Epilepsy Research Institute UK Sudden Unexpected Death in Epilepsy (SUDEP) Workshop: Identifying the pre-clinical and clinical priorities for SUDEP research

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Abstract

The Epilepsy Research Institute's Mortality, Morbidity and Risk Theme workshop on Sudden Unexpected Death in Epilepsy (SUDEP) brought together a diverse group of stakeholders, including basic science researchers, clinicians and clinical researchers, charity partners, bereaved individuals and people with epilepsy to identify important gaps in pre-clinical and clinical SUDEP research. Collectively, the SUDEP workshop highlighted recommendations for future research to address several identified gaps and the need to develop infrastructures that utilise data-driven approaches to reduce SUDEP risk. National and global cross-institution collaborations will be fundamental in driving these research efforts forward.

Key words

Epilepsy, mortality, research gaps, risk, seizure

Introduction

Every week in the UK there are 21 epilepsy-related deaths [1]. People with epilepsy are three times more likely to die prematurely than those without epilepsy [2]. The most common causes of mortality include Sudden Unexpected Death in Epilepsy (SUDEP), status epilepticus, severe injury and suicide [3,4]. Over the last 20 years there has been an increase in public awareness of SUDEP, prompting a surge in research interest.

Recognised significant risk factors for SUDEP include generalised tonic-clonic seizures, seizures from sleep, uncontrolled and persistent seizures [5], medication non-adherence [6-8], previous brain injury or CNS infection [9], alcohol and drug misuse [7] and pregnancy [10].

Pre-clinical research using brain tissue and animal models has identified several potential mechanisms for SUDEP, including respiratory dysfunction and changes in autonomic networks – cortical and brainstem structures – that regulate critical bodily functions: for example cardiovascular functions [11-13]. With regards to cardiovascular dysfunction, heart rate variability alterations are linked to SUDEP and, as such, may be an important biomarker for SUDEP risk [14,15]. The molecular mechanisms underpinning SUDEP are, however, poorly understood and it is likely multiple complex mechanisms contribute towards SUDEP risk. Discussions identifying research gaps around mechanisms and risk for SUDEP are therefore vital to support future recommendations for research and prevent avoidable deaths.

Epilepsy Research Institute and Mortality, Morbidity and Risk theme

The Epilepsy Research Institute (Institute) has become the central hub for the epilepsy research community in the UK. The Institute's mission is to radically advance research into the causes, prevention and treatment of epilepsy and its associated conditions. The Institute's research strategy is underpinned by six themed programmes of work. These themed programmes were based on the outcomes of the Institute's UK Priority Setting Partnership in 2022 [16,17] which identified the top research priorities for the epilepsy research community. The number one priority was to better understand the causes and contributing factors of epilepsy-related deaths, including SUDEP, and how these deaths can be prevented. In line with this, the 'Mortality, Morbidity and Risk' theme aims to accelerate research through multidisciplinary approaches to identify risk factors and prevent epilepsy-

related deaths. Within this broad work programme, the theme first prioritised the advancement of pre-clinical and clinical research into SUDEP.

The Epilepsy Research Institute SUDEP Workshop

The Institute's Mortality, Morbidity and Risk theme convened a one-day in-person SUDEP workshop in September 2024 to identify knowledge gaps in SUDEP research and propose recommendations for future research. The workshop was attended by experts from diverse backgrounds, including basic researchers (15%), clinicians and clinical researchers (45%), charities (25%), people with epilepsy and bereaved individuals (15%).

During the workshop, attendees reflected on the knowledge gaps in SUDEP research and summarised potential changes to better support individuals with epilepsy at risk of SUDEP. Some attendees were also invited to give their personal reflections on the risk of SUDEP and losing a loved one to SUDEP. A series of group-based roundtable discussions (8–10 attendees per group) were held, during which workshop attendees considered pre-clinical and clinical knowledge gaps in SUDEP research and identified recommendations for future research to maximise benefits for individuals living with epilepsy. These discussions highlighted key gaps in SUDEP research. Each of these are explored further below, although it is recognised that they may not encompass all gaps in the field.

Pre-Clinical Discussions

The group-based discussions identified several knowledge gaps for pre-clinical research into SUDEP. First, attendees noted a clear lack of suitable animal models that accurately replicate the human condition [18,19]. *In vitro* experiments on animal tissue are important to identify the molecular mechanisms of SUDEP. However, one of the major concerns with using *in vitro*/*ex vivo* models to understand the mechanisms of SUDEP is that these models do not fully replicate the dynamic changes that occur in response to seizures in the human brain. There is significant untapped potential in examining dynamic changes in *in vivo* models of SUDEP in mice.

During the workshop, discussions highlighted a gap in pre-clinical SUDEP research in the UK compared to other parts of Europe and the USA. The underlying reasons remain uncertain,

though stricter regulatory requirements in the UK were suggested as a potential factor. Research involving animal models, where death is expected in a subset of cases, naturally requires enhanced ethical and regulatory oversight. While the regulatory challenges associated with SUDEP-focused studies in the UK are generally manageable, it was suggested that some researchers opt to explore other fields within epilepsy, rather than focusing on SUDEP, due to the additional complexities involved in obtaining approvals.

Second, discussions identified the need to translate observations made by clinical staff and patients in primary, secondary and tertiary healthcare settings into research questions that can be mechanistically investigated in pre-clinical models. For example, it was evident that more research is needed to examine the impact of autonomic dysfunction following a seizure. The need for research to examine the impact of altered serotonin signalling in the brainstem on the risk of SUDEP, as well as the role of sleep disruptions, temperature [20], infection, neurodevelopment and mental health problems (e.g. stress, anxiety, depression) in increasing an individual's risk of SUDEP, were all highlighted. Discussants agreed that there is a need to disentangle the complex causal associations between identified mechanisms and SUDEP to better understand how therapeutic models can help reduce risk and prevent SUDEP.

Attendees mentioned the need for better infrastructure to develop and utilise existing national epilepsy brain banks, for example The Epilepsy Society Brain and Tissue Bank, to allow for the deep profiling of post-mortem human brain tissue of individuals who have died from SUDEP. Such work could help identify changes in brain structures and connectivity that could be validated in rodent models to understand the causal association between these changes and SUDEP. For example, research examining post-mortem brain tissue has found reductions of the neurotransmitter serotonin and an increase in adenosine [21,22] in the brainstem [23] and other brain regions that influence ictal apnoea, suggesting failure of arousal systems, particularly in the brainstem, as one pathway through which people succumb to SUDEP. Further pre-clinical research using animal models is required to investigate the causal associations between brainstem functionality and SUDEP.

Group discussions also identified a gap in animal research, specifically relating to the use of animal tissue to examine questions related to SUDEP. In its current state, brain tissue from rodents used in neuroscientific research that die as a consequence of seizure activity akin to

SUDEP is often discarded when the primary research question is not related to SUDEP. Going forward, the sharing of appropriate tissue samples relevant for SUDEP research (e.g. brainstem, thalamus), would help improve understanding of these underpinning mechanisms.

The attendees also highlighted the impact of anti-seizure medications (ASMs) on cardio-respiratory function and the subsequent risk for SUDEP as an understudied research area. Research examining these factors in animal models will play an important role in optimising recommendations for treatment. Discussions focussed on the challenges of modelling human profiles, for example the use of ASMs, in animal models, stating that inferences drawn from these models to inform knowledge around mechanistic pathways that influence the risk of SUDEP in humans would be less clear.

An additional identified knowledge gap included the impact of co-morbidities (e.g. depression, diabetes) and associated treatments (e.g. selective serotonin reuptake inhibitors) on SUDEP risk. There is a clear need to better understand the variability in seizures that lead to SUDEP. Whilst generalised tonic-clonic seizures are known to increase risk for SUDEP [24]; whether the mechanisms that contribute towards SUDEP risk in generalised versus focal seizures are distinct or overlapping remains uncertain.

Discussions also emphasised the importance of identifying biomarkers for SUDEP to inform prevention approaches. For example, research examining spreading depolarisation in the brainstem as a possible risk factor for SUDEP is needed. Prioritising the development and testing of models that predict the likelihood of spreading depolarisation reaching the brainstem, as well as investigating whether this process can be redirected or prevented to decrease the risk of SUDEP, will likely be insightful. Early warning detection systems, for example wearable devices and breath tests, to predict seizure onset were also deemed important to consider further. Attendees also highlighted the need for research to evaluate the efficacy of alternative interventions, including vagus nerve stimulation, stimulation of the arousal system or continuous supplementation of oxygen, to prevent SUDEP. Lastly, there is a pressing need to understand why pregnant women are at elevated risk for SUDEP [10], and whether this is a consequence of changes in hormonal systems or differences in drug metabolisation that impact on risk.

Clinical Discussions

Clinical group-based discussions identified several knowledge gaps for SUDEP research. First, poor 'risk communication' was identified as a key clinical priority. Discussions highlighted the importance of delivering risk information in an accessible format. It was also thought that research is needed to better understand the factors that influence risk communication, for example who, when and how risk is communicated. Attendees recognised the need to understand better people's *perceptions* of risk to inform personalised risk conversations that are more targeted based on an individual's risk profile. Potential barriers to risk communication were also highlighted, including the recognition of language barriers, clinical judgement around when to communicate risk and appointment time constraints. It was acknowledged that risk discussions should be informed by the lived experience of people with epilepsy, to better define the level of risk that is considered acceptable. Additionally, discussions emphasised the importance of following up risk communication with a clear plan or intervention. Without this, it could lead to increased stigma and negative impacts on mental health, as well as leaving flagged risks unaddressed.

Second, discussions highlighted the need for optimal capture of standardised routine patient care data across primary, secondary and tertiary centres in the UK National Health Service (NHS). Consensus regarding a standard set of data to be collected is needed to ensure that data can be collated across settings to better inform research examining an individual's risk and mechanisms underpinning SUDEP. Additionally, attendees mentioned the need to provide coroners and medical examiners with education about SUDEP and associated risks to ensure accurate recording of SUDEP on death certificates. This will ensure that risk data can be appropriately used to better inform outcomes.

It was recognised that identifying specific groups at increased risk for SUDEP, for example younger people (especially young men), older people, people from minority groups, those from lower socioeconomic groups, pregnant women, people with increased cardiovascular risk, people with specific epilepsies (e.g. Dravet Syndrome) and people with an intellectual disability, is of critical importance. Issues such as under-recognition and/or undertreatment of epilepsy in older adults were noted. There is a need for research to investigate the

intersectionality of risk across specific groups and the impact of compounding risk on SUDEP across the lifespan.

Attendees agreed that the current UK NHS system requires improved infrastructure and better integrated care for people with epilepsy, as well as capitalising on the harmonisation of data across primary, secondary and tertiary settings to improve service delivery. For example, improved access to emergency, tertiary, maternity and mental health care settings and better integration of information shared across these systems are vital. In addition, access to ASMs and reserves are required to minimise the impact of failures in supply chains and avoid a deterioration of seizure control that could lead to increased hospital admissions or mortality. Discussions also raised the need for a cultural shift to recognise the impact that epilepsy has on people's lives and focus on destigmatisation. This could be driven by, for example, providing education about epilepsy in education and care settings.

It was acknowledged that there is a need for an epilepsy biobank(s) to capture and collate big data containing genetic, biological and clinical information on people affected by epilepsy and their family members to better understand risk for SUDEP. Attendees identified the need to utilise wearable technologies to improve the capture and use of data related to seizure prediction and detection. Such devices could play a fundamental role in alerting people at risk and allowing them vital time to seek support. Lastly, discussions shed light on the gaps in current knowledge around the direct and indirect financial costs of SUDEP over the course of a lifetime, both for bereaved families and wider society. Research exploring the costs associated with SUDEP will play an important role in providing evidence to support increased research investment in this area.

Recommendations

Despite significant progress in epilepsy and SUDEP research, there remains an urgent need to identify individuals at elevated risk of SUDEP and the factors that increase risk, to enable proactive measures that prevent avoidable epilepsy-related deaths. By focusing on those people directly affected by epilepsy, this workshop prioritised recommendations that are meaningful for the epilepsy community. The discussions helped illuminate important recommendations to address pre-clinical (see Table 1) and clinical (see Table 2) research and knowledge gaps (see Figure 1).

Table 1. Preclinical group-based workshop recommendations to address knowledge gaps

Recommendation	Method to help close research gap
Facilitate pre-clinical animal research	
Guidance to support animal license approval	• Develop guidance that supports SUDEP researchers conducting animal research in the UK to receive the relevant regulatory approvals. This will help to develop suitable animal models of SUDEP and identify the molecular mechanisms.
Cross-institution collaborations	• Minimise wastage and maximise the use of animal tissue across research studies by promoting collaborations across institutions. By forming cross-institution partnerships, tissue samples can be shared and re-used for all relevant research purposes.
Global collaborations	• Build international collaborations between researchers conducting animals research to ensure that resources, models and expertise are shared. This will accelerate the progress of SUDEP research.
Attract and retain early career researchers	• Create SUDEP research funding calls with the aim of 1) raising the profile of SUDEP research in the UK, and 2) attracting and retaining early career researchers in this field. • Provide these researchers with resources to support their wider professional development.
Shared learning across associated conditions	
Utilise expertise beyond epilepsy	• Connect with basic and clinical researchers across adjacent fields, such as cardio-respiratory and autonomic systems, to better understand the mechanisms underlying SUDEP.
Research using animal models in relevant conditions	• Utilise animal models with co-morbidities that increase the risk of SUDEP in humans (e.g. stroke or heart failure) to establish whether the mechanisms underpinning these distinct conditions overlap with SUDEP.
National epilepsy brain banks	• Support the development of infrastructures that support existing epilepsy brain banks. • Establish several national epilepsy brain banks to accelerate pre-clinical SUDEP research.

Notes. SUDEP = Sudden Unexpected Death in Epilepsy.

Table 2. Clinical group-based workshop recommendations to address knowledge gaps

Recommendation	Method to help close research gap
Standardised data capture	
Collection of standardised data	• Develop a patient record template for primary, secondary and tertiary care settings across the UK NHS to collect standardised patient data on epilepsy (e.g. seizure occurrence) to better predict risk of SUDEP.
Data linkage across healthcare systems	• Develop infrastructure that supports data linkage across integrated care systems in the UK NHS. This will inform the identification of high-risk groups and discussions about risk with patients.
Coding for SUDEP on death certificates	• Develop best-practice guidelines that enable national medical examiners and coroners to accurately record SUDEP on death certificates. The accurate coding of SUDEP deaths will enable researchers to access data that is vital for predicting and ameliorating future risk.
Optimise risk communication	
Factors that influence risk communication	• Conduct research that explores the factors impacting communication of SUDEP risk (e.g. how/who is communicating) to improve delivery, impact and outcomes.
Promote transmission of risk	• Optimise the transmission of risk communication between healthcare professionals and patients to ensure information is shared effectively.
Risk perception through lived experience	• Work with people living with and bereaved by epilepsy to co-produce research that explores people's *perceptions* of risk, which will inform decision-making processes and support offered.
Identification of high-risk groups	

Better understanding of risk	• Capitalise on large available datasets to conduct research that helps identify 1. Who is at risk? 2. Why are they at risk? 3. How can this risk be effectively communicated? 4. What can be done to reduce this risk?
Dynamic risk stratification	• Develop systems for tracking dynamic risk throughout an individual's life to identify and predict when they are at increased risk of SUDEP.
Identification of modifiable risk factors	• Undertake research aimed at identifying risk factors (e.g. medication adherence, seizure control, environmental factors, life stages (e.g. pregnancy), cardiovascular co-morbidities) that can be targeted by interventions to reduce SUDEP risk.
Epilepsy biobank	• Develop an epilepsy biobank that captures genetic, biological and clinical data from people with epilepsy and their families to accelerate SUDEP risk prediction.

Notes. SUDEP = Sudden Unexpected Death in Epilepsy. NHS = National Health Service.

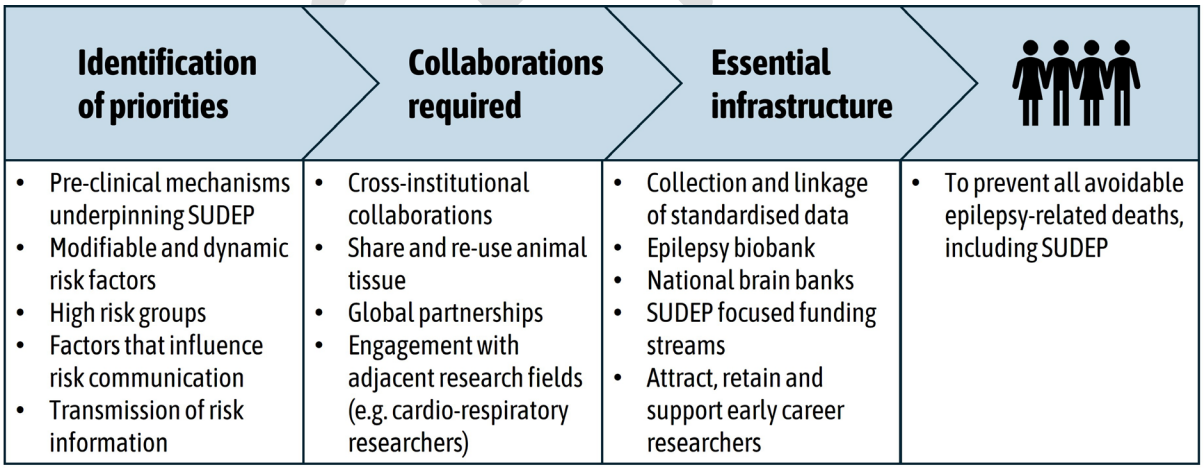

Figure 1. Intersection of pre-clinical and clinical recommendations. *Notes.* SUDEP = Sudden Unexpected Death in Epilepsy.

During the pre-clinical discussions, several key recommendations were prioritised. A clear need to facilitate and support pre-clinical SUDEP research was identified. This can be achieved through promoting international cross-institution collaborations that will maximise the use of data (e.g. tissue samples) and expertise from adjacent fields. A tangible goal is to develop guidance documents to support preclinical SUDEP researchers, particularly those new to the field, in navigating relevant regulatory approvals to conduct preclinical SUDEP research. There is also a global need to attract, retain and support early career researchers conducting SUDEP research to radically advance breakthroughs. To accomplish this, it will be important to leverage dedicated funding streams (e.g. research fellowships and project/programme grants) and provide professional development training opportunities where required.

Third, there is a pressing need for interdisciplinary research collaborations that utilise expertise across relevant fields (e.g. cardiovascular and respiratory) to advance our understanding of the common mechanisms underlying SUDEP. While there is a growing understanding of the fatal interplay between respiratory depression, autonomic dysfunction, and cardiac instability in SUDEP, there remains a lack of clarity on the precise mechanisms, individual risk factors, and effective interventions. Seizures that spread to the brainstem can disrupt autonomic and respiratory centres, contributing to the cascade of events leading to SUDEP. A more detailed understanding of this process requires a systematic collaboration between pre-clinical and clinical researchers including but not limited to neuroscientists, cardiologists, respiratory physiologists and neurologists. Additionally, geneticists, and molecular biologists can identify mutations that may predispose individuals to cardiorespiratory dysfunction, especially during periods of hypoxia and autonomic instability. Preventing SUDEP will require breaking down disciplinary and institutional silos, and fostering large-scale, cross-disciplinary collaborations to enable a more integrated, systems-level understanding of its underlying mechanisms. Alongside this, lobbying research councils to prioritise funding calls that require interdisciplinary research collaborations will play a fundamental role in driving research of this nature forward.

A final pre-clinical priority focused on the importance of establishing several national epilepsy brain banks and the infrastructures that support their sustainability to enable the collation and utilisation of tissue samples that will accelerate pre-clinical SUDEP research. To

implement this, it is critical to first understand the barriers that prevent the timely collection of brain tissue for research.

In addition, clinical discussions highlighted the value of collecting and linking standardised patient data on epilepsy across primary, secondary and tertiary UK NHS systems to support the identification and prediction of high-risk SUDEP groups. Similarly, global efforts to standardise the collection and harmonisation of patient data will be important for identifying risk predictors of SUDEP. There is also a need to develop best practice guidelines for national medical examiners and coroners to aid in the recognition and accurate recording of SUDEP on death certificates. Risk information across healthcare settings can then be used to identify groups at risk, with the aim of developing tailored prevention approaches. Furthermore, experts raised the need for future research examining the factors that influence risk communication and the transmission of risk information between healthcare professionals and patients to ensure that this process can be personalised (e.g. based on demographic factors, perception) and optimised. To inform this, it was acknowledged that research exploring people with epilepsies *perception* of risk is also of the upmost importance, as this information will influence when and how support is needed and offered.

More generally, discussions demonstrated the need for better identification and tracking of modifiable risk factors and how these change throughout the life course. To date, some risk factors for SUDEP are well characterised (e.g. generalised tonic-clonic seizures, medication non-adherence to ASMs [5-8]), but there is very large variation in SUDEP risk depending on individual circumstances and epilepsy characteristics [25]. A greater understanding of how risk fluctuates over time, for example tracking medication adherence rates, and the significance of time-limited social/lifestyle focused risk factors, will play an integral role in identifying when someone is at high risk and in need of targeted interventions. Lastly, the creation of an epilepsy biobank(s) that captures and collates in-depth big data from people with epilepsy and their families will play a fundamental role in disentangling mechanisms underpinning SUDEP [26] and should align with global standardised common data elements for data collection and reporting in epilepsy [27].

Table 3. Key priority areas for SUDEP research

Priority areas

1.	Pre-clinical research identifying mechanisms underpinning SUDEP is needed
2.	Infrastructure to support the collection and optimisation of epilepsy data is vital
3.	Better identification and communication of risk to those at highest risk is needed
4.	Engagement with wider stakeholders is critical for advancing research in this area
5.	Global research collaborations are essential to accelerate progress of SUDEP research

The SUDEP workshop highlighted key priority areas for research (see Table 3), including the examination of mechanisms underpinning SUDEP, modifiable risk factors (e.g. medication adherence) and factors that impact risk communication, especially during critical life stages. In line with this, personalised risk communication and personalised risk assessment for SUDEP will be important. Several recommendations for the development of infrastructure to support the collection, standardisation and optimisation of epilepsy patient data across several platforms, for example, healthcare systems, epilepsy brain banks and biobank(s) were proposed and could be fundamental in driving forward research efforts in this field. Engagement with the wider research community, as well as broader stakeholders, including people with epilepsy, charities, healthcare professional and government bodies, will be essential in the further development and implementation of these recommendations.

Workshop participants

The names and organisations of the workshop organising committee, speakers and attendees were (in alphabetical order): Sammy Ashby, SUDEP Action; Caoimhe Bennett, Epilepsy Research Institute; Amol Bhandare, University of Warwick; Kathryn Bush, Newcastle University; Beate Diehl, University College London; Ben Donovan, SUDEP Action; Martin Elliott, Gresham College; Hedley Emsley, Lancaster University; Thomas Jensen, University College London; Anthony Marson, University of Liverpool and The Walton Centre NHS Foundation Trust; Faye McLeod, Epilepsy Research Institute and Newcastle University; Marco Mula, St Georges NHS Trust; Hannah Pickard, Epilepsy Research Institute; Owen Pickrell, Swansea University; Laura Price, Epilepsy Research Institute; Rohini Rattihalli, Oxford University Hospitals; Arjune Sen, University of Oxford; David Sibree, SUDEP Action; Janine Winterbottom, The Walton Centre NHS Foundation Trust; and Rob Wykes, University College London and University of Manchester.

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