**National Quality Forum—Evidence (subcriterion 1a)**

**Measure Number** (*if previously endorsed*)**:** 1814

**Measure Title**: Counseling for Women of Childbearing Potential with Epilepsy

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** Click here to enter composite measure #/ title

**Date of Submission**: 1/15/2016

|  |
| --- |
| **Instructions**  *For composite performance measures:*  *A separate evidence form is required for each component measure unless several components were studied together.*  *If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.*   * Respond to all questions as instructed with answers immediately following the question. All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of *supplemental* materials may be submitted, but there is no guarantee it will be reviewed. * If you are unable to check a box, please highlight or shade the box for your response. * Maximum of 10 pages (*incudes questions/instructions*; minimum font size 11 pt; do not change margins). ***Contact NQF staff if more pages are needed.*** * Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx). |

|  |
| --- |
| **Note: The information provided in this form is intended to aid the Steering Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF’s evaluation criteria.**   1a. Evidence to Support the Measure Focus The measure focus is evidence-based, demonstrated as follows:   * Health outcome: [**3**](#Note3) a rationale supports the relationship of the health outcome to processes or structures of care. Applies to patient-reported outcomes (PRO), including health-related quality of life/functional status, symptom/symptom burden, experience with care, health-related behavior. * Intermediate clinical outcome: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4)that the measured intermediate clinical outcome leads to a desired health outcome. * Process: [**5**](#Note5) a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured process leads to a desired health outcome. * Structure: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured structure leads to a desired health outcome. * Efficiency: [**6**](#Note6) evidence not required for the resource use component.   **Notes**  **3.** Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.  **4.** The preferred systems for grading the evidence are the U.S. Preventive Services Task Force (USPSTF) [grading definitions](http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm) and [methods](http://www.uspreventiveservicestaskforce.org/methods.htm), or Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org/publications/index.htm).  **5.** Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement. Note: A measure focused only on collecting PROM data is not a PRO-PM.  **6.** Measures of efficiency combine the concepts of resource use and quality (see NQF’s [Measurement Framework: Evaluating Efficiency Across Episodes of Care](http://www.qualityforum.org/Publications/2010/01/Measurement_Framework__Evaluating_Efficiency_Across_Patient-Focused_Episodes_of_Care.aspx); [AQA Principles of Efficiency Measures](http://www.aqaalliance.org/files/PrinciplesofEfficiencyMeasurementApril2006.doc)). |

**1a.1.This is a measure of**: (*should be consistent with type of measure entered in De.1*)

Outcome

Health outcome: Click here to name the health outcome

Patient-reported outcome (PRO): Click here to name the PRO

*PROs include HRQoL/functional status, symptom/symptom burden, experience with care, health-related behaviors*

Intermediate clinical outcome (*e.g., lab value*): Click here to name the intermediate outcome

Process: Counseling for Women of Childbearing Potential with Epilepsy

Structure: Click here to name the structure

Other: Click here to name what is being measured

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**HEALTH OUTCOME/PRO PERFORMANCE MEASURE**  *If not a health outcome or PRO, skip to* [*1a.3*](#Section1a3)

**1a.2.** **Briefly state or diagram the path between the health outcome (or PRO) and the healthcare structures, processes, interventions, or services that influence it.**

Not Applicable

**1a.2.1.** **State the rationale supporting the relationship between the health outcome (or PRO) to at least one healthcare structure, process, intervention, or service (*i.e., influence on outcome/PRO*).**

Not Applicable

*Note: For health outcome/PRO performance measures, no further information is required; however, you may provide evidence for any of the structures, processes, interventions, or service identified above.*

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**intermediate outcome, PROCESS, or STRUCTURE PERFORMANCE measure**

**1a.3.****Briefly state or diagram the path between structure, process, intermediate outcome, and health outcomes**. Include all the steps between the measure focus and the health outcome.

|  |  |  |
| --- | --- | --- |
| Process | Intermediate Outcome | Outcome |
| Eligible patients counseled on how epilepsy and its treatment may affect contraception or pregnancy | Increased folic acid use in eligible population  Eligible patients receive appropriate obstetrical, prenatal and pre-pregnancy care in accordance with their wishes | Decreased number of unintended pregnancies for eligible population  Decreased complications during pregnancy for eligible patients  Increased number of children born at term for eligible patients  Decreased malformations in infants born to eligible patients |

**1a.3.1.** **What is the source of the systematic review of the body of evidence that supports the performance measure?**

Clinical Practice Guideline recommendation – ***complete sections*** [***1a.4***](#Section1a4)***, and*** [***1a.7***](#Section1a7)

US Preventive Services Task Force Recommendation – ***complete sections*** [***1a.5***](#Section1a5) ***and*** [***1a.7***](#Section1a7)

Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*) – ***complete sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)

Other – ***complete section*** [***1a.8***](#Section1a8)

*Please complete the sections indicated above for the source of evidence. You may skip the sections that do not apply.*

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION**

**1a.4.1.** **Guideline citation** (*including date*) and **URL for guideline** (*if available online*):

1. Pugh MJ, Berlowitz DR, Montouris G, et al. What constitutes high quality of care for adults with epilepsy? Neurology 2007;69:2020-2027
2. Harden CL, Hopp J, Ting TY, et al. Practice Parameter update: Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): Obstetrical complications and change in seizure frequency: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:126-132.
3. Harden CL, Meador KJ, Pennell PB, et al. Practice Parameter update: Management issues for women with epilepsy – Focus on pregnancy (an evidence-based review): Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:133-141.
4. National Institute of Clinical Health and Excellence. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (update). 2012. Clinical guideline 137. Available at: <http://www.nice.org.uk/Guidance/cg137> Accessed on February 18, 2014.

**1a.4.2.** **Identify guideline recommendation number and/or page number** and **quote verbatim, the specific guideline recommendation**.

Since the release of the original measure, the guideline statements have been updated, and additional guideline statements added supporting the need for counseling.

1. If a woman with epilepsy is of childbearing potential and receives oral contraceptives in conjunction with an enzyme inducing AED [Antiepileptic Drug], THEN decreased effectiveness of oral contraception should be addressed. (higher doses of the oral contraceptive, alternative birth control methods, or change AED). (Level A 2++/Primary)1
2. Patients with epilepsy should receive an annual review of information including topics such as: … Contraception, family planning, and how pregnancy and menopause may affect seizures (evidence grade C)1
3. Women with epilepsy (WWE) should be counseled that seizure freedom for at least 9 months prior to pregnancy is probably associated with a high rate (84%-92%) of remaining seizure-free during pregnancy. (Level B) 2
4. Women with epilepsy who smoke should be counseled that they possibly have a substantially increased risk of premature contractions and premature labor and delivery during pregnancy. There is possibly a substantially increased risk of premature contractions and premature labor and delivery during pregnancy for WWE who smoke. (Level C)2
5. Counseling of WWE who are contemplating pregnancy should reflect that there is probably no increased risk of reduced cognition in the offspring of WWE not taking AEDs (Level B).3
6. To reduce the risk of MCMs, avoidance of the use of VPA during the first trimester of pregnancy, if possible, may be considered, compared to the use of PHT or LTG. [MCMs=major congenital malformations; VPA=valproate; PHT=phenytoin; LTG=lamotrigine] (Level C)3
7. In order to enable informed decisions and choice, and to reduce misunderstandings, women and girls with epilepsy and their partners, as appropriate, must be given accurate information and counselling about contraception, conception, pregnancy, caring for children and breastfeeding, and menopause. (Level III)4
8. Information about contraception, conception, pregnancy, or menopause should be given to women and girls in advance of sexual activity, pregnancy or menopause, and the information should be tailored to their individual needs. This information should also be given, as needed, to people who are closely involved with women and girls with epilepsy. These may include her family and/or carers. (Level III)4
9. All healthcare professionals who treat, care for, or support women and girls with epilepsy should be familiar with relevant information and the availability of counselling. (Level III)4
10. Discuss with women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), and their parents and/or carers if appropriate, the risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child. Assess the risks and benefits of treatment with individual drugs. There are limited data on risks to the unborn child associated with newer drugs. Specifically discuss the risk of continued use of sodium valproate to the unborn child, being aware that higher doses of sodium valproate (more than 800 mg/day) and polytherapy, particularly with sodium valproate, are associated with greater risk. (Evidence comes from three systematic reviews; one review focused on incidence of malformation and the other two on child neurodevelopmental outcomes. No individual RCTs were reviewed. This recommendation was also based on GDG consensus opinion.)4
11. In women of childbearing potential, the possibility of interaction with oral contraceptives should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. (Level III)4
12. In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the possibility of interaction with oral contraceptives should be discussed with the child and/or her carer, and an assessment made as to the risks and benefits of treatment with individual drugs. (Level III)4
13. In women and girls of childbearing potential, the risks and benefits of different contraceptive methods, including hormone-releasing intrauterine devices (IUDs), should be discussed. (Level III)4
14. If a woman or girl taking enzyme-inducing AEDs chooses to take the combined oral contraceptive pill, guidance about dosage should be sought from the SPC and current edition of the BNF (available at http://bnf.org External Web Site Policy). (Level III)4
15. Women and girls with epilepsy need accurate information during pregnancy, and the possibility of status epilepticus and sudden death in epilepsy (SUDEP) should be discussed with all women and girls who plan to stop AED therapy (see the section 'Withdrawal of Pharmacologic Treatment' above).4

**1a.4.3.** **Grade assigned to the quoted recommendation with definition of the grade:**

1. Level A 2++/Primary A: Rated as appropriate
2. Evidence grade C
3. Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.
4. Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies
5. Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.
6. Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.
7. Level III-Well-designed non-experimental descriptive studies, case-control studies, and case studies
8. Level III-Well-designed non-experimental descriptive studies, case-control studies, and case studies
9. Level III-Well-designed non-experimental descriptive studies, case-control studies, and case studies
10. Following statement provided verbatim, “Evidence comes from three systematic reviews; one review focused on incidence of malformation and the other two on child neurodevelopmental outcomes. No individual RCTs were reviewed. This recommendation was also based on GDG consensus opinion.”
11. Level III-Well-designed non-experimental descriptive studies, case-control studies, and case studies
12. Level III-Well-designed non-experimental descriptive studies, case-control studies, and case studies
13. Level III-Well-designed non-experimental descriptive studies, case-control studies, and case studies
14. Level III-Well-designed non-experimental descriptive studies, case-control studies, and case studies
15. Women and girls with epilepsy need accurate information during pregnancy, and the possibility of status epilepticus and sudden death in epilepsy (SUDEP) should be discussed with all women and girls who plan to stop AED therapy (see the section 'Withdrawal of Pharmacologic Treatment' above).4

**1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)

**Pugh -**

**Ratings**

1-3 clearly appropriate/ reliable/ necessary

4-6 uncertain or equivocal

7-10 appropriate/ reliable/ necessary

**Levels of Evidence:** 31

1++ High quality meta-analyses, systematic reviews of RCTs or RCTs with low risk of bias

1+ Well conducted meta analyses, systematic reviews, or RCTs with low risk of bias

2++ High quality systematic reviews or studies without randomization, one or more high quality case-control or cohort study with low risk of confounding and high probability of a causal relationship

2+ Well conducted case-control or cohort study with low risk of confounding and moderate probability that the relationship is causal

3 Non-analytic studies (case reports/ case series)

4 Expert opinion

**AAN Classification Recommendations**

**Appendix e-5: Classification of Recommendations**

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)\*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

\*In exceptional cases, one convincing Class I study may suffice for an “A” recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).

**NICE Evidence**

NICE National Collaborating Centre for Primary Care. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. London (UK): Royal College of General Practitioners; 2004 Oct.

Rating Scheme for Strength of the Evidence

Ia-Systematic review or meta-analysis of randomized controlled trials

Ib-At least one randomized controlled trial

IIa-At least one well-designed controlled stud without randomization

IIb-At least one well-designed quasi-experimental descriptive studies, such as a cohort study

III-Well-designed non-experimental descriptive studies, case-control studies, and case studies

IV-Expert committee reports, opinions and/or clinical experience of respected authorities

Rating Recommendations

A\* Directly based on category I evidence (meta-analysis of randomized controlled trials (RCTs) or at least one RCT)

B\* Directly based on category II evidence (at least one controlled study without randomization or at least one other quasi-experimental study) or extrapolated from category I evidence

C\* Directly based on category III evidence (non-experimental descriptive studies) or extrapolated from category I or II evidence

D\* Directly based on category III evidence (expert committee reports or opinions and/or clinical experience of respected authorities) or extrapolated from category I, II or III evidence

N Recommendation taken from NICE guideline or technology appraisal guidance

**1a.4.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.4.1*)**:**

Pugh Same as above

AAN URL: <http://www.neurology.org/content/suppl/2009/04/27/WNL.0b013e3181a6b325.DC1.html>

NICE Same as above

**1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?**

Yes **→ *complete section*** [***1a.7***](#Section1a7)

No **→ *report on another systematic review of the evidence in sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)***; if another review does not exist, provide what is known from the guideline review of evidence in*** [***1a.7***](#Section1a7)

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.5.** **UNITED STATES PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

**1a.5.1.** **Recommendation citation** (*including date*) and **URL for recommendation** (*if available online*):

Not Applicable

**1a.5.2.** **Identify recommendation number and/or page number** and **quote verbatim, the specific recommendation**.

Not Applicable

**1a.5.3.** **Grade assigned to the quoted recommendation with definition of the grade**:

Not Applicable

**1a.5.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: the* *grading system for the evidence should be reported in section 1a.7.*)

Not Applicable

**1a.5.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.5.1*)**:**

Not Applicable

***Complete section*** [***1a.7***](#Section1a7)

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.6. OTHER SYSTEMATIC REVIEW OF THE BODY OF EVIDENCE**

**1a.6.1.** **Citation** (*including date*) and **URL** (*if available online*):

Not Applicable

**1a.6.2.** **Citation and** **URL for methodology for evidence review and grading** (*if different from 1a.6.1*)**:**

Not Applicable

***Complete section*** [***1a.7***](#Section1a7)

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE supporting the measure**

*If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.*

**1a.7.1.** **What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review?**

All guideline groups evaluated various forms of the question, do women with epilepsy have an increased risk of pregnancy-related complications? As well as an evaluation of evidence on seizure recurrence and birth defect potential.

**1a.7.2.** **Grade assigned for the quality of the quoted evidence with definition of the grade**:

See above evidence grades and verbatim recommendations

**1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system.**

See 1a.4.4

**1a.7.4.** **What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range**: Click here to enter date range

Pugh data previously provided in prior submissions.

AAN guidelines range - 1985-February 2008

NICE range June 2010 to September 2013 (Builds off of past NICE searches of evidence)

**QUANTITY AND QUALITY OF BODY OF EVIDENCE**

**1a.7.5.****How many and what type of study designs are included in the body of evidence**? (*e.g., 3 randomized controlled trials and 1 observational study*)

Details on Pugh data previously provided.

AAN Obstetrics guideline identified 9 studies graded Class III or higher. Regarding premature contractions and premature labor and delivery: “One Class I study5 showed no substantially increased risk of premature contractions or premature labor and delivery in WWE taking AEDs compared to control women without epilepsy (OR 0.51, 95% CI 0.19 –1.36). One Class II study12 showed an increased risk for WWE who were smokers compared to control women who were also smokers (OR 3.4, 95% CI

1.8–6.5) (data not given for all WWE compared to controls). One Class III study13 also showed an increased risk (*p* \_ 0.05). Another Class III study8 demonstrated no significant increased risk but was insufficiently sensitive to exclude a substantially increased risk (OR 8.24, 95% CI 0.92–70.32). A Class III study11 showed no significant increased risk but was not sufficiently sensitive to exclude an increased risk (RR 0.7, 95% CI 0.3–1.4). In a categorical,\_2 statistic, it was reported that the rates of premature births were not different than controls (*p* \_ 0.3),9 and another study found no differences in gestational ages in the offspring of WWE compared to controls (WWE \_ 38.06, SD 1.42 vs controls \_ 38.17, SD 3.58 weeks).”

Regarding Seizure Recurrence in previously seizure free WWE: “Two Class II articles16,17 showed that for WWE who were seizure-free for 9 months prior to pregnancy, 84%–92% remained seizure-free during pregnancy (table e-4). In one study, 38 of 45 (84%; CI 0.71– 0.92) pregnant WWE remained seizure-free,16 and in the other study, 47 of 51 (92%; CI 0.82– 0.97) pregnant WWE remained seizure-free.17 One larger Class III article22 showed that 80% of a group of WWE (n \_ 450) who were seizure-free at least 1 year prior to pregnancy remained seizure-free during pregnancy (exact number not provided). One Class III article showed that of 72 WWE who were seizure-free for 10 months, 74% (95% CI 0.62– 0.82) remained seizure-free during pregnancy.18 A second Class III article showed that of 54 WWE who were seizure-free for 9 months, 94% (95% CI 0.85– 0.98) remained seizure-free during pregnancy, and of 48 WWE who were seizure-free for 1 year, 92% (95% CI 0.80–0.98) remained seizure-free during pregnancy.19 These results are all fairly consistent across the class of evidence and sample size of the studies. *Conclusion.* Two Class II articles show the rate of remaining seizure-free during pregnancy if WWE are seizure-free for at least 9 months to 1 year prior to pregnancy is probably 84%–92%.”

Harden CL, Hopp J, Ting TY, et al. Practice Parameter update: Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): Obstetrical complications and change in seizure frequency: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:126-132.

AAN Management issues for women with epilepsy – focus on pregnancy guideline identified 9 studies graded Class III or higher. Regarding risk of reduced cognition, “Two Class II studies24,25 observed that cognition is not reduced in children of WWE unexposed to AEDs. One was a blinded observational study24 comparing the IQ of 64 children of WWE not taking AEDs with 121 controls. No important differences in IQ were found. The other study25 showed no difference in the IQ of 57 children of untreated WWE and 57 control children matched for age, race, and socioeconomic status. ***Conclusion.*** Cognition is probably not reduced in children of WWE who are not exposed to AEDs in utero (two Class II studies).”

Regarding relationship between AED and risk of MCMs: “All studies evaluated AED dose in the first trimester and MCMs. In one Class I study,10 a relationship between AED dose and risk of MCMs was reported for LTG but not VPA. Using the Cochran Armitage method,17 we found a significant dose relationship with VPA (exact tests one-sided *p* \_ 0.02, two-sided *p* \_ 0.04) and with LTG (exact tests one-sided *p* \_ 0.01, two-sided *p* \_ 0.02), but not with CBZ (exact tests one-sided *p* \_ 0.19, two-sided *p* \_ 0.31). Two Class II studies11,12 and six Class III studies13-15,18-20 also found a relationship between VPA dose and MCMs. The VPA dose above which MCMs were significantly more likely to occur was not consistent, but was approximately 1,000 mg daily in five studies.12,13,18-20 **Are there specific MCMs associated with specific** **AEDs?** One Class I study10 showed increased risk of neural tube defects and facial clefts with VPA (RR 5.32, CI 1.38 –20.50 for neural tube defects and RR 4.18, CI 1.55–11.25 for facial clefts). One Class II study8 showed increased risk for cleft palate with PHT and posterior cleft palate with CBZ. Another

Class II study12 showed increased risk of neural tube defects and hypospadias with VPA. Two Class III studies showed increased risk of spina bifida with VPA,9,21 and one showed increased risk of hypospadias.

9 Two Class III studies9,15 showed increased risk of cardiac malformations associated with PB.

***Conclusions***

• PHT exposure in utero possibly contributes to the risk of cleft palate (one Class II study).

• CBZ exposure in utero possibly contributes to the risk of posterior cleft palate (one Class II study).

• VPA exposure in utero probably contributes to neural tube defects and facial clefts (one Class I study) and possibly contributes to hypospadias (one Class II study).

• PB exposure in utero possibly contributes to cardiac malformations (two Class III studies).”

Harden CL, Pennel PB, Koppel BS, et al. Practice Parameter update: Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): Vitamin K, folic acid, blood levels and breastfeeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73:142-149.

NICE guideline statements were a reaffirmation of previous statements in 2004. These statements and evidence were previously reviewed during prior endorsement review.

**1a.7.6.** **What is the overall quality of evidence across studies in the body of evidence**? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)

See details provided in 1a.7.5

**ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE**

**1a.7.7.** **What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence**? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*)

See details provided in 1a.7.5

**1a.7.8.** **What harms were studied and how do they affect the net benefit (benefits over harms)?**

See details provided in 1a.7.5

**UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE**

**1a.7.9.** **If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review**.

NICE completed an update of the evidence in 2014, and complete details of their update can be found online at: <http://www.nice.org.uk/guidance/cg137/evidence/evidence-update-544389949> NICE found there was no potential impact on guidance for Women and girls with epilepsy previously published.

* Vajda FJ, O’Brien TJ, Lander CM, et al. Tertogenesis in repeated pregnancies in antiepileptic drug-treated women. Epilepsia 2013; 54(1):181-186.
* Campbell E, Devenney E, Morrow J et al. (2013) Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs in utero. Epilepsia 54: 165–71
* Meador KJ, Baker GA, Browning N et al. (2013) Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurology 12: 244–52

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.8 OTHER SOURCE OF EVIDENCE**

*If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.*

**1a.8.1** **What process was used to identify the evidence?**

**1a.8.2.** **Provide the citation and summary for each piece of evidence.**