

Seizure First Aid Training for people with epilepsy who attend emergency departments, and their family and friends: intervention development and pilot.

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General Information

This document describes the Seizure First Aid Training project (intervention development and pilot trial) and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated as appropriate. Clinical problems relating to this project should be referred to the Chief Investigator via the CTRC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, and CTRC Standard Operating Procedures.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for children (Medicines for Children Clinical Trials Unit – MC CTU), cancer (The Liverpool Cancer Trials Unit; LCTU), epilepsy, oral health and obstetrics and gynecology (<http://www.ctrc.org.uk/>). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

The CTRC epilepsy portfolio is part of the Liverpool Epilepsy Research Group (LERG), which has an international reputation for undertaking clinically - based research in epilepsy, and the group's portfolio ranges from fundamental science through to health service research. The Liverpool group has led the three largest randomized controlled trials in epilepsy to date, including SANAD I, MESS and the MRC antiepileptic drug withdrawal study.

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Glossary

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CTRC	Clinical Trials Research Centre
ED	Emergency Department
ES	Epilepsy Society
GP	General Practitioner
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
MREC	Multi-centre Research Ethics Committee
PI	Principal Investigator
PWE	People with epilepsy
RCT	Randomised Controlled Trial
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
TAU	Treatment As Usual
TMG	Trial Management Group
TSC	Trial Steering Committee

1 PROTOCOL SUMMARY

Title: Seizure First Aid Training for people with epilepsy who attend emergency departments, and their family and friends: intervention development and pilot.

Phase: Project PART A Intervention development: Develop Seizure First Aid Training for people with epilepsy (PWE) who attend emergency departments (ED) for epilepsy, and their informal carers.

Project Part B-Complete a pilot Randomised Controlled Trial (RCT) to assess the feasibility and optimum design of a future, definitive RCT to test Seizure First Aid Training's efficacy.

Population: Part A-Representatives from professional groups caring for PWE in some form will feedback on an existing seizure awareness course developed by the Epilepsy Society (ES) and changes needed for ED population.

20 PWE aged 16+ and one of their carers will also attend a development course and feedback on how the existing course should be refined.

Part B- EDs will help identify 80 patients (who will in turn identify a carer to take part with)

Patient inclusion criteria:

- Established diagnosis of epilepsy (1+ year);
- All epilepsy syndromes and all types of focal and generalised seizures;
- Currently being prescribed antiepileptic medication;
- Age 16+ (no upper age limit);
- Visited an ED for epilepsy on 2+ occasions within the previous 12 months (as reported by patient);
- Able to provide informed consent, participate in Seizure First Aid Training and independently complete questionnaires in English.

Patient exclusion criteria:

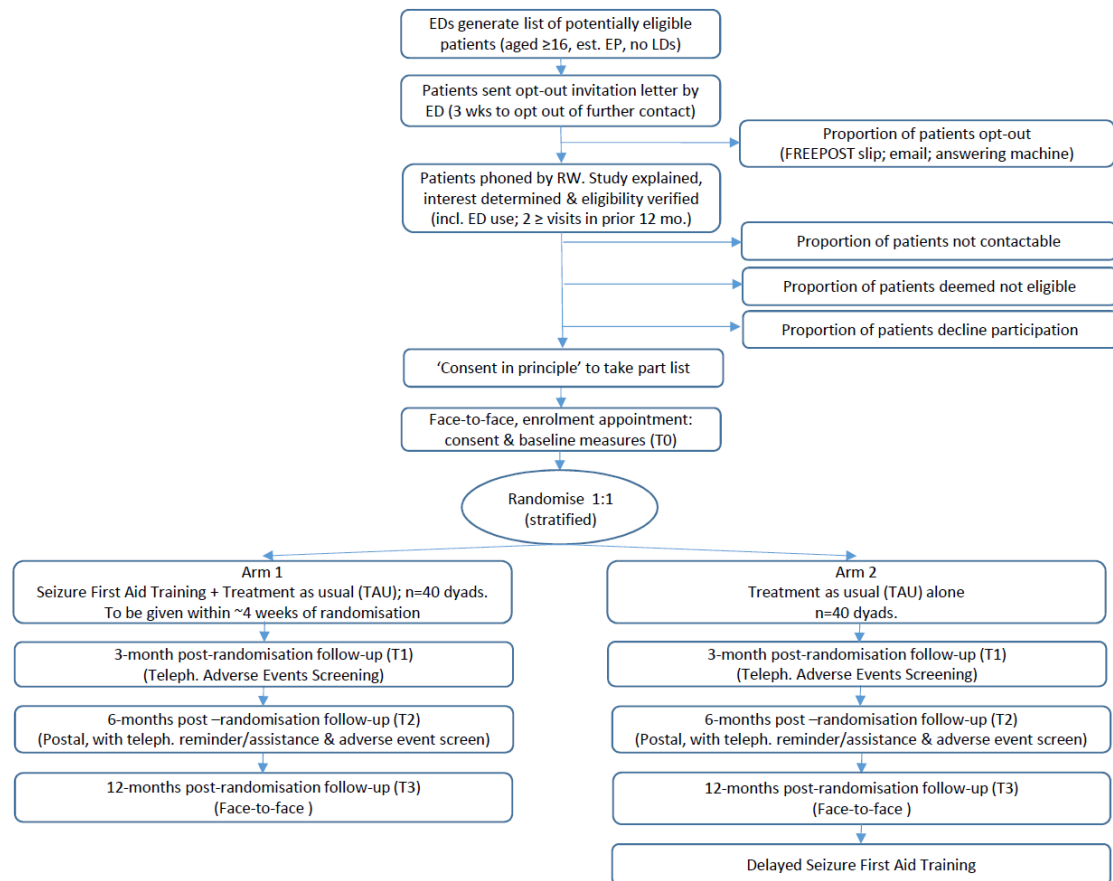
- Actual / suspected psychogenic non-epileptic seizures alone or in combination with epilepsy;
- Acute symptomatic seizures related to acute neurological illness or substance misuse;
- Severe current psychiatric disorders (e.g. acute psychosis) or life-threatening medical illness;
- Enrolled in other epilepsy-related non-pharmacological treatment studies.
- Home address is >25 miles from ED identified from.

Study Centres and Distribution:	<p>PART A Intervention development: 7 leading representatives from neurology, emergency medicine, GPs with special interest in epilepsy, epilepsy nursing, commissioning and user groups will provide feedback on behalf of professional groups caring for epilepsy.</p> <p>Regional and national partner user groups will help identify PWE and their carers who will provide feedback.</p> <p>PART B Pilot RCT: Three UK NHS (Merseyside) EDs.</p>
Study Duration:	<p>PART A Intervention development: 8 months.</p> <p>PART B Pilot RCT: 30 months</p>
Description of Agent/ Intervention:	<p>PART A Intervention development: None</p> <p>PART B Pilot RCT: In addition to their usual care, patients and carers in both treatment arms will be given the opportunity to attend the Seizure First Aid Training course developed during Part B of the project. It will be delivered by an Epilepsy Society trainer and aim to increase participants' confidence in seizure management, providing them with a practical understanding of what is required for different seizure scenarios. They will also learn what they can do to assist ambulance crews to manage seizures within the community.</p>
Primary Objective:	<p>PART A Intervention development:</p> <p>1) Optimise the content, delivery and behaviour change potential of the Epilepsy Society's existing course for PWE attending ED, and their informal carers. The resulting adapted package will be named Seizure First Aid Training.</p> <p>PART B Pilot RCT:</p> <p>2) Conduct a pilot RCT of Seizure First Aid Training vs. Treatment As Usual (TAU) alone to estimate likely recruitment, consent and follow-up rates in a future definitive trial.</p>
Secondary Objective/s:	<p>PART B Pilot RCT:</p> <p>3) Test acceptability of randomisation to participants.</p> <p>4) Calculate estimates of the annual rate of ED visits in the control group and the likely dispersion parameter to inform the sample size calculation of a future RCT.</p>

5) Conduct an analysis of the cost of implementing the Seizure First Aid Training programme.

Protocol Summary - continued

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



2 BACKGROUND INFORMATION

2.1 Introduction

Epilepsy and emergency hospital use

With a prevalence of ~1%, epilepsy is the most common serious neurological condition in the UK. NHS policy identifies this ambulatory care sensitive condition as an important cause of avoidable emergency hospital use and readmission.[1, 2] This is because 20% of people with epilepsy (PWE) visit emergency departments (ED) for seizures each year,[3-5] with one half being admitted.[5-7] Currently, six out of seven hospital admissions for epilepsy occur on an emergency, rather than planned basis.[8] Seeking emergency care for epilepsy can be appropriate, important, and even life-saving. Most emergency visits by PWE are, however, clinically unnecessary according to clinical guidelines. Our National Audits of Seizure Management in Hospitals (NASH) [9, 10] found that the majority of visits were by those with known, rather than new epilepsy and most people had experienced an uncomplicated seizure. Guidelines are clear that, with the correct training, such seizures can be safely managed by patients and their families in the community. [9-11].

Compared to the wider epilepsy population, PWE who attend ED have poorer health. They have had more seizures, poorer quality of life, are more distressed and feel more stigmatised by epilepsy. There is also inequality in terms of use of ED, with studies,[12, 13] including the NHS Atlas of Variation,[14] indicating that PWE who visit ED are more likely to reside in areas where social deprivation is high and seizure control the worst. Many though, have been receiving outpatient care consistent with excellence. This indicates they warrant additional support. Our NASH found ED visits do not typically lead to patients receiving extra support.

The reason services are not reactive to ED use may be because, as noted by the National Institute for Health and Care Excellence (NICE) (2012), a lack of research means it has been unclear what can help. The visits are, nevertheless, costly. In England in 2012/13, they cost the NHS >£57 million. [15, 16] One reason costs are so high is that PWE are frequently readmitted; ~60% of PWE re-attend ED within 12 months.[17] Epilepsy is the commonest neurological reason for repeat emergency admission within 12 months.[22]

Epilepsy self-management and current lack of routine support for it

Coping with life in the context of having epilepsy requires PWE to accept their diagnoses and adopt specific self-management behaviours to prevent seizures and manage consequences. To support them to do this, NICE [18] states that offering PWE and carers self-management education, including on first aid and safety, is essential. Self-management programmes have been tested and adopted by the NHS for other chronic conditions (e.g. diabetes: DAFNE[19], DESMOND[20]; X-PERT;[21] arthritis[22, 23]). The NHS has not though yet implemented routine self-management education for PWE or their carers and there is limited time for it within routine care appointments.[24, 25] Patients have summarised the current lack of information following diagnosis as “I was left high and dry”[26]. Studies have found that a proportion of PWE, particularly those with low educational levels, have low epilepsy knowledge [27, 28].

Importance of confidence in seizure management and first aid knowledge

Evidence from a recent mixed-methods study of ours has brought clarity to the reasons why PWE can attend ED. For it, we recruited 85 PWE from 3 NHS EDs and completed the first interviews with PWE about the circumstances of visits. Despite having a diagnosis for 10+ years, patients, particularly those who attended frequently, explained how they were unsure how to manage seizures and could not educate others about first aid. They felt that they had not been given sufficient information and had left consultations with unresolved questions and uncertainties. They were fearful of the consequences of their seizures, including the possibility of death. This often led them to call for an ambulance when they believed that they were about to have, or had had, a seizure:

“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!” (Male participant, 23) [29]

The results from an analysis of the quantitative data we collected as part of the same project offers some support for the role of patient confidence in ED use. We examined which participants’ characteristics predicted ED use over the 12-months following recruitment.[30] Factors such as medication management and seizures did not emerge as important. Instead, patients’ scores on a measure of epilepsy-related mastery [31] did. This measure captures the degree to which the patient perceives internal vs. external locus of control, with example items including “I often feel helpless in dealing with my seizures” and “Sometimes I feel that my epilepsy controls my life”. Those who reported the least sense of mastery subsequently visited ED the most.

We also found evidence to suggest that seizure first aid knowledge is particularly low in PWE visiting ED. Specifically, upon recruitment patients were tested using the Epilepsy Knowledge Profile-General (EKP-G).[32] Patients’ overall score’s on this questionnaire were not associated with their subsequent ED use. The EKP-G does though contain a single question on seizure first-aid. A third of the participants from our ED sample responded incorrectly to this item, stating that it was always necessary to call a doctor or ambulance if a person with epilepsy has a seizure, even if it occurred without complications.[17] Only 11% of the wider epilepsy population have been found to give this answer.[33]

Our interviews with patients also revealed how family and friends could have an important role in ED use. Patients explained how when they had a seizure, responsibility for their care and the decision to seek emergency care would need to be delegated to a family member, friend or work colleague. When these informal carers were not confident, they would call for an ambulance, regardless of whether the seizure involved complications. During one interview a carer who was accompanying a patient participant interjected with the following comment:

“[I was] just worried because I don’t know anything about epilepsy... I mean I only know the bad things, I know it can be quite serious... I know you can die... I was so worried I decided just to ring an ambulance...better safe than sorry.” (Friend of female participant, 60) [34]

The role which our qualitative data suggests family and friends can have in ED use concords with evidence that, despite greater social isolation, up to 90% of PWE still identify a significant other (e.g., spouse, parent, friend) who acts as an informal carer for them.[35] Such persons can provide a variety of forms of care, ranging from emotional support to reminders to take medication.

Importantly, it has also been found that most seizures leading to an ED visit occur within the patient’s home and are witnessed by someone else.[6, 36] Reuber et al.[6] found that in their area, only 15% of ED visits by PWE occurred because the person was alone and had a seizure in a public place.

2.2 Rationale

To date, no seizure management training intervention has been developed or tested for its ability to reduce ED use by PWE who attend ED or their carers. There is evidence, however, to suggest that such an intervention could be effective.

The evidence that self-care skills can be improved

Two Cochrane reviews [37, 38] found only three self-management studies targeting adults with epilepsy.[39-41] None of the programmes trialled focused exclusively on seizure management, or on those attending ED, none systematically involved carers, and none had

been trialled in the UK. The reviews did though conclude that there was some evidence that educational interventions can improve epilepsy self-care skills. Helgeson et al.'s [39] trial of the Sepulveda Epilepsy Education (SEE) programme warrants particular discussion as SEE did include some discussion of seizure first aid and so the outcome of participants is relevant.

SEE is a 2-day psychotherapeutic group-based programme. Participants for Helgeson et al.'s [39] RCT were recruited from those insured by Kaiser Permanente in the US. The quality of the trial was low, the specifics of what information patients received is unclear and only 38% of those randomised to SEE completed it.[37] Nevertheless, it is important that at 4-month follow-up, the SEE group demonstrated a significant increase in understanding of epilepsy, a decrease in fear of seizures, and decrease in hazardous medical self-management practices compared to wait-list control participants. No significant changes were though, seen on measures of anxiety or confidence managing epilepsy, and health service utilization was not measured.

As the number of studies conducted with adults with epilepsy is small, Lindsay and Bradley's [42] Cochrane review of self-management interventions for children with epilepsy and their parents is also instructive. It identified two RCTs of interventions which contained modules on seizure first aid.

The first was Tieffenberg et al.'s [43] evaluation of a Spanish programme called ACINDES which is for those aged 6-15 years. Delivered by trained teachers, ACINDES teaches children and parents about epilepsy. At 12-month follow-up, children in the intervention group showed significant improvements in epilepsy knowledge compared with the control group. There was also a significant reduction in their emergency hospital visits and a trend for their parents to show increased knowledge and less fear of their child's death.

The second RCT of note was by Lewis et al.[44, 45] Lewis et al. examined the effect of another Spanish intervention called the 'Children's Epilepsy Programme' (CEP). CEP teaches children about seizures, living with epilepsy and communication. At 5-month follow-up, children in the CEP group had significantly improved epilepsy first aid knowledge compared to controls.[44] Their parents also showed significantly greater reduction in anxiety than control parents.[45]

Evidence that ED use can be reduced

That interventions can lead to improvements in the seizure management skills of PWE and their carers accords with the wider literature on first aid education. This shows that even relatively brief, 2-hour interventions can improve the first aid skills of a variety of groups, including, children, parents and carers.[46-50] That training in self-care has been found to be associated with reduced service utilisation in epilepsy, without compromising patient outcome, concords with the large, high quality evidence base on interventions to reduce ED use by those with asthma – another chronic, relapsing condition.[51-53] Boyd et al. [51] 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 followed for on average 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.

On the basis of the aforementioned evidence, we theorize that PWE who frequently visit ED (here defined as 2+ visits in the prior year) could benefit from an intervention that improves their own and their informal carers' confidence and ability in managing seizures and empowers them to be able to tell others from their wider support network about how to help them if a seizure occurs.

An existing training course in seizure management

The Epilepsy Society is an English charity (ref. 206186) with a 120 year history. The Society has taken on an important role within the voluntary sector in producing information materials and offering epilepsy training for different audiences (epilepsysociety.org.uk/epilepsy-

[training](#)). Since 1998, it has been running a ½-day group-based training course titled 'Epilepsy awareness and seizure management' from its rooms in Buckinghamshire. People from a variety of backgrounds, including patients, carers, teachers and care home staff, can pay to attend the course.

The course was developed iteratively, with the involvement of PWE, by a multidisciplinary group including neurologists, psychologists and social workers. It has not been formally evaluated, but aims to increase participants' confidence in seizure management.

The course in its current form

The course consists of a number of components and so is a complex intervention.[54] It is delivered to groups of 10-20 people by a single educational facilitator who typically has a nursing or social care background, and experience of working with PWE. In order to deliver the course, an educational facilitator follows a standard training programme developed by the Society. The course lasts 3 hours, with breaks included. Educational aims for PWE and didactic aims for educational facilitators are specified.

It covers the following 8 topics:

- 1) What is epilepsy? Myths and truths about epilepsy are discussed, and a simple explanation is provided of what happens in the brain to produce seizures;
- 2) Different causes of epilepsy and seizure triggers;
- 3) Diagnosis: Important diagnostic tools are discussed;
- 4) Detailed discussion of seizure types, their effects, and how to manage each of them, including when to call an ambulance and demonstration of the recovery position. This includes video clips showing different types of seizures, with PWE and health professionals discussing them;
- 5) Status epilepticus;
- 6) Treatments: Medication and side-effects;
- 7) Risk management and support needs;
- 8) Sources of further information: Addresses of organisations offering assistance and information.

Materials for the delivery of the course include standardised slides, video clips and information booklets. An information pack provides participants with a permanent record of the material covered and includes space for notes to promote active processing of material, as well as participation.

Learning is elicited rather than taught, with the behaviour of the educational facilitator promoting a non-didactic approach. Course participants are encouraged to share experiences and ask questions.

Justification for choosing and adapting the ES's course

The Epilepsy Society's course holds the potential to increase patient and carer seizure management confidence and ultimately lead to fewer unnecessary hospital visits. In Appendix 1 we expand on how the specific content of the intervention might produce the anticipated reduction in ED use.

The format of the course and mode of delivery aligns with what service users have said they want and how they would prefer this to be delivered.[55-59] The intervention is also potentially generalizable and its mode of delivery sustainable within the NHS context. PWE have, for example, expressed a preference for people with knowledge of epilepsy to lead training.[55] As such, epilepsy nurse specialists and clinical physiologists have been asked to deliver other epilepsy self-management interventions.[37, 60] Forty-five percent of acute trusts in the UK do not, however, have access to an epilepsy nurse specialist [61, 62] and 60% have no EEG facilities.[5] Commissioning national third sector epilepsy organisations to deliver seizure-management training could create a more generalizable and financially sustainable model [18, 63, 64] . The ES charges a person £40 to attend its half-day seizure

management course. This is favourable when compared to the cost the NHS pays for a patient to attend one of the diabetes self-management courses (6 hour DESMOND course= £203 per patient;[65] 35 hour DAFNE type 1= £545 per patient [66]) or one of the generic expert patient courses (15 hour EPP course= £250 per patient [67]) .

In this project we propose to refine the content and format of the ES's programme for the target population and optimise its behaviour change potential. The reason that the ES's course needs to be refined is that it was developed for delivery to a broader, fee-paying audience. It has not been formally evaluated for delivery in the NHS context, nor specifically for PWE who visit EDs who, the evidence indicates, can be particularly challenged by epilepsy and who may have lower educational levels. Its developers also did not have a clear behaviour change model. The ES has agreed for their course to form the basis of a new, adapted course, called Seizure First Aid Training. Having developed the Seizure First Aid Training, we will obtain the design information necessary for a future, definitive trial of its effectiveness.

2.3 Objectives

This study will consist of two parts.

Part A will involve the development of the Seizure First Aid Training for people with epilepsy (PWE) who attend emergency departments (ED) for epilepsy, and their informal carers. To do this, experts from the professional groups supporting PWE will review the course and be interviewed about changes needed to ensure content accuracy and suitability (stage 1). Having done this, we shall then optimise the behaviour change potential of the course through the use of introducing a self-affirmation exercise at the start of the course (stage 2). Two Seizure First Aid Training courses using the initial iteration of the course will then be delivered to patient and carer user group members who have used ED for epilepsy (stage 3). They will, via group interviews, feedback on the course and identify required changes.

Part B will assess the feasibility and optimum design of a future RCT to test the Seizure First Aid Training's effectiveness.

The primary and secondary objectives for each part of the project are as follows:

Primary Objective:

PART A Intervention development:

1) Optimise the content, delivery and behaviour change potential of the Epilepsy Society's existing course for PWE attending ED, and their informal carers. The resulting adapted package will be named Seizure First Aid Training.

PART B Pilot RCT:

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

Secondary Objective/s:

PART B Pilot RCT:

3) Test acceptability of randomisation to participants.

4) Calculate estimates of the annual rate of ED visits in the control group and the likely dispersion parameter to inform the sample size calculation of a future RCT.

- 5) Conduct an analysis of the cost of implementing the Seizure First Aid Training programme.

2.4 Potential Risks and Benefits

The research workers recruiting persons for Parts A and B of the project will discuss the potential risks and benefits of participation with them prior to study entry. They will also be outlined in the applicable Participant Information Sheets.

2.4.1 Potential Risks

Ethical issues which may be relevant to this study include: the anxiety over audio-recording of sessions, and the potential for participants to have seizures during the Seizure First Aid Training sessions. To reduce concern about audio recording of sessions and qualitative phases, the purposes of this will be clearly explained in the information sheets, we shall always ask participants to provide permission for this to occur and explain that all study data will be kept in the strictest confidence.

Educational facilitators will have been trained by the Epilepsy Society to work with groups, deal with seizures and receive ongoing supervision. We will offer Seizure First Aid Training to PWE and carers within a local hospital. This will limit the distance that PWE will need to travel to attend the course and travel expenses will be reimbursed. It increases the likelihood of PWE being familiar with the area and may reduce anxiety about coming to unfamiliar settings. PWE and carers will be reassured that appropriate facilities will be available in the event of a seizure. For Part B of the project, we will run approx. 6 courses for the 40 dyads period to allow PWE to attend later courses if illness/seizures prevent earlier attendance/ completion of the course. Participants in both study arms will receive ongoing TAU and trial participation can be terminated at any time if clinicians think there is a risk in continued participation.

Please see section 9 for discussion of the ethical considerations involved with this project.

2.4.2 Known Potential Benefits

As well as continuing to receive their usual medical care, all patient and carer participants in Part B of the project will get to go on the Seizure First Aid Training course. This could enable patients to better self-manage their epilepsy, improve their quality of life and make fewer emergency visits. A potential benefit for society will be cost savings for NHS resources.

3 SELECTION OF CENTRES/CLINICIANS

PART A Intervention development:

Stage 1 Consultation with health professional representatives

Leading representatives from 7 groups supporting PWE in some form will provide feedback on the current content of the Epilepsy Society's course.

We have agreement from the following organisations:

1. The International League Against Epilepsy-UK Chapter (Neurologist representative);
2. College of Emergency Medicine (ED representative);
3. GPs with Special Interest in Epilepsy'
4. Epilepsy Specialist Nurses Association;
5. London Ambulance Service/ North West Ambulance Service NHS Trust);
6. Cheshire Merseyside Strategic Clinical Networks (Commissioning representative)'
7. Epilepsy Bereaved/SUDEP Action user group.

Stage 2 Optimisation of intervention's behaviour change potential

Not applicable.

Stage 3 Consultation with service user representatives

The Mersey Region Epilepsy Association and the Epilepsy Society have agreed to help the research workers identify and recruit 20 PWE aged 16+ and one of their carers to attend the 2 development courses and provide feedback on the course and changes needed.

Individual patient and carer participants can take part in this phase of the project even if they do not have a carer or patient taking part with them.

PART B Pilot RCT:

Participants will be recruited from the EDs of 3 NHS hospitals in the North West of England. Agreement to act as local principal investigators has been given by ED consultants at 3 Merseyside hospital EDs.

The 3 EDs have been specifically selected to be the research sites for the pilot trial for their ability to inform a future definitive trial which, given the inequality in terms of use of emergency services for epilepsy,[14] would likely focus recruitment in socially deprived areas, where ED use is highest and seizure control lowest.

Each of the EDs is consultant led and offers a 24-hour service with full resuscitation facilities. Together, they serve a local population of ~827,000, within which the prevalence of adult epilepsy is 0.98%.[68] This population features high levels of social deprivation [69, 70] and rates of emergency admissions for epilepsy that are amongst the highest in England (Liverpool 9th highest; Wirral 12th highest).[14] The level of epilepsy control in the area is also worse than the national average. Epilepsy control is defined here as the percentage of PWE prescribed antiepileptic medication in the local population who were seizure-free in the previous 12 months as recorded for the 2012/13 QOF. According to this measure, 70.9% of PWE from the Clinical Commission Group areas served by the hospitals were seizure free, whereas the national average was 75.4%.[68]

Recruitment from these study centres will be initiated once all global (e.g. local R&D approval) and study-specific conditions have been met, and all necessary documents have been returned to CTRC.

4 DESIGN

4.1 Primary Endpoint

PART A INTERVENTION DEVELOPMENT:

Stage 1 Consultation with health professional representatives

Consensus already exists on what constitutes appropriate seizure first aid [71] and so the representatives from the main professional bodies caring for PWE will be asked to help ensure that the medical information presented by the programme is correct and that Seizure First Aid Training could be a course which they could, in the future, support. In advance of their interviews, each representative will be provided with a summary of the study, its rationale and the course materials. Having scrutinised these materials, the representatives will be individually interviewed. The exact questions will vary depending on the representatives' expertise. However, key questions may include: i) identifying any inaccuracies in the content of the existing ES programme; ii) what they did and did not like about the current content and delivery; iii) for their suggestions of how to make the programme more helpful (including issues to do with how users might be supported to manage situations when an ambulance has been called, but the PWE does not need to be transferred to ED, such as carrying epilepsy ID and the contact details for a significant other [72]); and iv) how the intervention could 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 Seizure First Aid Training will consist of health-related information provision. Whilst information provision is usually a necessary precursor to behaviour change, it alone, is not always sufficient to change behaviour.[73] Self-Affirmation Theory [74, 75] states that people are motivated to preserve a positive, moral, and adaptive self-image and to maintain self-integrity. Many PWE to whom the Seizure First Aid Training will be delivered to will have visited ED for an uncomplicated seizure. Being informed that this conflicts with medical guidance could be construed as a threat to self-integrity.[74-76] Therefore, these persons might be at risk of rejecting or denigrating the information provided by the course. To mitigate against this and so maximise the behaviour change potential of the information presented by the course, a Self-Affirmation exercise shall be individually completed by participants at the start of the courses.

A large body of evidence now shows that having a person complete a Self-Affirmation activity prior to receipt of health risk messages reduces resistance to threatening or dissonant health-risk information.[77-81] The exercise that will be used is Reed and Aspinwall's [82] 'Kindness Questionnaire'. This brief (~5 mins), effective [80, 83] questionnaire requires the person to recall past acts of kindness. It consists of 10 questions, 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?" Participants are encouraged to elaborate on their recollection for 'Yes' responses by noting down instances on the questionnaire. Please see Section 8.2 for details of how the activity will be introduced to participants receiving the course.

Stage 3 Consultation with service user representatives

Patients and carers will be consulted to ensure that the content of the course addresses users' needs and that its delivery is optimised. PWE and carers dyads who agree to be consulted will be asked to attend a user feedback session. We shall run two user feedback sessions. On the day of a session, the format and purpose of the session will be reiterated to participants. They will then be asked to complete the initial iteration of the Seizure First Aid Training course resulting from Stages 1 and 2.

A research worker will attend the courses to record their impressions of participants' engagement with the materials, other members of the group and the educational facilitator. Having completed the course, a focus group will then be held to explore participants' views of the intervention, its content, the facilitator, scheduling and acceptability. It is anticipated

that the course and feedback session will last ~4 hours in total. This will include the 3 hour course, with breaks included, followed by a minute focus group of around 60 minutes.

PART B PILOT RCT:

The primary objective of the pilot RCT is not to measure effect, but rather generate the following: estimates of eligibility, consent, recruitment and retention rates and speed of recruitment; and estimates of completion rates of study assessment tools and rates of unblinding. Patient participants will be requested to complete self-report measures prior to randomisation (T0) and then 3- (T1), 6- (T2) and 12-months (T3) post-randomisation. Carer participants will be requested to complete self-report measures prior to randomisation (T0) and then 6- (T2) and 12-months (T3) post-randomisation.

4.2 Secondary Endpoint(s)

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

Whilst the pilot will not be powered to detect a clinically meaningful difference in outcome between treatment groups, summary statistics will be calculated to measure the effect of the intervention on the proposed primary and secondary outcome measures (except measures xiii and xiv, see below) for a future definitive trial and the precision of such estimates at the post-treatment time points. These estimates will be able to be used to inform a sample size calculation for a future definitive trial.

Proposed primary outcome measure for a future definitive trial

i) Epilepsy-related ED visits

The proposed primary outcome for a future definitive trial will be the number of epilepsy-related ED visits made over the 12 months following randomisation by patient participants which would be compared between the Seizure First Aid Training and TAU only control group.

In line with previous ED trials,[84-86] it is proposed that ED use should be measured using objective NHS data. The Hospital Episode Statistics (HES) system provides the only central record of an individual's use of all EDs in England and data will be extracted from this system (using participants' NHS numbers) to provide information on individual participants' use of ED at baseline and over the 12 months of follow-up. At present, primary care records are not sufficient as means of capturing information on a participants ED use as EDs inform primary care teams of only ~75% of all epilepsy visits.[9, 10]

HES data on participants use of ED will be requested at the start of Project Month 32, once all 12-month face-to-face follow-up assessments have been completed. This single tranche of data will cover their use over both the baseline and follow-up periods. The request will be submitted to the Data Linkage and Extract Service at the Health & Social Care Information Centre who process requests for HES data. With an expected processing time of 4-5 months, it is expected that the data will be received by the research team by Project Month 37/38.

Proposed secondary outcome measure for a future definitive trial

Secondary measures will be based on participant self-report measured using CRFs. Baseline (T0) and 12 month (T3) follow-up measures will be collected in face-to-face sessions by a research worker, blind to treatment allocation. Abbreviated assessments will occur at 3-months (T1) and 6 months (T2).

The 3-month (T1) assessment will be conducted by telephone and focus on patient participants' experience of Serious Adverse Events only. For the 6-month (T2) follow-up assessment, participants will be posted a set of questionnaires for completion on their own

and instructed to return them in a pre-paid envelope. The research workers will contact participants by telephone about a week after the questionnaires have been posted. This is to ensure that the questionnaires were received and to ask if help is needed with their completion. The telephone contact will also be used to collect data from patient participants on their experience of Serious Adverse Events. The research workers will follow a specific script to collect this information over the phone. If questionnaires are not received within 2 weeks, research workers will contact the participants again.

ii) Self-reported epilepsy-related ED visits (Patients only; T0, T2, T3)

As a separate means of capturing ED use, patient participants will be asked at baseline (T0) to self-report on their utilisation of ED for epilepsy in the 12 months preceding recruitment. At the 6-month (T2) and 12-month (T3) follow-ups they will be asked to report on their utilisation of ED for epilepsy in the time since their last assessment (typically ~6 months).

The reason for also asking participants to self-report on ED use is that HES is not a 'live', searchable system, visits are not coded by specific diagnosis and there can be a time between requesting data on a patient's service use and receiving it. Using this system to provide the primary outcome data would extend the timescale of a future trial and increase costs. At present, no evidence exists on how accurate PWE are at self-reporting on previous ED use. To be able to inform a future trial about how best to measure ED use, the coverage and accuracy of patient self-report will be compared to data from the HES system. This will help determine whether the expense associated with use of the HES system as the primary means of measuring ED use is warranted.

iii) Quality of life (QoL) (Patients only; T0, T2, T3)

This will be measured using the standardised, reliable and valid epilepsy-specific measure, the Quality of Life in Epilepsy Scale-31 (QOLIE31).[87] It has 7 subscales (emotional well-being, energy-fatigue, cognitive functioning, seizure worry, medication effects, social functioning, overall QoL). It has good construct and convergent validity and can be used to demonstrate a statistically significant, as well as clinically meaningful, change in patients with difficult to control epilepsy more precisely than generic measures, such as the Short Form-36.[88]

iv) Caregiver burden (Carers only; T0, T2, T3)

No epilepsy-specific measure is available. Therefore, the Zarit Caregiver Burden Inventory will be used.[89] Its 22 items evaluate the effect of a condition on a caregiver's 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 been used for epilepsy.[90-92]

v) Distress (Patients and Carers; T0, T3)

We will use the 14-item Hospital Anxiety and Depression Scale[93] to measure self-reported distress in patients and carers. It is a reliable, valid scale,[94, 95] widely-used in UK epilepsy research.

vi) Felt Stigma (Patients only; T0, T3)

Jacoby's [96, 97] 3-item Stigma of Epilepsy Scale, with revised 4-point scoring, will measure the extent to which PWE feel they are stigmatised by their epilepsy. The scale's internal consistency (Cronbach's $\alpha=.85$) is good.[97]

vii) Health economics (Patients only; T0, T3)

Using the Client Service Receipt Inventory (CSRI),[98] we will measure patient health service use (including use of ambulance services, regardless of whether transfer to ED happened), informal care (including work time lost by informal carers), benefits received and employment status during the 12 months prior to baseline and 12 following randomisation. The 5-item EQ-5D,[99] already shown to be valid in PWE,[100] will also be used.

viii) Knowledge and fear of seizures (Patients and Carers; T0, T3)

Both patients and carers will complete 5-items from the Fears subscale from the 60-item Epilepsy Knowledge and Management Questionnaire.[101] They focus on knowledge about seizures and on fears of death or brain damage. Example items include “I continually dread seizures”, “I always want an ambulance to be called” and “I am afraid to go out”. The measure is sensitive to change.[39, 102] and the 5-items have previously been used in isolation [33].

ix) Confidence managing seizures/ epilepsy (Patients and Carers; T0, T2, T3)

Patients: Wagner *et al.*'s [31] 6-item epilepsy-specific scale will be used. This measures PWEs' perception of epilepsy and its treatment and the extent to which they feel able to control these. This measure distinguishes between groups of PWE with differing levels of severity. It has adequate internal consistency (Cronbach's $\alpha = .7$) and test-retest reliability (.74).

Carers: The 6-item Condition Management subscale from Austin's Parents Response to Child Illness Scale will be completed by carers. It has been shown to have good internal consistency.[103] Example items include “I feel confident in my ability to handle my family or friend's epilepsy” and “I know what to do when the next seizure happens”. Carers respond to each item using a 5-point scale.

x) Knowledge of what to do when faced with a seizure (Patient and Carers; T0, T3).

Both patients and carers will complete a measure assessing their knowledge of what to do when faced with a seizure. The standardised questions come from Martiniuk *et al.*'s (2007) 'Thinking About Epilepsy Questionnaire'. Example items include “When someone is having a shaking seizure you need to hold him/her down to stop the shaking: True; False; Don't know?” and “When someone with epilepsy is having a seizure, an ambulance should be called: Always; Never; Only if the seizure lasts 5 minutes; If the person is unusually tired after the seizure; If there are two seizures in a row; If the person bumped his/her head?”

xi) Seizure control (Patients only; T0, T2, T3)

Patients only: At baseline (T0), patients will be asked to complete Thapar's seizure frequency scale for the prior 12 months.[104] At 6- (T2) and 12-months (T3) follow-up, PWE will be asked for the number of seizures (of any type) that they have experienced since the last assessment and the date of the first and most recent seizure (if applicable) since last assessment. To assist, patients to do this they will be provided with a seizure diary at T0 and instructed on how to complete this.

xii) Adverse events (Patients only; T1, T2, T3)

A standardised checklist will be used to ask PWE about any new symptoms or diagnoses occurring since randomisation and length of those symptoms. This will allow us to describe any potential complications that occur in the two treatment arms.

xiii) Patient Activation Measure (PAM) (Patients & Carers; T0, T3)

This 13-item questionnaire measures the latent construct of “patient activation,” which captures the degrees to which patients (and carers) perceive themselves to have the beliefs, knowledge, and skills to “manage their condition(s), collaborate with their providers, maintain their health functioning, and access appropriate and high-quality care.” Based on their PAM score, respondents are classified into one of four “stages” of activation where the first stage corresponds to the lowest level of activation and the fourth stage corresponds to the highest level [105].

xiv) Feedback on participation (Patients & Carers, T3)

To capture patient and carers feedback on what it was like taking part in the trial, we shall ask both parties to complete 3 study questions on withdrawal of the study. These are: (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 women’s experience of participating in the Magpie Trial [114].

5 STUDY POPULATION

5.1 Inclusion Criteria

PART A INTERVENTION DEVELOPMENT:

Stage 1 Consultation with health professional representatives

Leading adult representatives from the professional groups caring for epilepsy have already been identified and provided provisional agreement to be involved. They will provide signed informed consent in order to formally participate in the project.

Stage 2 Optimisation of intervention's behaviour change potential

Not applicable.

Stage 3 Consultation with service user representatives

Patients with the following characteristics will be eligible to participate in the Seizure First Aid Training development phase:

- A. Established diagnosis of epilepsy (1+ year);
- B. All epilepsy syndromes and all types of focal and generalised seizures;
- C. Currently being prescribed antiepileptic medication;
- D. Age 16 years or older (no upper age limit);
- E. Have visited ED at least once in the past 2 years for epilepsy (as reported by the patient);
- F. Live in the North-West area of England.
- G. Able to provide informed consent and participate in the Seizure First Aid Training course in English.

Carers with the following characteristics will be eligible to participate in the Seizure First Aid Training development phase:

- a) A significant other to the patient (e.g., family member, friend) who the patient identifies as providing informal support;
- b) Age 16 years or older (no upper age limit);
- c) Live in the North-West area of England.
- d) Able to provide informed consent and participate in the Seizure First Aid Training course in English.

Patient and carer eligibility will be ascertained by interviewing the patients and carers.

PART B PILOT RCT:

Patients with the following characteristics will be eligible for inclusion in the pilot trial:

- A. Established diagnosis of epilepsy (1+ year);
- B. All epilepsy syndromes and all types of focal and generalised seizures;
- C. Currently being prescribed antiepileptic medication;
- D. Age 16 years or older (no upper age limit);
- E. Visited an ED for epilepsy on 2 or more occasions within the previous 12 months (as reported by patient);
- F. Live in the North-West area of England (defined as having a home postcode which indicates they reside within 25 miles of ANY of the 3 ED recruitment sites; see Appendix 2 for list of included postcodes);
- G. Able to provide informed consent, participate in the Seizure First Aid Training and independently complete questionnaires in English.

Carers with the following characteristics will be eligible for inclusion in the pilot trial:

- a) A significant other to the patient (e.g., family member, friend) who the patient identifies as providing informal support;
- b) Age 16 years or older (no upper age limit);
- c) Live in the North-West area of England.
- d) Able to provide informed consent, participate in the Seizure First Aid Training and independently complete questionnaires in English.

Eligibility will be ascertained by examination of patient attendance triage cards by local investigative teams and by subsequently communicating with patients and carers.

Please note that whilst efforts should be made to maximise the recruitment of patient-carer dyads, patient participants can take part without a carer. It is possible that a minority of patients cannot identify someone to take on this role. Carers cannot, however, take part in this part of the project without a patient partner having at least been consented into the study.

5.2 Exclusion Criteria

PART A INTERVENTION DEVELOPMENT:

Patients with the following characteristics will be excluded from the Seizure First Aid Training development phase:

- I. Acute symptomatic seizures related to acute neurological illness or substance misuse (e.g., alcohol or drug-induced);
- II. Severe current psychiatric disorders (e.g. acute psychosis) or life-threatening medical illness;

Carers with the following characteristics will be excluded from the Seizure First Aid Training development phase:

- i. Severe current psychiatric disorders (e.g. acute psychosis) or life-threatening medical illness;

PART B PILOT RCT:

Patients with the following characteristics will be excluded from the pilot trial:

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

Carers with the following characteristics will be excluded from the pilot trial:

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

5.3 Participant Transfer and Withdrawal

5.3.1 Participant Transfers

PART A INTERVENTION DEVELOPMENT:

Not applicable to any of the 3 stages in this part of the project due to short duration of participation and that there is no follow-up.

PART B PILOT RCT:

For patients and carers moving away from the area, every effort should be made for them to be followed-up by the research team. This should occur even if their move occurs before they had a chance to attend a Seizure First Aid Training course.

A patient or carer participant is defined as someone who has formally provided consent. Before this point, they are NOT deemed a participant.

The CTIRC should be notified in writing of participants who move away from the area.

5.3.2 Withdrawal from Intervention

PART A INTERVENTION DEVELOPMENT:

Stage 1 Consultation with health professional representatives

Not applicable.

Stage 2 Optimisation of intervention's behaviour change potential

Not applicable.

Stage 3 Consultation with service user representatives

In consenting to participate in the development phase, patients and carers are each consenting to participate in a Seizure First Aid Training course and a focus group. When at a Seizure First Aid Training course, patients and carers are free to leave the course at any time without providing a reason. If the participant is agreeable, they should still be permitted to participate in the focus group to hear their views of the intervention.

If illness prevents a person from attending or completing their Seizure First Aid Training course and they wish to re-attend, an effort should be made by the research team to arrange for them to attend a subsequent course (if there is one). The educational facilitator will have a list of attendees at each course and will keep a record of attendance as well as any disruptions to the course (e.g., due to seizures). Partial attendance will be noted by the educational facilitator and logged on the treatment attendance form.

PART B PILOT RCT:

In consenting to participate in the pilot trial, patients and carers are each consenting to trial treatment, follow-up and data collection. When at a Seizure First Aid Training course, patients and carers are free to leave the course at any time without providing a reason.

The educational facilitator will have a list of attendees at each course and will keep a record of attendance as well as any disruptions to the course due to seizures. If a patient participant is physically present at the start and end of the course it will be considered that they and their carer received the intervention unless a major seizure prevented them to participate in considerable portion of the course. Partial attendance will be noted by the educational facilitator and logged on the treatment attendance form. The form will be returned immediately following a course to the study Administrator. These data will then be entered onto the treatment database by the study Administrator.

The administrator will contact participants to identify the reasons for non-attendance/partial attendance and offer alternative courses if appropriate. For example, if a person was unable to complete the course they should be offered the opportunity to attend a later

course, depending on availability. If the subject declines this offer, the Administrator will record this on the study treatment database.

If the participant withdraws from the randomly allocated treatment, patients and carers should still be followed up to allow a thorough assessment of the treatment policies. Participants in both arms of the trial are expected to complete two assessments during follow-up. If a participant wishes to withdraw from trial treatment, the research team should explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Follow-up will continue unless the patient explicitly also withdraws consent for follow-up.

5.3.3 Withdrawal from Project Completely

PART A INTERVENTION DEVELOPMENT:

Stages 1 & 3

Even if after deciding to take part, professional representatives, patients and carers are still free to change their mind at any time (including during an interview or focus group), without needing to give a reason. No new information would be collected on the participant. However, any information that has already been collected would be kept. If the health professional *explicitly* asked for their data to be withdrawn from the analysis this would be possible. However, the group nature of qualitative work with patients and carers means this would not be feasible in their case.

Stage 2

Not applicable.

PART B PILOT RCT:

Patients and carers are free to withdraw consent at any time without providing a reason. Patients and carers may also be withdrawn from the study if their usual care provider (specialist and/or GP) informs the research team that there has been any change in the patient's condition that justifies the discontinuation of participation.

For those participants who wish to withdraw, this will be recorded on a withdrawal form (included in the CRF) which will collect information on date and reasons for withdrawal (if the person is willing to provide this information and/or it is appropriate), how the withdrawal was initiated and describe the circumstances of withdrawal. When a complete withdrawal occurs, the single research worker who has had most contact with the participant should also complete the Research Worker Treatment Guess form (described in Section 8.4). A copy of both forms should be promptly sent to the CTRC.

Participants who withdraw consent for the trial will have data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the study (except for Hospital Episode Statistic data on their subsequent ED use).

If a patient participant withdraws, the carer they were participating with should, if the carer is agreeable, still be followed up and offered the allocated treatment. Similarly, if a carer participant withdraws, the patient participant they were taking part with should still be followed up if they are agreeable.

6 ENROLMENT AND RANDOMISATION

6.1 Screening

PART A INTERVENTION DEVELOPMENT:

Stage 1 Consultation with health professional representatives

In preparation for this project, the leading professional bodies caring for PWE have been identified, approached and provided provisional agreement to review and provide feedback on the ES's intervention. In some cases, individual representatives have already identified themselves and in other cases, they body will select a representative closer to the time.

Stage 2 Optimisation of intervention's behaviour change potential

Not applicable.

Stage 3 Consultation with service user representatives

Patient and carers will be recruited for the development phase via the Mersey Region Epilepsy Association and the Epilepsy Society. Advertisements will be placed in their publications, websites and at their meetings. Persons interested in receiving more information and participating will be requested to contact the team. Patient and carer participants will each receive a £10 voucher once they have attended a [Seizure First Aid Training](#) course and provided feedback.

PART B PILOT RCT:

There is no national record that codes ED visits in sufficient detail to identify epilepsy-related visits. Therefore, to identify eligible patient participants for the pilot trial the local attendance records of the participating EDs will be searched and a list of potentially eligible participants compiled.

As UK EDs code their attendances using their own presenting symptoms/ diagnoses (often variations of the Manchester Triage Presenting Complaints system [106]) an expert panel shall be convened to identify those symptoms and diagnoses by which the different EDs classify attendances that they consider potentially indicative of an epilepsy-related attendance.

With the support of local ED consultants and the research team, administrative clerks/ IT managers at each of recruitment site shall complete computer searches of their EDs' attendance records for the prior 12 months for patients who fall into the relevant categories. A list of potentially suitable patients will be compiled, along with their contact details. The electronic search will identify only those whose age at the time of presentation was ≥ 16 years old and exclude those not residing within 25 miles of *any* of the EDs (i.e., not having a postcode starting with any of those presented in Appendix 2)

The triage cards relating to ED visits that led to the patients being identified will be obtained (scanned copies are typically available). These will be reviewed by the local investigative teams to assess patient eligibility. The triage cards will typically allow screening will respect to whether the patient has established epilepsy or not, whether they have a profound intellectual disability, and whether or not they experience non-epileptic seizures).

After having pooled the lists from the 3 hospitals and removed duplications (to ensure a patient is not invited more than once), an invitation letter from the applicable local ED investigator will be sent to all patients who are ostensibly eligible. To ensure minimal disruption to clinical routines, the research team will, where necessary, assist local investigators with the preparation and distribution of invitation letters.

The invitation letter will explain the study to the patient. It will note that unless they return an included FREEPOST opt-out form within 3 weeks or opt-out by means of leaving a message on a dedicated telephone answer phone or email (Seizure_First_Aid_project@liv.ac.uk), that they will subsequently be telephoned by a research worker with more information. Patients opting out will be encouraged to detail any reasons for not wanting to participate. The initial invitation letter will contain a patient

Participant Information Sheet and also instruct patients interested in performing to identify a significant other who would be interested in taking part with them.

The telephone call that interested patients (i.e., those not having opted-out of further contact) will receive will involve the research worker verifying patient eligibility, explaining the study in more detail, answering any questions the patient may have and determining whether they would like to participate or not. To ensure consistency, quality and efficiency, the research workers shall be guided by a standardised script. The conversation regarding eligibility will focus on patient's medical history to establish epilepsy as the primary diagnosis (not resulting from a malignancy), to establish that the patient is receiving antiepileptic drugs and that they have made at least 2 ED visits for epilepsy in total in the previous 12 months. In addition, screening will seek to identify those who have psychosis and terminal illnesses as concurrent morbidities in order to exclude them from the study.

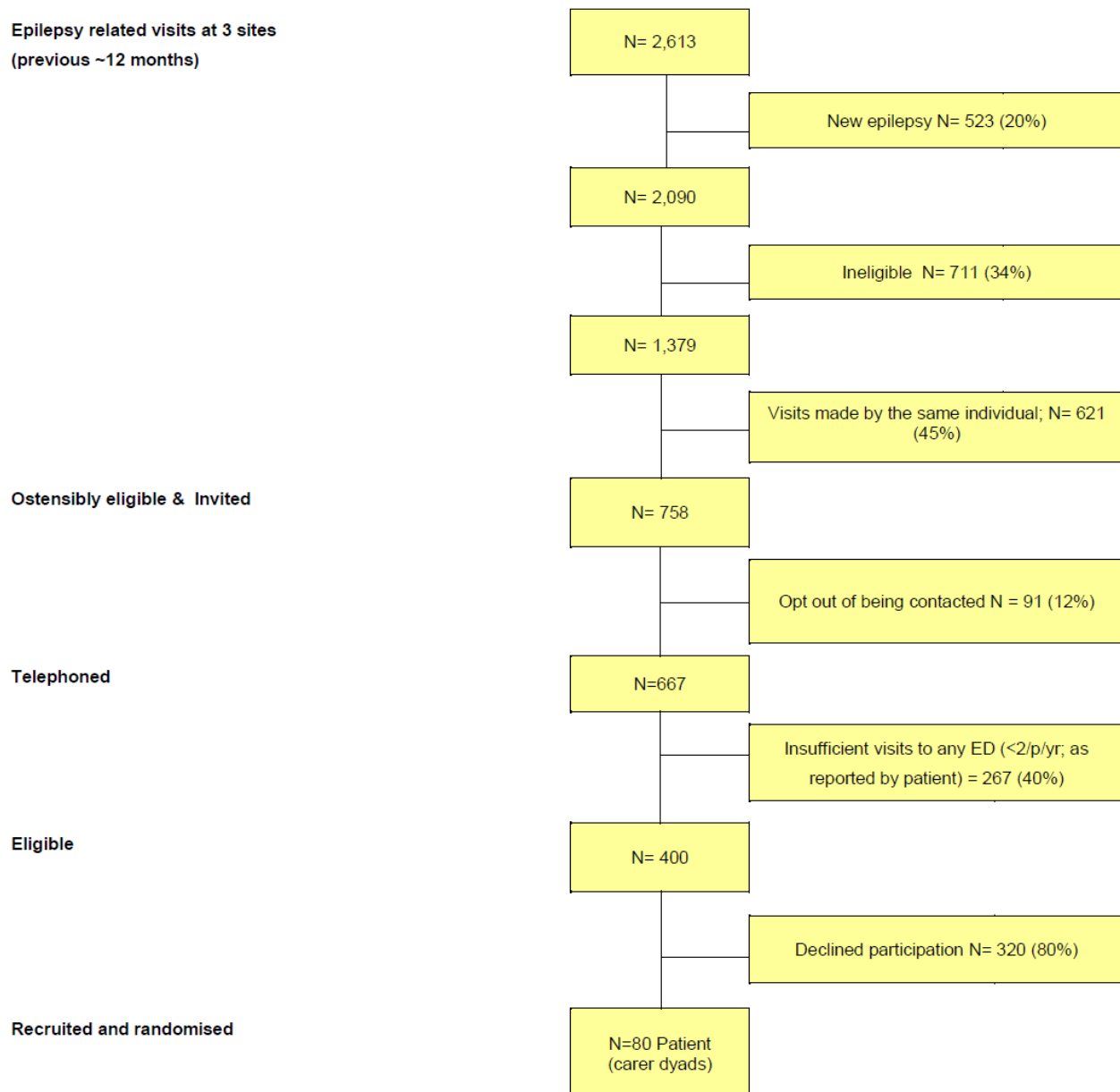
If a person is identified as eligible and willing to participate, then consent in principle will be taken over the telephone. These persons will then be added to a list of willing patients and be subsequently contacted by the research workers to arrange an enrolment appointment (see section 6.2).

It is anticipated that the majority of people will be identified as ineligible or decline participation during the telephone contact. It is also anticipated that some patients may not be available when the telephone call is made. A maximum of 2 calls will be made to make telephone contact with each person. Following this, it will be recorded that it was not possible to contact the individual. Efforts should be made to vary the times at which the calls to individuals are made. If a patient does not have an active telephone number then no attempt shall be made to contact them.

Evidence indicates that ~400 eligible PWE will have visited the 3 EDs over the 12 months preceding our recruitment phase. The anticipated recruitment for the trial is illustrated in Figure 2. The estimate for the number of attendances at the 3 EDs is based on Health and Social Care Information Centre data for these sites from 2012/13 [107] and published audit data which shows ~1% of all ED visits are for epilepsy [6, 108] and that of these, ~80% are by those with an established diagnosis.[6, 108] After factoring in evidence on the proportion of ED visits within a year that have been made by the same individual,[10] we estimated, using data from a previous study conducted by our group at University Hospital Lewisham's ED (which is most similar to North-West EDs), the number of PWE that would satisfy the inclusion/exclusion criteria.[109] On the basis of evidence about the preferences of PWE [110] and data from previous trials of self-management programmes,[19, 30, 53, 111] we estimate that $\geq 20\%$ of those who have visited ED on 2+ occasions in the prior 12 months will agree to participate. Experience from a current HTA trial of ours (09/144/09) indicates that ~12% of PWE will opt-out of being contacted by the research team when sent an invitation letter and that 1.5 research workers can make ~25 calls a day to participants to explain a study.

After having factored in staff annual leave and the 3-week opt-out period following invite, we estimate it will take the local ED consultants and 1.5 research workers ~11 months to screen, call, recruit and assess 80 patients and their 80 carers.

Figure 2 Estimated recruitment



6.2 Enrolment/ Baseline

PART A INTERVENTION DEVELOPMENT:

Stage 1 Consultation with health professional representatives

Closer to the study start date, each of the representatives/ organisations who have given their provisional agreement to participate will be contacted to verify willingness to participate and answer any questions they have. Each representative will be sent a Participant Information Sheet. If they are agreeable to participation they will be sent a consent form to sign and return before the interview. They will then be sent the materials for the Epilepsy Society's current package to review in preparation for their interview. Then ~2 weeks later they will provide feedback by means of an individual interview with a research worker. The interview will occur at a time and in a format that is convenient for the representatives (e.g., telephone, Skype, or face-to-face at the representatives office or the university). Each expert representative will receive a consultancy fee of £200 following completion of their interview in which they provide feedback.

Stage 2 Optimisation of intervention's behaviour change potential

Not applicable.

Stage 3 Consultation with service user representatives

Patients and carers who have expressed an interest in participating in the development phase will be contacted by phone. Their eligibility will be verified, they will be provided with more information, sent an Participant Information Sheet and, if appropriate, asked to identify a carer to participate with them. Those who remain interested will be booked to attend one of the two Seizure First Aid Training development courses that will be run in the summer period of 2015 (~June). They will be sent a Consent Form and an appointment booking letter and taxi travel arrangements made, if required. The two development courses will take place within a local education centre designed specifically for people with neurological conditions.

PART B PILOT RCT:

Patients who are on the list of those providing consent in principle to take part in the trial will be contacted ~2-4 weeks later to arrange and complete an enrolment appointment.

The reasons for the time gap between a patient providing consent in principle and their enrolment appointment are as the follows: Randomisation will be 1:1 intervention to control. The intervention is, however, group-based, with ~10 patients (and carers) attending each course. To generate a group of 10 patients (and carers) to receive a Seizure First Aid Training course, 20 patients need to be randomised. It may take the research team 2-4 weeks to complete a sufficient number of telephone calls to allow them to generate this number of patients. At the same time, the purpose of randomisation is to achieve balance between randomised groups. To minimise the likelihood of (measurable and unmeasurable) changes occurring between enrolment and randomisation, enrolment sessions will only be conducted when a sufficient number of willing patients has been generated to mean that randomisation will soon occur.

At the enrolment appointment (T0) the research worker will meet the patient face-to-face (and, if practicable, the family member or friend that they would like to take part with). Appointments will take place in the patients or carers home or at the university offices. The research worker will explain the study in detail and provide Participant Information Sheets. If applicable, they will then obtain informed, written consent from both parties and go on to complete the patient and carer baseline CRF to collect the required baseline (pre-randomisation) data.

Completion of the CRF will enable collection of the data necessary to deliver primary and secondary outcomes. To permit shorter appointment times and the possibility of patients and carers completing CRFs at the same time, CRFs will be worded so that they can be completed by participants in the company of a research worker or administered directly by the research worker. It may, for example, be possible for the research worker to ask the

carer participant to independently complete the CRF in one room, whilst the research worker assists the patient participant with the completion of their CRF in another room or vice-versa.

It is possible that during an enrolment session that a patient is determined to not actually be eligible to take part in the study (e.g., that they are not able to complete questionnaires or able to attend a Seizure First Aid Training course). Such patients will not be randomised and the screening database will be updated to reflect this.

6.3 Randomisation

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

Once the CRF has been completed by BOTH the patient and their carer, the research team should proceed to add the patient-carer dyad to the list to be randomised. When a sufficient number of dyads (i.e., 20) are on the list, a round of randomisation will occur.

Patient-carer dyads *should not* be add to the list to be randomised until:

- a) Consent has been obtained from the patient AND carer (if they are taking part with one);
- b) Eligibility criteria have been fulfilled
- c) The baseline CRFs have been completed by BOTH the patient and the carer (if they are taking part with one)

Patient-carer dyads will be randomised to one of the following treatment arms:

Arm 1: Seizure First Aid Training, plus treatment as usual (TAU)

OR

Arm B: Treatment as usual (TAU) alone

Participants will be randomised by the research worker using a secure web based randomisation programme controlled centrally by the Clinical Trials Research Centre (CTRC). Personal login username and password, provided by the CTRC, will be required to access the web based randomisation system.

The research workers obtaining consent will register a patient-carer dyad for the study by entering all the baseline data regarding them onto a master recruitment database (*Open Clinica*). The system will then assign a unique participant identification number (PIN) to the dyad which needs to be recorded on the copy of the consent form (hard copy to be stored in the Trial Master File). The PINs will be the primary identifier for participants in the study. The PIN will distinguish who is the patient participant and who is the carer participant from the dyad. The letter P will be appended to the end of the PIN to indicate that the person is the patient participant (e.g., "840P"), whilst the letter "C" will be appended to the PIN to indicate that the person is the carer participant (e.g., "840C").

Computer-generated randomisation will be conducted remotely by the CTRC.

We will maintain strict allocation concealment. Email confirmations will be automatically generated each time a randomisation is requested and will be sent to relevant staff with or without details of the treatment allocation included, depending on their role in the study. Specifically, the research workers will receive a confirmation of successful randomisation. A 0.20 FTE administrator will be informed of the details of each dyads randomisation and will liaise with patients and their carers to arrange their attendance at the course and travel.

Dyads randomised to the intervention arm will receive a letter from the administrator informing them that they are going to be invited to attend a Seizure First Aid Training course on a specified date. The dyad will be encouraged to attend the specific course they have been randomised to but will accommodate their need to change the dates whenever possible. Those who were randomised to the TAU alone (control) group will also receive a letter from the administrator to let them know that they will be offered to attend a course in a year's time, once they have completed all the study assessments.

The time between randomisation and the start of intervention will be kept as short as possible to minimise loss of participants prior to receiving the intervention, while allowing time to arrange transport to the courses for participants in the intervention group. We aim to deliver courses within 2 weeks of randomisation.

7 TRIAL TREATMENT/S

7.1 Introduction

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

Assessments that should be carried out prior to the start of the randomised treatment are detailed in the relevant sections of 4.2. Patient-carer dyads will be accrued over an 11 month period.

7.2 Arm A

7.2.1 *Intervention arm: Seizure First Aid Training (plus TAU)*

The exact content of the Seizure First Aid Training will have been determined during Part A of the project. Broadly speaking the Seizure First Aid Training will consist of a 3-hour course (with breaks included) run by locally-based Epilepsy Society-trained educational facilitators. See section 2.2 for a description of the current content of the Epilepsy Society's course on which Seizure First Aid Training will be based.

The courses will be delivered to groups of ~6-10 patient-carer dyads at a time. Both patients and carers will be expected to participate actively in the course. Seizure First Aid Training is a single day, course, with no additional booster sessions. Participants will, however, each be provided with permanent copies of course material in the form of an Information Pack which they can subsequently use as reminders of the topics covered by the course. Their packs will also contain Epilepsy Society identification cards, wallet sized first aid instructions cards and the contact details of further information. Participants will each also receive certificates of attendance,

As people with epilepsy may be reluctant to travel by public transport, funds are available to contribute towards taxis to transport dyads to and from the courses (up to £35 per dyad per course). If required, this will be arranged by the study Administrator. Refreshments will also be provided for participants

As noted in section 4.1, the behaviour change potential of Seizure First Aid Training will be maximised by asking participants to complete the 'Kindness Questionnaire' at the start of the course. It is a self-affirmation exercise. To reduce the exercise appearing odd, it will be introduced by the educational facilitator in the following way:

"Thank you for coming today. At this session we are going to talk about epilepsy and seizure first aid. This will involve me providing quite a bit of information to you. Before I do this, I would like you to each take a couple of minutes to fill in this following questionnaire. It is called the Kindness Questionnaire. It looks to get us in a positively frame of mind. This might seem a little strange but the reason we are asking everyone to do this is that we know that how we feel can improve how well we remember things. When we are in a good frame of mind, we generally remember things better. You will each fill in this questionnaire by yourselves and the answers you give to the questions are just for you. They are private and we will not be sharing them with the rest of the group"

In addition to receiving the Seizure First Aid Training course, participants will continue to receive their standard medical care. No restrictions shall be placed on the usual care participants can receive.

7.2.2 Assessment and Accountability Procedures for Study Treatment/s

Participants randomised to the intervention arm will be invited and encouraged to attend the course in full. If they are physically present at the start and end of the course we will consider that they received the intervention unless a major event (such as a significant seizure) prevented them to participate in considerable portion of the course delivered on the day.

The educational facilitators will have a list of attendees at each course and will keep a record of attendance as well as any disruptions to the course (e.g., due to seizures).

Partial attendance will be noted by the educational facilitators and logged on the record of attendance. This information will then be entered onto the intervention database by the study Administrator once the course has been delivered.

The study Administrator will be informed about non-attendance/ partial attendance by the record of attendance. They will then contact participants to identify the reasons for non-attendance and offer alternative courses if appropriate. If the participant declines this offer the administrator will record this on the intervention database.

The participants' usual care providers (GP and/or specialist) will remain responsible for their patient's ongoing care during their participation in the study. The usual care providers will be informed of their patient's participation in the study by the research worker who consented the patient into the study. Included in the letter will be the contact details of the study Administrator (who is not blind to treatment allocated) should the usual care provider want to find out to which treatment group the person has been allocated.

7.3 Arm B

7.3.1 Control arm: TAU only

The active intervention will be compared to TAU alone. The appropriate control comparison for the study will be TAU by the PWE's normal care team.

Delayed access to Seizure First Aid Training courses for control participants is being used as a recruitment/ retention incentive. These courses will be run once all retained patient and carer participants from both arms have completed their 12-month follow-up assessments. It is optional for control participants to attend one of the delayed courses and no further data will be collected upon them following their 12 month follow-up. Support with travel costs will not be provided for dyads, nor will refreshments (unless remaining budgets permit this).

7.3.2 Assessment and Accountability Procedures for Study Treatment/s

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

Those who were randomised to TAU (control) group will also receive a letter to let them know that they will be offered to attend a course in a year's time, once they completed all the study assessments.

The participants' usual care provider (GP and/or specialist) will remain responsible for the patient's ongoing care during their participation in the study. The usual care providers will be informed of the patient's participation in the study.

No restrictions shall be placed on the usual care participants can receive. In England all people with epilepsy are expected to have a structured medical review of their epilepsy at least yearly by either a generalist or specialist. NICE guidelines for epilepsy also recommend that when seizures are not controlled or treatment fails, it is expected that a patient will be referred to tertiary services for assessment.

7.4 Unblinding

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

This is a single-blind pilot trial. Participants will be aware of their treatment allocation, whilst research workers conducting the outcome assessments will not be informed of participants' treatment allocation.

Strict allocation concealment will be maintained. Email confirmations will be automatically generated each time a set of randomisations is requested and will be sent to relevant staff with or without details of the treatment allocation included, depending on their role in the study. Two databases will be created in order to maintain blinding. The first database will be for the participant registration, baseline and outcome measures (with data collected and entered by blinded research workers who will complete the baseline and follow-up assessments). The second intervention database will store the data related to the intervention (data relating to the Seizure First Aid Training sessions, including dates when delivered and attendance) and will be entered on the database by the administrator. Central data cleaning will be undertaken by a CTRC Data Manager who is not blind to treatment.

Participants will be asked not to inform the research workers of their treatment allocation and should be reminded of this at the start of each data collection point.

Blinding will be tested by asking the research workers to record which group they think a participant was allocated to after each of the participant follow-up assessments and if a participant completely withdraws from the study. The form used will be included in the T1, T2 and T3 CRF. This information will be recorded and stored on the database.

7.5 Concomitant Medications/Treatments

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

No restrictions will be placed on the usual care patient participants in either treatment group can receive during their participation in the study. Therefore, decisions about concomitant medications/treatments will depend on the patients' usual care providers.

It is possible that drug changes will take place in both treatment groups during the period of follow-up. Antiepileptic medication treatment may affect outcomes, but the allocation to Seizure First Aid Training and TAU is at random, so effects should be distributed randomly between groups. Prescribed medication changes for both groups will be recorded as part of health service use (see secondary outcomes section 4.2).

7.6 Co-enrolment Guidelines

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

To avoid potentially confounding issues, ideally patients should not be recruited into other epilepsy trials.

7.7 Schedule for Follow-up

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

The expected duration of follow-up for patient and carers participants in each treatment arm is approximately 12 months.

All participants will be followed up whether they actually received their allocated treatment or not. If a patient is randomised to the active treatment arm but withdraws from receiving it, the participant will be asked to continue with trial follow-up. If a participant does not wish to continue in the trial, a Withdrawal Form (included in the CRF) will be completed to capture the date and reason.

Patient participants will be requested to complete self-report measures at baseline (T0) and then 3- (T1), 6- (T2) and 12-months (T3) post-randomisation. Carer participants will be requested to complete self-report measures at baseline (T0) and then 6- (T2) and 12-months (T3) post-randomisation. The time window for self-report data to be collected will be set to ± 3 weeks of the scheduled date.

Depending on the follow-up point, an assessment will take from 10 minutes to an hour of the participant's time. The assessments at baseline (T0) and 12-months (T3) will involve face-to-face interaction with a research worker. The assessment at 3-months (T1) will be completed with patient participants by phone and focus on experience of Serious Adverse Events only. The assessment at 6-months (T2) will be completed by post, with telephone follow-up approximately one week after posting.

Please note that if a participant in the control arm wishes to attend one of the delayed [Seizure First Aid Training](#) courses that will be run for this group, they will be 'in' the study for longer than 12 months. This is because the delayed courses will not be run until all participants have completed their 12-month follow-up (T3) assessments. TAU group participants will, however, only contribute outcomes to the trial data set under the TAU condition, with no further data being collected upon them following their 12 month follow-up (T3). Participants recruited at the start of the trial recruitment phase and randomised to the control group will consequently be 'in' the study for the longest – up to 2 years in some cases.

The request for baseline and follow-up HES data on patient participants ED use will be submitted once all patient participants have completed their 12-month follow-up (T3) assessments.

Table 1: Trial Assessments/ Activities

					Follow-Up Schedule			
Procedures	Screening	Baseline (T0) ¹	Randomisation period	Intervention	Randomisation +3 months(T1) ⁵	Randomisation +6 months (T2)	Randomisation +12 months (T3)	Withdrawal
		SCREENING DATA BASE						
Demographics	X			-				
Assessment of Eligibility Criteria	X	X		-				
Willingness to participate and, of applicable, reasons for not wanting to participate	X			-				
		MAIN DATA BASE						
Registration Form		X		-				
Signed Consent Form		X		-				
Update Contact Details (including GP)		X	X	-	X	X		
Issue of Questionnaires in person ^{1,2}		X		-			X	
Use Randomisation Form to add person to list to be randomised		X		-				
Randomise patient-carer dyad			X	-				
Inform patient of randomisation outcome ³			X	-				
Inform Usual Care Provider of randomisation outcome			X	-				
Assessment of Adverse Events ⁴				-	X	X	X	
Issue of Questionnaire by post				-		X		
Telephone follow up of Questionnaire (~1 week later)				-		X		
Re-Issue of Questionnaire by post to non-responders (~2 weeks later)				-		(X)		
Withdrawal Form				-				(X)
Research Worker Treatment Guess				-	X	X	X	(X)
Submit request for data from HES				-			X	

					Follow-Up Schedule				
Procedures		Screening	Baseline (T0) ¹	Randomisation period	Intervention	Randomisation +3 months(T1) ⁵	Randomisation +6 months (T2)	Randomisation +12 months (T3)	Withdrawal
		TREATMENT DATA BASE							
Registration Form			X		(X)				
Course Attendance Log					(X)				
Course Adverse Events Form					(X)				

(X) – As indicated/required.

¹ At baseline, all procedures should be done before study intervention.

² Refer to section 4.2 for specification of questionnaires to be administered

³ To be completed by Study Administrator who is not blind to treatment allocation.

⁴ At T1 & T2 this is to be completed by telephone and at T3 this is to be completed face-to-face.

⁵ Patient participants only.

7.8 Procedures for Assessing Safety

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

The processes for monitoring and reporting of patient participants' experience of Serious Adverse Events (SAEs) for this non-CTIMP are informed by the Department of Health's Research Governance Framework for Health and Social Care (2005), National Research Ethics Service guidance (2015) and requirements set out by the study sponsor. The definitions used in this section have been adapted from the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031).

A SAE is defined here as any adverse event which results in any of the following:

- results in death
- is 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
- is otherwise considered medically significant.***

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does 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 have not worsened, do not constitute an SAE. Prolongation of hospital stay due to social factors, for example, geographical location of the participant's home which prevents discharge is not considered a SAE.

*** This does not include: 1) medical or surgical procedures. Only the condition leading to the procedure is a SAE, assuming it satisfies one of the other criteria for seriousness; 2) Pre-existing disease or conditions present before treatment that do not worsen; 3) Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery; 3) Overdose of medication without signs or symptoms; 4) The disease being treated or associated symptoms/signs unless it is severe enough to satisfy one of the other criteria for seriousness.

7.8.1 Monitoring of SAEs

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 following adverse events are expected in this study population. Whilst they will be captured as outcomes of the trial, they will not be 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 anti-epileptic medication;
- Diagnosis of a comorbid psychiatric condition.

7.8.2 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 Table 2.

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.

Table 2 Definitions of causality

	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 participant's clinical condition, other concomitant treatments).
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.

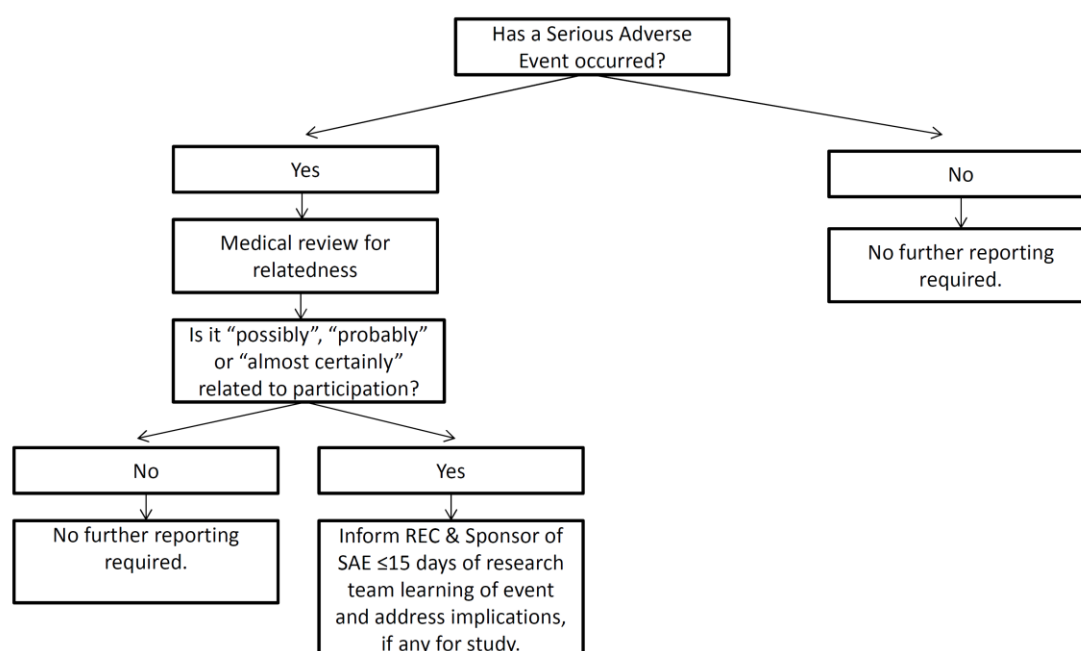
7.8.3 Reporting

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)

(<http://www.hra.nhs.uk/documents/2013/10/overview-of-safety-and-progress-reporting-requirements-non-ctimps.pdf>). 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 Seizure First Aid Training 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 Study Steering Committee (SSC) 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 3 Flowchart for determining of reporting requirements.



7.9 Substudies

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

Whilst funding has not currently been secured for its analysis, data on treatment fidelity – the extent to which an intervention was delivered by the educational facilitators as planned – will be collected for subsequent analysis, subject to resources being obtained.

The data that will be collected will consist of audio-recordings of the Seizure First Aid Training sessions. These recording will be made with the permission of participants. At a later date, a checklist of treatment components will be devised following consensus. Two independent raters will then listen to the audio-recordings and use the checklist to identify

the presence of treatment components and to determine whether specific modules were covered.

The checklist will be developed and piloted to assess variability across observers, clarify the meaning of individual items to improve coding rules and improve future inter-observer reliability. Course dates and details of the person facilitating the course will be associated with the recordings. The audio recordings of all the courses delivered will be securely stored on the University of Liverpool's firewall and password protected network.

7.10 Loss to Follow-up

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

Telephone reminders and checking if questionnaires were received are part of the strategy to improve adherence to the study protocol at 6-month (T2) follow up. An additional measure to increase adherence is distribution of £10.00 vouchers to patient and carer participants following completion of each of their assessments.

Despite encouragement to complete post-randomisation assessments we expect that about 25% of the participants may decline to complete the necessary assessments. This will be recorded on Withdrawal Form (included in the CRF) which will collect information on date and reasons for withdrawal, how the withdrawal was initiated and describe the circumstances of withdrawal. If any attempts to contact patient participants are unsuccessful because contact details are no longer current, then the patient participant's primary care practice will be contacted to obtain up to date details. In the case of carer participants, the patient they were taking part with should be contacted to obtain up to date details.

7.11 Trial Closure

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Study Steering Committee.

8 STATISTICAL CONSIDERATIONS

8.1 Introduction

A separate and full Statistical Analysis Plan (SAP) for the pilot RCT will be developed prior to the final analysis and approved by the SSC.

8.2 Method of Randomisation

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

The unit of randomisation will be the individual patient. Randomisation will be 1:1 intervention to control and will use a minimisation program with a built in random element utilising factors that will not be made known to individuals in charge of recruitment to minimise any potential for predicting allocation.

8.3 Sample Size

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

As this is a pilot RCT, a formal power calculation is not appropriate; the study will not be powered to detect a clinically meaningful difference in the primary outcome between the Seizure First Aid Training and TAU groups. Rather, the aim is 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.

We consider that 40 patients in each arm (Seizure First Aid Training v TAU) of the pilot study will provide these estimates with adequate precision. In particular, with a sample size of 80, we will be able to estimate an overall drop-out rate of 25% (approximate rate experienced by similar studies [37, 38, 109]) to within a 95% confidence interval of +/- 10% and a participation rate of 20% from an assumed 400 patients to within a 95% confidence interval of +/-4%. Assuming that ED data at 12 months is not available for whatever reason for 25% of patients, outcome data from 60 patients would still allow robust estimation of the ED rate and dispersion parameter, and sample sizes between 24 and 50 have been previously recommended as 'adequate' for pilot studies.[112, 113]

8.4 Monitoring and Analyses

A Study Management Group will oversee day-to-day running of the project and maintain close contact with local principal investigators. It will include the Chief Investigators, other applicants, and CTRC representatives.

An independent SSC will consider the progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question. The SSC will be Chaired according to HS&DR guidance, with PPI representation. Meeting minutes will be sent to NIHR regularly. HS&DR guidelines state a Data Monitoring and Ethics Committee is not required here (ssc-and-dmec-checklist-june13.doc). The study will be compliant with the research governance framework and Good Clinical Practice guidelines.

No interim analyses of the accumulating data will be performed.

Research workers will be based at the University of Liverpool to ensure a close working relationship with the Data Manager and Trial Statistician and to support them in their role. They will be mentored by a CTRC senior trial manager and line-managed and supervised by the CI. Study specific Standard Operating Procedures will be reviewed by CTRC. The Data Manager will undertake quality assurance checks to ensure integrity of randomisation, undertake source verification, monitor missing data, timeliness of data entry and check for illogical/inconsistent data. They will provide regular reports to the CI. The Trial Statistician, supervised by CTS, will carry out primary analyses. The Educational Facilitators will receive ongoing supervision from line managers at the Epilepsy Society. Audio-recordings of Seizure First Aid Training courses will be made available.

8.5 Analysis Plan

PART A INTERVENTION DEVELOPMENT:

The interviews with the representatives will be audio-recorded, fully transcribed and entered into NVivo10 and initial line by line open coding undertaken. Codes will then be grouped into themes, and these themes examined across the data set paying particular attention to similarities and variations among respondents and the explanation of 'deviant' cases. Two members of the research team will take part in analysis to reduce bias in the identification and interpretation of themes. The aim will be to identify the key, feasible changes to the ES's existing course that the experts consider are necessary.

A summary of the findings will be presented by research worker 1 to a programme development subgroup which will convene to oversee the development of the Seizure First Aid Training. Membership will include the two Chief Investigators (AN & LR) a psychologist and neurologist respectively who have expertise in complex intervention development; patient and carer representatives, a medical sociologist (MM), and a representative from the educational team at the Epilepsy Society. A research worker and the Epilepsy Society will work together to implement the modifications to the course content and teaching materials during Months 3-4.

The focus groups with patients and carers who have attended the initial version of Seizure First Aid Training will be audio-recorded and transcribed. This data, together with the notes recorded by the RW observing the course, will be analysed systematically using the same approach used for the interviews with the representatives. Any further modifications that are needed to the Seizure First Aid Training which arise from the interviews will be fed back to the programme development subgroup and changes will be made during Months 7-8 before the pilot RCT phase begins.

PART B PILOT RCT:

This is a pilot study and consequently not powered to detect a significant difference between groups, no comparative analyses are planned. The aim of the pilot RCT is rather 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.

From the quantitative data we will generate the following: point estimates and 95% confidence intervals (if applicable) for percentage eligible (percentage of patients screened that satisfy eligibility criteria), percentage of eligible participants that consent with description of reasons for non-consent, recruitment rate (number of patients randomised per month), retention rate (percentage of randomised participants that remain in the study to final follow-up visit and reasons for withdraw, where available) and speed of recruitment (number of months to randomise 80 participants); and estimates of completion rates of study assessment tools (percentage of randomised participants that complete study assessments) and rates of unblinding (percentage of randomised participants who the research workers are unblinded to during the study). We shall describe patient and carer feedback on what it

was like take part in the trial (see section 4.2 for questions to be asked). To inform a sample size calculation for a future definitive trial, summary statistics will be calculated to measure the effect of the intervention on the primary and secondary outcome measures and the precision of such estimates at each of the two post treatment time points.

To help determine the preferable method of capturing ED use in a future definitive trial we shall: 1) describe how ED use as captured by patient self-report at each follow-up point compares to that captured via the HES system; 2) report on any practical challenges that arose in using the different methods; 3) describe the resources each required; and 4) report for what proportion of participants the different methods were able to provide outcome ED data for.

For the pilot, NHS programme costs will be estimated on a per patient basis as the sum of costs of space rental, equipment (amortised over usual estimates of life cycles for such items), staff costs (using Epilepsy Society wage rates) and other programme consumable items (such as pamphlets, to be estimated from cost data from the Epilepsy Society). We will interview the Epilepsy Society education director in order to assess actual impacts of providing the programme on the costs listed above. These data will also provide a basis for making further assumptions about cost impacts in other geographical locations.

9 ETHICAL CONSIDERATIONS

9.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

Ethical issues which may be relevant to this study include:

The inconvenience of attendance at Seizure First Aid Training and dependence on carers/ others to be able to attend and potential for participants to have seizures during the Seizure First Aid Trainingsessions:

Educational facilitators will have been trained by the Epilepsy Society to work with groups, deal with seizures and receive ongoing supervision. During the pilot RCT phase Seizure First Aid Training courses will be offered to PWE and carers within a local hospital. This will limit the distance that PWE will need to travel to attend the course and funds are available to allow dyads to travel to the course by taxi. It increases the likelihood of PWE being familiar with the area and may reduce anxiety about coming to unfamiliar settings. PWE and carers will be reassured that appropriate facilities will be available in the event of a seizure. For Part B of the project, we will run approx. 6 courses for the 40 dyads randomised to the intervention arm to allow PWE to attend later courses if illness/seizures prevent earlier attendance/ completion of the course. Participants in both study arms will receive ongoing TAU and trial participation can be terminated at any time if clinicians think there a risk in continued participation.

Anxiety over audio-recording of sessions and qualitative interviews/ focus groups

To reduce concern about audio-recording of sessions and qualitative phases, the purposes of this will be clearly explained in the information sheets, participants will be asked to provide permission for this to occur and it will be explained that all study data will be kept in the strictest confidence.

Need to complete baseline and follow-up outcome questionnaire assessments and potential distress caused by completion.

We shall only recruit persons able to provide informed consent and independently complete questionnaires. Appointments will occur at a time and place that is convenient for the participant. The baseline and follow-up questionnaire packs have been designed to be as brief as possible so as to reduce the demands placed on participants. They include standardised and validated measures used extensively with no known adverse effect and their suitability has been considered by members of partner user group. However, given the potentially sensitive nature of questions about one's health in a vulnerable population, participants shall be advised at the outset that these questions may cause some additional upset and that they can stop filling in the questionnaires at any time should they wish to, without needing to give a reason and without this impacting on the quality of their care. We shall also request participants to inform us of any difficulties so we can monitor any difficulties participants are having with the study so changes can be taken if needed.

Deterring appropriate use of ED

One particular issue that the research team– which includes an epileptologist, neurologist and an emergency physician – has given detailed consideration to when considering the ethics of the project is whether the Seizure First Aid Training intervention might have the effect of deterring participants from accessing ED services when they were actually clinically required and so cause an adverse event. Most epileptic seizures in those with established epilepsy can be managed without emergency medical assistance. However, there are situations in which a person should seek emergency assistance. These include when the

person experiences a prolonged seizure, is slow in recovering, has repeated seizures and/or sustains a significant injury.

Considerations led contributors to conclude that it is unlikely that the Seizure First Aid Training intervention would inappropriately deter ED use. The reasons for this are as follows:

i) Firstly, an examination of previous trials of education focused on ED use shows that such a response to self-management education is not seen. Whilst education is typically associated with decreases in ED use, it is not accompanied by an increase in medical crises due to delays in patients seeking emergency treatment or a worsening of the patients' condition. Instead, the severity of participants' conditions can reduce and quality of life and satisfaction increase.

Boyd et al. [115], for example, completed a Cochrane review of trials examining interventions for educating children who are at risk of asthma-related ED attendance. Thirty-eight studies involving 7,843 children were included. In no study were adverse events raised. In another systematic review, Morgan et al. [116] examined non-ED based interventions aimed at reducing ED utilization by those with a variety of conditions. Seventeen of the 29 studies captured information on adverse events, but no significant events were attributed to the interventions.

ii) Secondly, the focus of the Seizure First Aid Training intervention will be on improving users' confidence in appropriately managing epileptic seizures. It will not instruct PWE and carers to never access ED for epilepsy or accuse patients of having previously made an "inappropriate" ED visit. Seizure First Aid Training will instead look to provide participants with a practical guide to help them correctly delineate what care is and is not required under different seizure circumstances. The risk of seizures will not be downplayed. In some circumstances, appropriate management consists of PWE visiting ED and participants will be informed of this. The Epilepsy Society's current course (on which Seizure First Aid Training will be based upon) already includes a discussion of what status epilepticus is and why emergency medical assistance should be sought for this.

To ensure that the information provided by Seizure First Aid Training is accurate and given in a sensitive manner, neurologists, nurses, emergency physicians, paramedics and users will – through Part A of the project – inform the development of Seizure First Aid Training. Importantly, Epilepsy Bereaved (now SUDEP Action) is one of the expert groups that has agreed to inform the development of Seizure First Aid Training. They are interested in the rare, but important event of sudden unexplained death in epilepsy.

iii) Finally, whilst the proposed primary outcome measure for a future trial is subsequent epilepsy-related ED use, the current study will not be promoted to participants as one which is seeking to reduce use of ED. Rather, it will be explained that this is a study which is responding to what many users have said they would like – namely, more information on epilepsy first aid. One way in which we intend to try to capture subsequent ED use is by asking participants to self-report on this at follow-up, as they will on a variety of other outcomes (e.g., other aspects of service use, seizures, quality of life). Under no circumstances, however, will the research staff who are recruiting and assessing participants give the patients any sense of reprimand should they report ED use at follow-up.

9.2 Ethical Approval

The study protocol has received the favourable opinion of the Multi-centre Research Ethics Committee (MREC) and will undergo independent review at the R&D offices at participating sites. A copy of local Research & Development (R&D) approval should be forwarded to CTRC before a site is initiated and patients recruited.

9.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a research study and continues throughout the individual's participation. Informed consent is required for all people participating in any phase of this project. In obtaining and documenting informed consent, the researchers should comply with applicable regulatory requirements and should adhere to Good Clinical Practice and to the ethical principles that have their origin in the Declaration of Helsinki.

Consent from health professional, patient and carer participants should be obtained prior to participation. Discussion of objectives, risks and inconveniences of the project and the conditions under which it is to be conducted are to be provided to potential participants by researchers with experience in obtaining informed consent. Participant Information Sheets and Consent forms, describing in detail the project, procedures and risks will be approved by an independent ethical committee and the participants will be asked to read and review the document. Upon reviewing the document, the researcher will explain the research study to the participant. This information will emphasise that participation in the project is voluntary and that the participant may withdraw from the study at any time and for any reason. All participants will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the project may be obtained will be provided.

The person will then sign and date the informed consent document. Both the person taking consent and the participant must personally sign and date the form. A copy of the informed consent document will be given to the person for their records. The original copy will be filed by the coordinating research team. For patient participants, a further copy of the signed consent form will (with the patient's consent) will be sent to their GP for their medical records.

Health professionals, patients and carers will have as long as they require to decide whether to take part in the project or not.

Only individuals able to independently provide informed consent will be able to participate in this project. Assent will not be obtained for the purposes of either Part A or B of this project.

Participants may, without being subject to any resulting detriment, withdraw from the project at any time by revoking the informed consent. The rights and welfare of the patient participants will be protected by emphasising to them and their family and friends that their quality of medical care will not be adversely affected if they decline to participate in the study.

9.4 Study Discontinuation

PART A INTERVENTION DEVELOPMENT:

Not applicable.

PART B PILOT RCT:

In the event that the study is discontinued, patient participants will be treated according to usual standard clinical care. The process for participants who withdraw early from trial treatment or from the trial completely is described in section 5.3.

10 STUDY MONITORING

Oversight Committees related to the monitoring of the project are detailed in section 13.

10.1 Source Documents

Part A

Not relevant

Part B

Source data: *All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*

Source documents: *Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information is the CRF. Data recorded in the CRF should be consistent and verifiable with source data in source documents other than the CRF.

Identified source documents other than the CRF for this trial are:

- Hard copy questionnaires
- Hospital Episode Statistics data sets
- Records of attendance for Seizure First Aid Training courses.

Therefore, for data where no prior record exists and which is recorded directly in the CRF, the CRF will be considered the source document, unless otherwise indicated by the investigator. All such exemptions should be identified prior to the trial. In addition to the above, the GPs (and specialists if applicable) of patient participants should, with the patient's permission (as specifically indicated on the consent) be sent a letter informing them of the patient's participation. This will include a copy the patient's signed and dated consent form. The letter will not note to which arm the patient has been randomised.

10.2 Data Capture Methods

Part A

Data capture will be in the form of audio-recordings, transcriptions and field notes.

Part B

Data capture will be in the form of paper copies.

10.2.1 Case Report Forms

PART A Intervention development:

In advance of the user feedback sessions, patients and carer participants will be sent the applicable, initial draft of the baseline outcome questionnaire pack. They will be asked to provide feedback on this during the focus group.

PART B Pilot RCT:

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. Patient and carer participants should be encouraged and strongly supported as necessary to provide answers to questions asked. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “ND”. If the item is not applicable to the individual case, write “NA”. Or if the data item is un-known, write “NK”. If a data item has not been recorded on source data then write ‘NR’. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

The research workers (and study administrator, where available) should aim to enter the data from the CRFs onto the data-set and file the original CRF at the coordinating centre within 3 days of the date at which data was collected or returned time specified for completion. Entering data in a timely fashion will allow an opportunity to identify early on any missing data and make attempts to obtain it.

Participant initials and participant identification number should be clearly labelled on all documents. For questionnaires that are posted by the research team to patient and carer participants for the 6-month (T2) follow-up, the header containing participant initials and identification number should be completed before sending by the research team.

10.3 Central Monitoring

Data stored at CTRC will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data from the CRF will be returned to the research workers in the form of data queries. Data query forms will be produced at the CTRC from the trial database and sent either electronically or through the post to the research workers. Research workers will promptly respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTRC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

10.3.1 Confidentiality

PART A Intervention development:

Individual participant medical information obtained as a result of this phase by the research team is considered confidential and disclosure to third parties is prohibited. This development phase of the project includes two Seizure First Aid Training courses and two focus groups. There is, however, the possibility that patient and carer participants could share personal information about themselves during the focus groups or Seizure First Aid Training courses and that another participant discusses this information with persons outside of the study. The research team will mitigate against this by firstly asking participants during the consent process to sign that they agree that personal information shared during group focus group/ Seizure First Aid Training course should remain confidential.

Secondly, before the focus groups and Seizure First Aid Training courses commence the researcher and facilitators respectively will reiterate this ground rule so as to increase the likelihood that personal information is kept confidential. The Participant Information Sheets shall, however, emphasise to those considering participation the possible limits to confidentiality.

PART B Pilot RCT:

CRFs will be labelled with the patient's initials and unique project identification number. The coordinating centre will collect, enter and file the CRFs. They will not need to typically transfer identifiable data. The exceptions to this are that:

1. With the patient's permission (as specifically indicated on the consent), the patient's GP (and specialist if applicable) will be sent a letter by the research worker informing them of the patient's participation.
2. The study administrator will need to receive attendance records from the educational facilitators for the Seizure First Aid Training courses that they run. This data will be uploaded to the intervention data-set. These records will include patient and carer contact details including name, address and participant identification numbers.

The research team will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted.

It is possible that a research worker or one of the educational facilitators delivering the full Seizure First Aid Training courses may become concerned about a patient participant's wellbeing (e.g., particularly low mood). In these circumstances there may be the need for disclosures to be communicated beyond the research team to the participant's GP. Where a research worker or educational facilitator has concern they will in the first instance discuss this with the Chief Investigator. A decision as to how to approach the issue will then be made. Where necessary the Chief Investigator will be able to seek the expertise of other principal research team investigators. This includes an epileptologist (AM), a GP (LR) and an emergency physician (SG).

If there is concern about a patient's wellbeing, the Chief Investigator will contact the patient and sensitively discuss the issue with them, the reason for concern and that it is felt that in this instance this information needs to be passed on to their GP. This limit to confidentiality and the circumstances under which action may be taken by the research team will be made clear to potential participants at the outset of the project in the patient Participant Information Sheets. We would highlight here however that whilst patient participants will complete a measure of emotional wellbeing in this study (i.e., the Hospital Anxiety and Depression Scale). It does not have a suicide item, nor is it diagnostic.

10.3.2 Quality Assurance and Control

Part A

Not relevant in the terms discussed here.

Part B

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. In accordance with the monitoring plan, source verification will be performed if indicated to be required as a result of central monitoring processes.

To this end:

- The Principal Investigator from each centre will have a site-set-up meeting with the Chief Investigator which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The Chief Investigator is to verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training;

- The Chief Investigator is to monitor screening, recruitment and drop-out rates between centres;
- The CTRC Data Manager is to conduct data entry consistency checks and follow-up data queries;
- Independent oversight of the trial will be provided by independent members of the Study Steering Committee. A Data and Safety Monitoring Committee is not required for the pilot trial phase.

10.4 Records Retention

Part A & Part B

The coordinating centre via the Research Workers and Administrator will undertake to store original qualitative data and originally completed CRFs until the Clinical Trials Unit informs the Chief investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest). The coordinating centre will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

11 INDEMNITY

The Seizure First Aid Training project is sponsored by the University of Liverpool, with the pilot trial phase being co-ordinated by the CTRC in the University of Liverpool. The University of Liverpool does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The University of Liverpool has clinical trials insurance and professional indemnity policies in place to cover its liabilities in regards to any work undertaken by its staff in the course of their employment at the University.

As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:

“A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process”.

12 FINANCIAL ARRANGEMENTS

This study is funded by the NIHR's Health Services and Delivery Research (HS&DR) Programme of the Department of Health.

12.1 Financial Support to Research Sites

Part A.

Not applicable.

Part B.

As the study is funded by the NIHR, it will be automatically adopted onto the NIHR Portfolio. This will allow trusts to apply to their comprehensive local research network for NHS support costs as required. The Coordinating Centre will also upload all participant accruals. Accrual data feeds in to the process of allocating future funding from the UKCRN to the CLRN, and from the CLRN to NHS Organisations to ensure that infrastructure resources are directed to where they are required. This infrastructure includes clinical research support staff and sessional support for clinical investigators of all professions to support studies on the UKCRN Portfolio.

12.2 Financial Support to Participants

Part A.

Each of the 7 expert representatives that will review the existing Epilepsy Society course material and then be interviewed about it will be paid a consultancy fee of £200 for their time. This will be transferred to them from the University following their interview.

Patient-carer dyads will be asked to attend a Seizure First Aid Training development course and then give feedback. This course will be held in the community. In preparation for the project we consulted with users. This identified that PWE can be reluctant to use public transport due to the possibility of seizures. Funds will be available to contribute towards return taxi travel for participants to attend the courses or otherwise reimburse them for costs incurred. A maximum of £30 is available for each dyad attending the course. Where travel costs have been individually incurred by participants, the person will be reimbursed from a petty cash allocation following production of a receipt or travel ticket. Each patient and carer who attends the course will also receive a £10 shopping voucher in acknowledgement of the time they have given to the project. This will be given to them following their participant in the focus group.

Part B.

We plan to maximise the uptake and retention of patients and carers by using shopping vouchers. There are 3 assessments that patient participants are requested to complete and 3 assessments that carer participants are requested to complete. For each assessment that a participant completes, they will receive a £10 shopping voucher immediately following completion of the assessment/ or receipt of their completed questionnaire in the case of the 6 month postal follow-up. Patient and carer receipt of vouchers will not depend on whether their carer or the patient they are participating with has completed their equivalent assessment.

The baseline and 12 month assessments of the patients and carers will typically be administered by the Research Workers in the patient and carers home/s. Where patients and/or carers visit the coordinating centre to complete the assessments and incur a cost, they will be reimbursed up to a cost £15 each. The group Seizure First Aid Training courses that participants will be asked to complete will take place outside of their homes. Funds will be available to contribute towards return taxi travel for participants to attend the Seizure First Aid Training courses or otherwise reimburse them for costs incurred. A maximum of £30 is available for each dyad attending the course. If necessary, the project administrator will be

available to help arrange taxi travel and charges made account the project account. Where travel costs have been individually incurred by participants, the person will be reimbursed from a petty cash allocation following production of a receipt or travel ticket.

12.3 Financial Support for Seizure First Aid Training courses

Part A.

Two courses will be run using the first iteration of the Seizure First Aid Training course. As these development courses are specific to this project the cost of running them will be covered by the NIHR research grant. The costs include a fee that will be paid to the Epilepsy Society for one of their educational facilitators to deliver the courses, the costs of room hire and for refreshments for participants.

Part B.

In addition to receiving usual medical care, all patients recruited from the EDs (and one of their carers) will get to go on the Seizure First Aid Training course at some point. There is an excess treatment cost (ETC) associated with participants receiving the specialist Seizure First Aid Training course as part of the pilot RCT. This results from the cost of room hire and the time of a trained Epilepsy Society educational facilitator (typically a nurse) to deliver the course. The cost for each patient-carer dyad to receive the Seizure First Aid Training is £84.38. As we anticipate recruiting 80 dyads for the pilot RCT, the total ETC is £6,750.

Research awards from the NIHR cover only research costs. They do not cover ETCs. Instead, their funding structure expects that NHS Trusts and Commissioners ensure the costs for a research study's intervention are provided and funded through normal commissioning. For purposes of the Seizure First Aid Training project, the ETCs are to be provided via the normal commissioning route.

The costs of refreshments for the courses will be met by the NIHR research grant.

13 STUDY COMMITTEES

13.1 Study Management Group (SMG)

A Study Management Group (SMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the CTRC. The SMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year. Refer to the TMG terms of reference and trial oversight committee membership document for further details.

13.2 Study Steering Committee (SSC)

As per the NIHR HS&DR guidelines, an independent Study Steering Committee (SSC) will be formed and approved by the funder.

The role of the SSC will be to provide overall supervision for the project on behalf of the Project Sponsor and Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The main features of the SSC are as follows:

- To provide advice, through the Chair, to the Chief Investigator, the Project Sponsor, the Project Funder, the Host Institution and the Contractor on all appropriate aspects of the project
- To concentrate on progress of the project, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question
- The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society
- To ensure appropriate ethical and other approvals are obtained and in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- To provide advice to the investigators on all aspects of the project

The SSC will have a minimum of 75% majority of independent members. The minimum quoracy for a meeting to conduct business is 67% of appointed members. It will be chaired by an independent Chair who is a Professor Emergency Medicine who is UK based and/or holding a substantive UK based appointment. Other independent members will include an independent neurologist, an independent representative from the ambulance service, an independent expert in the development and testing of complex health interventions and 2 individuals who are able to contribute a patient and care perspective.

Although there may be periods when more frequent meetings are necessary, the SSC will meet at least annually. Meeting minutes will be sent to all members, the sponsor, the funder and the study master file. The responsibility for calling and organising SSC meetings lies with the Chief Investigator, in association with the Chair.

The Seizure First Aid Training project does not require a DMEC as stated by the funder's guidelines.

Independence

The definition of independent is as follows:

- Not part of the same institution as any of the applicants or members of the project team
- Not part of the same institution that is acting as a recruitment or investigative centre
- Not related to any of the applicants or members of the project team
- For the Chair only – not an applicant on a rival proposal

13.3 Independent Data and Safety Monitoring Committee (IDSMC)

The Seizure First Aid Training project does not require an IDSMC as stated by the funder's guideline (www.nets.nihr.ac.uk/data/...doc/.../ssc-and-dmec-checklist-june13.doc)

14 PUBLICATION

The Study Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (<http://www.icmje.org/>) will be respected. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the SSC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

15 PROTOCOL AMENDMENTS

15.1 Version 1.0 (19/01/2015)

Original Approved version.

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17 APPENDICES

Appendix 1 The mechanisms by which the Seizure First Aid Training course might reduce unnecessary/ avoidable ED use

Appendix 2 Relevant postcodes for Part B screening exercise to identify patients who should be approached, subject to other inclusion/ exclusion criteria

Appendix 1 The mechanisms by which the Seizure First Aid Training course might reduce unnecessary/ avoidable ED use

Pathway of ED attendance	How might course reduce ED use by pathway?
<p>1. Patient self-referral</p> <p><i>Pathway 1.1:</i> Some patients' have low knowledge of epilepsy and seizures, have incorrect beliefs concerning seizure first aid, lack confidence managing seizures and can be disproportionately fearful of them (e.g., [117]). Consequently, some patients will 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.</p> <p><i>Pathway 1.2:</i> There is some 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) [118, 119].</p> <p><i>Pathway 1.3:</i> 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 [18]. They can empower patients and families to manage some seizures, without the need for medical assistance [120, 121]. Patients, however, might not be aware of them or their utility. They may also have incorrect beliefs about them which may act as a barrier to their use (e.g., that they all need to be rectally administered).</p>	<p><i>1.1</i> By covering the 8 topics listed earlier, the training course could help increase patients' knowledge of what seizures are, what their effects are and help patients to know when it is and is not necessary to seek emergency assistance. This information, which is delivered in everyday language, could serve to increase patients' confidence in managing seizures, including post-ictal states, and help them to delineate the critical circumstances that require emergency services to be contacted. The course could also help allay disproportionate fears that patients hold.</p> <p><i>1.2:</i> The ES's 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.</p> <p>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 patients' feelings of stigma and shame about their diagnosis. Stigma can be associated with willingness to accept one's diagnosis and antiepileptic treatments.</p> <p><i>1.3:</i> The ES's course includes the topic 'Treatments: Medication and side-effects'. This covers emergency medication. Sources of further information on this topic will also be provided. The information that is relayed to PWE could enable them to start a discussion with their usual care provider about whether such treatment is suitable for them. It is the usual care provider who would need to organise the prescription of such treatments and develop an action plan with the patient for their use. The GP (& specialist if applicable) of patient participants will have received a letter explaining the study and informing them of their patient's participation.</p>
<p>2. Referral by informal carer</p> <p><i>Pathway 2.1:</i> Responsibility for managing epileptic seizures is often delegated to informal carers; 90% of PWE identify an informal carer [35]. Some of these persons have low knowledge of epilepsy and</p>	<p><i>2.1:</i> The Seizure First Aid Training course could help increase carers' 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</p>

<p>seizures, have incorrect beliefs concerning seizure first aid, lack of confidence in helping managing them and can be fearful of them and their threat to the patients' life [34, 122]. This can mean some carers always call for emergency medical attention when the patient has or has had a seizure, regardless of whether it is medically required or not.</p> <p><i>Pathway 2.2:</i> There is some evidence that in a minority of 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., having forgotten doses) or epilepsy in an optimum manner (e.g., not taken precaution to avoid a seizure trigger) [118, 119].</p> <p><i>Pathway 2.3:</i> Portable emergency medications (e.g., buccal midazolam) can be prescribed to PWE who have had a previous episode of prolonged or serial convulsive seizures [18]. Their prescription can empower some carers to manage some seizures, without medical assistance and provide them and the patient with a greater sense of freedom [120, 121]. Carers, however, might not be aware of them or their utility. They may also have incorrect beliefs about them which may be a barrier to their use (e.g., that they all need to be rectally administered).</p>	<p>identify alternative pathways of support. It could also help allay disproportionate fears held by the carer.</p> <p>2.2 The course describes what antiepileptic medications do, explains why adhering to prescribed regimes is important and outlines potential seizure triggers. This information could help carers better support PWE to manage their medication (e.g., helping PWE with reminders) and risk management (e.g., helping the PWE to identify and avoid triggers, such as sleep deprivation, stress). It is possible that imparting appropriate information on carers means that they themselves could become powerful supporters of the development of self-management responsibility in the PWE that they know.</p> <p>2.3: The ES's course includes the topic 'Treatments: Medication and side-effects'. This covers emergency medication. Sources of further information on this topic will also be provided. The information that is relayed to carer could enable them to start a discussion with the patient's usual care provider about whether such treatment is suitable for the patient. It is the usual care provider who would need to organise the prescription of such treatments and develop an action plan for their use.</p>
<p><u>3. Referral by person in wider social network</u></p> <p><i>Pathway 3.1:</i> PWE will be able to attend the Seizure First Aid Training course with one informal carer. ED attendances can, however, also result from a person in the patients' social network lacking confidence in helping the patient or having incorrect beliefs [123].</p>	<p>3.1: By covering the 8 topics noted earlier, the ES's course could help PWE to feel more informed and comfortable with their diagnosis. This could increase their confidence and empower them to have a discussion with others about their epilepsy and relay correct information about how they can be helped if they have a seizure and what their preferences regard transportation to ED are. This could include telling them what constitutes typical and atypical seizure activity. To help PWE do this, the ES has a variety of resources which participants' will be given or have their attention drawn to. For example, in participants' take-away information pack, there will be a number of free wallet sized 'Seizure First Aid Cards' which can be given to friends and family members. These outline the steps of seizure management and note when it is necessary to call for emergency assistance. The card also provides the address of an ES webpage for carers, family and</p>

	friends and an information telephone number.
<p>4. Having had a seizure in a public place</p> <p><i>Pathway 4.1:</i> In a minority of cases (~15%, [6]), 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 (e.g., because they do not know the patient's medical history. The patient may also be in a post-ictal state and whilst it is not necessary to transport them to hospital, they do not have an alternative way of ensuring the patient's safety. There is also some evidence that due to low confidence in managing seizures, some ambulance staff can be insistent about transporting the patient to ED [72].</p>	<p>4.1. The ES's course does not currently cover this topic. However, with the help of experts and users consulted during the development phase, we intend to introduce this as a new topic. It is anticipated that this will involve briefly discussing with PWE and carers the challenges that face ambulance crews when managing seizures, the benefits of patients carrying easily accessible epilepsy identification cards (which the ES will provide for free to patients) 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 will also be advised on the rules and regulations concerning transportation to ED by paramedics.</p>

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Appendix 2 Relevant postcodes for Part B screening exercise to identify patients who should be approached, subject to other inclusion/ exclusion criteria

All relevant postcodes (excludes duplicates)	25 miles from Aintree Hospital (L9 7AL)	25 miles from Royal Liverpool Hospital (L7 8XP)	25 miles from Arrowe Park Hospital (CH49 5PE)
BB3	BB3	BL1	CH1
BL1	BL1	BL11	CH2
BL11	BL11	BL3	CH25
BL2	BL2	BL5	CH26
BL3	BL3	BL6	CH27
BL4	BL4	CH1	CH28
BL5	BL5	CH2	CH29
BL6	BL6	CH25	CH3
BL7	BL7	CH26	CH30
BL78	BL78	CH27	CH31
CH1	CH1	CH28	CH32
CH2	CH2	CH29	CH33
CH25	CH25	CH3	CH34
CH26	CH26	CH30	CH4
CH27	CH27	CH31	CH41
CH28	CH28	CH32	CH42
CH29	CH29	CH33	CH43
CH3	CH3	CH34	CH44
CH30	CH30	CH4	CH45
CH31	CH31	CH41	CH46
CH32	CH32	CH42	CH47
CH33	CH33	CH43	CH48
CH34	CH34	CH44	CH49
CH4	CH4	CH45	CH5
CH41	CH41	CH46	CH6
CH42	CH42	CH47	CH60
CH43	CH43	CH48	CH61
CH44	CH44	CH49	CH62
CH45	CH45	CH5	CH63
CH46	CH46	CH6	CH64
CH47	CH47	CH60	CH65
CH48	CH48	CH61	CH66
CH49	CH49	CH62	CH7
CH5	CH5	CH63	CH70
CH6	CH6	CH64	CH8
CH60	CH60	CH65	CH88
CH61	CH61	CH66	CH99
CH62	CH62	CH7	CW6
CH63	CH63	CH70	CW8
CH64	CH64	CH8	L1
CH65	CH65	CH88	L10
CH66	CH66	CH99	L11
CH7	CH7	CW6	L12
CH70	CH70	CW7	L13
CH8	CH8	CW8	L14

CH88	CH88	CW9	L15
CH99	CH99	FY0	L16
CW6	CW6	FY8	L17
CW8	CW8	L1	L18
CW9	CW9	L10	L19
FY0	FY0	L11	L2
FY1	FY1	L12	L20
FY3	FY3	L13	L21
FY4	FY4	L14	L22
FY8	FY8	L15	L23
L1	L1	L16	L24
L10	L10	L17	L25
L11	L11	L18	L26
L12	L12	L19	L27
L13	L13	L2	L28
L14	L14	L20	L29
L15	L15	L21	L3
L16	L16	L22	L30
L17	L17	L23	L31
L18	L18	L24	L32
L19	L19	L25	L33
L2	L2	L26	L34
L20	L20	L27	L35
L21	L21	L28	L36
L22	L22	L29	L37
L23	L23	L3	L38
L24	L24	L30	L39
L25	L25	L31	L4
L26	L26	L32	L40
L27	L27	L33	L5
L28	L28	L34	L6
L29	L29	L35	L67
L3	L3	L36	L68
L30	L30	L37	L69
L31	L31	L38	L7
L32	L32	L39	L70
L33	L33	L4	L71
L34	L34	L40	L72
L35	L35	L5	L73
L36	L36	L6	L74
L37	L37	L67	L75
L38	L38	L68	L8
L39	L39	L69	L9
L4	L4	L7	LL11
L40	L40	L70	LL12
L5	L5	L71	LL13
L6	L6	L72	LL15
L67	L67	L73	LL16
L68	L68	L74	LL17
L69	L69	L75	LL18

L7	L7	L8	LL19
L70	L70	L9	LL22
L71	L71	LL11	PR8
L72	L72	LL12	PR9
L73	L73	LL16	WA1
L74	L74	LL17	WA10
L75	L75	LL18	WA11
L8	L8	LL19	WA12
L9	L9	M28	WA2
LL17	LL17	M29	WA3
LL18	LL18	M31	WA4
LL19	LL19	M38	WA5
M27	M27	M41	WA55
M28	M28	M44	WA6
M29	M29	M46	WA7
M30	M30	PR25	WA8
M31	M31	PR26	WA88
M38	M38	PR4	WA9
M41	M41	PR6	WN1
M44	M44	PR7	WN2
M46	M46	PR8	WN3
PR0	PR0	PR9	WN4
PR1	PR1	WA1	WN5
PR11	PR11	WA10	WN6
PR2	PR2	WA11	WN8
PR25	PR25	WA12	
PR26	PR26	WA13	
PR4	PR4	WA14	
PR5	PR5	WA2	
PR6	PR6	WA3	
PR7	PR7	WA4	
PR8	PR8	WA5	
PR9	PR9	WA55	
WA1	WA1	WA6	
WA10	WA10	WA7	
WA11	WA11	WA8	
WA12	WA12	WA88	
WA13	WA13	WA9	
WA14	WA14	WN1	
WA2	WA2	WN2	
WA3	WA3	WN3	
WA4	WA4	WN4	
WA5	WA5	WN5	
WA55	WA55	WN6	
WA6	WA6	WN7	
WA7	WA7	WN8	
WA8	WA8		
WA88	WA88		
WA9	WA9		
WN1	WN1		

WN2	WN2		
WN3	WN3		
WN4	WN4		
WN5	WN5		
WN6	WN6		
WN7	WN7		
WN8	WN8		
CW7			
LL11			
LL12			
LL16			
LL13			
LL15			
LL22			

