META ANALYSIS AND SYSTEMATIC REVIEW

Heterogeneous outcome reporting in adult slow-transit constipation studies: Systematic review towards a core outcome set

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Key words
Core outcome set, OMERACT, Outcomes, Slow-transit constipation.

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Abstract

Background and Aim: Standardizing evaluative outcomes and their assessment facilitates comparisons between clinical studies and provides a basis for comparing direct effects of different treatment options. The aim of this study was to systematically review types of outcomes and measurement instruments used in studies regarding treatment options for slow-transit constipation (STC) in adults.

Methods: In this systematic review of the literature, we searched MEDLINE, Embase, and PsycINFO from inception through February 2018, for papers assessing any STC treatment in adult patients. Outcomes were systematically extracted and categorized in domains using the conceptual framework of the Outcome Measures in Rheumatology filter 2.0. Outcome reporting was stratified by decade of publication, intervention, and study type.

Results: Forty-seven studies were included in this systematic review. Fifty-nine different types of outcomes were identified. The outcomes were structured in three core areas and 18 domains. The most commonly reported domains were defecation functions (94%), gastrointestinal transit (53%), and health-care service use (51%). The most frequently reported outcomes were defecation frequency (83%), health-related quality of life (43%), and adverse events and complications (43%). In 62% of the studies, no primary outcome was defined, whereas in two studies, more than one primary outcomes were selected. A wide diversity of measurement instruments was used to assess the reported outcomes.

Conclusion: Outcomes reported in studies on STC in adults are heterogeneous. A lack of standardization complicates comparisons between studies. Developing a core outcome set for STC in adults could contribute to standardization of outcome reporting in (future) studies.

Introduction

Chronic constipation is a condition with a high reported prevalence ranging from 16% to 19.2% in Europe.1,2 Functional, or idiopathic, constipation is a subtype of chronic constipation that is associated with no clear organic cause.3 The diagnosis of functional constipation is based on the Rome IV criteria.4,5 These criteria define constipation as the presence of at least two symptoms of constipation, such as a low defecation frequency, straining, lumpy or hard stools, and a sensation of incomplete evacuation.4 Functional constipation can be classified in three (overlapping) subtypes: normal transit constipation, slow-transit constipation (STC), and evacuation disorders.5,6

Even though the 2013 medical position statement of the American Gastroenterological Association argues different treatment algorithms for patients with normal transit constipation or STC versus patients with evacuation disorders,6 clinical studies do not always distinguish between the various subtypes of functional constipation. Different treatment algorithms, however, may be associated with different relevant outcomes. Therefore, and also in order to facilitate epidemiological, etiological, pathophysiological, and therapeutic enquiry,5 it is relevant to take this subclassification into account when designing clinical studies.

This paper focuses on STC. STC is present in 15% to 42% of the patients diagnosed with functional constipation and is associated with slow transit of feces.3,7 First treatment options for STC consist of (a combination of) lifestyle changes, behavioral treatment, pharmacological treatment, or retrograde colonic irrigation.3,8,9 Patients not responding to conservative treatment might undergo surgical interventions such as sacral neuromodulation, subtotal colectomy, or colostomy.7

In the scientific literature, there is no formal consensus on the types of outcomes to be assessed or measurement instruments to be used in clinical studies in patients with STC. Formalization
could be achieved by the development of a core outcome set (COS). A COS is a minimal set of outcomes to be included in every (clinical) study regarding treatment for a certain health condition. Implementation of a COS can standardize evaluative outcomes and their assessment and decrease the likelihood of outcome reporting bias. It also facilitates comparisons between the direct effects of different treatment options, which is of importance when supporting the development of treatment guidelines and policies.

Databases of the International Consortium for Health Outcomes Measurement and Core Outcome Measures in Effectiveness Trials provide only one constipation-related COS for clinical trials in childhood constipation (0–18 years). This COS, however, does not specifically focus on STC as a subtype of functional constipation and focuses on outcome assessment in children and adolescents. Therefore, we argue that an additional COS will contribute to standardizing outcome reporting in studies on STC in adult patients.

Before the actual development of a COS, a comprehensive overview of the existing types of outcomes is required. Therefore, we systematically reviewed the literature and extracted the types of outcomes and measurement instruments reported in STC studies in adult patients. As our aim was to provide an overview of the existing types of outcomes in STC research, this review does not focus on the results of the included studies. This literature review could, in turn, provide a basis for future development of a COS for STC in adult patients.

Methods

Search strategy. The initial search was conducted in July 2016, followed by an updated search in February 2018. In the Supporting Information, the full search query is described. In short, the databases MEDLINE (PubMed), Embase (Ovid), and PsycINFO (EBSCO) were searched with a combination of disease terms (e.g., constipation, slow-transit, and idiopathic), treatment terms (e.g., treatment, therapy, laxatives, biofeedback, and colectomy), and outcome terms (e.g., effectiveness and outcome). The search was restricted to English articles using human subjects. If MeSH terms or subject headings existed, they were included in the search. Although the review focuses on STC, a broad search strategy was used to ensure that all potentially relevant articles were identified. Subsequently, articles on other (sub)types of constipation were excluded during eligibility assessment.

Eligibility assessment. Titles and abstracts were retrieved and imported in Endnote X7. Duplicates were removed. Titles and abstracts were screened for eligibility by the first reviewer (A. R. for the initial search or S. H. for the update) using the criteria outlined in Table 1. The second reviewer (M. K.) screened a subset of 3% randomly selected titles and abstracts for eligibility. As within this subset there was complete agreement between the reviewers, duplicate title and abstract screening of the full sample of papers was not considered necessary. After title and abstract screening, full-text articles were retrieved and screened for eligibility by the first reviewer (A. R. or S. H.).

Quality assessment of outcome reporting. The eligibility criterion “outcome reporting quality” was evaluated through a quality assessment. When articles were eligible based on the full text, the quality of reporting of the outcomes and measurement instruments was assessed. Table 2 shows the criteria of the quality assessment. Articles were included in the systematic literature review if they scored ≥3 points (out of 4 points) in the quality assessment. The assessment was performed using a selection of appropriate criteria regarding outcome reporting from the following existing quality checklists: STROBE, TREND, CONSORT, and MINORS.

Data extraction. The first reviewer (A. R. or S. H.) conducted the primary data extraction. Extraction included data on population age, treatment option(s), primary and secondary outcomes, study type, and reporting and measurement methods of the outcomes. The second reviewer (M. K.) extracted data from a subset of 15% randomly selected articles to check the comprehensiveness of the primary data extraction. As full consensus was reached between the two reviewers for this subset, duplicate data extraction was not deemed necessary.

| Table 1 | Eligibility criteria in chronological inclusion order |
|---|---|
| **Population** | Patients (humans) with slow-transit constipation aged ≥18 years. If patients <18 years were included, only outcomes assessed in participants ≥18 years were extracted |
| **Intervention** | Any treatment of constipation such as laxatives, biofeedback, physical exercise, subtotal colectomy, and sacral neuromodulation |
| **Comparator** | Any treatment of constipation such as laxatives, biofeedback, physical exercise, subtotal colectomy, and sacral neuromodulation or placebo, or a different patient group as comparator, or no control group |
| **Outcome** | Safety, efficacy, or effectiveness of constipation treatment, measured with any outcome |
| **Study type** | Case studies, cohort studies (prospective and retrospective), case-control studies, noncontrolled trials, cross-over studies, and ([non]randomized controlled) trials |
| **Language** | English |
| **Outcome reporting quality** | Studies were excluded when it was unclear which outcomes were used and/or how outcomes were measured |
| **Publication status** | Published |
| **Publication year** | No restriction |
| **Publication type** | Full-text articles (no conference abstracts) |
Classification of outcomes in domains. The Outcome Measures in Rheumatology (OMERACT) filter 2.0 was used to categorize the extracted primary and secondary outcomes. This conceptual framework follows the 1.0 version that has been used since 1998 to categorize outcomes in rheumatology.19 The 2.0 version has been developed for other health conditions and was successfully used in multiple systematic reviews.11,20–22 The framework covers two concepts: impact of health conditions and pathophysiological manifestations. These concepts cover four core areas: life impact, resource use and economical impact, pathophysiological manifestations, and death. All outcomes reported in the included papers were classified in domains by two authors (A. R. and S. H.). Each domain was classified under one of the four core areas. When more than six outcomes were categorized into the same domain, the domain was split in subdomains based on grouping of clinical symptoms. Adverse events and complications were reported as an additional concept of the OMERACT 2.0 filter.11 See Figure 1 for the conceptual framework.

Analysis. Primary, as well as overall, outcome reporting was analyzed. Results were summarized using frequencies and percentages. The frequency of outcome domain reporting was calculated for all included papers and for various subgroups of papers. Subgroups were made according to decade of publication (inception–1996, 1997–2007, and 2008–2018), study type (case report/case series, uncontrolled trials, retrospective cohort study, and [non]randomized controlled trials), and intervention category (pharmacological agents, stimulation therapy, resectional surgical techniques, and other treatments). Analyses were conducted using Microsoft Excel 2016.

Table 2 Three item assessment of reporting quality of outcomes and measurement instruments

| No. | Criterion                                                                                           | Yes | No  |
|-----|-----------------------------------------------------------------------------------------------------|-----|-----|
| 1   | Study outcomes and methods used to collect data are clearly described.                              | 2 points | 0 points |
|     | • The outcomes are clearly specified and defined.                                                    |     |     |
|     | • It is clearly described how the outcomes are measured.                                             |     |     |
|     | • It is clearly described by whom the outcomes are reported.                                        |     |     |
| 2   | All outcomes reported in the section are specified in the or section.                               | 1 point | 0 points |
|     | If there are any outcomes reported in the section that are not specified in the / section, 0 points are scored. |     |     |
| 3   | Unambiguous explanation of outcomes and outcome measures throughout the article.                   | 1 point | 0 points |
|     | The reporting of outcomes is consistent throughout the article. There is no unambiguous reporting that makes it confusing for the reader to assess what has been done. |     |     |

Figure 1 Conceptual framework OMERACT 2.0.11. International Classification of Functioning (ICF), Disability and Health
Results

Search results. MEDLINE, Embase, and PsycINFO were first searched in July 2016, identifying 1680 records (PubMed: 552; Embase: 1108; and PsycINFO: 20). The updated search in February 2018 revealed another 272 records (PubMed: 60; Embase: 205; and PsycINFO: 7), resulting in a total of 1952 records. After deducting duplicates, 1458 records were included in title and abstract screening, resulting in full-text screening of 229 records. Full-text screening followed by quality assessment of outcome reporting revealed 47 studies to be included. Figure 2 shows the PRISMA flow diagram.

Study characteristics. In total, 47 articles published between 1989 and February 2018 were included. Table S1 lists the included studies. Characteristics of the included studies are summarized in Table 3. The majority of the studies were conducted in both adults and elderly (55%). Twenty interventions were examined across the studies, classified in four categories. Most studies assessed the effect of stimulation therapy (34%), followed by surgical resections (28%), pharmacologic agents (24%), and other treatment modalities (14%). Various diagnostic methods and thresholds to define STC were applied in the study populations. Thirty-four (72%) studies used a radiopaque marker study to define STC, whereas four studies used colonic transit scintigraphy. Four studies combined both methods. A detailed overview can be found in Table S2.

Primary outcomes. In 29 (62%) studies, no distinction was made between primary and secondary outcomes. Sixteen studies defined one primary outcome: digestive functioning (n = 4), improvement in constipation symptoms or defecation frequency (n = 3), constipation severity (n = 3), defecation frequency (n = 3), treatment success (n = 2), and health-related quality of life (n = 1). One study defined a composite primary outcome: treatment success defined in terms of both the clinical cure and the clinical improvement rate. Another study defined four primary outcomes: treatment success, clinical improvement rate, stool consistency, and safety endpoints. In total, eight different (combinations of) primary outcomes were defined. Of the studies defining a primary outcome, 50% were uncontrolled trials, 39% were (non)randomized controlled trials, 39% were (non)randomized controlled trials, 39% were (non)randomized controlled trials, and one case study, and one retrospective cohort study.

Categorization of outcomes. In total, 59 different types of outcomes were assessed in the 47 included studies. On average, 6.9 (range 1–14) different outcomes were assessed per study. Of the 59 different types of outcomes, 23 outcomes were categorized in the concept impact of health conditions and 35 in the concept pathophysiological manifestations. Subsequently, the outcomes were categorized in three core areas and 18 domains. Complications and side effects were labeled as an additional concept. Outcomes within the core area death were not reported in any of the included studies. The most frequently reported domains are defecation functions, digestive functions, and health-care service use in 94%, 53%, and 51% of the studies, respectively.

The most frequently reported types of outcomes are defecation frequency in 83% of the studies, followed by 43% of the studies.
Table 3

Characteristics of the 47 included studies on any treatment options for adult patients with slow-transit constipation

| Study type                          | n (%) | Intervention                                                                 |
|-------------------------------------|-------|------------------------------------------------------------------------------|
| Case report and case study          | 17 (36) | Stimulation therapy††, Resectional surgical techniques†, Pharmacologic agents†† |
| Uncontrolled trial                  | 15 (32) | Biofeedback‡, Fecal microbiota transplantation‡‡, Abdominal wall massage‡‡ |
| Retrospective cohort study          | 1 (2)  | Body acupuncture‡‡                                                             |
| (Non)randomized controlled trial    | 14 (30) |                                                                              |

Publication year

- 1989–1996: 9 (19)
- 1997–2007: 15 (32)
- 2008–2018: 23 (49)

Population

- Adults (18–64 years): 20 (43)
- Elderly (> 64 years): 1 (2)
- Adults and elderly (18+ years): 26 (55)

Intervention

- Stimulation therapy††
- Resectional surgical techniques†
- Pharmacologic agents††
- Biofeedback‡
- Fecal microbiota transplantation‡‡
- Abdominal wall massage‡‡
- Body acupuncture‡‡

Comparator

- No control: 30 (64)
- Placebo: 13 (28)
- Fiber: 1 (2)
- Conventional treatment: 1 (2)
- Control is different patient group: 1 (2)
- Subtotal colectomy: 1 (2)

Core area life impact. The core area life impact consists of eight domains: health-related quality of life, treatment satisfaction, treatment success/improvement, self-care, domestic life, interpersonal interactions and relationships, well-being, and community, social, and civic life. In total, 64% of the studies reported 16 different types of outcomes in these domains. The domains most frequently reported were health-related quality of life (43%), treatment satisfaction (28%), and treatment success/improvement (26%).

Core area resource use and economical impact. The core area resource use and economical impact consists of two domains: health-care service use and compliance. In total, 49% of the studies reported seven different types of outcomes in these domains. The core area resource use and economical impact consists of two domains: health-care service use and compliance. In total, 49% of the studies reported seven different types of outcomes in these domains.

Core area pathophysiological manifestations. The core area pathophysiological manifestations consists of eight domains: defecation functions, digestive functions, sensation of pain, sensations associated with the digestive system, blood, ingestion functions, weight maintenance functions, and urinary functions. The domain defecation functions was divided into seven subdomains: defecation frequency, general defecation functions, defecation sensations, defecation consistency, defecation profile, defecation control, and other types of outcomes. All except two studies (i.e., 96%) reported on 35 different types of outcomes within this core area.
Domains most frequently reported were defecation functions (94%), 23–47, 49–54, 56–69 digestive functions (53%), 23–30, 33–35, 37, 40, 41, 44, 45, 47, 49, 53, 56–64 and sensations associated with the digestive system (32%), 23, 27, 32, 33, 41, 42, 45, 47, 49, 50, 52, 53, 56–60, 62, 64, 66 and elimination of feces (36%). 23–27, 29, 32, 33, 41, 42, 45, 47, 49, 50, 52, 53, 56–60, 62, 64, 66

The most commonly reported subdomains of defecation functions were defecation frequency (83%), 23–25, 29, 31–33, 35–43, 45–47, 49, 50, 52, 54, 56–64, 66–69 general defecation functions (53%), 28, 31–33, 40, 42, 46, 48–51, 54, 55, 57, 60, 62, 63, 65–68 and constipation severity (43%), 28, 31–33, 40, 42, 46, 48–51, 54, 55, 57, 60, 62, 63, 65–68 and colonic/whole-gut transit time (40%). 25–28, 33, 35–37, 40, 41, 47, 49, 53, 56–64–68

Table S3C lists the outcome reporting frequency in the core area pathophysiological manifestations.

### Outcome domains based on decade of publication.

Reporting of the health-related quality of life domain increased from zero studies published from inception to 1996 to 57% of the studies published after 2008. On the other hand, reporting of domains within the core area resource use and economic impact decreased from 67% of the studies published between 1997 and 2007 to 43% of the studies published after 2008. This also applies for reporting of the digestive function domain, decreasing from 89% to 43% of the studies over time. Domains of which reporting was stable over time were treatment...
Table 5  Reporting of outcome domains in the 47 included studies according to the OMERACT 2.0 filter core area “pathophysiological manifestations”

| Outcome (sub)domain | Outcome reporting in (sub)domains n studies (%) | Outcomes reported within domain | Measurement instruments |
|---------------------|-----------------------------------------------|---------------------------------|-------------------------|
| Defecation functions | 44 (94)                                        | Defecation frequency            | Patient diary           |
|                      | 39 (83)                                        | Defecation frequency associated with complete evacuation | Telephone interview |
|                      |                                                 |                                 | Undefined questionnaire(s) |
| Defecation frequency | 19,21,25,27,29,31,39,41,43,45,46,48–50,52–60,62–65 |                                 | VAS                     |
|                     |                                                |                                 | KESS score              |
|                      |                                                |                                 | Rome III criteria       |
|                      |                                                |                                 | SCL-90                  |
|                     |                                                |                                 | CAS                     |
|                      |                                                |                                 | PAC-SYM                 |
|                      |                                                |                                 | Wexner constipation score |
|                      |                                                |                                 | Agachan score           |
|                      |                                                |                                 | CCSS                    |
|                     |                                                |                                 | Patient diary           |
|                      |                                                |                                 | Undefined questionnaire(s) |
|                     |                                                | Constipation symptoms (general) | 5-point Likert scale    |
|                     |                                                |                                 | Anorectal manometry     |
| General defecation functions | 25 (53) | Constipation severity | Balloon expulsion test |
|                     | 28,31–33,40–42,46,48–51,54,55,57,60–69        |                                 | Stationary pull through |
|                     |                                                |                                 | Patient diary           |
|                     |                                                |                                 | Undefined questionnaire(s) |
| Elimination of feces | 17 (36)                                        | Straining, Incomplete evacuation | Bristol stool scale     |
|                     | 25–27,29,32,33,38,41,43,47,52,57–69,63–65      | Need to digitate/assisted defecation | Patient diary           |
|                     |                                                 | Difficulty with rectal evacuation | (Telephone) interview   |
|                     |                                                 | Anorectal motility              | Undefined questionnaire(s) |
| Fecal consistency   | 16 (34)                                        | Stool consistency               | Holschneider score      |
|                     | 23,26,35,38,39,41,47,52,57–60,64,66–68         |                                 | Telephone interview     |
| Fecal continence    | 10 (21)                                        | Anal/fecal incontinence         | Wexner incontinence score |
|                     | 34,39,42,50–52,58,65,62,63                     | Soiling                         | Vaizey incontinence score |
| Other               | 6 (13)                                         | Stool weight                     | Patient diary           |
|                     | 23,26,32,43,53,63                              | Time spent toileting            | Scale                   |
| Flatulence          | 2 (4)                                          | Flatulence                       | Interview               |
|                     | 23,64                                          |                                 | Patient diary           |
|                     |                                                 |                                 | 5-point Likert scale    |

(Continues)
success/improvement, treatment satisfaction, and defecation frequency. Reporting of outcomes in the domains sensation of pain and sensations associated with the digestive system ranged from 35% to 73% and 11% to 53% of the studies, respectively.

**Outcome domains based on intervention studied.**

In studies on resectional surgical techniques and studies on stimulation therapy, outcomes in the health-related quality of life domain were most frequently reported (77% and 50% of the studies, respectively). For resectional surgical techniques, this was followed by 69% of the studies reporting on outcomes in the treatment satisfaction domain. Reporting of the domain health-care service use ranged from 18% in studies on pharmacological agents to 62% in studies on resectional surgical techniques. Reporting of the defecation function domain was consistent between intervention categories, ranging from 82% to 100%. The digestive function domain was reported in 91% of the studies on pharmacologic agents compared with 50% of the studies on stimulation therapy.

**Outcome domains based on study type.** Reporting of the core area impact was most common in 88% of the case reports and case studies, followed by 73% of the uncontrolled trials and 21% of the (non)randomized controlled trials. Of the case reports and case studies, 65% reported on outcomes within the health-related quality of life domain, followed by 47% reporting on the satisfaction domain. For the uncontrolled trials, domains most frequently reported were health-related quality of life and treatment success/improvement, both in 40% of the studies. In the (non)randomized controlled trials, outcomes within the domains health-related quality of life, treatment success/improvement, and satisfaction were reported in 14% of the studies.

The core area resource use and economical impact was reported in 65% of the case reports and case series, 53% of the uncontrolled trials, and 21% of the (non)randomized controlled trials. Within the core area pathophysiological manifestations, reporting of the domain sensation of pain ranged from 40% in uncontrolled trials to 59% in case reports and case studies. The digestive function domain was only reported in 12% of the case reports and case studies, whereas reporting in other study type categories ranged from 71% to 87%. Reporting of the domain defecation functions ranged from 86% in (non)randomized controlled trials to 100% in uncontrolled trials.

**Adverse events and complications.** Reporting of any adverse events or complications occurred in 43% of the
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Studies. Adverse events and complications have been increasingly reported over time, from 22% in studies published before 1996 to 57% in studies published after 2008. Whereas 77% of the studies on resectional surgical techniques reported this outcome, reporting in studies on other intervention categories ranged from 27% to 31%. Looking at study types, reporting of adverse events and complications ranged from 29% in (non)randomized controlled trials to 59% in case reports and case studies. No data were gathered on the types of adverse events and complications assessed in the included studies.

**Measurement instruments.** The majority of the outcomes (83%) were at least partially patient reported. However, the measurement instruments that were used differed within and between most types of outcomes. Many studies did not define the type of questionnaire that was used to assess outcomes (they only reported that “a questionnaire” was used). Therefore, these are described as undefined questionnaires. A summary of the types of outcomes and the measurement instruments used per outcome is shown in Table S4.

All outcomes in the digestive functions domain were assessed by technical methods, as were improvement/response, anorectal motility, stool weight, and blood levels. The technical method most frequently used was a radiopaque marker study (n = 12) to assess colonic/whole-gut transit time. Adverse events and complications, compliance, hospitalization, and constipation drug use were either clinician reported, derived from hospital records, or measured using undefined questionnaires.

Defecation frequency was measured using patient diaries, undefined questionnaires, and telephone interviews. Health-related quality of life was assessed with various questionnaires of which the Short Form 36 was most often used (50%). Abdominal pain was assessed by seven different instruments of which a patient diary was used in 44% of the studies. Constipation severity was assessed by the Wexner constipation score questionnaire in 55% of the studies reporting this outcome.

**Discussion**

This systematic review categorizes the different types of outcomes and measurement instruments used to assess the efficacy and effectiveness of treatment options for STC in adult patients, based on the OMERACT 2.0 framework. We encountered heterogeneous reporting of different types of outcomes and measurement instruments in the reviewed literature. Across the 47 included studies, 59 types of outcomes were reported, classified into 18 domains within three core areas (life impact, resource use and economical impact, and pathophysiological manifestations). The core area death was not covered. The domain defecation functions was the most common domain, reported in 94% of the studies. Furthermore, many studies reported on digestive functions (53%), sensation of pain (49%), health-care service use (49%), health-related quality of life (43%), and adverse events and complications (43%). Other domains were reported in 40% of the studies or less. Types of outcomes most frequently reported were defecation frequency (83%), health-related quality of life (43%), adverse events and complications (43%), constipation severity (43%), and colonic/whole-gut transit time (40%). These results indicate a lack of consensus on criteria for assessing treatment efficacy and effectiveness, which makes it difficult to compare different treatment options for STC in adult patients.

Importantly, when zooming in on primary outcome reporting, as much as 62% of the studies (n = 29) did not define a primary outcome. In the remaining 38% of the studies (n = 18), eight different (combinations of) primary outcomes were reported. Compared with outcome reporting in all the 47 included studies, there is less heterogeneity when only taking into account the 18 studies defining a primary outcome. However, the most commonly reported primary outcome, digestive functioning, was only reported in 22% of these 18 studies.

Our results show increased reporting of health-related quality of life over time. This aligns with previous findings showing an increased number of publications addressing (health-related) quality of life over recent decades in gastroenterology. On the other hand, reporting of outcome domains within the core area resource use and economical impact decreased over the last two decades.

Next to the large variety of types of outcomes reported in the studies, there was a wide diversity in measurement instruments used within and between the reported outcomes. The majority (83%) of the outcome measures were at least partially patient reported, and many outcomes were assessed with undefined questionnaires. Not defining these questionnaires used limits the interpretability of the assessed outcomes as it is unknown whether validated measurement instruments were used. However, in some outcomes (e.g. defecation frequency), this might be of less importance compared with when more complex concepts (e.g. sensation of pain) are assessed. Technical measures were mostly used to assess colonic or oro-cecal transit time, but the use of these objective measures for outcomes in the digestive function domain decreased over time. This might be explained by the theory that these measures are currently being used in the diagnostic phase, rather than as a treatment outcome. Next to the standardization of types of outcomes to be used, standardization is required on which measurement instruments to use to assess certain outcomes. When instruments with sound psychometric properties are unavailable, they should be developed.

Comparing the results of this systematic review with the available COS for childhood constipation shows some agreements and discrepancies. Defecation frequency, (health-related) quality of life, and complications and side effects are included in the childhood constipation COS and are also reported in more than 43% of the literature on STC in adult patients. Stool consistency, however, was only reported in 34% of the studies in this literature review and is included in the childhood constipation COS. Another discrepancy with the COS is painful defecation. In the reviewed literature, painful defecation was not listed as a type of outcome in any of the studies. Assuming that this might be due to a lack of uniform definitions of the outcomes, painful defecation might be grasped in other outcomes included in this review such as straining, general constipation symptoms, difficulty with rectal evacuation, or pelvic and anorectal pain. However, the types of outcomes listed earlier are only reported in 21% of the studies or less. Furthermore, the COS for childhood constipation includes three outcomes only to be assessed when age appropriate (fecal incontinence, abdominal pain, and school attendance). One of these outcomes, abdominal pain, was reported in 38% of the studies in...
this literature review and might also be relevant for the adult population with STC.

To our knowledge, this is the first study providing a comprehensive overview of the types of outcomes and measurement instruments reported in studies on STC in adult patients. Our study has some limitations that need to be addressed. First, it is possible that not all relevant studies were included in the review due to the eligibility criteria, resulting in potentially missed types of outcomes. Second, one reviewer independently screened all records for eligibility, rather than the recommended two reviewers for systematic reviews. The second reviewer screened only a proportion of the titles and abstracts, and full-text papers. This was partly due to pragmatic reasons (i.e., the search identified almost 2000 abstracts and > 200 full-text papers), but more importantly, the aim of this review was to identify reported outcomes in clinical studies rather than synthesize effectiveness evidence. We feel that the potential risk (i.e., false exclusion or inclusion of a paper) of the screening approach used is minor, for several reasons: (i) there was full consensus between both reviewers for a proportion of the data, (ii) saturation of reported outcomes was most likely reached because the updated search resulted in six additional papers, but these revealed no new outcomes, and (iii) false inclusion of a paper in the initial screening of titles and abstracts would generally be noticed during the full-text screening, leading to exclusion at this stage. A third limitation was that our search for types of outcomes was limited to those reported in the existing literature. This could potentially lead to missing outcomes that are relevant to patients. For example, patients often report fatigue in daily life during outpatient visits at the clinic. However, fatigue was not reported as an outcome in any of the 47 reviewed studies. This example stresses the importance of patient involvement in the development of a COS. Finally, publication and outcome reporting bias may have led to missing other additional relevant outcomes. Outcomes that are not (positively) affected by current treatments may not be reported.

Whereas the updated search did not reveal new types of outcomes, it did reveal two new treatment options and one new control treatment used in studies on adult patients with STC. We see that research on STC treatment options is continuously evolving. Heterogeneity of types of outcomes and measurement instruments reported in studies on STC, as identified in this review, limits the comparability of the research conducted on treatment options. The development of a COS for this specific patient group is therefore of great importance. To achieve standardization, consensus must be reached on the core primary and secondary outcomes for STC studies. Therefore, the next step in the development of a COS for STC is to conduct a consensus study with various stakeholders such as patients and health-care professionals. This consensus study is best performed according to the Delphi methodology to achieve agreement on the outcomes and measurement instruments used.75

In conclusion, this systematic review reported on studies assessing the efficacy or effectiveness of treatment options for STC in adult patients. Results show a wide variety of types of outcomes reported and instruments used, with the majority of the studies not defining a primary outcome. To be able to compare future studies and synthesize evidence, developing a minimum COS for clinical research in adult patients with STC is recommended.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of the included studies for treatment options in slow-transit constipation.
Table S2. Diagnostic methods and applied thresholds to define STC.
Table S3A–C. Frequency of outcome reporting within the three core areas and outcome domains.
Table S4. Types of outcomes and measurement instruments used in the included studies categorized per core area.