

National Association of Medical Examiners Position Paper:

Recommendations for the Investigation and Certification of Deaths in People with Epilepsy

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Why a Position Paper?

- Investigation and certification of deaths related to epilepsy varies within and between jurisdictions.
- Terms and criteria to diagnose and classify seizures, seizure disorders and epilepsy vary.
- There were no guidelines for investigation and certification of epilepsy-related deaths.

The incidence of death due to epilepsy is likely underestimated by death certificate data.

Panel Members

Pathologists/Medical Examiners

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Goals of Panel

- Improve investigation and surveillance of epilepsy-related deaths by establishing recommendations for the practice and interpretation of:
 - Death investigation
 - Autopsy and ancillary test performance
 - Certification
- Better inform public health burden of seizure and epilepsy-related death.

Seizures, Seizure Disorder, or Epilepsy?

- Seizures ≠ epilepsy.
- A **seizure** is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
- **Epilepsy** is a *disease* characterized by an enduring predisposition to generate *unprovoked* seizures.
 - The term can be used whether or not an underlying etiology is known
 - Epilepsy may be due to a genetic, developmental, acquired (e.g. trauma, tumor, infarct), or unknown cause.

A person is considered to have epilepsy if they meet any of the following conditions.

- **Two or more unprovoked seizures** occurring greater than 24 hours apart, or
- One unprovoked seizure and a probability of further seizures occurring over the next 10 years, or
- **Diagnosis of an epilepsy syndrome** (e.g. West Syndrome/Infantile spasms, Dravet Syndrome, Juvenile Myoclonic Epilepsy, Lennox-Gastaut Syndrome etc.)

See definition by International League Against Epilepsy (ILAE), published in:
Fisher RS et al. A practical clinical definition of epilepsy. *Epilepsia* 2014; 55:475-482.

What is an “unprovoked” seizure?

Provoked seizure are caused by an acute, transient process

- drug/alcohol withdrawal or intoxication
- transient metabolic derangements (e.g. hypoglycemia, hyponatremia), or
- high fever

Unprovoked seizures are caused by

- genetic or developmental disorders
- chronic acquired conditions (e.g. trauma, tumor, infarct), or
- unknown causes

Risk Factors for Sudden Death due to Epilepsy

- Generalized Convulsive Seizures>Complex Partial Seizures
- Uncontrolled seizures
- Escalating seizure frequency
- Anti-epileptic drug non-compliance or recent need to increase AEDs
- Presence of structural brain lesions, intellectual disability, alcohol abuse, and anxiolytic use

Table 1: Questions Formulated by the Panel to Address Seizure- and Epilepsy-Related Deaths

Number	Question
1	Within the bounds of state law, which deaths require assumption of jurisdiction and performance of an autopsy?
2	What constitutes appropriate and necessary scene investigation, epilepsy screening, and follow-up?
3	When is it appropriate or necessary to perform toxicology and/or antiepileptic seizure medication testing?
4	What are the best samples to collect for laboratory testing and histologic analysis?
5	How are scene findings, autopsy findings, toxicology, and histology interpreted?
6	How are competing causes of sudden death assessed?
7	What are the optimal methods for determining and certifying cause of death, manner of death, and how injury occurred?

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When is it appropriate or necessary to perform toxicology and/or anti-epileptic seizure medication testing?

- When a specific anatomic cause of death is not identified at autopsy
- Toxicology testing should include quantification of anti-epileptic drugs

What are the *best* samples to collect for laboratory testing and histologic analysis?

- Blood, tissue, and other fluid samples should be retained as per the jurisdiction's usual protocol for routine toxicology testing.
- EDTA (purple top) tube of blood is **preferred**
- Blood spot card or frozen tissue (1 cubic centimeter of liver, spleen, or heart at -80°C) can also be used

What are the *best* samples to collect for laboratory testing and histologic analysis?

- **Brain examination after formalin fixation is recommended when possible.**
 - Examination by a neuropathologist is preferred but at the discretion of the autopsy pathologist.
 - Recommended CNS histology, even in grossly normal brain:
 - Both hippocampi, Both amygdala, Watershed cortex, Basal ganglia, Hypothalamus, Midbrain, Pons, Medulla (Reichard and Vaubel, 2014)
- **Heart** – examined at autopsy/histology recommended
 - Left ventricle x 3 and right ventricle x 1 (Royal College of Pathologists)
- **Lung** – histology recommended

How are scene findings, autopsy findings, toxicology and histology interpreted?

The following topics are reviewed in position paper:

- Livor pattern/Body position
- Tongue, Lip or Inner Cheek Trauma (supportive but not diagnostic)
- Incontinence of Urine
- Gastric Contents in Airway
- Pulmonary Edema
- Bronchopneumonia
- Neuropathologic Findings
- Alcohol and Drugs of Abuse
- Antiepileptic Drugs

How are competing causes of sudden death assessed?

• Comorbid Coronary Artery Disease

- Factors that support cardiac disease rather than epilepsy as the cause of death
 - Severe coronary stenosis,
 - Coronary thrombus,
 - Acute myocardial infarction in territories served by stenotic arteries, and/or
 - Cardiomegaly / large ventricular chambers
- When circumstances or findings suggest seizure (e.g., witnessed sz or tongue bite) but acute cardiac changes are present:
 - the elevated stress and sympathetic response to the seizure may have triggered the cardiac event
 - Can consider possibility of epilepsy as cause and acute cardiac even as mechanism.

How are competing causes of sudden death assessed?

• Comorbid Primary Cardiac Electric Disease

- Factors that support arrhythmogenic disorder rather than epilepsy as the cause of death
 - Personal or family history of arrhythmogenic disorder
 - Report of seizure activity following peak exercise
 - Ventricular tachycardia or fibrillation documented by EMS favors cardiac etiology

What are the optimal methods for determining and recording (certifying) cause of death, manner of death, and how injury occurred (including wording on the death certificate)?

- Sudden death in person diagnosed with epilepsy and no other cause identified, **any of the following** can be used for COD, but sudden nature should be emphasized:
 - “Sudden death due to epilepsy”
 - “Sudden unexpected death in epilepsy” (SUDEP)
 - “Epilepsy”
- “Seizure disorder” may be substituted for “epilepsy” when clinical diagnosis is not provided or history is inconsistent.

Cause of Death Certification continued.

- When there is a known underlying etiology for the epilepsy, it should be indicated:
 - Sudden death due to epilepsy due to blunt trauma of head
 - Sudden death due to epilepsy due to cerebral infarct due to cerebrovascular disease.
- Cardiac or pulmonary disease considered insufficient to cause death may be included in contributory causes (Part II).

Cause of Death Certification continued.

In unwitnessed, apparently ‘sudden’ death with competing causes that may be mechanistically related, inclusion of both possibilities is recommended. Possible wordings may be:

- Person with epilepsy dead in bed with 90% atherosclerotic stenosis of coronary artery:
 - Part I: Atherosclerotic Coronary Artery Disease
 - Part II: Epilepsy
- Person with epilepsy and alcohol intoxication
 - Part I: Sudden death due to epilepsy
 - Part II: Alcohol intoxication
 - (or vice versa depending on alcohol concentration)

Manner of Death Certification.

- **Person with epilepsy submerged in bathtub:**
 - Part I: Drowning, Part II: Epilepsy
 - MOD: Accident
- **Person with epilepsy due to prior brain injury:**
 - Part I: Sudden death due to epilepsy due to blunt trauma of head
 - MOD: Accident, Homicide or Suicide depending on circumstances of head trauma

Table 3. Case Vignettes with Recommended Death Certificate Wording

History	Cause of Death (Part I)	Other Significant Conditions (Part II)	How Injury Occurred	Manner
Decedent with epilepsy found dead in bed; no other cause of death discovered	Sudden death due to epilepsy		N/A	N
Decedent with epilepsy found dead in bed; competing cause of death such as severe coronary artery disease discovered	Atherosclerotic coronary artery disease	Epilepsy	N/A	N
Decedent with epilepsy found dead in bed; contributing factor such as moderate coronary artery disease discovered	Sudden death due to epilepsy	Atherosclerotic coronary artery disease	N/A	N
Decedent with epilepsy found dead in bed; ethanol concentration reported as 0.41 g/dL	Acute ethanol intoxication	Epilepsy	Decedent with epilepsy ingested an excess of ethanol	A
Decedent with epilepsy due to blunt head trauma occurring from an accidental fall 10 years prior	Epilepsy due to blunt head trauma due to fall		Decedent with epilepsy found dead; suffered head injury in fall 10 years prior	A
Decedent with epilepsy due to blunt head trauma occurring from an assault 10 years prior	Epilepsy due to blunt head trauma due to assault		Decedent with epilepsy found dead; suffered head injury in assault 10 years prior	H
Decedent with epilepsy found dead; submerged in bathtub; no other cause of death discovered	Drowning	Epilepsy	Decedent with epilepsy found submerged in bathtub	A
Driver with epilepsy had witnessed seizure in motor vehicle accident; examination revealed no competing cause of death	Sudden death due to epilepsy		N/A	N

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Vendor table at this NAME meeting
