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**Sudden Death in the Young: A Terrible Waste**

Professor Martin Elliott

**“People who die prematurely from avoidable causes lose an average of 23 potential years of life. For children and young people, this figure rises to 72 years.”**

Anne Campbell, Mortality Analysis Team, Office for National Statistics

**Introduction**

This is a challenging lecture for me, but one I have felt driven to deliver. Just over 7 years ago, on Friday the 13th of November 2009, my son Toby died suddenly, at home, during the night. He was 26, and apparently well. A year earlier, he had bitten his tongue in his sleep, during what he thought was a nightmare. He bit his tongue again the night before he died.

Undiagnosed, he died of **S**udden **U**nexpected **D**eath in **EP**ilepsy. **SUDEP**. Neither I, nor any of the five professors of medicine who came to his funeral, had ever heard of it.

We are not alone. In 2011, a survey of 2570 Canadian paediatricians[[1]](#footnote-1) revealed that only 34% of those caring for children with epilepsy had ever heard of the term SUDEP. In 2002, a national UK audit highlighted SUDEP as **‘deaths in the shadows’**, being systematically under-recognized, under-reported, and poorly investigated by health professionals1.

In my opening lecture, I dedicated this entire series to Toby’s memory, but I rededicate this specific one to him and to all those young people who have died suddenly. Losing a child is every parent’s nightmare, irrespective of the cause. Whilst I am concentrating on **sudden** death tonight, I want to make it clear that I do not underestimate the impact that *any* death has on a family, however long one has to prepare.

We are sadly aware through our daily news that young people (usually defined as those under 35 years of age) die in accidents, through violence, including war, and by their own hands. Much is made of our susceptibility to terrorism and conflict. There were 60 deaths in the entire UK armed forces in 2015, but only 1 was due to hostile action (<https://www.gov.uk/government/collections/uk-armed-forces-deaths-in-service-statistics-index)> . Since September 11 2001, 53 people have died in the UK as a result of terrorism (<http://researchbriefings.parliament.uk/ResearchBriefing/Summary/CBP-7613)> .

It is less well appreciated that hundreds of young people, not apparently in harm’s way, die suddenly and unexpectedly from often-undiagnosed medical conditions.

When a young person does die suddenly and unexpectedly there is no time to prepare or say goodbye. A future is lost, years of promise are unmet, society is deprived, friends and family are broken hearted and as I know personally, they are changed.

The immediate effects of a sudden death are hard for those affected to remember in detail, but they are well-described. There is overwhelming shock, manifest2 as numbness, anger, despair, disbelief, anxiety and guilt…surely we could have done something. There is some sort of denial…surely this can’t be happening? There is profound questioning ….why did this happen? How could this have happened?

Concentration, confidence and interest in life are lost. Sleep becomes difficult; eating a chore. There is desperate sadness. Thoughts can be irrational, and so can actions. One becomes very intolerant of the insensitivity and offhandedness of others, particularly those in officialdom.

It is exhausting. For ourselves, we could not have coped without the support of our families, dear friends and wonderful neighbours. Many of these people who helped us so much are here tonight, and again I want to thank you all. One does slowly come to terms with what has happened, but life is never the same again. The yearning to see Toby, even just once more, never goes away.

So what we can we do to avoid these terrible effects and to prevent young people dying suddenly? In this lecture, I want to define how frequent is such death; to outline the causes; to describe how research can be done; and how we might be able to prevent or reduce the incidence. Death from serious infection, asthma, pulmonary embolus and brain haemorrhage all occur in the young, but I am going to spend most of this lecture talking about sudden cardiac death (**SCD**) and sudden death in epilepsy (**SUDEP**). I will also discuss some of the legal and social issues related to the investigation of sudden death. I will end by suggesting some ways in which **you** can help.

**Incidence**

What constitutes a young person? Surprisingly, definitions vary; from 0-19y (the range used by the Office of National Statistics), and from 0-35 by those reporting epilepsy deaths and sudden cardiac deaths, and 0-25 by some reporting cardiac death, though in some studies the definition extends to <45 or even 50 years. In this talk, I am going to stick with up to the age of 35.

The available data relating to causes of death come from a variety of sources, but primarily from Death Certificates and are available from the Office of National Statistics [ONS] (<http://visual.ons.gov.uk/what-are-the-top-causes-of-death-by-age-and-gender/)>. The most recent available data (2013) from ONS on causes of death by age group reveal that deaths were rare in those aged 1-4 in 2013, with congenital anomalies (68), homicide (22), and epilepsy (22) topping the list of causes. Between the ages of 5-19, transport accidents were the most common cause (13% of deaths), being three times more common in males. Suicide was the second most common cause in males and the 6th in females. From 20 – 34, suicide, accidental poisoning[[2]](#footnote-2) and transport accidents predominate in both sexes. Sudden unexpected death from medical causes is rarer, but likely to be underestimated because of poor coding on the death certificate, itself caused by a combination of poor post-mortem investigation, inadequate or confusing definitions or lack of awareness of professionals about what to write on the death certificate. The impact of coding changes can be significant. Recent changes to diagnostic coding by the WHO have resulted in an **apparent** drop in mortality rates due to epilepsy, although the true rates (reported via registries) have remained constant (Jane Hanna, *personal communication*).

I am a paediatric cardiac surgeon. My life has been devoted to the heart, so I think it is right that I begin with sudden cardiac death in the young.

**Sudden Cardiac Death in the Young[[3]](#footnote-3)**

Sudden cardiac death (SCD) is an unexpected death due to cardiac causes occurring generally within one hour of the onset of symptoms in a person with known or unknown cardiac disease. Depending on the source, “young” is variably defined as those less than 25, 30, 35, or 40 years of age.

The incidence of SCD in the young has been estimated at 0.36-3.7 events per 100,000 patient years[[4]](#footnote-4), roughly equivalent to 1100 to 9000 deaths in Europe and 800 to 6200 in the USA per year. That would equate to between **150 and 1000 per year** in England and Wales[[5]](#footnote-5). That is the equivalent of several whole classrooms, lecture theatres or offices. The wide range is almost certainly due to misclassification, which has been said to occur in up to half of cases4. Such imprecise estimates of incidence and definition have important implications for health planning and resource allocation.

In older people like me, sudden cardiac death is usually related to degenerative conditions like coronary artery disease, valve abnormalities or heart failure. In the young, the most frequent diagnoses include heart muscle disease (cardiomyopathies), infections (myocarditis), rhythm problems (often ion channel abnormalities [channelopathies]) and a variety of rare congenital conditions. These diseases are often undetected before the SCD event.

In general, the risk of SCD in young people approximately doubles during physical activity, and is two to three times higher in athletes compared to non-athletes. The incidence of SCD in young athletes is in fact very low, at around 1-3 per 100,0005, 6, and most likely caused by pre-existing congenital or genetically mediated cardiovascular disease, rather than the sporting activity itself. In the USA, the National Registry of Sudden Death in Athletes was established in the 1980s and has reported7 on 1,866 sudden deaths in individuals under 40 years of age during a 27-year observational period. Their data show that 36% of all sudden deaths in this registry are attributed to confirmed cardiovascular causes, of which the most frequent are hypertrophic cardiomyopathy (36%), congenital anomalies of the coronary arteries (17%), myocarditis (6%), arrhythmogenic right ventricular cardiomyopathy (AVRC) (4%) and channelopathies (3.6%). Of these diagnoses, AVRC has been noted to be associated with death during sleep8. Male gender, black race, and basketball participation all appear to place an athlete at higher risk9.

**Diagnosis**

If someone dies during the day, in public and of an apparent cardiac arrest, the cause of death may be derivable from a history, direct observation or perhaps ECG evidence if resuscitation was attempted. These circumstances are not uncommon in SCD. However, often a cause is not immediately identifiable and the doctor looking after the patient does not feel comfortable in issuing a death certificate because he or she is not certain of the cause of death. In that case, either consent for a post-mortem (PM) will be requested of the family, or the case referred to the coroner (see later in this essay) who may order a post-mortem, irrespective of the wishes of the family. Yet even when a PM is performed, up to half of the deaths remain unexplained3. In the ideal world, such expert examination would take place promptly, using tightly defined protocols and to a high standard. Sadly, this is not always the case, despite the observation of many that it would be helpful to bereaved relatives to provide them with at least partial understanding and rationalisation of their tragedy; and to give them the comfort of trying to help other families avoid what they have gone through. Guidelines which define the PM protocols have indeed been produced for assumed cardiac death 10-12 to ensure that a proper examination is performed on the heart, and that detailed sampling is done of tissue and blood for histologic, molecular, genetic and toxicological measurement. As Priori and colleagues summarise3, a properly conducted [cardiac] PM should resolve the following issues:

1. Whether the death is attributable to a cardiac disease,
2. The nature of the cardiac disease (if present),
3. Whether the mechanism of death was arrhythmic,
4. Whether there is evidence of a cardiac disease that may be inherited and thus requires screening and counselling of relatives and
5. The possibility of toxic or illicit drug use or other causes of unnatural deaths.

Tissue samples should be obtained as early as possible for DNA and other molecular analyses, and tissue should be retained and shared with experts in the field. Without such detailed analyses, we will never get to the underlying causes of these diseases, especially in those genetic channelopathies which may cause arrhythmic death. In my view, there should be no variation in the quality or completeness of post mortems. The guidelines are clear, and this is the most important way we have of understanding more about these terrible events. I refer to this again later in this essay.

It is not surprising that many relatives, if not most, do not wish their loved one to undergo a post-mortem. It seems like a further and desperately unwelcome assault. Recently, MRI has been used to reduce the trauma of the post-mortem and to increase the quality of information derived13-15 8, 16. This is a rapidly developing field, and can provide hard evidence of tiny lesions missed by conventional PM. Using MRI, these lesions can be biopsied by needle rather a major disfiguring traditional PM. New technologies will allow faster and cheaper exome and potentially genome sequencing from such biopsies. We will soon know much more.

**Prediction of Risk**

Many in the field have described this as the philosopher’s stone. It is now clear that the likelihood of dying suddenly originates as a ‘**perfect storm’** of the interaction between a vulnerable substrate (genetic or acquired changes in the heart or brain) together with multiple, often poorly understood, factors that may trigger the fatal event. Although we know this, we do not yet know enough properly to assess or stratify the risk17.

**Screening**

Screening is always contentious. It can be expensive to identify small numbers of susceptible individuals; it can induce fear in families of victims, and it can create further anxiety in the worried well. Usefulness also depends on the simplicity, sensitivity and specificity of the screening tool used. Electrocardiography [ECG] is well established and almost omnipresent. It is useful in identifying certain abnormal rhythms which are associated with sudden death, and Italy and Japan have introduced screening programs designed to identify asymptomatic patients with inheritable arrhythmogenic disease18-20. Although there is consensus amongst experts in Europe and the USA that screening athletes is wise (and endorsed by the International Olympic Committee), a recent study from Israel showed21 no change in rates of sudden cardiac death after the introduction of screening. And, as Kaltman has reported22, cost estimates for screening athletes in the US lie between $300 million and $1 billion per year; a massive cost and greater, I calculate, than the amount invested in trying to identify causes and appropriate treatment. Despite this, pre-participation screening of athletes remains a recommendation3 in Europe.

**Should family members be screened?**

If the sudden death is clearly cardiac and especially arrhythmogenic (SADS), approximately 50% may be hereditable[[6]](#footnote-6) (e.g., long QT syndrome, Brugada syndrome, CPVT, some forms of cardiomyopathy [Hypertrophic Cardiomyopathy [HCM] and Arrhythmogenic Right Ventricular Cardiomyopathy [ARVC]). If the post mortem supports these diagnoses, and especially if molecular testing results are supportive, then there is a good case for screening family members to identify people at risk, and for some to reduce anxiety. For other families, such screening may **increase** anxiety, and so screening should be carried out in specialist centres with appropriate psychosocial support, sadly not available everywhere. Screening should take the form of a good history, ECG studies, echocardiography, perhaps MR imaging and molecular testing at specialist centres.

Knowing you are at risk is of little value if there is nothing you can do to prevent the consequences of that risk. This means that very great care and empathy is needed when discussing screening with relatives, and clear knowledge of both the risk of the disease and any treatment is crucial. We must never forget that are first duty is ‘To Do No Harm’, and be sure that the chosen methods of reducing the risk of sudden death do not so severely reduce the quality of life that death may seem a better option.

**Treatment**

It is perhaps bizarre to consider ‘treatment’ under the heading of sudden death, but since many SCDs occur during the day and are witnessed, we must remember that there are immediate resuscitative steps that can be taken. Evidence strongly suggests23, 24 that lives can be saved by having public-access defibrillators like those demonstrated at my last lecture (<http://www.gresham.ac.uk/lectures-and-events/the-rhythm-of-life-the-beat-and-dance-of-the-heart)> . It pays to learn how to use them. I urge all of you to learn how to resuscitate, and the BHF films I showed you in my last lecture are a good start[[7]](#footnote-7). Call for help, and start to massage.

**Prevention**

What can be done to prevent sudden cardiac death? Clearly you must be identified as being at risk, and that will come from either the identification of an underlying disorder like cardiomyopathy, or a previous rhythm problem, which predisposes you to severe and dangerous rhythm, changes. For those with a definite arrhythmic tendency, it is sensible to avoid those things (e.g. excess coffee or alcohol, large meals) known to exacerbate abnormal rhythms.

Treatment can be divided into drug therapy, device therapy, interventional therapy and surgical therapy. All are clearly dependent on the detailed underlying predisposing factor to SCD. A detailed description of these interventions is beyond the scope of this lecture, but they are well described by Priori et al3. Suffice it to say that both treatment *and* no treatment carry risks, as drugs, interventions and surgery may all have unwanted adverse effects.

Drug therapies target various aspects of the membrane polarisation processes that I outlined in my last lecture. Most drug trials have produced equivocal results, and some have actually made things worse. For those patients who have the tendency to go into ventricular fibrillation, automatic implantable defibrillators [ICD] have proven to be effective25 in reducing mortality associated with abnormal rhythms (by about 50%) and with overall mortality (by 28%), primarily in those with poor contractility of the heart (low left ventricular ejection fraction). The National Institute for Health and Care Excellence (NICE) recommends the insertion of a subcutaneous ICD for the prevention of sudden cardiac death in the short and medium term. The guidance states that evidence on short term safety is adequate, but there remains uncertainty about long-term durability (<https://www.nice.org.uk/guidance/ipg454/chapter/1-guidance)> . This is another area in which technology is progressing rapidly, resulting in greater reliability, less inappropriate defibrillations and miniaturisation of kit. For those who have a proven tendency to VF, ICDs can be truly life saving.

Destruction (ablation) of a proven arrhythmogenic focus in the heart either by a trans-catheter approach or if absolutely necessary by surgery may also be indicated, and is life-saving if successful.

**Cardiomyopathies** are well classified26 heart muscle disorders almost all of which can be associated with ventricular arrhythmias and an increased risk of sudden cardiac death, with the risk varying with the aetiology and severity of the disease. They are broadly divided into **dilated** cardiomyopathy when the wall of the heart is thinned out, often scarred and contracts poorly; and **hypertrophic** cardiomyopathy (HCM) in which the left ventricular wall is unusually thick. Both groups may be helped by drugs as before, and by the use of implantable defibrillators, but HCM patients are also advised to avoid competitive sports3.

Thus, we have some evidence about what to do for those at risk of sudden cardiac death, but there remain big gaps in the evidence base which must be filled if we are to change for the better the future for such people and avoid unexpected deaths. Apart from the obvious statement that we need to know much more about the basic biochemical and cellular mechanisms precipitating sudden death, Priori et al3 reviewed these gaps in evidence in SCD, and they are summarised below.

* Identification of those at risk. New approaches to genetic profiling, ECG screening and imaging need to be assessed. Simple and cheap methods will need to be found before mass screening is viable, and treatments must be better to justify it.
* Optimizing the chain of care for those whose ‘death’ is witnessed and may be reversible.
* Understanding the mechanism of sudden death in those with structurally normal hearts
* Assessment of new technology, like wearable defibrillators and remote monitors
* Understanding what psychosocial support works for families and patients at risk.
* Improving risk-stratification in inherited arrhythmias or cardiomyopathies

To these I would add that we need to understand more about the impact of specific genetic abnormalities not just on the cause of the disorder, but also on the response to treatment. It is already becoming clear that some genotypes influence the response to drugs in a variety of arrhythmic conditions27.

I now want to turn to the other major topic in this lecture, **S**udden **U**nexpected **D**eath in **Ep**ilepsy.

**SUDEP**

**Definition**

Epilepsy affects more than 500,000 people in the UK[[8]](#footnote-8); about 1 in 100 people. It is a condition that affects the brain and causes repeated seizures. During a seizure, brain cells (neurons) fire off abnormal bursts of electrical impulses, which may cause the brain or body to act strangely. Seizures vary from just an odd feeling, to a trance-like state and at the most extreme loss of consciousness and generalized convulsions; classic *‘grand mal* fits. As a result of these symptoms, people with epilepsy were often ostracized, stigmatized and even housed in asylums out of the public gaze, as was the case with George V’s son, Prince John. Yet epilepsy is a common presentation in general practice, second only to stroke in neurological conditions.

Sudden unexpected death in epilepsy (**SUDEP**) happens in people with epilepsy often occurring in the absence of a defined structural cause of death. There are many mechanisms described and circumstances observed28. Some victims, like my son Toby, are undiagnosed at the time of death, and the terminal seizure may be their first.

Although sudden death in epilepsy was mentioned 150 years ago, as an ‘urgent problem’, it was not until after I qualified in the 1970’s that it became better defined and scientifically studied. Indeed, it is hard to find any reference to it between 1920 and 1980. Drugs to treat epilepsy had been developed, and it was thought that the disorder had become, relatively, benign.

To be able to define the true incidence, design research and compare studies, clear definitions were needed, and the handful of scientists who recognised SUDEP as an issue worked hard to provide them. Two different definitions emerged in the 1990’s, but these were brought together by Lina Nashef of King’s College Hospital, London and her international colleagues in a 2012 paper28. For those seeking more detail, this paper includes helpful case scenarios to explain and aid classification.

**Incidence**

Sudden unexpected death in epilepsy (SUDEP) is the commonest cause of epilepsy-related premature mortality 29. More people die of SUDEP than in house fires every year. In 2011, the Joint Epilepsy Council estimated there to be at least 600 deaths per year in the UK. The risk of dying suddenly and unexpectedly is **increased 24- to 28-fold** among young people with epilepsy compared with the general population30, 31, but the incidence of SUDEP varies depending on the particular subset of people with epilepsy. The lowest incidence, 0.09 per 1,000 patient-years, has been reported in population-based studies in newly diagnosed epilepsy patients. The incidence is one hundred fold greater in those whose epilepsy does not respond to treatment32. Twenty deaths (out of 600 registered entries) of previously undiagnosed people have been reported to the SUDEP Action registry in the last three years alone. There is also a cumulative increase in risk of SUDEP with age (after diagnosis as a child), rising to a potential 40% risk in that group when they reach adulthood[[9]](#footnote-9).

Prevalence data for SUDEP are distorted by its underuse as a final diagnosis on death certificates due to a lack of detailed, high quality autopsies and neuropathology studies33. Each year in the UK the Charity **SUDEP Action** ([http://www.sudepglobalconversation.com/thurman](http://www.sudepglobalconversatio.com/thurman) ) support over 14,000 people with their services; including bereaved families, people with epilepsy & health professionals.

This staggering figure gives some indication of the current scale of the problem in this country (https://sudep.org/sites/default/files/accounts\_2016\_scanned.pdf ). The major predisposing risk factor for SUDEP is the occurrence of generalised tonic-clonic seizures (GTCS or ‘grand mal’ fits), and the risk rises with increasing frequency of GCTS34.

**Risk Factors**

Certain risk factors for SUDEP have been identified (for a good review see Tomson et al35, 36. The American Academy of Neurology and the American Epilepsy Society will publish further guidelines later this year). The most consistent factor is that of poor seizure control, and in particular of GTCS. Resistance to treatment also increases the risk. A pooled analysis of 4 case control studies reported37 that male sex, epilepsy onset below the age of 16, epilepsy of >15 years duration and a high frequency of GTCS were important risk factors. So-called ‘complicated’ epilepsy is also likely to pose an additive risk38.

Night time and sleep appear to be times of increased risk39, as does lack of supervision in established at-risk epilepsy patients; especially in those who have had nocturnal fits. SUDEP cases were more likely to be found in the prone, face down, position in one recent retrospective study of forensic autopsies40, 41. Being diagnosed, but on no anti-epileptic drugs or during tapering of therapy also present important risks42.

The so called MORTEMUS study which looked retrospectively at SUDEP occurring in epilepsy monitoring units (EMUs) has described43 the immediate events leading up to death in the victims. GTCS were followed by recurrent episodes of stopping breathing (apnoea) or continuous apnoea followed by absent heartbeat (asystole) after the seizure (the post-ictal phase). These changes are also well described by Friedman et al44, from whose paper is taken this summary diagram.



Ventricular arrhythmias may also occur, and indeed epilepsy appears to be a risk factor for sudden *cardiac* death in the general population45, when it can occur in the absence of precedent epileptic seizures. Indeed, about 10% of witnessed SUDEP cases occur without apparent seizure activity. And it is important to remember that a small but significant number of young people die of SUDEP without any diagnosis or awareness that they have epilepsy (20/600 over 3 years in the current data from the (voluntary) Epilepsy Death Register established by SUDEP Action. My son Toby is included in this statistic.

NICE guidelines for epilepsy management were developed in 2004. Guideline 1.4.5 recommended that all adults [and children] having a first seizure should be seen by a specialist as soon as possible to ensure precise diagnosis and initiation of therapy. These guidelines were not universally applied, but greater familiarity with guidelines and better IT access to them, together with patients being able to find them simply as well, will help ensure that more early referrals are achieved…if only the resources are there to be able to meet demand. The recent update is available here (<https://www.nice.org.uk/guidance/cg137>) . Sadly, however, there are still no reliable bio-markers, including both ECG and EEG, for SUDEP46, and these would be necessary to facilitate studies on preventative strategies.

**Aetiology**

The cause of SUDEP is likely to be multifactorial, involving underlying genetic susceptibility related to the individual epilepsy syndrome, functional and pathological characteristics within brain, uncontrolled generalised tonic–clonic seizures [GTCS], and the circumstances in which death occurs (e.g. prone position). However, the detailed genetic architecture of SUDEP remains elusive. Better understanding of the underlying causes of SUDEP is required both to create new and to improve existing preventative strategies. Leu and colleagues postulated47 that the genetic risk for SUDEP was not localized, but spread across the whole genome, and have shown in exome-sequencing studies that over a thousand genes contribute to the overall polygenic burden, some of which may be candidates for further detailed study. No single gene was common to all cases. In people who have succumbed to SUDEP, there is a higher burden of deleterious genetic variants, compared to the burden in people with epilepsy who have not succumbed to SUDEP, and to people without epilepsy 46.

Cardiovascular co-morbidities are quite common in epilepsy, and various arrhythmias have been described in association with seizures, including asystole (the absence of heart beat and pulse). The associations have recently been well reviewed by Shmuely S et al48. There is clearly an area of overlap between SUDEP and SCD, and increasing knowledge of the underlying genetic mechanisms suggests that the degree of overlap might be around 20% (Professor Helen Cross, *personal communication*), a view supported by exome-sequencing work by Bagnall et al49, demonstrating that some SUDEP victims have clinically relevant mutations in cardiac arrhythmia and epilepsy genes. The overlap is likely to reflect similar abnormalities in the ion-channels associated with cellular action potentials (e.g. long QT syndrome), so called channelopathies.

Investigations into rare syndromes associated either a higher incidence of SUDEP (e.g., Dravet’s Syndrome and alternating hemiplegia of childhood) also support this overlap between cardiac and neurological mechanisms associated with membrane depolarisation50, and may provide more clues as to aetiology. The relationship between cardiac dysfunction and epilepsy has been reviewed (Sisodiya, S *personal communication*), with particular reference to those with uncontrolled or drug-resistant epilepsy. Underlying abnormal ventricular arrhythmias increase the risk of SUDEP, and Chyou et al51 demonstrated abnormal ventricular conduction patterns in SUDEP patients not present in controls. Investigation into how epileptic seizures mess up the ‘brain-heart’ link may thus provide mechanistic insight to the association between epilepsy and cardiac dysfunction. From all these studies, it seems clear that patients with a new diagnosis of epilepsy should have a full, expert, cardiac assessment, including formal ECG and echocardiography testing. Whilst ideal, there is resistance from many cardiologists to do this, largely because of an already enormous workload and the current shortage of echo and ECG technicians.

Tissue mechanisms have also been investigated (as they have in many disease processes), but Sisodiya’s group at UCL were unable to identify any clear immuno-histochemical signature in autopsy specimens after SUDEP52.

All these studies highlight the importance of obtaining (and retaining) material from the victims of unexpected sudden death of all types. Science cannot progress without access to such tissue, and thus future deaths may not be prevented as they could be.

Nashef and Richardson53 recall that in 1997, *Epilepsia* published the proceedings of an international meeting on SUDEP, convened by the support group Epilepsy Bereaved (now SUDEP Action), at a time when the interests of self-help groups, clinical researchers, and the pharmaceutical industry converged. The event was unique then, as recognition of SUDEP was in its infancy. Bereaved relatives needed SUDEP to be recognized as a significant, tragic, yet hitherto neglected calamity that required attention. Researchers wanted SUDEP acknowledged as a reality, after years of denial except by a leading few and investigated, as was its due. As Nashef and Richardson explained, “*We now find ourselves, 18 years later, in an entirely different place. Yet, although knowledge about SUDEP has grown substantially, we are not where we need to be*”.

Much more needs to be done to understand the physiology of the events, and potential triggers,44, 54 leading up to or associated with sudden death. This can only happen in Epilepsy Monitoring Units (EMUs) where patients known to be at high risk can be monitored. Such patients include those with poor drug control. Measures that are not routinely monitored in EMUs, including blood pressure, overall and instantaneous heart rate variation, baroreflex sensitivity, blood catecholamines, breathing patterns (rate, O2, CO2, apnoea, and hypopnoea) are under study together with modern imaging studies. Because of the relatively low incidence, especially in hospital, multicentre collaboration is vital, and this is being undertaken in the US (and including University College London) via the NINDS Center for SUDEP research (CSR)54. This approach offers the best hope for the future, combining as it does advanced imaging, genetic, immunochemical and physiological monitoring, together with sophisticated data-analysis.

**Prevention**

What can we do to identify susceptible individuals, and how might we prevent them suffering the fate of SUDEP?

Who is at risk?[[10]](#footnote-10)

* We are now pretty sure that those patients having generalised tonic-clonic (GTCS) seizures are at increased risk of SUDEP, and the greater the frequency of GTCS, the greater the risk.
* A seizure occurring within the last year (and perhaps in the last 5 years) may also increase risk.
* It is also possible that either the absence of anti-epileptic drug treatment or the need for multiple drugs may be risk factors, but it may be that the need for multiple drugs is simply a reflection of the severity of the epilepsy. However, the failure to add a drug when needed also poses a moderate risk.
* There is some evidence that nighttime seizures may increase the risk.
* Women of childbearing age. It is challenging to get therapy right in this group of patients. There is anxiety that the anti-epileptic drugs may damage a fetus may cause a woman to reduce or alter her therapy, putting her at risk of SUDEP. SUDEP deaths during maternity are apparently increasing ([www.sudepglobalconversation.com/nashef-ckia](http://www.sudepglobalconversation.com/nashef-ckia)). Women with epilepsy need pre-conception counseling well ahead of any pregnancy both to explain relative risk and to advise re therapy.
* There may be reluctance to take the drugs; e.g. a student leaving home and suddenly reducing therapy.

Knowledge of these risk factors gives some indication of how we might be able to prevent SUDEP happening to patients.

* Newly diagnosed epileptic patients should be promptly and thoroughly investigated for both neurological and cardiac disorders, and anti-epileptic treatment should probably be started[[11]](#footnote-11). There is no cause for delay, and referral to a specialist unit should be urgent.
* Patients known to have epilepsy should be as well controlled as possible, and those with recent or frequent GTCS should have their drug therapy reviewed and monitoring increased. In the current NHS circumstances, this can be a tough ask for general practices. However, identification of those at risk should be helped by the development for use in general practice of the ‘SUDEP and Seizure Checklist’ (<https://www.sudep.org/checklist>)55, which includes assessment of 20 evidence-based risk factors. Gales and Shankar reported[[12]](#footnote-12) the identification of 5 /107 individuals with a risk score of 8 or 9 (http://www.rcgp.org.uk/clinical-and-research/bright-ideas/sudep-checklists-in-primary-care.aspx). Most worryingly though, there were no available data on any of the 107 patients on nocturnal seizures, surveillance at night, prone sleeping position or pregnancy data.
* Those experiencing nocturnal fits should receive special attention43. There is evidence42, sadly judged by a recent Cochrane review56 as ‘weak’, that night time supervision and/or the use of listening devices similar to baby alarms may be protective. Such strategies may not anyway be popular with teenagers or young adults. The use of support dogs, capable of detecting an imminent seizure may be of value in those patients lucky enough to have one (<https://supportdogs.org.uk)> , but more evidence is needed, and may be hard to obtain in adequate numbers.

New technology offers promise, but little strong evidence yet exists57. Fisher reviewed the topic in 201258 and I will not reiterate the detail here. Many proposed devices, even these days, are relatively cumbersome and it is hard to imagine that they would have been popular with those at risk…unlike a cuddly and lovable support dog! Cameras, seizure (movement) detecting mattresses, anti-suffocation pillows and smart watches have been deployed. In the last five years, there has been an explosion of interest in sensor technology, and wearable health monitoring devices. Some have already reached the market, and demand more extensive and objective trials (<http://www.healthline.com/health/bracelets-and-devices-epilepsy#Overview1> and Samson, K 201559). Whilst we must be cautious that aggressive Internet marketing doesn’t distort good evidence acquisition, it seems likely to me that something useful will emerge in this area, hopefully better than simply expecting a young person to have to sleep each night with a responsible other human. I cannot imagine how hard it would be for the person charged with the responsibility of overseeing an at risk person to sit there night after night worrying they might have to intervene; if they had to would they succeed, and how would they cope if they failed.

**Should at risk people be told?**

The broad ethical challenge**22** is to balance the potential benefits and risks of preventing sudden death in an environment in which there is uncertainty about its causes, measures to evaluate risk, and the effectiveness of interventions to reduce risk. The importance of knowing what to tell potential victims cannot be underestimated. But there are clear barriers to resolving the problem.

1. The persistent professional taboo that prevents half of epilepsy professionals from discussing the risk of sudden death with their patients. The situation in SCD is better, but far from perfect.
2. The lack of funding for both research and routine surveillance
3. Uncertainty over the value of screening.

The UK is very well positioned to answer these questions, if only it had the will and would expend the energy. Primary care IT systems are relatively well developed, and although hospitals have some way to go and data integration remains challenging, the very existence of a comprehensive health system means that important population studies, and public health interventions should be able to be done well here and have effective global impact.

We need to carry out more qualitative research to understand how potential victims and their families *feel* about such issues, and recognise that they are partners in care not victims of it. Interventions must be personalised, but to do that much more data are needed. Such qualitative research is the hardest to fund. Grant giving bodies are dominated by conventional scientists, or, as the cynics amongst us often say in private; drugs, genes and cytokines.

**System Problems and Insensitivities**

I now want to turn to the *process* that families go through after a sudden death, and consider how that gets in the way of both support and research. Let me first consider the time and location of sudden death.

Sudden cardiac death in the young usually takes place during the day, and is often witnessed, sometimes on the athletic field, as was the case with Fabrice Muamba playing for Bolton against Tottenham Hotspur in 2012. He was successfully resuscitated, but in 2016 Patrick Ekang of Dinamo Bucharest and 6 other professional footballers were not so lucky. Much research has been done about sudden death in athletes7, 60, 61, and because of their fame and, let’s face it, value, this research continues to attract a great deal of funding.

SUDEP by contrast often takes place at night, is usually un-witnessed and carries with it all the historic stigma which has become associated with epilepsy62. Victims are young and maybe living alone, and it may take days to discover the body. Perhaps because of the most common causes of death in this age group (suicide, drugs, trauma), many families find that the place of death is treated as a crime scene2[[13]](#footnote-13), with police separating loved ones from victim, and looking for evidence of foul play, suicide or drugs. In the USA, this has even ended up with full-blown murder investigations (<http://www.sudepglobalconversation.com/wannamaker-hanna>). There may be a lengthy and unfamiliar process of a coroner’s investigation, or at least a delay until a ‘forensic’ post mortem is carried out. Coroners and pathologists do not work at night. The law progresses slowly, and inquests may be delayed for weeks or months (SUDEP Action is aware of many such cases). There is little sense of urgency, and the family will remain in a state of limbo, uncertain of the cause of death or what is to happen. It is always intensely traumatic for the family.

Families welcome contact from the medical team that has been coordinating their care. Yet there is no established process for the Coroner’s office to notify the neurologist that a patient has died. A not uncommon scenario is that the first contact with the family is a reminder that their recently deceased loved one has failed to turn up for an appointment at the clinic.

In my own son’s case the paramedics, police, and our GP were all wonderful, for which we will always be grateful. Even so, Toby died on a Friday and time seemed to slow down, with no sense of urgency about the need to investigate the cause of death. Whilst something that no family wants to have to face, the post-mortem investigation of victims is crucial to provide information to help future, potentially savable, patients. The need to understand is profound. I remember being aware of this at the time. Sadly, there are significant problems with current post-mortems.

**Issues with Post-Mortems**

Kaltman et al for the American Heart Association, recommend the following for SCD22;

*Circumstances surrounding the deaths should be captured by death scene investigation, along with medical record, family history, and autopsy review. Demographic data about the decedent, activity level at the time of event, drugs or medications used (including stimulants for ADHD, psychotropic and asthma medications, etc.), antecedent symptoms, and family history of SCD or SCD-associated conditions will provide relevant information for the elucidation of associations with SCDY. Partnering with local medical examiners, especially forensic pathologists, may allow for standardization of autopsy protocols. Autopsies should include a comprehensive examination of the heart, including cardiac dimensions, weight, gross structure, coronary artery anatomy, and histological evaluation of the myocardium. A concerted effort to rule out non-cardiac causes of sudden death is critical. For cases with no definitive cause on general autopsy, appropriately preserved bio specimens should be collected for molecular autopsy (post-mortem genetic investigation). Through sequencing and genomic approaches, molecular autopsy may be able to identify pathological variants [specific to heart rhythm abnormalities] each of which predisposes to SCDY. Although primarily limited to research laboratories (health insurance does not currently pay for post mortem testing), molecular autopsy will be critical for full description of SCDY cases.*

Post-mortem (PM) examination is also required to confirm SUDEP, at the minimum through exclusion of other causes of death63. Correct classification of the cause of death in people with epilepsy is self-evidently essential to any future research, and to epidemiological studies. Examination of the brain offers a resource for further investigation and understanding of the different pathological mechanisms that lead to SUDEP. Detailed post-mortem examination guidelines were published by the Royal College of Pathologists as long ago as 2006 ([www.rcpath.org)](http://www.rcpath.org)). A recent review by Thom et al concluded63 that PMs have become better (at least in specialist centres) since the Sentinel audit in 2002, and diagnostic findings were made with greater frequency, making SUDEP less likely to be a diagnosis of exclusion as it used to be in the past. But such good practice is far from uniform64, 65. Fresh tissue is not always taken for detailed analysis, nor the brain examined appropriately. I described earlier the developments in post-mortem MR imaging to provide detailed anatomic information about the heart in SCD. Such structural information may be of great value in epilepsy too, as morphologic changes in the brain have recently been reported in victims of SUDEP66, 67. Imaging is not usually done post-mortem. Radiologists place PM scans low on their list of priority when faced with a waiting list of live patients, although some centres are pioneering out-of-hours MRI scanning for PMs. The attitude of coroners to the importance of science is also variable, but the importance of expert analysis of specimens and genetic material is clear63, and yet tissue and images are currently rarely shared with such experts.

The plethora of television programmes about forensic science leads one to imagine that huge resources are available to identify the cause of death, and thus must contribute to deeper understanding of the causes of disease. Sadly, this is not the case. Such resources are not universally available, are effectively rationed and certainly not deployed unless a serious crime is suspected. Unfortunately, not all forensic post mortems are performed to the standards required fully to understand sudden death in the young. Not all sudden deaths result in a coroner’s inquest, if a satisfactory cause of death has been identified.

One of the senior researchers in the field told me the story of a situation in which a coroner refused to let the research lab have tissue that was vital for research, and for which examination the family had not only given consent, but were enthusiastic. The researcher said; “*I found deeply depressing and frustrating, and I believe the family found it very upsetting at an already-difficult time, that we were unable to have transferred to us brain tissue from an individual who had succumbed to SUDEP which the family wanted to be used for research. There was no barrier except the attitude of the coroner involved. That simply cannot be right.”*  I completely agree.

The investigation of the *underlying* causes of disease is not the primary purpose of a Coroner’s post mortem or inquest. That is looking for a relatively *simple* cause of death, defined by certain limited categories, one of which, relevant here, is ‘natural causes’. These are listed below from section 9.1 of the Guide to Coroner Services ([www.gov.uk/moj)](http://www.gov.uk/moj)) [[14]](#footnote-14).

*9.1 Inquest conclusions – determinations and findings*

*The coroner (or jury where there is one) comes to a conclusion at the end of an inquest. This includes the legal ‘determination’, stating formally who died, and where, when and how they died. The coroner or jury may also make ‘ findings’ to allow the death to be registered). When recording the cause of death the coroner or jury may use one of the following terms:*

* *accident or misadventure*
* *alcohol/drug related*
* *industrial disease*
* *lawful/unlawful killing*
* *natural causes*
* *open (used when there is insufficient evidence for any other outcome)*
* *road traffic collision*
* *stillbirth*
* *suicide*

*Alternatively, or in addition, the coroner or jury may make a brief ‘narrative’ conclusion setting out the facts surrounding the death in more detail and explaining the reasons for the decision.*

Not only is there variation in the quality and completeness of post mortems, and their relevance to the underlying disease, but there is also variation between coroners in how they interpret the data. This has been shown recently in a study of suicides68. Reforms to the Coroner’s system were made in 2013 (<https://www.gov.uk/government/news/major-overhaul-of-coroner-services-in-england-and-wales>) , in response to such inconsistencies and ‘post-code lotteries’. A new post of Chief Coroner was created, with the specific responsibility of delivering national standards at local level, together with speeding up the whole process. The results have so far been deeply disappointing, despite the millions spent. Delays are common and regional variation has not been eliminated. Localism dominates, and according to affected families (SUDEP Action) the post-code lottery persists. A detailed critique of the Coroner’s system is beyond the scope of this lecture, but I feel justified in saying that, in its current form, it is not the perfect mechanism for getting to the root causes of SCD or SUDEP. The system won’t even permit (SUDEP Action *personal communication*) the use of a standardized *pro-forma* to ensure that all relevant parties are informed, and help form supportive organisations can be signposted. Most families have to resort to the Internet to find help, at a time of maximum stress. The Government was due to publish details of a public consultation on the effectiveness of the coroner reforms in early 2016. Now in early 2017, this has not yet appeared, (https://www.gov.uk/government/consultations/post-implementation- review-of-the-coroner-reforms-in-the-coroners-and-justice-act-2009. ). Those organisations involved in supporting the bereaved have felt that this consultation was anyway inadequate in scope and content.

The system could work better, with a few tweaks and with commitment from coroners and pathologists alike. There are grounds for optimism. Good working relationships and excellent practice have been established in the South West Region, and a recent conference in Oxford attended by relevant experts from medicine, the law and the Coronial service concluded69 that there should be much more collaboration between relevant parties, better protocols for post mortems and clarification of practices relating to genetic evidence in both post-mortem practices and the court. I applaud such collaboration and hope it bears fruit. The law should be helpful to society, not obstructive to scientific progress.

The comparison with the process for investigation of cot deaths is stark, particularly in Scotland, where there is a national protocol and integration with charity support services for the family (http://www.sudiscotland.org.uk/process-overview/). Local protocols for cot death also exist in England, again integrating family support with protocols for investigation.

(http://www.safeguardingshropshireschildren.org.uk/scb/files/west-midlands-sudi-guidance.pdf )

**Final Thoughts**

I suspect that most of us would like to die suddenly, preferably in our sleep and without suffering. One hopes that victims of SUDEP or SCD do just that. But we are talking about the young, and they should not die in the wrong generational order. Nothing can prepare the relatives and friends for the ‘overwhelming sense of disbelief’2 which is often experienced after sudden unexpected death, irrespective of the cause, and the loss of both life and opportunity. Families and friends can experience post-traumatic stress disorder, as indeed can GPs, nurses, police and paramedics. They are secondary victims and must not be forgotten.

As a society, we can and should do more to make the processes surrounding sudden unexpected death as simple, quick, effective and humane as possible. All opportunities to collect data, relevant biological samples and histories should be taken, and not obstructed. That means treating a sudden death as a something urgent, so that samples and scans can be obtained as ‘freshly’ as possible, and shared with relevant experts to perform the most up to date analyses.

Data should be shared, and all deaths submitted to Registers so that there are complete and accurate population-wide data to analyse. Such registries have begun (for example, SUDEP Action began the voluntary, all source, Epilepsy Death Register in 2013, over 600 cases have now been reported to it. An excellent response, but almost certainly a massive underestimate of the total number of cases), but need more funding, more work and more time to release their potential value. Their use should, in my view, be mandatory, as is the case for cardiac surgical data. I have discussed before[[15]](#footnote-15) the concept of **data donation as a public good**, and remain confident that the vast majority of families would be only too happy to share relevant data if they were used to help prevent future deaths. I for one would find comfort in knowing that knowledge gained from our family’s experience would help others.

The study of SUDEP has been hampered by poor diagnosis and under-reporting, particularly in the young. Thus, research is currently proposed (Cross & Abdel-Mannan, *personal communication*) prospectively to collect data on all incident cases of SUDEP in childhood, interviewing affected families using a ‘verbal autopsy’ technique. This will be linked to DNA sample collection and a full neuropathology review. Such detailed data linkage should provide more and necessary insights into the disorder.

SUDEP care in general is hampered by the marked resistance of professionals to discuss the risk, and by the extraordinary difficulty that the NHS has in spreading good practice from one area to another. Decades of political ‘localism’, often supported by communities, and professional certainty that ‘it won’t work here’ have contributed to this, but the current NHS structure of multiple semi-independent organisations means that the wheel is constantly having to be reinvented and lives are being put at risk. NICE remains a beacon of hope and good practice, envied throughout the world. We should support it.

Research is critical to understanding and treatment.. Epilepsy is associated with a negative social perception even to this day70, and funding for epilepsy research has always been harder to obtain than funding for cardiac research. Data from the Charity Commission Annual Report (2015-2016) reveal a 15-fold disparity in money raised for cardiac charities (almost £300m) and that raised for epilepsy charities (£50m). Most goes to the British Heart Foundation, and little in either is allocated primarily to sudden death, although the apparent ratio is approximately 2:1 in favour of cardiac research. This despite the fact that there is a common ‘middle ground’ of scientific importance, and the peri-mortem investigations ought to be identical. One could reasonably argue that research groups might be better combined into teams looking *together* at sudden death in the young, rather than within their own, siloed specialty. This has begun at UCL under the auspices of Professors Helen Cross and Sanjay Sisodaya, is supported by the views of Shmuely et al48 and receives support from Guidelines being developed by the American Academy of Neurology and the American Epilepsy Society (*in preparation*).

Not only are there differences in the funding of research, but there are also differences in the number of specialists and the distribution of services. There is a shortage of neurologists in England compared to other similar countries[[16]](#footnote-16), and wide differences in the provision of specialist services[[17]](#footnote-17). There is a particular shortage and poor distribution of epilepsy specialists [[18]](#footnote-18). Although this last report was published in 2008, there has been little improvement since71, and Epilepsy Action emphasised how critical the situation had become in 201372, listing the following, suggesting that our current *system* is putting patients at risk.

**[Service] Planning**

* 66%, 104/158 of Clinical Commissioning Groups (CCGs) do not have, or even intend to produce, a written needs assessment of the health and social care needs for people with epilepsy.
* Of the local authority responses, only 27% (27/102) of their Joint Strategic Needs Assessments (JSNAs) include a section that mentions the care of people with epilepsy.
* Only 17% (27/158) of CCGs or CCG confederations have appointed a clinical lead for epilepsy.

**[Service] Provision**

* **Only 20%** (8/40) of acute trusts stated that their average waiting time for an adult with suspected epilepsy to see an epilepsy specialist consultant was two weeks or less.
* Of those acute trusts that provide an epilepsy service, **only 66% (52/79)** offer their patients access to an adult epilepsy specialist clinician.
* **Only half** (52%, 475/905) of people with epilepsy told us that they have seen an epilepsy specialist nurse.
* **Only 14%** (128/947) of people with epilepsy report having a written care plan.
* **Over a third** (37%, 305/827) of patients (adults and children) were not offered an epilepsy review in the last twelve months. Of the adults, **68% (206/305) were still having seizures.**
* **Nearly three quarters** (73%, 495/682) of patients (adults and children) who are still having seizures have **never been referred** to a specialist tertiary epilepsy centre.

Not only are specialists lacking, but GP funding cuts have also reduced the formal requirement for epilepsy review to once per year. Patients with epilepsy (and indeed many other chronic conditions) are frequently left to self-manage, but do this without basic understanding of when and why to seek help. A&E may seem the natural place to go if uncertain, increasing NHS pressures.

Note that whilst the situation is clearly poor for epileptic services, even cardiac service provision is imperfect (http://www.phgfoundation.org/news/4671) . There is a lack of uniform access to inherited cardiac conditions services in many parts of the country, particularly in paediatrics.

This lecture has given me the opportunity to bring the issue of sudden unexpected death to your attention. Please make others aware, and look for these charities which support both research and the affected families.

They are:

**Cardiac Charities;**

Cardiac Risk in the Young (<http://www.c-r-y.org.uk)>

SADS UK (<http://sadsuk.org.uk/newsite/)>

Cazfest ([www.cazfest.com)](http://www.cazfest.com))

Vital Signs Foundation (<http://www.vsf.org.uk)>

**Epilepsy Charities;**

Epilepsy Research UK (<https://www.epilepsyresearch.org.uk)>

SUDEP Action (<https://sudep.org)>

Young Epilepsy (<http://www.youngepilepsy.org.uk>)

This is just a sample of the charities involved in the cardiac and epilepsy fields, but those with a declared interest in sudden death.

As Elisabeth Donner points out2, sudden unexpected death in the young leaves relatives with an overwhelming sense of disbelief and loss, and the terrible feeling that they could have done more. Even though experts know this not to be true, the feelings of guilt are profound and long-lasting. Many relatives of the deceased say that they do not want the death to be in vain. They do not want the death to be even more of a terrible waste than it already is. Some families will want to donate tissue; others will simply want recognition of the events leading up to the death and assurance that lessons have been learnt. There are strong feelings that even the most basic systems are not in place to keep people at risk safe, and basic information may not be freely available or given; for example, that showering is safer than taking a bath.

The lack of opportunity to say goodbye and say all the things you wish you could (or should) have said stays with you always. The lost opportunities for the victim prey on your mind. Toby, for example, loved American politics, and hated unfairness, injustice and war. It seems unbelievable to me that he wasn’t here to experience 2016, to shout at the television and appreciate, with his infectious laugh, the burning satire which the year induced.

Gresham lectures aim to educate. As both Elisabeth Donner 2 and Lina Nashef 73 have emphasised, we must **educate to protect**, and the most effective way of reducing the incidence and impact of sudden death in the young, whatever the cause, is to alert both patients and public alike to the problem and its potential solutions. And to continue to press our politicians to invest in health services and research. I hope I have helped that process tonight.

©Professor Martin Elliott, 2017

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1. Donner EJ, Jeffs T, Jette N. Are Canadian pediatricians aware of SUDEP? American Epilepsy Society Annual Meeting 2012. [↑](#footnote-ref-1)
2. There was a total of 518 homicides in 2014-15, 6188 suicides, and 3674 deaths in the same period related to drug poisoning [↑](#footnote-ref-2)
3. For a very thorough of sudden cardiac death in all age groups, read:*3. Priori SG, Blomström-Lundqvist C. 2015 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. Eur Heart J 2015;****36****(41): 2757-2759.*  [↑](#footnote-ref-3)
4. The calculation of events per patient-year(s) is the number of incident cases divided by the amount of person-time at risk. Make the calculation by adding the number of patients in the group and multiply that number by the number of the years that patients are being studied (or followed) in order to calculate the patient-years (denominator). Then divide the number of events (numerator) by the denominator.

   * Example: 100 patients are followed for 2 years. In this case, there are 200 patient-years of follow-up.
   * If there were 8 myocardial infarctions (MI) in the group, the rate would be 8 MIs per 200 patient years or 4 MIs per 100 patient-years.

   [↑](#footnote-ref-4)
5. including 25% of the deaths that occur during pregnancy (<https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/MBRRACE-UK%20Maternal%20Report%202016%20-%20website.pdf>) [↑](#footnote-ref-5)
6. The number is probably higher (Dr. Juan Kaski, *personal communication*), but published screening studies are limited by the fact that most of these conditions have significant clinical (and genetic) heterogeneity, so a single one-off assessment in a relative may not detect phenotypic features that would become apparent with ongoing investigations. In addition, as most of these conditions are autosomal dominant, thus at least 50% of relatives would be expected to be normal on screening, even if 100% of the conditions causing SCD were heritable. [↑](#footnote-ref-6)
7. <https://www.youtube.com/watch?v=ILxjxfB4zNk> and <https://www.youtube.com/watch?v=Ff_kalDZfzU> . For more information visit [www.bhf.org](http://www.bhf.org) [↑](#footnote-ref-7)
8. http://www.nhs.uk/conditions/Epilepsy/Pages/Introduction.aspx [↑](#footnote-ref-8)
9. Risk of SUDEP in children with epilepsy (aged 0­–17 years) is 0.22/1,000 patient-years (95% CI 0.16–0.31). The risk of SUDEP increases in adults to 1.2/1,000 patient-years (95% CI 0.64–2.32) [↑](#footnote-ref-9)
10. Many of these issues were identified in the 2004 NICE Guidelines, and the evidence has now strengthened. They will also be covered in Guidelines to be published in 2017 by the American Academy of Neurology and the American Epilepsy Society [↑](#footnote-ref-10)
11. https://www.nice.org.uk/guidance/cg137 [↑](#footnote-ref-11)
12. The check list was developed into a smartphone App called EpSMon (<https://www.youtube.com/watch?v=e3mECsSVgHI>) and more details can be found here [www.epilepsytoolkit.org.uk](http://www.epilepsytoolkit.org.uk) and at <https://www.sudep.org//epilepsy-self-monitor>) [↑](#footnote-ref-12)
13. http://www.scotland-judiciary.org.uk/10/794/Fatal-Accident-Inquiry-into-the-deaths-of-Erin- Casey-and-Christina-Fiorre-Ilia [↑](#footnote-ref-13)
14. The full 2009 Coroners Act can be found here <http://www.legislation.gov.uk/ukpga/2009/25/pdfs/ukpga_20090025_en.pdf> [↑](#footnote-ref-14)
15. <http://www.gresham.ac.uk/lectures-and-events/seeing-through-the-lies-innovation-and-the-need-for-transparency> [↑](#footnote-ref-15)
16. http://www.publications.parliament.uk/pa/cm201213/cmselect/cmhealth/6/6vw46.htm) [↑](#footnote-ref-16)
17. http://www.neural.org.uk/updates/253-First-ever%20data%20on%20neurology%20appointments%20shows%20significant%20variation%20in%20access%20to%20services [↑](#footnote-ref-17)
18. https://www.epilepsy.org.uk/sites/epilepsy/files/images/campaigns/Epilepsy\_in\_England\_-\_Time\_for\_change\_report.pdf [↑](#footnote-ref-18)