
	Median	-2	-2	-2
	Maximum	1	18	18
	Missing	10 (38.5%)	11 (44.0%)	21 (41.2%)

Notes:

a. Calculated only for patient participants with a baseline and 12 month measure reported.

b. Four participants reported no ED visits in the 12 months prior to baseline, even though the inclusion criteria for eligibility into the trial required at least two ED visits in the 12 months prior to baseline. This reflects inaccuracy and inconsistency in self-reporting.

Appendix 18 Baseline scores of patients and SO participants and change over follow-up on secondary outcome measures

Quality of Life – Total QOLIE-31-P score (patient participants with complete CRF data)

Outcome: Total QOLIE-31-P score (range 0 to 100) [a]		**SAFE + TAU**	**TAU**	**Total**
Total QOLIE-31-P score at Baseline (T0)	N	23 (88.5%)	16 (64.0%)	39 (76.5%)
	Mean	51.2	44.1	48.3
	Standard deviation	18.4	14.92	17.25
	Minimum	17.7	17.1	17.1
	Median	48.8	42.6	46.3
	Maximum	78.7	79.5	79.5
	Missing	3 (11.5%)	9 (36.0%)	12 (23.5%)
Total QOLIE-31-P score at 6 months (T2)	N	16 (61.5%)	12 (48.0%)	28 (54.9%)
	Mean	49.5	43.0	46.7
	Standard deviation	21.86	10.46	17.92
	Minimum	10.4	20.4	10.4
	Median	50.2	45.1	47.7
	Maximum	85.7	59.8	85.7
	Missing	10 (38.5%)	13 (52.0%)	23 (45.1%)
Total QOLIE-31-P score at 12 months (T3)	N	10 (38.5%)	8 (32.0%)	18 (35.3%)
	Mean	47.6	42.9	45.5
	Standard deviation	20.35	12.23	16.93
	Minimum	9.7	23.8	9.7
	Median	48.6	48.6	47.0
	Maximum	72.9	57.0	72.9
	Missing	16 (61.5%)	17 (68.0%)	33 (64.7%)
Change in total QOLIE-31-P score from baseline at 6 months (T2)[b]	N	14 (53.8%)	8 (32.0%)	22 (43.1%)
	Mean	-5.9	-0.7	-4.0
	Standard deviation	13.81	8.57	12.20
	Minimum	-33.7	-12.0	-33.7
	Median	-6.5	-1.8	-3.2
	Maximum	18.7	12.9	18.7
	Missing	12 (46.2%)	17 (68.0%)	29 (56.9%)
Change in total QOLIE-31-P score from baseline at12 months (T3)[b]	N	10 (38.5%)	6 (24.0%)	16 (31.4%)
	Mean	0.8	-2.18	-0.3
	Standard deviation	10.72	10.48	10.38
	Minimum	-14.9	-19.5	-19.5
	Median	1.0	-0.9	0.2
	Maximum	20.5	12.9	20.5
	Missing	16 (61.5%)	19 (76.0%)	35 (68.6%)

Quality of Life – Total QOLIE-31-P score (patient participants with complete data following data imputation)

Outcome: Total QOLIE-31-P score (range 0 to 100)[a]		**SAFE + TAU**	**TAU**	**Total**
Total QOLIE-31-P score at Baseline (T0)	N	25 (96.2%)	24 (96.0%)	49 (96.1%)
	Mean	51.6	44.3	48.0
	Standard deviation	18.63	16.38	17.77
	Minimum	17.7	12.3	12.3
	Median	48.8	42.6	46.3
	Maximum	78.7	79.5	79.5
	Missing	1 (3.8%)	1 (4.0%)	2 (3.9%)
Total QOLIE-31-P score at 6 months (T2)	N	21 (80.8%)	14 (56.0%)	35 (68.6%)
	Mean	47.8	42.6	45.7
	Standard deviation	21.67	9.76	17.86
	Minimum	10.4	20.4	10.4
	Median	49.7	43.6	44.4
	Maximum	85.7	59.8	85.7
	Missing	5 (19.2%)	11 (44.0%)	16 (31.4%)
Total QOLIE-31-P score at 12 months (T3)	N	18 (69.2%)	12 (48.0%)	30 (58.8%)
	Mean	51.0	44.0	48.2
	Standard deviation	20.43	11.72	17.58
	Minimum	9.7	23.8	9.7
	Median	48.6	47.3	47.3
	Maximum	82.8	57.0	82.8
	Missing	8 (30.8%)	13 (52.0%)	21 (41.2%)
Change in total QOLIE-31-P score from baseline at 6 months (T2)[b]	N	20 (76.9%)	13 (52.0%)	33 (64.7%)
	Mean	-3.0	-0.8	-2.2
	Standard deviation	13.16	9.07	11.61
	Minimum	-33.7	-12.3	-33.7
	Median	-2.4	-1.6	-1.6
	Maximum	18.7	15.7	18.7
	Missing	6 (23.1%)	12 (48.0%)	18 (35.3%)
Change in total QOLIE-31-P score from baseline at12 months (T3)[b]	N	18 (69.2%)	12 (48.0%)	30 (58.9%)
	Mean	2.2	-1.9	0.6
	Standard deviation	11.27	12.13	11.59
	Minimum	-20.5	-22.7	-22.7
	Median	2.1	-0.9	1.0
	Maximum	20.5	18.6	20.5
	Missing	8 (30.8%)	13 (52.0%)	21 (41.2%)

a. Total QOLIE-31-P score ranges from 0 to 100, where higher scores correspond to a better quality of life

b. Calculated only for patient participants with a baseline and 12 month measure reported.

Caregiver Burden – Total burden score (significant other participants with complete CRF data)

Outcome: Total burden score (range 0 to 88)[a]		**SAFE + TAU**	**TAU**	**Total**
Total burden score at Baseline (T0)	N	17 (94.4%)	17 (89.5%)	34 (91.9%)
	Mean	15.8	20.6	18.2
	Standard deviation	11.01	13.59	12.42
	Minimum	0	0	0
	Median	14.0	19.0	15.5
	Maximum	45	45	45
	Missing	1 (5.6%)	2 (10.5%)	3 (8.1%)
Total burden score at 6 months (T2)	N	15 (83.3%)	8 (42.1%)	23 (62.2%)
	Mean	19.7	22.7	20.7
	Standard deviation	12.13	11.3	11.68
	Minimum	0	13	0
	Median	19	20	19
	Maximum	42	48	48
	Missing	3 (16.7%)	11 (57.9%)	14 (37.8%)
Total burden score at 12 months (T3)	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	19.5	24.9	22.1
	Standard deviation	16.24	15.83	15.88
	Minimum	0	7	0
	Median	15	20	18
	Maximum	48	54	54
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)
Change in total burden score from baseline at 6 months (T2)[b]	N	14 (77.8%)	7 (36.8%)	21 (56.8%)
	Mean	2.7	1.6	2.3
	Standard deviation	7.01	6.21	6.62
	Minimum	-9	-5	-9
	Median	1	1	1
	Maximum	20	12	20
	Missing	4 (22.2%)	12 (63.2%)	16 (43.2%)
Change in total burden score from baseline at 12 months (T3)[b]	N	10 (55.6%)	9 (47.4%)	19 (51.4%)
	Mean	1.4	0.8	1.1
	Standard deviation	10.04	8.38	9.04
	Minimum	-20	-12	-20
	Median	0.5	2.0	1.0
	Maximum	15	14	15
	Missing	8 (44.4%)	10 (52.6%)	18 (48.6%)

a. Total burden score ranges from 0 to 88 where higher scores correspond to a greater level of burden

b. Calculated only for SO participants with a baseline and 12 month measure reported

Caregiver Burden – Burden Categories (significant other participants with complete CRF data)

Outcome: Burden categories		SAFE + TAU	TAU	Total
Burden Categories at Baseline (T0)	Little or no burden	12 (66.7%)	10 (52.7%)	22 (59.5%)
	Mild to moderate burden	4 (22.2%)	5 (26.3%)	9 (24.3%)
	Moderate to severe burden	1 (5.6%)	2 (10.5%)	3 (8.1%)
	Severe burden	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	1 (5.6%)	2 (10.5%)	3 (8.1%)
Burden Categories at 6 months (T2)	Little or no burden	9 (50.0%)	4 (21.1%)	13 (35.1%)
	Mild to moderate burden	5 (27.7%)	3 (15.8%)	8 (21.6%)
	Moderate to severe burden	1 (5.6%)	1 (5.3%)	2 (5.4%)
	Severe burden	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	3 (16.7%)	11 (57.8%)	14 (37.8%)
Burden Categories at 12 months (T3)	Little or no burden	6 (33.3%)	5 (26.3%)	11 (29.7%)
	Mild to moderate burden	4 (22.2%)	3 (15.8%)	7 (18.9%)
	Moderate to severe burden	1 (5.6%)	2 (10.5%)	3 (8.1%)
	Severe burden	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

Caregiver Burden – Total burden score (all significant other participants, including those with missing CRF data)

Outcome: Total burden score (range 0 to 88)[a]		SAFE + TAU	TAU	Total
Total burden score at Baseline (T0)	N	18 (100.0%)	19 (100%)	37 (100.0%)
	Mean	17.1	20.7	18.9
	Standard deviation	12.00	13.03	12.51
	Minimum	0	0	0
	Median	14.5	19.0	16.0
	Maximum	45	45	45
	Missing[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total burden score at 6 months (T2)	N	16 (88.9%)	10 (52.6%)	26 (70.3%)
	Mean	19.4	22.7	20.7
	Standard deviation	11.78	9.98	11.04
	Minimum	0	13	0
	Median	19.0	22.0	19.5
	Maximum	42	48	48
	Missing[b]	2 (11.1%)	9 (47.4%)	11 (29.7%)
Total burden score at 12 months (T3)	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	19.5	24.9	22.1
	Standard deviation	16.24	15.83	15.88
	Minimum	0	7	0
	Median	15	20	18
	Maximum	48	54	54

	Missing[b]	7 (38.9%)	9 (47.4%)	16 (43.2%)
Change in total burden score from baseline at 6 months (T2)[c]	N	16 (88.9%)	10 (52.6%)	26 (70.3%)
	Mean	1.4	2.0	1.7
	Standard deviation	7.89	6.96	7.41
	Minimum	-15	-7	-15
	Median	0.0	1.5	0.5
	Maximum	20	13	20
	Missing	2 (11.1%)	9 (47.4%)	11 (29.7%)
Change in total burden score from baseline at 12 months (T3)[c]	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	2.1	0.9	1.5
	Standard deviation	9.79	7.91	8.74
	Minimum	-20	-12	-20
	Median	1	2	1
	Maximum	15	14	15
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

a. Total burden score ranges from 0 to 88 where higher scores correspond to a greater level of burden
b. 'Missing' participants had no data recorded for the outcome
c. Calculated only for SO participants with a baseline and 12 month measure reported

Caregiver Burden – Burden Categories (all significant other participants, including those with missing CRF data)

Outcome: Burden Categories		**SAFE + TAU**	**TAU**	**Total**
Burden Categories at Baseline (T0)	Little or no burden	12 (67.7%)	11 (57.9%)	23 (62.2%)
	Mild to moderate burden	5 (27.8%)	6 (31.6%)	11 (29.7%)
	Moderate to severe burden	1 (5.6%)	2 (10.5%)	3 (8.1%)
	Severe burden	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Burden Categories at 6 months (T2)	Little or no burden	10 (55.6%)	4 (21.1%)	14 (37.8%)
	Mild to moderate burden	5 (27.8%)	5 (26.3%)	10 (27.0%)
	Moderate to severe burden	1 (5.6%)	1 (5.3%)	2 (5.4%)
	Severe burden	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	2 (11.1%)	9 (47.4%)	11 (29.7%)
Burden Categories at 12 months (T3)	Little or no burden	6 (33.3%)	5 (26.3%)	11 (29.7%)
	Mild to moderate burden	4 (22.2%)	3 (15.8%)	7 (18.9%)
	Moderate to severe burden	1 (5.6%)	2 (10.5%)	3 (8.1%)
	Severe burden	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

Distress – Total anxiety score (patient participants with complete CRF data)

Outcome: Total anxiety score (range 0 to 21)[a]		**SAFE + TAU**	**TAU**	**Total**
Total anxiety score at Baseline (T0)	N	25 (96.2%)	25 (100.0%)	50 (98.0%)
	Mean	10.2	10.4	10.3
	Standard deviation	5.22	4.54	4.84
	Minimum	2	0	0
	Median	11	11	11
	Maximum	20	18	20
	Missing	1 (3.8%)	0 (0.0%)	1 (2.0%)
Total anxiety score at 12 months (T3)	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	10.8	10.6	10.7
	Standard deviation	5.49	3.18	4.46
	Minimum	3	5	3
	Median	10.5	10.0	10.0
	Maximum	19	16	19
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)
Change in total anxiety score from baseline at 12 months (T3)[b]	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	0.2	-0.6	-0.2
	Standard deviation	3.91	3.26	3.58
	Minimum	-7	-7	-7
	Median	-0.5	-1	-1
	Maximum	13	6	13.0
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

a. Total anxiety score ranges from 0 to 21, where higher scores correspond to higher levels of anxiety
b. Calculated only for patient participants with a baseline and 12 month measure reported

Distress – Anxiety Categories (patient participants with complete CRF data)

Outcome: Anxiety Categories		**SAFE + TAU**	**TAU**	**Total**
Anxiety Categories at Baseline (T0)	Normal range	9 (34.6%)	5 (20.0%)	14 (27.5%)
	Suggestive of anxiety	3 (11.5%)	7 (28.0%)	10 (19.6%)
	Probable anxiety	13 (50.0%)	13 (52.0%)	26 (50.9%)
	Missing	1 (3.8%)	0 (0.0%)	1 (2.0%)
Anxiety Categories at 12 months (T3)	Normal range	6 (33.3%)	2 (8.0%)	8 (15.6%)
	Suggestive of anxiety	3 (16.7%)	8 (32.0%)	11 (21.6%)
	Probable anxiety	9 (50.0%)	7 (28.0%)	16 (31.4%)
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

Distress – Total anxiety score (patient participants with complete data following data imputation)

Outcome: Total anxiety score (range 0 to 21)[a]		**SAFE + TAU**	**TAU**	**Total**
Total anxiety score at Baseline (T0)	N	25 (96.2%)	25 (100.0%)	50 (98.0%)
	Mean	10.2	10.4	10.3
	Standard deviation	5.22	4.54	4.84
	Minimum	2	0	0
	Median	11	11	11
	Maximum	20	18	20
	Missing	1 (3.8%)	0 (0.0%)	1 (2.0%)
Total anxiety score at 12 months (T3)	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	10.8	10.6	10.7
	Standard deviation	5.49	3.18	4.46
	Minimum	3	5	3
	Median	10.5	10.0	10.0
	Maximum	19	16	19
	Missing	8 (30.8%)	8 (40.0%)	16 (31.4%)
Change in total anxiety score from baseline at 12 months (T3)[b]	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	0.2	-0.6	-0.2
	Standard deviation	3.91	3.26	3.58
	Minimum	-7	-7	-7
	Median	-0.5	-1	-1
	Maximum	13	6	13.0
	Missing	8 (30.8%)	8 (40.0%)	16 (31.4%)

a. Total anxiety score ranges from 0 to 21, where higher scores correspond to higher levels of anxiety
b. Calculated only for patient participants with a baseline and 12 month measure reported

Distress – Anxiety Categories (patient participants with complete data following data imputation)

Outcome: Anxiety Categories		**SAFE + TAU**	**TAU**	**Total**
Anxiety Categories at Baseline (T0)	Normal range	9 (34.6%)	5 (20.0%)	14 (27.5%)
	Suggestive of anxiety	3 (11.5%)	7 (28.0%)	10 (19.6%)
	Probable anxiety	13 (50.0%)	13 (52.0%)	26 (50.9%)
	Missing	1 (3.8%)	0 (0.0%)	1 (2.0%)
Anxiety Categories at 12 months (T3)	Normal range	6 (33.3%)	2 (8.0%)	8 (15.6%)
	Suggestive of anxiety	3 (16.7%)	8 (32.0%)	11 (21.6%)
	Probable anxiety	9 (50.0%)	7 (28.0%)	16 (31.4%)
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

Distress – Total depression score (patient participants with complete CRF data)

Outcome: Total depression score (range 0 to 21)[a]		**SAFE + TAU**	**TAU**	**Total**
Total depression score at Baseline (T0)	N	23 (88.5%)	24 (96.0%)	47 (92.2%)
	Mean	6.6	8.7	7.7
	Standard deviation	4.51	4.67	4.66
	Minimum	0	0	0
	Median	7.0	8.5	7
	Maximum	17	19	19
	Missing	3 (11.5%)	1 (4.0%)	4 (7.8%)
Total depression score at 12 months (T3)	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	7.2	8.6	7.9
	Standard deviation	4.07	3.46	3.80
	Minimum	1	4	1
	Median	7	9	8
	Maximum	14	16	16
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)
Change in total depression score from baseline at 12 months (T3)[b]	N	16 (61.5%)	16 (64.0%)	32 (62.7%)
	Mean	-0.5	0.1	-0.2
	Standard deviation	1.97	2.90	2.46
	Minimum	-3	-5	-5
	Median	-0.5	1.0	0.0
	Maximum	3	5	5
	Missing	10 (38.5%)	9 (36.0%)	19 (37.3%)

a. Total depression score ranges from 0 to 21, where higher scores correspond to higher levels of depression
b. Calculated only for patient participants with a baseline and 12 month measure reported

Distress – Depression Categories (patient participants with complete CRF data)

Outcome: Depression Categories		**SAFE + TAU**	**TAU**	**Total**
Depression Categories at Baseline (T0)	Normal range	14 (53.9%)	10 (40.0%)	24 (47.1%)
	Suggestive of depression	5 (19.2%)	7 (28.0%)	12 (23.5%)
	Probable depression	4 (15.4%)	7 (28.0%)	11 (21.6%)
	Missing	3 (11.5%)	1 (4.0%)	4 (7.8%)
Depression Categories at 12 months (T3)	Normal range	10 (38.4%)	7 (28.0%)	17 (33.3%)
	Suggestive of depression	4 (15.4%)	4 (16.0%)	8 (15.7%)
	Probable depression	4 (15.4%)	6 (24.0%)	10 (19.6%)
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

Distress – Total depression score (patient participants with complete data following data imputation)

Outcome: Total depression score (range 0 to 21)[a]		**SAFE + TAU**	**TAU**	**Total**
Total depression score at Baseline (T0)	N	25 (96.2%)	25 (100.0%)	50 (98.0%)
	Mean	6.7	8.6	7.6
	Standard deviation	4.36	4.61	4.53
	Minimum	0	0	0
	Median	7	8	7.5
	Maximum	17	19	19
	Missing	1 (3.8%)	0 (0.0%)	1 (2.0%)
Total depression score at 12 months (T3)	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	7.2	8.6	7.9
	Standard deviation	4.07	3.46	3.80
	Minimum	1	4	1
	Median	7	9	8
	Maximum	14	16	16
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)
Change in total depression score from baseline at 12 months (T3)[b]	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	-0.2	0.5	0.1
	Standard deviation	2.39	3.16	2.77
	Minimum	-3.0	-5.0	-5.0
	Median	-0.5	1.0	0.0
	Maximum	5.8	6.2	6.2
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

a. Total depression score ranges from 0 to 21, where higher scores correspond to higher levels of depression
b. Calculated only for patient participants with a baseline and 12 month measure reported

Distress – Depression Categories (patient participants with complete data following data imputation)

Outcome: Depression Categories		**SAFE + TAU**	**TAU**	**Total**
Depression Categories at Baseline (T0)	Normal range	14 (53.8%)	11 (44.0%)	25 (49.0%)
	Suggestive of depression	7 (26.9%)	7 (28.0%)	14 (27.5%)
	Probable depression	4 (15.3%)	7 (28.0%)	11 (21.6%)
	Missing	1 (3.8%)	0 (0.0%)	1 (2.0%)
Depression Categories at 12 months (T3)	Normal range	10 (38.4%)	7 (28.0%)	17 (33.3%)
	Suggestive of depression	4 (15.3%)	4 (16.0%)	8 (15.7%)
	Probable depression	4 (15.3%)	6 (24.0%)	10 (19.6%)
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

Distress – Total anxiety score (significant other participants with complete CRF data)

Outcome: Total anxiety score (range 0 to 21)[a]		**SAFE + TAU**	**TAU**	**Total**
Total anxiety score at Baseline (T0)	N	17 (94.4%)	18 (94.7%)	35 (94.6%)
	Mean	8.4	7.9	8.1
	Standard deviation	4.21	4.37	4.24
	Minimum	2	0	0
	Median	9	10	9
	Maximum	15	14	15
	Missing	1 (5.6%)	1 (5.3%)	2 (5.4%)
Total anxiety score at 12 months (T3)	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	9.2	8.2	8.7
	Standard deviation	5.15	2.39	4.01
	Minimum	1	4	1
	Median	9	9	9
	Maximum	16	12	16
	Missing	7 (38.9%)	9 (47.8%)	16 (43.2%)
Change in total anxiety score from baseline at 12 months (T3)[b]	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	0.5	-0.5	0.0
	Standard deviation	2.70	3.13	2.88
	Minimum	-3	-5	-5
	Median	1	-1.5	-1
	Maximum	3	5	5
	Missing	7 (38.9%)	9 (47.8%)	16 (43.2%)

a. Total anxiety score ranges from 0 to 21, where higher scores correspond to higher levels of anxiety
b. Calculated only for SO participants with a baseline and 12 month measure reported

Distress – Anxiety Categories (significant other participants with complete CRF data)

Outcome: Anxiety Categories		**SAFE + TAU**	**TAU**	**Total**
Anxiety Categories at Baseline (T0)	Normal range	7 (38.9%)	7 (36.8%)	14 (37.8%)
	Suggestive of anxiety	4 (22.2%)	3 (15.8%)	7 (18.8%)
	Probable anxiety	6 (33.3%)	8 (42.1%)	14 (37.8%)
	Missing	1 (5.6%)	1 (5.3%)	2 (5.4%)
Anxiety Categories at 12 months (T3)	Normal range	4 (22.2%)	4 (21.1%)	8 (21.7%)
	Suggestive of anxiety	2 (11.1%)	5 (26.3%)	7 (18.9%)
	Probable anxiety	5 (27.8%)	1 (5.3%)	6 (16.2%)
	Missing	7 (38.9%)	9 (47.8%)	16 (43.2%)

Distress – Total anxiety score (significant other participants with complete data following data imputation)

Outcome: Total anxiety score (range 0 to 21)[a]		**SAFE + TAU**	**TAU**	**Total**
Total anxiety score at Baseline (T0)	N	18 (100.0%)	19 (100.0%)	37 (100.0%)
	Mean	8.4	8.3	8.3
	Standard deviation	4.09	4.47	4.23
	Minimum	2	0.0	0.0
	Median	9.0	10.0	9.3
	Maximum	15	14	15
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total anxiety score at 12 months (T3)	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	9.2	8.2	8.7
	Standard deviation	5.15	2.39	4.01
	Minimum	1	4	1
	Median	9	9	9
	Maximum	16	12	16
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)
Change in total anxiety score from baseline at 12 months (T3)[b]	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	0.5	-0.5	0.0
	Standard deviation	2.70	3.13	2.88
	Minimum	-3	-5	-5
	Median	1.0	-1.5	-1.0
	Maximum	3	5	5
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

a. Total anxiety score ranges from 0 to 21, where higher scores correspond to higher levels of anxiety
b. Calculated only for SO participants with a baseline and 12 month measure reported

Distress – Anxiety Categories (significant other participants with complete data following data imputation)

Outcome: Anxiety Categories		**SAFE + TAU**	**TAU**	**Total**
Anxiety Categories at Baseline (T0)	Normal range	7 (38.9%)	7 (36.8%)	14 (37.8%)
	Suggestive of anxiety	5 (27.8%)	3 (15.8%)	8 (21.7%)
	Probable anxiety	6 (33.3%)	9 (47.4%)	15 (40.5%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anxiety Categories at 12 months (T3)	Normal range	4 (22.2%)	4 (21.1%)	8 (21.7%)
	Suggestive of anxiety	2 (11.1%)	5 (26.3%)	7 (18.9%)
	Probable anxiety	5 (27.8%)	1 (5.3%)	6 (16.2%)
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

Distress – Total depression score (significant other participants with complete CRF data)

Outcome: Total depression score (range 0 to 21)[a]		**SAFE + TAU**	**TAU**	**Total**
Total depression score at Baseline (T0)	N	18 (100.0%)	19 (100.0%)	37 (100.0%)
	Mean	4.3	3.4	3.8
	Standard deviation	4.40	2.65	3.59
	Minimum	0	0	0
	Median	2.5	3.0	3.0
	Maximum	12	8	12
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total depression score at 12 months (T3)	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	5.2	5.1	5.1
	Standard deviation	3.60	3.60	3.51
	Minimum	0	0	0
	Median	5	5	5
	Maximum	12	11	12
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)
Change in total depression score from baseline at 12 months (T3)[a]	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	-0.4	1.3	0.4
	Standard deviation	3.14	1.83	2.68
	Minimum	-9	-1	-9
	Median	0	1	1
	Maximum	3	4	4
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

a. Total depression score ranges from 0 to 21, where higher scores correspond to higher levels of depression
b. Calculated only for SO participants with a baseline and 12 month measure reported

Distress – Depression Categories (significant other participants with complete CRF data)

Outcome: Depression Categories		**SAFE + TAU**	**TAU**	**Total**
Depression Categories at Baseline (T0)	Normal range	14 (77.8%)	18 (94.7%)	32 (86.5%)
	Suggestive of depression	1 (5.6%)	1 (5.3%)	2 (5.4%)
	Probable depression	3 (16.7%)	0 (0.0%)	3 (8.1%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Depression Categories at 12 months (T3)	Normal range	7 (38.9%)	8 (42.1%)	15 (40.6%)
	Suggestive of depression	3 (16.7%)	1 (5.3%)	4 (10.8%)
	Probable depression	1 (5.6%)	1 (5.3%)	2 (5.4%)
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

Distress – Total depression score (significant other participants with complete data following data imputation)

Outcome: Total depression score (range 0 to 21)[a]		**SAFE + TAU**	**TAU**	**Total**
Total depression score at Baseline (T0)	N	18 (100.0%)	19 (100.0%)	37 (100.0%)
	Mean	4.3	3.4	3.8
	Standard deviation	4.40	2.65	3.59
	Minimum	0	0	0
	Median	2.5	3.0	3
	Maximum	12	8	12
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total depression score at 12 months (T3)	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	5.2	5.1	5.1
	Standard deviation	3.60	3.60	3.51
	Minimum	0	0	0
	Median	5	5	5
	Maximum	12	11	12
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)
Change in total depression score from baseline at 12 months (T3)[a]	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	-0.4	1.3	0.4
	Standard deviation	3.14	1.83	2.68
	Minimum	-9	-1	-9
	Median	0	1	1
	Maximum	3	4	4
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

a. Total depression score ranges from 0 to 21, where higher scores correspond to higher levels of depression

a. Calculated only for SO participants with a baseline and 12 month measure reported

Distress – Depression Categories (significant other participants with complete data following data imputation)

Outcome: Depression Categories		**SAFE + TAU**	**TAU**	**Total**
Depression Categories at Baseline (T0)	Normal range	14 (77.8%)	18 (94.7%)	32 (86.5%)
	Suggestive of depression	1 (5.6%)	1 (5.3%)	2 (5.4%)
	Probable depression	3 (16.7%)	0 (0.0%)	3 (8.1%)
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Depression Categories at 12 months (T3)	Normal range	7 (38.9%)	8 (42.1%)	15 (40.6%)
	Suggestive of depression	3 (16.7%)	1 (5.3%)	4 (10.8%)
	Probable depression	1 (5.6%)	1 (5.3%)	2 (5.4%)
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

Stigma – Total stigma score (patient participants with complete CRF data)

Outcome: Total stigma score (range 0 to 9)[a]		**SAFE + TAU**	**TAU**	**Total**
Total stigma score at Baseline (T0)	N	24 (92.3%)	24 (96.0%)	48 (94.1%)
	Mean	3.2	4.1	3.6
	Standard deviation	2.45	3.26	2.89
	Minimum	0	0	0
	Median	3	3	3
	Maximum	7	9	9
	Missing	2 (7.7%)	1 (4.0%)	3 (5.9%)
Total stigma score at 12 months (T3)	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	3.2	3.9	3.5
	Standard deviation	2.57	3.03	2.79
	Minimum	0	0	0
	Median	3.5	3.0	3.0
	Maximum	8	9	9
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)
Change in total stigma score from baseline at 12 months (T3)[a]	N	17 (65.4%)	17 (68.0%)	34 (66.7%)
	Mean	-0.1	0.3	0.1
	Standard deviation	2.30	1.79	2.04
	Minimum	-6	-2	-6
	Median	0	0	0
	Maximum	4	4	4
	Missing	9 (34.6%)	8 (32.0%)	17 (33.3%)

a. Total stigma scores (ranging from 0 to 9 where higher scores correspond to higher levels of stigma)
b. Calculated only for patient participants with a baseline and 12 month measure reported

Stigma – Stigma Categories (patient participants with complete CRF data)

Outcome: Stigma Categories		**SAFE + TAU**	**TAU**	**Total**
Stigma Categories at Baseline (T0)	No stigma	4 (15.4%)	3 (12.0%)	7 (13.7%)
	Mildly to moderately stigmatized	13 (50.0%)	13 (52.0%)	26 (51.0%)
	Highly Stigmatized	7 (26.9%)	8 (32.0%)	15 (29.4%)
	Missing	2 (7.7)	1 (4.0%)	3 (5.9%)
Stigma Categories at 12 months (T3)	No stigma	4 (15.4%)	3 (12.0%)	7 (13.7%)
	Mildly to moderately stigmatized	10 (38.4%)	8 (32.0%)	18 (35.3%)
	Highly Stigmatized	4 (15.4%)	6 (24.0%)	10 (19.6%)
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

Stigma – Total stigma score (all patient participants, including those with missing CRF data)

Outcome: Total stigma score (range 0 to 9)[a]		**SAFE + TAU**	**TAU**	**Total**
Total stigma score at Baseline (T0)	N	25 (96.2%)	24 (96.0%)	49 (96.8%)
	Mean	3.2	4.1	3.6
	Standard deviation	2.41	3.26	2.87
	Minimum	0	0	0
	Median	3	3	3
	Maximum	7	9	9
	Missing[b]	1 (3.8%)	1 (4.0%)	2 (3.9%)
Total stigma score at 12 months (T3)	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	3.2	3.9	3.5
	Standard deviation	2.57	3.03	2.79
	Minimum	0	0	0
	Median	3.5	3.0	3.0
	Maximum	8	9	9
	Missing[b]	8 (30.8%)	8 (32.0%)	16 (31.4%)
Change in total stigma score from baseline at 12 months (T3)[c]	N	17 (65.4%)	17 (68.0%)	34 (66.7%)
	Mean	-0.1	0.3	0.1
	Standard deviation	2.30	1.79	2.04
	Minimum	-6	-2	-6
	Median	0	0	0
	Maximum	4	4	4
	Missing	9 (34.6%)	8 (32.0%)	17 (33.3%)

a. Total stigma scores (ranging from 0 to 9 where higher scores correspond to higher levels of stigma)
b. 'Missing' participants had no data recorded for the outcome
c. Calculated only for patient participants with a baseline and 12 month measure reported

Stigma – Stigma Categories (all patient participants, including those with missing CRF data)

Outcome: Stigma Categories		**SAFE + TAU**	**TAU**	**Total**
Stigma Categories at Baseline (T0)	No stigma	4 (15.4%)	3 (12.0%)	7 (13.7%)
	Mildly to moderately stigmatized	14 (53.9%)	13 (52.0%)	27 (52.9%)
	Highly Stigmatized	7 (26.9%)	8 (32.0%)	15 (29.4%)
	Missing	1 (3.8%)	1 (4.0%)	2 (3.9%)
Stigma Categories at	No stigma	4 (15.4%)	3 (12.0%)	7 (13.7%)
	Mildly to moderately stigmatized	10 (38.4%)	8 (32.0%)	18 (35.3%)

12 months (T3)	Highly Stigmatized	4 (15.4%)	6 (24.0%)	10 (19.6%)
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

Fear of seizures – Total fear score (patient participants with complete CRF data)

Outcome: Total fear score (range 5 to 30)[a]		**SAFE + TAU**	**TAU**	**Total**
Total fear score at Baseline (T0)	N	16 (61.5%)	9 (36.0%)	25 (49.0%)
	Mean	16.4	17.6	16.8
	Standard deviation	5.48	4.77	5.16
	Minimum	6	8	6
	Median	17	18	17
	Maximum	24	25	25
	Missing	10 (38.5%)	16 (64.0%)	26 (51.0%)
Total fear score at 12 months (T3)	N	8 (30.8%)	5 (20.0%)	13 (25.5%)
	Mean	15.5	20.8	17.5
	Standard deviation	5.32	2.49	5.07
	Minimum	8	17	8
	Median	16	21	18
	Maximum	23	23	23
	Missing	18 (69.2%)	20 (80.0%)	38 (74.5%)
Change in total fear score from baseline at 12 months (T3)[b]	N	6 (23.1%)	3 (12.0%)	9 (17.6%)
	Mean	-1.5	2.0	-0.3
	Standard deviation	2.66	1.00	2.78
	Minimum	-6	1	-6
	Median	-1.5	2.0	0.0
	Maximum	2	3	3
	Missing	20 (76.9%)	22 (88.0%)	42 (82.4%)

a. Total fear scores (ranging from 5 to 30, where higher scores correspond to greater levels of fear)

b. Calculated only for patient participants with a baseline and 12 month measure reported

Fear of seizures – Total fear score (all patient participants, including those with missing CRF data)

Outcome: Total fear score (range 5 to 30)[a]		**SAFE + TAU**	**TAU**	**Total**
Total fear score at Baseline (T0)	N	23 (88.5%)	23 (92.0%)	46 (90.2%)
	Mean	15.2	13.6	14.4
	Standard deviation	5.32	5.80	5.56
	Minimum	5	3[d]	3[d]
	Median	16	14	14
	Maximum	24	25	25
	Missing[b]	3 (11.5%)	2 (8.0%)	5 (9.8%)
Total fear score at 12 months (T3)	N	16 (61.5%)	17 (68.0%)	33 (64.7%)
	Mean	14.4	16.0	15.2
	Standard deviation	4.88	4.15	4.52
	Minimum	5	10	5
	Median	15	16	16
	Maximum	23	23	23
	Missing[b]	10 (38.5%)	8 (32.0%)	18 (35.3%)
Change in total fear score from baseline at 12 months (T3)[c]	N	15 (57.7%)	17 (68.0%)	32 (62.8%)
	Mean	0.6	1.5	1.1
	Standard deviation	4.03	7.25	5.89
	Minimum	-6	-10	-10
	Median	0	1	0
	Maximum	9	18	18
	Missing	11 (42.3%)	8 (32.0%)	19 (37.2%)

a. Total fear scores (ranging from 5 to 30, where higher scores correspond to greater levels of fear)
b. Missing' participants had no data recorded for the outcome
c. Calculated only for patient participants with a baseline and 12 month measure reported
d. Minimum reported score less than minimum possible score of 5 due to missing data treated as zeros

Fear of seizures – Total fear score (significant other participants with complete CRF data)

Outcome: Total fear score (range 5 to 30)[a]		**SAFE + TAU**	**TAU**	**Total**
Total fear score at Baseline (T0)	N	6 (33.3%)	4 (21.1%)	10 (27.0%)
	Mean	15.5	16.0	15.7
	Standard deviation	3.45	3.92	3.43
	Minimum	10	11	10
	Median	15.5	16.5	15.5

	Maximum	20	20	20
	Missing	12 (66.7%)	21 (78.9%)	27 (73.0%)
Total fear score at 12 months (T3)	N	6 (33.3%)	2 (10.5%)	8 (21.6%)
	Mean	20.7	22.5	21.1
	Standard deviation	3.78	0.71	3.31
	Minimum	16	22	16
	Median	22.0	22.5	22.5
	Maximum	24	23	24
	Missing	12 (67.7%)	17 (89.5%)	29 (78.4%)
Change in total fear score from baseline at 12 months (T3)[b]	N	3 (16.7%)	0	3 (8.8%)
	Mean	6.7	NA	6.7
	Standard deviation	7.02	NA	7.02
	Minimum	0	NA	0
	Median	6	NA	6.0
	Maximum	14	NA	14
	Missing	15 (83.3%)	19 (100.0%)	34 (91.2%)

a. Total fear score ranges from 5 to 30, where higher scores correspond to greater levels of fear
b. Calculated only for SO participants with a baseline and 12 month measure reported

NA – no SO participants in the TAU group had complete CRF data at both Baseline (T0) and at 12 months (T3), therefore change in total fear score could not be calculated

Fear of seizures – Total fear score (all significant other participants, including those with missing CRF data)

Outcome: Total fear score (range 5 to 30)[a]		**SAFE + TAU**	**TAU**	**Total**
Total fear score at Baseline (T0)	N	16 (88.9%)	17 (89.5%)	33 (89.2%)
	Mean	13.8	12.4	13.1
	Standard deviation	4.83	5.10	4.95
	Minimum	4[d]	1[d]	1[d]
	Median	14.5	13.0	14.0
	Maximum	20	20	20
	Missing[b]	2 (11.1%)	2 (10.5%)	4 (10.8%)
Total fear score at 12 months (T3)	N	11 (61.1%)	9 (47.4%)	20 (54.0%)
	Mean	15.6	16.0	15.8
	Standard deviation	6.59	5.00	5.78
	Minimum	5	9	5
	Median	16	16	16
	Maximum	24	23	24
	Missing[b]	7 (38.9%)	10 (52.6%)	17 (46.0%)
Change in total fear score from	N	9 (50.0%)	8 (42.1%)	17 (45.9%)
	Mean	2.2	1.9	2.1
	Standard deviation	5.40	4.76	4.96
	Minimum	-4	-5	-5

baseline at 12 months (T3)[c]	Median	0.0	2.5	0.0
	Maximum	14	7	14
	Missing	9 (50.0%)	11 (57.9%)	20 (54.1%)

a. Total fear score ranges from 5 to 30, where higher scores correspond to greater levels of fear
b. 'Missing' participants had no data recorded for the outcome
c. Calculated only for SO participants with a baseline and 12 month measure reported
d. Minimum reported score less than minimum possible score of 5 due to missing data treated as zeros

Confidence in managing seizures/ epilepsy – Total mastery score (patient participants with complete CRF data)

Outcome: Total mastery score (range 6 to 24)[a]		**SAFE + TAU**	**TAU**	**Total**
Total mastery score at Baseline (T0)	N	26 (100.0%)	21 (84.0%)	47 (92.3%)
	Mean	13.9	12.1	13.1
	Standard deviation	2.86	2.95	3.00
	Minimum	8	7	7
	Median	14	12	13
	Maximum	20	19	20
	Missing	0 (0.0%)	4 (16.0%)	4 (7.8%)
Total mastery score at 6 months (T2)	N	21 (84.6%)	15 (60.0%)	36 (70.6%)
	Mean	12.7	11.7	12.3
	Standard deviation	3.89	2.97	3.53
	Minimum	7	6	6
	Median	11	12	11
	Maximum	21	17	21
	Missing	4 (15.4%)	10 (40.0%)	15 (29.4%)
Total mastery score at 12 months (T3)	N	18 (69.2%)	16 (64.0%)	34 (66.7%)
	Mean	13.8	11.3	12.6
	Standard deviation	3.47	2.60	3.29
	Minimum	9	6	6
	Median	13.5	12.0	12.0
	Maximum	21	16	21
	Missing	8 (30.8%)	9 (36.0%)	17 (33.3%)
Change in total mastery score from baseline at 6 months (T2)[b]	N	21 (80.8%)	12 (48.0%)	33 (64.7%)
	Mean	-0.7	-1.4	-0.9
	Standard deviation	3.71	3.34	3.54
	Minimum	-8	-8	-8
	Median	-1	-2	-1
	Maximum	8	4	8
	Missing	5 (19.2%)	13 (52.0%)	18 (35.3%)
Change in total mastery score	N	18 (69.2%)	14 (56.0%)	32 (62.7%)
	Mean	0.2	-1.1	-0.4
	Standard deviation	2.96	3.41	3.17
	Minimum	-5	-9	-9

from baseline at 12 months (T3)[b]	Median	0.5	-1.0	0.0
	Maximum	6	3	6
	Missing	8 (30.8%)	11 (44.0%)	19 (37.3%)

a. Total mastery score ranges between 6 and 24, where higher scores correspond to higher levels of mastery
b. Calculated only for patient participants with a baseline and 12 month measure reported

Confidence in managing seizures/ epilepsy – Total mastery score (all patient participants, including those with missing CRF data)

Outcome: Total mastery score (range 6 to 24) [a]		**SAFE + TAU**	**TAU**	**Total**
Total mastery score at Baseline (T0)	N	26 (100.0%)	25 (100.0%)	51 (100%)
	Mean	13.9	11.4	12.7
	Standard deviation	2.86	3.50	3.40
	Minimum	8	3[c]	3[c]
	Median	14	12	13
	Maximum	20	19	20
	Missing[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total mastery score at 6 months (T2)	N	22 (84.6%)	17 (68.0%)	39 (76.5%)
	Mean	12.3	11.4	11.9
	Standard deviation	4.32	2.91	3.76
	Minimum	3[d]	6	3[d]
	Median	11	11	11
	Maximum	21	17	21
	Missing[b]	4 (15.4%)	8 (32.0%)	12 (23.5%)
Total mastery score at 12 months (T3)	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	13.8	11.5	12.7
	Standard deviation	3.47	2.60	3.25
	Minimum	9	6	6
	Median	13.5	12.0	12.0
	Maximum	21	16	21
	Missing[b]	8 (30.8%)	8 (32.0%)	16 (31.4%)
Change in total mastery score from baseline at 6 months (T2)[c]	N	22 (84.6%)	17 (68.0%)	39 (76.5%)
	Mean	-1.2	-0.2	-0.8
	Standard deviation	4.35	4.25	4.28
	Minimum	-12	-8	-12
	Median	-1	-1	-1
	Maximum	8	11	11
	Missing	4 (15.4%)	8 (32.0%)	12 (23.5%)
Change in total mastery score	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	0.2	-0.5	-0.2
	Standard deviation	2.96	3.36	3.13
	Minimum	-5	-9	-9

from baseline at 12 months (T3)[c]	Median	0.5	0.0	0.0
	Maximum	6	3	6
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

a. Total mastery score ranges between 6 and 24, where higher scores correspond to higher levels of mastery
b. 'Missing' participants had no data recorded for the outcome
c. Calculated only for patient participants with a baseline and 12 month measure reported
d. Minimum reported score less than minimum possible score of 6 due to missing data treated as zeros.

Confidence in managing seizures/ epilepsy – Total confidence score (significant other participants with complete CRF data)

Outcome: Total confidence score (range 1 to 5)[a]		**SAFE + TAU**	**TAU**	**Total**
Total confidence score at Baseline (T0)	N	18 (100.0%)	19 (100.0%)	37 (100.0%)
	Mean	3.5	3.8	3.6
	Standard deviation	0.62	0.72	0.69
	Minimum	2.0	2.3	2.0
	Median	3.5	3.8	3.7
	Maximum	4.5	5.0	5.0
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total confidence score at 6 months (T2)	N	16 (88.9%)	9 (47.4%)	25 (67.6%)
	Mean	4.2	3.9	4.1
	Standard deviation	0.75	0.71	0.73
	Minimum	2.7	2.8	2.7
	Median	4.1	4.0	4.0
	Maximum	5.0	4.8	5.0
	Missing	2 (11.1%)	10 (52.6%)	12 (32.4%)
Total confidence score at 12 months (T3)	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	4.3	4.1	4.2
	Standard deviation	0.57	0.99	0.78
	Minimum	3.5	2.2	2.2
	Median	4.2	4.7	4.3
	Maximum	5.0	5.0	5.0
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)
Change in total confidence score from baseline at 6 months (T2)[b]	N	16 (88.9%)	9 (47.4%)	25 (67.6%)
	Mean	0.6	0.2	0.5
	Standard deviation	0.70	0.32	0.61
	Minimum	-0.8	-0.2	-0.8
	Median	0.6	0.2	0.2
	Maximum	1.7	0.8	1.7
	Missing	3 (11.1%)	10 (52.6%)	12 (32.4%)
Change in total confidence score	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	0.7	0.3	0.5
	Standard deviation	0.49	0.43	0.50

from baseline at 12 months (T3)[b]	Minimum	0.0	-0.2	-0.2
	Median	0.7	0.3	0.5
	Maximum	1.7	1.0	1.7
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

b. Total confidence score range between 1 and 5, where higher scores correspond to higher levels of confidence
c. Calculated only for SO participants with a baseline and 12 month measure reported

Confidence in managing seizures/ epilepsy – Total confidence score (all significant other participants, including those with missing CRF data)

Outcome: Total confidence score (range 1 to 5)[a]		**SAFE + TAU**	**TAU**	**Total**
Total confidence score at Baseline (T0)	N	18 (100.0%)	19 (100.0%)	37 (100.0%)
	Mean	3.5	3.8	3.6
	Standard deviation	0.62	0.72	0.69
	Minimum	2.0	2.3	2.0
	Median	3.5	3.8	3.7
	Maximum	4.5	5.0	5.0
	Missing[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total confidence score at 6 months (T2)	N	16 (88.9%)	9 (47.4%)	25 (67.6%)
	Mean	4.2	3.9	4.1
	Standard deviation	0.75	0.71	0.73
	Minimum	2.7	2.8	2.7
	Median	4.1	4.0	4.0
	Maximum	5.0	4.8	5.0
	Missing[b]	2 (11.1%)	10 (52.6%)	12 (32.4%)
Total confidence score at 12 months (T3)	N	11 (61.1%)	10 (52.6%)	21 (56.6%)
	Mean	4.3	4.1	4.2
	Standard deviation	0.57	0.99	0.78
	Minimum	3.5	2.2	2.2
	Median	4.2	4.7	4.3
	Maximum	5.0	5.0	5.0
	Missing[b]	7 (38.9%)	9 (47.4%)	16 (43.24%)
Change in total confidence score from baseline at 6 months (T2)[c]	N	16 (88.9%)	9 (47.4%)	25 (67.6%)
	Mean	0.6	0.2	0.5
	Standard deviation	0.70	0.32	0.61
	Minimum	-0.8	-0.2	-0.8
	Median	0.6	0.2	0.2
	Maximum	1.7	0.8	1.7
	Missing	3 (11.1%)	10 (52.6%)	12 (32.4%)
Change in total confidence score	N	11 (61.1%)	10 (52.6%)	21 (56.8%)
	Mean	0.7	0.3	0.5
	Standard deviation	0.49	0.43	0.50
	Minimum	0.0	-0.2	-0.2

from baseline at 12 months (T3)[c]	Median	0.7	0.3	1.0
	Maximum	1.7	1.0	1.7
	Missing	7 (38.9%)	9 (47.4%)	16 (43.2%)

a. Total confidence score range between 1 and 5, where higher scores correspond to higher levels of confidence
b. Missing' participants had no data recorded for the outcome
c. Calculated only for SO participants with a baseline and 12 month measure reported

Knowledge of what to do when faced with a seizure – Total knowledge score (patient participants)

Outcome: Knowledge score (range 0 to 13)[a]		**SAFE + TAU**	**TAU**	**Total**
Knowledge score at Baseline (T0)	N	26 (100.0%)	25 (100.0%)	51 (100%)
	Mean	9.0	9.0	9.0
	Standard deviation	4.05	4.19	4.08
	Minimum	0	0	0
	Median	10	11	11
	Maximum	13	13	13
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Knowledge score at 12 months (T3)	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	9.4	9.4	9.4
	Standard deviation	3.68	3.69	3.63
	Minimum	1	3	1
	Median	10.5	11.0	6.0
	Maximum	13	13	13
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)
Change in knowledge score from baseline at 12 months (T3)[b]	N	18 (69.2%)	17 (68.0%)	35 (68.6%)
	Mean	-0.4	0.8	0.1
	Standard deviation	3.62	3.15	3.41
	Minimum	-8	-8	-8
	Median	0	1	0
	Maximum	7	5	7
	Missing	8 (30.8%)	8 (32.0%)	16 (31.4%)

a. Knowledge score is calculated based on the number of questions about epilepsy answered correctly out of a total of 13
b. Calculated only for patient participants with a baseline and 12 month measure reported

Knowledge of what to do when faced with a seizure – Total knowledge score (significant other participants)

Outcome: Knowledge score (range 0 to 13)[a]		**SAFE + TAU**	**TAU**	**Total**
Knowledge score at Baseline (T0)	N	18 (100.0%)	19 (100.0%)	37 (100.0%)
	Mean	9.9	7.7	8.8
	Standard deviation	3.07	4.19	3.81
	Minimum	4	1	1
	Median	11	7	9
	Maximum	13	13	13
	Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Knowledge score at 12 months (T3)	N	15 (83.3%)	13 (68.4%)	28 (75.7%)
	Mean	7.4	8.15	7.8
	Standard deviation	5.36	5.40	5.29
	Minimum	0	0	0
	Median	9	11	9.5
	Maximum	13	13	13
	Missing	3 (16.7%)	6 (31.6%)	9 (24.3%)
Change in knowledge score from baseline at 12 months (T3)[b]	N	15 (83.3%)	13 (68.4%)	28 (75.7%)
	Mean	-2.0	-0.8	-1.5
	Standard deviation	5.03	5.01	4.96
	Minimum	-12	-12	-12
	Median	0	0	0
	Maximum	4	8	8
	Missing	3 (16.7%)	6 (31.6%)	9 (24.3%)

a. Knowledge score is calculated based on the number of questions about epilepsy answered correctly out of a total of 13

b. Calculated only for SO participants with a baseline and 12 month measure reported

Appendix 19 Adverse events occurring during pilot trial in descending order, according to frequency overall

Adverse event		**SAFE + TAU**		**TAU**		**Total**	
Category of events (e.g. body system)	Event	Events (n)	Patients [n(%)]	Events (n)	Patients [n(%)]	Events (n)	Patients [n(%)]
Eyes, ear, nose, throat	Problem with eyes and sinuses	0	0 (0.0%)	1	1 (9.1%)	1	1 (5.6%)
Genito-urinary	Overnight hospital admission required due to urinary tract infection (pre existing)	0	0 (0.0%)	1	1 (9.1%)	1	1 (5.6%)
Haematological	Dislocated shoulder	0	0 (0.0%)	1	1 (9.1%)	1	1 (5.6%)
Neoplasia	Change in seizure pattern [a]	1	1 (14.3%)	0	0 (0.0%)	1	1 (5.6%)
	Increase in seizure frequency [a]	1	1 (14.3%)	0	0 (0.0%)	1	1 (5.6%)
Neurological	Increased seizures, medications changed	1	1 (14.3%)	3	3 (27.3%)	4	4 (22.2%)
	Increased seizures (shift patterns at work)	1	1 (14.3%)	0	0 (0.0%)	1	1 (5.6%)
	New seizure type; frequent absence seizures as well as usual seizure types	1	1 (14.3%)	0	0 (0.0%)	1	1 (5.6%)
	Seizure frequency sodium levels requiring in patient monitoring	0	0 (0.0%)	1	1 (9.1%)	1	1 (5.6%)
	Seizures more severe (tonic clonic)	0	0 (0.0%)	1	1 (9.1%)	1	1 (5.6%)
	Vagus Nerve Stimulation not working properly, going to hospital for observation	0	0 (0.0%)	1	1 (9.1%)	1	1 (5.6%)
Respiratory	Increases number of seizures due to chest infection and antibiotics	0	0 (0.0%)	1	1 (9.1%)	1	1 (5.6%)
Other:	Gynae-pregnancy. Increase in the number of fits due to being pregnant / just given birth	0	0 (0.0%)	2	1 (9.1%)	2	1 (5.6%)
	Diagnosis of status epilepticus	1	1 (14.3%)	0	0 (0.0%)	1	1 (5.6%)
	Vertigo	0	0 (0.0%)	1	1 (9.1%)	1	1 (5.6%)
Total		6	6 (100.0%)	13	11 (100.0%)	19	18 (100.0%)

Notes: Two participants were under investigation to determine whether a brain tumour could be the cause of their seizure changes; hence 'Body System' is classified as 'Neoplasia' rather than 'Neurological.'