NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of assessing motility of the gastrointestinal tract using a wireless capsule

In this procedure a capsule with a tiny wireless transmitter is swallowed, and transmits information about the movements and contents of the gut to an external device. The capsule moves through the gut and is passed out with the faeces.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in January 2014.

Procedure name

- Assessing motility of the gastrointestinal tract using a wireless capsule

Specialist societies

- British Society of Gastroenterology
- Association of Upper GI surgeons

Description

Indications and current treatment

The procedure is used to investigate gastrointestinal (GI) motility-related symptoms. In particular, it is intended for use in people with suspected gastroparesis or slow transit constipation.

Gastroparesis is a chronic disorder of the stomach characterised by delayed gastric emptying in the absence of mechanical obstruction. Treatment includes: medical therapies (for example, antibiotics and metoclopramide), botulinum toxin, gastric electrical stimulation, jejunostomy, and parenteral nutrition.

Slow transit constipation comprises a number of symptoms including straining, hard stools, sensation of incomplete evacuation and infrequent bowel movements. Treatment includes medical therapies (such as laxatives) and lifestyle advice (for example, increase exercise, water and fibre intake).

The standard procedure used to assess upper GI motility is gastric emptying scintigraphy. It involves ingesting a standardised radiolabelled meal. An X-ray is taken after 4 hours and delayed gastric emptying is diagnosed if less than 90% of the gastric content has emptied.

Radiopaque marker examination is used to detect slow transit constipation. The patient ingests a number of radiopaque markers on day 0 and has an X-ray after a predefined time period (usually 4 or 5 days). Marker retention identifies patients with slow transit.

Small intestinal barium radiography is used to assess transit time in the small bowel. The patient ingests a barium drink. As the barium passes through the digestive tract it fills and coats the oesophagus, stomach, and first part of the small intestine, making them more visible in an X-ray.

Colon scintigraphy uses X-rays to follow an ingested radiolabelled meal or tracer from caecal instillation to defecation.

Colonoscopy is an endoscopic examination of the large bowel and the distal part of the small bowel with a fibre optic camera on a flexible tube passed through the anus.

What the procedure involves

The aim of the wireless capsule system is to measure gastrointestinal (GI) motility (that is, gastric emptying time, small bowel transit time and/or colonic transit time) by assessing temperature, pressure and pH in the GI tract.

The system consists of a single-use non digestible, wireless transmitting capsule, a receiver for acquiring and storing signals from the capsule and software for displaying data on a personal computer. Before the procedure the patient fasts for 8 hours, and then drinks some water and eats a standardised meal replacement then swallow the capsule. The patient then fasts for a further 6 hours and is advised to avoid vigorous exercise. While in the body, the capsule can sample bowel contents and transmits data about pH, pressure and temperature to a portable receiver (worn by the patient) at regular intervals as it travels through the GI tract. The patient may be instructed to manually record meals, sleep and bowel movements by pushing an event button on the portable receiver. The capsule is passed out of the bowel with the faeces. If not seen in the stool, a loss of the recording signal and/or abrupt temperature drop on the recording profile confirm passage of the capsule from the body.

Clinical assessment

The Rome III criteria define functional constipation as follows:

- 2 or more of the following for at least 25% of defecations for 3 or more months:
  - straining
  - lumpy or hard stools
  - sensation of incomplete evacuation

  - sensation of anorectal obstruction/blockage
  - manual manoeuvres to facilitate defecation (such as digital evacuation , support of the pelvic floor)
- loose stools rarely present without the use of laxatives
- insufficient criteria for irritable bowel syndrome.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to assessing motility of the gastrointestinal tract using a wireless capsule. Searches were conducted of the following databases, covering the period from their commencement to 2 January 2014: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. If selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with gastroparesis or chronic constipation
Intervention/test	Assessing motility of the gastrointestinal tract using a wireless capsule
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 745 patients with suspected GI motility problems from 1 comparative effectiveness review[1]. Data from 340 healthy people are also included in this review. The remaining 6 studies[2,3,4,5,6,7] in table 2 are included in the comparative effectiveness review[1].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on assessing motility of the gastrointestinal tract using a wireless capsule

Study 1 Stein E (2012)[1]

Details

Study type	**Comparative effectiveness review**
Country	All 12 included studies are from US
Recruitment period	Studies included if published by July 2012
Study population and number	n=**745 patients (12 studies, 18 publications) with suspected motility problem. Data on 340 healthy patients is also included. [calculated by IP analyst from evidence tables]**
Age and sex	Mean 49.7 years (6 studies) [calculated by IP analyst from evidence tables] 86.3% female (9 studies) [calculated by IP analyst from evidence tables]
Patient selection criteria	Patients with suspected gastroparesis or slow transit constipation.
Technique	Wireless motility capsule (SmartPill) compared with gastric scintigraphy/antroduodenal manometry/endoscopy/radiopaque marker
Follow-up	**Range: 1–21 days (10 studies)**
Conflict of interest/source of funding	Technical experts, advisers and reviewers who worked on the review had to disclose only financial conflicts of interest greater than $10,000. However, it is unclear whether any of those involved did declare any conflicts of interest.

Analysis

Follow-up issues: See individual study reports in table 2 for further information.

Study design issues: Searched MEDLINE and EMBASE up to 1 July 2012. Two independent reviewers assessed each title, abstract and full article and any differences were resolved by consensus adjudication. Only selected studies that compared wireless motility capsule (WMC) with other diagnostic tests. All studies were assessed for quality by using a modified QUADAS-2 quality assessment tool and the strength of the evidence was based on an adapted GRADE system (categories: high, moderate, low and insufficient). Seven of the included studies are prospective, 4 are retrospective and 1 paper did not specify a study design.

Study population issues: Three studies focused on patients with gastroparesis, 5 studies on patients with constipation and the remaining studies either did not specify or patients had suspected GI dysmotility.

Other issues: Authors had planned to conduct meta-analyses if sufficient data available. Authors decided that the included studies were not amenable to pooling. The authors also point out that no standards exist in the field of motility assessment for determining the minimum improvement of diagnostic accuracy that will identify one test as superior to another test. There are no standards to establish the equivalence of motility tests. The authors arbitrarily chose a 10% difference in sensitivity or specificity as a potential important difference between tests.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **varies depending on outcome (745 across 12 studies)**

Diagnostic accuracy

	Sensitivity (Range)	**Specificity** (Range)	**Strength of evidence**
WMC compared with clinical diagnosis of gastroparesis (N=560, 6 studies)	65 to 68%	82 to 87%	NR
WMC compared with gastric scintigraphy (N=560, 7 studies)	59 to 86%	64 to 81%	Low
WMC compared with ROM (N=78, 1 study)	37%	95%	Low
WMC plus other diagnostic tests compared with other diagnostic tests alone (N=79, 2 studies)	42 to 51%	60 to 66%	Low

Concordance between WMC and scintigraphy: 35% to 81% (range)
Concordance between WMC and ROM: 65 to 87%

Transit times - correlation
Kuo 2008 (61 patients with gastroparesis compared with 87 healthy subjects) reports a GET correlation coefficient (WMC compared with scintigraphy at 4 hours) of 0.73. The same study reports a GET correlation coefficient (WMC compared with scintigraphy at 2 hours) of 0.63. Authors calculated area under the curve for GET assessed by WMC of 0.94 (sensitivity 87%, specificity 92%).

Pressure patterns (2 studies – data presented separately)
Lee 2012: 47.6% (10/21) of patients with normal GET using scintigraphy had pressure abnormalities identified by WMC. Diagnostic gain of using scintigraphy and WMC compared with. scintigraphy alone was significant (p=0.002).
Reddymasu 2010: when looking at gastric pressure patterns in isolation from transit times compared with clinical diagnosis of gastroparesis based on symptoms and prior scintigraphy, the sensitivity of WMC is 88% and specificity is 30%.

Treatment decisions (3 studies)
WMC testing alters management in patients with suspected gastroparesis (50% to 69% change in management for medicine, diet or surgery [Low])

Safety

Number of patients analysed: **381 patients with motility problems and 114 healthy subjects (5 studies).**

No serious adverse events reported in the 5 studies. Strength of evidence: Low

Study	**Non-serious adverse events**	**Retained capsule**
Rao 2009	NR	0 in healthy subjects 21% (14/67) of patients with constipation retained the capsule at day 5 X-ray. Of these, 78.6% (11/14) had no capsule at the day 21 X-ray and the other 3 recovered it from their stools.
Camilleri 2010	31 (possible for person to have more than 1 event)*	0
Rao 2011	NR	0
Rao 2009a	None	0
Rao 2012	NR	NR

*see next study table for full details of this paper

Abbreviations used: AUC, area under the curve; CAT, computed axial tomography; CI, confidence interval; CMT, conventional motility tests; CTT, colonic transit time; GES, gastric emptying scintigraphy; GET, gastric emptying time; GI; gastrointestinal; IQR, interquartile range; LGI, lower gastrointestinal; NTC, normal transit constipation; NR, not reported; NS, not significant; OTT, orocaecal transit time; PPI, proton pump inhibitor; SBTT, small bowel transit time; ROC, receiver operating characteristic; ROM, radiopaque markers ; SITT, small intestinal transit time; SLBTT, small and large bowel transit time; STC, slow transit constipation; UGI, upper gastrointestinal; WGTT, whole gut transit time; WMC, wireless motility capsule

Study 2 Camilleri M (2010)[2]

Details

Study type	**Comparative study (within patients)** [included in Stein 2013]
Country	US
Recruitment period	NR
Study population and number	n=**187 patients with symptomatic constipation**
Age, sex and ethnicity	Mean 42.5 years; 87.3% (138/158) female; 83% Caucasian, 13% black, 2% Asian/Pacific islanders, 1% Hispanic and 1% other.
Patient selection criteria	Patients aged 18–80 years with symptoms of chronic functional constipation for at least 1 year (self-reported hard stool at least 25% of the time with at least 1 of 6 symptoms of functional constipation defined in Rome III criteria).
Technique	Wireless motility capsule (SmartPill) compared with radiopaque marker (all patients underwent both techniques simultaneously) Radiopaque marker: 24 markers are ingested each day for 3 successive days with abdominal X-rays on 4th and 7th day to count the amount of radiopaque marker remaining in the abdomen.
Follow-up	**2 weeks (approximate)**
Conflict of interest/source of funding	Lead author is a consultant for the SmartPill manufacturer with compensation paid to the Mayo clinic. The study was funded by a grant from the manufacturer. One of the other authors (Semler) is employed by and owns stock in the manufacturer.

Analysis

Follow-up issues: 187 patients were eligible for the study, 3.7% (7/187) then withdrew consent. Of those who ingested the wireless motility capsule 12.2% (22/180) were disqualified (8 had a device malfunction, 5 took disallowed concomitant medication [such as antibiotics, laxatives, opiate medication or proton pump inhibitor] and 5 did not comply with the study protocol).

Study design issues: Multicentre prospective study. Main objective was to demonstrate statistical equivalence between wireless motility capsule and radiopaque marker (current clinical standard). Participating centres prohibited medications. Patients were asked to maintain a daily diary to record stool consistency according to the Bristol stool form scale and were encouraged to maintain usual daily fibre intake and exercise routine. Study required 150 patients in order to achieve 0.83 power to detect a difference of 10 percentage points. For colonic transit time, wireless motility capsule was cut off at more than 59 hours and radiopaque marker was cut off at more than 67 hours. Delayed colonic transit time defined as more than 59 hours. Delayed small and large bowel transit time defined as more than 65 hours.

Study population issues: none.

Other issues: none.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **157**

Diagnostic accuracy

	%	95% CI (p value)
Sensitivity for CTT (N=157)	79.7%	67 to 98% (0.01)*
Specificity for CTT (N=157)	90.8%	83 to 96% (0.00001)*
Sensitivity for SLBTT (N=154)	79.3%	67 to 89% (0.01)*
Specificity for SLBTT (N=154)	90.6%	83 to 96% (0.00001)*

*compared with null hypothesis of 65% agreement

Overall device agreement for CTT: 87% (95% CI 80 to 92%)
Overall device agreement for SLBTT: 86% (95% CI not reported)

Relationship between WMC and ROM estimates of colonic transit

Significant correlation between WMC and ROM for CTT (r=0.707, p<0.001) and SLBTT (r=0.704, p<0.001)

Transit times

		Median time in hours classified by WMC (IQR)	Median time in hours classified by ROM (IQR)
CTT	**All**	43.5 (21.7 to 70.3)	55 (31 to 85)♦
SLBTT	**All**	47 (25.8 to 75.1)[§]	NR
GET	**NTC**	179 (152 to 243)	179 (148 to 244)
	STC	197 (165 to 292)	196 (166 to 259)
	All	185 (157 to 248)	NR
SBTT	**NTC**	232 (194 to 285)	234 (199 to 285)
	STC	236 (205 to 322)	233 (201 to 315)
	All	234 (201 to 293)	NR
OTT	**NTC**	425 (374 to 528)	505 (419 to 618)
	STC	429 (380 to 528)	479 (389 to 622)
	All	437 (381 to 531)	NR

♦p<0.001
[§]p=0.013 compared with CTT classified by ROM

Prevalence of WMC gastric emptying time > 5 hours suggesting gastroparesis
In patients with constipation: 18.3% (28/152)
In patients with slow colonic transit: 13
In patients with normal colonic transit: 15

Safety

Authors reported adverse events as being not related, probably not related, possibly related, probably related or definitely related to the procedure. The authors identified 7 adverse events as being possibly or definitely related to the procedure as follows:

	Possibly related	Definitely related
Abdominal pain	1	1
Diarrhoea	1	0
Dysphagia	0	2
Nausea	2	0

There were no incidents of capsule retention.

Abbreviations used: AUC, area under the curve; CAT, computed axial tomography; CI, confidence interval; CMT, conventional motility tests; CTT, colonic transit time; GES, gastric emptying scintigraphy; GET, gastric emptying time; GI; gastrointestinal; IQR, interquartile range; LGI, lower gastrointestinal; NTC, normal transit constipation; NR, not reported; NS, not significant; OTT, orocaecal transit time; PPI, proton pump inhibitor; SBTT, small bowel transit time; ROC, receiver operating characteristic; ROM, radiopaque markers ; SITT, small intestinal transit time; SLBTT, small and large bowel transit time; STC, slow transit constipation; UGI, upper gastrointestinal; WGTT, whole gut transit time; WMC, wireless motility capsule

Study 3 Rao SS (2011)[3]

Details

Study type	**Comparative study (within patients)** [included in Stein 2013]
Country	US
Recruitment period	2007–2009
Study population and number	n=**86 patients with suspected symptoms of upper GI or lower GI dysmotility**
Age, sex and ethnicity	Mean 44.5 years; 89.5% (77/86) female; 89.5% (77/86) white, 4.7% African–American and 5% (5.8%) other.
Patient selection criteria	Patients with suspected symptoms of upper GI or lower GI dysmotility for at least 6 months and had normal endoscopy and/or colonoscopy, normal haematology and metabolic profiles, normal abdominal ultrasound and normal CAT scan evaluations. Patients with a history of severe dysphagia, bezoars, GI obstruction, inflammatory bowel disease, previous gastrectomy, colectomy or other abdominal pelvic surgeries were excluded.
Technique	Wireless motility capsule (SmartPill) compared with CMT (radiopaque marker colonic transit test [in patients with LGI symptoms] or nuclear scintigraphy gastric emptying test[(in those with UGI symptoms])
Follow-up	**120 hours**
Conflict of interest/source of funding	Lead author is an advisory board member and has received research funding from the manufacturer. Other authors have no conflicts of interest.

Analysis

Follow-up issues: 93 patients had the wireless motility capsule test but 7.5% (7/93) were excluded because they either did not fulfil the symptom criteria or did not undergo comparative CMT.

Study design issues: Retrospective chart review. Patients asked to discontinue all laxatives and drugs that affect motility and continue their usual diet. Gastric emptying time defined as time between ingestion of wireless motility capsule and abrupt rise in pH (more than 2 pH units from gastric baseline). Small bowel transit time defined as time between capsule entry into the small bowel and its entry into the caecum (entry into caecum: drop >1 pH unit sustained for 10 minutes and 30 minutes after entry into the small bowel). Colonic transit time was defined as the time interval between the points of entry into the caecum and the capsule exit from the body. Whole gut transit time was defined as the time between capsule ingestion and its exit from the body. Patients completed validated symptom questionnaire before tests started. The responses were used to determine if patients were in the upper gastrointestinal (3 or more of the following symptoms scoring >1.5 on a 4 point scale: nausea, vomiting, epigastric pain, bloating or postprandial fullness) or lower gastrointestinal group 3 or more of the following symptoms scoring >1.5 on a 4-point scale: constipation, excessive straining, feeling of incomplete evacuation, hard stools, use of digital manoeuvres, lower abdominal pain, discomfort with altered bowel habit, gas and bloating). All patients were asked to maintain a stool diary for 5 days after ingesting the wireless motility capsule.

Study population issues: Mean duration of symptoms for suspected LGI symptom group (n=50, 58%) and upper gastrointestinal symptom group (N=36, 42%) were 5.8 years and 10.1 years respectively. GI related medications taken at baseline in lower gastrointestinal group: prescription laxatives (44%), antidepressants (30%), fibre supplements (16%), PPIs (12%), antiemetics (8%), prokinetics (6%) and narcotics (6%).GI related medications taken at baseline in upper gastrointestinal group: PPIs (58%), antidepressants (44%), prescription laxatives (19%), antiemetics (17%), prokinetics (14%) and narcotics (8%).

Other issues: none.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **86**

Confirmation of clinical diagnosis

	LGI group (N=50)	UGI group (N=36)	All patients (n=86)
WMC	52% (26/50)	66.7% (24/36)*	58.1% (50/86)*
CMT	46% (23/50)	42.9% (15/35)	44.2% (38/86)

*significantly different from CMT ($p<0.05$)

Diagnostic agreement

	LGI group (n=50)	UGI group (n=86)
Colonic transit +ve agreement	34% (17/50)	-
Colonic transit –ve agreement	28% (14/50)	-
GET +ve agreement	-	33.3% (12/36)
GET –ve agreement	-	16.7% (6/36)

Overall diagnostic disagreement for LGI group: 8% (4/50)
Overall diagnostic agreement for UGI group: 14% (5/36)

Device agreement

	LGI group (n=50)	UGI group (n=86)
Colonic transit +ve agreement	87% (20/23)	-
Colonic transit –ve agreement	66.7% (18/27)	-
GET +ve agreement	-	80% (12/15)
GET –ve agreement	-	81% (17/21)

Overall device agreement for LGI group: 76%
Overall device agreement for UGI group: 81%

New diagnostic information with WMC

Overall, 43% (37/86) of all patients received a new additional diagnosis after WMC test.

	LGI group (n=50)	UGI group (n=36)	All patients (n=86)
Prolonged gastric emptying♦	28% (14/50)	25% (9/36)	26.7% (23/86)
Rapid gastric emptying♦	4% (2/50)	8.3% (3/36)	5.8% (5/86)
Prolonged small bowel transit	14% (7/50)	16.7% (6/36)	15.1% (13/86)
Prolonged colon transit∞	6% (3/50)	8.3% (3/36)	9.3% (8/86)
Diffuse or generalised GI motility disorder	52% (26/50)[§]	47.2% (17/36)	51.2% (44/86)

[§]p=0.006 compared with CMT
♦Abnormal GET classified by scintigraphy defined as >10% retention at 4 hours (prolonged gastric emptying) or <20% retention at 1 hour (rapid gastric emptying).
∞Prolonged colonic transit classified by ROM defined as retention of 6 or more radiopaque markers at 120 hours.

Influence of WMC on patient management

		LGI group (n=50)	UGI group (n=36)
Treatment	**Prokinetic agents**	6%	36%
	Prescription laxatives	20%	33%
	Nutritional and behavioural therapies	4%	19%
	Antidepressants	12%	14%
	Withdrawal of opioids	6%	8%
	Antiemetics	6%	44%
Further diagnostic testing	**Anorectal manometry**	28%	25%
	Breath testing for bacterial overgrowth or carbohydrate intolerance	16%	18%

Overall, WMC influenced management in 30% of LGI group and 50% of UGI group.

Safety

Authors state that no serious adverse events were reported during the study. The WMC was successfully expelled from the body in all patients.

Abbreviations used: AUC, area under the curve; CAT, computed axial tomography; CI, confidence interval; CMT, conventional motility tests; CTT, colonic transit time; GES, gastric emptying scintigraphy; GET, gastric emptying time; GI; gastrointestinal; IQR, interquartile range; LGI, lower gastrointestinal; NTC, normal transit constipation; NR, not reported; NS, not significant; OTT, orocaecal transit time; PPI, proton pump inhibitor; SBTT, small bowel transit time; ROC, receiver operating characteristic; ROM, radiopaque markers ; SITT, small intestinal transit time; SLBTT, small and large bowel transit time; STC, slow transit constipation; UGI, upper gastrointestinal; WGTT, whole gut transit time; WMC, wireless motility capsule

Study 4 Kuo B (2011)[4]

Details

Study type	**Comparative study (within patients)** [included in Stein 2013]
Country	US
Recruitment period	Sept 2007 – May 2010
Study population and number	n=**83 patients with suspected gastroparesis, intestinal dysmotility or slow transit constipation**
Age and sex	Mean 43.7 years; 79.5% (66/83) female
Patient selection criteria	Patients undergoing WMC to exclude delayed gastric, small intestinal or colonic transit.
Technique	WMC (SmartPill) compared with CMT (gastric scintigraphy, small intestinal barium radiography, radiopaque marker, anorectal manometry) CMTs were conducted before WMC test. radiopaque marker protocol involved performance of a single X-ray 5 days after swallowing a marker capsule.
Follow-up	**5 days**
Conflict of interest/source of funding	Lead author is an advisory board member and has received research funding from the manufacturer. Other authors: Dr Chey is on the advisory board for the manufacturer, Dr Wilding is a consultant for the manufacturer and Dr Hasler is a consultant and has received research funding from the manufacturer.

Analysis

Follow-up issues: complete wireless motility capsule data for 92.8% (77/83) of patients. Two patients did not exhibit pH decreases reflecting ileocaecal junction transit and 2 patients had not evacuated the capsule at the time the data recorder was returned (both capsules were passed after the study was completed).

Study design issues: Retrospective review of patients from 2 centres. Authors state that most prior conventional motility tests were conducted at outside community institutions and many did not adhere to published practice guidelines. Methodologies employed were diverse and inconsistent and the definitions for transit abnormality were frequently not validated. Methods to measure small intestinal transit were not rigorously validated and in the absence of widely accepted techniques, barium radiography was used (normal range definitions varied). Patients were asked to discontinue PPIs for 7 days, histamine H_2 receptor antagonists for 3 days, laxatives fir at least 3 days and anticholinergic agents for 3 days before wireless motility capsule.

Study population issues: 14.6% (12/82) with diabetes, 7.2% (6/82) with prior gastrointestinal surgery or resection, 8.5% (7/82) with prior malignancy, 52.4% (43/82) with psychiatric disease and 26.8% (22/82) with neurologic disease. 19.4% (13/67) have a BMI>30 kg/m^2.

CMT details:84.6% (44/52) of patients with suspected delayed gastric emptying underwent gastric scintigraphy, 46.2% (6/13) of patients with suspected delayed small intestinal transit underwent small bowel barium radiography and 26.2% (16/61) of patients with suspected slow colonic transit underwent radiopaque marker and 68.9% (43/61) of patients with suspected slow colonic transit underwent anorectal outlet function testing.

Other issues: none.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **77**

Confirmation of Clinical Diagnosis (NB. patients can be included in more than one of the 3 'suspicion' categories)

	CMT sensitivity	WMC sensitivity in target region	WMC specificity in target region	WMC abnormal transit in other region
Suspected gastric emptying delay (N=52)	38.6% (17/44)	46.2% (24/52)	67.9% (19/28)	Small intestine: 20.4% (10/49) Colon: 53.2% (25/47)
Suspected small intestinal transit delay (N=13)	66.7% (4/6) [Barium]	9.1% (1/11)	84.4% (54/64)	Stomach: 38.5% (5/13) Colon: 40% (4/10)
Suspected colonic transit delay (N=61)	56.2% (9/16)	58.2% (32/55)	61.1% (11/18)	Stomach: 41.7% (25/60) Small intestine: 14.3% (8/56)

Gastric emptying delay defined as > 5 hours, small intestinal transit delay defined as >6hours and colonic transit delay defined as>59 hours.

Overall, new diagnosis observed by WMC in 53% (44/83) of patients (7 new gastroparesis diagnoses, 3 new small intestinal dysmotility diagnoses, 11 new slow transit constipation diagnoses and 23 new generalised dysmotility diagnoses)
Overall, regional isolated delays observed in 32% of patients (9% stomach, 5% small bowel and 18% colon).
Overall, transits normal in 32% and generalised delays in 35%.
Symptom profiles similar for normal transit, isolated delayed gastric, small intestinal and colonic transit and generalised delay p=NS)

Test agreement

		CMT normal	CMT abnormal	+ve test agreement (sensitivity)	−ve test agreement (specificity)
GET	**WMC Normal**	18	7	58.8%	64.3%
	WMC Abnormal	10	10		
SITT	**WMC Normal**	9	3	0%	75%
	WMC Abnormal	3	0		
CTT	**WMC Normal**	3	1	85.7%	42.9%
	WMC Abnormal	4	6		

Overall discordance: 38%

Changes in clinical management following WMC (N=66)

	Change to medication regimen	Change in nutritional programme	Referral to surgery
Isolated abnormal gastric emptying (N=7)	57.1% (4/7)	28.6% (2/7)	0%
Isolated small intestinal transit (N=4)	75% (3/4)	0%	0%
Isolated abnormal colon transit (N=14)	71.4% (10/14)	7.1% (1/14)	21.4% (3/14)
Abnormal generalised transit (N=23)	73.9% (17/23)	21.7% (5/23)	4.3% (1/23)
Normal transit throughout (N=18)	27.8% (5/18)	5.6% (1/18)	0%

Overall influence on management:60% (39/65) new medication, 13.8% (9/65) modified nutritional regimens, 6.2% (4/65) surgical referrals and eliminated the need for testing not already done (17.3% (9/52) gastric scintigraphy, 53.8% (7/13) small bowel barium transit and 68.3% (41/60) radiopaque colon marker tests).

Safety

Not reported

Abbreviations used: AUC, area under the curve; CAT, computed axial tomography; CI, confidence interval; CMT, conventional motility tests; CTT, colonic transit time; GES, gastric emptying scintigraphy; GET, gastric emptying time; GI; gastrointestinal; IQR, interquartile range; LGI, lower gastrointestinal; NTC, normal transit constipation; NR, not reported; NS, not significant; OTT, orocaecal transit time; PPI, proton pump inhibitor; SBTT, small bowel transit time; ROC, receiver operating characteristic; ROM, radiopaque markers ; SITT, small intestinal transit time; SLBTT, small and large bowel transit time; STC, slow transit constipation; UGI, upper gastrointestinal; WGTT, whole gut transit time; WMC, wireless motility capsule

Study 5 Rao SS (2009)[5]

Details

Study type	**Comparative study** [included in Stein 2013]
Country	US
Recruitment period	Not reported
Study population and number	n=**165 (78 patients with chronic constipation compared with 87 healthy subjects)**
Age and sex	Patients with constipation: 88.5% (69/78) female; Mean age (women): 45 years, (men): 53 years. Healthy subjects: 46% (40/87) female; Mean age (women): 39 years, (men): 36 years.
Patient selection criteria	Constipated patients had to meet Rome II criteria for chronic functional constipation and report at least 2 of the 6 symptoms of constipation. People with previous abdominal surgery were excluded except those with uncomplicated appendectomy, cholecystectomy or caesarean section. Healthy subjects recruited after screening with Mayo GI Disease questionnaire.
Technique	Wireless motility capsule (SmartPill) compared with radiopaque marker (abdominal X-rays on day 2 and 5)
Follow-up	**21 days (maximum)**
Conflict of interest/source of funding	Authors serve as speakers, consultants or advisory board members for the wireless motility capsule manufacturer and have received research funding from the manufacturer. This study was funded by the manufacturer.

Analysis

Follow-up issues: wireless motility capsule transit parameters were not available for 12 participants because of a software malfunction. Caecal arrival time was not available in 5 other participants. Overall, wireless motility capsule data from 85.9% (67/78) of patients with constipation and 93.1% (81/87) of healthy subjects was available. Two participants did not have X-rays on day 2 or day 5 and 10 other participants had X-rays on day 4 rather than day 5. Overall, radiopaque marker data were available from 85.9% (67/78) of patients with constipation and 98.9% (86/87) of healthy subjects.

Study design issues: Prospective study. All patients with constipation were asked to discontinue all laxatives, drugs that affect motility and PPIs from 48 hours before starting the study. Use of stable doses of antidepressants, oral contraceptives and lipid lowering drugs were allowed. All participants were asked to keep a stool diary for 5 days after swallowing the wireless motility capsule and eat their usual diet. Gastric emptying time was defined as the time interval between ingestion of wireless motility capsule and point where there is an abrupt change in pH profile (≥2 pH units from gastric pH at baseline). Gastric emptying time determined by 2 independent reviewers. Small bowel transit time defined as the time interval between capsule entry into the small bowel and entry into the caecum. Caecal entry defined as a distinct decrease in pH (≥1 pH unit sustained for ≥10 minutes and at least 30 minutes after capsule entry into the small bowel). Colonic transit time defined as time interval between point of entry into the caecum and exit of the capsule from the body. Capsule exit time confirmed by abrupt loss of signal and/or abrupt decrease in temperature. Whole gut transit time defined as the time interval between capsule ingestion and exit from the body. All X-rays read by 2 independent reviewers. Discrepancies in radiopaque marker count were resolved by mutual consultation. Testing null hypothesis that radiopaque marker and wireless motility capsule are equivalent as defined by a correlation of 0.7 or higher. Power was 90% in detecting true correlations of 0.56 or smaller using a total sample of 150 subjects. Upper limit of gastric emptying time was 6 hours. Upper limit for whole gut transit time was 120 hours.

Study population issues: none.

Other issues: none.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **67 with constipation, 81 healthy subjects**

Median (25th to 75th percentile) transit times in hours (constipated patients only)

	All constipated (N=67)	Women (N=59)	Men (N=8)	p value
CTT	46.7 (24 to 91.9)	46.7 (24 to 91.9)	50.9 (25.2-)*	NR
WGTT	59.3 (39.7 to 97.9)	58 (39.7 to 97.9)	72.2 (36.3-)*	0.73
GET	3.5 (3 to 4.2)	3.4 (3 to 4.1)	4.2 (3.6-)*	NR
SBTT	4.2 (3.5 to 5.1)	4.2 (3.5 to 5.2)	4.4 (3.4 to 4.8)	NR

*The second values in these ranges were not reported in the study.

Correlation of CTT and WGTT measured by WMC with number of retained ROMs

	WMC parameters	
	CTT	**WGTT**
All participants day 2 ROM (95% CI)	0.78 (0.7-0.84)	0.77 (0.68 to 0.84)
Day 2 ROMs in healthy subjects	0.7	0.74
Day 2 ROMs in constipated subjects	0.74	0.67
All participants day 5 ROM (95% CI)	0.59 (0.46-0.69)	0.58 (0.45 to 0.69)
Day 5 ROMs in healthy subjects	0.4	0.39
Day 5 ROMs in constipated subjects	0.69	0.66

32.8% (22/67) of patients with constipation retained more than 5 markers a day 5 X-rays. Median 22 ROMs retained at day 2 X-rays by constipated patients.
Overall correlation of the number of ROMs that were seen on day 2 with that of day 5 was 0.62. This was 0.44 for healthy subjects and 0.58 for patients with constipation.

Diagnostic utility: AUC of the ROC curve, sensitivity and specificity for WMC and day 5 ROM (all participants)

Parameter	AUC (95% CI)		Cut off value	Sensitivity	Specificity
CTT	0.73 (0.65 to 0.82)	**All**	59 hours	0.46	0.95
		Men	44 hours	0.5	0.9
		Women	59 hours	0.46	0.92
WGTT	0.76 (0.68 to 0.84)	**All**	73 hours	0.42	0.95
		Men	52 hours	0.63	0.9
		Women	73 hours	0.41	0.92
ROM (Day 5)	0.71 (0.63 to 0.78)	**All**	>5 markers	0.37	0.95

23 patients with constipation were delayed according to ROM criteria and 82.6% (19/23) of these also had delayed CTT as measured by WMC. 21 patients with constipation had delayed transit by day 5 ROM criteria.

Safety

No adverse events reported during the study.

20.9% (14/67) patients with constipation had retained the capsule at day 5 X-ray. At day 21 X-ray, 78.6% (11/14) of these patients had expelled the WMC. The other 3 recovered the capsule from their stools.

Abbreviations used: AUC, area under the curve; CAT, computed axial tomography; CI, confidence interval; CMT, conventional motility tests; CTT, colonic transit time; GES, gastric emptying scintigraphy; GET, gastric emptying time; GI; gastrointestinal; IQR, interquartile range; LGI, lower gastrointestinal; NTC, normal transit constipation; NR, not reported; NS, not significant; OTT, orocaecal transit time; PPI, proton pump inhibitor; SBTT, small bowel transit time; ROC, receiver operating characteristic; ROM, radiopaque markers ; SITT, small intestinal transit time; SLBTT, small and large bowel transit time; STC, slow transit constipation; UGI, upper gastrointestinal; WGTT, whole gut transit time; WMC, wireless motility capsule

Study 6 Kuo B (2008)[6]

Details

Study type	**Comparative study** [included in Stein 2013]
Country	US
Recruitment period	March 2005 to November 2005
Study population and number	n=**148 (61 patients with gastroparesis compared with 87 healthy subjects)**
Age and sex	Patients with gastroparesis: 83.6% (51/61) female; Mean age: NR; Ethnicity: 82% (50/61) Caucasian, 11.5% (7/61) black and 6.6% (4/61) Hispanic. Healthy subjects: 36.8% (32/87) female; Mean age: NR; Ethnicity 79.3% (69/87) Caucasian, 8% (7/87) black, 5.7% (5/87) A/P Island, 4.6% (4/87) Hispanic, 2.3% (2/87) other.
Patient selection criteria	All participants: subjects with previous gastro-oesophageal surgery were excluded except those with uncomplicated appendectomy and/or laparoscopic cholecystectomy. Drugs such as cisapride, domperidone, metoclopramide, macrolide antibiotics, $5HT_4$ partial agonists and antiemetics were held. No narcotic drugs were allowed for 1 week before starting the study. Prescription medication such as antilipidaemics, antidepressants and oral contraceptives were permitted if the condition and dose had been stable for 6 months before enrolment. Nonsteroidal anti-inflammatory drugs were stopped 1 week before the study and other over the counter drugs were stopped 3 days before the study started. Patients with gastroparesis: aged 18 to 65 years with a history of nausea, vomiting, early satiety, epigastric pain or discomfort for at least 6 months and documented abnormal scintigraphy as defined by local medical centre standards within 2 years of enrolment. People with excessively delayed GET (>90% standard meal retained after 2 hours) , average bowel movement frequencies exceeding 72 hours, evidence of gastric bezoar within last 3 years, stricture, peptic ulcer, severe dysphagia to food and pills, severe vomiting, severe abdominal pain, severe weight loss (>4.5 kg in past 2 months) or diabetes with a haemoglobin A1C>10 were excluded. PPIs stopped for 1 week, histamine-2 blockers for 2 days and antacids for 1 day before starting study. Medication affecting GI motility was stopped 48 hours before starting the study. Healthy subjects: aged 18 to 65 years, screened using the Mayo GI Disease questionnaire. People with cardiovascular, endocrine, renal or chronic disease were not recruited. Healthy subjects also had to fulfil the following criteria: at least 1 bowel movement per 48 hours, no pregnancy, no surgery within the past 3 months, no clinical evidence of diverticulitis, no medications that could alter GI motility, BMI<35, no tobacco use within 8 hours before and after wireless motility capsule ingestion and no alcohol 24 hours before or during the monitoring period.
Technique	Wireless motility capsule (SmartPill) compared with GES Participants ingested the scintigraphy meal within 20 minutes of ingesting wireless motility capsule. Scintigraphic images taken immediately after the meal and every 30 minutes for 4 hours. An additional image was taken at 6 hours.
Follow-up	**72 hours**
Conflict of interest/source of funding	Authors serve as speakers, consultants or advisory board members for the wireless motility capsule manufacturer and have received research funding from the manufacturer. This study was funded by the manufacturer, a NYSTAR grant and an NIH grant.

Analysis

Follow-up issues: 2 participants did not participate after enrolment. 98.6% (146/148) had complete gastric emptying scintigraphy data. 10.8% (16/148) had missing gastric emptying time data measured by wireless motility capsule because of prototype equipment malfunctions. An additional 5 participants had gastric emptying time recorded as missing because the emptying

time was<30 minutes. Overall 84.5% (125/148) are included in the analysis for gastric emptying time.

Study design issues: Prospective study. Gastric emptying time defined as the time from wireless motility capsule ingestion to an abrupt pH rise (usually >3 pH units form gastric baseline) as the capsule passes from the acidic antrum into the more alkaline duodenum. Gastric emptying time determined by 2 independent reviewers and by computer software. Discrepancies were resolved by further review and consultation with an additional reviewer. Null hypothesis: correlation between gastric emptying time and gastric emptying scintigraphy of ≤0.7. Power of 80% in detecting a true correlation of 0.58 with a total sample size of 130.

Study population issues: none.

Other issues: none.

Key efficacy and safety findings

Efficacy

Number of patients analysed:
GES: 146 (59 patients with gastroparesis compared with 87 healthy subjects)
GET: 125 (48 patients with gastroparesis compared with 77 healthy subjects)

Median (95% CI) gastric emptying measures

	Patients with gastroparesis	Healthy subjects
GET (minutes)	>360 (320 to >360) n=48	215 (199 to 225) n=77
GES at 2 hours (% of meal retained)	51% (42 to 58%) n=59	25% (23 to 37%) n=87
GES at 4 hours (% of meal retained)	9% (4 to 13%) n=59	1% (1 to 1.4%) n=87

26 patients with gastroparesis and 6 healthy subjects had GET times >360 minutes.

Correlation of GES-2hrs and GES-4hrs with GET, Sensitivity and Specificity (n=125)

	Scintigraphy-GET correlation (95% CI)	Sensitivity	Specificity	AUC (95% CI)
GES 2 hours	0.63 (0.5 to 0.75)	0.34	0.93	0.79 (0.71 to 0.88)
GES 4 hours	0.73 (0.61 to 0.82)	0.44	0.93	0.82 (0.77 to 0.91)
GET	Not applicable	0.65	0.87	0.83 (0.74 to 0.9)

No statistical difference observed between AUCs for GET and GES-4hrs (p>0.05).

47.9% (23/48) of patients with gastroparesis and 6.5% (5/77) of healthy subjects had abnormal scinitgraphic emptying at 4 hours. For these people, the AUC for GET was 0.94, sensitivity was 0.87 and specificity was 0.92. Using this analysis, the cut-off point for GET that provides optimum balance of sensitivity and specificity for clinical use is 300 minutes.

Safety

Passage of WMC confirmed in all participants (46% had an abdominal X-ray to evaluate capsule presence). Authors state that no serious adverse events or unanticipated device-related adverse events occurred.

Adverse events

	Total	Not related to device	Probably not related to the device	Definitely related to the device
Dizziness upon standing	1	1	0	0
Bloating	1	0	1	0
Capsule retention[§]	1	0	0	1
Nausea	1	1	0	0
Vomiting*	2	1	1	0
Stomach pain	1	1	0	0
Abdominal pain	1	1	0	0
Bitter taste	1	1	0	0
Local skin burn	1	0	1	0
Total	10	6	3	1

*2 reports of vomiting: both cases occurred well after ingestion of WMC and the capsule remained in the body.
[§]1 report of the capsule retention in a viscous jelly like mass after the patient with gastroparesis ingested Citrucel (a bulk forming laxative). An endoscopy was performed but it was not possible to retrieve the capsule. Erythromycin IV (200mg) was administered and the capsule subsequently emptied the stomach after 30 minutes.

Abbreviations used: AUC, area under the curve; CAT, computed axial tomography; CI, confidence interval; CMT, conventional motility tests; CTT, colonic transit time; GES, gastric emptying scintigraphy; GET, gastric emptying time; GI; gastrointestinal; IQR, interquartile range; LGI, lower gastrointestinal; NTC, normal transit constipation; NR, not reported; NS, not significant; OTT, orocaecal transit time; PPI, proton pump inhibitor; SBTT, small bowel transit time; ROC, receiver operating characteristic; ROM, radiopaque markers ; SITT, small intestinal transit time; SLBTT, small and large bowel transit time; STC, slow transit constipation; UGI, upper gastrointestinal; WGTT, whole gut transit time; WMC, wireless motility capsule

Study 7 Lee A (2012)[7]

Details

Study type	**Comparative study (within patients)** [included in Stein 2013]
Country	US
Recruitment period	March 2005 to October 2007
Study population and number	n=**43 patients with gastroparesis** (subset of patients from Kuo 2011[6])
Age and sex	Mean 42 years; 81.4% (35/43) female
Patient selection criteria	See study 6 (Kuo 2011[6]) for details
Technique	Wireless motility capsule (SmartPill) compared with GES
Follow-up	**Not reported**
Conflict of interest/source of funding	Two of the 3 authors are consultants for the manufacturer and have performed clinical trials funded by the manufacturer. The lead author has no conflicts of interest and the study was supported by the International Foundation of Functional Gastrointestinal disorders and the NIH.

Analysis

Follow-up issues: none

Study design issues: Prospective study involving 7 centres.

Study population issues: 62.8% (27/43) had idiopathic gastroparesis and 37.2% (16/43) had gastroparesis secondary to underlying diabetes mellitus.

Other issues: none.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **43** 60.5% (26/43) had an abnormal GET and 51.2% (22/43) had an abnormal GES. Overall device agreement between GET and GES: 77% (positive agreement: 86%, negative agreement: 66%) Overall, 47% had abnormal gastric and small bowel pressure measurements. Of these, 40% had an abnormal gastric pressure measurement (contractions and / or motility index) and 40% had abnormal small bowel pressure measurements. The remaining 20% had both. Overall, 30% had abnormal gastric contractions and 16% had abnormal small bowel contractions. Overall, 21% had an abnormal gastric motility index and 23% had an abnormal small bowel motility index. 47.6% (10/21) of those with normal GES had abnormalities identified by WMC. There were 2 participants who had normal GET but abnormal GES. The overall diagnostic gain with WMC compared with GES was 19% (p=0.04). Compared with GES, there was significant improvement in diagnostic gain from GET+GES (p=0.02), GES + gastric pressure measurement + small bowel pressure measurement (p=0.03), GES + GET +gastric pressure measurement (p=0.02), GET + gastric pressure measurement + small bowel pressure measurement (p=0.04) and GES + GET+ gastric pressure measurement + small bowel pressure measurement (p=0.002).	Not reported
Abbreviations used: AUC, area under the curve; CAT, computed axial tomography; CI, confidence interval; CMT, conventional motility tests; CTT, colonic transit time; GES, gastric emptying scintigraphy; GET, gastric emptying time; GI; gastrointestinal; IQR, interquartile range; LGI, lower gastrointestinal; NTC, normal transit constipation; NR, not reported; NS, not significant; OTT, orocaecal transit time; PPI, proton pump inhibitor; SBTT, small bowel transit time; ROC, receiver operating characteristic; ROM, radiopaque markers ; SITT, small intestinal transit time; SLBTT, small and large bowel transit time; STC, slow transit constipation; UGI, upper gastrointestinal; WGTT, whole gut transit time; WMC, wireless motility capsule	

Efficacy

Transit times

A case series of 187 patients with constipation reported significantly lower median colonic transit time of 43.5 hours (interquartile range [IQR)] 21.7–70.3 hours) classified by wireless motility capsule compared with 55 hours (IQR 31 to 85 hours) when classified by radiopaque markers ($p<0.001$)[2].

A comparative study of 165 (78 patients with chronic constipation and 87 healthy subjects) reported median transit times assessed by the capsule of 3.5 hours for gastric emptying time , 4.2 hours for small bowel transit time , 46.7 hours for colonic transit time and 59.3 hours for whole gut transit time for patients with constipation[5]. A comparative study of 148 (61 patients with gastroparesis and 87 healthy subjects) reported median gastric emptying time assessed by the capsule of more than 360 minutes (95% confidence interval [CI] 320 to more than360 minutes) in patients with gastroparesis and 215 minutes (95% CI 199 to 225 minutes) in healthy subjects[6].

The comparative study of 148 (61 patients with gastroparesis and 87 healthy subjects) reported median gastric emptying scintigraphy at 2 hours of 51% of meal retained (95% CI 42 to 58%) in patients with gastroparesis and 25% of meal retained (95% CI 23 to 37%) in healthy subjects[6].

Diagnostic accuracy

Wireless motility capsule compared with clinical diagnosis

A review of 560 patients with suspected motility problems (6 studies) reported sensitivity of the capsule compared with clinical diagnosis of gastroparesis to be 65 to 68% and specificity to be 82 to 87%[1].

Wireless motility capsule compared with scintigraphy

The review of 560 patients with suspected motility problems (7 studies) reported sensitivity of the capsule compared with gastric emptying scintigraphy to be 59

to 86% and specificity to be 64 to 81%. The strength of this evidence was reported to be low[1].

The comparative study of 148 (61 patients with gastroparesis and 87 healthy subjects) reported area under the curve of 0.79 (95% CI 0.71 to 0.88), sensitivity of 0.4 and specificity of 0.93 between gastric emptying scintigraphy at 2 hours and the capsule[6]. The same comparative study reported that 48% (23/48) of patients with gastroparesis and 7% (5/77) of healthy subjects had abnormal GES at 4 hours. For these people, the area under the curve for gastric emptying time was 0.94, sensitivity was 0.87 and specificity was 0.92. Using this analysis, the cut-off point for gastric emptying time that provides optimum balance of sensitivity and specificity for clinical use is 300 minutes[6].

Wireless motility capsule compared with radioactive marker

The review of 78 patients with suspected motility problems (1 study) reported sensitivity of the capsule compared with radiopaque marker assessment to be 37% and specificity to be 95%. The strength of this evidence was reported to be low[1]. The case series of 187 patients with constipation reported sensitivity of the capsule compared with radiopaque marker assessment for colonic transit time of 80% (95% CI 67 to 98%, p=0.01) and specificity of 91% (95% CI 83 to 96%, p=0.00001)[2].

The case series of 187 patients with constipation reported sensitivity of the capsule compared with radiopaque marker assessment for small and large bowel transit time of 79% (95% CI 67 to 89%, p=0.01) and specificity of 91% (95% CI 83 to 96%, p=0.00001)[2].

The comparative study of 165 (78 patients with chronic constipation and 87 healthy subjects) reported an area under the curve for colonic transit time of 0.73 (95% CI 0.65 to 0.82) with a sensitivity of 0.46 and specificity of 0.95 for the capsule compared with day 5 radiopaque marker assessment for all participants (cut off value of 59 hours)[5]. The same comparative study reported an area under the curve for whole gut transit time of 0.76 (95% CI 0.68 to 0.84) with a sensitivity

of 0.42 and specificity of 0.95 for the capsule compared with day 5 radiopaque marker assessment for all participants (cut off value of 73 hours)[5].

The same study also reported an area under the curve for day 5 radiopaque marker assessment of 0.71 (95% CI 0.63 to 0.78) with a sensitivity of 0.37 and specificity of 0.95 for all participants (cut off value >5 markers retained)[5].

Wireless motility capsule compared with common motility tests (gastric scintigraphy, small intestinal barium radiography, radioactive markers or anorectal manometry)

A case series of 83 patients with suspected gastroparesis, intestinal dysmotility or slow transit constipation reported that positive test agreement for assessment of GET by WMC and common motility tests was 59% and negative test agreement was 64%[4]. The same case series reported that positive test agreement for assessment of small intestine transit time by the capsule and common motility tests was 0% and negative test agreement was 75%[4]. The case series also reported that positive test agreement for assessment of colonic transit time by the capsule and common motility tests was 86% and negative test agreement was 43%[4].

WMC plus other diagnostic tests compared with other diagnostic tests alone

The review of 79 patients with suspected motility problems (2 studies) reported sensitivity of the capsule plus other diagnostic tests compared with other diagnostic tests alone to be 42 to 51% and specificity to be 60 to 66%. The strength of this evidence was reported to be low[1].

Concordance

The review of 745 patients with suspected motility problems reported concordance between the capsule and scintigraphy within a range of 35 to 81%[1]. The same review reported concordance between the capsule and radiopaque marker assessment within a range of 65 to 87%[1].

The case series of 83 patients with suspected gastroparesis, intestinal dysmotility or slow transit constipation reported overall discordance of 38% between the capsule and common motility tests[4].

Device agreement

The case series of 187 patients with constipation reported overall device agreement between the capsule and radiopaque marker assessment for colonic transit time of 87% (95% CI 80 to 92%)[2].The same case series reported overall device agreement between the capsule and radiopaque marker assessment for small and large bowel transit time of 86%[2].

The case series of 86 patients with suspected symptoms of upper GI or lower GI dysmotility reported overall device agreement between the capsule and radiopaque marker assessment/scintigraphy of 76% for patients with lower GI symptoms and 81% for patients with lower GI symptoms[3]. A case series of 43 patients with gastroparesis reported overall device agreement between gastric emptying time and gastric emptying scinitgraphy of 77% (positive agreement of 86% and negative agreement of 66%)[7].

Diagnostic agreement

The case series of 86 patients with suspected symptoms of upper GI or lower GI dysmotility reported overall diagnostic disagreement between the capsule and radiopaque marker assessment/scintigraphy of 8% (4/50) for patients with lower GI symptoms and overall diagnostic agreement of 14% (5/36) for patients with lower GI symptoms[3].

Confirmation of diagnosis or new diagnosis

The case series of 86 patients with suspected symptoms of upper GI or lower GI dysmotility reported that the capsule confirmed the clinical diagnosis in 58% (50/86) of patients and radiopaque marker assessment or scintigraphy confirmed the clinical diagnosis in 44% (38/86) of patients ($p<0.05$)[3].

The case series of 83 patients with suspected gastroparesis, intestinal dysmotility or slow transit constipation reported that new diagnosis was observed using the

capsule in 53% (44/83) of patients[4]. The case series of 43 patients with gastroparesis reported overall diagnostic gain of using the capsule of 19% (p=0.04)[7].

Correlation

The case series of 187 patients with constipation reported significant correlation between the capsule and radiopaque marker assessment for colonic transit time (r=0.707, p<0.001) and small and large bowel transit time (r=0.704, p<0. 001)[2].

The comparative study of 165 (78 patients with chronic constipation and 87 healthy subjects) reported correlation coefficients of 0.78 (95% CI 0.7 to 0.84) for colonic transit time and 0.77 (95% CI 0.68 to 0.84) for whole gut transit time between the capsule and day 2 radiopaque marker assessment for all participants[5].The same comparative study reported correlation coefficients of 0.59 (95% CI 0.46 to 0.69) for colonic transit time and 0.58 (95% CI 0.45 to 0.69) for whole gut transit time between the capsule and day 5 radiopaque marker assessment for all participants[5].

The comparative study of 148 (61 patients with gastroparesis and 87 healthy subjects) reported correlation coefficient of gastric emptying scintigraphy at 2 hours compared with the capsule of 0.63 (95% CI 0.5 to 0.75)[6].

Treatment decisions

The review of 745 patients with suspected motility problems reported that the capsule testing altered management (medicine, diet or surgery) in 50 to 69% of patients with suspected gastroparesis. The strength of this evidence was reported to be low[1].

The case series of 86 patients with suspected symptoms of upper GI or lower GI dysmotility reported that the capsule influenced management in 30% of patients with lower GI symptoms and 50% of patients with upper GI symptoms[3].The case series of 83 patients with suspected gastroparesis, intestinal dysmotility or slow transit constipation reported that the capsule influenced management; 60%

(39/65) received new medication, 14% (9/65) had modified nutritional regimens, 6% were referred for surgery and had the need for further test eliminated[4].

Safety

Device failure

Device malfunction was reported in 4% (8/180) of those who ingested the capsule in the case series of 187 patients with symptomatic constipation[2]. Software malfunction resulting in missing capsule transit parameters was reported in 12 participants (group not specified) in the comparative study of 165 (78 patients with chronic constipation and 87 healthy subjects)[5]. Prototype equipment malfunctions resulting in missing gastric emptying time data was reported in 11% (16/148) of participants (group not specified) in the comparative study of 148 (61 patients with gastroparesis and 87 healthy subjects)[6].

Capsule retention

Capsule retention at day 5 X-ray was reported in 21% (14/67) of patients with constipation in the comparative study of 165 (78 patients with chronic constipation and 87 healthy subjects). At day 21 X-ray 79% (11/14) of these patients had expelled the capsule. The other 3 recovered the capsule from their stools[5].

Capsule retention was reported in 1 patient with gastroparesis in the comparative study of 148 (61 patients with gastroparesis and 87 healthy subjects). The capsule was retained in a viscous jelly like mass after the patient ingested Citrucel (a bulk forming laxative). An endoscopy was performed but it was not possible to retrieve the capsule. Erythromycin IV (200 mg) was administered and the capsule subsequently emptied from the stomach after 30 minutes[6].

Other adverse events

The case series of 187 patients with constipation reported 7 adverse events as being possibly or definitely related to the capsule; 2 cases of abdominal pain, 1 case of diarrhoea, 2 cases of dysphagia and 2 cases of nausea[2].

Validity and generalisability of the studies

- The key study[1] includes all relevant peer reviewed papers on this procedure and reports that the strength of the evidence as low.
- Only evidence from the United States has been published.
- All included studies were either funded by the manufacturer or conducted by researchers who were consultants for the manufacturer.

Existing assessments of this procedure

In 2011, the American and European Neurogastroenterology and Motility Societies published a position paper on evaluation of the gastrointestinal transit. The paper stated that 'the capsule is recommended for an assessment of gastric emptying and regional and whole gut transit time in individuals with suspected gastroparesis and symptoms of upper GI dysmotility. It is particularly useful for testing individuals with suspected alterations of GI motility in multiple regions'[8].

In 2014, another American health insurance (Blue Cross and Blue Shield Medical) advisory panel stated that 'the evidence is insufficient to make conclusions regarding whether SmartPill either improves the net health outcome or is as beneficial as established alternatives for diagnosis and evaluation of either gastroparesis or slow-transit consitpation'[9].

In 2014, an American managed health care company (Aetna) published a policy on gastrointestinal function tests and stated that 'Aetna considers a wireless capsule for measuring gastric emptying parameters (SmartPill GI Monitoring System) experimental and investigational for the evaluation of gastric disorders (for example, gastroparesis), intestinal motility disorders (such as chronic constipation), and all other indications because of inadequate published evidence of its diagnostic performance and clinical utility over conventional means of measuring gastric emptying'[10].

In 2013, an American health insurance company (United Healthcare) published a medical policy on gastrointestinal motility, diagnosis and treatment. The policy

stated that ‘the SmartPill wireless gastrointestinal motility monitoring system is proven for diagnosing and evaluating gastrointestinal motility disorders including gastroparesis when used according to FDA labeled indications’. In addition, the policy also states that ‘the SmartPill wireless gastrointestinal motility monitoring system is medically necessary when earlier diagnostic tests have failed to identify the cause of symptoms consistent with a gastrointestinal motility disorder’[11].

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Catheterless oesophageal pH monitoring. NICE interventional procedure guidance 187 (2006). Available from http://guidance.nice.org.uk/IPG187
- Gastroelectrical stimulation for gastroparesis. NICE interventional procedure guidance 103 (2004). This guidance is currently under review and is expected to be updated in 2014. For more information, see http://guidance.nice.org.uk/IPG103
- Wireless capsule endoscopy for investigation of the small bowel. NICE interventional procedure guidance 101 (2004). Available from http://guidance.nice.org.uk/IPG101

Specialist advisers’ opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Dr Anton Emmanuel (British Society of Gastroenterology), Professor Robin Spiller (British Society of Gastroenterology) and Dr Natalia Zarate-Lopez (British Society of Gastroenterology)

- Title should be altered to ‘Wireless capsule assessment of transit and motility in the gastrointestinal tract’ or ‘Assessing regional and global gut transit using a wireless non-digestible capsule’.
- Two of the specialist advisers have performed the procedure at least once and 1 specialist adviser has never performed the procedure.
- Two specialist advisers consider the procedure to be novel and of uncertain safety and efficacy. One specialist adviser considers the procedure to be a minor variation on an existing procedure (GIVEN endo capsule).
- The comparator is multiple assessment by whole gut and colonic transit (radio-isotope or marker), small bowel manometry and gastric scintigraphy or the GIVEN endo capsule.
- Theoretical adverse events: impaction of the capsule in patients with strictures, or capsule not progress beyond the stomach in patients with severe gastroparesis.
- Anecdotal adverse events: difficulty swallowing the capsule and software failure.
- Training and facilities are not available outside of research centres. In those centres where it is undertaken, training has occurred at international meetings and from the company distributing the product. This training and support is mostly in the form of optimising software analysis. It is important that the person administering the capsule can interrogate and confirm that the patient has the ability to swallow appropriately and to confirm that there are no contraindications for the use of the device.
- Controversy or uncertainty:
  - Cost utility – unlikely to be used outside of specialist centres in its current form.
  - There is uncertainty about the validity of measurements of upper GI (especially gastric) motility. There is no controversy about its ability to measure GI tract. It is more controversial in its ability to provide relevant information of GI tract motor patterns.

  - The device measures gut transit using the advance through the GI tract of the capsule and this might not reflect the true speed of transit of a given meal.
  - Gut transit depends of regional motility and this is influenced by the luminal contents and it is unclear whether the device elicits non-standard patters on GI motility. Measurement of GI motility by the device is limited by the fact that it has only 1 pressure sensor and therefore direction of contractions and speed of propagating contractions cannot be established.
  - The capsule can be used to assess gastric and intestinal motor patterns but whether this alters clinical outcome is not known.
- One specialist adviser stated that the procedure would have moderate impact and 1 specialist adviser stated that the procedure would have minor impact on the NHS.
- Other issues: avoids exposure to radiation as standard methods to determine gut transit, colonic transit time and scintigraphy, involve patient exposure to radiation.

Patient commentators' opinions

NICE's Public Involvement Programme sent 5 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received 1 completed questionnaire.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Issues for consideration by IPAC

Future or ongoing studies:

- NCT02022826: 'Clinical management with SPM System and validation of the SPM 5 hour cutoff in patients with symptoms of gastroparesis' (patients will undergo concurrent gastric scintigraphy and SmartPill Motility Monitoring

System (SPM) testing to determine the presence or absence of delayed gastric emptying based on predetermined diagnostic cut-offs for each technique). Case series, expected enrolment: 250 patients. Expected completion date: December 2015. (Manufacturer study)

- NCT01890616: ’Constipation and gut transit in DMD patients’ (determining gut transit times using SmartPill in patients with Duchenne Muscular Dystrophy older than 18).Case series, estimated enrolment: 20. Final data collection: October 2013.

References

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9. Mark DH. (2012) Wireless motility capsule in the diagnosis and evaluation of gastroparesis or slow-transit constipation (Provisional abstract). Database of Abstracts of Reviews of Effects 1-

10. Aetna. (2014) Clinical Policy Bulletin: Gastrointestinal Function: Selected Tests (Number: 0396).

11. United HealthCare Services. (2013) Gastrointestinal motility disorders, diagnosis and treatment.

Appendix A: Additional papers on assessing motility of the gastrointestinal tract using a wireless capsule

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Gelfond D, Ma C, Semler J & Borowiz D (2013) Intestinal pH and gastrointestinal transit profiles in cystic fibrosis patients measured by wireless motility capsule. Digestive Diseases & Sciences 58(8):2275-81	N= 10 patients with cystic fibrosis Follow-up: 1 hour for pH data [Comparative data on 10 healthy subjects is also reported]	In patients with cystic fibrosis, there was a significant delay in time interval required to reach and sustain pH 5.5 and pH 6.0 ($p < 0.001$), which is required for pancreatic enzyme replacement therapy dissolution. Only small bowel transit in patients with cystic fibrosis was noted to be significantly delayed ($p = 0.004$) without a compensatory increase in whole gut transit time.	No comparator test Larger studies in table 2
Hasler WL, Saad RJ, Rao SS et al. (2009) Heightened colon motor activity measured by a wireless capsule in patients with constipation: relation to colon transit and IBS American Journal of Physiology - Gastrointestinal & Liver Physiology 297(6):G1107-G1114	N=36 patients with self reported constipation Follow-up: maximum 100 hours [Comparative data on 53 healthy subjects is also reported]	Constipated patients with normal or moderately delayed transit showed increased motor activity that is partly explained by IBS.	No comparator test Larger studies in table 2
Kloetzer L, Chey WD, McCallum RW et al. (2009) Motility of the antroduodenum in healthy and gastroparetics characterized by wireless motility capsule. Neurogastroenterology & Motility 22:527-533.	N= 42 patients with gastroparesis Follow-up: not reported [Comparative data on 71 healthy subjects is also reported]	Median number of contractions: Gastroparesis:47 Healthy: 72 Median motility index score: Gastroparesis:11.12 Healthy: 11.83	No comparator test Larger studies in table 2
Saad RJ and Hasler WL. (2011) A technical review and clinical assessment of the wireless motility capsule. Gastroenterology & Hepatology 7(12):795-804	N= 3 case reports (1 refractory gastroparesis, 1 constipation and 1 upper and lower gastrointestinal	Case 1: 35 year old female. Capsule data indicated markedly delayed small bowel transit time of 23 hours and 15 minutes and a	No comparator test Larger studies in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
	symptom complex)	normal colon transit time of 47 hours. This indicates intestinal pseudo obstruction with a contractile profile consistent with visceral neuropathy. Treatment: intermittent use of antibiotics and treatment trials of octreotide and pyridostigmine. An earlier gastrectomy could have been avoided if wireless motility capsule used earlier. Case 2: 21 year old female. Colon transit time: 116 hours, normal small bowel transit time and normal gastric emptying time. Patient referred for elective colectomy (medical therapy was ineffective). Case 3: 19 year old female. Normal small bowel transit time, gastric emptying time and colon transit time. Treatment: low dose mirtazaine and antiemetic as required. Patient reported symptom improvement.	
Saad RJ, Rao SSC, Koch KL et al (2010) Do stool form and frequency correlate with whole-gut and colonic transit? Results from a multicentre study in constipated individuals and healthy controls. The American Journal of Gastroenterology 105:403-11.	N= 46 patients with chronic constipation Follow-up= 5 days	Moderate correlation between stool form and whole-gut transit measured by WMC ($r=-0.61$, $p<0.0001$) or ROM ($r=-0.45$, $p=0.0016$).	This is an additional analysis of patients are already included in Rao 2009 in table 2 (which is included in Stein 2013 in table 2).
Sarosiek I, Selover KH, Katz LA et al. (2010) The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. Alimentary Pharmacology & Therapeutics 31(2):313-22	N=34 patients with gastroparesis Follow-up: maximum approx. 170 hours [Comparative data on 53 healthy subjects is also reported]	Median gastric emptying time, colon transit time and whole gut transit time was significantly longer in patients with gastroparesis compared with healthy controls. Small bowel transit time was not significantly different	No comparator test Larger studies in table 2

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
		between the groups.	
Wiliams III RE,Bauman WA, Spungen AM et al. (2012). SmartPill technology provides safe and effective assessment of gastrointestinal function in persons with spinal cord injury. Spinal Cord 50(1):81-4	N= 10 patients with spinal cord injury Follow-up: maximum approx. 100 hours [Comparative data on 10 healthy subjects is also reported]	Gastric emptying time (GET), colonic transit time (CTT) and whole gut transit time (WGTT) were prolonged in patients with spinal cord injury compared with health subjects (GET: 10.6±7.2 compared with 3.5±1.0 h, P<0.01; CTT: 52.3±42.9 compared with 14.2±7.6 h, P=0.01; WGTT: 3.3±2.5 compared with 1.0±0.7 days, P<0.01). No complications or side effects were reported.	No comparator test Larger studies in table 2 [Excluded by Stein 2013 as it 'does not apply to the key question]

Appendix B: Related NICE guidance for assessing motility of the gastrointestinal tract using a wireless capsule

Guidance	Recommendations
Interventional procedures	**Catheterless oesophageal pH monitoring. NICE interventional procedure guidance 187 (2006)** 1.1 Current evidence on the safety and efficacy of catheterless oesophageal pH monitoring appears adequate to support the use of this technique provided that normal arrangements are in place for consent, audit and clinical governance. **Gastroelectrical stimulation for gastroparesis. NICE interventional procedure guidance 103 (2004) [under review]** Current recommendations: 1.1 Current evidence on the safety and efficacy of gastroelectrical stimulation for gastroparesis does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake gastroelectrical stimulation for gastroparesis should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear, written information. Use of the Institute's information for the public is recommended. • Audit and review clinical outcomes of all patients having gastroelectrical stimulation for gastroparesis. 1.3 The procedure should only be performed in specialist gastroenterology units with expertise in gastrointestinal motility disorders. 1.4 Current evidence on the efficacy of the procedure relates mainly to relief from nausea and vomiting, which occurs in some patients. There is little evidence that the procedure improves gastric emptying. Further research will be useful, and the Institute may review the procedure upon

	publication of further evidence. **Provisional recommendations [consultation closed 22 January 2014]:** 1.1 Current evidence on the efficacy and safety of gastric electrical stimulation for gastroparesis is adequate to support the use of this procedure with normal arrangements for clinical governance, consent and audit. 1.2 During the consent process clinicians should inform patients considering gastric electrical stimulation for gastroparesis that some patients do not get any benefit from it. They should also give patients detailed written information about the risk of complications, which can be serious, including the need to remove the device. 1.3 Patient selection and follow-up should be done in specialist gastroenterology units with expertise in gastrointestinal motility disorders and the procedure should only be performed by surgeons working in these units. 1.4 Further publications providing data about the effects of the procedure on symptoms in the long term and on device durability would be useful. **Wireless capsule endoscopy for investigation of the small bowel. NICE interventional procedure guidance 101 (2004)** 1.1 Current evidence on the safety and diagnostic yield of wireless capsule endoscopy appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Clinicians should consider the use of other investigations before wireless capsule endoscopy, particularly in patients with Crohn's disease in whom strictures are suspected.

Appendix C: Literature search for assessing motility of the gastrointestinal tract using a wireless capsule

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	02/01/2014	Issue 12 of 12, December 2013
Database of Abstracts of Reviews of Effects – DARE (CRD website)	02/01/2014	Issue 4 of 4, October 2013
HTA database (CRD website)	02/01/2014	Issue 4 of 4, October 2013
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	02/01/2014	Issue 12 of 12, December 2013
MEDLINE (Ovid)	02/01/2014	1946 to November Week 3 2013
MEDLINE In-Process (Ovid)	02/01/2014	December 31, 2013
PubMed	02/01/2014	n/a
EMBASE (Ovid)	02/01/2014	1974 to 2013 Week 52
BLIC	02/01/2014	n/a

Trial sources searched on 03/01/2014:

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials metaRegister of Controlled Trials – mRCT
- Clinicaltrials.gov

Websites searched on 03/01/2014:

- National Institute for Health and Clinical Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)

- Conference websites

General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Wireless Technology/
2	wireless*.tw.
3	exp Telemedicine/
4	(telemed* or telehealth or ehealth or telemetr* or biotelemetr* or radiotelemet* or teleradiometr* or telemonitor*).tw.
5	Capsules/
6	(motility adj4 (capsul* or pill* or device*)).tw.
7	((nondigest* or "non digest" or non-digest* or indigest*) adj4 (capsule* or pill*)).tw.
8	((gastrointestin* or GI) adj4 monitor* adj4 (system* or device*)).tw.
9	((gastrointestin* or GI) adj4 monitor* adj4 system*).tw.
10	or/1-9
11	Gastroparesis/
12	gastropare*.tw.
13	Gastric Emptying/
14	(delay* adj4 gastr* adj4 empt*).tw.
15	Gastrointestinal Motility/
16	Gastrointestinal Transit/
17	((gastrointestin* or GI or gastric or gut) adj4 (transit or motility)).tw.
18	Constipation/
19	(chronic adj4 constip*).tw.
20	or/11-19
21	10 and 20
22	SmartPill.tw.
23	21 or 22
24	animals/ not humans/
25	23 not 24