

Evidence-based Practice Center Systematic Review Protocol

Project Title: Treatments for Fecal Incontinence

I. Background and Objectives for the Systematic Review

Fecal incontinence (FI) involves recurrent involuntary loss of fecal material.^{1,2} FI is defined by the frequency of episodes (such as daily or weekly episode counts) and by the consistency of the fecal material (solid, liquid, or mucus).^{1,3} FI severity varies widely and the amount of leakage can vary across episodes. The negative psychological effects, social stigma, and reduced quality of life surrounding FI can be devastating.³ The condition can dramatically impede daily activities and socialization because those affected aim to avoid embarrassment. FI can also result in severe skin breakdown and ulceration, particularly in nursing home residents and immobile adults.

FI prevalence estimates vary across patient populations and by FI definition. FI prevalence increases with age and varies by sex. Among community-dwelling adults, the prevalence of FI is 8.3 percent,² with slightly higher prevalence in women (9 percent) than men (7.7 percent).² FI affects less than 3 percent of young adults age 20 to 29 but more than 15 percent of adults age 70 and older.² Women over age 40 are disproportionately affected due to pelvic floor dysfunction after childbirth or obstetrical trauma. At least half of all nursing home residents and 83 percent of residents with severe cognitive impairment have experienced FI.⁴ Monthly FI occurs in 6 percent to 25 percent⁴ of adults, with weekly prevalence less than 3 percent.² Of the 8.3 percent of affected community-dwelling adults, 6.2 percent experience FI with liquid stool, 1.6 percent with solid stool, and 3.1 percent with mucus.²

FI can result from a number of causes that fall into two broad categories: nonneurological or neurological. Nonneurological causes of FI may be structural (e.g., muscle damage after episiotomy or surgery), functional (e.g., post-radiation or muscle atrophy), due to an underlying gastrointestinal (GI) disorder (e.g., inflammatory bowel disease), due to stool consistency issues, or from other factors. Neurological causes of FI include damage to the nervous system or advanced cognitive impairment. Multiple causes of FI in individual patients are common. In patients with FI due to multiple etiologies, a dominant etiology may not be determinable. Risk factors for FI include increasing age, female sex, chronic diarrhea, nerve damage (such as from injury, multiple sclerosis, or chronic diabetes), post-surgical or post-radiation complications, cognitive impairment, or other factors such as severe constipation (stool impaction).^{4,5}

Treatments for FI may be nonsurgical or surgical. Nonsurgical treatments include pelvic floor muscle training exercises (PFMT),^{6,7} dietary modification (including dietary fiber),⁵ medications,⁸ biofeedback,⁶ bowel schedules, anal plugs, rectal irrigation,^{9,10} or combinations thereof.^{5,6} Injections of biocompatible tissue-bulking agents into the anal canal walls are a newer, more invasive nonsurgical procedure.¹¹ Surgical procedures used to treat FI in the United States include implanted sacral nerve stimulators, radiofrequency anal sphincter remodeling, anal sphincter repair (sphincteroplasty or muscle transposition), sphincter replacement (artificial anal sphincter), surgical correction of conditions that can result in FI (rectal prolapse, hemorrhoids, or rectocele), or, when all other treatments fail, colostomy.^{1,5,12,13} Many new treatments for FI have been developed within the last decade. However, not all conventional or modern treatments are FDA-approved (or seeking FDA-approval) for use in the United States; some treatments are in the earlier stages of clinical evaluation, others are used in Europe but are not approved for use in

the United States (rectal irrigation, magnetic anal sphincter, some anal plugs), or are approved for use in the United States by one manufacturer only (tissue bulking agent, anal plug).

FI etiologies and other patient factors dictate feasible treatment options.¹ For example, the range of treatment approaches used for FI in adults with spinal cord (neurologic) injury would differ from those used to treat pelvic floor muscle atrophy (structural weakness) or anal sphincter injury (structural damage). Treatment goals are to decrease the frequency and severity of FI episodes in affected adults. In general, initial FI treatments tend to be conservative (diet, drugs, exercises, etc.) and become progressively more invasive (local injections of tissue-bulking material, surgical procedures) if desired treatment effects are not obtained with less invasive approaches. Conversely, the ultimate treatments may be aimed at mitigating earlier FI treatment failures. For example, surgical treatments that do not achieve the desired level of continence may be augmented by dietary changes, exercises, or drugs.

Although many recent systematic reviews have assessed the effectiveness of component treatments for FI,^{6-8,11-21} none have yet examined the collective evidence for FI treatment effectiveness, reported overall and subgroup treatment effects (when available), or examined the long-term treatment effects across all FI treatments. Given the heterogeneous population of adults afflicted with FI (see Populations below), information on subgroup treatment outcomes across that range of available FI treatments would advance knowledge and have the potential to improve patient care and outcomes.³

This systematic review will synthesize the available evidence on treatment outcomes and identify gaps in the evidence base for treatment-subgroup combinations to provide current and potentially better information to aid decisionmaking for both patients and physicians. Additional information on baseline patient factors that could modify treatment effects, such as age, sex, FI severity, comorbidities, and prior FI treatments, will be addressed when available.

Potential challenges in conducting the proposed systematic review are discussed under Methods (section E below). These may include etiologically heterogeneous patient samples, the use of varied outcomes scales and measures, a lack of measures for some patient-important outcomes (such as urgency), limited long-term outcomes information, and differences in the timing of outcomes assessments across studies.

Our findings will provide evidence support for FI treatment guidelines by physicians' groups and for clinical decisionmaking in general, with the goal of improving treatment and outcomes for adults with FI.

II. The Key Questions

The draft key questions were posted for public comment on AHRQ's Effective Health Care Web site from September 2, 2014, through September 22, 2014. Comments were received from a clinical expert, professional association, industry, and one anonymous individual. Most comments were requests for clarification of items already listed in the PICOTS or on the breadth of the key questions; one requested the addition of a physical therapist to our panel of expert advisors for the systematic review. No changes were made to the Key Questions or PICOTS but the protocol text clarifies that the PICOTS list outcome categories and not all specific measures, since these are numerous. We requested a representative from the American Physical Therapy Association (APTA) for the Technical Expert Panel for the systematic review.

Key Question 1: What is the comparative effectiveness of treatments to improve quality of life and continence and lessen the severity of fecal incontinence in affected adults?

Key Question 2: What adverse effects are associated with specific treatments for adults with fecal incontinence?

The PICOTS Framework (Population, Intervention, Comparator, Outcomes, Timing, Setting) will be identified for each key question.

Population: by etiologic categories:

We will include adults with FI and classify them within the etiologic categories listed below, and by adult age groups (geriatric versus other). Whenever possible, we will examine treatment effects within etiologic subgroups of adults, since affected individuals are highly heterogeneous and not all treatments are feasible for specific subgroups. Patients with FI due to spinal cord injury will be separately evaluated. Adults with fistulas will be excluded. The possible associations of treatments and etiologic subgroups are shown in Appendix A. Potential subgroups include:

1) Structural (damage or variants)

- Anal sphincter
 - Injury (often due to episiotomy): from muscle damage and/or nerve damage
 - Damage from surgery (for hemorrhoids or cancer [after anal, rectal or colon resection]) or underlying systemic condition (such as scleroderma)
- Pelvic floor
 - Weakening (atrophy), prolapse (pelvic organs, rectal), or stretching (chronic constipation)
- Rectal
 - Post-radiation (mainly for prostate and rectal cancer)
 - Rectal filling and storage problems
 - Hemorrhoids
 - Rectocele
- Congenital malformations (anorectal, anal sphincter)

2) Alterations in gastrointestinal (GI) motility or fecal texture (due to conditions or ingestibles)

- Crohn's disease, ulcerative colitis, irritable bowel syndrome (IBS)
- Medications
- Autoimmune disorders (such as systemic lupus erythematosus)

3) Neurogenic etiologies

- Nerve injury to pelvic floor
- Spinal cord injury, spina bifida
- Traumatic brain injury (TBI)
- Stroke
- Neurodegenerative diseases (such as multiple sclerosis, multiple system atrophy (MSA), Shy-Drager syndrome, etc.)

4) Multiple

- Any combination of above etiologies

5) Unknown

- FI etiology(ies) unknown or not reported

Interventions

We will include FDA-approved treatments for FI and FDA-approved medications used off-label (not specifically approved for the treatment of FI) and available for use in the United States. Interventions that do not require FDA approval and are used in the United States will be included. Since a number of treatments that are not FDA-approved are commonly used in Europe, the following additional specifications will apply:

- If the device is FDA approved for an indication and is used off label for FI, we will include the studies (e.g., rectal irrigation)
- If a device is FDA approved under a certain brand name for FI (e.g., anal plugs), and there are studies that compare it to other brands approved only in Europe, we will include those studies.

Colostomy, treatments for diarrhea (not FI), and laxatives used to treat stool impaction will be excluded.

Key Questions 1 and 2:

- Nonsurgical
 - Functional enhancement therapies (muscle training/biofeedback/electrostimulation):
 - Pelvic floor muscle training exercises (PFMT)
 - PFMT with biofeedback (using electrical or ultrasound sensors)
 - PFMT with biofeedback, plus electrostimulation
 - Dietary modifications: fiber, probiotic supplements, other
 - Medications: such as
 - Antidiarrheal or constipating drugs (such as loperamide hydrochloride [e.g., Imodium®], diphenoxylate plus atropine [e.g. Lomotil®], codeine)
 - Sphincter function enhancers (topical phenylephrine gel, sodium valproate)
 - Other bowel-affecting drugs: anticholinergics (hyoscyamine sulfate), tricyclic agents (amitriptyline, imipramine)
 - Behavior modification
 - Stool consistency management
 - Devices: anal plugs
 - Rectal irrigation
 - Injections of local biocompatible tissue-bulking agent (into the anal canal walls)
 - Dextranomer in stabilized sodium hyaluronate (Solesta®)
- Surgical:
 - Implanted neurostimulation (sacral nerve stimulators)
 - Radiofrequency anal sphincter remodeling (SECCA) – (may be in-office procedure)
 - Anal sphincter repair (sphincteroplasty or muscle transposition)
 - Sphincter replacement (artificial anal sphincter)
 - Surgical correction of condition that led to FI (such as rectal prolapse, hemorrhoids, or rectocele)

- Combined treatments: any combination

Comparators

- All other treatment options, alone or in combination. Where available, trials with placebo or sham controls will be included.

Outcomes

The review will focus on patient-important outcomes as listed below. Intermediate outcomes, such as physiologic measures of sphincter function^{22,23} (EMG recruitment, direct EMG [pudendal nerve terminal motor latency test], anorectal manometry, defecography, etc.), will not be examined due to the lack of correlation with patient-important outcomes.^{23,24}

Key Question 1

- Final health outcomes
 - Quality of Life (multiple scales, such as the Fecal Incontinence Quality of Life [FIQL],²⁵ Gastrointestinal Quality of Life Index,²⁶ or the Medical Outcomes Survey 36-item health survey (SF-36)²⁷, others)
 - Reduced frequency of incontinence episodes (bowel diaries, episode counts, etc.)
 - Reduced severity of incontinence (volume and type of leakage; the use of coping behaviors): multiple scales such as the Fecal Incontinence Severity Index [FISI],²⁸ Jorge/Wexner (Cleveland Clinic²⁹) Incontinence Score,³⁰ Vaizey/St. Mark's Hospital incontinence score,³¹ Pescatori,³² Miller Incontinence Score,³³ and others.³⁴
 - Urgency
 - Emotional and psychological outcomes (fear, shame, embarrassment, depression, humiliation, anger, etc.): FIQL subscales,²⁵ Euro-QoL 5D (anxiety/depression subscale)³⁵
 - Change (reduction) in coping behaviors relative to FI management
 - Social activity
 - Sexual function

Key Question 2

- Adverse effects of treatment(s):
 - Pain: abdominal, other
 - Worsening of FI (frequency, severity)
 - Constipation and/or diarrhea
 - Other gastrointestinal symptoms (such as cramping, bloating, etc.)
 - Difficulty evacuating bowels
 - Headache
 - Nausea
 - Change in appetite
 - Local dermatitis
 - Surgical complications (infection, revision surgery, etc.)
 - Negative emotional/psychological effects (depression, anger, etc.)
 - Other adverse effect(s) related to treatment (skin breakdown, urinary tract infection, etc.)

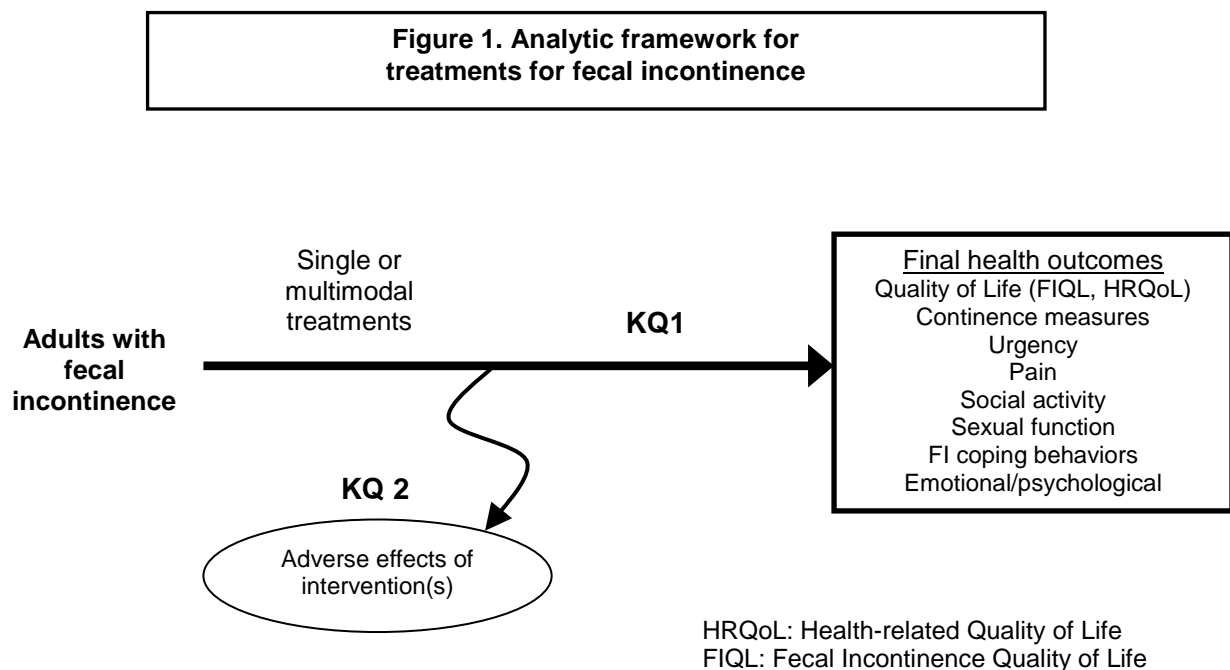
Timing

- Duration of followup: Since FI is a chronic condition, studies with at least 3 months of followup after treatment initiation are the main focus of the review. However, since some interventions may have only short followup (such as medications or dietary interventions), we will include all studies that otherwise meet the selection criteria to allow us to make overarching comments about the status of the FI treatment-outcomes literature in the final report.

Setting

- Any setting (community dwelling, long-term care, other)

III. Analytic Framework



IV. Methods

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

Studies for this comparative effectiveness review of treatments for FI will be selected based on the PICOTS framework outlined in Section II above, and the study-specific inclusion criteria described in Table 1 below.

Table 1. Study inclusion criteria fecal incontinence

Category	Criteria for Study Inclusion
Population	<ul style="list-style-type: none"> Enrolled adults (age 18 and older) with fecal incontinence (FI) at the time of study enrollment in studies that tested the effectiveness of treatments for FI and reported at least one outcome in affected adults (as identified in the PICOTS above). Diagnostic criteria: Patient-reported or investigator-identified FI Other etiologic subgroups will be included if identified in the literature.
Interventions	<ul style="list-style-type: none"> Studies of treatments targeted at existing FI due to any etiology will be included as follows: Pharmacologic treatments that are FDA approved for use in the United States for FI or FDA-approved and used off-label for FI will be included. Nonpharmacologic interventions that are FDA approved or were available for use in the U.S. (FDA approval was not necessary) will be included. Additional nondrug intervention specifications include: <ul style="list-style-type: none"> If a device is FDA-approved for some indication and is used off-label for FI, we will include the studies (e.g., rectal irrigation units) If a device is FDA-approved for FI under a certain brand name (e.g., an anal plug), and there are studies that compare it to other brands approved only in Europe, we will include those studies.
Study designs	<ul style="list-style-type: none"> Published systematic reviews, randomized clinical trials (RCTs), nonrandomized controlled trials, and prospective or retrospective cohort studies will be included. Observational studies without control groups will be included only if they assessed treatment harms (Key Question 2). Cohort studies must include appropriate analytic techniques to address bias, such as propensity scores, instrumental variables, or multivariate analysis.
Time of publication	<ul style="list-style-type: none"> English language RCTs and observational studies published from 1980 forward (to include early studies of drugs that are currently used in the treatment of FI); systematic literature reviews from 2007 forward.
Language of publication	<ul style="list-style-type: none"> We will limit included studies to English language publications because that literature best represents FDA-approved and/or available interventions in the United States. However, we will not limit our search strategy by language so that potential language bias can be assessed
Study quality	<ul style="list-style-type: none"> Systematic reviews must include transparent risk of bias assessment that used validated tools. All studies that meet the inclusion criteria will be screened for eligibility Studies that do not adequately report study information to allow the abstraction of outcomes identified in the key questions, or have indeterminate numerators and denominators for outcomes and adverse event rates, will be excluded.

KQ = key question; RCT = randomized controlled trial

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

Bibliographic database searches will identify randomized controlled trials and observational studies published from 1980 to the present on treatments for adults with FI. Relevant bibliographic databases for this topic include Ovid MEDLINE[®], Embase, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid Physiotherapy Evidence Database (PEDro), and Allied and Complementary Medicine (AMED).

Additionally, we will search for systematic reviews published since 2007 that evaluated treatments for FI. For reviews that were published previously on the same topic by the same author(s), only the most recent update will be included. We will use the 2007 look-back boundary to avoid the inclusion of outdated reviews, obsolete treatments, or interventions that have been replaced with newer approaches.

Our preliminary MEDLINE search strategy through April 2014 is in Appendix B. An experienced librarian in the Minnesota Evidence-based Practice Center developed the MEDLINE search strategy; the search will be modified for other databases. The search strategies will be peer reviewed by an independent biomedical librarian. The search strategy employs relevant

Medical Subject Headings (MeSH[®]) and natural language terms to identify terms related to FI (fecal, faecal, or anal and incontinence or accidental bowel leakage), and specific filters to identify study designs. Bibliographic database searches will be supplemented with backward citation searches of highly relevant systematic reviews. We will update the literature searches while the draft report is under public and peer review.

Two independent investigators will review titles and abstracts of bibliographic database search results to identify studies that examined interventions for FI. Citations determined potentially eligible by either investigator will undergo full text screening. Two independent investigators will screen full text articles to determine if all inclusion criteria are met. Differences in screening decisions will be resolved by consultation between investigators and a third investigator.

We will conduct additional grey literature searches to identify relevant completed and ongoing studies. Relevant grey literature resources include trial registries and the U.S. Food and Drug Administration (FDA) databases. Grey literature search results will be used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias. We will search ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP) for studies on treatments for FI in their study protocol. We will also review Scientific Information Packets sent by manufacturers for relevant pharmaceuticals, devices, and interventions.

C. Data Abstraction and Data Management

Recent, relevant systematic reviews determined to have fair or good quality will be used to replace *de novo* extraction for the specific population/treatment/outcome comparisons to which they apply, when feasible.³⁶ Items that will impact the feasibility of using existing systematic review individual study data in our review include review quality, their use of published (versus unpublished) data, and whether or not all included studies and patient samples meet our inclusion criteria. For systematic reviews that do not meet all the feasibility criteria but are of fair or good quality, we may use their abstracted study, population, and outcome data, which will be verified by a trained abstractor. If a fair or good quality systematic review included both published and unpublished data, we will abstract only the published individual study data rather than the systematic review data. From systematic reviews, we will extract author, year of publication, literature search dates, eligibility criteria, relevant synthesis results, and strength of evidence assessment (see section F below). We will use data provided by the systematic review to assess strength of evidence for results that lack strength of evidence assessments, if risk of bias assessments were provided in the review. Studies included in the prior published systematic reviews will be tracked for contribution to unique population-treatment-outcome comparisons to avoid double-counting study results. Etiologic subgroup outcomes will be identified whenever possible.

For individual trials, one investigator trained in research methodology will extract relevant study, population, risk of bias, and outcomes data. Initial data abstraction will be quality checked by a second trained investigator. Data fields to be extracted will be determined based upon the proposed summary analysis. These fields will include author, year of publication, setting, subject inclusion and exclusion criteria, etiologic subgroup(s) included, intervention(s) and control characteristics (intervention delivery, timing, frequency, duration), followup duration, participant baseline demographics, comorbidities, fecal incontinence diagnostic and severity criteria, descriptions and results of primary outcomes and adverse effects, study funding source, and

conflict of interest information. Data will be entered into Excel spreadsheets by one trained investigator and checked for accuracy by a second.

D. Assessment of Methodological Risk of Bias of Individual Studies

The risk of bias of eligible studies will be assessed by two independent investigators using instruments specific to each study design (RCT, observational). Two independent investigators will consult to reconcile any discrepancies in overall risk of bias assessments. When agreement cannot be reached through consultation between the two reviewers, a third investigator will be consulted to reconcile the summary judgment.

For RCTs, we will assess the risk of bias using a modified Cochrane Risk of Bias tool.³⁷ The seven domains of the tool are sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias (i.e., problems not covered by other domains). Outcomes measurement issues inherent in the psychometric properties of the questionnaires used to measure outcomes and assessment methods used to detect change in those questionnaire results will be specifically evaluated for detection bias. Additional items may be necessary to evaluate potential risk of bias associated with treatment definition and implementation (treatment fidelity) for nonpharmacologic treatments.

Overall summary risk of bias assessments for each study will be classified as low, moderate, or high based on the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations.³⁷ Elements contributing to a low risk of bias assessment include whether a study used a random sequence generation, concealed allocation of treatment assignments, blinded outcomes assessors, demonstrated treatment fidelity, had minimal to modest missing outcomes data or balanced missing data across groups with similar reasons for missing data across groups.³⁷ High risk of bias elements include nonrandom sequence generation, lack of blinding of outcomes assessors when the outcome was likely to be affected by the lack of blinding, or had high and/or differential losses to followup across treatment groups when missing outcomes data may have been related to real outcomes. Moderate risk of bias will be assigned to studies that are challenged across several of the domains but the study was blinded or, if blinding was not possible, outcome assessors were blinded to treatment assignment.

We developed an instrument to assess risk of bias for observational studies using the RTI Observational Studies Risk of Bias and Precision Item Bank³⁸ (Appendix C) because concerns about selection bias and blinding make the use of observational studies debatable in comparative effectiveness reviews. We selected items most relevant in assessing risk of bias from observational studies of FI, and to foster consistency with the risk-of-bias instrument for randomized controlled trials.³⁷ Bias issues common to observational studies involve the nonrandom selection of subjects, the completeness and validity of the recording of baseline patient information, attrition, and the ascertainment of outcomes. Items included from the RTI Item Bank address participant selection, group membership, efforts to address selection bias, identification of baseline effect modifiers and confounders, and appropriateness of analytic methods for observational studies. The overall summary risk-of-bias assessments for each observational study will be classified as low, moderate, or high based on the collective risk of bias inherent in each outcome domain and confidence that the results are believable given the study's limitations. Similar to risk of bias for RCTs, the overall summary risk of bias will be weighted lower for studies that demonstrate comparability across groups. Moderate risk of bias may be assigned to large cohort studies with a sample size for adequate power to detect

differences, moderate to large effect sizes, and strong evidence of attempting to control for plausible confounders.

Systematic review quality will be assessed by two independent reviewers using the AMSTAR criteria.^{36,39,40} We will also perform a quality assessment of 10 percent of abstracted data to assure that systematic review data are accurate. Systematic reviews' risk of bias and strength of evidence methods must meet accepted AHRQ EPC standards (such as Cochrane review methods or GRADE).

E. Data Synthesis

For each Key Question, we will summarize the results into evidence tables and synthesize evidence by the type of study (RCT, observational) for each unique population, comparison, and outcome combination within specific followup time periods.

When a comparison has been adequately addressed by a previous systematic review of acceptable quality (fair or high quality according to AMSTAR) and no new studies are available, we will reiterate the conclusions drawn from that review. We plan to use relevant systematic reviews of published data that have assessed study risk of bias and outcome strength of evidence. If this information is not clear or not present, we will use the data abstracted from the review, supplemented as necessary with de novo abstraction, to assess risk of bias and strength of evidence using the methods noted in Sections D and F. Since the use of a validated risk of bias tool is an inclusion criterion, we anticipate consistency across risk of bias approaches. However, if reviews used different tools to assess risk of bias in individual studies, we will determine if the main elements that address sources of potential bias were covered by their assessment/tool. If the risk of bias assessment tool is similar to our approach, we will separately assess risk of bias on only a sample of primary studies from prior reviews. If the tool is not similar or misses important potential bias elements, we will reassess risk of bias using our approach. When new trials are available, previous systematic review data will be synthesized with data from the additional trials, when possible. If there have been substantial numbers of new studies since the review was published, we may opt to create a new study pool for re-analysis. We will analyze included studies in these systematic reviews to assess the balance of publication dates and study-level risk of bias relative to the original research we will include.

We will emphasize patient-centered outcomes in the evidence synthesis. The primary outcomes for the review are outcomes most important to patients; quality of life²⁵ and FI severity,²⁸ including episode frequency, type and amount of leakage, as identified in the literature and by Key Informants (consumers, clinical experts and FI researchers).⁴¹

Outcomes will be reported by class of FI etiology whenever possible (Appendix A). We plan to pool data from multiple studies if we find two or more studies for the same etiology-treatment-outcome comparison. If that is not possible due to the inclusion of adults with mixed or unknown FI etiologies in individual studies, we plan to pool data from multiple studies based on treatment-outcome comparisons only. If there are variations in issues such as patient samples or measures that might affect pooling, we will conduct sensitivity analyses to assess their effects. If, as we anticipate, outcomes measures are varied and/or not comparable on scoring characteristics (including weighted versus unweighted measures), we will summarize evidence qualitatively and report as much etiologic information as is feasible. Standardized mean differences will be calculated for different measures of the same outcome if pooling is possible. We will categorize treatment effects by the clinical importance of differences, if known.

We will assess the heterogeneity among clinical, methodological and PICOTS elements to determine the appropriateness of pooling data.⁴² Pooling criteria will include the same definitions of FI interventions and outcomes for similar etiologic subgroups.⁴² If pooling is possible, we will pool by study design; RCT and observational studies will not be combined. When a quantitative analysis is not appropriate or possible due to lack of comparable studies for given etiology-treatment-outcome combination, qualitative synthesis will be conducted. Our preliminary examination of the literature suggests that study heterogeneity will allow only minimal opportunity for pooling; if this proves to be the case, a qualitative synthesis will be conducted for those etiologic subgroup-treatment-outcome combinations.

Potential issues in data synthesis that would impede our ability to quantitatively aggregate data include but are not limited to:

- Differences in FI severity scales:²⁴ Scales differ in range, minimum/maximum episode frequencies assessed, weighting (versus not), and whether or not the measure provides a composite or subscale scores.^{28,30,31,33}
- FI episode counts/bowel diaries: denominators differ (day, number of weeks, month, any)
- Etiologic subgrouping: FI causes are heterogeneous. Key Informants suggest that most studies will include adults with FI due to mixed etiologies, and that, as in clinical practice, the dominant etiology may not be determinable in many cases.
- Timing of outcomes assessments: Evidence may be for short-term rather than longer term (3 or more months) outcomes that are of greatest interest to patients and providers.
- Lack of measures for some outcomes (e.g., urgency)

F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes

The overall strength of evidence for select clinical outcomes within each comparison will be evaluated based on five domains: (1) study limitations (internal validity); (2) directness (single, direct link between the intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate) with the study limitations domain having considerable importance.⁴³ A fifth domain, reporting bias,⁴³ will be evaluated by the potential for publication bias, selective outcome reporting bias, and selective analysis reporting bias by comparing reported results with those mentioned in the methods section, and an assessment of the grey literature (such as ClinicalTrials.gov, unpublished abstracts, and Scientific Information Packets) to assess potentially unpublished studies.

Study limitations will be rated as low, moderate, or high according to study design and conduct. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study). Directness will be rated as either direct or indirect. Precision will be rated as precise or imprecise. Reporting bias will be rated as detected or not detected. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association.

Deficiencies in the five domains will lower the strength of evidence grade.⁴³ We will require the existence of at least two moderate risk of bias studies or one appropriately powered RCT to assign a low strength of evidence rather than considering it to be insufficient. We will require at least one good study (low risk of bias) for moderate strength of evidence and two good studies (low risk of bias) for high strength of evidence. In addition, to be considered as moderate or higher, intervention-outcome pairs need a positive response on two out of the three domains other than risk of bias. Based on these factors, the possible SOE grades are:⁴³

- **High.** Very confident that the estimate of effect lies close to the true effect. Few or no deficiencies in body of evidence; findings believed to be stable.
- **Moderate.** Moderately confident that the estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable but some doubt.
- **Low.** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient.** No evidence, unable to estimate and effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

For prior systematic reviews that provided acceptable strength of evidence, strength of evidence domains will be extracted to assess the impact of new articles on the overall body of evidence. We will take into consideration the differences in strength of evidence domains and the relative contributions of the prior review and the new articles. For published systematic reviews that did not provide a strength of evidence assessment based on a GRADE or GRADE-equivalent method, we will assess strength of evidence by replacing de novo review processes and incorporating all relevant articles, including new articles identified in bridge searches.

G. Assessing Applicability

Applicability of studies will be determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, enrollment of adults with heterogeneous etiologic factors, narrow (or excessively broad) inclusion criteria, or patient and intervention characteristics different than those described by population studies of FI interventions. Not all treatments are feasible for all types of FI, so sample differentiation will be important for applicability. Adults in clinical trials of FI treatments may be higher functioning, younger, and/or less impaired than the FI patient population as a whole. Comparator interventions may be available outside of the United States only and may never be considered for use in the United States. Followup timing on interventions may be short and therefore less helpful or applicable to the long-term management of chronic FI for patients and providers.

V. References

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VI. Definition of Terms

AMED	Allied and Complementary Medicine
APTA	American Physical Therapy Association
CENTRAL	Cochrane Central Register of Controlled Trials
FDA	Food and Drug Administration
FI	Fecal Incontinence
FIQL	Fecal Incontinence Quality of Life

FISI	Fecal Incontinence Severity Index
GI	Gastrointestinal
HRQoL	Health-related Quality of Life
IBS	Irritable bowel syndrome
ICTRP	International Controlled Trials Registry Platform
KI	Key Informant
KQ	Key Question
MeSH	Medical Subject Headings
MSA	Multiple system atrophy
PEDro	Physiotherapy Evidence Database
PFMT	Pelvic floor muscle training
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, Setting
RCT	Randomized controlled trial
TBI	Traumatic brain injury

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

AHRQ posted the key questions on the Effective Health Care Web site for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

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 healthcare 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 Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multidisciplinary 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. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in 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 recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or 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 Task Order Officer 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. The EPC considers all peer review comments on the draft report in preparation of 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 three months after the publication of the evidence report.

Potential Peer 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

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. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHS A290201200016I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed 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 the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A: Possible Associations Between Fecal Incontinence Treatments and Etiologic Subgroups for the Systematic Literature Review

Treatment	Etiology				
	Structural	Stool	Neurogenic	Mixed	Unknown
Nonsurgical					
PFMT					
Biofeedback					
Diet					
Medications (by type)					
Behavior modification					
Devices (plugs)					
Rectal irrigation					
Tissue-bulking injections					
Surgical					
Implanted neurostimulation					
Radiofrequency anal sphincter remodeling (SECCA)					
Anal sphincter repair					
Sphincter replacement					
Surgical correction: rectocele, etc. rectal prolapse, etc.					
Combined treatments (specify)					

PFMT: pelvic floor muscle training

Appendix B: Search Strategy: MEDLINE®

Database: Ovid MEDLINE(R) <1946 to April Week 2 2014> Search Strategy:

- 1 meta analysis as topic/ (13660)
- 2 meta-analy\$.tw. (54127)
- 3 metaanaly\$.tw. (1217)
- 4 meta-analysis/ (46905)
- 5 (systematic adj (review\$1 or overview\$1)).tw. (44526)
- 6 exp Review Literature as Topic/ (7463)
- 7 or/1-6 (107419)
- 8 cochrane.ab. (25887)
- 9 embase.ab. (24212)
- 10 (psychlit or psyclit).ab. (857)
- 11 (psychinfor or psycinfo).ab. (7828)
- 12 or/8-11 (40459)
- 13 reference list\$.ab. (8747)
- 14 bibliograph\$.ab. (10598)
- 15 hand search.ab. (792)
- 16 relevant journals.ab. (656)
- 17 manual search\$.ab. (2067)
- 18 or/13-17 (21325)
- 19 selection criteria.ab. (18411)
- 20 data extraction.ab. (8689)
- 21 19 or 20 (25615)
- 22 review/ (1860178)
- 23 21 and 22 (18203)
- 24 comment/ (534380)
- 25 letter/ (808206)
- 26 editorial/ (336293)
- 27 animal/ (5281074)
- 28 human/ (13356171)
- 29 27 not (28 and 27) (3832160)
- 30 or/24-26,29 (5028311)
- 31 7 or 12 or 18 or 23 (132997)
- 32 31 not 30 (124092)
- 33 randomized controlled trials as topic/ (91978)
- 34 randomized controlled trial/ (370164)
- 35 random allocation/ (80059)
- 36 double blind method/ (124975)
- 37 single blind method/ (18853)
- 38 clinical trial/ (486017)
- 39 clinical trial, phase i.pt. (13981)
- 40 clinical trial, phase ii.pt. (22475)
- 41 clinical trial, phase iii.pt. (8783)
- 42 clinical trial, phase iv.pt. (921)

43 controlled clinical trial.pt. (88103)
44 randomized controlled trial.pt. (370164)
45 multicenter study.pt. (169875)
46 clinical trial.pt. (486017)
47 exp Clinical trials as topic/ (278463)
48 or/33-47 (1017339)
49 (clinical adj trial\$.tw. (196096)
50 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. (122378)
51 placebos/ (32469)
52 placebo\$.tw. (149639)
53 randomly allocated.tw. (15467)
54 (allocated adj2 random\$.tw. (17908)
55 49 or 50 or 51 or 52 or 53 or 54 (390513)
56 48 or 55 (1136146)
57 case report.tw. (181365)
58 case report.tw. (181365)
59 letter/ (808206)
60 historical article/ (299983)
61 57 or 58 or 59 or 60 (1278357)
62 56 not 61 (1106770)
63 exp cohort studies/ (1334416)
64 cohort\$.tw. (249257)
65 controlled clinical trial.pt. (88103)
66 epidemiologic methods/ (29664)
67 limit 66 to yr=1971-1983 (5334)
68 63 or 64 or 65 or 67 (1501811)
69 (fecal and incontin*).ti. (1195)
70 (anal and incontin*).ti. (732)
71 exp *Fecal Incontinence/ (5028)
72 (faecal and incontin*).ti. (630)
73 69 or 70 or 71 or 72 (5152)
74 73 and 32 (108)
75 73 and 62 (525)
76 68 and 73 (1351)
77 76 not (75 or 74) (1065)
78 75 or 76 or 77 (1597)
79 limit 78 to "all child (0 to 18 years)" (432)
80 limit 79 to "all adult (19 plus years)" (264)
81 78 not 79 (1165)
82 80 or 81 (1429)

Appendix C. Risk of Bias Assessment for Observational Studies

Question	Response		Criteria	Justification
			Internal Validity	
1. Study design: prospective, retrospective, or mixed?	Prospective	<input type="checkbox"/>	Outcome had not occurred when study was initiated; information was collected over time	
	Mixed	<input type="checkbox"/>	One group was studied prospectively; other(s) retrospectively	
	Retrospective	<input type="checkbox"/>	Analyzed data from past records, claims	
2. Were inclusion/exclusion criteria clearly stated?	Yes	<input type="checkbox"/>	Clearly stated	
	Partially	<input type="checkbox"/>	Some, but not all criteria stated or some not clearly stated.	
	No	<input type="checkbox"/>	Unclear	
3. Were baseline characteristics measured using valid and reliable measures <u>and</u> are they equivalent in both groups?	Yes	<input type="checkbox"/>	Valid measures, groups ~ equivalent	
	No	<input type="checkbox"/>	Nonvalidated measures or nonequivalent groups	
	Uncertain	<input type="checkbox"/>	Could not be ascertained	
4. Were important variables known to impact the outcome(s) assessed at baseline?	Yes	<input type="checkbox"/>	Yes, most or all known factors were assessed	
	No	<input type="checkbox"/>	Critical factors are missing	
	Uncertain	<input type="checkbox"/>		
5. Is the level of detail describing the intervention adequate?	Yes	<input type="checkbox"/>	Intervention sufficiently described	
	Partially	<input type="checkbox"/>	Some of the above features.	
	No	<input type="checkbox"/>	Intervention poorly described	
6. Is the selection of the comparison group appropriate?	Yes	<input type="checkbox"/>	Other adults with fecal incontinence with similar etiologic, demographic, severity and comorbid features	
	No	<input type="checkbox"/>		
7. Was the impact of a concurrent intervention or an unintended exposure that might bias results isolated?	Yes	<input type="checkbox"/>	By inclusion criteria, protocol, or other means	
	Partially	<input type="checkbox"/>	Some were isolated, others were not	
	No	<input type="checkbox"/>	Important concurrent interventions were not isolated or prohibited	
8. Were there attempts to balance the allocation across groups? (e.g., stratification, matching or propensity scores)	Yes	<input type="checkbox"/>	<i>(If yes, what method was used?)</i>	
	No	<input type="checkbox"/>		
	Uncertain	<input type="checkbox"/>	Could not be ascertained	
9. Were outcomes assessors blinded?	Yes	<input type="checkbox"/>	Who assessed outcomes?	
	No	<input type="checkbox"/>		
	Uncertain	<input type="checkbox"/>	Not reported	
10. Were outcomes assessed using valid and reliable measures, and used consistently across all study participants?	Yes	<input type="checkbox"/>	Measures were valid and reliable (i.e., objective measure, validated scale/tool); consistent across groups	
	Partially	<input type="checkbox"/>	Some of the above features	
	No	<input type="checkbox"/>	None of the above features	
	Uncertain	<input type="checkbox"/>	Could not be ascertained.	
11. Was length of followup the same for all groups?	Yes	<input type="checkbox"/>		
	No	<input type="checkbox"/>		
	Uncertain	<input type="checkbox"/>	Could not be ascertained	
12. Did attrition result in differences in group characteristics between baseline and followup?	Yes	<input type="checkbox"/>	<i>(If yes, for which followup period(s)?)</i>	
	No	<input type="checkbox"/>		
	Uncertain	<input type="checkbox"/>	Could not be ascertained	
13. If dissimilar baseline	Yes	<input type="checkbox"/>	What method?	

Question	Response		Criteria	Justification
	Internal Validity			
characteristics, does the analysis control for baseline differences between groups?	No	<input type="checkbox"/>		
	Uncertain	<input type="checkbox"/>	Could not be ascertained	
14. Were confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?	Yes	<input type="checkbox"/>		
	No	<input type="checkbox"/>		
	Uncertain	<input type="checkbox"/>	Could not be ascertained (i.e., retrospective designs where eligible at baseline could not be determined)	
	NA	<input type="checkbox"/>	No confounders or effect modifiers included in the study.	
15. Were important confounding and effect modifying variables taken into account in design and/or analysis? (e.g., matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)	Yes	<input type="checkbox"/>		
	Partially	<input type="checkbox"/>	Some variables taken into account or adjustment achieved to some extent.	
	No	<input type="checkbox"/>	Not accounted for or not identified.	
	Uncertain	<input type="checkbox"/>	Could not be ascertained	
16. Are statistical methods used to assess the primary outcome appropriate to the data?	Yes	<input type="checkbox"/>	Statistical techniques used must be appropriate to the data.	
	Partially	<input type="checkbox"/>		
	No	<input type="checkbox"/>		
	Uncertain	<input type="checkbox"/>	Could not be ascertained	
17. Is there suggestion of selective outcome reporting?	Yes	<input type="checkbox"/>	Partial reporting of prespecified outcomes (e.g., secondary not primary outcomes; only significant outcomes; beneficial not adverse outcomes, etc.)	
	No	<input type="checkbox"/>		
	Uncertain	<input type="checkbox"/>	Could not be ascertained	
18. Was the funding source identified?	Yes	<input type="checkbox"/>	Who provided funding?	
	No	<input type="checkbox"/>		
	Uncertain	<input type="checkbox"/>		
Overall Assessment				
Overall Risk of Bias Assessment	Low	<input type="checkbox"/>	Results are believable taking study limitations into consideration	
	Moderate	<input type="checkbox"/>	Results are probably believable taking study limitations into consideration	
	High	<input type="checkbox"/>	Results are uncertain taking study limitations into consideration	