Evidence-based Practice Center Systematic Review Protocol

Project Title: Breastfeeding and Health Outcomes for Infants and Children

I. Background and Objectives for the Systematic Review

Breastfeeding – the feeding of human milk at the breast or expressed – is widely accepted as the most beneficial feeding method for infants. Decades of research showing that breastfeeding is associated with short- and long-term benefits for children and mothers has led multiple national and international organizations, including the American Academy of Pediatrics (AAP),1 the American Academy of Family Physicians,2 the American Congress of Obstetrics and Gynecology,3 the Canadian Pediatric Society,4 the 2020–2025 Dietary Guidelines for Americans,5 and the World Health Organization (WHO)6 to recommend that infants be fed breastmilk exclusively for the first 6 months of life. Additionally, WHO and AAP support continued breastfeeding, along with appropriate complementary foods introduced at about 6 months, as long as mutually desired for 2 years or beyond.1,7

Globally, breastfeeding initiation rates vary widely, with more developed countries having lower rates of breastfeeding initiation and continuation than less developed countries.8 In the United States, rates of ever and exclusive breastfeeding are lower among Black persons, persons with lower socioeconomic status, persons who are unmarried, persons from rural areas, and those in younger age groups compared with their counterparts.9-12 These groups disproportionately face several barriers to breastfeeding, including needing to return to work, inflexible work hours, inequities in access to resources and services that support breastfeeding and expressing milk, and less cultural acceptance of breastfeeding.13-18 Understanding how the association between breastfeeding and health outcomes varies by social and demographic characteristics may help identify structural barriers and other areas to prioritize for intervention. Evidence exists that interventions to support breastfeeding can be effective in increasing the rates and duration of breastfeeding, though greater effort is needed to address the inequities in access to these programs.19-21

To date, the most comprehensive and widely cited systematic review on the relationship between breastfeeding and infant and maternal health outcomes is a 2007 report by Ip and colleagues.22 Guideline developers and decision makers throughout the United States2,23 and internationally4 have relied on this report, which synthesized both primary studies and existing systematic reviews. The 2007 report was critically important in building federal efforts to support breastfeeding in the United States and in helping to inform the Centers for Disease Control and Prevention’s (CDC’s) program development activities. In 2018, the report was partially updated, focusing only on the maternal health benefits of breastfeeding.20 Several recent reviews, including those from the Pregnancy and Birth to 24 Months Project24-29 and others30-36 have examined specific infant and child outcomes. However, no review has comprehensively updated the 2007 report’s evidence on the link between breastfeeding and infant and child outcomes.
It is well-established that breastfeeding and the consumption of human milk is beneficial for infants. However, our understanding of the nuanced benefits of breastfeeding for specific health outcomes, the magnitude of those benefits, and how they vary with the intensity, duration, mode of feeding, and source of human milk continues to evolve. It is important to understand this evidence base to inform guidelines and help clinicians support patients in making feeding decisions.

**Purpose of the Review**

The purpose of this review is to provide a synthesis of the current evidence on the association between breastfeeding/consumption of human milk and a range of health outcomes in infants and children. The systematic review was nominated by the Centers for Disease Control and Prevention (CDC) to inform their program development activities. The intended audience includes guideline developers, maternal and infant health programmatic leaders, research funders and researchers, and clinicians who provide care to persons planning to become parents or expecting a birth.

**II. Key Definitions**

- **Breastfeeding**: Feeding human milk alone or in combination with commercial milk formula and/or complementary foods or beverages. Breastfeeding includes feeding at the breast (direct breastfeeding) or feeding expressed human milk from mother, lactating parent, or donor source

- **Breastfeeding initiation**: A measure of whether an infant has started consuming human milk

- **Breastmilk**: Human milk

- **Commercial milk formula**: Commercially prepared milk formula meeting U.S. Food and Drug Administration and/or Codex Alimentarius international food standards; also referred to as infant formula or breastmilk substitute

- **Complementary foods and beverages**: Foods and beverages other than human milk or commercial milk formula (liquids, semisolids, and solids) provided to an infant or young child to provide nutrients and energy

- **Donor human milk**: Human milk that has been expressed by someone other than the mother or lactating parent and donated. Includes either pasteurized donor milk from certified milk banks or uncertified, informally donated human milk

- **Duration of breastfeeding**: Length of time infant was fed human milk. Typically calculated based on point-in-time or current breastfeeding status (e.g., 24-hour recall) or reported as time when human milk consumption ceased

- **Early initiation of breastfeeding**: Fed human milk within one hour of birth
• **Ever breastfed**: A measure of consumption of human milk at any point during a child’s life. Is often compared to “never breastfed”

• **Exclusive breastfeeding**: Feeding with human milk alone, not in combination with commercial milk formula and/or complementary foods or beverages. Can include limited quantities of prescribed medicines, vitamins, minerals, and oral rehydration solution but does not include water. Measured scientifically as “exclusivity”

• **Expressed human milk**: Human milk that has been expressed by hand or with a pump

• **Intensity of breastfeeding**: A measure of the proportion of total feedings in a given time period that include human milk, including the degree of exclusivity

• **Mixed feeding**: Feeding with human milk and commercial milk formula but not complementary foods or beverages

• **Mode of feeding**: A measure of how an infant consumes human milk, such as at the breast (direct breastfeeding) or previously expressed human milk via bottle or spoon

• **Predominant breastfeeding**: Feeding with human milk alone (not in combination with commercial milk formula and/or complementary foods or beverages), but can include limited quantities of (a) drops or syrups containing vitamins, minerals, or medicines, (b) water and water-based drinks such as sweetened water and teas, (c) fruit juice, (d) oral rehydration salts solution, or (e) ritual fluids

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Feeding an infant at the breast and producing and expressing human milk are frequently discussed solely in relation to mothers and within a woman’s domain. However, not all people who give birth or feed their infants human milk identify as a woman or mother. Transgender men and gender nonbinary individuals can and do become pregnant and give birth and therefore may be candidates for breastfeeding their infants. As such, the word “breastfeeding” itself may be less accurate for gender-diverse parents, who may prefer the term “chestfeeding,” which is more inclusive of lactation in the context of varying physiologic anatomies. Acknowledging this diversity, we have elected to use the terms “breastfeeding” and “mother” in this document since these terms more accurately describe the populations in the anticipated body of evidence and are more easily understood in the United States and internationally, particularly by non-native English speakers and those with lower literacy levels. Moreover, we want to ensure this systematic review accurately highlights important research gaps, such as the need for more studies conducted among gender-diverse individuals. Therefore, we will strive to ensure the terms we use are accessible to a wide variety of audiences and accurately describe the populations in the included body of evidence. As studies report on populations and infant feeding in more gender-inclusive language, we will bring that language forward.
III. Key Questions

This review will be guided by one Key Question (KQ 1) that addresses the infant and child health outcomes associated with breastfeeding and consuming human milk. One sub-KQ (KQ 1a) addresses variation in the associations by important variables related to breastfeeding and human milk consumption.

1. What is the association between breastfeeding/human milk consumption and health outcomes among infants and children?

   a. How do these associations vary by intensity (including exclusivity), duration, and mode of feeding, and by source of human milk?

IV. Methods

Our methods follow guidance provided in the AHRQ Effective Health Care Program Methods Guide for Effectiveness and Comparative Effectiveness Reviews.43

The original questions provided in the scope of work were revised by the systematic review project team in partnership with the AHRQ Task Order Officer, CDC, Key Informants (KIs), and input received while the KQs were posted for public comment (from January 3, 2023, to February 1, 2023). A draft protocol was reviewed by our Technical Expert Panel and was subsequently revised to reflect greater clarity in our inclusion and exclusion criteria and methods.

Criteria for Inclusion and Exclusion of Studies in the Review

The following inclusion and exclusion criteria will be used to guide the literature search and to determine whether identified studies should be included in the systematic review (Table 1).

<table>
<thead>
<tr>
<th>PICOTS</th>
<th>Inclusion</th>
<th>Exclusion</th>
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<tr>
<td>Populations</td>
<td>Full term infants (≥ 37 and 0/7 weeks gestation)</td>
<td>Studies exclusively among:</td>
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<tr>
<td></td>
<td></td>
<td>• Preterm (gestational age &lt;37 weeks) infants</td>
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<td>• Low birth weight (&lt;2500 grams) or small for gestational age infants</td>
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<td>• Women with medical conditions contraindicated for breastfeeding (e.g., breast cancer, HIV)</td>
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<td>Exposures</td>
<td>Any exposure to human milk, including feeding at the breast; consuming expressed human milk; or a combination</td>
<td>Application of human milk to skin</td>
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<td>PICOTS</td>
<td>Inclusion</td>
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| **Comparators** | • No exposure to human milk  
• Less intensive exposure (e.g., mixed feeding or commercial milk formula consumption vs. exclusive consumption; lower proportion of feedings that are human milk)  
• Shorter duration of exposure  
• Different mechanism of exposure (e.g., feeding at the breast [direct breastfeeding] vs. feeding expressed human milk)  
• Different source of human milk (e.g., milk from lactating parent vs. milk from donor) | All other comparisons; no comparison |

| **Outcomes** | Health outcomes observed at any point in the life course, specifically:  
• Allergies, specifically:  
  o Atopic dermatitis  
  o Allergic rhinitis  
  o Food allergies  
• Asthma  
• Celiac disease  
• Cognitive development (e.g., measures of IQ and other cognitive development measures)  
• Childhood cancer  
• Cardiovascular disease outcomes, specifically:  
  o Blood lipid levels, hyperlipidemia  
  o Blood pressure, elevated blood pressure  
  o Arterial stiffness, intima-media thickness, atherosclerosis  
  o Metabolic syndrome  
  o Incidence and prevalence of CVD  
  o CVD-related mortality  
• Diabetes, specifically  
  o Type I  
  o Type II  
• Infectious diseases, specifically:  
  o Otitis media  
  o Diarrhea/GI infection  
  o Upper and lower respiratory tract infections including COVID-19  
• Oral health outcomes, specifically:  
  o Dental caries  
  o Malocclusions  
• Sudden infant death syndrome / sudden unexpected infant death  
• Infant mortality  
• Inflammatory bowel disease  
• Weight-related outcomes, specifically:  
  o Weight gain velocity (birth to 24 months)  
  o Obesity | Any other outcome not specified, including maternal health outcomes |

| **Country setting** | Studies conducted in a more developed country, defined as "very high" on the 2021 human development index per the United Nations Development Programme | Studies conducted in other countries |
PICOTS | Inclusion | Exclusion
--- | --- | ---
**Study designs** | • Existing systematic reviews\(^c\) | All other designs, including:
• Observational studies comparing health outcomes among 2 or more groups with different exposures to human milk, including cohort and case-control\(^d\) studies and studies with observational follow-up of health outcomes from randomized or non-randomized clinical trials of breastfeeding support interventions | • Studies of breastfeeding support interventions without observational follow-up of health outcomes
• Studies with no comparison groups
• Cross-sectional studies\(^e\)
• Case series

**Publication language** | Studies published in English | Studies published in languages other than English

Abbreviations: ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorder; COVID-19 = coronavirus disease 2019; GI = gastrointestinal; HIV = human immunodeficiency virus; NICU = neonatal intensive care unit

\(^a\) The full report will contextually consider the unique feeding needs of this population and will discuss what we know about the association between breastfeeding and health outcomes for preterm infants. This evidence will not be systematically reviewed

\(^b\) The full report will contextually discuss potentially harmful unintended consequences related to breastfeeding such as excessive weight loss, hyperbilirubinemia, and hypoglycemia. This evidence will not be systematically reviewed

\(^c\) Well-conducted systematic review, with or without meta-analysis, that aligns with these PICOTS criteria and is not rated as “critically low” according to systematic review credibility criteria using AMSTAR 2\(^{45}\)

\(^d\) Case-control studies will be considered only in cases in which the outcome is rare (<1/1000) and/or this is the only evidence available for that particular outcome.

\(^e\) Cross-sectional studies will be excluded except in cases in which the study compares outcomes between twins or siblings with different exposures.

**Literature Search Strategies**

A medical research librarian will develop and execute the literature searches, which will be peer-reviewed by a second research librarian. We will search MEDLINE, Embase and CINAHL to identify English-language literature (existing systematic reviews [ESRs] and primary studies) published between 2005 and the present. The literature searches of the previous review were completed in November 2005. We will supplement our searches by examining the reference lists of other previously published reviews, meta-analyses, primary studies, and studies suggested by experts. A Supplemental Evidence and Data for Systematic review (SEADS) portal will be available for this review. Additional articles suggested to us from any source, including peer and public review, will be screened applying identical eligibility criteria.

While the draft report is under peer review and open for public comment, we will update the search and incorporate any eligible studies identified either during that search or through peer or public reviews into the final report.

**Process for Study Selection**

Given the number of outcomes and comparisons of interest and the time that has elapsed since the last comprehensive report on this subject, we will use a combination of methods to identify
and synthesize the evidence. This will include using ESRs and, where appropriate, summarizing newer evidence alongside ESRs.

First, we will screen the titles and abstracts of all records identified in the searches against the inclusion and exclusion criteria. Since we expect the literature searches to yield a high number of citations, we will develop, pilot, and use a single screen process (one reviewer) at this stage to identify clearly ineligible records based on keywords (e.g., animal, preterm, ovarian, depression) if necessary. Two reviewers will independently review all remaining titles and abstracts. Because we plan to use ESRs where possible, we will code all tentatively included citations according to their outcome and study design (i.e., ESR or primary study).

Once the title and abstract screening stage is complete, two reviewers will independently assess the full text of all publications identified during title and abstract review prioritizing the review of ESRs first and primary studies if necessary. All full-text articles will be coded for tentative inclusion or exclusion, including reasons for exclusion.

We will first triage full-text articles by outcome and according to study design (i.e., ESR or primary study). We will consider two scenarios in the use of ESRs: (1) using an ESR’s results only or (2) using an ESR’s results plus a “bridge” search for newer evidence and/or results for additional comparison(s). In the former example and in the case of no incorporation of new primary evidence, the results of an ESR will be presented as reported by review authors with no updating of the primary evidence or re-analysis of results. In the latter scenario, part of the ESR may be used as a starting point for an update to the evidence, with additional searching to bridge the gap in time between the ESR’s last search date and the present and/or to address additional comparisons not included in the base ESR. Our determination of whether incorporation of newer primary evidence is necessary will be based on the recency of the ESR’s last search date and the certainty of the underlying strength of the evidence (based on the limitations, directness, consistency, and precision as discussed below).

In instances where we identify more than one ESR that addresses a particular outcome and/or comparison, we will identify one review that represents the most current, credible, and applicable evidence for each outcome-by-comparison of interest. These reviews will serve as the basis for the main findings. Other ESRs will be coded for exclusion as being superseded by a more recent ESR. To select an ESR for each outcome-comparison pair, we will abstract minimal pertinent information about each review, including the last search date, number of included studies, and all PICOTS criteria. When comparing ESRs for the same outcome-comparison, we will use the following criteria to determine which ESR to include:

- Dates of search;
- Relevance of inclusion/exclusion criteria to our review criteria (i.e., based on included study designs, population, comparators, countries, and outcomes);
- Number of included studies; and/or
- Credibility of review (see Assessment of Methodological Risk of Bias).
We will not compare the included studies within each review to evaluate comprehensiveness, concordance, or discordance in the included primary evidence except in cases where the search dates and eligibility criteria are nearly identical.

In cases where there is no recent ESR or there is a signal that newer evidence might change the findings of the ESR (e.g., based on the design or size of the study or magnitude of relative association) we will review all primary literature identified in our search for that outcome-comparison.

All stages of study selection will be conducted in DistillerSR (Evidence Partners, Ottawa, Canada). We will keep detailed records of inclusion and exclusion decisions to report reasons for full-text exclusions for both ESRs and primary studies. Disagreements will be resolved by team discussion and consensus.

Assessment of Methodological Risk of Bias of Systematic Reviews and Individual Studies

We will assess the credibility of all ESRs being considered for inclusion using an adapted version of the AMSTAR 2 (Assessment of Multiple Systematic Reviews) tool.\textsuperscript{45, 48} The AMSTAR 2 tool contains 10 domains and 16 items that relate to the planning and conduct of the review. We will rate our confidence in the results of each ESR according to written guidance\textsuperscript{45} as: high (zero or one non-critical weakness), moderate (more than one non-critical weakness), low (one critical flaw with or without non-critical weaknesses or more than one non-critical weakness downgraded from moderate), or critically low (more than one critical flaw with or without non-critical weaknesses). One reviewer will complete the AMSTAR 2 tool for all provisionally included reviews; reviews that are rated critically low will be reviewed independently by a second reviewer using the same tool. ESRs rated as critically low by two reviewers according to AMSTAR 2 criteria will be excluded.

We will assess the risk of bias of primary studies being considered for inclusion according to the major risk of bias domains defined in the AHRQ Methods Guide\textsuperscript{49, 50} and using an adapted version of the Risk Of Bias In Non-randomized Studies – of Exposures (ROBINS-E) tool.\textsuperscript{51, 52} Risk of bias domains include bias due to confounding, bias in selecting participants into the study or analysis, bias arising from measurement of the exposure, bias due to post-exposure interventions, bias from missing data, bias from measurement of the outcome, and bias in reporting outcomes selectively. Important confounding or mediating variables related to the KQ include, for example, family household income and insurance status, maternal education, maternal employment, maternal race/ethnicity, immigrant status, maternal health status, maternal dietary intake, maternal smoking, family history of outcome, environmental exposures (e.g., pets), birthweight, type of infant formula, timing and type of complementary foods and beverages. We will rate the risk of bias for each study by domain and overall, as low, moderate, or high risk of bias. Two independent reviewers will assess the risk of bias for each primary study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team.

We will incorporate the credibility assessments and risk of bias results into our strength of evidence assessments and downgrade our confidence in evidence summaries in the presence of critical study limitations.
**Data Abstraction and Data Management**

We will abstract descriptive and outcome data from each included study into detailed abstraction forms in DistillerSR. One reviewer will complete primary data abstraction and a secondary reviewer will check the data for accuracy and completeness. Data abstraction forms will differ according to whether the study is an ESR or primary study.

For ESRs, we will abstract the pertinent methods of the review, including the last search date and PICOTS criteria and will note the analytic approach used, including any attempts to explore heterogeneity. We will abstract the total number of included studies and number of included studies by comparison. We will abstract details about how the breastfeeding exposures, comparisons, and outcome(s) were defined and will report the results of the ESR’s analysis, including pooled results, where available. If available, we will abstract what method was used to grade the strength of evidence for particular comparisons and/or outcomes and the results of those assessments. We will note the ESR-reported limitations in the body of evidence and any other important details that contextualize the findings of the review.

For primary studies, we will abstract general characteristics of the study (e.g., author, year, study design, purpose); clinical characteristics of the sample (e.g., age, race, setting, country); description of potential confounding factors and how the study accounted for those confounders; description of the breastfeeding exposures and comparisons; definitions of outcomes; analytic methods including adjustment for confounding factors; and results (e.g., absolute and relative risks of the outcome) favoring those that are adjusted for potential confounders rather than unadjusted results when both are provided and including credible, prespecified findings by subgroups. Additionally, we will note to what extent any adjustment impacted the findings to aid in interpretation of the results.

**Data Synthesis and Analysis**

We will synthesize the results of the review by health outcome. We will develop an overall figure or table to present the results for all outcomes.

If using an ESR as is (with no updating with newer evidence), we will report the review findings (narrative and/or quantitative estimates) as reported by review authors. In cases where we incorporate newer primary evidence, we will present the results of the primary evidence alongside the results of the ESR and will note the concordance or discordance in the consistency, precision, directness, and limitations of the newer evidence. Where appropriate, we will consider meta-analyzing data from ESRs with newly identified primary studies for specific outcomes-by-comparisons. We will consider performing meta-analysis for specific comparisons by outcomes when there is a signal that newer evidence may change the results reported in the ESR (e.g., several newer primary studies with large relative effects). We will require at least three unique studies of low or medium risk of bias that we deem sufficiently similar (i.e., in population, comparator, and outcome) in order to perform meta-analysis. If a meta-analysis is not possible, we will present the results of an ESR along with an updated narrative synthesis describing the results of the newly identified studies.
For ESRs and primary studies that report data from both developed and developing countries, we will report only those results pertaining to developed countries if the reported data allow us to do so. In instances where that is not possible, we will exclude the study.

Although this review is a partial update of the 2007 AHRQ review, in most cases we will not integrate the findings of that review with evidence from newer ESRs given the high likelihood of overlap in evidence between systematic reviews. Rather, the discussion section of our report will compare pooled estimates and strength of evidence assessments from the 2007 report with the results found in our update. For outcomes for which there is no recent ESR identified, we will examine the included studies from the 2007 review for potential inclusion in addition to newer primary evidence.

**Grading the Strength of Evidence for Major Comparisons and Outcomes**

We will rate the SOE for each outcome using the approach described in the AHRQ Methods Guide. We will abstract SOE judgments made in ESRs if available, and will reassess and assign our own SOE assessments considering all available data if necessary. The primary domains we will assess as part of our SOE assessment are study limitations, directness, consistency, and precision as described below:

- **Study limitations** (low, medium, high): The degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias (i.e., good internal validity).
- **Directness** (direct or indirect): The degree to which the outcome is directly or indirectly related to health outcomes of interest.
- **Consistency** (consistent, inconsistent, or unknown/not applicable): This is the degree to which studies report similar magnitudes of effect (i.e., range sizes are similar) or same direction of effect (i.e., effect sizes have the same sign)
- **Precision** (precise or imprecise): Describes the degree of certainty surrounding an effect estimate with respect to a given outcome, based on the width of confidence intervals relative to a clinically important effect estimate, sufficiency of sample size, and number of events.

Because methods to detect reporting bias in observational studies are less certain, we will not assess this domain as part of our rating. We may assess additional domains when appropriate, including dose-response association, strength of association, and the possibility that controlling for plausible confounders would increase or decrease the effect size. One reviewer will rate the SOE; at least one additional reviewer will independently review each rating.

The SOE for each outcome will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale (Table 2) by evaluating and weighing the combined results of the above domains.
Table 2. Description of the strength of evidence grades

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<th>Strength of Evidence</th>
<th>Description</th>
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<tr>
<td><strong>High</strong></td>
<td>We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.</td>
</tr>
<tr>
<td><strong>Insufficient</strong></td>
<td>We are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. The body of evidence has unacceptable deficiencies which precludes reaching a firm conclusion. If no evidence is available, it will be noted as “no evidence”</td>
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</table>

Source: Berkman et al.54

Assessing Applicability

Applicability will be assessed in accordance with AHRQ’s Methods Guide.53, 54 Several factors may limit the applicability of findings, including the extent to which the results from included studies may or may not apply to the full spectrum of families and exposures in developed countries. Some factors identified *a priori* that may limit the applicability of evidence to persons with full-term infants in developed countries include the race and ethnicity of enrolled populations (and underlying inequities and structural social constructs), the setting and geographic locations of enrolled populations, and the availability of health insurance and employment status of enrolled populations. We will also pay attention to the time frame between exposure to breastfeeding and the outcomes of interest and will note the extent to which secular trends in rates of breastfeeding or the outcomes may confound the observed associations. Findings linking breastfeeding to infant and child health outcomes from observations made decades ago may not be generalizable to contemporary populations. Based on EPC guidance, the SOE rating will be uninfluenced by these factors.43, 53, 54 Instead, we will discuss applicability in a separate section, using the PICOTS as a guiding framework to ensure that we consider several components of applicability.
V. References


VI. Summary of Protocol Amendments
[to be completed if protocol is modified]

VII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized them after reviewing of the public comments and seeking input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the Key Questions are specific and relevant.
VIII. Key Informants

Key Informants are the end-users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

IX. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.
Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

**XI. EPC Team Disclosures**

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

**XII. Role of the Funder**

This project was funded under Contract No. 75Q80120D00004 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by either the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

**XIII. Registration**

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).