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

**Measure Number** (*if previously endorsed*)**:** 1858

**Measure Title**: Trastuzumab administered to patients with AJCC stage I (T1c) – III human epidermal growth factor receptor 2 (HER2) positive breast cancer who receive adjuvant chemotherapy

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** N/A

**Date of Submission**: 11/12/2019

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| **Instructions**  *Complete 1a.1 and 1a.2 for all measures. If instrument-based measure, complete 1a.3.*  *Complete* ***EITHER 1a.2, 1a.3 or 1a.4*** *as applicable for the type of measure and evidence.*  *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.*   * 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. * Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx). |

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| **Note: The information provided in this form is intended to aid the Standing 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:   * Outcome: [**3**](#Note3) Empirical data demonstrate a relationship between the outcome and at least one healthcare structure, process, intervention, or service. If not available, wide variation in performance can be used as evidence, assuming the data are from a robust number of providers and results are not subject to systematic bias. * 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. * For measures derived from patient reports, evidence should demonstrate that the target population values the measured outcome, process, or structure and finds it meaningful. * Process measures incorporating Appropriate Use Criteria: See NQF’s guidance for evidence for measures, in general; guidance for measures specifically based on clinical practice guidelines apply as well.   **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 Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org) and/or modified GRADE.  **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

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.* (*A PRO-based performance measure is not a survey instrument. Data may be collected using a survey instrument to construct a PRO measure.)*

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

Process: Administration of trastuzumab

Appropriate use measure: Click here to name what is being measured

Structure: Click here to name the structure

Composite: Click here to name what is being measured

**1a.2** **LOGIC MODEL** Diagram or briefly describe the steps between the healthcare structures and processes (e.g., interventions, or services) and the patient’s health outcome(s). The relationships in the diagram should be easily understood by general, non-technical audiences. Indicate the structure, process or outcome being measured.

The process evaluated in this measure is a patient being administered trastuzumab within 12 months of a breast cancer diagnosis. Multiple randomized controlled trials have demonstrated that administration of trastuzumab improves a patient’s disease-free survival (DFS) and overall survival (OS). Additionally, this measure is directly supported by recommendations in National Comprehensive Cancer Network (NCCN), Cancer Care Ontario (CCO), and American Society of Clinical Oncology(ASCO)-CCO clinical practice guidelines.

The role of trastuzumab in adjuvant and neoadjuvant therapy in women with

HER2/neu-overexpressing breast cancer. Madarnas Y, Tey R, reviewers. Toronto

(ON): Cancer Care Ontario; 2011 Sep 15 [Endorsed 2010 Jun 11]. Program in

Evidence-based Care Evidence-Based Series No.: 1-24 Version 2

<https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13890>

Gradishar WJ, Anderson BO, Abraham J, et al. NCCN Guidelines Panel. NCCN Clinical Practice Guidelines

in Oncology – Breast Cancer. Version 3. 2019. September 6, 2019.

<https://www.nccn.org> (free account is required to view guideline)

Denduluri, N., et al., *Selection of Optimal Adjuvant Chemotherapy and Targeted*

*Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused*

*Update.* J Clin Oncol, 2018. **36**(23): p. 2433-2443.

<https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/11081>

Eisen A, Fletcher GG, Gandhi S, Mates M, Freedman OC, Dent SF, et al. Optimal systematic therapy for early female breast cancer. Toronto (ON): Cancer Care Ontario; 2014 Sep 30 [In Review 2019 Jan]. Program in Evidence-Based Care Evidence-Based Series No.: 1−21 IN REVIEW.

<https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/331>

**1a.3** **Value and Meaningfulness:**  **IF** this measure is derived from patient report, provide evidence that the target population values the measured ***outcome, process, or structure*** and finds it meaningful. (Describe how and from whom their input was obtained.)

**\*\*RESPOND TO ONLY ONE SECTION BELOW -EITHER 1a.2, 1a.3 or 1a.4) \*\***

**1a.2** **FOR OUTCOME MEASURES including PATIENT REPORTED OUTCOMES - Provide empirical data demonstrating the relationship between the outcome (or PRO) to at least one healthcare structure, process, intervention, or service.**

**1a.3.****SYSTEMATIC REVIEW(SR) OF THE EVIDENCE (for intermediate outcome, PROCESS, or STRUCTURE PERFORMANCE measures, including those that are instrument-based) If the evidence is not based on a systematic review go to section 1a.4) If you wish to include more than one systematic review, add additional tables.**

**What is the source of the systematic review of the body of evidence that supports the performance measure? A systematic review is a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. It may include a quantitative synthesis (meta-analysis), depending on the available data. (IOM)**

Clinical Practice Guideline recommendation (with evidence review)

☐ US Preventive Services Task Force Recommendation

☐ Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*)

☐ Other

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| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | NCCN Guidelines Version 3.2019 Breast Cancer  National Comprehensive Cancer Network  Version 3.2019 – September 6, 2019  NCCN Clinical Practice Guidelines in Oncology™. Breast Cancer, V.3.2019 (MS-30)  <https://www.nccn.org> (free account is required to view the guideline, however full pdf is attached below) |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the conclusions from the SR. | “The panel recommends HER2-targeted therapy in patients with HER2-positive tumors. Trastuzumab is humanized monoclonal antibody with specificity for the extracellular domain of HER2. All of the adjuvant trials of trastuzumab have demonstrated clinically significant improvements in DFS, and the combined analysis from the NSABP B31 and NCCTG N9831 trials, and the HERA trial, showed significant improvement in OS with the use of trastuzumab in patients with high-risk, HER2-positive breast cancer. Therefore, regimens from each of these trials are included as trastuzumab-containing adjuvant regimen choices in the guideline. The benefits of trastuzumab are independent of ER status. Based on these studies, the panel has designated use of trastuzumab with chemotherapy as a category 1 recommendation in patients with HER2-positive tumors greater than 1 cm.” (MS-44-MS-46) |
| Grade assigned to the **evidence** associated with the recommendation with the definition of the grade | Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate |
| Provide all other grades and definitions from the evidence grading system | NCCN Categories of Evidence and Consensus:  Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.  Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.  Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.  Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |
| Grade assigned to the **recommendation** with definition of the grade | Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate |
| Provide all other grades and definitions from the recommendation grading system | NCCN Categories of Evidence and Consensus:  Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.  Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.  Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.  Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | The NCCN guideline notes that results of nine randomized trials testing trastuzumab as adjuvant therapy have been reported, and recounts detailed results for four RCTs of adjuvant trastuzumab, including NSABP B-31, NCCTG N9831, HERA, and BCIRG 006. NCCN’s analysis of these trials includes the following summary (MS-44-MS-46):   * “The panel recommends HER2-targeted therapy in patients with HER2-positive tumors. Trastuzumab is humanized monoclonal antibody with specificity for the extracellular domain of HER2. All of the adjuvant trials of trastuzumab have demonstrated clinically significant improvements in DFS, and the combined analysis from the NSABP B31 and NCCTG N9831 trials, and the HERA trial, showed significant improvement in OS with the use of trastuzumab in patients with high-risk, HER2-positive breast cancer. Therefore, regimens from each of these trials are included as trastuzumab-containing adjuvant regimen choices in the guideline. The benefits of trastuzumab are independent of ER status. Based on these studies, the panel has designated use of trastuzumab with chemotherapy as a category 1 recommendation in patients with HER2-positive tumors greater than 1 cm.” |
| Estimates of benefit and consistency across studies | See Body of Evidence section. |
| What harms were identified? | See Body of Evidence section. |
| Identify any new studies conducted since the SR. Do the new studies change the conclusions from the SR? | Updated guidelines continue to support this measure. |

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| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | Optimal Systemic Therapy for Early Female Breast Cancer  Andrea Eisen, Glenn G. Fletcher, Sonal Gandhi, Mihaela Mates, Orit C. Freedman, Susan F. Dent, Maureen E. Trudeau, and members of the Early Breast Cancer Systemic Therapy Consensus Panel  September 30, 2014  Eisen A, Fletcher GG, Gandhi S, Mates M, Freedman OC, Dent SF, et al. Optimal systematic therapy for early female breast cancer. Toronto (ON): Cancer Care Ontario; 2014 Sep 30 [In Review 2019 Jan]. Program in Evidence-Based Care Evidence-Based Series No.: 1−21 IN REVIEW. (pgs. 17-18)  <https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/331> |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the conclusions from the SR. | R27. Trastuzumab plus chemotherapy is recommended for all patients with HER2+ node positive breast cancer and for patients with Her2+ node negative breast cancer greater than 1 cm in size |
| Grade assigned to the **evidence** associated with the recommendation with the definition of the grade | This guideline utilized a modified Delphi technique to reach consensus on final recommendations.  The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial caner system, Cancer Care Ontario (CCO). The PEBC produces evidence-based and evidence-informed guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle. The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence be our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. |
| Provide all other grades and definitions from the evidence grading system | See Body of Evidence section. |
| Grade assigned to the **recommendation** with definition of the grade | See Body of Evidence section. |
| Provide all other grades and definitions from the recommendation grading system | See Body of Evidence section. |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | Key Evidence and Qualifying Statements   * Phase III clinical studies have demonstrated improved DFS and OS with the addition of trastuzumab to chemotherapy compared with chemotherapy alone in HER2+ early breast cancer (see Table 14 for Evidentiary Base). * The majority of adjuvant trastuzumab trials included patients with lymph node positive breast cancer, or lymph node negative disease with one of the following high-risk features: ER-, grade 2 or 3, T ≥1cm, or age <35 years. Trastuzumab may still be considered in patients with HER2+ disease outside these features. Although most studies excluded patients with tumors <1 cm, the benefit of trastuzumab was equivalent in both node negative and node positive tumors in the HERA trial which included small N0 tumours (1 cm was the formal inclusion criteria, although 60 patients with tumors <1 cm were also enrolled). The BCIRG 006 trial analysis by tumour size found benefit in tumours <1 cm, <2 cm, and ≥2 cm, but not for tumours 1-2 cm in size; however, interpretation is limited because of the small number of patients in each category. The review by Petrelli and Barni concluded that patients with HER2+ tumours have a higher rate of recurrence and poorer survival rate than patients with HER2- cancer of the same size/stage, confirming that HER2 positivity itself is a risk factor. There does not appear to be a threshold according to tumour size, and size alone should not be the deciding factor in whether to administer trastuzumab to patients with tumours <1 cm. In Ontario, tumours <1 cm can be treated under the Evidence Building Program (EBP). * The meta-analysis by Moja et al (Cochrane Collaboration) found that the hazard ratio for trastuzumab-containing regimens vs. chemotherapy alone was 0.66 for OS and 0.60 for DFS (p<0.00001 for both). The risk of congestive heart failure and left ventricular ejection decline were higher with trastuzumab (RR=55.1, p<0.00001 and R=1.83, p<0.0008, respectively). In patients at high risk of recurrence without cardiac problems, there is clear survival rate benefit for trastuzumab. |
| Estimates of benefit and consistency across studies | See Body of Evidence section |
| What harms were identified? | See Body of Evidence section |
| Identify any new studies conducted since the SR. Do the new studies change the conclusions from the SR? | Updated guidelines continue to support this measure. |

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| **Source of Systematic Review:**   * **Title** * **Author** * **Date** * **Citation, including page number** * **URL** | The role of trastuzumab in adjuvant and neoadjuvant therapy in women with  HER2/neu-overexpressing breast cancer. Madarnas Y, Tey R, reviewers. Toronto  (ON): Cancer Care Ontario; 2011 Sep 15 [Endorsed 2010 Jun 11]. Program in  Evidence-based Care Evidence-Based Series No.: 1-24 Version 2  <https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/pebc1-24f.pdf> (a pop-up box will appear, click “OK”)    Please note the verbatim recommendation (below) appeared in the above  Cancer Care Ontario guideline, which is no longer available via PubMed. This  recommendation was reaffirmed in the following 2018 ASCO and Cancer Care  Ontario guideline update:  Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early  Breast Cancer  Denduluri, N., et al., *Selection of Optimal Adjuvant Chemotherapy and Targeted*  *Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused*  *Update.* J Clin Oncol, 2018. **36**(23): p. 2433-2443.  <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/11081> |
| Quote the guideline or recommendation verbatim about the process, structure or intermediate outcome being measured. If not a guideline, summarize the conclusions from the SR. | “Trastuzumab should be offered for one year to all patients with HER2  Positive node-positive or node-negative, tumour greater than 1 cm in size,  and primary breast cancer and who are receiving or have received  (neo)adjuvant chemotherapy. Trastuzumab should be offered after  chemotherapy.” (CCO guideline, development and methods pg 3/ pdf pg  29; <https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/pebc1-24f.pdf> (a pop-up box will appear, click “OK”).  Please note this original recommendation was reaffirmed in a 2018 ASCO and Cancer Care Ontario guideline update, available at: <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer#/11081> |
| Grade assigned to the **evidence** associated with the recommendation with the definition of the grade | CCO guidelines use a narrative approach in grading the quality of the evidence. |
| Provide all other grades and definitions from the evidence grading system | CCO guidelines use a narrative approach in grading the quality of the evidence. |
| Grade assigned to the **recommendation** with definition of the grade | The guideline provides strong support for the use of trastuzumab  in all patients with HER2 positive primary breast cancer.  Strong Recommendation: There is high confidence that the recommendation  reflects best practice. This is based on (1) strong evidence for a true net effect  (e.g., benefits exceed harms); (2) consistent results, with no or minor  exceptions; (3) minor or no concerns about study quality; and/or (4) the extent  of panelists’ agreement. Other compelling considerations (discussed in the  guideline’s literature review and analyses) may also warrant a strong  recommendation. |
| Provide all other grades and definitions from the recommendation grading system | Strong Recommendation: There is high confidence that the recommendation  reflects best practice. This is based on (1) strong evidence for a true net effect  (e.g., benefits exceed harms); (2) consistent results, with no or minor  exceptions; (3) minor or no concerns about study quality; and/or (4) the extent  of panelists’ agreement. Other compelling considerations (discussed in the  guideline’s literature review and analyses) may also warrant a strong  recommendation.  Moderate Recommendation: There is moderate confidence that the  recommendation reflects best practice. This is based on (1) good evidence for a  true net effect (e.g., benefits exceed harms); (2) consistent results, with minor  and/or few exceptions; (3) minor and/or few concerns about study quality;  and/or (4) the extent of panelists’ agreement. Other compelling considerations  (discussed in the guideline’s literature review and analyses) may also warrant a  moderate recommendation.  Weak Recommendation: There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists’ agreement. Other considerations (discussed in the guideline’s literature review and analyses) may also warrant a weak recommendation. |
| Body of evidence:   * Quantity – how many studies? * Quality – what type of studies? | Six randomized controlled trials were considered in the original CCO  recommendation. |
| Estimates of benefit and consistency across studies | The evidence described in the RCTs is directly relevant to the measure (use of  trastuzumab in patients with HER2/neu positive breast cancer). All studies  considered women with invasive breast cancer that overexpressed HER2/neu  and outcomes associated with the inclusion of trastuzumab. Five trials included  chemotherapy plus or minus trastuzumab. Some of those also investigated the  schedule for trastuzumab delivery; considering schedules concurrent with  chemotherapy, or following chemotherapy completion with various time  periods in between completion of chemotherapy and the start of trastuzumab.  Duration of trastuzumab was also investigated. One trial specifically considered  cardiac adverse events to assess potential harms, other trials considered  adverse events in addition to disease-specific outcomes.  The outcome of disease-free survival is more precise given the limited long-term  follow-up, with more events for consideration, compared to overall survival.  This limits issues with insufficient events. Notably, both outcomes were  reported for consideration, though benefits in overall survival were noted in  two individual studies and the combined analysis from NSABP B31 and NCCTG  N9831.  Results were consistent with respect to improvements in disease-free survival  among women randomized to trastuzumab-containing arms. Hazard ratios  reported for disease free survival were 0.54, 0.55, 0.45 and 0.48. The results for  disease-free survival across trials were statistically significant for the treatment  arm including trastuzumab.  Studies were consistent with respect to the direction of effect. Differences in  magnitude were noted, but can be attributed to various chemotherapies  regimens across the studies, as well as slightly different patient populations.  All of the adjuvant trials of trastuzumab have demonstrated clinically significant  improvements in disease-free survival. The combined analysis from NSABP B31  and NCCTG N9831, BCIRG 006, and the HERA trial showed significant  improvement in overall survival with the use of trastuzumab in patients with  high-risk, HER2 positive breast cancer.  Based on preliminary reports of three large RCTs, the addition of one year of  trastuzumab, following a variety of adjuvant or neoadjuvant chemotherapy  regimens, significantly improved the primary endpoint of DFS in patients with  HER2/neu positive early breast cancer. Secondary endpoints of RFS, DDFS, and  TTR in all studies, and OS in one combined study, were also significantly  improved with the addition of trastuzumab. Those results are only applicable to  women with HER2/neu overexpressing breast cancer who complete a minimum  of four cycles of adjuvant or neoadjuvant chemotherapy. Although the majority  of the patients in those studies had node-positive breast cancer, women with  high-risk node-negative breast cancer were also included in HERA (32% were N0  but had T1c tumors) and NCCTG 9831 (11% were N0 but had tumours >1cm if  ER negative, >2cm if ER positive). Therefore, those results are also generalizable  to women with node-negative breast cancer who meet those criteria. The  magnitude of incremental benefit conveyed by adjuvant trastuzumab well  exceeds the gains accrued by over three decades of adjuvant chemotherapy  use. |
| What harms were identified? | Based on the current reports, the cardiac toxicity with adjuvant trastuzumab  appears to be acceptable. Notably, the reported rate of cardiac events was  higher in the concurrent versus sequential trastuzumab arm (in NSABP B31 4.1%  vs. 0.7%, HR of 7.2; in NCCTG 9831 3.3% vs. 2.2%). The toxicity is considered  acceptable, given the increase in survival. |
| Identify any new studies conducted since the SR. Do the new studies change the conclusions from the SR? | A 2018 ASCO and Cancer Care Ontario guideline update reaffirmed this recommendation on the use of trastuzumab, following a systematic review. No new studies changing the conclusions reached by the 2018 guideline update were found in subsequent literature reviews. |

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**1a.4 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.4.1** **Briefly SYNTHESIZE the evidence that supports the measure.** A list of references without a summary is not acceptable.

**1a.4.2 What process was used to identify the evidence?**

**1a.4.3.** **Provide the citation(s) for the evidence.**