Horizon Scanning Research & Intelligence Centre

Emerging technologies for the diagnosis, treatment and management of epilepsy

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This review is based on information that was publicly available at the time of research and may include opinions from a small number of clinical experts, patients and the public. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technologies included and should not be used for commercial purposes, the development of clinical trials or commissioning without additional information.

Due to the nature of innovation being driven to answer unknown questions and deliver solutions to unmet clinical needs, it should be noted that the health technologies discussed in this report may not have sufficient clinical exposure and clinical expertise to address the potential benefits and harms of the technologies in detail.

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EXECUTIVE SUMMARY

This horizon scanning review was conducted by the NIHR Horizon Scanning Research & Intelligence Centre (HSRIC) to identify emerging technologies for the diagnosis and management (including treatment) of epilepsy. In addition, we explored the perspectives of healthcare professionals and people affected by epilepsy on the technologies identified in terms of their potential for impact on people with epilepsy and on health services.

Epilepsy is a common neurological condition that affects more than half a million people in the UK (around 1 in 100 people). It is characterised by a tendency to have sudden and unprovoked seizures that start in the brain. There are over 40 different types of epilepsy, and the condition can affect people of all ages.

We searched a wide variety of sources of intelligence to identify technologies at an early stage of development (equivalent to phase I/II). These sources included horizon scanning databases, clinical trial registries, commercial and bibliographical databases, and online news sources. Once the initial data had been collected the technologies were filtered against predetermined inclusion and exclusion criteria using publicly available information. This filtration process produced a final list of technologies believed to be in early clinical development.

This report presents a summary of the 114 new and emerging technologies that were identified, comprising 27 drugs and 87 medical devices, procedures and techniques. Advances are being made across a wide range of technology areas, including drugs, neurostimulation devices, imaging and genetic techniques, and new surgical, digital and cognitive technologies. The technologies that we identified were for applications across the entire care pathway for epilepsy, from diagnosis, through treatment and on to mobile technologies for real-time self-management.

The report also summarises the views of clinical experts and members of the public affected by epilepsy on the technologies and their potential for impact. People affected by epilepsy considered a number of the emerging technologies to have great potential. Their main concerns about new technologies included the risks and side-effects of new invasive procedures, the reversibility of implanted devices if they prove problematic or do not work as intended, the effectiveness, safety, cost, availability of new technologies, and their impact on quality of life. The importance of having more individualised approaches to therapy and technologies that empower people to self-manage their condition more effectively was emphasised. The technologies that we identified were in early clinical development, and research is ongoing. As the experts and people affected by epilepsy stressed, for many of the technologies further evidence is needed to support or negate their use by individuals and the National Health Service (NHS).
ACKNOWLEDGEMENTS

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- Mr Jibril Farah, Consultant Neurosurgeon, Walton Centre NHS Foundation Trust, Liverpool.
- Dr Nigel Hoggard, Clinical Senior Lecturer in Radiology, Royal Hallamshire Hospital NHS Foundation Trust, Sheffield.

Patient and public involvement and engagement (PPIE): people affected by epilepsy
The charity Epilepsy Action enabled us to involve four members of the public in the review who are members of their Epilepsy Action Research Network (EARN).

The NIHR Horizon Scanning Research and Intelligence Centre is grateful to all those who helped us to include both a healthcare professionals’ and potential users’ perspective in this report. We thank Epilepsy Action and all the clinical experts and people affected by epilepsy for their time and valuable contributions.
INTRODUCTION

This horizon scanning review presents the findings of a project that aimed to identify emerging technologies for the diagnosis and management (including treatment) of epilepsy. It was conducted by the NIHR Horizon Scanning Research and Intelligence Centre (HSRIC) to provide early intelligence for the MRC/NIHR Efficacy and Mechanism Evaluation (EME) Programme about developments in this field.

1.1. DIFFERENT TYPES OF EPILEPSY

The term epilepsy covers a heterogeneous group of disorders; there are around 40 different types of seizure and over 30 epilepsy syndromes.

Epilepsy is characterised by recurring seizures, and is defined by any of the following criteria:

a) At least two unprovoked (or reflex) seizures occurring more than 24 hours apart.
b) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
c) Diagnosis of an epilepsy syndrome.

For each person with epilepsy, the aim is to apply a diagnostic framework that includes three domains: (i) aetiology, (ii) electroclinical syndrome, and (iii) seizure type.

1.1.1. CLASSIFICATION BY CAUSE

The World Health Organization (WHO) classifies epilepsy according to cause (aetiology) as follows:

1. Idiopathic epilepsy
   The most common type of epilepsy (affecting six out of ten people with the disorder), in which there is no identifiable cause.

2. Symptomatic epilepsy
   Epilepsy in which there is a known cause (also known as secondary epilepsy). Examples of such causes include:
   - Brain damage from prenatal or perinatal injuries (e.g. a loss of oxygen or trauma during birth, low birth weight).
   - Congenital abnormalities or genetic conditions with associated brain malformations.
   - Severe head injury.
   - Stroke that restricts the amount of oxygen to the brain.
   - Infection of the brain such as meningitis, encephalitis, neurocysticercosis.
   - Certain genetic syndromes.
   - Brain tumour.

The International League Against Epilepsy (ILAE) uses a classification system based on six categories that affect therapeutic approaches. These categories are not independent and a person’s aetiology may fit into two or more categories:

1. Genetic - Genetic factors (both inherited and de novo) are presumed to play a major role in causation, although in most cases the underlying genes are not yet known. A major subgroup called genetic generalised epilepsy (GGE) (also known as ‘idiopathic’ generalised epilepsy, IGE) accounts for one third of all epilepsies.
2. Structural - There is a distinct structural abnormality, e.g. focal cortical dysplasia, trauma, and hypoxic-ischemic damage. The underlying basis for a structural abnormality may be genetic and/or acquired.

3. Metabolic - There is a well delineated metabolic defect with manifestations or biochemical changes throughout the body such as porphyria, uraemia, amino-acidopathies or pyridoxine dependent seizures. It is likely that most metabolic epilepsies will have a genetic basis but some may be acquired.

4. Immune - There is evidence of autoimmunity-mediated inflammation in the central nervous system.

5. Infectious - Associated with infections affecting the central nervous system, such as tuberculosis, HIV and cerebral malaria.

6. Unknown - Where it is not possible to make a specific diagnosis apart from the basic electroclinical semiology (e.g. frontal lobe epilepsy).

### 1.1.2. CLASSIFICATION BY ELECTROCLINICAL SYNDROME

Epilepsies may also be classified into around 31 different syndromes (sometimes referred to as electroclinical syndromes). Each syndrome refers to a distinctive disorder identifiable on the basis of a set of features including typical age of onset, seizures types, and specific electroencephalogram (EEG) characteristics, imaging features and specific co-morbidities.

### 1.1.3. CLASSIFICATION BY SEIZURE TYPE

For a significant group of people with epilepsy (around a third) the type of epilepsy cannot be diagnosed in terms of either aetiology or syndrome. A classification by seizure types has been proposed by ILAE for purposes of communication in clinical care, teaching and research.

1. Focal seizures (also known as partial seizures)
   - Motor: tonic, atonic myoclonic, clonic, epileptic spasms, hypermotor.
   - Non-motor: sensory, cognitive, emotional and autonomic.

2. Generalised seizures
   - Absence: typical. Atypical, myoclonic, eyelid myoclonia.

3. Unknown onset
   - Motor: tonic-clonic, tonic, epileptic spasms.
   - Non-motor.

Note: If a seizure is unusually prolonged (lasting five minutes or more) or seizures occur repeatedly (three or more within an hour) with no recovery between, this is known as status epilepticus (SE). SE can be potentially dangerous and can even lead to death if it is not identified and treated early.
1.2. CLINICAL NEED AND BURDEN OF DISEASE

Epilepsy is the most common serious brain disorder worldwide\(^9\) and the fourth most common neurological condition\(^10\). The estimated proportion of the general population that have active epilepsy (i.e. continuing seizures or with the need for treatment) at a given time is 4-10 per 1,000 people\(^11\). There are around 600,000 people living with epilepsy in the UK\(^12\), and around 1,000 people die annually from epilepsy-related causes\(^13\). The incidence of Sudden Unexpected Death In Epilepsy (SUDEP) is estimated to be around one death per 1,000 people with epilepsy per year\(^14\). In financial terms it has been estimated that the annual cost of established epilepsy in the UK is around £2 billion\(^15\).

The diverse nature of epilepsy means that it can be difficult to diagnose accurately, and estimates suggest that 5-30% of diagnoses may be incorrect\(^15\). Although epilepsy can start at any age, it is most commonly diagnosed in people under the age of 20 (accounting for 70% of cases\(^16\)) and adults over 65 years\(^17\). For some people their epilepsy only lasts for a short time (due to spontaneous remission) while in others it is a lifelong condition.

Around 354,000 people in England are currently receiving anti-epileptic drugs (AEDs) (of which 90% are adults and 10% are children and young people)\(^18, 19\). In England, prescriptions for AEDs cost £433 million in 2013 (which was a 13% increase on the previous year)\(^20\).

1.3. CURRENT CLINICAL PRACTICE

1.3.1. CARE PATHWAY\(^21\)

Diagnostic investigations\(^15\)

- Electroencephalogram (EEG) – a test in which electrical activity in the brain is recorded for analysis via electrodes attached to the head at standardised points.
- Brain imaging (neuroimaging) – used to identify structural abnormalities that cause certain epilepsies:
  - Magnetic Resonance imaging (MRI)
  - Computerised axial tomography (CAT) – used to identify underlying gross pathology if MRI is not available or is contraindicated.
- Other tests:
  - blood tests (e.g. plasma electrolytes, glucose, calcium) - used in adults to identify potential causes and/or to identify any significant co-morbidity
  - blood and urine biochemistry - used in children and young people to exclude other diagnoses, and to determine an underlying cause of the epilepsy
  - 12-lead electrocardiography (ECG) - used in adults with suspected epilepsy and in children and young people in cases of diagnostic uncertainty.
- Neuropsychological assessment – used in children, young people and adults in whom it is important to evaluate learning disabilities and cognitive dysfunction, particularly in regard to language and memory.
There is no cure for epilepsy. While up to 70% of people with active epilepsy have their condition controlled satisfactorily with AEDs\textsuperscript{15, 17, 19}, a substantial proportion (estimates range from around 30-48%\textsuperscript{22, 23}) of people with epilepsy do not respond to medication. Other treatment options include:

- Psychological interventions:
  - relaxation techniques, cognitive behaviour therapy (CBT) and biofeedback may be used in conjunction with AED therapy in adults where seizure control is inadequate with optimal AED therapy
  - relaxation techniques and CBT may be used in children and young people with drug-resistant focal epilepsy.

- Ketogenic diet (KD) - a high fat, low carbohydrate, controlled protein diet used in children and young people with epilepsy whose seizures have not responded to appropriate AEDs.

- Vagus Nerve Stimulator (VNS, an implanted medical device):
  - adjunctive therapy to reduce the frequency of seizures in adults, young people and children who are refractory to antiepileptic medication but who are not suitable for surgery.

- Brain surgery (neurosurgery) - to remove a specific area of the brain which is thought to be causing the seizures, or to separate the part of the brain that is causing seizures from the rest of the brain\textsuperscript{24}.

### 1.3.2. CLINICAL GUIDELINES

Clinical guidelines relevant to the diagnosis and management of epilepsy include:

- NICE clinical guideline. Epilepsies: diagnosis and management. CG137, January 2012 (updated February 2016)\textsuperscript{15}.
- NICE quality standard. Epilepsy in adults. QS26, February 2013\textsuperscript{19}.
- NICE quality standard. Epilepsy in children and young people. QS27, February 2013\textsuperscript{18}.
- SIGN national clinical guideline. Diagnosis and management of epilepsy in adults. SIGN143, May 2015\textsuperscript{25}.
- SIGN national clinical guideline. Diagnosis and management of epilepsy in children and young adults. SIGN81, March 2005\textsuperscript{26}.

### 2 AIM

To identify emerging technologies for the diagnosis and management of epilepsy, and to engage with experts and people affected by epilepsy to gain an insight into the potential of these technologies for impact on people with epilepsy and the national health service (NHS).

### 3 METHODS

Initial scoping searches were undertaken to obtain background information about epilepsy, including clinical need, burden of disease, and the various terms and definitions used in relation to this heterogeneous condition. Scoping the field informed the development of appropriate search terms, inclusion and exclusion criteria, and the formulation of a bespoke search strategy. The following methods were used to conduct this horizon scanning review.
3.1. IDENTIFICATION

3.1.1. SEARCH OF ELECTRONIC SOURCES

We searched the following electronic sources of intelligence to identify relevant emerging health technologies:

- Horizon scanning databases
- Commercial pharmaceutical and medical technology databases
- Clinical trial registries and research funding databases
- Industry news websites
- Bibliographical databases
- Professional conference proceedings
- Websites of key organisations and networks.

A detailed list of the sources of intelligence searched for this review is presented in Appendix 1. A list of search terms used when searching for relevant emerging technologies can be found in Appendix 2.

3.1.2. INVOLVEMENT OF EXPERTS

We contacted clinical experts and relevant professional organisations to obtain intelligence on relevant technology developments that they were aware of, and any relevant identification sources, such as conference proceedings that may provide information on emerging technologies. A list of individual experts and organisations contacted can be found in Appendix 3.

3.1.3. INVOLVEMENT OF PEOPLE AFFECTED BY EPILEPSY

Through patient group/advocacy organisations we contacted people with epilepsy and/or their representatives or caregivers to obtain intelligence on relevant technology developments that they were aware of. A list of the patient group/advocacy organisations contacted can be found in Appendix 3.

3.2. INVESTIGATION AND FILTRATION

Primary Filtration stage

The technologies identified as being potentially relevant were checked against the pre-defined inclusion and exclusion criteria (Table 1), using the information available from the source/s searched. Any obvious duplicates were removed. This process yielded an initial long-list of technologies.
## Table 1: Review inclusion and exclusion criteria used for filtration

<table>
<thead>
<tr>
<th>Filtration point</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
</table>
| **Type of technology**      | • Drugs  
  • Medical devices – including diagnostics (e.g. predictive, prognostic, diagnostic tests) and digital technologies  
  • Cellular and biological therapies (e.g. antibodies)  
  • Medical procedures  
  • Vaccines                                                                                                                                                                                                 | • Dietary interventions  
  • Complementary therapies                                                                                                             |
| **Place in pathway**        | • Diagnosis  
  • Management (including treatment)                                                                                                                                                                                  | • Screening  
  • Prevention                                                                                                                                                                                                 |
| **Clinical indication**     | • Epilepsy (ICD-10 G40)  
  • Status epilepticus (ICD-10 G41)                                                                                                                                                                                   | All other related ICD-10 codes, including:  
  • Acquired aphasia with epilepsy (Landau-Kleffner syndrome) (ICD-10 F80.3), classified under ‘Specific developmental disorders of speech and language’  
  • Seizure (convulsive) NOS (ICD-10 R56.8), classified under ‘Convulsions, not elsewhere classified’  
  • Todd paralysis (post-epileptic) (ICD-10 G83.8), classified under ‘Cerebral palsy and other paralytic syndromes’                                                                 |
| **Stage of development**    | Clinical research phases I and II (or the equivalent)                                                                                                                                                                 | Preclinical stage research  
  • Clinical research phases III and IV  
  • Technologies already in routine NHS use                                                                                                      |
| **Type of research study**  | • Interventional  
  • Primary purpose: diagnosis or management                                                                                                                                                                       | Observational  
  • Expanded access studies  
  • Other primary purposes (e.g. basic science, prevention, screening, health services research)                                                                                      |
| **Recruitment status of research study** | • Open  
  • Closed: active but not recruiting, enrolling by invitation, suspended, and completed within the last 2 years                                                                                              | Other ‘closed’ statuses (e.g. withdrawn and terminated), status unknown, and clinical trial records not updated within the last 2 years. |
| **Research location/s**     | Any (UK, EU, non-EU)                                                                                                                                                                                              | ---                                                                                                      |
| **Developer/research sponsor type** | Any (commercial, academic, etc)                                                                                                                                         | ---                                                                                                      |

### Secondary Filtration stage

The initial long-list of technologies was then investigated further by searching online for publically available information to confirm that (i) individual technologies met the inclusion criteria, and (ii) were not duplicates. This detailed research covered key aspects such as development status, indication and mode of action, and phase and status of any clinical trials. In addition, information was collected (where available) on estimated licence and launch dates. The technologies remaining after primary and secondary filtration are presented in this report.
3.3. ASSESSMENT OF POTENTIAL FOR IMPACT

Having identified a wide range of technologies that are in early clinical development for epilepsy, we involved health professionals, patients and carers to gain an insight into the potential impact that the identified technologies might have on people affected by epilepsy and on health services.

3.3.1. HEALTHCARE PROFESSIONALS’ PERSPECTIVE

We approached nine clinical experts to invite them to provide comments on the technologies that we had identified. The guide questions asked were:

- Do you believe this technology has the potential to diagnose, treat or manage epilepsy?
- Innovation: what features of the technology (if any) do you believe to be innovative?
- Impact: what is the potential impact of the technology on outcomes for people with epilepsy and NHS systems and resources?
- Are there any particular groups of people with epilepsy that this technology may benefit (e.g. young children, adolescents, those with co-morbidities)?
- Barriers: what potential barriers might there be to this technology being adopted into the NHS?

3.3.2. POTENTIAL USERS’ PERSPECTIVE

We collaborated with the charity Epilepsy Action, to involve six members of their Epilepsy Action Research Network (EARN) whom we invited to provide comments on the technologies that had been identified. The guide questions asked of the people affected by epilepsy were:

- How do you think the technology could impact on your quality of life (QOL)?
- What do you like about the technology?
- What do you dislike about the technology?

4 RESULTS

4.1. TECHNOLOGIES IDENTIFIED

A summary of the number of technologies identified and excluded through the identification and filtration processes is presented in Figure 1. By applying HSRIC horizon scanning methods, 1,595 (93.4%) of the technologies identified from the initial search were eliminated through two rounds of research and filtration. The final set of technologies that met the inclusion criteria represented 6.7% of the total identified at the outset.
A total of 114 technologies that met the inclusion criteria were identified (Table 2). Of these, 27 (24%) were drugs and 87 (76%) were non-drug technologies. Ninety-one technologies (80%) were for the management/treatment of epilepsy, and twenty-three technologies (20%) were for diagnostic use. The full results are presented at Appendix 4 for drug technologies and Appendix 5 for non-drug technologies.

Table 2: Number of technologies identified – by type

<table>
<thead>
<tr>
<th>Technology type</th>
<th>Number identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic: drugs n=27</td>
<td>27</td>
</tr>
<tr>
<td>Therapeutic: non-drug n=38</td>
<td></td>
</tr>
<tr>
<td>Neuromodulation therapies</td>
<td>21</td>
</tr>
<tr>
<td>Surgical techniques</td>
<td>10</td>
</tr>
<tr>
<td>Other therapeutic techniques</td>
<td>7</td>
</tr>
<tr>
<td>Management n=26</td>
<td></td>
</tr>
<tr>
<td>Digital and wearable technologies (seizure tracking/alert)</td>
<td>18</td>
</tr>
<tr>
<td>Management interventions and devices</td>
<td>8</td>
</tr>
<tr>
<td>Diagnostic n=23</td>
<td></td>
</tr>
<tr>
<td>Electroencephalogram (EEG) techniques</td>
<td>9</td>
</tr>
<tr>
<td>Brain imaging techniques</td>
<td>7</td>
</tr>
<tr>
<td>Other diagnostic tests</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total technologies</strong></td>
<td><strong>114</strong></td>
</tr>
</tbody>
</table>
Phase of development

A summary of the information obtained about the phases of technology development is presented in Table 3. A total of 54 (47.4%) of the technologies identified were in phase I, I/II or II clinical research (27 drugs and 27 non-drugs). A further 47 (41.2%) were in early development or clinical trials, and 13 (11.4%) were available with research ongoing or were provided as a testing service. This timeframe information was obtained between May and July 2016, and was not verified directly with the developers.

Table 3: Number of technologies identified – by phase of development

<table>
<thead>
<tr>
<th>Technology type</th>
<th>Phase I (n)</th>
<th>Phase II (n)</th>
<th>Phase I/II (n)</th>
<th>Sub-total</th>
<th>In early development (n)</th>
<th>In clinical trials, phase not specified (n)</th>
<th>Sub-total</th>
<th>Available with research ongoing/ testing service (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>10</td>
<td>12</td>
<td>5</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Non-drugs</td>
<td>13</td>
<td>12</td>
<td>2</td>
<td></td>
<td>37</td>
<td>10</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>24</td>
<td>7</td>
<td>(54)</td>
<td>37</td>
<td>10</td>
<td>(47)</td>
<td>13</td>
</tr>
</tbody>
</table>

Location of research

A summary of the information obtained about the locations of research development is presented in Table 4. A total of 21 (18.4%) of the technologies were being researched at centres in the United Kingdom (UK). A further 7 (6.1%) were being researched at centres elsewhere in the European Union (EU), and 42 (36.9%) at centres in non-EU countries. For the remaining 44 technologies (38.6%) information on location was not available.

Table 4: Number of technologies identified – by location of research development

<table>
<thead>
<tr>
<th></th>
<th>UK (or including UK)</th>
<th>EU (or including EU)</th>
<th>Non-EU</th>
<th>Location/s not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Non-drugs</td>
<td>20</td>
<td>5</td>
<td>35</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>7</td>
<td>42</td>
<td>44</td>
</tr>
</tbody>
</table>

4.2. ASSESSMENT OF POTENTIAL FOR IMPACT

Of the nine clinical experts that we approached, four provided comments on the technologies that had been identified. Four out of the six people affected by epilepsy that we approached also provided comments on the technologies that had been identified. Their comments are provided in full in Appendix 4 for drugs and Appendix 5 for non-drug technologies.

One healthcare professional provided brief comment on 15 of the 27 drugs identified. Brief comments were also received on four of the drugs from people affected by epilepsy. More detailed and numerous sets of comments were received from both healthcare professionals and people with
epilepsy on all of the 87 non-drug technologies identified. The following technologies were highlighted as having potential for significant impact on those with epilepsy and health services.

**Drugs**

Both the clinical experts and people affected by epilepsy highlighted the potential for impact of Designer Receptor Exclusively Activated by Designer Drugs (known as DREADDS or chemogenetics27, Appendix 4, technology 13). This is a new therapeutic development which aims to create a set of genetically modified chemical signal (neurotransmitter) receptors in a particular part of the brain. These are triggered only by the administration of the corresponding designer drug to inhibit seizure onset. The concept of designer drugs – which have a very targeted mode of action – was considered to have great promise for epilepsies that are so individual in nature.

Drugs that are being developed in the form of edible oil and topical gels were also of great interest. For example it was thought that triheptanoin edible oil (Appendix 4, technology 23) would be good if it worked without the need for a ketogenic diet, and topical cannabidiol gel (Appendix 4, technology 27) might offer a useful way for carers to administer the drug easily, and might provide a useful alternative option for people who have difficulty swallowing tablets. Expert advisors identified three other drugs in development as being innovative, with a novel mechanism of action (Appendix 4, technologies 18, 21 and 22).

**Neuromodulation therapies**

The largest group (n=21) of non-drug technologies identified covered a number of neuromodulation therapies. Comments from clinical experts and people affected by epilepsy included the view that having both non-invasive and minimally-invasive trigeminal and vagal neurostimulation available could improve quality of life for people for whom AEDs do not reduce seizures completely, especially if they could be used instead of AEDs (rather than in combination).

One Vagal Nerve Stimulation (VNS) device (Appendix 5, technology 32) was considered to be innovative in that it can monitor heart rate and deliver automatic neurostimulation in response to rapid increases in heart rate that may be associated with seizure onset. It was considered to offer greater potential for impact than other VNS systems that do not have this heart rate feature. Responsive Neurostimulation (RNS, Appendix 5, technologies 35 and 36), although probably costly and requiring the implantation of a device into the brain, was thought to offer the potential to serve as an internal ‘pacemaker’ to prevent seizures in people with severe intractable focal onset epilepsy.

It was thought that Cortical Electrical Stimulation (CES, Appendix 5, technology 37) could be useful in blocking the focal area where a mild seizure originates before it can spread and become more generalised, which would be of great potential benefit to people with severe intractable focal onset epilepsy. Repetitive Transcranial Magnetic Stimulation (rTMS, Appendix 5, technologies 38-40) was thought to have the potential to non-invasively lower the seizure threshold for significant amounts of time. If it could be developed for use in the home setting it might be a useful way of stopping status epilepticus events. The related technique of transcranial Direct Current Stimulation (tDCS, Appendix 5, technologies 41-44) was also considered to be of interest if it could be used in the home setting to painlessly target the focal site of onset to reduce seizure threshold.

**Surgical techniques**

It was thought that two new techniques: Laser Interstitial Thermal Therapy (LITT, Appendix 5, technologies 52-54) and Stereotactic Electronecephalography (SEEG) electrode-guided radiofrequency thermocoagulation (Appendix 5, technology 55) might be more accurate than
standard surgical techniques, potentially leading to better outcomes for people with deep-seated or multiple lesions. Tightly-Focused Femtosecond Laser microsurgery (Appendix 5, technology 58) was also highlighted as having potential for preserving radial pathways while minimising damage to surrounding areas in people with deep-seated lesions.

Other therapeutic techniques

The new therapeutic field of optogenetics (Appendix 5, technology 60) in which gene therapy enables the use of light to control seizure activity was considered to be exciting, potentially offering an innovative way of improving seizure management.

Management

Developments in digital and wearable (also known as ‘mobile’) technologies for seizure tracking and alert (Appendix 5, technologies 66-83) were welcomed by both the clinical experts and people affected by epilepsy. For example, being able to video record seizures as and when they occur may improve the accuracy of diagnosis. The remote sharing of information with healthcare professionals and researchers could be useful (both informative and time-saving), and there is also potential for researchers to be able to collect valuable information from Big Data sources. Whilst it was noted that several applications (apps) are already available to download for free, it was thought that commercial competition should be encouraged to drive further improvements in the technology and to reduce prices. Digital technologies that could accurately predict seizure onset (i.e. provide a robust alert function), e.g. by incorporating the real-time monitoring of key biometrics such as body movement, heart rate and temperature, were of great interest to our advisors (Appendix 5, technologies 75 and 76). It was thought that if alerts proved to be reliable, they could significantly reduce seizure falls and improve peace of mind for those affected by epilepsy.

The advisors were also very interested in new learning strategies that were based on biofeedback (Appendix 5, technologies 84 and 85). With these, the person gets information about how normally subconscious aspects of their bodily state (e.g. their blood pressure and brainwave activity) fluctuate in real-time, and can then learn how to modify them using the power of thought to help reduce and control seizures. Cognitive-based self-management was also an area of interest, for example home-based Problem Solving Therapy (Appendix 5, technology 86) may help to manage cognitive dysfunction and improve quality of life. A specialist nurse-led intervention (Appendix 5, technology 87) was thought to offer a potentially empowering and cost-effective option for use in the community setting. In terms of new safety equipment, a movement-activated inflatable hood-shaped airbag (Appendix 5, technology 91) was also of interest as a new potential alternative to helmets and face masks for children to reduce fall injury.

Diagnostics

The use of new wireless temporary ‘tattoo’ electrodes for EEG recording (Appendix 5, technology 93) was thought to be potentially useful for babies, and EEG-functional Magnetic Resonance Imaging (EEG-fMRI, Appendix 5, technology 100) might be a more child-friendly way of accurately localising the epileptogenic zone\(^4\) (EZ) prior to surgery. Simultaneous Positron Emission Tomography (PET)-MR ±EEG (Appendix 5, technology 101) might reduce the number of scans and clinic attendances needed, and in children it may reduce the need for sedation and general anaesthetic. The genetic technique of Whole-Exome Sequencing (WES, Appendix 5, technologies 113 and 114) was thought to be an important method for discovering new epilepsy-related genes to improve diagnosis and inform research.

---

\(^4\) The area of the brain in which the seizure starts
In this review we present an overview of emerging technologies in development for the diagnosis and management of epilepsy. A total of 114 technologies were identified: 27 drugs, and 87 medical devices, procedures and techniques. In addition, we explored the perspectives of healthcare professionals and people affected by epilepsy on the technologies identified in terms of their potential for impact on people with epilepsy and on health services. The technologies that we identified were in early clinical development, and research is ongoing. As the clinical experts and people affected by epilepsy stressed, for many of the technologies further evidence is needed to support or negate their use by individuals and the NHS.

The central strategy used for the management of epilepsy is drug therapy using AEDs. People affected by epilepsy and clinicians consulted in the review wanted to see: (a) more effective drugs with fewer side-effects, (b) more easily administered formulations of drugs (e.g. edible oils and topical gels), and (c) drugs that work in a much more targeted way using more individualised approaches, with areas such as ‘designer’ drugs, gene therapy and optogenetics seen as potentially ground breaking.

However, despite advances in drug development, a significant area of clinical need is for alternative treatment approaches for the estimated 30-48% of people who have medically intractable epilepsy. Surgical interventions to treat people who have medically intractable epilepsy are generally under used, and may not be appropriate for people with multifocal or generalised seizures, or where the EZ cannot be identified. Major advances in surgical and non-surgical diagnostic and therapeutic strategies may make surgery a viable option for many more people who cannot currently benefit from this treatment modality. Key challenges are to localise and evaluate the EZ more accurately and, where possible, less-invasively, and to achieve more effective resection whilst minimising collateral damage to surrounding tissues.

An example of a promising new non-invasive technique for EZ identification is dense-array EEG, which uses many more scalp electrodes than standard EEG to give a more accurate diagnosis. Another new way of localising the EZ is by functional mapping of cortical activity through the scalp using a technique called transcranial magnetic stimulation (TMS). The information obtained using TMS can then be used during surgery to navigate more accurately to the target site.

New methods to enhance the resolution of MRI neuroimaging using quantitative structural analyses may increase diagnostic accuracy to a level at which lesions can be identified which do not show up using current techniques. This could enable more people to access surgical therapy. Computer software based on sophisticated algorithms is also being developed to enhance brain mapping for diagnostic purposes and to improve 3D modelling of brain structures for pre-surgical planning and for navigation during surgery.

Stereo-EEG (SEEG) is a new invasive intracranial robot-assisted technique that has generated much excitement as a new way of recording brain activity deeper within the brain using multiple-depth electrodes to localise EZs. This may find more lesions than current techniques (e.g. recording using subdural electrodes), and could therefore make surgery possible for people with multiple lesions and deep-seated EZs.

MRI-guided laser interstitial thermal therapy (MRgLITT) is a novel minimally invasive ablative treatment in which cooled stereotactic lasers are placed into the target area of the brain and the EZ is heat-ablated using real-time monitoring with MR thermography. The potential advantages of this exciting new therapeutic approach may include the ability to target deep lesions such as those close to the base of the skull.
A promising new VNS device (Appendix 5, technology 32) has the innovative feature of including a sensor for monitoring heart rate. It is intended to identify and automatically inhibit seizures when, or even just before, they occur and was highlighted by review advisors as being a potentially important advance in VNS therapy.

There was also considerable interest in another new seizure modifying treatment called Responsive Neurostimulation (RNS), which could potentially serve as an internal ‘neural pacemaker’. RNS differs from other forms of neurostimulation in that the focal EEG signal is monitored continuously using intracranial electrodes placed over an ictal onset zone. Cortical stimulation is based on computer analysis of EEG signal input to block seizure onset. Again, RNS may provide an important new therapeutic option for those who are not candidates for conventional surgery or for whom other treatments have not worked.

Another important area of technology development was mobile digital devices (e.g. phone apps and wearable devices) that track and raise alerts of seizure onset. Several such technologies are already available (both commercially and for free), and are becoming increasingly widely used to help empower people in the self-management of their condition. There is also important potential for the information recorded by such devices to be usefully shared in real-time with caregivers and clinicians. The sharing of such information via social media to generate Big Data sets that can be analysed may help researchers to gain a better understanding of the condition and its management. The related field of self-management using biofeedback and cognitive modification interventions was also of considerable interest to the review advisors.

This review has shown that significant advances are being made across a wide range of technology areas, including drugs, neurostimulation devices, imaging and genetic techniques, and new surgical, digital and cognitive technologies. The technologies that we identified were for applications right across the care pathway for epilepsy, from diagnosis, through treatment and on to mobile technologies for real-time self-management.

The assessment of potential impact proved insightful, with extensive comments received from clinical experts and people affected by epilepsy on all of the 87 non-drug technologies identified, along with some more brief and general comments on the drugs in development. The people affected by epilepsy considered a number of the emerging technologies to be of potential significance. Their main concerns about new technologies included the risks and side-effects of new invasive procedures; the reversibility of implanted devices if they prove problematic or do not work as intended; the effectiveness, safety, cost, and NHS availability of new technologies; and their impact on quality of life.

People affected by epilepsy emphasised the importance of having more individualised approaches to therapy and technologies that empower people to self-manage their condition more effectively. Further investment in basic research into the mechanisms that underlie the many different forms of epilepsy is needed to drive technological innovation in new directions.
### APPENDIX 1. ELECTRONIC SOURCES OF INTELLIGENCE USED TO IDENTIFY TECHNOLOGIES

<table>
<thead>
<tr>
<th>Type of identification source</th>
<th>Horizon scanning databases</th>
<th>Commercial drug (i.e. pharmaceutical)/medical technology databases</th>
<th>Clinical trial registries</th>
<th>Industry news sites</th>
<th>Bibliographic databases</th>
<th>Scientific conference proceedings</th>
<th>Key organisations and networks</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHR HSRIC technology database</td>
<td>PharmaProjects</td>
<td>ClinicalTrials.gov</td>
<td>MedGadget</td>
<td>OVID Medline</td>
<td>American Epilepsy Society (AES) 69th Annual Meeting (Dec 2015, USA): abstracts search available for 2015 using key words</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EuroScan</td>
<td>Adis Insight</td>
<td>UKCRN portfolio database</td>
<td>Medical News Today</td>
<td>EMBASE</td>
<td>Epilepsy Foundation</td>
<td>Epilepsy Foundation</td>
<td></td>
</tr>
<tr>
<td>ECRI Institute</td>
<td>GlobalData Healthcare (Medical)</td>
<td>WHO International Clinical Trials registry platform (ICRTP)</td>
<td>Fierce Network</td>
<td></td>
<td>EpiNet</td>
<td>Epilepsy Foundation, Elephants</td>
<td></td>
</tr>
<tr>
<td>AHRQ Healthcare Horizon Scanning System</td>
<td>i4i portfolio of funded projects</td>
<td>i4i portfolio of funded projects</td>
<td>Clinica MedTech</td>
<td></td>
<td>International League Against Epilepsy (ILAE)</td>
<td>Epilepsy Society</td>
<td></td>
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<tr>
<td>CADTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Citizens United for Research in Epilepsy (CURE)</td>
<td>Epilepsy Action</td>
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<tr>
<td>HealthPACT</td>
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<td></td>
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<td></td>
<td>Finding a Cure for Epilepsy and Seizures (FACES) Human Epilepsy Research Opportunities (HERO)</td>
<td>Epilepsy Action</td>
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<td>ASERNIP–S</td>
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<td></td>
<td>Epilepsy Research UK</td>
<td>Epilepsy Society</td>
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<td></td>
<td>Epilepsy Action</td>
<td>Young Epilepsy</td>
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<td></td>
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<td></td>
<td>SUDEP Action (Sudden Unexpected Death in Epilepsy)</td>
<td>SUDEP Action (Sudden Unexpected Death in Epilepsy)</td>
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<td></td>
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<td></td>
<td></td>
<td>Action Medical Research for Children</td>
<td>Action Medical Research for Children</td>
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# APPENDIX 2. SEARCH TERMS

<table>
<thead>
<tr>
<th>Search dimension</th>
<th>Text search terms</th>
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<td>Clinical</td>
<td>Epilepsy</td>
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<tr>
<td></td>
<td>Epilepsies</td>
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<tr>
<td></td>
<td>Epileptic</td>
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<td></td>
<td>Epilepticus</td>
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<tr>
<td></td>
<td>Seizure</td>
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<tr>
<td>Place in pathway</td>
<td>Diagnosis</td>
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<tr>
<td></td>
<td>Therapeutics</td>
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<tr>
<td></td>
<td>Treatment</td>
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<td></td>
<td>Management</td>
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### MeSH heading search terms and strategy for bibliographic databases

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<thead>
<tr>
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<tr>
<td>2</td>
<td>Exp Diagnosis/</td>
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<td></td>
<td>OR</td>
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<td></td>
<td>Exp Therapeutics/</td>
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<td></td>
<td>OR</td>
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<td></td>
<td>Exp Disease management/</td>
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<td>3</td>
<td>1 and 2</td>
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<td>4</td>
<td>LIMIT to:</td>
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<td></td>
<td>Humans</td>
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<td></td>
<td>English language</td>
</tr>
<tr>
<td></td>
<td>Publication Types: Clinical Trials, Reviews</td>
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<td></td>
<td>Publication Year: Last 2 years</td>
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</table>
APPENDIX 3. CLINICAL EXPERTS, PROFESSIONAL & PATIENT GROUP ORGANISATIONS CONTACTED

<table>
<thead>
<tr>
<th>Professional organisations contacted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Association of British Neurologists - Epilepsy Advisory Group</td>
</tr>
<tr>
<td>British Paediatric Neurology Association - British Paediatric Epilepsy Group (BPEG)</td>
</tr>
<tr>
<td>Royal College of Psychiatrists - Epilepsy Working Group</td>
</tr>
<tr>
<td>Society of British Neurological Surgeons</td>
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<tr>
<td>Epilepsy Nurses Association</td>
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<tr>
<td>International League Against Epilepsy - British Chapter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individual experts contacted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Mark Richardson, Kings College London, Institute of Psychiatry</td>
</tr>
<tr>
<td>Dr Nigel Hoggard, Royal Hallamshire Hospital, Sheffield</td>
</tr>
<tr>
<td>Dr Arjune Sen, John Radcliffe Hospital, University of Oxford</td>
</tr>
<tr>
<td>Professor Helen Cross, Great Ormond Street Hospital for Children</td>
</tr>
<tr>
<td>Mr Ellamushi Habib, St Bartholomew's Hospital, Royal London Hospital</td>
</tr>
<tr>
<td>Mr Richard Walsh, Birmingham Children's Hospital</td>
</tr>
<tr>
<td>Dr Anita Devlin, Great North Children's Hospital, Newcastle upon Tyne</td>
</tr>
<tr>
<td>Professor Leone Ridsdale, King’s College London</td>
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</table>

<table>
<thead>
<tr>
<th>Patient group/advocacy organisations contacted</th>
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<tbody>
<tr>
<td>Epilepsy Action</td>
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<td>Epilepsy Society</td>
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<tr>
<td>Epilepsy Research UK</td>
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<tr>
<td>Young Epilepsy</td>
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</table>
### APPENDIX 4. EMERGING DRUGS IDENTIFIED FOR THE TREATMENT OF EPILEPSY (N=27)

<table>
<thead>
<tr>
<th>n</th>
<th>Technology name</th>
<th>Developer</th>
<th>Indication</th>
<th>Technology description</th>
<th>Status</th>
<th>Clinical trial info</th>
<th>Further information</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Alprazolam (Staccato, AZ002, AZ-002)</td>
<td>Alexza Pharmaceuticals</td>
<td>Epilepsy acute repetitive seizures (ARS)</td>
<td>A formulation of alprazolam, using its proprietary Staccato system, which enables rapid, aerosolized delivery of alprazolam into the lungs under development. Alprazolam is licensed to treat anxiety disorders and panic disorder and is in a class of medications called benzodiazepines. It works by decreasing abnormal excitement in the brain.</td>
<td>Phase II</td>
<td>NCT02351115 (USA).</td>
<td><a href="https://ClinicalTrials.gov/show/NCT02351115">https://ClinicalTrials.gov/show/NCT02351115</a></td>
</tr>
</tbody>
</table>

**Expert comments:** Aerosol would have to be used up the nose for nasal absorption but if this is possible then it is worth exploring further.

**People affected by epilepsy comments:**
- I wonder if there are any side-effects on the lungs?
- Am surprised the web link seems to state use just for photosensitive epilepsy (not very common?). Similar benzodiazepine such as Frisium (clobazam) has a wider usage? QOL Impact – will need to wait until full details of how successful the trial has actually been.

<p>| 4 | Ataluren (PTC-124, Translarna) | PTC Therapeutics | Dravet syndrome | An orally-active small molecule that promotes read-through of nonsense mutations in mRNA. | Phase II | NCT02758626 | <a href="https://ClinicalTrials.gov/show/NCT02758626">https://ClinicalTrials.gov/show/NCT02758626</a> |</p>
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<tbody>
<tr>
<td><strong>Expert comments:</strong> As part of gene therapy portfolio this is definitely worth exploring further with animal models of Dravet.</td>
<td></td>
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<tr>
<td><strong>5</strong></td>
<td>BGG 492, selurampanel</td>
<td>Novartis Pharmaceuticals UK Ltd</td>
<td>Epilepsy, partial (focal, local)</td>
<td>An orally available, AMPA/kainate receptor antagonist. AMPA receptors are abundantly expressed in virtually all excitatory neuronal synapses, and are key mediators of seizure spread in the central nervous system (CNS). There is emerging evidence that AMPA receptors could play a role in the pathology of epilepsy and in seizure-induced brain damage.</td>
<td>Phase II, complete d</td>
</tr>
<tr>
<td><strong>Expert comments:</strong> Further study worth exploring.</td>
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<tr>
<td><strong>6</strong></td>
<td>BIS-001 huperzine, huperzine, Biscayne Pharmaceuticals</td>
<td>Adults with complex partial seizures (CPS) Children with Dravet syndrome</td>
<td>A highly potent and selective acetylcholinesterase (AChE) inhibitor that is a synthetic form of the traditional Chinese medicine huperzine A.</td>
<td>Phase I Phase Ib/IIa proof-of-concept trial for complex partial epilepsy is planned for 2016</td>
<td>Phase Ib/IIa proof-of-concept trial for complex partial epilepsy is planned for 2016</td>
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<tr>
<td><strong>Expert comments:</strong> QOL Impact – a must for further research due to lack of medication AEDs available for Dravet Syndrome. Likes: presumably very limited. No dislikes.</td>
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<tr>
<td><strong>7</strong></td>
<td>Brabafen, fenfluramine hydrochloride, fenfluramine hydrochloride</td>
<td>Zogenix, Inc. Katholieke Universiteit</td>
<td>Lennox Gastaut Syndrome</td>
<td>Low-dose fenfluramine hydrochloride also in development for Dravet syndrome (phase III) and</td>
<td>Phase II NCT02655198</td>
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<tr>
<td>Zogenix, ZX-008</td>
<td>Leuven</td>
<td>unspecified epilepsy (pre-clinical).</td>
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</table>

**Expert comments:** Animal data suggests that this may be helpful in Dravet along with historical human data, so worth taking forward.

| 8 | Bumetanide (BUMEX) | Hoffman-La Roche | Neonatal seizures | In the brain, bumetanide blocks the NKCC1 cation-chloride co-transporter, and thus decreases internal chloride concentration in neurons. In turn, this concentration change makes the action of GABA more hyperpolarizing, which may be useful for treatment of neonatal seizures that quite often are not responsive to traditional GABA-targeted treatment, such as barbiturates. | Phase I Licensed for other indications | NCT00830531 | [https://clinicaltrials.gov/show/NCT00830531](https://clinicaltrials.gov/show/NCT00830531) |

| 9 | Cannabidivarin (GWP42006, CBDV) | GW Pharmaceuticals | Epilepsy/Focal Seizures | A cannabinoid extract featuring cannabidivarin (CBDV) as the primary cannabinoid. | Phase II | NCT02369471NCT02365610NCT01918735 | [https://ClinicalTrials.gov/show/NCT02369471](https://ClinicalTrials.gov/show/NCT02369471) [https://ClinicalTrials.gov/show/NCT02365610](https://ClinicalTrials.gov/show/NCT02365610) [http://clinicaltrials.gov/show/NCT01918735](http://clinicaltrials.gov/show/NCT01918735) |

**Expert comments:** Undoubtedly cannabinoids will come into treatment possibilities and offer the usual efficacy of a new drug but are unlikely to be of revolutionary benefit on the basis of current trial result.


| 11 | CPP 115 | Catalyst Pharmaceutical Partners | Epilepsy | 4-aminobutyrate transaminase inhibitors. CPP-115 is One of a group of novel GABA-aminotransferase inhibitors. CPP-115 binds to GABA-AT (GABA-aminotransferase, also known as GABA transaminase or GABA-T), causing increased levels of GABA, gamma-aminobutyric acid, the chief inhibitory neurotransmitter in humans. It plays a | Phase I Orphan drug designation in both the US and Top-line adverse events and pharmacodynamics data from a phase lb trial in healthy | [http://www.catalystpharma.com/cpp-115.shtml](http://www.catalystpharma.com/cpp-115.shtml) |
role in regulating neuronal excitability throughout the nervous system. In humans, GABA is also directly responsible for the regulation of muscle tone.

Early development for a broad range of central nervous system indications, such as infantile spasms, epilepsy, Tourette Syndrome and Post Traumatic Stress Disorder (PTSD).

- **Expert comments:** Potentially useful particularly if blood levels and therefore potential effects on the liver are reduced.

| 12 | DP-VPA; RAP-valproate; SPD-421 | D-Pharm (Originator) - Israel, Jiangsu Nhwa Pharmaceutical (Licensee), China | Epilepsy, partial (focal, local) | An oral prodrug of the antiepileptic valproic acid (VPA). It is based on D-Pharm's proprietary drug targeting technology, Regulated Activation of Prodrugs (RAP), which enables preferential bio-activation of the drug within the epileptic focus. A derivative of VPA is linked to a lipid vector to form the prodrug, which is activated by PLA2 at the site of seizure activity in the brain. | Phase II | the EU for infantile spasms volunteers released Dec 2015 |

- **Expert comments:** Very innovative and new. Would be a real frontier. Further data required.

*People affected by epilepsy comments:* Designer drugs might have promise for epilepsies that are so individual in nature.
<table>
<thead>
<tr>
<th></th>
<th>Drug Name</th>
<th>Company</th>
<th>Indication</th>
<th>Description</th>
<th>Phase</th>
<th>NCT Number</th>
<th>ClinicalTrials.gov Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Ganaxolone (CCD-1042, Epalon 1000)</td>
<td>Marinus Pharmaceuticals</td>
<td>Epilepsy, PCDH19-related female-limited; Status epilepticus</td>
<td>A synthetic analogue (epalon) of a naturally-occurring neuroactive steroid and positive allosteric modulator of the GABA-A receptor (allopregnanolone). Also in development for partial epilepsy (focal, local) – Phase III.</td>
<td>Phase I &amp; II</td>
<td>NCT00465517NCT02358538</td>
<td><a href="https://ClinicalTrials.gov/show/NCT00465517">https://ClinicalTrials.gov/show/NCT00465517</a> <a href="https://ClinicalTrials.gov/show/NCT02358538">https://ClinicalTrials.gov/show/NCT02358538</a></td>
</tr>
<tr>
<td>15</td>
<td>ICA-105665 (Icagen-2)</td>
<td>Pfizer</td>
<td>Epilepsy</td>
<td>An oral selective opener of KCNQ potassium channel subtypes. The compounds act on channels located on central and peripheral neuron cell membranes, resulting in a more negative resting membrane potential and decreased electrical excitability.</td>
<td>Phase I/II</td>
<td>NCT01281956 (USA)</td>
<td><a href="https://guidebook.com/guide/27988/poi/2777673/">https://guidebook.com/guide/27988/poi/2777673/</a></td>
</tr>
<tr>
<td>16</td>
<td>Naluzotan (PRX00023, PRX-00023)</td>
<td>Proximagen National Institute of Neurological Disorders and Stroke</td>
<td>Epilepsy, localization related</td>
<td>An small molecule dual serotonin (5-HT)1A receptor agonist and sigma-1 receptor antagonist. Patients with localization-related epilepsy have reduced 5HT1A receptor binding on 18FCWAY positron emission tomography (PET). Increasing neurotransmitter activity at 5HT1A receptor sites might ameliorate seizures.</td>
<td>Phase II</td>
<td>NCT01281956 (USA)</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT01281956">https://clinicaltrials.gov/ct2/show/NCT01281956</a></td>
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</table>

**Expert comments:** Similar to fenfluramine as SHT. Further data required.

<p>| Expert comments: Novel action. Further data required. |
|---|---|---|---|---|
| 22 | <strong>Tonabersat</strong> (SB-220453, USL-260) | Proximagen | Epilepsy, unspecified | A fluorobenzoyl amino benzopyran, it is a gap junction blocker that inhibits cortical spreading depression and release of nitric oxide. | Phase II. |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Study Name</th>
<th>Sponsor</th>
<th>Diseases</th>
<th>Description</th>
<th>Phase</th>
<th>ACTRNs</th>
<th>URL</th>
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</thead>
<tbody>
<tr>
<td>23</td>
<td>Triheptanoin (triglyceride of heptanoate) oil</td>
<td>Ultragenyx, University of Queensland, Australia</td>
<td>Epilepsy</td>
<td>A stable, edible tasteless triglyceride oil that has been used in patients with metabolic disorders.</td>
<td>Phase I-II, (Australia)</td>
<td>ACTRN12614000187640, ACTRN12615000406505</td>
<td><a href="http://www.anzctr.org.au/ACTRN12614000187640.aspx">http://www.anzctr.org.au/ACTRN12614000187640.aspx</a></td>
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<tr>
<td>25</td>
<td>UCB-0942</td>
<td>UCB</td>
<td>Epilepsy: treatment resistant; Highly Drug-resistant Focal Epilepsy; partial (focal, local)</td>
<td></td>
<td>Phase II</td>
<td>EudraCT2015-001268-20 (Netherlands), EudraCT2014-003330-12 (Germany and Netherlands) NCT02625090 NCT02495844</td>
<td><a href="https://ClinicalTrials.gov/show/NCT02625090">https://ClinicalTrials.gov/show/NCT02625090</a> <a href="https://ClinicalTrials.gov/show/NCT02495844">https://ClinicalTrials.gov/show/NCT02495844</a></td>
</tr>
<tr>
<td>27</td>
<td>ZYN002 (Topical cannabidiol gel)</td>
<td>Zynerba Pharmaceuticals Inc</td>
<td>Epilepsy</td>
<td>ZYN-002 is a non-psychotropic synthetic cannabinoid (CBD) transdermal gel, under development by Zynerba Pharmaceuticals for the treatment of adult and childhood epilepsy. It is formulated as a permeation-enhanced gel</td>
<td>Phase I-II (Australia)</td>
<td>ACTRN12615001025527, ACTRN12616000104459, ACTRN1261600</td>
<td><a href="http://www.anzctr.org.au/ACTRN12615001025527.aspx">http://www.anzctr.org.au/ACTRN12615001025527.aspx</a></td>
</tr>
</tbody>
</table>
and being developed to deliver 1-2 times/day, through the skin into the bloodstream via a clear, odourless gel.

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**Expert comments:** Need to establish efficacy and indication for Cannabinoids orally absorbed in the first instance.

**People affected by epilepsy comments:**
- This sounds fantastic because it’s not always possible for someone else to get medication in someone and be a great way for a carer to make sure when taking medicine it is done as easily as possible.
- Dose mechanism may be good for slow release dose and for people who have difficulty taking tablets.
APPENDIX 5. EMERGING NON-DRUG TECHNOLOGIES IDENTIFIED FOR THE DIAGNOSIS AND MANAGEMENT OF EPILEPSY (N=87)

Questions asked of clinical experts (for reference):

1. Do you believe this technology has the potential to diagnose, treat or manage epilepsy?
2. Innovation: what features of the technology (if any) do you believe to be innovative?
3. Impact: what is the potential impact of the technology on outcomes for people with epilepsy and NHS systems and resources?
4. Are there any particular groups of people with epilepsy that this technology may benefit (e.g. young children, adolescents, those with comorbidities)?
5. Barriers: what potential barriers might there be to this technology being adopted into the NHS?

<table>
<thead>
<tr>
<th>n</th>
<th>Technology name</th>
<th>Developer</th>
<th>Indication</th>
<th>Technology description</th>
<th>Status</th>
<th>Clinical trial info</th>
<th>Further information</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>Trigeminal Nerve Stimulation</td>
<td>Boston Scientific Corporation, Olive View-UCLA Education &amp; Research Institute, Epilepsy Foundation</td>
<td>Epilepsy</td>
<td>An implantable neurostimulation device designed to stimulate deep branch of the trigeminal nerve to reduce the frequency and severity of seizures.</td>
<td>Phase II, completed (has results)</td>
<td>USA: NCT01159431 (n=50, completed)</td>
<td><a href="https://ClinicalTrials.gov/show/NCT01159431">https://ClinicalTrials.gov/show/NCT01159431</a></td>
</tr>
</tbody>
</table>

**Expert comments:**
- Similar to VNS therefore has potential to treat symptoms (seizures [sometimes abbreviated to Sx]) but would need to see efficacy data from a trial. If efficacious then fewer hospital admissions. Costs quite high.
- Experimental device proven safety but not efficacy. Not currently suitable for clinical use outside trials. 1. No, 2. No, 3. No.
### People affected by epilepsy comments:
- If this has results and has been completed then I would think it may help many people who struggle to get control through medication alone.
- QOL Impact – certainly helpful to have both eTNS and sTNS available to patients having problems finding routine AEDs/ alternative drugs that reduce seizures completely.
  - Likes: choice available ref e and s types. Patients wishing to try these stimulation devices I think will increase, to help reduce seizures when mono/poly therapy use of available AEDs have failed and where surgery is not a viable option. Dislikes: possibility of more side-effects where invasive systems are used but at least treatment can be reversed if not successful or side effects unpleasant. Possible dislike with all TNS/VNS is that they are used in conjunction with AEDs – not as an alternative.
- Blurb in link says it’s an external device. This would be good if it means no surgery like VNS, as if it didn’t work could easily be removed…but concerned what it would look like. Cautious of claims based on seizure reduction as personal experience of VNS is of alertness improvement rather than seizure reduction.

### Expert comments:
- Similar to VNS therefore has potential to treat Sx but would need to see efficacy data from a trial. If efficacious then fewer hospital admissions. Costs quite high.
- Experimental device proven safety but not efficacy. Not currently suitable for clinical use outside trials.

### People affected by epilepsy comments:
- I would personally like to see this approved first and then work from there.
- QOL Impact: certainly helpful to have both eTNS and sTNS available to patients having problems finding routine AEDs/ alternative drugs that reduce seizures completely. Likes: choice available ref e and s types. Patients wishing to try these stimulation devices I think will increase, to help reduce seizures when mono/poly therapy use of available AEDs have failed and where surgery is not a viable option. Dislikes: possibility of more side-effects where invasive systems are used but at least treatment can be reversed if not successful or side effects unpleasant. Possible dislike with all TNS/VNS is that they are used in conjunction with AEDs – not as an alternative.
- An external device would be good if it means no surgery like VNS, as if it didn’t work could easily be removed…but concerned what it would look like. Cautious of claims based on seizure reduction as personal experience of VNS is of alertness improvement rather than seizure reduction.

<table>
<thead>
<tr>
<th>29</th>
<th>Trigeminal Nerve Stimulation (eTNS™) device</th>
<th>NeuroSigma Inc</th>
<th>Epilepsy</th>
<th>An implantable neurostimulation device designed to stimulate deep branch of the trigeminal nerve to reduce the frequency and severity of seizures.</th>
<th>Phase II. USA approval expected May 2019 and launch Aug 2019. Approved in other jurisdictions</th>
<th>USA: NCT01978470 (n=20, end date Aug 2016)</th>
<th><a href="http://www.sciencedirect.com/science/article/pii/S1525505014005897">http://www.sciencedirect.com/science/article/pii/S1525505014005897</a></th>
<th><a href="https://clinicaltrials.gov/ct2/show/NCT01978470?term=neurosigma&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT01978470?term=neurosigma&amp;rank=1</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Monarch eTNS System - external trigeminal nerve stimulation device</td>
<td>NeuroSigma Inc and Boston Scientific</td>
<td>Epilepsy</td>
<td>A non-invasive, home based neuromodulation system. Mild electrical signals pass through electrodes placed on the patient’s forehead. eTNS is intended to transcutaneously stimulate the various branches of the trigeminal nerve to reduce the frequency and severity of seizures.</td>
<td>Phase II. CE marked and available in EU. USA approval</td>
<td>USA: NCT01978470 (n=20, ongoing,</td>
<td><a href="http://www.monerch.etns.com/etns-therapy/epilepsy">http://www.monerch.etns.com/etns-therapy/epilepsy</a></td>
<td></td>
</tr>
<tr>
<td>Corporation</td>
<td>trigeminal nerve (the largest cranial nerve), which projects to the amygdala. The stimulation is controlled by an external pulse generator worn by patients during sleep.</td>
<td>(PMA) expected Sept 2018 and launch Dec 2018</td>
<td>end date Aug 2016</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

**Expert comments:**
- Not practical for work or everyday living. Can only apply intermittently if know when going to have Sx. Probably more applicable to migraine.
- Experimental device proven safety but not efficacy. Not currently suitable for clinical use outside trials. 1. No, 2. No, 3. No.

**People affected by epilepsy comments:**
- This sounds good but I’d be worried about the size of the hole needed in the forehead. However if it worked and stopped my seizures a mark on my forehead I could put up with.
- For some people non-invasive help to reduce seizures would be less frightening I would think.
- QOL Impact: certainly helpful to have both eTNS and sTNS available to patients having problems finding routine AEDs/ alternative drugs that reduce seizures completely. Likes: choice available ref e and s types. Patients wishing to try these stimulation devices I think will increase, to help reduce seizures when mono/poly therapy use of available AEDs have failed and where surgery is not a viable option. Dislikes: possibility of more side-effects where invasive systems are used but at least treatment can be reversed if not successful or side effects unpleasant. Possible dislike with all TNS/VNS is that they are used in conjunction with AEDs – not as an alternative.
- This gives a picture so understand what it would look like. Doesn’t look very comfy to sleep in...thinking sweaty forehead, and will it stick? Connected up to a battery pack making movement difficult. Seizure reduction claims sound too good to be true. 18 weeks doesn’t seem a very long time over which to assess the effectiveness. Is it claiming to work only when in use? Or is it meant to be effective all the time? Good thing is that it’s non-invasive so no surgery....but wouldn’t want to pay for it without a money back guarantee!

| 31 | Trigeminal Nerve Stimulation Device | NuroRestor e Inc | Epilepsy | An implantable percutaneous stimulation device that stimulates deep branch of the trigeminal nerve that reduces the frequency and severity of seizures. | Phase I |

**Expert comments:**
- Not practical for work or everyday living. Can only apply intermittently if know when going to have Sx. Probably more applicable to migraine.
Experimental device proven safety but not efficacy. Not currently suitable for clinical use outside trials. 1. No, 2. No, 3. No.

**People affected by epilepsy comments:**
- QOL Impact: certainly helpful to have both eTNS and sTNS available to patients having problems finding routine AEDs/alternative drugs that reduce seizures completely. Likes: choice available ref e and s types. Patients wishing to try these stimulation devices I think will increase, to help reduce seizures when mono/poly therapy use of available AEDs have failed and where surgery is not a viable option. Dislikes: possibility of more side-effects where invasive systems are used but at least treatment can be reversed if not successful or side effects unpleasant. Possible dislike with all TNS/VNS is that they are used in conjunction with AEDs – not as an alternative.
- Implantable so would want to be fairly sure of a reasonable probability of positive impact.

### Vagal Nerve Stimulation (VNS)

| 32 | AspireSR vagus nerve stimulation (VNS) therapy generator, model 106 | LivaNova Inc (formerly Cyberonics Inc) | Partial onset seizures - refractory | This is the only VNS device that can adjust its neurostimulation in response to changes in the patient’s heart rate. Since a suddenly increasing heart rate in epileptics often signals the start of a seizure, the AspireSR may be capable of stopping seizures at an earlier stage. Model 106 includes a new Seizure Detection Algorithm (SDA) and corresponding Automatic Magnet Mode (AMM) feature. Study completed July 2015, n=31. EU, Including UK: King's College Hospital. | Available since 2015 | UK and other countries: NCT01325623 (n=31, ended July 2015, and reported in abstract). NCT01846741 | http://us.livanova.com/en/vns-therapy-for-epilepsy/health-care-professionals/vns-therapy/about-products/ | [https://clinicaltrials.gov/ct2/show/NCT01978470](https://clinicaltrials.gov/ct2/show/NCT01978470) | [https://clinicaltrials.gov/show/NCT01325623](https://clinicaltrials.gov/show/NCT01325623) |

**Expert comments:**
- Offers definite potential over and above that offered by ordinary VNS to those who respond to magnet or to those with ictal tachycardia. Larger studies needed to know real benefit and the algorithm may need adjusting to preserve battery life. Reduces hospital admissions and potentially SUDEP with automated feature able to fire during sleep. Need to work on rechargeable model to reduce battery replacements.
- This adjunction to current VNS system has the potential to improve palliation of seizure. 1-Yes, 2-Yes, 3-Improve outcome, 4-all groups, 5-No.
### People affected by epilepsy comments:
- This one sounds very interesting for people with epilepsy. I found that the increase in heart rate interesting and wondered if this device would have a double use for the heart too if it showed up a problem at the start or during a seizure.
- QOL Impact: as per TNS comments, plus that it’s a more advanced and ‘improved’ model – hence the adjustment of neurostimulation in relation to heart rate. Likes: as above in terms of advancement of research ref VNS. Research should continue as progress has been proved via trials. No dislikes.
- Sounds like it might be a good additional feature to VNS. Not clear from what I read whether it was claiming better outcome than standard VNS (with manual swipe magnet). Could currently fitted devices be “upgraded” to this?

| 33 | GammaCore - External Vagal Nerve Stimulator (also known as transcutaneous VNS, tVNS) | ElectroCore | Epilepsy | A portable handheld device that transmits electrical impulses to the vagus nerve without direct contact but through the skin on the right or left side of the patient’s neck. The device is designed to be easy to use – it is turned on and off with a simple switch – and allows the patient to control the intensity of the stimulation themselves. | Phase I. CE marked (date of info Aug 2014) | UK | [http://www.fiercemedicaldevices.com/story/electrocore-talks-potential-pharma-partners/2014-08-18](http://www.fiercemedicaldevices.com/story/electrocore-talks-potential-pharma-partners/2014-08-18) [http://gammacore.com/en/patients/about-gammacore](http://gammacore.com/en/patients/about-gammacore) |

### Expert comments:
- As long as small and discrete and works as well as implanted model would have real potential as rechargeable.
- Experimental device not currently for clinical use outside trials. Possibly may improve outcome if efficacy proven in trials.

### People affected by epilepsy comments:
- It sounds good but it only sounds useful in patients who can detect their seizures early.
- When I read this it just made me think of those collars you put around dogs that transmit a shock to stop them barking and the owner controls them. I hope it isn’t like that. I know someone who tried one who said it was pretty intense on high!
- QOL Impact: as per TNS comments, plus the obvious advantage of patient control. Likes: as above ref patient control and that the product is non-invasive.
- Sounds good but feel dubious about its effectiveness. Primary claims seem to be for headache and migraine rather than epilepsy. Presume one just uses it if you feel a seizure coming on... but would have to be aware and able to do that. Given that the jury is still out on the effectiveness of full-time implanted devices, it seems unlikely to me that an occasional zap with an external device is doing to make much difference.
NEMOS transcutaneous vagus nerve stimulation (tVNS, t-VNS) CerboMed, University of Cambridge, UK (PI: Dr Howard Ring) Uncontrolled epilepsy Non-invasive VNS device that consists of a stimulation unit and a dedicated ear electrode. The stimulation unit, having approximately the size of a common mobile phone, sends out the electrical impulses. It is connected with the ear electrode, which patients wear like an earphone. The impulses are transferred via the ear electrode through the skin to a branch of the vagus nerve.

UK: EpAID trial (HTA code 10/104/16)

Expert comments:
- As long as no interference with hearing and of equal efficacy as implantable one then in theory has potential but many may find it too restrictive socially and interferes with hearing/listening.
- Experimental device not for clinical use outside trials. Possibly may improve outcome if efficacy proven in trials. 1. No, 2. No, 3. No.
- This has the potential to treat epilepsy. The innovation is that it can deliver stimulation to the vagus nerve non-invasively unlike conventional VNS which requires surgical implantation. If it proves to be successful, it may allow patients to receive VNS without the need to undergo surgery. Also, if response to tVNS correlates with responses to conventional VNS, it may allow patients to be screened prior to surgical implantation with VNS with increased confidence that implanted VNS will be efficacious. We do not yet have confidence that outcome with tVNS is equivalent to that of implanted VNS. Also, it will be difficult to get funding for tVNS via the NHS until it is proven to be as efficacious as implanted VNS.

People affected by epilepsy comments:
- This sounds good because people could mistake it for someone listening to music.
- From reading comments from people who have uncontrolled epilepsy they seem to have a pretty miserable time when their seizures are really bad. If this type of device could give them some good quality of life it would be really good for them.
- QOL Impact – as per TNS comments, plus the unique access to the ear of this device. Likes: even more non-invasive to many patients. Also fMRI evidence in patients. If satisfactory, it is sure to progress regarding use. No dislikes.
- Sounds good but feel dubious about its effectiveness. Primary claims seem to be for headache and migraine rather than epilepsy. Presume one just uses it if you feel a seizure coming on... but would have to be aware and able to do that. Given that the jury is still out on the effectiveness of full-time implanted devices, it seems unlikely to me that an occasional zap with an external device is doing to make much difference. Maybe slightly more promising than GammaCore as says to use continuously for 3x1 hour long stints. Still dubious about its claims and only 7 subjects in the trial reported, with no control.

Responsive Neurostimulation (RNS)

Responsive neurostimulation (RNS) – ‘closed-loop’ cortical stimulation Various (including NeuroPace Inc) Refractory, partial-onset seizures A novel treatment paradigm for seizure modification that is distinct from other types of neurostimulation because it employs continuous monitoring of a focal EEG signal via intracranial electrodes placed over an ictal onset zone, with cortical stimulation based on In clinical research. One system FDA approved to date 35

http://www.cerbomed.com/Publications-86.html

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4855197/

http://www.sciencemag.org
For severe intractable focal onset epilepsy could present real opportunity. For those not suitable for surgery.

- 1-Yes. 2-Yes with significant potential impact on epilepsy treatment and outcome. 3-Improved outcome. 4-all groups. 5-Cost could be a problem although selection criteria should limit the number of implants.

Expert comments:

- QOL Impact: as per TNS comments. Likes: if potential programming successful, then I’m assuming great progress can be achieved if aiming for eventual ‘pace-maker’ benefits, due to continuous monitoring of a focal EEG signal. Dislikes: none if working hand in hand with NeuroPace RNS® System.
- Link doesn’t say anything about the treatment except that it is a poor substitute for TLE surgery! Still if surgery is not an option, yet an onset zone can be identified, it might be useful. Guess it’s a brain invasive operation, which obviously makes it a big decision to take, would need to be desperate and/or feel there was a high chance of improvement.

| 36 | NeuroPace RNS® System (procedure used: responsive neurostimulation, RNS) | NeuroPace Inc | Mesial Temporal Lobe Epilepsy | Claimed to be the first and only closed-loop brain-responsive neurostimulation system. It is intended to detect abnormal electrical brain signals that precede seizures and deliver electrical stimulation in response to try to normalize electrical brain activity and prevent seizures. The device includes a neurostimulator that is placed in the skull and leads that are placed in the seizure-originating areas of the brain. Intended benefits: seizure prevention, fewer adverse events than other neurostimulation methods, and data transmission by patients to clinicians. | CE marking expected 2018 (info from developer). Available in the USA (FDA approved 2013) | USA: NCT02403843 (n=375, post approval study, end date May 2023) | http://www.neuropace.com/the-rns-system/#overview | http://www.fiercebiotech.com/special-report/neuropace-2014-fierce-15 | https://clinicaltrials.gov/ct2/show/NCT02403843 | ncedirect.com/science/article/pii/S152550501502024 |
Cortical Electrical Stimulation (CES)

| 37 | Cortical electrical stimulation | King’s College Hospital, London, UK | Drug-resistant focal epilepsies | The technique involves ‘blocking’ the abnormal area using an electrical current, and it has already been trialled in two people at King’s College Hospital, London. According to the researchers this technique will not only provide improved quality of life, it will potentially help to reduce epilepsy-related injuries and even healthcare costs. | Early clinical research | UK: King’s College Hospital and the National Hospital for Neurology and Neurosurgery (n=25) | https://www.epilepsysresearch.org.uk/research_portfolio/cortical-electrical-stimulation-for-the-treatment-of-focal-epilepsy/ |

**Expert comments:**
- For severe intractable focal onset epilepsy could present real opportunity. For those not suitable for surgery.
- Experimental device with potential of improving seizure outcome if efficacy proven in trials. 1. No, 2. No, 3. No.

**People affected by epilepsy comments:**
- Sounds great.
- Sounding positive and hopeful.
- QOL Impact – as stated in the web link ref ERUK, QOL will be helped if trialling successful, especially as it involves ‘focal’ seizures. From my own experience, these are sometimes the hardest to eradicate with AEDs – tonic clonic seizures weren’t. Likes: the extra information on how stimulation affects seizure frequency and epilepsy ‘like’
activity between seizures - maybe of particular importance for future research ideas. The blocking of the focal area would be of huge benefit, if this means controlling these type of ‘mild’ seizures (let’s say ‘simple partial’), plus blocking the source i.e. focal area, of what then can spread to become ‘generalised tonic-clonic seizures’. Both sets of symptoms if reduced from a physical point of view would be of benefit – hence the comment about reducing ‘injuries’ as stated. Dislikes: none really as potential impact is impressive.

- Potential for those with focal seizures that are not able to be operated on. Not clear how it would be applied so how invasive or risky it might be. Not clear if it is meant to work whilst in operation or later. Think the claims might be a bit grand for a treatment that is likely to be applicable to a small group only.

### Repetitive Transcranial Magnetic Stimulation (rTMS)

<table>
<thead>
<tr>
<th></th>
<th>MagStim RapidStim2 - repetitive transcranial magnetic stimulation (rTMS)</th>
<th>Temporal Lobe Epilepsy</th>
<th>Functional MRI (fMRI) Guided repetitive TMS Enhancement of Associative Memory Networks. Repetitive TMS (rTMS) stimulates the brain with a series of magnetic pulses and has an inhibitory effect on the neuronal activity when applied at a low (≤ 1 Hz) frequency [3]. Low frequency rTMS applied for 15–30 min can reduce regional cortical excitability, and when targeted to an epileptic focus, this can suppress seizures in patients with neocortical epilepsy and interrupt ongoing seizures in status epilepticus.</th>
<th>Phase I, not yet recruiting</th>
<th>USA: NCT02749422 (n=40, end date Nov 2016)</th>
<th><a href="https://ClinicalTrials.gov/show/NCT02749422">https://ClinicalTrials.gov/show/NCT02749422</a></th>
<th><a href="http://www.sciencedirect.com/science/article/pii/S221332321630007X">http://www.sciencedirect.com/science/article/pii/S221332321630007X</a></th>
<th><a href="http://www.sciencedirect.com/science/article/pii/S1935861X14001697">http://www.sciencedirect.com/science/article/pii/S1935861X14001697</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>MagStim RapidStim2</td>
<td>Magstim Inc., New York University, USA</td>
<td>Functional MRI (fMRI) Guided repetitive TMS Enhancement of Associative Memory Networks. Repetitive TMS (rTMS) stimulates the brain with a series of magnetic pulses and has an inhibitory effect on the neuronal activity when applied at a low (≤ 1 Hz) frequency [3]. Low frequency rTMS applied for 15–30 min can reduce regional cortical excitability, and when targeted to an epileptic focus, this can suppress seizures in patients with neocortical epilepsy and interrupt ongoing seizures in status epilepticus.</td>
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<td><a href="https://ClinicalTrials.gov/show/NCT02749422">https://ClinicalTrials.gov/show/NCT02749422</a></td>
<td><a href="http://www.sciencedirect.com/science/article/pii/S221332321630007X">http://www.sciencedirect.com/science/article/pii/S221332321630007X</a></td>
<td><a href="http://www.sciencedirect.com/science/article/pii/S1935861X14001697">http://www.sciencedirect.com/science/article/pii/S1935861X14001697</a></td>
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<tr>
<td></td>
<td>H-Coil repetitive transcranial magnetic stimulation (rTMS)</td>
<td>Children's Hospital Boston, Focal temporal lobe</td>
<td>A non-invasive low frequency magnetic coil rTMS device designed to inhibit the abnormal electrical activity through deep brain stimulation. While conventional</td>
<td>In clinical research</td>
<td>In clinical research</td>
<td><a href="http://www.ncbi.nlm.nih.gov/pubmed/2711490">http://www.ncbi.nlm.nih.gov/pubmed/2711490</a></td>
<td><a href="http://www.ncbi.nlm.nih.gov/pubmed/2711490">http://www.ncbi.nlm.nih.gov/pubmed/2711490</a></td>
<td></td>
</tr>
<tr>
<td>Harvard Medical School, USA</td>
<td>epilepsy (TLE)</td>
<td>rTMS stimulators activate only superficial cortical areas, reaching deep epileptic foci, for example in TLE it is possible using specially designed H-coils. Deeper and larger volumes of stimulation can be induced by the unique shape of H-coils containing an array of elements which are contoured to the shape of the skull.</td>
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**Expert comments:**
- This has the potential to lower the Sx threshold for significant amounts of time. Barriers include access to guided TMS and the frequency of visits. Perhaps if designed TMS which could be used at home would be of definite value. Safety data and adverse effects on memory and other cognitive function would need to be assessed particular if areas of brain targeted were large.
- Very interesting has potential to improve seizure outcome and is minimally invasive. Still experimental and should be considered within the remit of clinical trials.

**People affected by epilepsy comments:**
- If I thought it worked and with no side effects it would be great. The only concern would be what happens to the patient when the device needs maintaining.
- QOL Impact – promising as most regarding reduction of seizures. Very much in its infancy stage as used elsewhere in other areas such as depression plus alternative areas.
- Non-invasive is good, but seems like a lot of daily sessions required which I imagine would require being at a centre. Subjective assessment of its impact on just one person, so obviously need more data. Might be a useful option if it can stop Status events. Need to be able to identify a focus area.

| Geodesic Transcranial Electrical Neuromodulation (GTEN) Device - low frequency repetitive transcranial magnetic stimulation (rTMS) | Electrical Geodesics Inc and Stanford University, USA | Epilepsy | A neurostimulation device designed to deliver small amounts of highly targeted electrical current through a changing pattern of the devices 256 electrodes. It is based on ADAPT Amplifier Technology. It directs the treatment to the focal area and spares the treatment to non-target areas. It records the brain activity during and after the treatment, and comprises of GES 400 dense array EEG platform. | Phase I. USA approval expected June 2016 and launch Sept 2016 | USA: NCT02757547, RESET (n=10, primary end date Dec 2016, study completion Sept 2017) |

**Expert comments:**
- In suitable patients where treatment demonstrated to reduce Sx threshold this could really be feasible as seemingly low risk and can administer at home. Lower cost than TMS. May have beneficial long term network adapting effects.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- QOL Impact – promising as most regarding reduction of seizures. Very much in its infancy stage as used elsewhere in other areas such as depression plus alternative areas.
- Seems like a variation on the above, although I guess the more targeted the better. Needs identification of focal onset site, and if one can do this then surgery might be the best option. Would need to assess how long benefit lasts or would you need to keep doing it.
## Transcranial Direct Current Stimulation (tDCS)

**People affected by epilepsy comments:** Concern with all of these stimulation devices are how long they will be effective for and possible long term impact on memory etc. If there is no real understanding of how they work, what else might they be doing? People used to think electric shock treatment was a good idea!


**Expert comments:**
- In suitable patients where treatment demonstrated to reduce Sx threshold this could really be feasible as seemingly low risk and can administer at home. Lower cost than TMS. May have beneficial long term network adapting effects.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- It sounds great especially if it allows painless targeting of the brain and spinal cord.
- QOL Impact – promising as most regarding reduction of seizures. Very much in its infancy stage as used elsewhere in other areas such as depression plus alternative areas.
- Seems like a variation on the above. Needs identification of focal onset site, and if one can do this then surgery might be the best option. Would need to assess how long the benefit lasts or would you need to keep doing it?

43 Starstim - Transcranial Direct Current Stimulation (tDCS) device

| NeuroElectrics | Drug-resistant Partial Epilepsy | A research-class multichannel transcranial current stimulator (including tDCS, tACS and tRNS), an EEG and acelerometry recording system a single lightweight, wireless package. tDCS, a non-invasive technique already used in other areas of neurology, may be efficient on some partial epilepsies, in particular through the individual configuration of stimulation, made possible by recent technological advances. | Phase II. CE marked | France: NCT02465970, BRAINSTIM (n=12, recruiting, end date June-Dec 2017) | http://www.neuroelectrics.com/products/starstim/ https://ClinicalTrials.gov/show/NCT02465970 http://www.sciencedirect.com/science/article/pii/S1935861X15004246 |

**Expert comments:**
- In suitable patients where treatment demonstrated to reduce Sx threshold this could really be feasible as seemingly low risk and can administer at home. Lower cost than TMS. May have beneficial long term network adapting effects.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- The only concern I’d have with this I think is what the side-effects are like.
- QOL Impact – promising as most regarding reduction of seizures. Very much in its infancy stage as used elsewhere in other areas such as depression plus alternative areas.
- Seems like a variation on the above. Needs identification of focal onset site, and if one can do this then surgery might be the best option. Would need to assess how long benefit lasts...or would you need to keep doing it.

- 1-No, 2-No, 3-not applicable (experimental), 4-n/a, 5-n/a.

**Expert comments:**
- In suitable patients where treatment demonstrated to reduce Sx threshold this could really be feasible as seemingly low risk and can administer at home. Lower cost than TMS. May have beneficial long term network adapting effects.
- 1-No 2-No. Experimental and will require further trials before considering clinical use in the NHS.

**People affected by epilepsy comments:**
- QOL Impact – promising as most regarding reduction of seizures. Very much in its infancy stage as used elsewhere in other areas such as depression plus alternative areas.
- Seems like a variation on the above. Needs identification of focal onset site, and if one can do this then surgery might be the best option. Would need to assess how long benefit lasts or would you need to keep doing it.
### Deep Brain Stimulation (DBS)

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Condition</th>
<th>Summary</th>
<th>Clinical Trials</th>
<th>USA: NCT02383407 (n=20), NCT02235792 (n=15)</th>
<th>Link</th>
</tr>
</thead>
</table>

**Expert comments:**

- Trials need to continue to decide optimal placement of the electrodes, in whom and which stimulation protocols. Ad hoc implantation of expensive devices is unlikely to represent good value for money for the NHS.
- This is an established mode of treatment of drug resistant epilepsy with published clinical trials. Specific subgroup of patients with drug resistant epilepsy can benefit from DBS with improved outcome. 1-Yes 2-Yes 3-Improved outcome 4-specific sub group of patients with epilepsy (bitemporal etc) 5-cost can be a problem but selective criteria for implantation should reduce overall numbers.

**People affected by epilepsy comments:**

- If I thought it worked and with no side effects it would be great and I’d be able to put up with the thought of wires in me. The only concern would be what happens to the patient when the device needs maintaining.
- QOL Impact – early stages in a way. Likes: end result hopefully of use but needs more evidence/research. Dislikes: invasive to the patient so PWE will be sometimes difficult to be trialled.
- Requires “proper” brain surgery, so never an easy decision. Need to be able to identify onset site. Developer link seems to claim it will work for a load of conditions… can’t actually see epilepsy mentioned. Would need to be in a quite desperate situation before thinking it was worth a try…particularly when not much data available to support claims.
| 46 | Deep Brain Stimulation (DBS) and cortical stimulation | Institute of Psychiatry, Psychology & Neurosciences, King’s College London, UK (PI: Dr Antonio Valentin) | Children with uncontrolled seizures | Treatment involves stimulating very specific parts of the brain using electrodes placed under the skull. Two techniques are being used in an ongoing UK study: cortical stimulation and deep brain stimulation. | In early clinical research | UK study (GN2380) started Feb 2016 (due to end Jan 2018) | [https://www.action.org.uk/our-research/epilepsy-new-way-treat-children-uncontrolled-seizures](https://www.action.org.uk/our-research/epilepsy-new-way-treat-children-uncontrolled-seizures) |

**Expert comments:**
- Carefully controlled trials to optimise patient selection, stimulation regimens and network modifying effects long-term need to proceed before they are approved for general use at great expense. Adverse event profiles particular in children who are likely to have this for a long time are required.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- QOL Impact: early stages in a way. Likes: end result hopefully of use but needs more evidence/research. Dislikes: invasive to the patient so PWE will be sometimes difficult to be trialled.
- Requires “proper” brain surgery, so never an easy decision. Need to be able to identify onset site. Developer link seems to claim it will work for a load of conditions... can’t actually see epilepsy mentioned. Would need to be in a quite desperate situation before thinking it was worth a try, particularly when not much data available to support claims. Cortical seems less risky, but either sounds like something one would only want to do if all other options fail and seizures are very bad.
## Other forms of neuromodulation

<table>
<thead>
<tr>
<th>#</th>
<th><strong>Device</strong></th>
<th><strong>Institution</strong></th>
<th><strong>Disease</strong></th>
<th><strong>Details</strong></th>
<th><strong>Status</strong></th>
<th><strong>Additional Info</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>Closed-Loop Multi-Electrode System</td>
<td>Emory University, USA</td>
<td>Epilepsy</td>
<td>Uses microstimulation by a multi-electrode array for seizure reduction. This approach has advantages over macro-electrode stimulation because more neurons can be activated with lesser tissue damage and multi-electrodes can deliver different spatio-temporal patterns of stimulation, which are not possible with macro-electrode. Research focus is on closed-loop stimulation where electrical stimulation is continuously modulated depending on ongoing neural activity at the seizure focus.</td>
<td>In early clinical research</td>
<td><a href="http://neurosurgery.emory.edu/research/translational-neuro-engineering/current-studies.html">http://neurosurgery.emory.edu/research/translational-neuro-engineering/current-studies.html</a></td>
</tr>
<tr>
<td>48</td>
<td>Low-intensity Focused Ultrasound Pulsation (LIFUP) device (Brain Neuromodulation Platform)</td>
<td>BrainSonix Corporation</td>
<td>Temporal Lobe Epilepsy</td>
<td>A medical technology platform based on proprietary Low Intensity Focused Ultrasound Pulsation (LIFUP) to modulate the brain function non-invasively without any harmful or irreversible effects on the brain and body. The patented technology allows targeting of specific neuronal circuits using fMRI, identification of malfunctioning circuits using fMRI “feedback” and repair of the circuits using LIFUP to activate or inhibit them.</td>
<td>In early clinical research</td>
<td>USA: NCT02151175 (n=12, recruiting, end date Feb 2017)</td>
</tr>
</tbody>
</table>

**Expert comments:**
- Limiting tissue damage and a multi-planar approach offers real promise and should be explored with all of the provisos above.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- How does this work if the person has seizures where different parts of the brain are affected?
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: the advantages stated over macro-electrode stimulation plus the comment re: stimulation being continuously modulated depending on ongoing neural activity at the seizure focus. Dislikes: some maybe unhappy re: way carried out physically perhaps?
- Think this is non-surgical? Sounds like it’s more targeted/specific.
**Expert comments:**
- Worth looking at preliminary data and animal studies.

*People affected by epilepsy comments:*
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: non-invasive. No dislikes.
- Sounds harmless enough, but the claim to “repair” neuro circuits seems a bit grand.

### Surgical techniques (n=10)

| # | Procedure                                      | Institution                | Technique                           | Advantages                                                                                                                                  | In clinical research                  | China          | NCT | [Link](http://ac.els-cdn.com/S1525505015002024/1-s2.0-S1525505015002024-main.pdf?_tid=38b31176-4370-11e6-957f-00000aab0f27&acdnat=1467806174_3d5ac7b1546cb1e0ab51d3fbe97dd93d) | [Link](http://www.sciencedirect.com/science/article/pii/S0035378715005871) | [Link](https://clinicaltrials.gov/ct2/show/NCT02089243) |
|---|-----------------------------------------------|----------------------------|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|----------------|-----|-------------------------------------------------|
| 49 | Selective amygdalohippocampectomy (SAH)       | Xijing Hospital, China (PI: Yanchun YC Deng) | Anterior temporal lobe epilepsy     | Advantages reported to be the preservation of the lateral cortex and temporal stem, smaller incision and craniotomy, but slightly worse seizure outcomes than with the gold standard procedure of anterior temporal lobectomy (ATL) and it still requires open surgery. | China NCT02089243 (n=40, end date July 2016) | [Link](http://ac.els-cdn.com/S1525505015002024/1-s2.0-S1525505015002024-main.pdf?_tid=38b31176-4370-11e6-957f-00000aab0f27&acdnat=1467806174_3d5ac7b1546cb1e0ab51d3fbe97dd93d) | [Link](http://www.sciencedirect.com/science/article/pii/S0035378715005871) | [Link](https://clinicaltrials.gov/ct2/show/NCT02089243) |
### Expert comments:
- This is a longstanding debate and fully depends on whether get additional cognitive benefits from more limited procedure – further data from trials will be useful in patient selection.
- This is a surgical procedure available for epilepsy since the 80s, currently used in the UK on selective basis (I prefer the transsyllivan approach).

### People affected by epilepsy comments:
- QOL Impact: useful alternative but as stated, needs extra research. Although in early stages, this could be of use to many PWE. Likes: side effects could be reduced. Some do not insist 100% seizure freedom is always the key as the QOL balance needs to be appropriate to the patient not necessarily the ‘surgeon’/‘specialist’. Dislikes: Open surgery still needed? Abstract shows difficulty of the outcome compared to ATL. Work may be needed concerning pre assessment accuracy. If improved this could be advantageous due to initial note stated.
- If one was taking the big step of surgery one would want the “gold standard” procedure not something lesser, although I suppose it depends on what risks come from the collateral damage caused.

### ExAblate - MR-Guided Focused Ultrasound (MRgFUS)

| ExAblate | InSightec, University of Virginia, USA (PI: Nathan Fountain) | Subcortical Lesional Epilepsy | An incision-less high intensity system designed to ablate targeted tissue in the human brain by delivering ultrasound waves. | Phase I. USA approval expected April 2018 and launch July 2018 | USA: NCT02804230 (n=10, end date June 2017) | [http://www.insightec.com/clinical/neurosurgery](http://www.insightec.com/clinical/neurosurgery) / [https://clinicaltrials.gov/ct2/show/NCT02804230](https://clinicaltrials.gov/ct2/show/NCT02804230) |

### Expert comments:
- Would need to consider collateral damage very carefully. How well targeted is this? If well targeted and efficacious then it has real possibilities.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials. Moreover this device allows ablation of only deep seated foci and this is a significant limitation. 1. No 2. No

### People affected by epilepsy comments:
- I don’t know all the research techniques used but I haven’t heard of the ultrasound waves being used before.
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: very much less invasive but evidence still needed as to how successful the controlling of tremors (in small areas) will be achieved. Procedure to be continued. Not sure of numbers of patients who can benefit? No dislikes.
- If you could have the benefit of surgery without the actual surgery, then great! Only sounds like it would be applicable to very specific types of epilepsy. Would be concerned if errors or inaccuracies could lead to damage of other areas of the brain.

### Laser thermal hippocampectomy (LTH)

| University of Pennsylvan a, USA (PI: Mark Attiah) | Anterior Temporal Lobectomy (ATL) | This is a new procedure that may offer a less invasive alternative to the standard open approach. Early data support LTH as a potentially comparable less invasive alternative to the gold standard anterior temporal lobectomy (ATL) in refractory TLE. | In clinical research | USA |
| 52 | Medtronic Visualase® MRI-Guided Laser Ablation System (procedure used: Laser Interstitial Thermal Therapy, MRigLITT), also known as stereotactic laser ablation (SLA) | Medtronic plc | Medically refractory Mesial Temporal Lobe epilepsy | A minimally invasive MRI (Magnetic Resonance Imaging) guided laser induced device. According to the company the ability to use laser ablation in a minimally invasive manner under MRI guidance provides a real-time estimate of the thermal damage incurred at the targeted lesion. This near instant information of the thermal damage is presented to the surgeon in the innovative software that is part of this device system. The innovative thermal damage estimate gives the surgeon the ability and confidence to ablate a lesion or anatomy with precision, thereby minimizing (collateral) damage to the non-diseased surrounding tissue/anatomies. (Note: NIHR HSRIC MedTech Alert on this topic due to be published July 2016.). | In clinical research. Estimated EU approval July 2018 and launch Oct 2018. (FDA approved) | USA: NCT01703143 (phase I), GDME201446, 10-007909 (completed studies), GDME2031637 (planned USA study) 10-007909GDM E2014446 10-007909 | http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=RssLanding&cat=news&id=2178428 https://clinicaltrials.gov/ct2/show/NCT01703143 |

**Expert comments:**
- Worth looking at trial data and costs of equipment.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: new procedure, plus as above - evidence still needed in addition to the early data support comparisons. Procedure to be continued. Not sure of numbers of patients who can benefit? No dislikes.
- If you could have the benefit of surgery without the actual surgery, then great! Only sounds like it would be applicable to very specific types of epilepsy. Would be concerned if errors or inaccuracies could lead to damage of other areas of the brain. All sounds a bit Star Trek/ Dr MaCoy.

- Seizure outcome and cognitive outcome data in sufficient amounts to be meaningful is required. If successful then could be less risky than open surgery with less collateral damage.
- This device for ablation of epileptic foci is available in the USA for clinical use. There are several reports and clinical studies showing efficacy in ablation of seizure foci (hypothalamic hamartomas, hippocampus, etc). Minimally invasive. 1-Yes 2-Yes 3-Improved outcome, decrease length of stay 4-all groups 5-Cost can be a limitation but small numbers of patients eligible should limit exposure.

**People affected by epilepsy comments:**
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: Real time estimate of thermal damage looks to be of use to the surgeon in this case, helping
with removal of problematic areas with minimal damage to close areas that aren’t a problem. Procedure to be continued. Not sure of numbers of patients who can benefit?

- No dislikes.
- If you could have the benefit of surgery without the actual surgery, then great! Only sounds like it would be applicable to very specific types of epilepsy. Would be concerned if errors or inaccuracies could lead to damage of other areas of the brain. All sounds a bit Star Trek/ Dr MaCoy.

| NeuroBlate Laser Interstitial Thermocoagulation Therapy - (procedure used: Laser Interstitial Thermal Therapy, MReLIT) | Monteris Medical Inc | Mesial temporal lobe epilepsy (MTLE); Medically Refractory Epilepsy | Designed to ablate and coagulate soft tissue during neurosurgery procedures through laser thermotherapy. Procedure is done as day-case under general anaesthetic. Using stereotactic guidance a laser probe is inserted into the brain. Patient is placed in the MRI scanner and laser is turned on – the MRI records real-time thermometry delivered to the lesion. Benefits – can treat deep-seated unresectable tumours, minimally invasive, day case. | Phase I. Not yet CE marked. FDA approval expected Feb 2019 and launch May 2019 | USA: NCT02820740 (n=45, not yet open for recruitment, end date Dec 2019) | https://clinicaltrials.gov/ct2/show/NCT02820740 |

**Expert comments:**
- Seizure outcome and cognitive outcome data in sufficient amounts to be meaningful is required. If successful then could be less risky than open surgery with less collateral damage.
- Similar system to Visualase (no.52) and comments for Visualase apply for this system.

**People affected by epilepsy comments:**
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: again, if laser treatment is to be found to be beneficial then will obviously become advantageous. Procedure to be continued re: clinical trials. Not sure of numbers of patients who can benefit? No dislikes.
- If you could have the benefit of surgery without the actual surgery, then great! Only sounds like it would be applicable to very specific types of epilepsy. Would be concerned if errors or inaccuracies could lead to damage of other areas of the brain. All sounds a bit Star Trek/ Dr MaCoy.

| MRI-guided laser interstitial thermal therapy (MRgLITT) | Various (including Medtronic plc and Monteris Medical Inc - see device-specific entries) | Drug-resistant epilepsy, paediatric, Mesial temporal lobe epilepsy, Medically refractory epilepsy; | This emerging surgical procedure utilises an optical fibre with a diffusing tip heated by a diode laser insulated in an outer cannula that cools the laser with either saline or carbon dioxide. The probe is delivered by frame-based stereotaxis, robotic stereotaxis, or MRI-based frameless stereotactic techniques to a defined target. The advantages of MRgLITT include the ability to target deep lesions via a minimally invasive approach and monitoring of the treatment in real time. This contrasts with other minimally invasive or non-invasive treatment methods (such as gamma knife radiosurgery or | Two systems FDA approved, research ongoing | http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4855197/ |
| 55 | Stereotactic electroencephalography (SEEG) electrode-guided radiofrequency thermocoagulation | Researchers | Drug resistant focal epilepsy, not eligible for conventional surgery | Facilitates a three-dimensional spatiotemporal understanding of seizure onset and progression. In comparison to surface electrode monitoring with subdural electrodes, SEEG may be particularly useful in the evaluation of children with multiple lesions including tuberous sclerosis complex, as well as for sampling deep targets such as insular cortex, the cingulate gyrus, and mesial temporal structures. In addition, placement does not require craniotomy. Robotic assistance in depth electrode placement has demonstrated benefits in planning safe trajectories and reducing operating time. Associated with excellent target accuracy of 1–3 mm. | In clinical research | http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4855197/ |
### Expert comments:
- This has real potential for the populations they describe. Definitely worth supporting in my view for use at specialised centres. Definite way forward for deep seated or multiple lesions.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

### People affected by epilepsy comments:
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: seems to have come back into the domain recently due to the ability to spot problematic areas which standard EEG’s cannot trace. Research must be of benefit. Procedure to be continued re: clinical trials. Although drug resistant focal epilepsy is referred to, am not sure of numbers of patients who can benefit? No dislikes.
- Sounds more like a technique for pinpointing focal onset sites which can then hopefully be treated by one of the above techniques. Sounds good. Love the potential these techniques offer to treat severe childhood epilepsies before repeated seizures have caused too much life-long damage. Holds out the prospect of a normal life for kids that would have poor outcomes otherwise and for whom social support costs could be massive, so well worth exploring.

<table>
<thead>
<tr>
<th>56</th>
<th>Stereotactic radiosurgery (SRS)</th>
<th>Researchers</th>
<th>Intractable mesial temporal lobe epilepsy</th>
<th>A novel technique for selective ablation of the mesial temporal structures which may have potential as a therapy for MTLE when open surgery is not an option.</th>
<th>In clinical research</th>
</tr>
</thead>
</table>

### Expert comments:
- Other techniques without radiation are preferable and I think are the future.
- SRS for epilepsy did not show significant improvement in outcome and currently is not an alternative to respective surgery.

### People affected by epilepsy comments:
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: does state it ‘may’ have potential so should be investigated. Procedure to be continued re: clinical trials. Not sure of numbers of patients who can benefit? No dislikes.
- Sounds more like a technique for pinpointing focal onset sites which can then hopefully be treated by one of the above techniques. Sounds good. Love the potential these techniques offer to treat severe childhood epilepsies before repeated seizures have caused too much life-long damage. Holds out the prospect of a normal life for kids that would have poor outcomes otherwise and for whom social support costs could be massive, so well worth exploring.

| 57 | robot CAS-R-2 frameless stereotactic system - robot-assisted stereotactic system for radiofrequency thermocoagulation (RF) | Beijing University and Navy General Hospital, China | Temporal lobe epilepsy | This robot-assisted system provides accurate RF treatment of the cranium and assists in deep electrode implantation. The deep electrodes are stereotactically implanted into the brain to identify the exact locations of the epileptogenic zones (EZs) and the pathways of seizure propagation. An advantage of this method is that it is possible to define EZs without performing a craniotomy. | In early clinical research | China: n=7 (completed) | http://www.neurologytimes.com/aan-2016/overcoming-epilepsy-self-management-barriers | https://www.spanidos-publications.com/10.3892/etm.2014.10892 |
### Expert comments:
- As above electro definition alongside imaging offers real potential.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

### People affected by epilepsy comments:
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: benefit stated concerning not having to perform a craniotomy to discover locations of EZ’s. Procedure to be continued re: clinical trials. Not sure of numbers of patients who can benefit? No dislikes generally except implants may be problematic to some PWE.
- Sounds more like a technique for pinpointing focal onset sites which can then hopefully be treated by one of the above techniques. Sounds good. Love the potential these techniques offer to treat severe childhood epilepsies before repeated seizures have caused too much life-long damage. Holds out the prospect of a normal life for kids that would have poor outcomes otherwise and for whom social support costs could be massive, so well worth exploring.

### Tightly-Focused Femtosecond Laser (optical microsurgery device)

<table>
<thead>
<tr>
<th>Coordinating Institution</th>
<th>Specialty</th>
<th>Description</th>
<th>Research Status</th>
<th>FDA Approval</th>
<th>USA: One-year Research Study Started</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornell University, USA (PI: Theodore Schwartz)</td>
<td>Focal neocortical epilepsy</td>
<td>A special kind of laser to make very fine cuts in the cortex without cutting the surface of the brain. A combination of in vivo two-photon imaging, ultrafast femtosecond laser cutting, electrophysiological recording, laser Doppler flowmetry, oxygen microsensor, and optical mapping will be used. The advantage of these ultrafast laser pulses is their ability to evaporate an extremely small volume of tissue without heating or damaging the surrounding tissue. Tightly focused femtosecond laser pulses provide a unique means to make micrometer-scale cuts more than a mm within the bulk of a tissue that cause minimal collateral damage.</td>
<td>In clinical research. FDA approval in USA expected April 2017 and launch July 2017</td>
<td>USA: one-year research study started Sept 2015</td>
<td><a href="http://weillcornellbrainandspine.org/femtosecond-laser-surgical-therapy-neocortical-epilepsy-optical-cutting-microsurgery">http://weillcornellbrainandspine.org/femtosecond-laser-surgical-therapy-neocortical-epilepsy-optical-cutting-microsurgery</a></td>
<td></td>
</tr>
</tbody>
</table>

### Expert comments:
- Of significant interest particularly if preservation of radial pathways in functional cortex.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

### People affected by epilepsy comments:
- This sounds good if it doesn’t cut the surface of the brain and can be so precise.
- QOL Impact: although in early stages, this could be of use to many PWE. Likes: successful laser treatment without nearby harm of surrounding areas. Procedure to be continued re: clinical trials. Not sure of numbers of patients who can benefit? No dislikes.
- Sounds more like a technique for pinpointing focal onset sites which can then hopefully be treated by one of the above techniques. Sounds good. The more focused in on the onset site the better. Love the potential these techniques offer to treat severe childhood epilepsies before repeated seizures have caused too much life-long damage. Holds out the prospect of a normal life for kids that would have poor outcomes otherwise and for whom social support costs could be massive, so well worth exploring.
### Other therapeutic techniques (n=7)

| 59 | Autologous mesenchymal stem cell (MSC) therapy | Ministry of Public Health, Belarus | Drug-resistant symptomatic epilepsy | Safety of Autologous MSC Infusion to Treat Epilepsy: Autologous bone marrow-derived mesenchymal stem cells, expanded ex vivo and neuro-induced (a portion of the cells). The final autologous cultured MSCs (0.7 - 1.4 x 10^6 cells/kg of weigh) and autologous neuro-induced MSCs (0.04 - 0.1 x 10^6 cells/kg of weigh) were used for intravenous administration (cultured MSCs) and a subsequent endoluminal injection (neuro-induced MSCs) one week later in the patients in an autologous manner. | Phase I/II | Belarus: NCT02497443 (n=60, currently suspended, end date Dec 2018) | https://ClinicalTrials.gov/show/NCT02497443 |

**Expert comments:**
- A lot more work in animal models required. No evidence to my knowledge that you can grow a new hippocampus.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- QOL Impact: difficult to assess due to ‘dislike’ comments below. Likes: none. Dislikes: participant recruitment suspended due to unfavourable reactions to the MSC injections.
- If this offered the possibility to reverse some of the damage from seizures then that would be marvellous…. Maybe too much to hope for? Maybe hope is to reduce seizures only…. Early days but if it worked then this could have wide applicability and improve outcomes. If stem cells can be got from discarded placenta etc. then no ethical issues to worry about.

| 60 | Optogenetics | Researchers | Astrocyte-related epilepsy | Optogenetics is a relatively new field that uses gene therapy techniques to promote the expression of genes that encode for light sensitive proteins called opsins. It targets seizure activity by incorporating light-sensitive proteins into neurons and then controlling their activity with the application of light. Optogenetics has not yet translated into clinical approaches with humans, although advances in wireless light delivery have already been made, and an implantable device to monitor seizure activity in humans was recently tested for the first time. | Phase I/preclinical | http://www.ncbi.nlm.nih.gov/pubmed/23642342 | http://www.neuroscientificallychallenged.com/blog/new-approaches-epilepsy-optogenetics-dreadds | http://link.springer.com/article/10.1007%2Fs00415-014-7294-y |
## Expert comments:
- Really exciting field which offers potential for Sx management. The light sensitivity part is really innovative. As gene therapy could provide a longer term solution as cells remain light sensitive.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials. Being a pre-clinical project and idea will require several years for development although is a good idea.

### People affected by epilepsy comments:
- QOL Impact: huge QOL issues as most people are already aware. Behaviour of genes and helping to understand neurone activity is so important. Likes: updated technology to help everyone involved in the learning process. No dislikes.
- Seems like this is mixing up two different things. The gene therapy sounds good if it offers to stop the triggering of seizure activity without the general brain dampening effect of conventional drugs. Would need to be able to identify if seizures are triggered in this way. The other seems to be a monitoring device rather than a treatment. Maybe this is the means by which one would identify if the patient was suitable for the gene therapy?

| 61 | Nano particles for the delivery of AEDs | Researchers | Drug Resistant Epilepsy | AEDs-loaded in nanosystems could be a promising new approach for the treatment of pharmaresistant epilepsy. | Early research | https://www.researchgate.net/publication/262844613_Pharmaresistant_epilepsy_and_nanotechnology |

## Expert comments:
- Further animal research.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials. Again pre-clinical.

### People affected by epilepsy comments:
- QOL Impact: will be of great help to the percentage of PWE affected re: drug resistant. Likes: to lessen the percentage of patients who are drug resistant. Would be very
useful as this figure has been static for a long time. No dislikes.

- Nanotechnology....its heralded as the solution to everything! If delivery of AEDs is the issue for resistant E, then maybe it would be a useful mechanism to get them across the blood brain barrier. However as most AEDs are general brain dampeners then would be concerned that side effects would be increased too.

<table>
<thead>
<tr>
<th>62</th>
<th>Electroconvulsive therapy (ECT)</th>
<th>Researchers</th>
<th>Refractory Status Epilepticus (RSE)</th>
<th>A novel treatment to stimulate extra GABA release. According to a 2016 systematic review Oxford level 4, GRADE D evidence exists to suggest an improvement in seizure control with ECT application for RSE, although routine use cannot be recommended at this time.</th>
<th>In early clinical research (14 papers published with a total of 19 patients)</th>
</tr>
</thead>
</table>

http://www.jnaccjournal.org/article.asp?issn=2334-0548;year=2016;volume=3;issue=2;spage=83;epage=95;aulast=Gupta

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>Researchers Status Epilepticus (RSE)</th>
<th>The identification of autoimmune encephalitis as a mechanism for SE raises the possibility of immunotherapeutic strategies as a potential SE treatment. For example, anti-NMDA receptor encephalitis often responds to immunotherapy (e.g. Corticosteroids, immunoglobulins).</th>
<th>Unclear</th>
</tr>
</thead>
</table>

**Expert comments:**
- Definite way forward in this group and we already know that this group can respond well to immunomodulation.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.
<table>
<thead>
<tr>
<th>64</th>
<th>Cooling Grid - Seizures</th>
<th>University of Minnesota, USA</th>
<th>Epilepsy</th>
<th>An implantable neurological device designed to cool the brain by reducing its temperature, to reduce the epileptiform activity in the seizures. Reduces the epileptiform activity in the seizures by cooling the brain.</th>
<th>In clinical research. Approval (USA: PMA) expected April 2018 and launch July 2018</th>
</tr>
</thead>
</table>

**Expert comments:**
- If successful most applicable in drug resistant status in ITU. If smaller and portable then adverse effects of cooling functional networks for the individual would have to be considered. Susceptible to electrical malfunction as with all stimulator devices. As far as we know offers no network modifying effects.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- QOL Impact: not as important at this time due to initial research. Likes: satisfactory, but to be carried out at the appropriate time. No dislikes.
- Would it "kick in" when a seizure starts or be cooling the brain all the time? Sounds like something that might be useful in minimising damage... maybe before operation can be performed etc. but would be looking for a better treatment/cure for the seizures if possible.

<table>
<thead>
<tr>
<th>65</th>
<th>Induced mild hypothermia</th>
<th>Assistance Publique - Hôpitaux de Paris, France (PI: S Legriel)</th>
<th>Super-Refractory Status Epilepticus (RSE)</th>
<th>A novel treatment in which a target temperature of 32-35°C is induced by either surface or endovascular cooling for a period of 24-48 hours. In addition to an antiepileptic effect, hypothermia is neuroprotective and can reduce the intensity of brain oedema caused by SE. Note: other potential management for super-refractory SE includes vagal nerve stimulation, electroconvulsive therapy, deep brain stimulation, transcranial magnetic stimulation and cerebrospinal fluid drainage (although the evidence base is limited at present).</th>
<th>In clinical research</th>
</tr>
</thead>
</table>

**France:**
- NCT01359332 (n=270, ongoing, end date Aug 2017 - phase III for moderate hypothermia)

http://www.jnaccjournal.org/article.asp?issn=2348-0548;year=2016;volume=3;issue=2;spage=83;epage=95;aulast=Gupta
http://www.antnsjournal.com/Mag_Files/24-4/001.pdf
https://clinicaltr...
### Management technologies (n=26)

#### Digital and wearable technologies for seizure tracking/alert (n=18)

<table>
<thead>
<tr>
<th>#</th>
<th>Technology</th>
<th>Description</th>
<th>Developer</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>66</td>
<td>EpiNav™ (Epilepsy Navigator) software</td>
<td>Combines information from an array of imaging technologies including MRI (for brain structure, blood vessels, white matter tracts), fMRI (for speech and motor function) and PET to provide an integrated 3D image of multiple brain structures and functions in order to assist in accurate surgical planning and electrode placement. The EpiNav™ software is custom-designed for multimodality image integration, advanced 3D visualisation and epilepsy surgery planning. The pioneering system will enable neurosurgeons to plan the best operative approach for inserting recording electrodes in the brain and for removing parts of the brain that give rise to seizures.</td>
<td>University College London (PIs: Professor John Duncan and Professor Sebastien Ourselin). Uses platform from Medtronic NeuroNavi gation</td>
<td>Beginning to introduce this into epilepsy surgery in a clinical trial at the National Hospital for Neurology and Neurosurgery. UK. Research grant running 2012-2016</td>
</tr>
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<td><strong>Expert comments:</strong></td>
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<td>Improved targeting of investigation and resection has got to be beneficial. Advanced co-registration of data must be the way forward. Interesting as a concept but not sure it will be possible to create such software to automate SEEG and surgical planning for epilepsy cases with integration of fMRI, PET and anatomical data set. Experimental software with potential to treat epilepsy but still use limited in clinical trials and will require multicentric approach to be successful.</td>
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</table>

**People affected by epilepsy comments:**

- QOL Impact: huge impact due to information stated from very important sources. Likes: Imaging technologies taken into account and used for the ‘best operative approach’. No dislikes.
- Confidence in epilepsy surgery is key to improving uptake, and if risk of damage (particularly to memory and personality) can be reduced then more people are likely to be brave enough to go for it. Tools like this must help.

| 67 | Decision Support System | Henry Ford Health System, USA | Epilepsy | A web-based device designed to process multi-modality medical images and extract quantitative information from patients. It uses image analysis results along with the results of other clinical tests as well as the patients’ history and characteristics to reduce the need for intracranial electrographic studies, predict post-operative outcomes, and suggest optimal treatment options for the new patients. | In clinical research. Approval (USA: 510k) expected Oct 2017 and launch Jan 2018 | USA study ending Aug 2016 (project No. 1R01EB01327-01A1) | [http://grantome.com/grant/NIH/R01-EB01327-01A1](http://grantome.com/grant/NIH/R01-EB01327-01A1) |

**Expert comments:**

May have its place but need to be careful of following computer based algorithms too closely.

**People affected by epilepsy comments:**

- QOL Impact: DSS difficult to follow even though I have TLE myself. Presume it’s all about collation of appropriate information. How widespread would this be? Likes: useful but areas covered may be restricted? Dislikes: as above.
- Confidence in epilepsy surgery is key to improving uptake, and if risk of damage (particularly to memory and personality) can be reduced then more people are likely to be brave enough to go for it. Tools like this must help.

| 68 | Computer software model based on MRI imaging: structural connectome based simulations | Newcastle University, UK (PI: F Hutchings) | Drug resistant temporal lobe epilepsy (TLE) | The software uses patient MRI scans to create a model that it can manipulate. The model consists of the neural network represented by nodes and connections between them. The simulator mimics the removal of different nodes to see how they affect the activity in the rest of the network. The researchers compared the | Phase I (a computer-based simulation study reported, using MRI scan from 22 | UK | [http://journals.plos.org/ploscompbio/article?id=10.1371/journal.pcbi1000531](http://journals.plos.org/ploscompbio/article?id=10.1371/journal.pcbi1000531) | [http://www.medgadget.com/2015/12/computer-simulation-predicts-treatment-targets.html](http://www.medgadget.com/2015/12/computer-simulation-predicts-treatment-targets.html) |
response of targeting of commonly removed areas to
those selected uniquely for each patient, showing a
marked improvement in ability to fight seizures. But
since this is still entirely a computer-based simulation,
the researchers will have to compare the software
against real patient cases to see whether it actually
works.


**Expert comments:**
- Definite potential to add to a suite of co-registered data and attempt to model outcomes although as stated needs more work including animal studies.
- Experimental software with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- Sounds a quite interesting study if it does work.
- QOL Impact: good, if this brings more accuracy ref not missing patients with or without drug resistance epilepsy types. Likes: clever concept but have these process steps already been covered elsewhere. Believe they have been – but if this idea is to combine then – in one study, then fine. No dislikes.
- Sounds like an interesting idea. If one could have a virtual operation that reliably predicted the outcome of the actual operation then that would be a huge confidence boost.... Some way off yet though I guess.
<p>| EpSMon - Epilepsy Self Monitor (App for smartphones) | Plymouth University; Cornwall Foundation NHS Trust; Royal Cornwall Hospital and SUDEP Action | Epilepsy, patients at risk of SUDEP | A mobile app for people with epilepsy to help them self-monitor their health risks in between visits to their doctors. It shows the user which health risks are getting better, which have worsened and which have stayed the same to encourage a discussion about these risks with their GP or epilepsy specialist. It can also help them to decide whether to seek help earlier than their next planned appointment. EpSMon is designed to help people with epilepsy be aware of why and when a medical review of their epilepsy is important. After the initial assessment of risk, it reminds them every three months to reassess. Adopted into the national epilepsy commissioning toolkit UK in 2015. | Launched July 2015 and available | UK | <a href="http://www.epsmmon.com/">http://www.epsmmon.com/</a> <a href="https://sudep.org/article/epilepsy-self-monitor">https://sudep.org/article/epilepsy-self-monitor</a> <a href="https://www.epilepsy.org.uk/news/news/epilepsy-self-monitoring-app-launched-64851">https://www.epilepsy.org.uk/news/news/epilepsy-self-monitoring-app-launched-64851</a> |</p>
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<th>People affected by epilepsy comments:</th>
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<tr>
<td>- Sounds reasonable and zero costs.</td>
<td>- QOL Impact: excellent tool for continuously updating patient’s individual ‘RISK’ of their epilepsy on a 3 month ‘reminder’ basis. Keeps the patient aware of risks involved – and when further action should be taken e.g. to see GP/specialist. Likes: I use this myself and it’s good, even for those with controlled epilepsy. I was one of the Patient advisors to the Safety Checklist which the app is based on. This information is for professionals, whilst the phone questions are simple for the PWE to answer on an ongoing basis. Three month phone reminder is perfect timing for ‘update’ self-assessment. No dislikes.</td>
</tr>
<tr>
<td>- Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.</td>
<td>- If users find it useful then it is useful! If it’s free that’s great. Probably appeal to the younger app generation who manage everything via their phone. There are a number of Apps around and if they are to be useful for professionals then I think there needs to be some coordination between what is being produced so look and feel is standardised and data could be collated for “big data” harvesting.</td>
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<tr>
<td>- Recording seizures is a good idea and video them as a great way of showing consultants exactly what happens. It can be very embarrassing at a young age to try and show a consultant what a seizure is like. Consultants have to realise the embarrassment and that the person is in the middle of the seizure even if it is only lasting seconds they’re not thinking about what it is like.</td>
<td>- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their GP/consultant plus researchers. Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle</td>
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| Young Epilepsy App | Design and Prosper Ltd (with Young Epilepsy) | Epilepsy | The "Learn section" of the app gives users quick access to information relevant to both teens and parents. The diary function enables young people and their families to log seizures, recording their severity and the situation in which they occurred. A quick, easy video function means seizures can be recorded for later reference. This helps families identify patterns. The app makes sharing data with doctors, teachers and others fast and accurate - profile and emergency first aid data can be logged and shared in moments. | Available and free to download | UK | http://www.designandprosper.com/our-work/young-epilepsy.aspx http://www.youngepilepsy.org.uk/for-parents-and-carers/help-and-advice/at-diagnosis/app.html |

71
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<th>72</th>
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<tr>
<td><strong>EpiWatch ResearchKit (app for use on the Apple Watch and iPhone)</strong></td>
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| Johns Hopkins University, USA (PIs: Gregory Krauss and Nathan Crone), THREAD Research and Acuma Health (a division of Smart Monitor) | Patients with epilepsy who may experience an 'aura' that signals an oncoming seizure | The onboard gyroscope and accelerometer data from Apple Watch and iPhone are combined with Apple Watch heart rate data when a participant chooses to track a seizure episode. The app also provides helpful tracking of seizures, prescription medication use and drug side effects — activities that are important in helping patients manage their condition. The developers state that it is not a seizure detector, but the data will help influence the creation of a seizure detection app in the future. | Research use at present. Available to download for free from the App Store (uses: to self-track seizures and participate in the research study) | USA |

**Expert comments:**

- This is a field which will just get bigger and better at movement and heart rate detection and sharing of data between apps and ultimately remotely to medical services. We should try to combine it with telemetry data or ambulatory data from EEG so that we can identify those with ictal tachycardia who may benefit from devices such as VNS 106. Commercial competition in this area is to be encouraged as improves technology and prices come down.

- Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.

**People affected by epilepsy comments:**

- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their friends, GP/consultant plus Researchers. Also, there are several devices like this one that include the tracking of seizures/contacts/timings. Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle ref: these Apps is similar in a way especially having the ability to record in more detail, the patient’s experiences and filming, if deemed appropriate. No dislikes.
• Aspect of prediction is interesting. If people had warning signs from heart beat or temp, etc and this could reliably be used to pre-empt major seizure onset, then that might be very useful in preventing injury from seizure falls. Injury from seizure falls are a huge concern, and fear of it a huge limiter. Anything to help reduce that would be great!

| 73 | Neutun (app for use on the Pebble SmartWatch) | Neuton Labs Inc | Epilepsy | A new app that was designed to work with smartwatches to accurately track and record seizures. It uses the motion sensors inside smartwatches to spot seizures, immediately beginning to record the intensity and lengths of the events. It can immediately notify loved ones that a seizure is occurring by sending a text message to people on a pre-set list. It also includes built-in medication reminders. Currently, the app only works with the popular Pebble smartwatch, but plans are in the works to be compatible with other devices. | Available to download from Google Play and Apple App Store | http://www.neutun.com | http://www.medgadget.com/2015/04/neutun-app-works-smartwatches-track-seizures-notify-loved-ones.html |

**Expert comments:**
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- Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.

**People affected by epilepsy comments:**
- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their friends, GP/consultant plus Researchers. Also, there are several devices like this one that include the tracking of seizures/contacts/timings. Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle ref: these Apps is similar in a way especially having the ability to record in more detail, the patient’s experiences and filming, if deemed appropriate. No dislikes.
- [See comments for EpiWatch, including: might be very useful in preventing injury from seizure falls] though better still if you can know before it starts! Need to be wary of false alarm risk. Good that it is a “normal” device that people likely to be using anyway...will help make it more acceptable especially to young.

<p>| 74 | SmartWatch - Wrist Accelerometer as a Biosensor for Tracking Seizures | SmartMonitor Corporation, Stanford University, USA | Generalized tonic-clonic epilepsy | A Biosensor for Tracking Seizures: Linking a Wrist Accelerometer to an Online Epilepsy Diary. Study will assess whether a movement detecting wristwatch can accurately detect seizures and seizure characteristics and record them into an online epilepsy diary. The patients may manually record a description into the online epilepsy diary of the symptoms they experienced before, during or after the seizure. | Phase II. FDA approval in process. Available to purchase from company website | USA: NCT02177877 (n=10, recruiting, end date Dec 2015) | <a href="http://smart-monitor.com/about-smart-watch/">http://smart-monitor.com/about-smart-watch/</a> | <a href="http://smart-monitor.com/wp-content/upload">http://smart-monitor.com/wp-content/upload</a> |</p>
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<td>• Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.</td>
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**People affected by epilepsy comments:**

- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their friends, GP/consultant plus researchers. Also, there are several devices like this one that includes the tracking of seizures/contacts/timings Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle ref: these Apps is similar in a way especially having the ability to record in more detail, the patient’s experiences and filming, if deemed appropriate. No dislikes.
- [See comments for EpiWatch and Neutun, including: might be very useful in preventing injury from seizure falls]. Seizure diaries seem to be of limited value as they are only as good as the entries made. Bit of a concern with these that one could obsessively record stuff and it all become a bit obsessive. Need to be able to easily summarise data for consultant meetings...you don’t get long!

| 75 | Embrace and Alert App (smartwatch device) | Empatica Inc | Epileptic and Psychogenic Non-Epileptic Seizures | A smart watch intended for ambulatory monitoring. It is designed to monitor physiological stress, arousal, sleep and physical activity using sensors. It sends an alert when an unusual event happens, like a convulsive seizure, warning the patients. It integrates with an event detector app which sends an alert when the user’s electrodermal response reaches a pre-set level that is customized based on the patient history and health profile, and a diary app which helps monitor and manage everyday routines. | In clinical research. CE marking in process. Preregistration in the USA (date of info Nov 2015) | https://www.empatica.com/  
http://www.me |
**Expert comments:**
- This is a field which will just get bigger and better at movement and heart rate detection and sharing of data between apps and ultimately remotely to medical services. We should try to combine it with telemetry data or ambulatory data from EEG so that we can identify those with ictal tachycardia who may benefit from devices such as VNS 106. Commercial competition in this area is to be encouraged as improves technology and prices come down.
- Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.

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- [See comments for EpiWatch, Neutun and SmartWatch, including: might be very useful in preventing injury from seizure falls]. Concern with these things that they might be smarter than the users! Software developers tend to get carried away with functionality but it needs to be of use and easy to use.

Expert comments:
- This is a field which will just get bigger and better at movement and heart rate detection and sharing of data between apps and ultimately remotely to medical services. We should try to combine it with telemetry data or ambulatory data from EEG so that we can identify those with ictal tachycardia who may benefit from devices such as VNS 106. Commercial competition in this area is to be encouraged as it improves technology and prices come down.
- Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.

People affected by epilepsy comments:
- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their friends, GP/consultant plus researchers. Also, there are several devices like this one that includes the tracking of seizures/contacts/timings. Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle ref: these Apps is similar in a way especially having the ability to record in more detail, the patient’s experiences and filming, if deemed appropriate. No dislikes.
- Interesting, but a bit weird! I don’t think many people would be happy to go around in this sort of outfit. Maybe if worn under other clothing. Would have to be giving something much more valuable than one can get from the Smart Watch type approach, before anyone is likely to go with it. Can you bung it in the wash?

| Wearable Seizure Sensor (automated wireless accelerometer) | Royal Melbourne Hospital, University of Melbourne, Australia | An automated mobile wireless accelerometer for detecting and classifying convulsive epileptic and Psychogenic Non-Epileptic Seizures. It detects abnormal movements and alert patients when seizures are severe. It consists of accelerometer sensors that can monitor the patient on an outpatient basis. It produces an automated response of either ES (Epileptic Seizures) or PNES (Psychogenic Non-Epileptic Seizures) to a convulsive seizure. | In clinical research. Approval expected July 2017 and launch Oct 2017 | Australia: study reported 2015 | Melbourne Health Research Week 28 May - 4 June 2015 (report) |

Expert comments:
Interesting concept worth exploring in those with intractable psychogenic Sx to reassure care givers as long as the algorithm is accurate.

People affected by epilepsy comments:
- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to...
| 79 | ESAP wearable device | RTI International | Epilepsy | A system that detects seizures based on a multiparametric approach and an adaptive algorithm. ESAP senses heart-rate patterns as recorded by electrocardiogram (ECG) as well as movement and respiration. The current prototype consists of a sensor (the Zephyr BioPatch) that is worn on the chest and which communicates via Bluetooth to a processing module. An adaptive algorithm that “learns” from its successes and mistakes for a particular patient is being developed and will eventually be integrated into the sensor to send an alarm locally or remotely. | Clinical research | USA | http://ac.els-cdn.com/S1525505015000931/1-s2.0-S1525505015000931-main.pdf?_tid=ec1cb1c6-4367-11e6-8a6f-00000aab0f6c&acdnat=1467802610_52ac66ed123c85cb492a7fd58e7c4c9 | ESAP wearable device | RTI International | Epilepsy | A system that detects seizures based on a multiparametric approach and an adaptive algorithm. ESAP senses heart-rate patterns as recorded by electrocardiogram (ECG) as well as movement and respiration. The current prototype consists of a sensor (the Zephyr BioPatch) that is worn on the chest and which communicates via Bluetooth to a processing module. An adaptive algorithm that “learns” from its successes and mistakes for a particular patient is being developed and will eventually be integrated into the sensor to send an alarm locally or remotely. | Clinical research | USA | http://ac.els-cdn.com/S1525505015000931/1-s2.0-S1525505015000931-main.pdf?_tid=ec1cb1c6-4367-11e6-8a6f-00000aab0f6c&acdnat=1467802610_52ac66ed123c85cb492a7fd58e7c4c9 |
| 80 | NeuroMedic Seizure Detection Device | NeuroWave Systems Inc | Focal and generalized seizures | A field-deployable device designed for the automated detection of seizures in patients undergoing long-term monitoring using retrospective EEG. | Prospective clinical evaluation underway | USA | http://www.neurowavesystems.com/research_efforts.html#seiz | Expert comments:  
- Interesting concept worth exploring in those with intractable psychogenic Sx to reassure care givers as long as algorithm accurate. It will get better and better.  
- Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.  
People affected by epilepsy comments:  
- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their friends, GP/consultant plus Researchers. Also, there are several devices like this one that includes the tracking of seizures/contacts/timings. Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle ref: these Apps is similar in a way especially having the ability to record in more detail, the patient’s experiences and filming, if deemed appropriate. No dislikes.  
- Useful if it was more accurate than the Smart Watch approach... so long as it was discrete enough. |
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<tr>
<th>No.</th>
<th>Device Description</th>
<th>NHS/University</th>
<th>Diagnosis</th>
<th>Key Features</th>
<th>Clinical Trial Details</th>
<th>Financial Support</th>
<th>Website/Details</th>
</tr>
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</table>

**Expert comments:**
- Sounds like community-based ambulatory monitoring which could be useful.
- Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.
- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their friends, GP/consultant plus Researchers. Also, there are several devices like this one that includes the tracking of seizures/contacts/timings. Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle ref: these Apps is similar in a way especially having the ability to record in more detail, the patient’s experiences and filming, if deemed appropriate. No dislikes.
- Depends how wearable it is for general public use. Chilling to think it has come out of military research into detectors of soldiers exposed to nerve gas.

**People affected by epilepsy comments:**
- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their friends, GP/consultant plus Researchers. Also, there are several devices like this one that includes the tracking of seizures/contacts/timings.
- Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle ref: these Apps is similar in a way especially having the ability to record in more detail, the patient’s experiences and filming, if deemed appropriate. This device may also help reduce SUDEP situations – especially regarding sleep seizures.
- No dislikes.
- Sounds like in-hospital use device. Might be useful if it is as good as EEG.

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| 82  | myCareCentric Epilepsy | Epilepsy Care Alliance | Combines wearable technologies, shared care records, machine learning, and data analysis tools. It can detect seizures using machine learning using the Microsoft | Launched in the UK Sept 2016. Being piloted by | | | [http://www.graphnethealth.com/what-we-](http://www.graphnethealth.com/what-we-)

**Expert comments:**
- Sounds like remote EEG monitoring feeding back to video EEG. Remote EEG recording can be helpful if accurate and unobtrusive looking.
- Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.
- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their friends, GP/consultant plus researchers. Also, there are several devices like this one that includes the tracking of seizures/contacts/timings. Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle ref: these Apps is similar in a way especially having the ability to record in more detail, the patient’s experiences and filming, if deemed appropriate. This device may also help reduce SUDEP situations – especially regarding sleep seizures.
- No dislikes.
- Sounds like an in-hospital use device. Might be useful if it is as good as EEG.
<table>
<thead>
<tr>
<th>Periictal cardiorespiratory dysfunction detection devices (e.g. Nexfin monitor)</th>
<th>Various (e.g. Edwards Life Sciences Corp)</th>
<th>Patients at risk of SUDEP</th>
<th>Non-invasive devices designed to detect periictal cardiorespiratory dysfunction in an outpatient setting are being developed for this indication, and show promise in providing early warning of potentially catastrophic events.</th>
<th>In development</th>
</tr>
</thead>
</table>

**Expert comments:**
- Alerting early that the patient is at high or imminent risk of SUDEP is highly important area of research and should be supported.
- Experimental tool.

**People affected by epilepsy comments:**
- QOL Impact: tremendous move within the charity/medicinal industry to encourage these sort of patient tools, not just to help the patient but also to pass on information to their friends, GP/consultant plus Researchers. Also, there are several devices like this one that includes the tracking of seizures/contacts/timings. Likes: In a way it saves time ref routine questions that used to be asked – so now allows QOL issues to be discussed. Content in principle ref: these Apps is similar in a way especially having the ability to record in more detail, the patient’s experiences and filming, if deemed appropriate. Paper is very well written by Professor F-G. His presentation (ES conference, London, early 2016) on SUDEP, highlighted many of the areas in the abstract above. This device is especially critical regarding possibility of reducing SUDEP due to possible detection of breathing dysfunction as stated. No dislikes.
- Good if something can identify those at high SUDEP risk, but difficult if there is little one can do to mitigate the risk.
### Management interventions and devices (n=8)

<table>
<thead>
<tr>
<th>No.</th>
<th>Intervention Details</th>
<th>Institution and Contact Information</th>
<th>Description</th>
<th>Funding Details</th>
<th>Additional Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>EEG-biofeedback learning strategy</td>
<td>Birmingham Children’s Hospital NHS Trust, UK (PI: Gina Parker)</td>
<td>EEG-biofeedback is a non-invasive learning strategy that can enable a person to alter his/her brain wave activity. According to the researchers, it has already been shown to be a safe and effective therapeutic option for some adults with epilepsy, but as yet there are no data available for children.</td>
<td>UK: pilot study (1 year, grant awarded 2014)</td>
<td><a href="https://www.epilepsyresearch.org.uk/research_portfolio/">https://www.epilepsyresearch.org.uk/research_portfolio/</a></td>
</tr>
<tr>
<td>85</td>
<td>Autonomic Cognitive Rehabilitation Training (ACRT) - biofeedback</td>
<td>University of Sussex, UK. PI: Dr Yoko Naga</td>
<td>ACRT is an online digital therapy platform that combines biofeedback and cognitive (brain) training. Therapy consists of 12 sessions, each lasting about 45 minutes. During each session, users will receive instructions and practice the technique which they will then be able to start applying in daily life. Biofeedback works by monitoring body signals that we are not usually aware of, like blood pressure or brainwaves. These signals are then displayed on a screen, allowing the person to see them change and learn to increase or decrease them. The system uses electrodermal activity – detecting changes in the bodily state of alertness using sensors on the skin.</td>
<td>Available at one private clinic (in Brighton). Researcher raising funding for research via crowd-funding website</td>
<td><a href="https://www.epilepsy.org.uk/research/take-part/projects-you-can-take-part-in/can-biofeedback-help-seizure-control">https://www.epilepsy.org.uk/research/take-part/projects-you-can-take-part-in/can-biofeedback-help-seizure-control</a></td>
</tr>
</tbody>
</table>

**Expert comments:**
- Very interesting area for adults and children cognitively over the age of 9 years. Self-modification if possible would offer very empowering way forward.
- 1-No, 2-No

**People affected by epilepsy comments:**
- Don’t really understand how it works, but if it does then it sounds great especially if it avoids need for AEDs. Talks about night seizures. How do you consciously train your brain to respond appropriately in sleep?
### Expert comments:
- Very interesting area for adults and children cognitively over the age of 9 years. Self-modification if possible would offer very empowering way forward. Also useful for management of anxiety in those worried about having Sx or in those with panic attacks with and without epilepsy.
- Not sure of the utility.

### People affected by epilepsy comments:
- This sounds like a good thing because I remember using biofeedback and it did help to an extent so had I explored it more I may have had fewer seizures.
- QOL Impact: having experienced simple partial seizures for 28 years myself – I’d imagine this to be very useful if reductions could take place for patients. Likes: cannot see any harm to try this as especially being safe. Would also help those whose auras lead on to more powerful seizures perhaps? No dislikes – especially again due to safety.
- If it works - great. Not clear what the skin sensors are like. If too obtrusive then might not be acceptable.

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#### Home Based Self-management and Cognitive Training Changes lives (HOBSCOTCH)

**Dartmouth-Hitchcock Medical Center, USA (PI: Barbara Jobst)**

A home-based self-management program to treat cognitive symptoms and improve quality of life, while minimizing the barriers of access to care. The program is based on Problem Solving Therapy (PST) and teaches problem solving strategies and compensatory mechanisms to help manage cognitive dysfunction and enhance quality of life.

**Phase II**

**USA:** NCT02394509 (n=88, recruiting, end date Oct 2019)

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### Expert comments:
- Very interesting area for adults and children cognitively over the age of 9 years. Self-modification if possible would offer very empowering way forward. Also useful for management of anxiety in those worried about having Sx or in those with panic attacks with and without epilepsy.
- Useful for patients and clinician. 1-Yes, 2-Yes, 3-Yes, 4-all group, 5-cost maybe limited.

### People affected by epilepsy comments:
- Sounds good to do when patients are well enough.
- QOL Impact: good, but a certain amount of scepticism may occur if not in a ‘clinical’ setting perhaps. Likes: OK to try but not convinced it will help all due to above. Dislikes – see above.
- If it works - great. Not clear what the skin sensors are like. If too obtrusive then might not be acceptable. Maybe of concern that it blurs the boundary of physical & mental illness (which of course is blurred) and possibility that epilepsy might be perceived as mental health issue with the stigma that has.

**Expert comments:**
- May result in fewer hospital admissions and doctor led consultations and empowerment of caregivers in a population where epilepsy very prevalent so would be cost effective training compared with district nurses in general.

**People affected by epilepsy comments:**
- This would be fantastic because everyone is different and need treating in different ways.
- QOL Impact: have spoken to Nurses at their National Conference recently and found the literature very professional. Likes: as above. Must be continued as the area does need more input and work carried out. No dislikes.
- Complex document but good to see a focus on Epilepsy with LD, as this is common and the specific needs of LD patients does not always seem to be well catered for. Role of carer in adult services does not seem to be adequately acknowledged.

| Self-Management education for adults with poorly controlled | King’s College | Poorly controlled | This 2-day information course is organised into a number of modules. These teach people with epilepsy | Phase II UK (King’s College) | http://www.net s.nihr.ac.uk/proj
| epilepsy (SMILE) | London, Institute of Psychiatry (funded by NIHR) | epilepsy (adults) | about very practical things like helping you understand what kinds of seizures you might have. Also, what features you need to be able to tell your doctor about so they can make a better diagnosis or offer a better management strategy. There is information about the kinds of tests you might have, so that you aren’t daunted by them. | London): ISRCTN57937389 RCT is ongoing (n=428; no longer recruiting, end date Dec 2016) | london:ects/hta/0916501 | https://www.epilepsy.org.uk/news/features/empowering-people-manage-theirepilepsy-smile-project http://www.isrctn.com/ISRCTN57937389 http://bmcneurol.biomedcentral.com/articles/10.1186/1471-2377-14-69 http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-0788-9 http://www.isrctn.com/ISRCTN57937389 |

**Expert comments:**
- Care is needed as we do not want patients to perfect their story before attendance at clinic. If they pre-diagnose and make their Sx fit in then incorrect diagnosis may be reached. Timing of this intervention is therefore crucial.
- This could be potentially a good idea similar in format to the pain management program for chronic pain condition. 1-Yes, 2-Yes

**People affected by epilepsy comments:**
- This is always a good thing but the day to be taught would have to be chosen very carefully as from my experience of epilepsy, I wasn’t always up for learning about something
I didn’t want and often made me anxious when I was unwell.

- QOL Impact: Very good in theory but quite hard to be put into practice especially getting PWE together, e.g. for a full weekend. It’s very much based on the MOSES system brought out in Germany several years ago. Likes: as above but communication is a real issue although the course is exceptional in terms of Quality. Dislikes: not exactly a dislike but the only suggestion I could make was the lecturers and helpers going to the PWE, i.e. customers, to residential addresses where PWE stay on a long term basis?
- Sounds useful for people recently diagnosed, and possibly for those diagnosed some time ago who are not up to speed with recent advances. If it is an attended course then might be difficult for people to attend. It seems diagnosis often occurs in children / young adults, who might be less inclined to attend a course unless tailored to them. Could be scary for recently diagnosed.

| 89 | Self-help stress reduction booklet | Sheffield Teaching Hospitals NHS Foundation Trust, UK (PI: Professor Markus Reuber) | Epilepsy | This study evaluates whether a self-help intervention in the form of a brief booklet can improve the quality of life and reduce the levels of stress of people who experience seizures. In addition, the study will explore the associations between seizure severity and frequency, physiological and self-reported stress, and anxiety and depression. | Clinical research | UK (Sheffield Teaching Hospitals: NCT02465047 (n=82, completed Sept 2015)) | https://clinicaltrials.gov/ct2/show/NCT02465047?term=NCT02465047&rank=1 |

**Expert comments:**
- Stress reduction may result in more attendance at work and better QoL.
- This could be potentially a good idea similar in format to the pain management program for chronic pain condition. 1-Yes, 2-Yes

**People affected by epilepsy comments:**
- Very useful but from my experience of epilepsy, I wasn’t always in the right kind of mind to read books.
- QOL Impact: a very good idea as too many ‘specialists’ say seizure freedom is the one and only key. I don’t agree (I have epilepsy as you know). To me, where PWE have spent years swapping medication to no avail, other issues as you state are easily as important if not more, than just stopping seizures. My brother was a very good example. Likes: opening up the epilepsy picture for PWE with alternative education (other than ‘stopping seizures) can be taught. No dislikes at all.
- Got my doubts that a booklet will help much. Stress will peak and trough and hopefully people manage better over time, especially if they learn more about their own triggers etc. so if success is based on follow up 6 months after, it may well have improved. Still would be happy to be proved wrong!

| 90 | PatientsLikeMe - online digital health platform for epilepsy self-management | University of California, USA (PI: John Hixton) | Epilepsy | An internet-based on-demand self-management programme intended to augment drug therapies and improve health metrics. It is an online epilepsy-specific platform with self-seizure-tracking tools and discussion fora. | Clinical research | USA (n=249, reported in abstract) | http://www.medscape.com/viewarticle/848737 | http://www.neurology.org/content
### Expert comments:
- Feeling part of a community is always beneficial and self-management important to feeling empowered. Good for adults and those with intractable Sx.
- This could be potentially a good idea similar in format to the pain management program for chronic pain condition. 1-Yes, 2-Yes.

### People affected by epilepsy comments:
- This sounds good and be a good addition to seizure diaries.
- QOL Impact: a little weak in a way due to the enormous amount of information trying to be covered – Youth Talk and Health Talk on Line is probably a better option. Likes: none really for the PWE. Dislikes – in a way, as above.
- I have never been tempted to take up these seizure diary tools, apps, etc. and I guess that is because I feel more comfortable with the seizure diary I created myself (basically just an excel spreadsheet, which I print off and manually record onto, then update at the end of each month). I guess other people have their own formats that contain all their past data and so might be reluctant to change too.

### Airbag Head Protection
- **Hovding Sverige AB**
- **Epilepsy**
- A single-use hood-style airbag which uses sensors and an algorithm to detect indicative movement patterns and inflates automatically with helium gas to protect the head from fall injury. It has been developed as an alternative to conventional crash helmets for use by cyclists.
- The Epilepsy Foundation have awarded the’ Epilepsy Innovation Seal of Approval, which will provide funding for further development of the product for this market.
- **Phase I.**
- CE marked and available as an head-surrounding airbag for cyclists (costing £219)

### Expert comments:
- Particularly useful for those with drop attacks and falls associated with Sx. Particularly useful for children with very frequent atonic Sx who otherwise wear helmets. Could be less stigmatising than a helmet. Need to be careful about effects of bouncing on neck.
- This could be potentially a good idea similar in format to the pain management program for chronic pain condition. 1-Yes, 2-Yes

### People affected by epilepsy comments:
- This sounds like a good idea but my thoughts would be could it burst and suffocate the patient if the seizure causes anything like it to happen.
- QOL Impact: very clever idea looking at the videos on the Hovding website. Likes: would people want to wear the clothing all the time that contains the Airbag itself – only time will tell – as opposed to Protective Headgear as used at the moment. Dislikes maybe the above. Would the Airbag have to be altered technically? There may be
differences between how a person goes down or gets hit – when comparing ‘accidents’ from epilepsy, or ‘accidents’ being hit by vehicles, etc.

- We were looking online at something like this for our daughter who recently had (another) nasty seizure fall that caused facial injuries. Seems like a great idea in principle but doesn’t seem to do much to protect the face (especially chin) or teeth. Also looks quite bulky around the neck, and is expensive. Like the idea in principle as the alternative (helmets and face masks, etc) are not something she would find acceptable to wear, and seem OTT given her day time seizures are (thankfully) rare. However damage especially to her teeth is a big concern.

### Diagnostics (n=23)

### Electroencephalogram (EEG) techniques (n=9)

<table>
<thead>
<tr>
<th>#</th>
<th>Description</th>
<th>Manufacturer</th>
<th>Overview</th>
<th>Author</th>
<th>Reference</th>
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<tbody>
<tr>
<td>#</td>
<td>Description</td>
<td>Hospital/Manufacturer Details</td>
<td>Data/Device Details</td>
<td>Warrented?</td>
<td>USA/FDA Approval</td>
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<tr>
<td>93</td>
<td>Hydrogel EKG - wireless temporary tattoo electrode (Epidermal electronic</td>
<td>Sharp HealthCare</td>
<td>A slim new temporary tattoo technology that can easily be applied to the skin without</td>
<td>FDA approved</td>
<td>USA: NCT02451618 (n=60, primary end date Nov 2017)</td>
</tr>
<tr>
<td></td>
<td>system (EES)</td>
<td></td>
<td>requiring a technician or scrubbing and preparation as with standard EEG lead. The</td>
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<td>experimental aspect of this study will be the application of test electrodes (EES or EKG) to evaluate if the electrodes can be used to produce a continuous bedside recording of brain activity in the same manner as an EEG recording, while ideally producing less irritation of newborn skin than conventional EEG electrodes.</td>
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</tr>
<tr>
<td>94</td>
<td>EEG Patch™ (based on the Epoch system from Epitel Inc)</td>
<td>Universities of Utah and Colorado, USA, Epitel Inc (manufacturer)</td>
<td>A wearable device (1-inch square, worn on the scalp for 7 days) that can detect and record seizure activity in the home setting. It is intended to perform wireless biopotential recording for long-term continuous monitoring of seizure activity in the everyday home environment and advance warning of an impending attack. The patch is waterproof and relies on two electrodes to record EEG data during all aspects of everyday life. Can operate 7 days on a single charge, and data can be downloaded. An epileptologist must</td>
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</table>

**Expert comments:**
- Await results of trials to see if sensitive and specific enough to be diagnostically useful or useful for Sx prevention.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials. 1-Yes, 2-No, 3-all group, 4-n/a, 5-Potential cost saving.

**People affected by epilepsy comments:**
- If this is as I imagine it to be then it will be quite unobtrusive and yet will provide the details which can’t always be obtained by a EEG in a hospital setting. Everyday life affects whether a seizure happens or if a person is too hot at night or too tired.
- QOL Impact: useful in a way as long as the specialist is confident the area tracked is the only specific area? Likes: ease of wearing, non-intrusive. Dislikes: must rely very much on initial testing if used in just one area. If the original EEG recorded in hospital is not 100% perfect then some epileptic activity can be missed.
- Sounds good compared to the bulky “ambulatory” EEG device my daughter had to lug around with her for a week! Maybe useful in deciding appropriate treatments in some cases, although for most that seems to be a range of “suck it and see” AEDs. Seems like something that might make “big data” collection easier. This may have lots of research applications, but not much short term benefit for patients.

| 95 | ANI-Si system - ‘dry electrode’ EEG Headset | Advanced NeuroMetri cs Inc | Epilepsy. Diagnostic /monitoring (home use) | A novel dry electrode headset that records EEG without requiring extensive and time-consuming patient skin preparation, head measurements or gels. The system can position electrodes in the current industry-standard international 10-20 system without a certified technician and may thus be applicable to the primary care and home setting. | Phase I/II | http://advancedneurometrics.com/ 

**Expert comments:**
- Would have to be carefully evaluated in terms of accuracy.
<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
<th>Company</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wireless EEG headset with dry electrodes</td>
<td>Imec and Holst Centre</td>
<td>Epilepsy. Diagnostic /monitoring (home use)</td>
</tr>
</tbody>
</table>

This EEG-cap (min. 21 electrodes) with active dry electrodes aims to combine meeting user expectations of comfort and aesthetics with high quality EEG. The headset is manufactured in one piece using 3D printing techniques, after which the electronic components are applied and covered by a 3D-printed rubber inlay. The mobile app relates the user’s emotional state to environmental information. Phase I. Launched in Aug 2015 for other indications (e.g. ADHD) Belgium (enrolling studies): NCT02394639 (n=10, end date Sept 2016), NCT02428348, NCT02408627

Expert comments:
- Would have to be carefully evaluated in terms of accuracy.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

People affected by epilepsy comments:
- Sounds interesting.
- QOL Impact: not huge as only carried out in private, there again if private, numerous tests can take place if the patient requires/wants this. Likes: as above. Dislikes: none because of above.
- If it makes it easier to get good EEG then great, getting sticky bits out is a nuisance. I guess the real skill is in interpreting the results though... and then having appropriate treatment.

97 | Prototype QUASAR EEG system - neonatal EEG Monitor using dry sensors | QUASAR Inc | Epilepsy (acute) and Status Epilepticus Monitoring (ICU) |

A portable, wireless, dry-sensor system intended for EEG monitoring. It is adapted to record EEG and monitor to treat critically ill neonates. It is based on Dry-Sensor EEG Technology. It helps to reduce infant’s mortality from seizures or other neurological disorders. The ultra-high impedance amplifier of the dry sensors allows In clinical research. Approval (USA: 510k) expected May 2018 and launch Aug

### Robot-assisted Stereoelectroencephalographic Electrode (SEEG, or stereo EEG) Implantation

**Setting:** Cleveland Clinic (Epilepsy Centre), USA

**Presurgical planning:** SEEG electrodes may be used to localize the focal point of seizure activity in patients with medically intractable epilepsy in whom magnetic resonance imaging and electroencephalography (EEG) with videotaping of spontaneous seizure events (video/EEG) have not been sufficiently precise to locate the seizure focal point before surgery. The types of electrodes used are epidural, subdural, and intracerebral depth electrodes.

**Phase:** Early clinical research

**Website:** [ducts_dsi.htm](http://www.ncbi.nlm.nih.gov/pubmed/26418870)

**Expert comments:**
- Technique already in use and any improvement in electrode placement with reduction in need for surgery is a definite advantage.
- Not novel there are currently robotic arm for SEEG delivery. Possibly they are looking at automated system.

**People affected by epilepsy comments:**
- QOL Impact: could be enormous for specific patients. Likes: a must due to the product accuracy – compared to routine equipment. Also because it is essential to pre-surgery. No dislikes.
- Sounds like it could be useful in specific situations. Improving accuracy of surgery has to be a good thing.

### Neural implant (small mesh of electrodes)

**Setting:** University of Pennsylvania, USA (PI: M Kahana)

**Presurgical planning:** Patients requiring surgery receive a small mesh of electrodes under their skulls, which they wear for two to seven weeks. The electrodes collect EEG recordings that are used to calculate where in their brains their seizures are originating, in preparation for surgery to remove the malfunctioning tissue.

**Phase:** Phase I

**Website:** [https://www.technologyreview.com/s/536331/work-begins-on-brain-stimulator-to-correct-memory/](https://www.technologyreview.com/s/536331/work-begins-on-brain-stimulator-to-correct-memory/)

**Expert comments:**
- If it offers similar performance then would be especially good for infants and neonates and neonatal units. Good for ambulatory recording in children.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

**People affected by epilepsy comments:**
- QOL Impact: not huge as only carried out in private, there again if private numerous tests can take place if the patient requires/wants this. Likes: as above. Dislikes: none because of above.
- Good if it helps monitoring of babies with less invasiveness.
Expert comments:
- The mesh still has to be placed in a targeted area but useful if Sx not that frequent and need to record for longer over a particular area.
- Experimental device with potential to treat epilepsy but still use limited in clinical trials.

People affected by epilepsy comments:
- This sounds like it could be useful as if it shows that seizures are in several areas it may show that surgery is not an option. It is better to know beforehand.
- QOL Impact: could be crucial with specific patients. Generally – not sure of already covered by others. Likes: useful if appropriate for the individual patient. Dislikes: not sure whether covered elsewhere in other techniques?
- The data recording for pre op might be useful. The link article is mainly about using this data to look at memory loss and possibility of improving this which sounds very interesting. If “lost” memory could be regained, that would be quite remarkable… though may be optimistic… who knows!


Expert comments:
- Excellent way forward for localising onset zone and assessing for surgery.
- The role of fMRI in detecting epileptogenic focus is interesting and has potential applications. 1-Yes, 2-Yes, 3-Yes, 4-Yes, 5-could be cost savings for NHS.

People affected by epilepsy comments:
- QOL Impact: essential as for young people being drug resistant. Likes: combination of EEG and MRI and child centred approach. As stated, a lot more ‘child friendly’. No dislikes.
- Sounds useful to focus on techniques as applicable to children, as its all well and good having a wonderful scanning technique, but if it requires a child to stay still for 20 mins it probably won’t happen!

Brain imaging techniques (n=7)

| 101 | Simultaneous PET-MR (±EEG) | King’s College London, UK | Epilepsy. Presurgical planning | Simultaneous acquisition of two imaging modalities often indicated in the presurgical evaluation. Faster, more efficient interpretation of both modalities. Added | In early use for other indications | UK (Kings College London) | Expert happy to discuss (contact: |
| 102 | Diffusion Tensor Imaging (DTI) - using BrightMatter device suite | Synaptive Medical | Temporal Lobe Epilepsy (TLE). Diagnostic | A new relatively new functional MRI imaging technique. Research suggests that it could provide clinically unique information for predicting neuropsychological status and provide additional insight into underlying structure/function relationships in TLEA. One study aims to investigate whether the use of Synaptive Medical's BrightMatter technology can help neurosurgeons to better visualize and plan surgeries by considering the white matter tracts, and whether it results in improved clinical outcomes. This study will investigate the preservation of the optic radiations in anterior temporal lobectomy epilepsy surgeries. | In clinical trials | Canada: NCT02590419 (n=40, end date Nov 2016) | [https://clinicaltrials.gov/ct2/show/NCT02590419](https://clinicaltrials.gov/ct2/show/NCT02590419) | [http://www.sciencedirect.com/science/article/pii/S003537871500259](http://www.sciencedirect.com/science/article/pii/S003537871500259) |

**Expert comments:**
- Tractography definite way forward in surgical planning and anything which better defines lesion and reduces respective area is of benefit.
- Still resolution DTI is limited as well as integration in neuro-navigational system. Preservation optic radiation is a well-established application. 1-No, 2-No
- Other similar software packages are available. I am not a surgeon and therefore cannot comment on usability of the various packages from surgical perspective but then who can without bias towards what they are used to using? Neurosurgical planning incorporating DTI data has been around for some years. In our local experience the utility has
been limited but has been used for demonstration of Meyer’s loop over the years when necessary before temporal lobe resections. Utility of these DTI software packages tend to be inversely related to the experience of the surgeon and has not been substitute for awake craniotomies in the wider neuro-oncological world.

**People affected by epilepsy comments:**
- QOL Impact: as with other similar pieces of research, can only improve QOL if studies work and can help the patient. Likes: possible outcome - if improvement takes place due to helping neurosurgeon taking into account white matter tracts. No dislikes.
- Important if it can help focus in on the site of epileptic activity and minimise collateral damage. If people have better assurances that surgery won’t have impact on memory, etc, then likely to be more confident to give it a try.

| 103 | Cone Beam Computed Tomography (CBCT) Three-Dimensional Digital Subtraction Angiography (3D DSA), CBCT 3D DSA | Niguarda Hospital, Italy (PI: Francesco Cardinale) | Epilepsy. Presurgical planning | This is a novel cerebrovascular imaging technique for the safe and accurate planning of Stereo-ElectroEncephaloGraphy (SEEG) electrode trajectory. | In clinical research | Italy | [http://www.sciencedirect.com/science/article/pii/S187887501502958](http://www.sciencedirect.com/science/article/pii/S187887501502958) |

**Expert comments:**
- Important to avoid vessels but could this not be incorporated into MRI rather than have additional radiation.
- This application is well suited for SEEG and particular exploration of the insula cortex. It is experimental but has application in epilepsy. 1-Yes, 2-Yes, 3-Yes, 4-all groups, 5-minimal costs.
- In a Swedish study of complications from invasive electrode use for epilepsy investigation the 10 haematomas in the 271 patient were 7 sub-durs and 3 epidurals. This suggests that the existing approaches used to avoid vessels are relatively good; the haematomas came from grid placement. Also it is unclear why this technique should be any better than CTA/CTV for delineation of all vessels for planning of trajectory.

**People affected by epilepsy comments:**
- QOL Impact: results so far look impressive according to the website like. Likes: safety and accuracy plus results of work so far is critical and very important for pre-surgical planning. No dislikes.
- 3D imaging sounds useful.

| 104 | Arterial Spin Labelling (ASL) MRI | University College London, UK (PI: Gavin Winston) | Refractory focal epilepsy: MRI-negative | A novel quantitative MRI image acquisition technique for the detection of abnormalities in patients who have normal structural MRI scans (around 20-30% of patients). | In clinical research | USA: NCT01772654 (completed Nov 2013) | [https://www.uc.ac.uk/ion/departments/epilepsy/themes/imaging/research](https://www.uc.ac.uk/ion/departments/epilepsy/themes/imaging/research) |

**Expert comments:**
- Await outcome of research data to assess added value but an important Sx group who currently can miss out of respective options. ASL MRI, NODDI and DESPOT imaging could all be supported as a research package.
- Very interesting but still experimental as application. 1-Yes, 2-Yes
- We have been assessing this technology for some years. It may have a modest role but is really a substitute for a PET or SPECT study. However it has lower signal to noise than either, but is sometimes useful.
### People affected by epilepsy comments:
- QOL Impact: a must for all PWE as this is an important part of accurate diagnosis. This can lead to surgery if appropriate. Likes: as above. No dislikes.
- The web link talks about possibility of identifying markers for SUDEP risk. That would be interesting as little progress in understanding of this....however it would beg the question of what one was to do with that info. If identified as high risk!

| 105 | Microstructural imaging (NODDI) | University College London, UK (PI: Gavin Winston) | Refractory focal epilepsy: MRI-negative | A novel quantitative image acquisition technique for the detection of abnormalities in patients who have normal structural MRI scans (around 20-30% of patients). | In early research | https://www.uc.l.ac.uk/ion/departments/epilepsy/themes/imaging/research |

### Expert comments:
- Await outcome of research data to assess added value but an important Sx group who currently can miss out of respective options. ASL MRI, NODDI and DESPOT imaging could all be supported as a research package.
- Very interesting but still experimental as application. 1-Yes, 2-Yes
- I find this very interesting but as you indicate there is limited evidence for clinical efficacy at this stage. However it may be feasible for it to be adopted into clinical practice. My concern is that the brains of patients with epilepsy are widely abnormal at this micro-structural level. The size of the studies is too small to be confident of its value, there will have been a lot of patient selection bias. For example in Pantangco et al 5 patients with TLE and for FCD it is a case report. We need some evidence that this technique can be used in real world circumstances. Preferably away from the cosy world of where it has been developed. For example: scan rescan reproducibility data is limited. The most commonly cited article has this calculated on one healthy volunteer. The acquisition takes 30 minutes! We need reproducibility in patient cohorts not volunteers. How many patients with epilepsy will manage to stay still for a 30 acquisition? In my clinical experience this will be a small percentage.

### People affected by epilepsy comments:
- QOL Impact: a must for all PWE as this is an important part of accurate diagnosis. This can lead to surgery if appropriate. Likes: as above. No dislikes.
- The web link talks about possibility of identifying markers for SUDEP risk. That would be interesting as little progress in understanding of this....however it would beg the question of what one was to do with that info. If identified as high risk!

| 106 | FreeSurfer software | FreeSurfer Wiki | Drug-resistant epilepsy | A software package for the computational analysis and visualisation of structural and functional MRI neuroimaging data, to identify lesions. It automatically estimates the thickness of the cerebral cortical, using a surface-based method that allows for the quantification of surface-based features such as gyrification index, curvature and sulcal depth. | In early research. Available for free download | http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview http://www.sciencedirect.com/science/article/pii/S22131582163 |
### Expert comments:
- Our personal experience is that we can use Freesurfer to identify lesions that we can see are there, much the same as all of the other newer imaging techniques that we have evaluated such as ASL. We haven’t assessed NODDI yet though. If NODDI shows changes in fibre density and orientation which work in opposing directions to leave the overall FA and mean diffusivity unchanged which is all that is available in conventional DTI we would be very interested. But as yet we’ve not seen it published. What we are currently trying to do get funding for is a pilot of FreeSurfer use in lesion negative scans which is where it needs to work to be useful.

| 107 | T1 and T2 mapping (DESPOT) imaging | University College London, UK (PI: Gavin Winston) | Refractory focal epilepsy: MRI-negative | A novel quantitative image acquisition technique for the detection of abnormalities in patients who have normal structural MRI scans (around 20-30% of patients). | In early research | https://www.ucl.ac.uk/ion/departments/epilepsy/themes/imaging/research |

### Expert comments:
- Await outcome of research data to assess added value but an important Sx group who currently can miss out of respective options. ASL MRI, NODDI and DESPOT imaging could all be supported as a research package.
- These techniques have been around a long time, my personal experience of relaxometry of the hippocampus was that it was rather unhelpful; I could almost always predict when it was going to be statistically reliably abnormal by just looking at the images (I have reviewed and used this technique in 100s of patients). However, it may well have a role in multispectral imaging models though.

**People affected by epilepsy comments:**
- QOL Impact: a must for all PWE as this is an important part of accurate diagnosis. This can lead to surgery if appropriate. Likes: as above. No dislikes.
- The web link talks about possibility of identifying markers for SUDEP risk. That would be interesting as little progress in understanding of this….however it would beg the question of what one was to do with that info. If identified as high risk!
<table>
<thead>
<tr>
<th><strong>Other diagnostic tests</strong></th>
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<td><strong>108</strong></td>
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<tr>
<th>109</th>
<th>epiSEEK® Comprehensive Sequence Analysis test</th>
<th>Courtagen Life Sciences Inc</th>
<th>Syndromic and non-syndromic epilepsy</th>
<th>Provides genetic analysis and clinical interpretation of data generated by the complete sequencing of 471 genes associated with epileptic and seizure disorder phenotypes.</th>
<th>USA-based testing service (saliva sample, turnaround time: 4-6 weeks)</th>
<th><a href="http://www.courtagen.com/test-menu-genetic-test-episeek.htm">http://www.courtagen.com/test-menu-genetic-test-episeek.htm</a></th>
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<tbody>
<tr>
<td>Expert comments:</td>
<td>• The bigger the better in many ways as long as bioinformatics also supplied – interpretation of the data is the challenge currently.</td>
<td>People affected by epilepsy comments:</td>
<td>• QOL Impact: again huge and relatively new area overall. Likes: very interesting information on the website. Dislikes: none, for obvious reasons.</td>
<td>• Worry that these have been developed as marketing opportunities. It is very easy to send off samples and get results, but need expert support to interpret and possibly counselling w.r.t. implications. Concern that within US such testing might become required by insurance companies ... (maybe even pre-birth) to assess risk and disadvantage groups of people.</td>
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| 110 | epiSEEK® Focus Epilepsy Panel | Courtagen Life Sciences Inc | Early onset epilepsy | This test includes syndromic and non-syndromic disorders associated with epilepsy such as Angelman, Angelman-like syndromes, Rett, atypical Rett syndromes, Cerebral folate deficiency, Creatine deficiency syndromes, Mowat-Wilson syndrome, West syndrome, Ohtahara syndrome, Early onset epileptic encephalopathy, Idiopathic generalized epilepsy, Benign familial neonatal seizures (BFNS), Familial infantile myoclonic epilepsy (FIME), Juvenile myoclonic epilepsy, Progressive myoclonic epilepsy, Epilepsy with behavioural and learning disorder. | USA-based testing service (saliva sample, turnaround time: 4-6 weeks) | http://www.courtagen.com/test-menu-genetic-test-episeek.htm http://www.cureepilepsy.org/news/news.asp http://www.courtagen.com/test-menu-episeek-focus.htm |
**Expert comments:**
- The bigger the better in many ways as long as bioinformatics also supplied – interpretation of the data is the challenge currently.

**People affected by epilepsy comments:**
- [As for the Comprehensive version] worry that these have been developed as marketing opportunities. It is very easy to send off samples and get results, but need expert support to interpret and possibly counselling w.r.t. implications. Concern that within US such testing might become required by insurance companies ...(maybe even pre-birth) to assess risk and disadvantage groups of people. Also appreciate that diagnosis is important… but in itself it doesn’t necessarily help anyone. If you have a child with Epilepsy with behavioural and learning disorder….. you don’t need a genetic test to tell you that you have problems!

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Provider</th>
<th>Description</th>
<th>Test Details</th>
<th>Website</th>
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</thead>
<tbody>
<tr>
<td>rxSEEK™ Epilepsy Drug</td>
<td>Courtagen Life Sciences Inc</td>
<td>Tests an individual’s ability to metabolize anti-epileptic drugs (AEDs) based on the haplotype sequence of certain liver enzymes involved in drug and chemical metabolism.</td>
<td>USA-based testing service (saliva sample, turnaround time: 4-6 weeks)</td>
<td><a href="http://www.courtagen.com/test-menu-rxseek.htm">http://www.courtagen.com/test-menu-rxseek.htm</a></td>
</tr>
<tr>
<td>Serum procalcitonin (PCT) testing</td>
<td>Researchers epilpticus (SE)</td>
<td>Serum PCT (an acute-phase protein) measured at SE onset is independently associated with death but does not predict emergence of infections during SE. Procalcitonin may increase the predictive value of clinical scoring systems allowing for rapid risk stratification early in the course of SE.</td>
<td>Early research Switzerland: observational cohort study reported (n=91)</td>
<td><a href="http://www.ncbi.nlm.nih.gov/pmc/articles/PM">http://www.ncbi.nlm.nih.gov/pmc/articles/PM</a> C4598971/</td>
</tr>
</tbody>
</table>

**Expert comments:**
- This could really help in the management of AEDs. Caution could be exerted in those known to be slow metabolisers and susceptible to toxicity. In presence of encephalopathy where not known if drug related or Sx related may help to identify.

**People affected by epilepsy comments:**
- Sceptical that side-effects are likely to be effectively predicted by such testing, as so individual. With AEDs it tends to be that a “suck it and see” test is the most effective… again seems like a marketing ploy.
| 113 | Neurome Test - Whole-Exome Sequencing (WES) | Personalis (available through Quest Diagnostics Athena Division) | Genetic epilepsy in children | Unlike whole-genome sequencing, which looks at single-nucleotide variants or alterations in DNA sequences, exome sequencing focuses on codes for proteins and specific segments of DNA where disease-causing variants occur. Neurome uses Personalis’ ACE Exome technology to screen certain areas of the genome that affect the nervous system, potentially providing diagnoses for certain forms of developmental delay, epilepsy and muscular dystrophy. | Testing service launched in the USA (date of info March 2015) | http://www.personalis.com/clinical/the-neurome-test/ http://www.fiercemedicaldevices.com/story/quest-and-personalis-dive-exome-sequencing-rare-pediatric-neurological-diso/2015-03-10 |

**Expert comments:**
- Definite way forward in future for finding additional mutations in known genes more quickly and extensively – should become widely available in due course to replace panel testing.

**People affected by epilepsy comments:**
- QOL Impact: new area but still crucial. Likes: background work, bit still very much needed. Links with other conditions/diseases make this extremely interesting. No dislikes.
- Needs further work to establish any cause and affect link. I never knew about increased infection risk with SE…. how bad can things get!

| 114 | Whole-Exome Sequencing (WES) | Royal Melbourne Hospital, University of Melbourne, Australia | Focal epilepsies of suspected genetic aetiology | A research report suggests that WES may identify pathogenic or likely/potentially pathogenic mutations in more than one in five patients with common focal epilepsy.

Another small study (n=50) reported that WES analysis had immediate treatment implications in 8 (16%) of the patients studied. | In early clinical research | Australia (study reported 2015, n=36) | Melbourne Health Research Week report 28 May - 4 June 2015 (report) https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/2325259 |
**Expert comments:**
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REFERENCES