

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 12: Pregnancy, Including Preterm Birth

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 750 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of about 195 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COIs).

Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the single topic for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before November 6, 2015, in this priority area; and (3) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Seven topics in this priority area were being tracked in the system as of November 6, 2015.)

We present a summary on this topic, which was deemed to have high-impact potential on the basis of expert comments. Readers are encouraged to read the detailed information on the intervention that follows the Executive Summary.

Priority Area 12: Pregnancy Including Preterm Birth Interventions and Programs

Topic	High-Impact Potential
1. Elagolix for treatment of endometriosis	Lower end of the high-impact-potential range

Discussion

We have found relatively few innovations in the pregnancy and preterm birth priority area for the Healthcare Horizon Scanning System despite extensive scanning since the system’s inception. In the past 12–15 months, even fewer topics have met criteria for tracking because so few of the leads we identify are interventions that truly address an unmet need. Consequently, for this edition of the report, a single topic was eligible for consideration. We are tracking six other interventions. These include an antibody infusion to prevent congenital cytomegalovirus infection, a biologic agent to prevent bronchopulmonary dysplasia in preterm infants, interventions intended to target both the pregnant woman and fetus (a drug for treating preeclampsia, another for preventing preterm birth, and a weight-management program), and a program for treating depression and anxiety in mothers of preterm infants. These topics were ineligible for consideration in this report because no phase III data were available, although trials are ongoing.

The paucity of new interventions might reflect an incomplete understanding of gestation and ways to enhance fetal development. According to the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), about half of stillbirths (i.e., miscarriages that occur after 20 weeks of gestation) occur with no known cause. Contributing conditions cited by

NICHD include chromosomal abnormalities, placental abnormalities, poor fetal growth, chronic maternal health issues, and infections. NICHD has developed a scientific vision for the next decade, including goals for pregnancy and reproductive research. NICHD states that scientists should be able to establish the causes of stillbirth and prematurity and to develop evidence-based preventive measures. NICHD's goals for reproductive science include developing new male and nonhormonal contraceptives and elucidating mechanisms for three major gynecologic disorders (i.e., endometriosis, pelvic floor disorders, fibroids). The American Congress of Obstetricians and Gynecologists' Making Obstetrics and Maternity Safer (MOMS) initiative to improve maternal health focuses on prematurity causes and interventions, obesity treatments and prevention, and maternal and fetal health-outcomes disparities. We expect that new interventions may develop in these areas.

Since the last Potential High-Impact Interventions report in June 2015, one topic in this priority area was eligible for consideration for high-impact potential.

Elagolix for Treatment of Endometriosis

- **Key Facts:** Pharmacologic interventions for moderate or severe endometriosis include peptide gonadotropin-releasing hormone (GnRH) receptor agonists such as leuprolide and goserelin. However, these must be injected via a depot formulation, can take weeks to work, and may induce menopause-like symptoms. Elagolix is a new, oral, fast-acting, nonpeptide GnRH receptor antagonist for treating endometriosis that is intended to reduce secretion of follicle-stimulating hormone and luteinizing hormone by blocking the GnRH receptor. According to the manufacturer, its rapid onset prevents hormonal flare associated with GnRH receptor agonist treatment, and it can be titrated to avoid bone density loss. In a phase III clinical trial, elagolix is being administered at a dosage of 150 mg once daily or 200 mg twice daily, orally. The developers are AbbVie (North Chicago, IL), in collaboration with Neurocrine Biosciences, Inc. (San Diego, CA).
Three phase III trials are ongoing. According to a manufacturer press release, positive preliminary results reported from a completed phase III trial (n=872) indicate that elagolix reduced menstrual pain and nonmenstrual pelvic pain. Additional smaller trials reported similar pain improvements, and bone mineral density loss was comparable to placebo. AbbVie expects to complete pivotal trials by November 2016 and then submit a new drug application. No cost, coverage, coding, or payment information is available yet, but elagolix is expected to cost more than available peptide GnRH receptor agonists, some of which are available in generic formulations, if it shows improved safety and efficacy. If the U.S. Food and Drug Administration approves elagolix, third-party payers may decline to cover the drug without data supporting its superiority to other treatments or payers may require a step-therapy approach starting with existing endometriosis treatments before using elagolix.
- **Key Expert Comments:** Overall, experts commenting on this topic thought that elagolix addresses an unmet need for an endometriosis treatment that is convenient, has manageable side effects, and provides symptom relief; however, it does not cure or prevent endometriosis, which limits its impact on patient health. Experts also noted that patients may prefer this oral drug over injectable alternatives. Experts suggested elagolix's presumed high price may increase overall health care costs.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Pregnancy Including Preterm Birth Intervention

Elagolix for Treatment of Endometriosis

Unmet need: Endometriosis is a painful disorder in which endometrium grows outside the uterus, commonly in the ovaries, bowel, or tissue lining the pelvis. Pharmacologic interventions for moderate or severe endometriosis include peptide gonadotropin-releasing hormone (GnRH) receptor agonists such as leuprolide and goserelin. However, these must be injected via a depot formulation, can take weeks to work, and may induce menopause-like symptoms. In patients whose disease does not respond to medical management, surgery to remove lesions or hysterectomy may be indicated.¹ Elagolix is a new, oral, fast-acting, nonpeptide GnRH receptor antagonist in development for treating endometriosis and has potential to avoid the undesirable side effects of existing treatments.

Intervention: As part of the menstrual cycle, the hypothalamus stimulates the pituitary gland with GnRH. Then the pituitary gland produces follicle-stimulating hormone (FSH) and luteinizing hormone (LH) that induce the ovaries to produce estrogen and progesterone. Natural secretion of GnRH by the hypothalamus occurs in pulses, and continuous GnRH receptor stimulation (e.g., as produced by administration of GnRH receptor agonists) can desensitize the pituitary gland to GnRH, reducing FSH and LH secretion. Alternatively, a competitive antagonist of the GnRH receptor could occupy receptors, also reducing FSH and LH secretion.²

Elagolix is such a nonpeptide GnRH receptor antagonist. It purportedly has a rapid onset, prevents hormonal flare associated with initiation of GnRH receptor agonist treatment, and can be titrated to avoid bone density loss.³ In a phase III clinical trial, elagolix is administered at a dosage of 150 mg once daily or 200 mg twice daily, orally.⁴ The most commonly reported adverse events in clinical trials are hot flashes, headache, nausea, nasopharyngitis, and fatigue.⁴⁻⁶ Hot flashes and bone mineral density loss are dose dependent.⁴ Women who are pregnant or who have received a diagnosis of osteoporosis are excluded from elagolix clinical trials, potentially indicating that elagolix would be contraindicated in these patients.

Clinical trials: Three phase III trials are ongoing;⁷⁻⁹ positive preliminary results have been reported from a completed phase III trial, M12-665.¹⁰ That trial (n=872) is evaluating the change in pain, bone mineral density, endometrial biopsy findings, and transvaginal ultrasound findings during elagolix treatment. In preliminary results derived from the first 6 months of study, a manufacturer's press release reported the following:⁴

Results from the trial show that after six months of treatment, both doses of elagolix (150 mg once daily and 200 mg twice daily) met the study's coprimary endpoints ($p < 0.001$) of reducing scores of non-menstrual pelvic pain (NMPP) and menstrual pain (or dysmenorrhea), associated with endometriosis, at month three, as well as month six, as measured by the Daily Assessment of Endometriosis Pain scale.

Additional, smaller trials reported improvements in bone mineral density loss, menstrual pain, and nonmenstrual pelvic pain.^{5,6,11}

Manufacturer and regulatory status: AbbVie (North Chicago, IL), in collaboration with Neurocrine Biosciences, Inc. (San Diego, CA), is developing elagolix. AbbVie expects to complete the pivotal phase III trials by November 2016, after which the manufacturers are expected to submit a new drug application to the U.S. Food and Drug Administration (FDA).⁴

Cost implications: No cost information is available yet, but elagolix is expected to cost more than available peptide GnRH receptor agonists, some of which are available in generic formulations, if it shows improved safety and efficacy.¹² For comparison, one dose of generic leuprolide reportedly costs about \$180.¹³

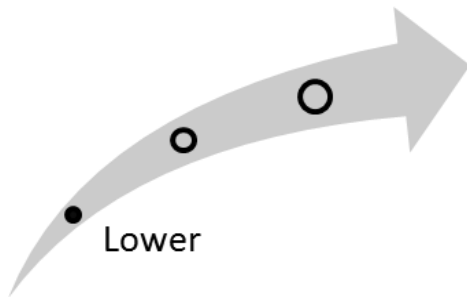
No coverage, coding, or payment information is available. If FDA approves elagolix, third-party payers may decline to cover it without data supporting its superiority to other treatments or payers

may require step therapy in which patients try existing endometriosis treatments before using elagolix.

Clinical Pathway at Point of This Intervention

Women with moderate to severe endometriosis may use peptide GnRH receptor agonists such as goserelin and leuprolide, which reduce the ovaries' production of hormones (estrogen and progesterone) by blocking GnRH's effect on the pituitary gland. However, peptide GnRH receptor agonists must be injected via a depot formulation, can take weeks to work, and may induce menopause-like symptoms. Treatment with peptide GnRH receptor agonists is usually limited to six monthly injections because further use may cause irreversible bone mineral density loss. Add-back therapy, which uses low-dose estrogen to partially restore estrogen levels, may also be needed while patients are receiving these drugs.¹⁴ Injectable peptide GnRH receptor antagonists have fewer side effects than agonists; however, injection site reactions and the inability to quickly discontinue therapy are issues with this approach.¹⁵ Elagolix, a nonpeptide GnRH receptor antagonist, is expected to compete with these treatments.

Figure 1. Overall high-impact potential: elagolix for treatment of endometriosis



Overall, experts commenting on this intervention thought that an unmet need exists for more convenient and effective endometriosis treatment with a better side effect profile than existing treatments. The experts thought elagolix could provide this option in an oral form likely to be preferred by patients. They noted its anticipated higher cost than alternative therapies available as generics may increase overall health care costs if patients drive demand for this drug. However, experts also stated that clinicians may require longer-term data before widely prescribing elagolix. Although elagolix addresses an unmet need, experts pointed out that it does not cure or prevent endometriosis, and thus will have limited effect on patient health overall. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.¹⁶⁻²¹ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for effective treatment of endometriosis that does not cause significant side effects such as bone mineral density loss or menopause-like symptoms, the experts agreed. Elagolix may improve patient health outcomes by reducing pain from endometriosis, avoiding side effects, and providing convenient oral option, the experts thought. However, two experts stated that the more important unmet need for preventive or curative treatments is not addressed by elagolix.^{16,21}

Acceptance and adoption: Clinicians may be more likely to prescribe an oral drug of similar safety and efficacy as an injectable option, making acceptance of elagolix likely, most experts thought. However, two experts were skeptical of clinician acceptance because of the lack of long-term data.^{16,21} Patient acceptance is likely to be high because of the ease of administration and good safety profile, most of the experts thought. However, one expert with a health systems perspective differed, suggesting that the side effects reported in trials and the dropout rate may reduce patient acceptance.²¹

Patients and third-party payers may realize a small to moderate increase in costs because elagolix is likely to be more expensive than other options, the experts stated. Two experts noted that surgical procedures and infertility treatments may be avoided with use of elagolix, which may decrease overall costs.^{18,20}

Health care delivery infrastructure and patient management: As an oral drug, elagolix is likely to exert minimal effects on health care delivery infrastructure and patient management, the experts agreed.

Health disparities: Two experts who focused on health disparities related to the cost of elagolix anticipated a small impact because other options are inexpensive.^{16,20} Two other experts noted that a small improvement in health disparities may be realized because of elagolix's easier oral administration compared with injectable options.^{17,19}

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