Appendix A. Search Strategies

We employed different searches for different sections of the report, including different searches for different questions. The strategies for these different searches, given in PubMed/Medline syntax, are provided below.

Searches for general information on treatment-resistant epilepsy

S1 epilepsy OR “convulsive disorder” OR “convulsive disorders” OR “seizure disorder” OR “seizure disorders”
S2 (seizure*[ti] OR epilepsy[ti] OR epileptic[ti]) AND (premedline[sb] OR publisher[sb])
S3 #1 OR #2
S4 #3 AND english[la] AND (human[mh] OR premedline[sb] OR publisher[sb])
S5 #4 AND (intract* OR “treatment-resistant” OR “treatment resistant” OR “drug-resistant” OR “drug resistant” OR “therapy-resistant” OR “therapy resistant” OR uncontrol* OR persistent OR refractory OR fail* OR continu* OR repeated* OR multiple OR “pseudo-intractability”)

Searches for Question #1 (What are the definitions of treatment-resistant epilepsy in the literature?)

S1 epilepsy AND (intract* OR “treatment-resistant” OR “treatment resistant” OR “drug-resistant” OR “drug resistant” OR “therapy-resistant” OR “therapy resistant” OR uncontrol* OR persistent OR refractory OR fail* OR continu* OR repeated* OR multiple OR “pseudo-intractability”)
S2 #1 AND review[pt] AND english[la] AND (human[mh] OR premedline[sb] OR publisher[sb]) AND 1985:2001[dp]
S3 #2 NOT (letter[pt] OR editorial[pt] OR news[pt] OR comment[pt] OR case report[mh])

Searches for Question #2 (Which methods of rediagnosing or re-evaluating treatment-resistant epilepsy lead to, or can be expected to lead to improved patient outcomes?)

To answer this question, we searched for information on diagnosis and misdiagnosis, and we separately present the search strategies below.

Searches on Diagnosis:

S1 epilepsy/di[mh] OR seizures/di[mh] OR convulsions/di[mh]
S2 (epilepsy OR seizure* OR convulsion OR fit OR fits) AND (diagnosis OR diagnose* OR diagnostic OR identif* OR classif* OR detect*) AND (premedline[sb] OR publisher[sb])
S3 (#1 OR #2) AND english[la] AND 1985:2001[dp]
S4 #3 AND (“gold standard” OR “ROC” OR “receiver operating characteristic” OR sensitivity OR specificity OR sensitivity and specificity[mh] OR likelihood OR “false positive” OR “false negative” OR “true positive” OR “true negative” OR “predictive value” OR accuracy OR precision)

S5 #3 AND (clinical trials[mh] OR clinical trial[pt] OR controls[ab] OR randomized controlled trials[mh] OR random allocation[mh] OR randomized controlled trial[pt] OR double-blind method[mh] OR single-blind method[mh] OR "single blind" OR "double blind" OR "single-dummy" OR "double-dummy" OR sham OR controlled clinical trials[mh] OR controlled clinical trial [pt] OR multicenter study[pt] OR meta-analysis OR meta-analysis[pt] OR placebo* OR outcomes research[mh] OR prospective studies[mh])

S6 #4 OR #5

S7 #3 AND ("EEG" OR "VEEG" OR electroencephalogra* OR ct[tiab] OR tomography, x-ray computed[mh] OR "cat scan"[tiab] OR "SPECT" OR magnetic resonance imaging OR "MRI" OR "MR" OR tomography, emission-computed[mh] OR "PET"[tiab] OR "positron emission tomography")

S8 #7 AND (intract* OR "treatment-resistant" OR "treatment resistant" OR "drug-resistant" OR "drug resistant" OR "therapy-resistant" OR "therapy resistant" OR uncontrol* OR persistent OR refractory OR fail* OR continu* OR repeated* OR multiple OR "pseudo-intractability")

S9 #1 AND (enzymes/blood[mh] OR hormones/blood[mh]) AND 1980:2001[dp] AND english[la] AND human[mh]

S10 epilep* AND (prolactin OR creatine kinase OR enolase) AND english[la] AND (premedline[sb] OR publisher[sb])

S11 #6 OR #8 OR #9 OR #10

S12 #11 NOT (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR case report[mh])

Searches on Misdiagnosis:

S1 epilepsy AND (reevaluat* OR "re-evaluate" OR "re-evaluation" OR "re-evalauted" OR "re-evaluating" OR reassess* OR "re-assess" OR "re-assessment" OR "re-assessed" OR "re-assessing" OR rediagnos* OR "re-diagnosis" OR "re-diagnose" OR "re-diagnosed" OR "re-diagnosing" OR misdiagnos* OR diagnostic errors[mh])

S2 epilepsy AND (syncope OR asystole OR bradyarrthymia OR anoxic OR cardiogenic OR neurocardiogenic OR psychogenic OR hypoxia OR syncopal)

S3 epilepsy AND (error* OR mistake*)

S4 #1 OR #2 OR #3

S5 #4 AND (di[sh] OR diagnosis[mh] OR du[sh])

S6 #5 AND epilepsy[majr]

S7 #4 AND (premedline[sb] OR publisher[sb])

S8 (#6 OR #7) AND english[la] AND 1985:2001[dp]

S9 #8 NOT (letter[pt] OR editorial[pt] OR news[pt] OR comment[pt] OR case report[mh])

Searches for Questions #3 (Which drug treatment strategy, (A) sequential monotherapy, (B) polytherapy, or (C) optimized current therapy leads to improved outcomes for patients with treatment-resistant epilepsy, and (D) What are the relative improvements obtained with each strategy?)

These searches included searches for "overall" information, searches on the natural history of epilepsy, and searches for articles on seizure frequency patterns. Below, we separately present information on each of these searches.

Searches for "overall" information:

S1 epilepsy OR "convulsive disorder" OR "convulsive disorders" OR "seizure disorder" OR "seizure disorders"

S2 (seizure*[ti] OR epilepsy[ti] OR epileptic[ti]) AND (premedline[sb] OR publisher[sb])

S3 (#1 OR #2) AND 1975:2001[dp] AND english[la]

S4 #3 AND drug therapy[sh] AND ("add-on" OR "sequential monotherapy" OR adjunct* OR drug therapy, combination[mh] OR "consecutive monotherapy" OR polytherapy)

S5 #3 AND (anticonvulsants OR acetozolamide OR "apo-acetaxolamide" OR diamox OR "adrenocorticotropic hormone" OR "ACTH" OR corticotropin OR cortitrophin OR allopurinol OR zyloprim OR antiepilepsirine OR "BR 16A" OR mentat OR carbamazepine OR tegretol OR "apo-carbamazepine" OR epitol or mazepine or novocarbamaz or sinemet or carnitine or carnitor or levocarnitine or frisium or clonazepam or klonopin or clonopam or rivotril or clorazepate or tranxene or clozapine or clorzaril OR dexamethasone or cortastat or dalalone or decadrol or decadron or decaject or dexacorten or dexasone or dexone or hexadrol or mymethasone or primethasone or solurex or dextromethorphan or benylin or "crough x" or "creo-terpin" OR "delsym cough" or "diabe TUSS dm" or "hold dm" or "pertussin dm" OR robitussin or sucrets or trocal or "Vicks 44" or diazepam or valium or dichlorphenamide or diclofenamide or daranide or ethosuximide or zarontin or felbamate or felbatol or fenfluramine or flumazenil or romazicon or funarizine OR cinnarizine or sibelium or fosphenytoin or cerebyx or gabapentin or neurontin or imipramine or tofranil or lamotrigine or lamictal or keppra or lorazepam or ativan or methsuximide or celontin OR nifedipine or adalat or procradia or nimodipine or nimotop or oxcarbazepine or trileptal or Phenobarbital or luminal or phenytoin or dilantin or piracetam or primidone or remacemide or ecovia OR "Thyrotropin releasing hormone" or trh or tiagabine or topiramate or trimethadione or tridione or tmo or trimethinum or troxidone or "valproic acid" or depakene or depakote or epival or zonisamide or zonegran)

S6 #5 AND (intract* OR "treatment-resistant" OR "treatment resistant" OR "drug-resistant" OR "drug resistant" OR "therapy-resistant" OR "therapy resistant" OR uncontrol* OR persistent OR refractory OR fail* OR continu* OR repeated* OR multiple OR "pseudo-intractability")

S7 #5 AND (blood[sh] OR optimiz* OR dosage OR dose* OR dosing OR titrat* OR "maximum tolerable" OR "blood level monitoring" OR "drug tolerance")

S8 #4 OR #5

S9 #8 AND ("polytherapy reduction" OR withdrawal OR remove OR removal)

S10 #4 OR #6 OR #7 OR #9

S11 #10 AND (clinical trials[mh] OR clinical trial[pt] OR controls[ab] OR randomized controlled trials[mh] OR random allocation[mh] OR randomized controlled trial[pt] OR double-blind method[mh] OR single-blind method[mh] OR "single blind" OR "double blind" OR "single-dummy" OR "double-dummy" OR sham OR controlled clinical trials[mh] OR controlled clinical trial[pt] OR multicenter study[pt] OR meta-analysis OR meta-analysis[pt] OR placebo* OR outcomes research[mh] OR prospective studies[mh] OR evidence-based medicine[mh])

S12 #11 NOT (letter[pt] OR editorial[pt] OR news[pt] OR comment[pt] OR case report[mh])

Searches on the natural history of epilepsy:

S1 epilepsy[majr] OR epilep*[ti]

S2 #1 AND ("natural history" OR developing countries[mh] OR untreated[tw] OR "natural progression" OR "clinical progression" OR "disease progression" OR "neurological course" OR "clinical course" OR time factors[mh] OR remission
OR remission, spontaneous[mh] OR transient[ti])

S3 #2 AND english[la] AND 1985:2001[dp] AND (human[mh] OR premedline[sb] OR publisher[sb])

S4 #3 NOT (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR case report[mh])

Searches on seizure frequency patterns:

S1 seizure* AND (frequency OR occurrence) AND (increase* OR decrease* OR chang* OR variation*)

S2 #1 AND (regression* OR sn[sh] OR statistic*)

S3 #1 AND "seizure frequency"[ti]

S4 "seizure frequency scoring system"

S5 #1 AND (circadian OR pattern* OR season*)

S6 #2 OR #3 OR #4 OR #5

Searches for Question #5 (Which methods of nondrug treatment for epilepsy after initial treatment failure lead to improved outcomes for patients with treatment-resistant epilepsy?)

S1 epilepsy[mh] AND human[mh]

S2 (epilep* OR seizure[ti]) AND (premedline[sb] OR publisher[sb])

S3 #1 OR #2

S4 #3 AND (alternative medicine[mh] OR acupuncture OR anthroposophy OR aromatherapy OR biofeedback OR chiropract* OR "color therapy" OR eclecticism OR homeopath* OR imagery OR kinesiology OR massage OR acupressure OR (medicine AND traditional) OR herbal OR "mental healing" OR "mind-body relations" OR metaphysics OR moxibustion OR naturopath* OR organother* OR radiesthesia OR reflexother* OR rejuvenation OR relaxation OR meditation OR "therapeutic touch")

S5 #3 AND ((vagal OR vagus nerve[mh] OR thalamic OR subcortical OR "deep brain") AND (electric stimulation[mh] OR electric stimulation therapy[mh] OR (electric* AND stimulation))

S6 #3 AND (diet therapy[sh] OR ketogenic OR vitamins/tu[mh] OR vitamin*)

S7 #3 AND (hyperbaric oxygenation[mh] OR hyperbaric OR "HBO" OR "cranial realignment" OR "magnetic therapy")

S8 #3 AND (surgery OR surgical OR surgery[sh] OR resect* OR hemispherectomy OR hemispherotomy OR “temporal lobe resection” OR “temporal lobectomy” OR “neocortical resection” OR “corpus callosotomy” OR “MST” OR “multiple subfield transections”)
S9 #4 OR #5 OR #6 OR #7 OR #8
S10 #9 AND 1985:2001[dp] AND english[la]
S11 #10 NOT (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR case report[mh])

Searches for Questions #6 (Which services for treatment-resistant epilepsy lead to, or can be expected to lead to improved patient outcomes?) and Question #7 (What characteristics of treatment-resistant epilepsy interfere with ability to obtain and maintain employment, or attend and perform well in school?)

S1 epilepsy
S2 #1 AND (psychology[sh] OR psychotherapy OR psychotherapeutic OR counseling OR cognitive therapy OR behavior therapy OR behavior modification OR group therapy OR family therapy OR psychoanaly* OR hypnosis OR “self-help” OR art therapy OR music therapy OR movement therapy)
S3 #1 AND (rehabilitation[sh] OR rehabilit* OR hospice OR home care OR educational counseling OR vocational counseling OR occupational therapy OR physical therapy OR speech language therapy OR community health services OR “nurse specialist service” OR self care)
S4 #1 AND (education OR patient education OR (nurs* AND special))
S5 #1 AND (psychosocial OR neuropsychosocial OR social skill* OR social adapt* OR social work OR coping skill* OR stress management)
S6 #1 AND (neuropsychological tests[mh] OR (neuropsychological AND (test* OR assess* OR evaluat*)))
S7 #1 AND (education OR remedial education OR special education OR ability grouping OR (academic AND (achievement OR aptitude)) OR educational placement OR mainstream* OR ((school OR classroom) AND (adjustment OR attendance OR dropout* OR readiness OR transition)) OR (student AND (attitudes OR characteristics)) OR study habits OR teacher student interaction)
S8 #1 AND (occupations OR (occupational AND (adjustment OR aspirations OR attitudes OR choice OR guidance OR interests OR mobility OR preference OR safety OR status OR stress OR success)))
S9 #1 AND (employment status OR unemployment OR employability OR employment history OR reemployment OR employ* OR unemploy* OR “quality of work life” OR “work adjustment training” OR work schedule tolerance[mh] OR job*)
S10 #1 AND (cognition OR (cognitive AND (ability OR assessment OR processes OR development OR rehabilitation))
S11 #1 AND (intelligence OR IQ)
S12 #1 AND (Quality of life[mh] OR QOL OR “life satisfaction” OR activities of daily living[mh] OR “activities of daily living” OR “ADL” OR “HRQOL” OR “HQOL”)
S13 #1 AND (driving OR drive OR accidents[mh])
S14 #1 AND (disable* OR disabil* OR handicap* OR psychomotor performance[mh] OR task performance and analysis[mh] OR “functional status” OR “functional ability”)

S15 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
S16 #15 AND english[la] AND 1985:2001[dp]
S17 #16 NOT (letter[pt] OR news[pt] OR comment[pt] OR editorial[pt] OR case report[mh])

Searches for Questions #8 (What is the mortality rate of patients with treatment-resistant epilepsy?) and Question #9 (Is there a correlation between the number and/or type of seizure and sudden death?):

S1 epilepsy/epidemiology[majr]
S2 epilepsy/mortality[majr]
S3 (epilepsy OR “convulsive disorder” OR “convulsive disorders” OR “seizure disorder” OR “seizure disorders”) AND (epidemiology OR mortality OR “sudden death” OR sudden death[mh] OR “SUDEP”) AND (premedline[sb] OR publisher[sb])
S4 epilepsy[majr] AND (sudden death[mh] OR “sudden death” OR “SUDEP”)
S5 epilepsy AND accidents[mh] AND human[mh]
S6 #1 OR #2 OR #3 OR #4 OR #5
S7 #6 AND 1985:2001[dp]
S8 #7 NOT (letter[pt] OR editorial[pt] OR news[pt] OR comment[pt] OR case report[mh])

Appendix B. Internal Validity

Question 2

Which methods of rediagnosing or re-evaluating treatment-resistant epilepsy lead to, or can be expected to lead to improved patient outcomes?

Internal Validity for Question 2A

Do all patients diagnosed with epilepsy that is deemed to be treatment-resistant truly have epilepsy?

The five studies addressing Questions 2A and the potential biases in each are list in Table 49. The following is a more detailed description of the biases found in each of theses studies.

Sampling bias. The patients in all five studies were consecutively enrolled during a fixed period. Consecutive enrollment reduces bias because it increases the likelihood that these patients are representative of the population of interest (the population defined by the inclusion/exclusion criteria of each study) and decreases the likelihood that they were selected from the population of interest because they were more or less likely to have been misdiagnosed.

Reference standard bias. Presently, no "gold-standard" for diagnosing epilepsy is available for routine use in clinical practice. Implanted electrodes may be considered a true "gold standard" but they cannot be routinely used in practice. Therefore, having perfect confidence in the results of any diagnostic reassessment is not possible.

All of the studies included in the present evidence base relied on continuous EEG monitoring (Evidence Table 6), usually in conjunction with video recording (video-EEG), in their diagnostic reassessment. The diagnosis of epileptic seizure was confirmed if patients experienced a typical seizure with the appearance of a true epileptic seizure (defined by some accepted criteria such as those proposed by the International League Against Epilepsy),[5,14] and if this seizure was simultaneously accompanied by abnormal EEG activity. A seizure was deemed nonepileptic if a patient experienced a typical seizure, but was not simultaneously accompanied by abnormal EEG activity. The accuracy of such diagnostic criteria relies on the supposition that an abnormal EEG always accompanies a true epileptic seizure. While this may be true for many seizures, this does not always hold, particularly when the EEG is performed using scalp electrodes. Seizures resembling tonic-clonic convulsions, absence seizures, or complex partial seizures with automatism that are unaccompanied by an ictal EEG abnormality can confidently be classified as nonepileptic.

In the absence of a true, practical, "gold-standard," confidence in the diagnosis made at reassessment can be increased if patients are followed and the results of the reassessment are shown to lead to improvements in patient outcome (e.g. decreased seizure frequency from baseline levels). Of the five studies included in the present evidence base, three reported on patient followup after the diagnostic re-assessment. However, none of these studies followed all of the patients in the study. In two studies, only those patients found to have nonepileptic seizures upon reassessment were followed and, in the remaining study, only those whose diagnosis of epileptic seizures was confirmed were followed.

Table 49. Potential biases for Question 2A

Reference	Potential Biases		
	Sampling Bias	Reference Standard Bias	Diagnostic Yield Bias
Studies performed in the United States			
Holmes (1998)[39]	No	Yes	Yes
Henry (1998)[37]	No	Yes	No
Arnold (1996)[40]	No	Yes	Yes
Slater (1995)[41]	No	Yes	No
Studies performed outside of the United States			
Zaidi (2000)[38]	No	Yes	No

Internal Validity for Question 2B

Which diagnostic modalities are useful in differentiating seizure types commonly mistaken for epilepsy from true epileptic seizures

The five studies addressing Questions 2B and the potential biases in each are listed in Table 50. The following is a more detailed description of the biases found in each of theses studies.

Imperfect reference standard bias. As discussed earlier, no true "gold standard" for diagnosing epileptic seizures is available for routine use in clinical practice. Consequently, the effectiveness of a diagnostic for epilepsy is usually measured against some less than perfect "reference" standard. A number of difficulties associated with the use of imperfect "reference" standards have been discussed in the literature, all of which may lead to biased estimates of test performance.[382-384]

In the literature considered here, the "reference" standard was usually the clinical opinion of one or more specialists who categorized patients into distinct diagnostic groups based on information from different sources. These sources included medical history, routine EEG (rEEG), ambulatory EEG (aEEG), or video-EEG, imaging data, psychological evaluations, cardiac monitoring data, etc. The exact reference standards and the criteria used to categorize the patients in four of the five included studies are provided in Evidence Table 15. The remaining two articles did not present any details of the reference standard that was used to categorize the included patients. Given that no practical, perfect reference standard exists, the fact that this information was not reported by these two studies may not be a major concern.

Differential reference standard bias. As mentioned above, two of the five included studies did not present details of the reference standard(s) used to categorize the patients included in the studies. This becomes a concern when looking for evidence of differential reference standard bias. Whether patients were allocated to the epileptic seizure or nonepileptic groups using the same or different reference standards cannot be known in these studies. Only one of the remaining three studies appears to have allocated patients into epileptic seizure or nonepileptic seizure groups using the same reference standard. Although all patients in the remaining three studies were allocated to a diagnostic category based on clinical opinion, this opinion was derived from the results of tests that were specific for each diagnostic category. Furthermore, the criteria used within a study to categorize patients differed greatly between studies, even for the same diagnosis.

Prevalence bias. This bias is common in diagnostic case-control studies, and affects the validity of positive and negative predictive values (PPV and NPV, respectively). In a typical case-control study, the numbers of cases (epileptic seizures) and controls (nonepileptic seizures) are artificially chosen to be equal (the prevalence of patients with nonepileptic seizures in the five studies included in the present evidence base ranged from 25.9 percent to 45.5 percent). This artificial prevalence introduces a bias that influences the PPV and NPV in a manner described by Bayes' theorem.[29]

If the true underlying prevalence of nonepileptic seizures in the population of interest is known (in this case patients deemed to have treatment-resistant epilepsy), adjustments to the PPV and NPV are possible to compensate for the effects of this bias. However, as per our analysis of prevalence data for Question 2A, only the nonepileptic seizure prevalence for a very specific patient subpopulation could be estimated, those with a diagnosis of treatment-resistant epilepsy referred to a specialist clinic for further diagnostic evaluation (estimated prevalence of

NES less than 35 percent, CI: 29 percent to 41 percent). The prevalence of patients with nonepileptic seizures among the general population of patients with a diagnosis of treatment-resistant epilepsy remains unknown.

Spectrum bias. Four of the five included studies, all of which were case-controlled, are clearly affected by this bias. In these studies, patients were selected from among patients who presented at the study centers for evaluation of seizures. These patients were selected because they suffered unequivocally from either epileptic or nonepileptic seizures. In other words, the patients included in these studies were those patients that were the most easily diagnosed. For example, although Anzola[45] considered all patients who were consecutively admitted for inclusion, only those patients who suffered unequivocally from epileptic seizures or unequivocally from noncardiac syncope attacks were actually enrolled. Thus, the patients of most clinical interest for this question, those in whom a misdiagnosis is most likely to be made, were not considered in these four studies.

Whether spectrum bias affects the fifth study in the evidence base is less clear. Wroe, Henry, John, et al.[50] reported that the patients enrolled in their study were "not specifically selected for this study." However, because the authors did not report any more details on the sampling methodology, this study may not have been protected from spectrum bias.

Interpretation bias. Blood prolactin levels are influenced by a number of conditions unrelated to epileptic seizures. Certain conditions, principally pituitary diseases, hypothyroidism, renal failure, and severe liver disease, contribute to elevated levels of blood prolactin levels, and the effects of diseases on the temporal blood prolactin level profile following a seizure is not known. None of the included studies reported comorbidities or specifically stated that they excluded patients because of the previously mentioned comorbidities. Therefore, these conditions could potentially have affected the blood prolactin levels in any of the relevant studies and, if so, whether these patients were evenly distributed between the diagnostic groups is not known. Consequently, this bias cannot be ruled out in any of the studies

Patient bias. None of the patients enrolled in any of the five included studies were blinded to the diagnostic category to which they were allocated. Nor were the patients blinded to the results of the blood prolactin level measurements. Because neither the allocation of patients to diagnostic categories nor the measurement of blood prolactin levels involved patient input, this potential bias is unlikely to have weakened the internal validity of any of the studies.

Investigator bias. This bias is unlikely to have weakened the internal validity of any of the studies included in the present evidence base. Although only one of the five included articles used blinded investigators, the remainder of the studies allocated patients to a diagnostic category group prior to the onset of the study and blood prolactin levels were measured objectively using commercial radioimmunoassay methods.

Diagnostic yield bias. Because all of the patients in all of the included studies experienced a typical seizure just prior to measurement of blood prolactin levels, the diagnostic yield of all of the studies was 100 percent. Therefore, this potential bias did not affect any of the studies we evaluated.

Verification bias. This bias is only relevant to studies that used followup to confirm the accuracy of the diagnostic of interest and occurs when only one group of patients is followed. This group typically consists of only those with a positive diagnosis. For example, only those diagnosed by the test of interest might be followed up. Since none of the studies in the present evidence base followed their patients after diagnoses, this bias clearly had no effect on the present evidence base.

Table 50. Internal validity of blood prolactin studies (Question 2B)

Reference	Potential bias								
	Imperfect Reference Standard Bias	Differential Reference Standard Bias	Prevelance Bias	Spectrum Bias	Interpretation Bias	Experimenter Bias	Patient Bias	Diagnostic Yield Bias	Verification Bias
Lusic (1999)[53]	Yes	?	Yes	Yes	?	No	No	No	No
Anzola (1993)[45]	Yes	Yes	Yes	Yes	?	Yes	No	No	No
Zelnik (1991)[56]	Yes	Yes	Yes	Yes	?	No	No	No	No
Mishra (1990)[57]	Yes	?	Yes	Yes	?	No	No	No	No
Wroe (1989)[50]	Yes	No	No	?	?	No	No	No	No

Question 4

Which drug treatment strategy, 1) sequential monotherapy, 2) polytherapy, or 3) optimized current therapy leads to improved outcomes for patients with treatment-resistant epilepsy, and what are the relative improvements obtained with each strategy?

Internal Validity for Sequential Monotherapy

The 13 studies addressing sequential monotherapy and the potential biases in each are listed in Table 51. The following is a more detailed description of the biases found in each of theses studies. In evaluating internal validity, we determined whether the results were potentially biased by the factors discussed in the Methodology section and appearing in the column headers of Table 51. Other questions in this report consider the potential for attrition bias, but for sequential monotherapy, we did not consider it because attrition was a study outcome.

Sampling bias. None of the trials was potentially affected by sampling bias because all enrolled patients were reported.

Sample specification bias. Only one of the trials reported that patients had received the maximum tolerable dose of prior AEDs. Thus, the remaining 12 trials were susceptible to sample specification bias.

Selection bias. For the purpose of this question, all of the included studies were considered uncontrolled case series (only data from treated groups was analyzed). Thus, selection bias is not applicable to the studies of sequential monotherapy.

Regression bias. All of the trials were potentially affected by regression bias because improvements could have been due to regression-to-the-mean.

Investigator bias and patient bias. Twelve trials were double-blinded. Consequently, neither investigator bias nor patient bias was likely to have affected these trials. However, the remaining trial was not blinded, thus it may have been affected by both of these biases.

Measurement bias. Ten trials reported that patients used seizure diaries to record seizures, thus these trials were potentially affected by measurement bias. In one trial, patients were monitored continuously via EEG, and thus this trial had no measurement bias. In the remaining two trials, the specific method of measurement was not reported.

Extraneous event bias. All of the trials were potentially affected by extraneous event bias.

In summary, the trials of sequential monotherapy were potentially affected by many threats to internal validity. All were potentially affected by both regression bias and extraneous event bias. Most trials were potentially affected by sample specification bias (12 of 13) and measurement bias (10 of 11). Only one trial was potentially affected by either investigator or patient bias, and no trials were affected by sampling bias.

Table 51. Internal validity of trials of sequential monotherapy

Reference	Potential Biases							
	Sampling Bias	Sample Specification	Selection Bias	Regression Bias	Investigator Bias	Patient Bias	Measurement Bias	Extraneous Event Bias
Sachdeo (2001)[68]	No	Yes	NA	Yes	No	No	Yes	Yes
Beydoun (2000)[86]	No	Yes	NA	Yes	No	No	Yes	Yes
Kanner (2000)[87]	No	No	NA	Yes	Yes	Yes	Yes	Yes
Schachter (1999)[79]	No	Yes	NA	Yes	No	No	No	Yes
Gilliam (1998)[76]	No	Yes	NA	Yes	No	No	Yes	Yes
Bergey (1997)[78]	No	Yes	NA	Yes	No	No	?	Yes
Beydoun (1997a)[85]	No	Yes	NA	Yes	No	No	Yes	Yes
Beydoun (1997b)[83]	No	Yes	NA	Yes	No	No	Yes	Yes
Sachdeo (1997a)[84]	No	Yes	NA	Yes	No	No	Yes	Yes
Devinsky (1995)[75]	No	Yes	NA	Yes	No	No	Yes	Yes
Schachter (1995)[88]	No	Yes	NA	Yes	No	No	Yes	Yes
Theodore (1995)[89]	No	Yes	NA	Yes	No	No	?	Yes
Faught (1993)[77]	No	Yes	NA	Yes	No	No	Yes	Yes

NA Not applicable

Internal Validity for Polytherapy

The 30 studies addressing polytherapy and the potential biases in each are list in Table 52. The following is a more detailed description of the biases found in each of theses studies. For each trial of polytherapy, we determined whether the results were potentially biased by the factors noted in the Methodology section. Other questions in this report consider the potential for attrition bias, but for polytherapy, we did not consider it because attrition was a study outcome.

Selection bias. All of the included trials were randomized. As in the section on sequential monotherapy, however, we tested for the possibility of selection bias in each trial. We performed two sets of analyses: one in which we individually tested each trial for between groups differences in patient characteristics, and another in which we searched for any consistent tendencies across trials. In the first set, we determined whether any statistically significant pretrial differences existed between the placebo group and the treated groups in each trial in the following patient characteristics:

- Mean age
- Percentage of patients who were female
- Mean duration of condition
- Mean baseline seizure frequency
- Percentage of patients with generalized vs. partial seizures
- Number of patients with known etiology
- Numbers of patients on one, two, three, or more drugs prior to the trial

The characteristics listed above were the only patient characteristics that could be tested for potential selection bias. The statistical details of the selection bias tests appear in Evidence Table 54. For each trial, we performed a Bonferroni correction to ensure that the trial-level Type I error rate was 0.05. In two of the 30 trials, the proportion of patients who were female was significantly different between groups. In the trial by Faught, Ayala, Montouris et al.,[94] 59 percent of placebo patients were female whereas 42 percent of zonisamide patients were female ($\chi^2(1)=5.91$, $p=0.015$). In the trial by Matsuo, Bergen, Faught et al.,[115] the percentages of females among placebo patients, lamotrigine 300 mg/day patients, and lamotrigine 500 mg/day patients were 70 percent, 58 percent, and 79 percent, respectively ($\chi^2(2)=7.71$, $p=0.021$). Thus, these two trials had potential selection bias. None of the other patient characteristics was significantly different between groups in any of the 30 trials.

Next, we investigated whether any patient characteristics demonstrated consistent selection bias across trials. For example, the mean age of patients in add-on placebo groups may have been higher compared to the mean age in add-on drug groups. Four patient characteristics were testable in five or more trials: mean age, proportion female, mean duration of condition, and proportion of patients who received two or more AEDs prior to the trial. For each of these patient characteristics, we performed a meta-analysis to determine whether there was a bias in the assignment of patients to groups. The details of these meta-analyses appear in Evidence Table 55 through 58. None of the analyses revealed any selection bias. Apparently, the potential for gender selection bias was unique to the two trials mentioned earlier, rather than a general trend among the group of 30 polytherapy trials.

Investigator, patient, regression, sampling and extraneous event biases. Because the trials were double blinded, neither investigator bias nor patient bias was likely to have affected these trials. Further, there was no evidence in any of the trials of sampling bias, regression bias, or extraneous event bias.

Measurement bias. All of the trials included for this question were potentially affected by measurement bias because all trials used seizure diaries to record seizure frequency (see Methodology section for a discussion of the potential difficulties with seizure diaries).

Sample specification bias. Twenty-seven of the 30 trials (90 percent) did not report whether patients had received the maximum tolerable dose of prior AEDs. Therefore, these trials were susceptible to sample specification bias.

In summary, the trials of polytherapy had few potential biases of internal validity. All of the trials were free from five potential biases (sampling, regression, investigator, patient, and extraneous event). However, all of the trials had potential measurement bias. In addition, 90 percent of the trials had sample specification bias, and two trials had potential selection bias.

Table 52. Internal validity of trials of polytherapy

Reference	Potential Bias							
	Sampling Bias	Sample Specification Bias	Selection Bias	Regression Bias	Investigator Bias	Patient Bias	Measurement Bias	Extraneous Event Bias
Faught (2001)[94]	No	Yes	Yes	No	No	No	Yes	No
Ben-Menachem (2000)[95]	No	Yes	No	No	No	No	Yes	No
Betts (2000)[96]	No	Yes	No	No	No	No	Yes	No
Cereghino (2000)[97]	No	Yes	No	No	No	No	Yes	No
Glauser (2000)[98]	No	Yes	No	No	No	No	Yes	No
Appleton (1999)[99]	No	Yes	No	No	No	No	Yes	No
Biton (1999)[100]	No	Yes	No	No	No	No	Yes	No
Duchowny (1999)[30]	No	Yes	No	No	No	No	Yes	No
Elterman (1999)[101]	No	Yes	No	No	No	No	Yes	No
KTSG (1999)[102]	No	No	No	No	No	No	Yes	No
Sachdeo (1999)[103]	No	Yes	No	No	No	No	Yes	No
Uthman (1998)[104]	No	Yes	No	No	No	No	Yes	No
Sachdeo (1997b)[105]	No	Yes	No	No	No	No	Yes	No
Ben-Menachem (1996)[90]	No	Yes	No	No	No	No	Yes	No
Chadwick (1996)[106]	No	Yes	No	No	No	No	Yes	No
Faught (1996)[91]	No	No	No	No	No	No	Yes	No
Privitera (1996)[107]	No	Yes	No	No	No	No	Yes	No
Sharief (1996)[108]	No	Yes	No	No	No	No	Yes	No
Tassinari (1996)[109]	No	Yes	No	No	No	No	Yes	No
Willmore (1996)[110]	No	Yes	No	No	No	No	Yes	No
Anhut (1994)[111]	No	No	No	No	No	No	Yes	No
Messenheimer (1994)[112]	No	Yes	No	No	No	No	Yes	No
Bourgeois (1993)[113]	No	Yes	No	No	No	No	Yes	No
FSG (1993)[114]	No	Yes	No	No	No	No	Yes	No
Matsuo (1993)[115]	No	Yes	Yes	No	No	No	Yes	No
McLean (1993)[116]	No	Yes	No	No	No	No	Yes	No
Schmidt (1993)[117]	No	Yes	No	No	No	No	Yes	No
Sivenius (1991)[118]	No	Yes	No	No	No	No	Yes	No

Table 52. Internal validity of trials of polytherapy (continued)

Reference	Potential Bias							
	Sampling Bias	Sample Specification Bias	Selection Bias	Regression Bias	Investigator Bias	Patient Bias	Measurement Bias	Extraneous Event Bias
UKGSG (1990)[119]	No	Yes	No	No	No	No	Yes	No
Jawad (1989)[70]	No	Yes	No	No	No	No	Yes	No

Internal Validity for Optimized Current Therapy

The results of our evaluation of potential sources of bias that may potentially weaken the internal validity of the seven studies addressing optimized current therapy are presented in Table 53. The following is a more detailed description of the biases found in each of theses studies.

Sampling bias. Only one article reported the sampling technique used to enroll patients into the study. Specht, Boenigk, Wolf, et al.[123] reported that their sample consisted of consecutive patients who met the inclusion criteria for the study. This can be an acceptable (albeit imperfect; see the description of selection bias in the Methodology section) sampling technique because it ensures that all patients who meet the inclusion criteria for a study are included. None of the remaining six articles reported on the sampling technique used to recruit the patients included in the study. Consequently, the presence of sampling bias cannot be determined in these studies.

Selection bias. Since none of three controlled trials included in the present evidence-base randomized patients to either the drug reduction or control arm, all three are potentially weakened by this bias.

Comparison of pretreatment demographic data for patients in the treatment and control arms of the controlled trials (Evidence Table 101) provided some evidence that selection bias was present in at least two of the three controlled trials (May, Bulmahn, Wohlhuter, et al.[121] and Duncan, Shorvon, and Trimble[122]). In addition, Duncan, Shorvon, and Trimble[122] reported that their control group consisted of patients recruited from the same population of patients as the drug reduction arm of the study, but that the patients in this group "…did not have a need for an immediate change in drug therapy." Thus, the patients in the control arm of this study were clearly different from the patients included in the drug reduction arm.

Although the demographic data does not provide clear evidence (statistically significant) for the presence of selection bias in the study by Thompson and Trimble,[126] this does not mean that selection bias is not present in the study. In fact, when considering all of the available pretreatment data abstracted from this study (Evidence Table 99), clearly, despite a lack of significant between group differences, the patients in the drug reduction arm were far more severely affected by epilepsy compared to the patients in the control arm. For example, the mean pretreatment frequency for partial seizures in the drug reduction group was 21.1 (SD: 34.6) seizures per week compared to 6.8 (SD: 9.7) per week in the control group. Although this difference was not statistically significant, selection bias may still have been present in this study. The average patient in the drug reduction arm was experiencing more than three times the number of seizures per week compared to the average patient in the control arm at study onset, and baseline memory, concentration, psychomotor speed, and mood were all better in the control group. These are all indications of selection bias.

Sample specification bias. None of the included articles stated that the patients entering a study were at maximum tolerable doses of their current AED regimen. Thus, this bias potentially affected all studies.

Patient reporting bias. Only one of the three controlled trials (Duncan, Shorvon, and Trimble[122]) blinded patients to treatment regimen, and was thus protected against the effects of this potential bias. Since none of the remaining two controlled trials blinded patients to treatment allocation, and all four of the case series were open, all six of the remaining included studies are potentially weakened by this bias.

Investigator bias. In all three of the included controlled trials, investigators were blinded to treatment regimen. As a result, these studies were provided some protection against this bias. Having said this, only one of the studies (Duncan, Shorvon, and Trimble[122]) blinded the patients in their studies to treatment regimen. Consequently, information gained from contact with patients may have broken the blinding of the investigators in these studies. Thus, we cannot assume that these two controlled trials were truly protected from investigator bias. The remaining four studies were open case series and, therefore, the internal validity of all of them may have been weakened by this potential bias.

Attrition bias. Although two studies suffered some attrition (Duncan, Shorvon, and Trimble[122] and Callaghan, O'Dwyer, and Keating[124]), rates in only one study exceeded 10 percent. The attrition rate in Callaghan, O'Dwyer, and Keating[124] was 17.1 percent.

Measurement bias. This bias potentially affects all of the studies included in the present evidence base and occurs when the outcome measure used to determine treatment effectiveness systematically under or overestimates the true measure of that outcome. In all of these studies, seizure frequency data was collected using patient or caregiver maintained seizure diaries. The problems associated with the use of seizure frequency data that was derived from patients or caregiver maintained diaries is discussed in the Methodology section of this report.

Although we required that data pertaining to quality of life and cognitive function be collected using a validated measurement instrument, this does not ensure that these data are unbiased. The instruments used in these studies were not validated in a population of patients with treatment-resistant epilepsy and thus their data may be biased.

Regression bias. Only studies that randomly assigned patients to treatment groups are free from this bias. Since the controlled trials were not randomized, they are susceptible to regression bias. The remaining studies were uncontrolled case series, which also renders them susceptible to regression bias.

Extraneous event bias. Only studies that randomly assigned patients to treatment groups can be free from this bias. Since none of the controlled trials was randomized and the remaining studies were uncontrolled case series, this bias may have weakened the internal validity of all of the studies in the present evidence base.

Table 53. Potential biases in studies of drug reduction strategies

Reference	Potential Bias								
	Sampling Bias	Selection Bias	Investigator Bias	Patient Reporting Bias	Attrition Bias	Measurement Bias	Regression To Mean	Extraneous Event Bias	Sample Specification Bias
Controlled trials performed outside of the United States									
May (1992)[121]	?	Yes	?	Yes	No	Yes	Yes	Yes	Yes
Duncan (1990)[122]	?	Yes	No	No	No	Yes	Yes	Yes	Yes
Thompson (1982)[126]	?	Yes	?	Yes	No	Yes	Yes	Yes	Yes
Case series performed in the United States									
Mirza (1993)[120]	?	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Case series performed outside of the United States									
Specht (1989)[123]	No	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Callaghan (1984)[124]	?	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schmidt (1983b)[125]	?	NA	Yes	Yes	No	Yes	Yes	Yes	Yes

NA Not applicable

Question 5

Which methods of nondrug treatment for epilepsy after initial treatment failure lead to improved outcomes for patients with treatment-resistant epilepsy

Internal Validity for Vagal Nerve Stimulation

The results of our evaluation of the internal validity of the 14 studies relevant to Question 5B are presented in Table 54. The following is a more detailed description of the biases found in each of theses studies.

Sampling bias. Of the 14 studies in the present evidence base, eight did not report on the sampling method used to recruit patients. Thus, these studies may be prone to sampling bias. The remaining six studies reported that they recruited and followed all patients who met the inclusion criteria for their study. Thus, this bias is unlikely in these latter studies.

Sample specification bias. None of the included articles specifically stated that patients entering the study were at the maximum tolerable doses of their current AED regimen. Thus, this bias potentially affected all studies in the present evidence base.

Selection bias. As discussed in the Methodology section, selection bias can only influence the outcome of a controlled trial. Between-groups analysis of both the available baseline patient demographic data and the outcome data abstracted from the two RCTs in the present evidence base (Evidence Tables 218 and 226) did not identify evidence for the presence of selection bias in these studies.

Investigator bias. The investigators in both of the included RCTs were reportedly blinded to how patients were allocated to treatment groups, so this potential source of bias should not have affected these studies. As the investigators of one of these RCTs points out (Clinical Trial EO3[331]), however, the blinding of these studies could have been broken. These investigators stated that, "A possible problem of the study design (which was used in both of the RCTs) was with regard to the blinding of patients and investigators. Although patients were not told which stimulation regimen they received, some may have correctly surmised that they were in the treatment group based on the stimulation cycling time and intensity. Comments from these patients could have influenced the blinded investigators."[331] The investigators of Clinical Study EO5 tried to minimize this problem by instructing patients not to inform blinded personnel of how often their stimulation device turned on and not to discuss their experiences with other patients. Furthermore, the investigators of Clinical Trial EO5 stated that they hired an "independent monitoring corporation" to monitor the study and "ensure" adherence to protocol and blinding procedures.[331] Because the methods used by the independent monitoring corporation to ensure adherence to the blinding procedures were not described, however, blinding of Clinical Trial EO5 may not have remained intact.

The remaining studies, including the two RCT followup case series, were all nonblinded, single arm studies. Thus, the study investigators had full knowledge that the patients in these studies were receiving VNS at levels believed to be therapeutic. Consequently, these case series may have investigator bias.

Patient reporting bias. All of the patients in the included case series were aware that they were being treated with VNS. Consequently, all of these studies have the potential for patient reporting bias. Furthermore, as discussed above, although both of the RCTs included in the

present evidence base reported that patients were blind to whether they were allocated to the treatment or active control arm of the study, blinding may have been broken.

Attrition bias. Attrition rates in the included studies tended to be low (ranging from 0 percent in the majority of studies to 6 percent in one small study). The only exception was the study of Lundgren, Amark, Blennow, et al.,[341] that reported attrition rates of 31.3 percent at 18-month followup and 87.5 percent at 24-month followup. Consequently, we have not included these longer-term data, and have only considered the 12-month followup data from this study when attrition rates were zero.

Because of the low attrition rates, the effects of attrition bias on the evidence base are likely to be small. In addition, for all studies in which attrition did occur, we explicitly implemented the intent-to-treat principle when performing an analyses by making the conservative assumption that all patients lost to followup were treatment failures.

Measurement bias. This bias potentially affects all of the studies included in the present evidence base. In all of these studies, seizure frequency data were collected using patient or caregiver maintained seizure diaries. The difficulties associated with the use of seizure frequency data that was derived from patients or caregiver maintained diaries is discussed in the Methodology section of this report.

Regression bias. The effects of this bias can only be avoided by performing a well-designed RCT. Thus, with the exception of two trials (RCTs EO3 and EO5), the remaining studies are potentially affected by this bias.

Extraneous event bias. The effects of this potential bias can only be avoided by performing a well-designed RCT. Thus, with the exception of two trials (RCTs EO3 and EO5), the remaining studies are potentially affected by this bias.

Maturation bias. Eight of the studies in the present evidence base had followup times of greater than 1 year. All of these studies are case series, and are thus potentially affected by this bias.

Table 54. Potential biases in studies of vagal nerve stimulation

Reference	Potential Biases									
	Sampling Bias	Sample Specification Bias	Selection Bias	Investigator Bias	Patient Reporting Bias	Attrition Bias	Measurement Bias	Regression to Mean	Extraneous Event Bias	Maturation Bias
RCT's performed in the United States										
Clinicial Study EO5 Handforth (1998)[332]	No	Yes	No	No	Yes	Yes	Yes	No	No	NA[a]
Clinical Trial EO3 The VNS Group (1995)[331]	No	Yes	No	No	Yes	No	Yes	No	No	NA[a]
Followup studies of RCT's performed in the United States										
De Giorgio (2000)[333] Followup of Clinical Study EO5	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Salinski (1996)[31] Followup of Clinical Trial EO3	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Case series performed in the United States										
Chayasirisobhon (2001)[346]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	NA[a]
Ergene (2001)[335]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Hosain (2000)[336]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	NA[a]
Clinical Trial EO4, Labar (1999)[334]	?	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA[a]
Case series performed outside of the United States										
Aldenkamp (2001)[337]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	NA[a]
Hoppe (2001)[339]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Ben-Menachem (1999)[343]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Boon (1999)[338]	No	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Parker (1999)[340]	?	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lundgren (1998)[341]	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Question 8

What is the mortality rate of patients with treatment-resistant epilepsy?

The results of our evaluation of the internal validity of the 10 studies relevant to Question 8 are presented in Table 55. The following is a more detailed description of the biases found in each of theses studies.

Cause validation bias. The methods that researchers use to determine cause of death have an impact on study quality. Autopsy findings can be considered the "gold standard" method for diagnosis of sudden unexpected death and other epilepsy-related deaths, because autopsies represent the most comprehensive effort to identify a cause of death. Diagnosis of cause of death is less reliable in cases where no autopsy had taken place, even though an expert or group of experts usually makes this determination. We refer to instances where the cause of death was determined by a less reliable method as instances of cause validation bias. This bias only affects cause-specific mortality rates; it has no effect on overall mortality rates.

All studies that presented information on how cause of death was determined (6/10 studies) reported that at least some patients had not been autopsied. Also, note that, although autopsy is the "gold standard" for diagnosis of epilepsy-related deaths, it is not always definitive because the thoroughness of autopsies varies considerably. A recent national study in the United Kingdom found that 87 percent of autopsies of patients with epilepsy were inadequate in at least one of the following areas: external examination, internal examination, further investigations, and cause of death report.[385]

Mortality ratio bias. Another important aspect of study quality and design is whether mortality in persons with epilepsy is compared to those who do not have epilepsy. In practice, this type of comparison is usually conducted using a reference population that includes all individuals in a national database (of which less than 1 percent of the population has epilepsy). Without a comparison between those who do and do not have epilepsy, determining whether an increased risk of death is associated with epilepsy is extremely difficult. Five studies (42 percent of all included studies) reported an SMR (at least for all-cause mortality); these studies in effect are cohort studies (one prospective and four retrospective).[354,356,360,362,363] In addition, one retrospective study (Racoosin, Feeney, Burkhart, et al.[357]) presented mortality rates and enough information about the study group structure (including number of patients in different age subgroups) from which we could calculate approximate SMRs.[a] These six studies were the most useful for addressing this question.

The four studies that did not calculate SMRs are of lesser quality, but we included them because they provided data for certain cause-specific types of mortality for which none of the included studies presented SMRs. These case series presented only mortality rates or number of deaths without comparing these numbers to a reference population.[355,358,359,361] They did not present enough information about their study groups to allow independent calculation of SMRs. Therefore, only CMRs could be calculated, which could not be standardized for age. Therefore, mortality comparisons between patients in these studies and reference populations are vulnerable to mortality ratio bias.

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[a] Because information was presented only for age bands spanning 15-20 years, our calculated SMRs are less precise than those derived from studies wherein SMRs were calculated by the study authors. Therefore, we consider the SMRs we calculated from Racoosin et al. to be approximate rather than exact.

Sampling bias. All of the retrospective studies (9/10 studies) were vulnerable to sampling bias (for a definition of this bias, see Methodology section of this document). Patient selection in the one prospective study appeared to preclude this bias.[360]

Sample specification bias. Because none of the included studies specified that patients described as "refractory" or "treatment-resistant" had received at least one AED at the maximum tolerated dosage, all of the studies were potentially affected by sample specification bias (see Methodology section for more detailed description of this bias).

Table 55. Internal validity of studies of mortality rate

Reference	Country	Potential bias			
		Mortality Ratio Bias (Overall Mortality)	Mortality Ratio Bias (Cause-Specific Mortality)	Sampling Bias	Sample Specification Bias
Physician's desk reference, Gabapentin trial data (2001)[358]	United States	No	Yes	Yes	Yes
Racoosin (2001)[357]	United States	No	Yes	Yes	Yes
Wong (2001)[353]	United Kingdom	No	Yes	Yes	Yes
Annegers (2000)[356]	United States	No	Yes	Yes	Yes
Hennessy (1999)[362]	United Kingdom	No	Yes	Yes	Yes
Sperling (1999)[360]	United States	No	Yes	No	Yes
Vickrey (1997)[361]	United States	Yes	Yes	Yes	Yes
Leestma (1997)[355]	United States, United Kingdom, Europe, Australia, South Africa	Yes	Yes	Yes	Yes
Leppik (1995)[359]	United States, Europe, Australia	Yes	Yes	Yes	Yes
Klenerman (1993)[354]	United Kingdom	No	Yes for some causes, no for others	Yes	Yes

Question 9

Is there a correlation between the number and/or type of seizure and sudden death?

The results of our evaluation of the internal validity of the 10 studies relevant to Question 9 are presented in Table 56. The following is a more detailed description of the biases found in each of theses studies.

Cause validation bias. How the diagnosis of SUDEP was determined is among the important aspects of study quality relevant to the present question. Autopsy findings can be considered the "gold standard" method for diagnosing SUDEP because autopsies represent the most comprehensive effort to identify a cause of death. Diagnosis of SUDEP in cases where there was no autopsy is less reliable, even though an expert or group of experts usually makes this determination. This latter type of definition is therefore subject to cause validation bias.

Clinical diagnoses of the cause of death may be less reliable compared to autopsy-determined causes. For example, a study of general surgery patients (none with epilepsy) that compared the cause of death determined first by clinical diagnosis and subsequently by autopsy found a discrepancy in 63 percent of cases.[386] This meant that the preautopsy clinical diagnosis was incorrect 63 percent of the time.

This does not imply that autopsy reports are always correct. One important difference between this surgical study and the determination of SUDEP is that, in the former study, there was an apparent cause of death prior to autopsy. There may or may not be such a significant discrepancy in the diagnosis of SUDEP cases by different methods. Furthermore, as discussed under Question 8, a recent audit of epilepsy-related deaths in the United Kingdom found that even autopsy reports might be inadequate in one respect or another.[385] Thus, although autopsies are the "gold standard" for determination of SUDEP, they are by no means perfect.

Of the studies included in the analysis for this question, three did not report the proportion of SUDEP cases determined by autopsy.[360,375,379] Of the six studies that did report this information, two diagnosed all SUDEP cases from autopsy findings,[378,380] while the remaining four contained at least some cases in which no autopsy was performed.[369,374,376,377] These latter cases were labeled by investigators as "probable" SUDEP in two studies,[369,374] while the other two studies did not make this distinction.[376,377] All studies that contained "probable SUDEP" cases included such cases in their analysis. The possibility exists that some or all of these cases had an explainable cause of death that would have been detected upon autopsy. Inclusion of these cases could have obscured any potential correlation between SUDEP and seizure type and/or frequency in these studies. However, since a separate independent analysis cannot be conducted without these cases in the four studies that presented them, we have included these cases in our analysis for this question. Table 56 shows that at least four of nine studies were vulnerable to cause validation bias (three additional studies did not report enough information to confirm this).

Study design is another factor that can affect a study's susceptibility to bias. All of the studies that we included for this question employed a type of nested case-control design. A nested case-control study is a prospective or retrospective cohort study in which all of the cases (in this instance, sudden deaths) are compared to a selected number of controls. This design is often used when the incidence of a condition is low (as are sudden deaths), meaning that the proportion of patients who do not become cases is large. Therefore, evaluating only a fraction of the control patients for exposure information becomes less expensive and time-consuming.[387] The primary difficulty with this design is its vulnerability to a number of biases (such as

selection of nonrepresentative controls or failure to identify or control for confounding variables) that could lead to spurious or uninterpretable results.[388]

Sampling bias. All retrospective studies (7/9 studies) were vulnerable to sampling bias (see Methodology section for a detailed description of this bias). Patient selection in the two prospective studies appeared to preclude this bias.[360,369]

Control selection bias. Biases can arise from using an inappropriate control group, which we refer to in this report as control selection bias. Inappropriate controls could lead to the finding of a correlation between SUDEP and another variable when no such correlation exists, or vice versa. However, we identified no control group in the studies included in this analysis as being particularly inappropriate. At least four studies[b] used living epilepsy patients as controls,[369,374,377,378] and three of these four performed some type of matching (Evidence Table 251 has specific matching information).[369,374,378] These are most likely appropriate control groups for studies of SUDEP cases.

Since the purpose of these studies was to identify variables that might increase the risk of SUDEP, we expect a difference between cases and controls in at least one variable. However, cases and controls may differ on unknown variables. At least two studies used all patients (living and deceased) as controls, which limits the possibility of selection bias in these studies.[360,376] In one study, whether living and deceased patients were used was unclear.[375] One study had two control groups: epilepsy patients who died of causes other than SUDEP, and living epilepsy patients.[379] In this study, only patients who died of other causes were compared to the group of SUDEP cases. We have used the group of living patients for an additional independent comparison. One study employed epilepsy patients who died of causes other than SUDEP as the sole control group.[380] The remaining study was unclear as to which patients were included in their control group.[375] What effect the use of living vs. deceased controls would have on the results in these studies is unclear. However, studies that used matched controls, randomly selected controls or all controls available, are less susceptible to bias compared to studies not using these groups.

Statistical control bias. One way to minimize the effect of the potential biases discussed above is through statistical correction of the data. In addition, such adjustment reduces possible confounding from other variables. Statistical attempts to correlate seizure type and/or frequency with sudden death were reported in seven out of nine studies (Evidence Table 251). Studies that used inappropriate statistical methods (or no statistical methods) to control for confounding are vulnerable to statistical control bias. Two studies attempted to control for confounding using multiple regression.[369,374] Because multiple regression can adjust for the effects of differences between patients who did and did not experience SUDEP, studies using multiple regression are of higher quality compared to studies that do not use multiple regression. If these differences are not adjusted, a true correlation between SUDEP and seizure type or frequency may be obscured or a spurious correlation created.

The potential differences between patients examined in these studies included the number of AEDs used, type of AEDs used, changes in dose of AEDs used, compliance with AED regimen (determined by AED blood levels), mental retardation, duration of epilepsy, psychotropic drug use, presence of epileptogenic structural lesions, age at epilepsy onset, and presence of comorbidities. Not all relevant differences may have been examined (or known), so a study that employed this statistical technique is not automatically of the highest quality. It is simply less vulnerable to confounding compared to studies that do not control for any variables.

[b] The study by Timmings[375] may also have used living controls, but this could not be determined from the published information.

Five studies did not control for the effects of any potential differences among patients. Two of these five studies did not perform any statistical comparisons and, therefore, we consider these low quality studies.[376,378] We independently calculated log odds ratios from the data presented in these studies, but not enough information was available to allow multiple logistic regression. Therefore, adjusting for the potential effects of other variables was not possible.

An additional problem in studies with a relatively small sample size is the lack of adequate statistical power to detect a statistically significant relationship between SUDEP and a relevant variable when such a relationship exists. We have performed independent calculations to determine the minimum detectable difference in studies that did not show a statistically significant relationship between SUDEP and seizure type or frequency. This enabled us to determine whether any of these studies lacked adequate power to detect a statistically significant relationship.

Although two studies controlled for potential confounding variables with multiple regression,[369,374] they nevertheless are imperfect. The biggest potential weakness in both studies is the reporting of some SUDEP cases that were not diagnosed by autopsy. This problem affected only 9 percent of cases in the study by Nilsson, Farahmand, Persson, et al.,[374] but it affected 50 percent of cases in the study by Walczak, Leppik, D'Amelio, et al.[369] Thus, the results of Nilsson, Farahmand, Persson, et al.[374] may be more reliable compared to those of Walczak, Leppik, D'Amelio, et al.[369] However, Walczak, Leppik, D'Amelio, et al.[369] compared compliance rates between cases and controls, a potential confounding variable not evaluated in Nilsson, Farahmand, Persson, et al.[374]

Neither study included age or gender, two potentially relevant variables, in their multiple regression analyses. Younger age has been associated with SUDEP rates in some studies,[354,368,376] while there is conflicting evidence in the literature concerning a possible relationship between SUDEP and gender. SUDEP appeared to be more prevalent in females in at least one report,[356] but has been reported to be more prevalent among males in another.[389] Nilsson, Farahmand, Persson, et al.[374] did not use these variables in multiple regression because they matched cases and controls by age and gender. If age did have an influence on SUDEP rates, matching cases and controls by age could effectively prevent detection of the correlation. Walczak, Leppik, D'Amelio, et al.[369] randomly selected controls from a cohort of living patients, but did not compare the age or gender frequencies of cases and controls. However, both studies compared the seizure frequency between cases and controls stratified by gender. Thus, the potential relationship between SUDEP and seizure type or frequency is unlikely to be obscured by not adjusting for age and gender.

Table 56. Internal validity in studies of mortality related to seizure type and frequency

Reference	Country	Potential Bias			
		Cause Validation Bias	Sampling Bias	Statistical Control Bias	Possible Confounding Variables Unaccounted For
Walczak (2001)[369]	United States	Yes	No	No	Yes
McKee (2000)[377]	United States	Yes	Yes	Yes	Yes
Kloster (1999)[380]	Norway	No	Yes	Yes	Yes
Nilsson (1999)[374]	United Kingdom	Yes	Yes	No	Yes
Sperling (1999)[360]	United States	?	No	Yes	Yes
Nashef (1995)[376]	United Kingdom	Yes	Yes	Yes	Yes
Timmings (1993)[375]	United Kingdom	?	Yes	Yes	Yes
Jick (1992)[378]	United States	No	Yes	Yes	Yes
Birnbach (1991)[379]	United States	?	Yes	Yes	Yes