Evidence-based Practice Center Systematic Review Protocol

Project Title: Wireless Motility Capsule Versus Other Diagnostic Technologies for Evaluating Gastroparesis and Constipation: A Comparative Effectiveness Review

I. Background and Objectives for the Systematic Review

Delayed gastric emptying and slow-transit constipation are difficult entities to measure. Clinicians proceed to diagnostic tests based on patients' initial symptomatic presentation. Empiric therapy is often employed; however, when this is unsuccessful or symptoms are severe enough to prompt further investigation, then diagnostic evaluation of gastrointestinal physiology is often employed. However, these tests are not perfect and have limitations that will be addressed later in this section.

GASTROPARESIS

Definition and Prevalence

Gastroparesis is a condition in which patients experience the symptoms of delayed gastric emptying in the absence of an actual physical blockage.[1] The most common symptoms are nausea, vomiting, early satiety, bloating, abdominal pain, and postprandial fullness.[2] Detection of gastric emptying delay is the essence of diagnosing gastroparesis. Since the common symptoms for gastroparesis overlap with symptoms of functional gastrointestinal (GI) disorders such as dyspepsia, cyclical vomiting, and irritable bowel syndrome, a more stringent definition of gastroparesis has been established. For clinical research, gastroparesis has been defined as delayed gastric emptying as detected by clinical testing and the presence of symptoms of nausea and/or vomiting, postprandial fullness, early satiety, bloating, or epigastric pain for more than 3 months. Using this definition, the cumulative incidence of gastroparesis is 4.8 percent in people with type 1 diabetes, 1.0 percent in people with type 2 diabetes, and 0.1 percent in people without diabetes but who may have idiopathic gastroparesis or other rarer etiologies.[2] A multicenter study revealed that 88 percent of patients with idiopathic gastroparesis were female, and the average age at the time of diagnosis was 41 years.[3,4] The prevalence of gastroparesis was estimated by a community-based study in 2007 to be 9.6 per 100,000 for men and 37.8 per 100,000 for women.[2]

Etiology and Clinical Course

The etiologies of gastroparesis are most often idiopathic, diabetic, and postsurgical but can also rarely be autoimmune, paraneoplastic, and neurologic. Idiopathic gastroparesis is the most common etiology, estimated by some small studies to range between 36 and 64 percent of patients with the condition; diabetes is the primary cause of gastroparesis in 29 to 31 percent of patients. Assessment usually takes place in the outpatient setting, but some patients become severely ill with intractable vomiting and dehydration and must be admitted to the hospital. Hospitalizations for gastroparesis increased by 158 percent between 1995 and 2004.[5] In

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individuals with diabetes and gastroparesis, digestion of food is unpredictable, and wild swings in blood glucose can require medical care and increase morbidity. This unpredictability highlights the need for accurate diagnosis of gastroparesis so that available treatments can be applied.

Standard Evaluation

Standard assessment for patients with typical symptoms (nausea, vomiting, bloating, abdominal pain, early satiety) of gastroparesis begins with exclusion of mechanical causes of disease. A typical assessment starts in the office of a physician, where a careful medical history is taken and a physical examination is performed.[6] If mechanical disease it not suspected, then exclusion of medication-induced symptoms must also be performed. Delay of gastric emptying is commonly caused by the use of certain medications such as narcotics or glucagon-like peptide agonists. If there is any clinical suggestion of mechanical obstruction as the etiology, then imaging with x-rays or computed tomography can confirm obstruction and exclude gastric emptying delay as a primary etiology. If there is any possible offending medication in use, it can be stopped and the patient can be observed for improvement of symptoms. Methods of testing include gastric emptying scintigraphy, antroduodenal manometry, and now wireless motility capsule technology. Electrogastrography is an older form of testing that is no longer available even in most academic centers.[1]

Gastric Scintigraphy

According to the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA), gastric emptying scintigraphy of a radiolabeled solid meal is the most recognized method, or reference standard, by which delayed gastric emptying can be determined.[6] Gastric scintigraphy is the ingestion of a meal commonly standardized to toast, jam, juice, and radiolabeled eggs, which are visible on passage through the GI tract during subsequent timed imaging. Most radiology centers require that all possible interfering medications such as narcotics, motility agents, and glucagon-like peptide agonists be withheld for 5 to 7 days before scintigraphic testing. According to the consensus statement issued by the American Neurogastroenterology and Motility Society (ANMS) in 2011,[7] gastric scintigraphy should ideally be performed over a period of 4 hours after consumption of a standardized meal to be reproducible and to detect more abnormalities among symptomatic patients. Motility specialists find that community-based radiology practices more often offer shorter versions of the scintigraphic examination with durations between 60 and 120 minutes. Full 4-hour testing is more commonly available at regional referral centers or tertiary care centers with established practices of motility specialists.[7] Standards of abnormal emptying have been established for 1, 2, 3, and 4 hours. Generally, delayed gastric emptying is confirmed if more than 90 percent of the gastric content has not emptied at 4 hours, meaning that more than 10 percent of the content was retained. Current scintigraphy has been shown to predict a much longer delay in gastric emptying when more than 35 percent of gastric content is retained at the end of 4 hours. Scintigraphy has not been shown to be useful as a diagnostic tool to judge response to treatment. Scintigraphy has other disadvantages such as low-dose radiation exposure, lack of sensitivity, lack of a standardized protocol in widespread use, duration of up to 4 hours, a half-day lost from work for the patient, and a high cost of interpretation.

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Antroduodenal Manometry

Antroduodenal manometry is a technically cumbersome technology, offered in a few specialized centers that can provide information about gastric emptying. In this testing procedure, a manometry catheter is inserted into the pyloric channel with endoscopic guidance and sedation of the patient. Then pressure measurements are captured, which provide information about the small bowel and gastric pressure ratio during resting, mealtime, and after medication usage. Antroduodenal manometry can differentiate myopathic and neuropathic etiologies of symptoms. Myopathy is present if amplitude muscle pressures of less than 30 mmHg are documented, and neuropathy is present if discoordinated bursts of muscle activity are detected.

Wireless Motility Capsule

A new modality, the wireless motility capsule, is available and has been approved by the U.S. Food and Drug Administration (FDA) for identifying motility disorders. This new modality is a portable, small capsule that, when swallowed, records and transmits data to a receiver as it travels through the gut. The capsule can measure pH, pressure, and temperature to track location, gastric contents, and expellation time from the different regions of the bowel. Wireless motility capsule testing has been studied in small trials to assess gastric emptying. It has been recommended by the ANMS and designated a technology to be watched by the ACG. The capsule is a one-time use device that is activated and then swallowed by the patient who has suspected symptoms of gastric emptying delay. The device provides frequent measures of pH, temperature, and pressure to determine its approximate location along the gut at any given time. The patient takes the pill after eating a standardized meal and wears a small monitor that allows the telemetry recordings to be made. Gastric emptying time is assessed from ingestion of the capsule, a point at which there is a low pH reading, to an abrupt rise in pH after it moves into the small bowel.[8] A cutoff point for gastric emptying time has been established to be 300 minutes in a tandem scintigraphic study of the capsule alone in comparison to a radiolabeled meal.[9] Disadvantages of the capsule include failure of the capsule to capture data (requiring repeat testing), delay or total failure of the capsule to pass (requiring serial x-rays to document passage or endoscopic or surgical removal, respectively), and inability to use the capsule for anyone with a possible stricture, altered anatomy, or severe pyloric stenosis.[10] Most patients do not mind wearing the data receiver during testing, but this may limit some patients in their daily life. Also, patients must be able to tolerate stopping all proton pump inhibitors and histamine 2 blockers before testing.[10] Advantages of testing with the wireless motility capsule include that it is wireless and painless, can be used in an office setting without sedation or radiation, and provides information for the whole gut in addition to the area of interest for gastric emptying.[11,12] Most physicians would assess patients for evidence or history of stricture before using the capsule; this assessment might include additional imaging studies that would not have been performed otherwise.

Use of Gastric Emptying Testing To Guide Treatment Options

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Documentation of gastric emptying delay guides physicians in their recommendations for nutrition, medication, and surgical therapies. Testing can also inform physicians about the length and severity of delay; thus, changes in diet can be made to accommodate better gastric emptying. Recommended changes in diet may include a low-fat diet, a low-residue (low fiber, easy to digest) diet, a liquid diet, or increasing consumption to multiple small meals taken 4 to 6 times per day. Prokinetic treatment, like erythromycin, is often used to treat patients who have documented gastroparesis. Patients can make better decisions about using prokinetics such as oral, intravenous, and sublingual preparations of metoclopramide, based on the confirmation of the gastroparesis with testing. This is important to patients because there is an FDA black box warning about the side effects of metoclopramide when used beyond 3 months. Some research protocols involve the use of domperidone (Motilium®). Without documentation of gastroparesis, most physicians would be reluctant to use domperidone. Patients with severe symptoms and severe emptying delay despite dietary changes may need feeding tubes such as jejunostomy or gastrojejunostomy tubes that bypass the stomach entirely. Patients with total failure of gastric emptying may not tolerate feeding tubes and may require intravenous nutrition. As patients undergo consideration for compassionate use of gastric pacer therapy, one of the key eligibility criteria is the presence of gastric emptying delay on testing. Thus, accurate diagnosis of gastroparesis is integral to decisions about management.

Outcomes

The main outcomes of interest are assessment of motility and diagnosis of gastric emptying delay. Other outcomes include the ability of testing to influence treatment decisions by changes in medications or nutrition or to affect patient-centered outcomes such as symptom improvement, need for surgery, quality of life, and patient satisfaction. It is important to consider potential harms of testing such as capsule retention, radiation exposure, and mortality. Clinicians and policymakers may also be interested in the effects on resource utilization such as the need for additional tests, physician services, or hospitalizations.

Controversy

The controversy surrounding the accuracy of the cutoff point for scintigraphy in differentiating patients with true gastroparesis from those with more functional symptoms was acknowledged at the 2011 American Neurogastroenterology and Motility Society meeting. A suggestion was made to use stricter criteria for diagnosing gastroparesis: only patients who were off all possible offending medications and who had retained at least 25 percent of gastric content at 4 hours would be diagnosed with the condition. Greater retention of gastric content is related to greater severity of disease, which may have implications for how patients with abnormal gastric emptying on capsule testing get stratified for treatment. Previous consensus recommendations from 2008 established baseline standards for scintigraphy and discussed grading severity of the gastric emptying delay as relevant to clinical research, but did not establish how that grading would affect decisions about patients.[13] We will address this issue by looking for data on how treatment decisions differ between testing methods. Another controversy was the lack of information regarding whether or not scintigraphy or wireless motility capsule testing could offer any guidance in assessing response to treatment or whether they would remain purely diagnostic tools. We will address this issue by looking for data on treatment response in

terms of patient-reported outcomes. It is also unclear at this time which populations would benefit most from the wireless motility capsule or which order of testing is best to diagnose patients. Currently, wireless motility capsule testing is being used in a complementary fashion as an addition to reference standard tests like scintigraphy. Whether it can replace or should supersede other testing methods is controversial.

CONSTIPATION

Incidence and Diagnostic Criteria

Constipation is a common symptom, reportedly occurring in 15 to 20 percent of the U.S. population. The definition of constipation has been established with slight variation by multiple professional societies, but usually constipation is defined as fewer than two bowel movements per week or a decrease in a person's normal frequency of stools that is accompanied by straining, difficulty passing stool, or passage of hard solid stools.[10] Patients with symptoms of constipation must be assessed by their medical history and a physical examination to exclude malignant or organic causes of constipation. A careful history should be able to elicit warning signs such as new onset of symptoms, obstructive symptoms, rectal bleeding, unintentional weight loss, or family history of early colon cancer. A rectal examination can further delineate rectal function and tone, and it can help to exclude a low rectal cancer. Investigation with colonoscopy is indicated if fecal occult blood or iron deficiency anemia are detected. Patients with symptoms of constipation and warning signs should be investigated with colonoscopy, as should all patients over 50 years of age who have never received a screening colonoscopy.[14] Once organic causes of constipation are excluded, a diagnosis of functional constipation can be made. For individuals who are less than 50 years of age without "red flag" symptoms, there is no required basic testing to make a diagnosis of constipation if they meet the Rome III criteria. The Rome III criteria define functional constipation as follows:

- Must include *two or more* of the following:

  a. Straining during at least 25 percent of defecations
  b. Lumpy or hard stools in at least 25 percent of defecations
  c. Sensation of incomplete evacuation for at least 25 percent of defecations
  d. Sensation of anorectal obstruction/blockage for at least 25 percent of defecations
  e. Manual maneuvers to facilitate at least 25 percent of defecations (e.g., digital evacuation, support of the pelvic floor)
  f. Fewer than three defecations per week

- Loose stools are rarely present without the use of laxatives
- Insufficient criteria for irritable bowel syndrome

Two or more of the above criteria must be fulfilled for the last 3 months, with symptom onset being at least 6 months prior to diagnosis.

Basic Management

Lifestyle changes and medical management should be used for all patients with symptoms of constipation. Lifestyle changes include drinking appropriate quantities of liquid, removing all possible offending medications, and eating a sufficient amount of vegetables, fruit, and fiber as recommended by the U.S. Department of Agriculture. Medical management includes avoiding constipating medications and initiating bulking agents (fiber supplements), stool softeners (Colace®, mineral oil), osmotic and stimulant laxatives (lactulose, milk of magnesia, magnesium citrate, senna, Dulcolax®), or prokinetics (prucalopride, linaclotide, lubiprostone, erythromycin) as indicated. Thus, the initial evaluation of constipation symptoms does not often involve colonic transit testing.

Indications for Colonic Transit Testing

For certain individuals with suspected slow-transit constipation—defined as persistent symptoms of constipation despite medical management and lifestyle changes—colon transit testing can provide insight into the etiology of the constipation. Testing can be used to explain the patient who fails first-line therapy and thus assist in identifying or excluding patients as surgical candidates.[10] It is most strongly indicated for anyone considering colon resection or surgery. Transit disorders include slow colonic transit or colonic inertia, a hypomotile disorder of the colon where transit in the proximal colon is slow without evidence of retropulsion of the markers from the left colon and without evidence of anorectal dysfunction. Outlet dysfunction, a category of slow-transit constipation, is the presence of discoordinated motion of the rectal muscles causing ineffective, weak, or reverse motion of stool. Idiopathic megacolon (primary or secondary), a pathological enlargement of the colon, can also be present and may occur in conjunction with longstanding neurological diseases or Hirschsprung's disease, a failure of the development of the nerve cells within the colon wall.[15] The main diagnostic methods used to test for colonic motility are radiopaque marker examination, colonic scintigraphy, colonic and anal manometry, and wireless motility capsule testing.[16,17] The reference standard has been radiopaque markers; however, scintigraphy has also been selected as a comparable measure of colonic transit. Other investigatory tools that can provide complementary information are imaging tests such as defacography with barium or magnetic resonance imaging, barium enema, endorectal ultrasound, and magnetic resonance imaging of the pelvis.

Radiopaque Markers

Slow-transit constipation is defined by the reference standard of radiopaque marker testing (commonly known as Sitz Markers).[16,17] Such testing is performed by having the patient ingest the radiopaque markers on day 0 and then taking x-ray images at intervals to document the excretion of those markers by 5 days after ingestion. Retention of markers after the initial observation period allows identification of patients with slow transit and focuses on the area of the colon that has the greatest delays.[8,10] One disadvantage to radiopaque marker testing is x-ray exposure in individuals with constipation. However, the test has been validated and in use since the late 1960s.[8]

Colonic Scintigraphy

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Colon scintigraphy can also be performed but is rarely used outside of highly specialized motility research centers. It involves ingestion of a radiolabeled meal or radiolabeled charcoal to follow the sequence of transit from the upper to lower GI tract. This method has been validated and has been used to study treatment response in several drug trials. Two protocols exist. The one from Temple University is based on a seven-region analysis in which a numeric value represents overall colon transit and emptying of the ascending colon, summarized in terms of the half-life of the radiolabeled substance. The one from the Mayo Clinic combines the results of only a five-region analysis. An advantage of colon scintigraphy is that testing can be completed in 1 to 2 days. Studies have assessed the validity relative to radiopaque markers.[18,19] The ANMS guidelines recommend colon scintigraphy as a test for evaluating colon transit.

Total Colonic Manometry

Colonic manometry has been described more recently but is not widely available and is only performed in specialized centers. For this test, the manometry catheter is placed with endoscopic and fluoroscopic guidance after a full bowel preparation. The catheter is left in place in some cases for up to 24 hours, and recordings are obtained after sedation wears off from the procedure used to place the catheter. One disadvantage of this method is its limited availability, which is due to the specialized technical expertise that is required to perform and interpret this labor-intensive procedure.

Wireless Motility Capsule

Wireless motility capsule testing involves ingesting a capsule and wearing a receiver to collect data. Cecal entry is defined as a sustained drop in pH of greater than 1 unit that occurs more than 30 minutes after gastric emptying. Colonic transit time is the time between cecal entry and rectal exit. Transit time within the colon can be calculated from the cecal transit time until the capsule exits the body, which is marked by a large temperature reduction.[10] One disadvantage is that 5 percent of patients undergoing capsule testing may not collect cecal entry-time data, thus limiting the diagnostic potential of the study.[8] Other disadvantages are that radiographic imaging must be used to confirm elimination of the capsule when it fails to pass spontaneously and that the device can fail at a rate up to 3 percent in some studies. One advantage of capsule testing is the simultaneous collection of data for the whole gut with one test. Other advantages include the lack of radiation exposure when the capsule is passed spontaneously and is observed in the stool after safe passage and the fact that it can be performed in the outpatient setting and thereby provide accurate information about real-life conditions. Of note, testing does take about 6 hours of observation to properly perform, if carried out as the original study suggested,[12] which might require patients to take time off from their work. Capsule testing cannot be performed in any patient expected to have stricture or stenosis. Other testing might be required to ensure that no narrowing is present. Another advantage of capsule testing is that it provides a more complete picture of colonic transit (like whole-bowel scintigraphy might if it were more widely available); whereas, radiopaque marker testing only offers static imaging. It is uncertain at this point whether all the extra data will be useful to change outcomes in any way. More studies must be done as this technology gets adopted into wider use.

Use of Colon Transit Testing

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Most patients with chronic constipation have improvement of symptoms with medical therapy and/or lifestyle changes. For some patients, all measures fail and their motility disorders may be identified with colon transit testing. When anorectal or outlet dysfunction is identified, biofeedback therapy can be used for treatment. Evidence of Hirschsprung's disease is an indication for surgical segmental resection. Megacolon requires medical therapy tailored to reducing gas formation, and reduction of fiber intake may paradoxically relieve symptoms. If these conservative measures fail, then megacolon may warrant segmental or total colectomy. If testing confirms the presence of slow-transit constipation (colonic inertia) without use of laxatives, then the next step in evaluation is transit testing with use of laxatives. Only after demonstrating colonic inertia in both of these settings should surgery be considered as a potential therapy.[20] Clear demonstration of severe total or segmental slow-transit constipation is an indication for colectomy; however, most clinicians reserve colectomy for patients with the most terminal or untreatable conditions. Sometimes an individual may have features of both outlet dysfunction and inertia; in these cases, outlet dysfunction must be addressed before making decisions about slow transit. If outlet dysfunction does not improve with biofeedback therapy, then surgical options may be limited to ileostomy rather than primary anastomosis. Therefore, accurate diagnosis is essential to proper management of slow-transit motility disorders.

Outcomes

The main outcome of interest to both stakeholders and clinicians is the ability to characterize transit time and to diagnose slow-transit constipation. Other outcomes include the ability of testing to influence treatment decisions such as change in medications or change in nutrition or to affect patient-centered outcomes such as symptom improvement, need for surgery, quality of life, and patient satisfaction. It is important to consider potential harms such as capsule retention, radiation exposure, and mortality. Clinicians and policymakers may also be interested in the effects on resource utilization such as the need for additional tests, physician services, and hospitalizations.

Controversy

Controversy regarding the role of capsule testing in the diagnostic evaluation of constipation was addressed at the 2011 American Neurogastroenterology and Motility Society conference. Some experts thought that it would likely be a complementary test rather than an independent test for patients with this disease.

Planning of the Review

The planned review is meant to summarize the available literature and to analyze the available data to help guide decisionmakers and clinicians on how useful current testing modalities for colonic and gastric motility are for diagnosing disease. The review may help to determine whether wireless motility capsule testing is useful in conjunction with or instead of other testing modalities for diagnosing and managing motility disorders. Most of the current data on wireless motility capsule testing comes from corporately sponsored studies at respected research centers, and there is not a large amount of independent data to support its use. That said, there appear to be studies available for further evidence-based review. Our goal would be to

define the populations who would benefit most from motility testing, including wireless motility capsule testing, and identify them for physicians and payers.

II. The Key Questions

Our draft Key Questions (KQs) were posted on the Agency for Healthcare Research and Quality's Effective Health Care Program Web site for public comment from December 7, 2011, through January 4, 2012. The comments raised some methodological concerns, which will be addressed below. Our finalized KQs are:

Question 1

In the evaluation of gastric dysmotility, how does the wireless motility capsule alone compare with gastric scintigraphy, antroduodenal manometry, and endoscopy in terms of diagnostic accuracy of gastric emptying delay, motility assessment, treatment decisions, patient-centered outcomes, harms, and resource utilization?

Question 2

When gastric scintigraphy, antroduodenal manometry, or endoscopy is used in the evaluation of gastric dysmotility, what is the incremental value of also using the wireless motility capsule in terms of diagnostic accuracy of gastric emptying delay, motility assessment, treatment decisions, patient-centered outcomes, harms, and resource utilization?

Question 3

In the evaluation of colonic dysmotility, how does the wireless motility capsule alone compare with radiopaque markers and scintigraphy in terms of diagnostic accuracy of slow-transit constipation, motility assessment, treatment decisions, patient-centered outcomes, harms, and resource utilization?

Question 4

When a radiopaque marker or scintigraphy is used in the evaluation of colonic dysmotility, what is the incremental value of also using the wireless motility capsule in terms of diagnostic accuracy of slow-transit constipation, motility assessment, treatment decisions, patient-centered outcomes, harms, and resource utilization?

PICOTS Framework

- **Population(s)**
    - The target population for KQs 1 and 2 will be patients with suspected gastroparesis who tend to have a history of nausea, vomiting, bloating, early satiety, epigastric pain, suspected gastric emptying delay, and no evidence of gastric outlet or other obstruction.

- For KQs 1 and 2, subgroups of interest include patients with idiopathic, diabetic, and postsurgical gastroparesis.

- The population for KQs 3 and 4 will be patients with suspected slow-transit constipation who are defined as having persistent symptoms of constipation despite medical management and lifestyle changes.
- For the assessment of harms, we will include wireless motility capsule testing conducted in any population.
- All KQs will be limited to adult patients.

- **Interventions**

  - The test of interest is the wireless motility capsule testing, alone (KQs 1 and 3) or in combination with other tests (KQs 2 and 4).

- **Comparators**

  - For KQs 1 and 2, the comparators are conventional diagnostic tests for suspected gastroparesis, including scintigraphy, antroduodenal manometry, and endoscopy.
  - For KQs 3 and 4, the comparators are conventional diagnostic tests for suspected slow-transit constipation, including scintigraphy and radiopaque markers.

- **Outcomes Measures for Each KQ**

  - The outcomes of interest were selected based on the experience of our clinical experts and what they thought would be most important to clinicians and patients. These are:

    - Diagnostic accuracy

      1. Gastroparesis: The reference standard is a 4-hour gastric emptying study.
      2. Slow-transit constipation: There is no consensus on a standard, so we will examine this outcome relative to each existing standard (radiopaque markers and colonic scintigraphy).

    - Motility assessment

      1. Transit time (including time to stomach emptying, time to small bowel emptying, time to colon emptying, total transit time)
      2. Pressure patterns

    - Treatment decisions

      1. Change in medications
      2. Change in nutrition
      3. Need for surgery

4. Need for a referral

- Patient-centered outcomes

1. Symptom improvement
2. Quality of life
3. Patient satisfaction

- Resource utilization

1. Test failure (unable to read test results)
2. Need for additional tests because of continued uncertainty about diagnosis
3. Utilization of other health care services such as hospitalizations and physician visits

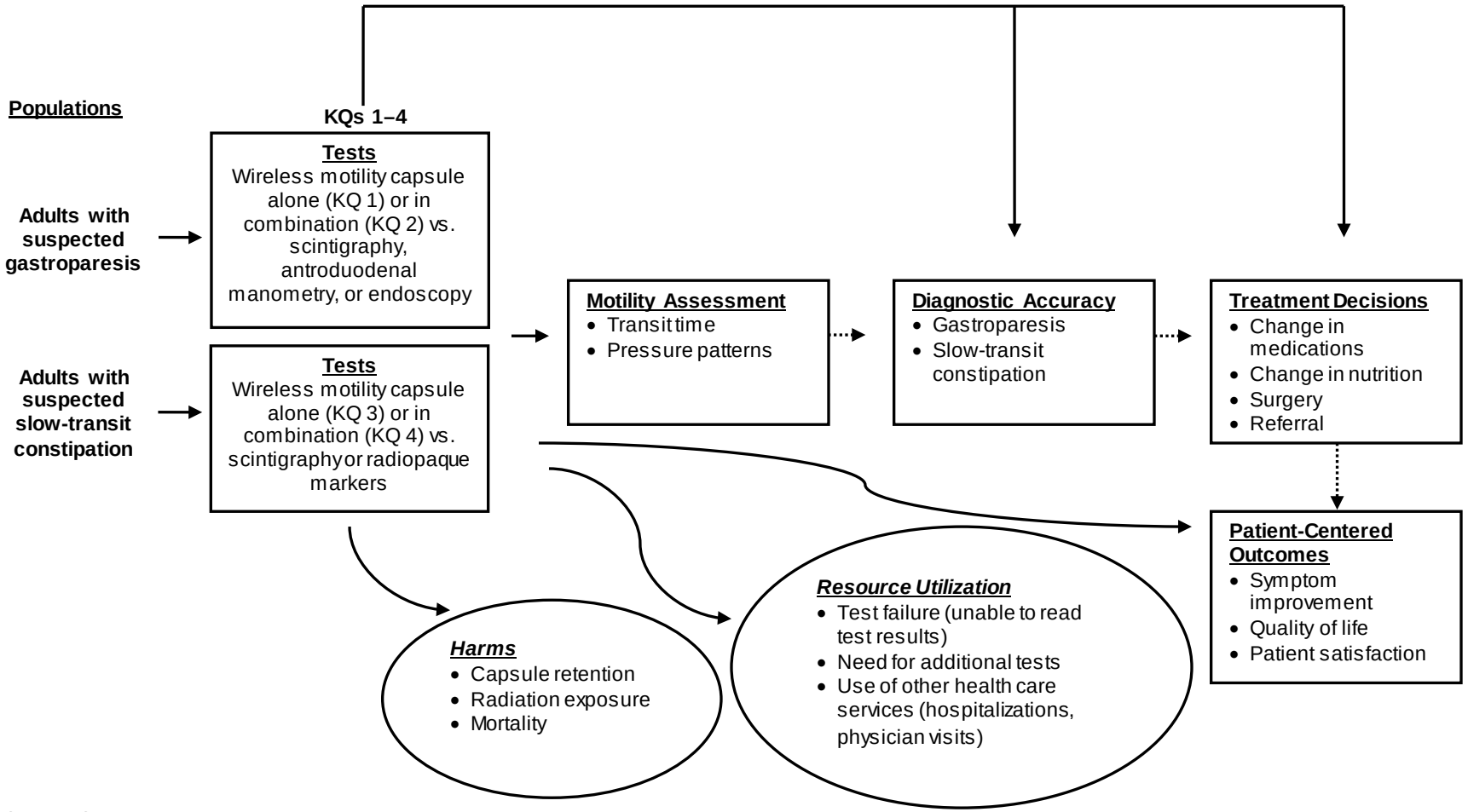
- Harms, such as capsule retention, radiation exposure, and mortality

- **Timing**
  - We plan to consider all lengths of followup for all the outcomes, but our desired length of followup for symptom improvement, quality of life, and need for additional tests would be at least 3 months.

- **Settings**
  - We plan to include all clinical settings in developed countries.

III. Analytic Framework

Figure 1. Analytic framework of the comparative effectiveness of diagnostic technologies for evaluating gastroparesis and constipation



KQ = Key Question

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IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

See Table 1 for a list of the inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria

Population and conditions of interest	• We will include studies that evaluate patients with suspected gastroparesis and/or slow-transit constipation. For the assessment of harms, we will be including any patient population that was evaluated with the wireless motility capsule test. • We will include only adult human subjects.
Diagnostic test of interest	• We will include all studies that evaluate the wireless motility capsule alone or in combination with other tests.
Comparisons	• For KQs 1 and 2, we will include studies that compare the wireless motility capsule with other conventional diagnostic tests for suspected gastroparesis, including scintigraphy, antroduodenal manometry, and endoscopy. • For KQs 3 and 4, we will include studies that compare the wireless motility capsule with other conventional diagnostic tests for suspected slow-transit constipation, including scintigraphy and radiopaque markers. • For the outcome of harms, we will not require a comparison group.
Outcomes	• We will include studies that report on at least one of the following outcomes: ○ Diagnostic accuracy – Gastroparesis: The reference standard is a 4-hour gastric emptying study. – Slow-transit constipation: There is no consensus on a standard, so we will examine this outcome relative to each existing standard (radiopaque markers and colonic scintigraphy). ○ Motility assessment – Transit time – Pressure patterns ○ Treatment decisions – Change in medications – Change in nutrition – Need for surgery – Need for a referral ○ Patient-centered outcomes – Symptom improvement – Quality of life – Patient satisfaction ○ Resource utilization – Test failure (unable to read test results) – Need for additional tests because of continued uncertainty about diagnosis – Utilization of other health care services such as hospitalizations and physician visits ○ Harms, such as capsule retention, radiation exposure, and mortality
Type of study	• We will exclude articles with no original data (e.g., editorials, commentaries, reviews). • We will include all types of studies (e.g., randomized controlled trials, cohort studies, case series, case reports) that evaluate the wireless motility capsule or similar devices in terms of harms. For all other outcomes, we will only include studies with an appropriate comparison group.
Timing and setting	• We will include all clinical settings in developed countries. • We will include all durations of followup, but our desired length of followup for symptom improvement, quality of life, and need for additional tests would be at least 3 months.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

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We will search the following databases for primary studies: MEDLINE® and EMBASE®. We will develop a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text words of key articles identified a priori. Our search strategy for MEDLINE is presented in Table 2.

Table 2. Proposed search string for identifying studies that evaluate the wireless motility capsule

Search #	Search String
#1	"Capsule Endoscopy"[mh]
#2	(Wireless[tiab] OR radiotelemetr*[tiab]) AND (motility[tiab] OR capsule*[tiab])
#3	Smartpill*[tiab]
#4	#1 OR #2 OR #3
#5	(animal[mh] NOT human [mh])
#6	#4 NOT #5

Our search will be updated during the peer review process.

We will search clinicaltrials.gov to identify any relevant registered trials. We will review the Scientific Information Packets provided by the manufacturer. Since many studies are likely to be published in abstract form only, we will review the major gastrointestinal conference proceedings, including Digestive Disease Week, ACG, and ANMS, for the past 2 years.

C. Data Abstraction and Data Management

Two independent reviewers will conduct title scans. For a title to be eliminated at this level, both reviewers will need to indicate that the study was ineligible. If the reviewers disagree, the article will be advanced to the abstract review.

The abstract review phase will be designed to identify studies reporting the diagnostic accuracy of the wireless motility capsule. Abstracts will be reviewed independently by two investigators and will be excluded if both investigators agree that the article meets one or more of the exclusion criteria (see the inclusion and exclusion criteria listed in Table 1). Differences between investigators regarding the inclusion or exclusion of abstracts will be tracked and resolved through consensus adjudication.

Articles promoted on the basis of the abstract review will undergo another independent parallel review to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will be tracked and resolved through consensus adjudication.

We will use a systematic approach to extract all data to minimize the risk of bias in this process. We plan to extract data directly into tables.

Each article will undergo double review by the study investigators for data abstraction. The second reviewer will confirm the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs will be formed to include personnel with both clinical and methodological expertise. A third reviewer will audit a random sample of articles to ensure consistency in the data abstraction of the articles. Reviewers will not be masked to the authors of the articles, their respective institutions, nor the journals in which their articles were published.

For all articles, the reviewers will extract information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, race, weight, prior testing, type of disease [diabetic, idiopathic, etc.], use of narcotics, blood sugar, smoking status), diagnostic tests of interest (e.g., type of capsule, prototype pill or capsule, endoscopy capsule used for motility purposes, if a preparation was used to prepare the capsule, and if a standardized

meal was used), comparisons, outcome measures, definitions, and the results of each outcome, including measures of variability. For endoscopy, we would capture the number of hours without anything by mouth before the procedure and the method of sedation. For gastric scintigraphy, we would collect data on duration of testing (e.g., 4 hours), the protocol used (e.g., Tougas[13,21]), and if liquid or solid components were used. For antroduodenal manometry, we would collect data on which catheter was used, how the catheter was placed, what amplitude and frequency were measured. For radiopaque markers, we would collect data on the type of radiopaque markers used, the timing of dosing of markers and the surveillance x-rays, and if counts were recorded in each segment of the colon, or if a total count was used, or both. For colon scintigraphy, we would collect data on type of labeled marker used, type of protocol used, and the duration of testing. For each of the diagnostic tests, we would collect information on the criteria used to make a diagnosis of gastroparesis and slow-transit constipation.

D. Assessment of Methodological Quality of Individual Studies

Article quality will be assessed independently by two reviewers. We will use the closed-ended questions from the QUADAS-2 quality assessment tool.[22] We will supplement this tool with additional quality-assessment questions (e.g., to assess spectrum bias) based on recommendations in the *Methods Guide for Medical Test Review*.[23]

E. Data Synthesis

We will conduct meta-analyses when there are sufficient data (at least three studies) and studies are sufficiently homogenous with respect to key variables (population characteristics, study duration, and treatment). Since none of the comparators is a "gold standard," we will follow the meta-analytic methods for when there is an imperfect reference standard.[23]

We will analyze studies published in abstract form only separately from the peer-reviewed literature.

For KQs 1 and 2, subgroups of interest include patients with idiopathic, diabetic, and postsurgical gastroparesis. Potential effect modifiers will be age and weight.

F. Grading the Evidence for Each Key Question –

At the completion of our review, we will grade the strength of the best available evidence addressing KQs 1-4 by adapting an evidence grading scheme recommended in the *Methods Guide for Medical Test Review*[23] and in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[24,25] Both of these evidence grading schemes are based on GRADE.[26] We will apply evidence grades to the bodies of evidence about each diagnostic test comparison for each outcome. We will assess the strength of the best available evidence by assessing the risk of bias, consistency, directness, precision, and the magnitude of effect. We will consider spectrum bias as part of the assessment of how well studies address the entire population of interest (i.e., directness of the population).

We will classify evidence pertaining to the KQs into four basic categories: 1) "high" strength of evidence (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect); 2) "moderate" strength of evidence (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change

the estimate); 3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and 4) "insufficient strength of evidence (evidence is unavailable).[26]

G. Assessing Applicability

We will assess the applicability of studies in terms of the degree to which the study population (age, etiology, comorbidities, prior surgery or gastric pacer), interventions (use of narcotics during testing, use of bowel motility-altering agents, such as laxatives or prokinetic agents), outcomes, and settings (referral center) are typical for the treatment of individuals with suspected gastroparesis or slow-transit constipation.

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VI. Definition of Terms

ACG = American College of Gastroenterology
AGA = American Gastroenterological Association
ANMS = American Neurogastroenterology and Motility Society
FDA = U.S. Food and Drug Administration
GI = gastrointestinal

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including 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 identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for 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 and have not reviewed 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 $10,000 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 TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes, as well as identifying particular studies or databases to search. They are selected to

provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or 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 recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 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 TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

There are no conflicts of interest to disclose.

XIII. Role of the Funder

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