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Manuscript title

Feasibility Study of a New MRI Mini-Capsule Device to Measure Whole Gut Transit Time in Pediatric Constipation.

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ABSTRACT

Objective: In England, 27,500 children are referred annually to hospital with constipation. An objective measure of whole gut transit time (WGTT) could aid management. The current standard WGTT assessment, the X-ray radiopaque marker (ROM) test, gives poor definition of colonic anatomy and the radiation dose required is undesirable in children. Our objective was to develop an alternative MRI WGTT measure to the X-ray ROM test and to demonstrate its initial feasibility in pediatric constipation.

Methods: With the Nottingham Young Person's Advisory Group (YPAG) we developed a small (8mm×4mm), inert polypropylene capsule shell filled with MRI-visible fat emulsion. The capsule can be imaged using MRI fat and water in-phase and out of phase imaging. Sixteen patients with constipation and 19 healthy participants aged 7-18 years old were recruited. Following a common ROM protocol, the participants swallowed 24 mini-capsules each day for 3 days and were imaged on day 4 and 7 using MRI. The number of successful studies (feasibility) and WGTT were assessed. Participants' EQ-VAS were also collected and compared between the day before the taking the first set of mini-capsules to the day after the last MRI study day.

Results: The mini-capsules were imaged successfully in the colon of all participants. The WGTT was 78 ± 35 hours (mean±SD) for patients, and 36 ± 16 hours, $P < 0.0001$ for healthy controls. Carrying out the procedures did not change the EQ-VAS scores before and after the procedures.

Conclusions: MAGIC (Magnetic Resonance Imaging in Pediatric Constipation) was a first-in-child feasibility study of a new medical device to measure WGTT in pediatric constipation using MRI. The study showed that the new method is feasible and was well tolerated.

Key Words: Magnetic Resonance Imaging, X-ray Radiopaque markers, Gastrointestinal Tract, TransiCapTM mini-capsules, MAGIC

What Is Known

- Current methods for assessing whole gut transit time (WGTT) include the traditional abdominal X-ray and radiopaque markers (ROM).
- X-ray ROM methods expose children and young people ionising radiation in the range 0.03-0.11 mSv.
- X-ray ROMs produce two-dimensional radiographs where the bowel and location of the ROM markers may be difficult to distinguish.

What Is New

- We developed a new, magnetic resonance imaging (MRI) visible mini-capsule, specifically aimed at children and young adults.
- This first-in-child feasibility study showed that WGTT can be measured in pediatric constipation using the new mini-capsule device in conjunction with MRI.

INTRODUCTION

Functional constipation in childhood is common, with estimated prevalence of 14% (1-5). The diagnosis is based on symptom and is defined according to the Rome IV diagnostic criteria (6-8) which for a child over 4 years of age must include two or more of the following (7): 1) two or fewer defecations in the toilet/week. 2) At least one episode of fecal incontinence/week. 3) History of retentive posturing or excessive volitional stool retention. 4) History of painful or hard bowel movements. 5) Presence of a large fecal mass in the rectum. 6) History of large diameter stools that can obstruct the toilet. Managing this condition can be challenging. Whole gut transit time (WGTT) imaging studies have long been used (9) as an objective measure which can assist in stratifying patients and directing management. Gut transit studies have been reported to help characterise normal transit (10), anorectal retention (outlet obstruction) (11), non-retentive faecal incontinence (12) and slow transit constipation (11, 13) and can be particularly useful when medical history and/or physical examination is unreliable (13).

Current methods include both gamma scintigraphy and X-ray radiopaque markers (ROMs). Both techniques involve exposure to ionising radiations, which is undesirable in young persons (14, 15). The effective exposure dose provided can vary considerably depending on isotopes and techniques. Radiolabelled meals in gamma scintigraphy can provide between 0.1 mSv (16, 17) up to 1-4 mSv (18) and X-ray can provide between 0.03 and 0.11 mSv (19). Scintigraphy uses radiolabelled tracers to determine transit time. Lack of standardisation (20) and limited availability make its use problematic. In the conventional Metcalf ROMs method (21), the patients ingest a number of small, inert plastic pellets on 3 consecutive days after which a series of abdominal radiographs are taken to assess the location of the markers inside the gastrointestinal tract (GI), thereby determining WGTT. The ROMs method is more widely available than scintigraphy. However, it is often difficult to determine the

location of the radiopaque markers accurately on an X-ray film due to the tortuous structure of the large bowel and the limitations of two-dimensional X-ray projection imaging.

Magnetic resonance imaging (MRI) has already revolutionised diagnostics in many fields and is recently coming of age for the assessment of functional GI diseases (22). WGTT has been recently measured using adult-sized, MRI visible capsules in health and constipation but the size of the capsules make them unsuitable for children (23-26).

This study aimed therefore at developing an MRI alternative to the X-ray ROMs, specifically targeted for the first time at children and young adults, and at demonstrating feasibility of the test in pediatric constipation.

METHODS

Study Participants

The Rome IV criteria was used to identify patients with childhood functional constipation following a referral either from primary or secondary care into a specialist clinic at Nottingham University Hospitals NHS Trust were recruited between April 2018 and June 2019 (Fig. 1). By the time they reached the specialist clinic, these patients were at various stages of treatment and there was no expectation that they would change treatment plan whilst participating as this was a feasibility study of the new methodology. During the same period healthy participants, who had normal bowel habit and did not suffer from constipation or diarrhoea, were recruited by advertisement from the local community. The CONSORT Diagram (27) is shown in Fig. 1. All participants were aged between 7 and 18 years old. A minimum age of 7 was selected as at this age participants are more likely to have had some experience of swallowing tablets. In participants younger than that age compliance with MRI procedures could also have been lower and motion artifacts could have been more frequent, precluding analysis. Participants with existing antegrade colonic enema (ACE) procedure were excluded as well as patients with a history of GI surgery that could affect GI function, including colectomy or small

bowel resection. Exclusion criteria included inability to lie flat and relatively still for less than 5 minutes and typical MRI scanning contraindications such as presence of metallic implants, pacemakers, history of metallic foreign body in eyes. This study was approved by the UK National Research Ethics Committee (17/WM/0049), by the Medicines and Healthcare products Regulatory Agency (MHRA) (CI/2017/0054) and registered on Clinicaltrials.gov (NCT03564249).

Study Design

This was an open label, feasibility, case-control study in a University setting. The intervention in this study mirrored a common X-ray ROM protocol (21). The rationale behind it is to load the gastrointestinal tract with repeated daily doses of a plurality of markers to achieve a steady state and then image the location of the markers in the gastrointestinal tract at predetermined time points (9). Many variants of this type of protocol have been proposed and we have chosen the one involving 3 daily doses of 24 markers each, which was also used for example for the common Sitzmarks[®] ROMs product (9, 28).

More specifically: participants were asked to swallow 24 mini-capsules each morning at home for 3 consecutive days (72 mini-capsules in total), by either mixing the mini-capsules in yoghurt, or swallowing with water or fruit juice. The participants underwent a short MRI scan on day 4. If mini-capsules were still seen in the bowel, a second short MRI scan was performed on Day 7. If mini-capsules were still seen in the bowel, they underwent a third MRI scan around day 26-28. This last scan was not part of the WGTT test but performed to collect data on possible retention of mini-capsules. EQ-VAS (visual analogue scale) questionnaire data (29) was collected at baseline and each day of the study (day 0, before they started taking the mini-capsules to day 8). EQ-5D-Y data (30) was also collected at baseline. The questionnaire evaluates health-related life domains such as mobility, self-care and pain. The lowest scores set possible for the EQ-5D-Y is 1,1,1,1,1 indicating no issues with any of the 5 domains. Scores higher than 1 in one or more domains indicate loss of QoL. All questionnaires used with permission. In addition to the Consort Diagram at Fig. 1, a CONSORT

Checklist (27) was also used to standardize reporting; this is shown in Supplemental Digital Content 1 (Suppl CONSORT Checklist).

The patients who completed the feasibility study were to be invited to undergo an exact repeat of the protocol after approximately 6 months (Part 2 of the study), to collect more pilot data and also start assessing potential changes in WGTT due to treatment. Due to project delays and funding timelines only 6 patients were able to come back and repeat the protocol. Whilst all 6 additional Part 2 studies were completed safely, the numbers are too small for meaningful paired comparison and they are not included in this analysis or the results section.

Study Objectives and Endpoints

The primary objective of this study was to develop the new device and technique and to assess its feasibility on pediatric constipation. The secondary objectives were: (i) to describe WGTT of controls and patients. (ii) to describe the safety of the technique. (iii) to describe the effect of the technique on Quality of Life (QoL).

The primary endpoint for feasibility was the number of successful measurements. The secondary endpoints were WGTT of controls and patients, the number of Adverse Events (AE) for all participants, the change in EQ-VAS scores (young people health on the day) (30) and the baseline EQ-5D-Y.

Mini-capsules

The mini-capsules are classed as an inert marker ingestible medical device (European Union Class IIa) designed in partnership with our Young Person Advisory Group (YPAG, see Suppl Text on Supplemental Digital Content 2) and manufactured by JEB Technologies Limited (Hampstead Avenue, Mildenhall, UK). They enter the body via the oral cavity and travel inside the GI tract where they can be located using MRI (in good analogy with X-ray ROMs). The mini-capsules (Fig. 2) were made from medical grade polypropylene polymer (8mm×4mm). The shell is invisible to MRI thus the mini-capsules were filled with a MRI-visible solution comprising oil and water, with trace amounts

(1 μ M) of Gadolinium (Gd) contrast agent for increased visibility, and the shell is designed to ensure that the contents are not released in the GI tract. The combination of fat, water and Gd allowed us to exploit standard fat and water MRI sequences providing a unique, positive signal, MRI signature for the mini-capsules in the large bowel. At the time of the study, the mini-capsules were non-CE marked and not FDA approved. They have subsequently been trademarked as TransiCap™.

MRI

A 3T, wide-bore Ingenia scanner (Philips, Best, The Netherlands) was used to acquire MRI. For the MRI the participants were not sedated and lay feet first on the scanner bed, in the supine position. A 3-dimensional 2-echo, mDIXON scan was then acquired to locate the mini-capsules. This provided 4 image types for each slice acquired: water only, fat only, fat and water in-phase and out-of-phase images (31). The liquid filling of the mini-capsules was optimised in conjunction with the imaging sequence parameters so that on a derived subtraction of the out-of-phase image from the in-phase image the signal of the mini-capsules would be maximised compared to gastrointestinal chime, intestinal water and surrounding organs, facilitating their detection. The sequence was acquired both in coronal and axial planes, breaking down the 3D volume into stacks of short breath-holds to minimise respiratory motion. Five breath holds of 12.3 s each were required to collect the axial image set and 6 breath holds of 13.5 s were required for the coronal image set. The whole MRI procedure took approximately 15-20 minutes. The MRI sequence parameters including length in seconds are provided in Supplemental Digital Content 3 (Suppl Table 1).

Counting of the mini-capsules was performed preferentially on the coronal plane views because the anatomy of the colon is simpler to follow in that orientation. If the coronal images were blurred by motion or partly obscured by a very full bladder, then the axial images were of additional value for the counting. These were observations made at post-processing stage. Four participants had some data sets that were more difficult to read because of blurring induced by respiratory motion caused by poor breath-holding during some of the imaging image acquisitions but possibly also by gastrointestinal

motility due to a recent meal. When blurring was noted by the radiographer at the time of scanning some image sets could be repeated immediately, which only required a few additional breath-holds. Acquiring both axial and coronal data sets and in separate stacks further helped because if one set was found to be blurry a different one could be analyzed. Analysis of one data set took approximately 10 minutes.

Data Analysis

After each scan, the mini-capsules remaining in the gut were located and counted on the derived in-phase minus out-of-phase images and the WGTT calculated following the Sitzmarks ROM method (21). The calculation of WGTT assumes that that by loading the gut with repeated ingestion of the mini-capsules over three days, a steady state is reached so that: $\text{WGTT in hours} = (72 \text{ hours} / \text{the number of mini-capsules ingested over three days}) \times \text{the total number of mini-capsules remaining in the colon}$. The total number of mini-capsules ingested in this study over 3 days, 72, simplifies the multiplying factor so that $\text{WGTT} = \text{the total number of mini-capsules remaining in the colon at Day 4}$. When some mini-capsules are remaining at Day 7, their contribution to the total transit time is simply added to the count at day 4 using the same method. The principle of the WGTT marker method relies on loading of the bowel with a plurality of markers not necessarily on their specific total number (9) hence the formula above can be adapted in case some of the mini-capsules were mistakenly not ingested, by simply changing the denominator for ‘the number of mini-capsules ingested over three days’. This happened in one instance in this study leading to one data imputation. All image data were analysed by a researcher with MRI radiographer background. The feasibility study was open label and they were not blind to which group the patients or controls belonged to, but they did not have knowledge of the individual patient histories. All statistical analyses were carried out using Prism version 6.07 (Graph Pad Software Inc., La Jolla, CA, USA). Normality of the data was assessed using D’Agostino and Pearson test. The comparison of WGTT and EQ-VAS between patients and controls was carried out *post-hoc*. The WGTT data were normally distributed and differences in WGTT

between the patients and controls were compared using two-tailed, unpaired t test. The EQ-VAS were compared between the baseline time point before the start of the study procedures and the day after the study procedures were completed (Day 8). Data were considered significantly different at $P < 0.05$. There was no prior data on the new mini-capsules to estimate sample size and 25 controls as an acceptable sample size for a feasibility study (32, 33) and allowing for dropouts.

RESULTS

Thirty five young persons were studied (Fig. 1). These comprised 16 patients (7 male; 9 female; 11 ± 3 years old; BMI 25 ± 9 kg/m²) and 19 healthy young controls (8 male; 11 female; 16 ± 2 years old; BMI 25 ± 5 kg/m²). The age between the two groups had a modest but significant difference (Mann Whitney $P < 0.001$) The individual participants' characteristics are provided in Supplemental Digital Content 4 (Suppl Table 2).

Number of successful measurements and feasibility

All the 35 participants that ingested the mini-capsules completed the study. Only one of the subjects forgot to ingest one of the daily doses and the WGTT calculation was corrected for this. This showed very good acceptability of the mini-capsules and MRI procedures. Feedback from the participants and the parents, albeit not formally recorded, was positive.

The mini-capsules were imaged successfully in the colon of all participants using MRI.

Fig. 4 (a) shows the image of a single coronal image slice clearly showing the mini-capsules with bright, positive signal against the darker colon contents of a participant. The image shown in Fig. 4 (b) is a projection reconstructed from a multi-slice three-dimensional set of the whole abdomen of another participant. The appearance of the markers in the segmented colon here is more similar to X-ray imaging with radiopaque markers, an example of which from a different study is shown in Fig. 4 (c) for comparison.

Whole Gut Transit Time

From the MRI images, it was possible to count the mini-capsules in the gastrointestinal tract of all the participants. The WGTT (Fig. 3), calculated from the mini-capsules count, was 78 ± 35 hours for the young patients with constipation, significantly longer than that for the healthy controls 36 ± 16 hours, $P < 0.0001$.

Number of Adverse events and safety

There were no Serious Adverse Events (SAEs) in the study. There was only one Adverse Event (AE) in the study. This was a single episode of vomiting. It was categorised as mild and quickly resolved, requiring no follow up and possibly related to the study procedures.

The number of mini-capsules detected in the gut decreased with time for all participants. In the patient group, the number significantly decreased from 57 ± 11 mini-capsules at day 4 to 19 ± 26 mini-capsules at day 7, $P = 0.02$. For the healthy controls the count significantly decreased from 31 ± 13 at day 4 to 4 ± 6 at day 7, $P < 0.0001$.

Some mini-capsules were present at day 7 in $n=11$ patients and $n=9$ healthy controls. These participants were recalled for a final scan at day 26-28 post ingestion. No mini-capsules were detected in any of the participants at this final time point, thus in part confirming the European Union Class IIa classification of the device.

EQ-VAS scores

There was no significant difference in EQ-VAS visual analogue scores provided by all participants pooled together at baseline before any procedure (87 ± 13) and after completing the mini-capsules and MRI intervention at Day 8 (85 ± 18), Wilcoxon's $P = 0.79$.

The young patients' EQ-VAS grand mean was about 10% lower than for healthy controls with no significant differences between groups ($P = 0.78$). There are also no significant differences in EQ-VAS scores before and after the mini-capsules and MRI test for patients (Wilcoxon's $P = 0.54$) and

for healthy controls (Wilcoxon's $P = 0.55$). A breakdown of data by patient group is shown in Supplemental Digital Content 5 (Suppl Fig 1).

EQ-5D-Y

All healthy controls scored their QoL at the lowest score 1 for all dimensions on the EQ-5D-Y questionnaires. Four patients indicated a loss of QoL in the questionnaires. A clerical error prevented the administration of the second batch of questionnaires after the MRI study procedures therefore those data are not available.

DISCUSSION

The MAGIC study was a 'first-in-child' clinical investigation of a novel medical device. As such we set out to assess feasibility, safety and performance of using the new device in the intended population, for the intended purpose. The study was successful on various points.

Assessing feasibility of the new technique was the primary objective of the study. The data showed that using the new device and the MRI methods were feasible and the procedures acceptable with 35 pediatric participants ingesting the mini-capsules and undergoing MRI without refusal and completing the study. The intended method to image the mini-capsules, using a derived in-phase minus out-of-phase fat and water MRI images worked well. The mini-capsules appeared distinctively, with a high positive contrast against the colonic chyme.

Another strength of the whole project was the active participation of children and young persons in the co-design of the mini-capsules and of the feasibility study.

Having imaged the mini-capsules in the colon of these participants we have been able to count them, which provided a successful measure of WGTT using the simple algorithm described in the methods. Therefore, the new device met the intended purpose of being imaged and identified in the gut, monitoring gut transit time using MRI and of measuring the intended WGTT end point of the study in pediatric constipated participants and healthy controls. We have also collected a reference mean and a

range of whole gut transit time for the healthy controls, which was a secondary objective of the study. The new data on mean and standard deviation of WGTT for a reasonable number of pediatric patients and controls will also allow us initial inferences on sample size power calculations for future pediatric intervention studies.

When comparing our transit time results with other pediatric data in the literature, Gutierrez et al. (34) found transit time in a constipated group of 49.6h versus 29.1 hours in a control non-constipated group. They used a radiopaque marker method involving ingestion of 10 markers per day for 6 days followed by an X-ray on day 7. Zaslavsky et al. (35) similarly found a transit time of 54.3h in an adolescent constipated group versus 30.2 hours in a control non-constipated group, a delay in transit time of 40% compared to controls. They used 20 radiopaque markers ingested each day for 3 days followed by an X-ray on day 4. The data collected here with our new mini-capsules showed a highly significant difference of 54% in whole gut transit time between our young patients with constipation and healthy controls. This further corroborates evidence that the new device was able to detect a clinically significant difference between pediatric constipation and healthy controls.

In this study we measured WGTT by counting the number of capsules remaining in the bowel at predetermined time points. Measuring segmental transit times in different tract of the colon was not an outcome for this study. Segmental transit times were once more popular particularly to inform segmental surgical resection but recently controversy has been reported about this treatment and its uncertain benefits (36, 37). The cross-sectional quality of MRI can provide an advantage over X-ray to assign the location of markers as bowel loops can overlap in the two-dimensional X-ray abdominal film, thought this needs to be assessed formally.

The study had a very good safety record. There was only one episode of vomit categorised as an adverse event. It is worth noting that this participant continued the study, completed the rest of the procedures and agreed to come back for one of the Part 2 studies which they completed successfully, further illustrating the mild nature of that adverse event.

The EQ-VAS scores showed no difference before and after the study procedures indicating that undergoing the study and the procedures did not alter the score of the patients and of the healthy participants.

The study had some limitations. The baseline EQ-5D-Y for the participants were not repeated after the study due to a clerical error thus preventing an appropriate assessment of changes in QoL.

The patient participants reached the specialist clinics in the hospital as they required expertise more than that available within primary and secondary care. Our pool included also those referred from other community paediatric clinics and general paediatric clinics within the region. As such, they were at various stages of treatment, when they participated in the study. There was no expectation that patients would change treatment plan whilst being investigated. It is interesting that despite this and their heterogeneity we demonstrated a longer WGTT in the patient group. At the same time this did not allow us to collect meaningful data on changes in gut transit upon treatment. The original design included an invitation to all patients to come back to repeat the feasibility study as a 'Part 2' approximately 6 months after the first participation. Due to delays in recruitment and funding timelines, and also some difficulty in communicating with the satellite district hospitals and practitioners, we were able to re-test only 6 patients. They all repeated the MRI study safely, but the sample is too small to provide meaningful comparisons and these repeated data were excluded from the analysis. There was a significant difference in age between the two groups though this was modest and did not seem to affect this feasibility study.

Some of the youngest participants reported feeling nervous at the start of the study, which is understandable for people who had not previously participated in a clinical investigation or had an MRI scan, but this did not stop any of them participating and they quickly relaxed and came back very happily for all the other visits. A further limitation of this study is that we did not set out to collect formal questionnaire feedback on how the procedures were perceived, the burden of attending and of going in the MRI scanner. A few data sets were blurred by motion. An observation made at post-

processing was that the large region of high intensity signal from a full bladder may make mini-capsule detection more difficult, particularly in the distal colon / rectum area, on the coronal image plane orientation although further post-processing techniques could overcome some difficulties. We also noted that participants who came in having just recently eaten a large breakfast or meal showed higher stomach and small bowel motility, which can also blur some image sets, particularly in the upper abdomen. Possible suggestions for improvement for the future could include more detailed explanations of the breath-holding and training young participants to hold their breath before the MRI scans, and recommending emptying of the bladder before going in the MRI scanner and a couple of hours of fasting before the MRI test. Clearly the utility of this mode of investigation is one to evaluate further. Constipation is a very common problem and whilst the vast majority of children and young persons will respond to simple treatment with stool softeners and bowel stimulant, there is a significant proportion of patients who do not show signs of improvement despite follow up. It is important to in these cases to evaluate the WGTT in order then to individualise therapy.

A non-contrast paediatric MRI scan to a single area of the body cost more than an X-ray (in the UK health system about 4 times more) so MRI cost and availability are issues to be taken into account. In the paediatric population, avoiding ionizing radiation exposure is a definite advantage of the new technique that should counterbalance the economic argument. The additional cross sectional imaging additional information on the bowel anatomy that can be gathered within the same scan is also an advantage of MRI. In terms of availability, it is true that MRI units are particularly busy with clinical routine. However, when new bowel imaging scans prove their worth they enter that clinical routine as it happened for MRI cholangiopancreatography and MRI enterography.

Here the primary aim of the study was simply to evaluate the feasibility of this test in children being looked after in a typical clinic set up. A full health economics evaluation needs to follow to evaluate the cost benefit analysis, taking into account not only the total duration of treatment and continued follow up within a paediatric clinic but also school days lost because of faecal incontinence, and the

impact of productivity for carers as they take time off to look after children with chronic constipation with overflow. The X-ray ROM protocol that we have copied for this initial study (3 daily doses of 24 markers) is a common one but it is not necessarily the only one used in past literature. The new MRI mini-capsules could be used in the future with other imaging protocols such as a single dose, single imaging time point (9) and also in adults, though further investigation and validation will be needed. A new multi-centre study of the mini-capsules in pediatric constipation was funded and is under way (Trial ID: ISRCTN42273449).

CONCLUSIONS

MAGIC was a first-in-child feasibility study of the new mini-capsule medical device (TransiCap™) to measure whole gut transit time in pediatric constipation using MRI. The study showed that the device met safety and performance objectives as per the intended purpose, with excellent feasibility and safety of using the new device in conjunction with MRI. The new device may represent a modern alternative to current X-ray ROM methods whilst not exposing the young patients to any ionizing radiation and at the same time providing high quality cross sectional images of the bowel. The clinical efficacy of using the mini-capsule test in clinical practice remains to be determined.

REFERENCES

- 1 Yong D, Beattie RM. Normal bowel habit and prevalence of constipation in primary school children. *Ambul Child Health* 1998;4:277-82.
- 2 Afzal NA, Tighe MP, Thomson MA. Constipation in children. *Ital J Pediatr* 2011;37.
- 3 van den Berg MM, Benninga MA, Di Lorenzo C Epidemiology of childhood constipation: A systematic review. *Am J Gastroenterol* 2006;101:2401-09.
- 4 Robin SG, Keller C, Zwiener R, et al. Prevalence of pediatric functional gastrointestinal disorders utilizing the Rome IV criteria. *J Pediatr* 2018;195:134-39.
- 5 Scarpato E, Kolacek S, Jojkic-Pavkov D, et al. Prevalence of functional gastrointestinal disorders in children and adolescents in the mediterranean region of Europe. *Clin Gastroenterol Hepatol* 2018;16:870-76.
- 6 Benninga MA, Nurko S, Faure C, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2016;150:1443-55.
- 7 Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2016;150:1456-68.
- 8 Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. *Gastroenterology* 2016;150:1262-79.
- 9 Sharif H, Devadason D, Abrehart N, et al. Imaging measurement of whole gut transit time in paediatric and adult functional gastrointestinal disorders: a systematic review and narrative synthesis. *Diagnostics* 2019;9.
- 10 Benninga MA, Tabbers MM, van Rijn RR. How to use a plain abdominal radiograph in children with functional defecation disorders. *Arch Dis Child Educ Pract Ed* 2016;101:187-93.
- 11 Hutson JM, Chase JW, Clarke MCC, et al. Slow-transit constipation in children: our experience. *Pediatr Surg Int* 2009;25:403-06.

- 12 Bongers MEJ, Tabbers MM, Benninga MA. Functional nonretentive fecal incontinence in children. *J Pediatr Gastroenterol Nutr* 2007;44:5-13.
- 13 Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr* 2014;58:258-74.
- 14 Miglioretti DL, Johnson E, Williams A, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. *JAMA Pediatr* 2013;167:700-07.
- 15 Shah DJ, Sachs RK, Wilson DJ. Radiation-induced cancer: a modern view. *Br J Radiol* 2012;85:E1166-E73.
- 16 Khalaf A, Hoad CL, Blackshaw E, et al. Simultaneous measurement of gastric emptying of a soup test meal using MRI and gamma scintigraphy. *Diagnostics* 2020;10,170.
- 17 Ziessman HA. Gastrointestinal transit assessment: role of scintigraphy: where are we now? Where are we going ? *Cuu Treat Options Gastro* 2016;14:452-60.
- 18 Knight LC. Update on GI radiopharmaceuticals and dosimetry estimates. *Semin Nucl Med* 2012;42:138-44.
- 19 Ward R, Carroll WD, Cunningham P, et al. Radiation dose from common radiological investigations and cumulative exposure in children with cystic fibrosis: an observational study from a single UK centre. *BMJ Open* 2017;7.
- 20 Rao SSC, Camilleri M, Hasler WL, et al. Evaluation of gastrointestinal transit in clinical practice: position paper of the American and European Neurogastroenterology and Motility Societies. *Neurogastroenterol Motil* 2011;23:8-23.
- 21 Metcalf AM, Phillips SF, Zinsmeister AR, et al. Simplified assessment of segmental colonic transit. *Gastroenterology* 1987;92:40-47.

- 22 Alyami J, Spiller RC, Marciani L. Magnetic resonance imaging to evaluate gastrointestinal function. *Neurogastroenterol Motil* 2015;27:1687-92.
- 23 Chaddock G, Lam C, Hoad CL, et al. Novel MRI tests of orocecal transit time and whole gut transit time: studies in normal subjects. *Neurogastroenterol Motil* 2014;26:205-14.
- 24 Lam C, Chaddock G, Marciani L, et al. Distinct abnormalities of small bowel and regional colonic volumes in subtypes of irritable bowel syndrome revealed by MRI. *Am J Gastroenterol* 2017;112:346-55.
- 25 Lam C, Chaddock G, Marciani L, et al. Colonic response to laxative ingestion as assessed by MRI differs in constipated irritable bowel syndrome compared to functional constipation. *Neurogastroenterol Motil* 2016;28:861-70.
- 26 Zhi M, Zhou Z, Chen H, et al. Clinical application of a gadolinium-based capsule as an MRI contrast agent in slow transit constipation diagnostics. *Neurogastroenterol Motil* 2017;29:e13020.
- 27 Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med* 2010;8,18.
- 28 Kim ER, Rhee PL. How to interpret a functional or motility test - colon transit study. *J Neurogastroenterol Motil* 2012;18:94-99.
- 29 van Reenen M, Janssen B, Oppe M, et al. EQ-5D-Y user guide: basic information on how to use the EQ-5D-Y instrument. Rotterdam: EuroQol Group; 2014.
- 30 Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res* 2010;19:875-86.
- 31 Eggers H, Brendel B, Duijndam A, et al. Dual-echo Dixon imaging with flexible choice of echo times. *Magn Reson Med* 2011;65:96-107.
- 32 Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat* 2005;4:287-91.

- 33 Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol* 2012;65:301-08.
- 34 Gutierrez C, Marco A, Nogales A, et al. Total and segmental colonic transit time and anorectal manometry in children with chronic idiopathic constipation. *J Pediatr Gastroenterol Nutr* 2002;35:31-38.
- 35 Zaslavsky C, da Silveira TR, Maguilnik I. Total and segmental colonic transit time with radio-opaque markers in adolescents with functional constipation. *J Pediatr Gastroenterol Nutr* 1998;27:138-42.
- 36 Bharucha AE, Pemberton JH, Locke GR. American Gastroenterological Association technical review on constipation. *Gastroenterology* 2013;144:218-38.
- 37 Knowles CH, Grossi U, Chapman M, et al. Surgery for constipation: systematic review and practice recommendations: Results I: Colonic resection. *Colorectal Dis* 2017;19:17-36.

FIGURES AND SUPPLEMENTARY MATERIAL LEGENDS

Figure 1. CONSORT diagram for the study.

Figure 2. Mini-capsule MRI device markers pictured near a 20 pence coin (21 mm in diameter) for size comparison.

Figure 3. Whole gut transit time (mean and SD) for young patients with constipation (n=16) and healthy controls (n=19). * $P < 0.0001$.

Figure 4. (A) A coronal, derived in-phase minus out-of-phase MRI image of a 7 year old patient participant, showing in the sigmoid/rectum 6 mini-capsules with positive signal against the chime. The mini-capsules are indicated by the white arrows in the corresponding expanded area on the right hand side. (B) An axial, derived in-phase minus out-of-phase MRI image of the same patient participant, showing in the descending colon 2 mini-capsules with positive signal against the chyme. The mini-capsules are indicated by the white arrows in the corresponding expanded area on the right hand side.

Supplemental Digital Content 1 – Suppl CONSORT checklist. CONSORT checklist of reported trial information.

Supplemental Digital Content 2 – Suppl Text Patient Involvement. Patient and Public Involvement and Engagement.

Supplemental Digital Content 3 – Suppl Table 1. MRI sequence parameters.

Supplemental Digital Content 4 – Suppl Table 2. Individual participants' characteristics.

Supplemental Digital Content 5 – Suppl Figure 1. Young participants' EQ-VAS scores before and after undergoing the mini-capsules ingestion and MRI scan procedures. The values shown are mean±standard deviation. Wilcoxon's $P = 0.54$ the patients and $P = 0.55$ for the healthy controls comparing before and after the study procedures respectively.

MAGIC study CONSORT Diagram



Fig 1

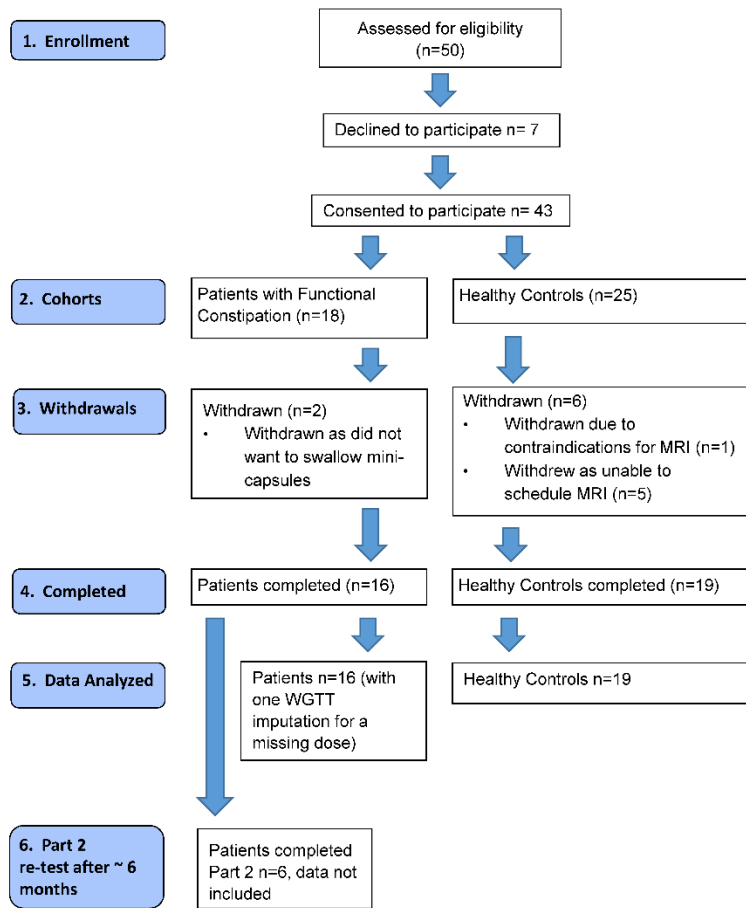


Fig 2



Fig 3

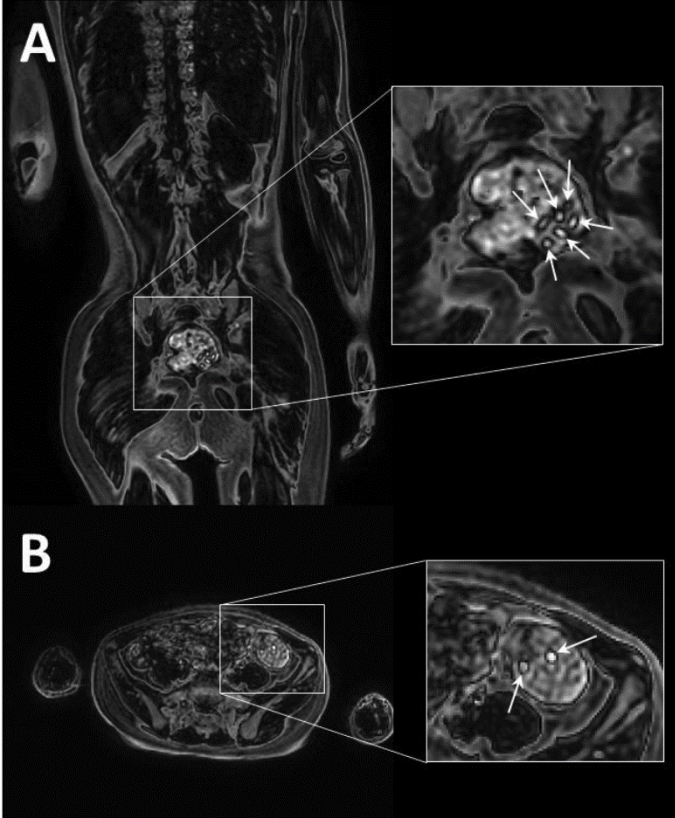
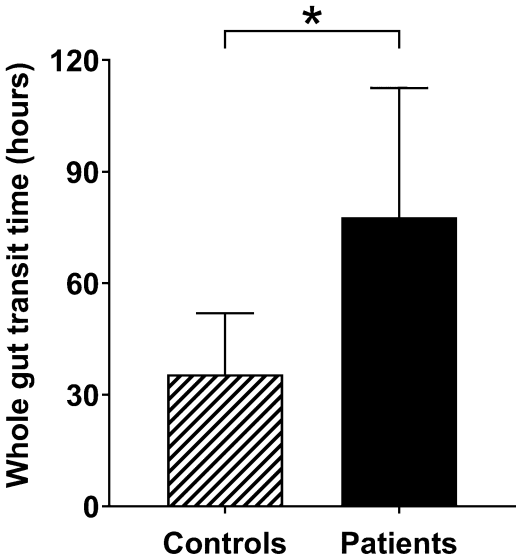
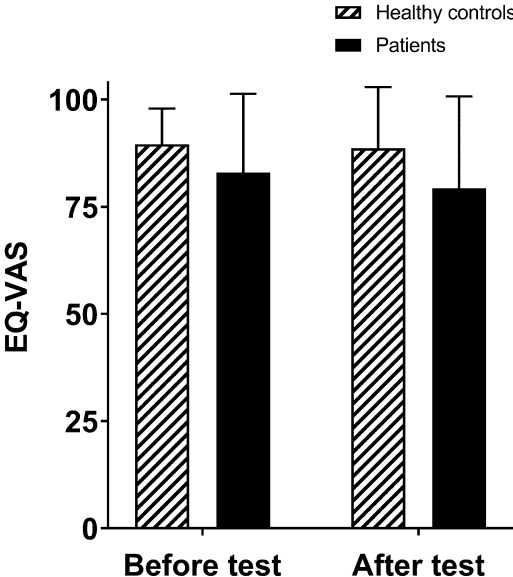


Fig 4



Supplemental Fig 1



Supplemental Digital Content 1: CONSORT checklist



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Not applicable
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4, 6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	11
Sample size	7a	How sample size was determined	Not applicable
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Not applicable
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Not applicable
Allocation concealment	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Not applicable

mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Not applicable
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Not applicable
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8-9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8-9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9, Suppl Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9-11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Not applicable
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Title page

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Supplemental Digital Content 2: Supplemental Text

Patient and Public Involvement and Engagement



The patient and public involvement and engagement (PPI/E) in this project was recurrent and meaningful since inception. We co-designed and co-produced the Transicap™ mini-capsules and the packaging, with the Young Person Advisory Group (YPAG) working in person with the designers at Renfrew Group International (Abbey Meadows, Leicester, UK) and the technology consultants from the NIHR from the Enteric Health Technology Cooperative. Together with the YPAG members we designed the MAGIC project website www.gastrointestinalmri.org.uk, we scripted, produced and narrated two novel, animated pediatric video info sheets, now Ethics approved and on YouTube <https://youtu.be/luvIutiTvr4> and <https://youtu.be/w5O8lhZqEs8>.



We wrote age-appropriate Ethics information sheets (praised by the Ethics Committee) and presented together at the podium of the Nottingham Pediatric Research Showcase 2018 (winning 2nd best oral presentation) and at the UK Clinical Research Facilities conference 2019.

We continue working with the YPAG and some of their comments on the progress of the co-production can be seen on this video edited from a round-table discussion about the YPAG's participation in the MAGIC programme <https://www.youtube.com/watch?v=tPRt75xdq2k>.



Supplemental Digital Content 3: Table 1

SUPPLEMENTAL TABLE 1. MRI sequence parameters

MRI sequence	3D T1 weighted TFE *	
	Axial	Coronal
Image orientation	Axial	Coronal
Field of View	350 mm (RL) × 280 mm (AP)	348 mm (RL) × 250 mm (HF)
Image stacks †	5 ‡	6 §
Slices per stack	33	27
Length of breath hold per stack	12.3 s	13.5 s
SENSE acceleration factor	2	2
Signal averaging	1	1
Flip angle	20°	20°
Repetition time TR	10 ms	10 ms
Echo times TE ₁ / TE ₂	1.32ms / 2.2 ms	1.32ms / 2.2 ms
Reconstruction matrix	400 × 400	400 × 400
Acquired image resolution	1.8 mm × 1.8 mm × 4.4 mm	1.8 mm × 1.8 mm × 4.4 mm
Reconstructed image resolution	0.88 mm × 0.88 mm × 2.2 mm	0.87 mm × 0.87 mm × 2.2 mm

* mDIXON sequence on Philips MRI scanner used

† The image stacks (packages) were acquired with no gaps between them, reconstructed independently and then put back together as a full section.

‡ The scanner table moved between each stack

§ The scanner table moved between a 'top' and a 'bottom' sections and then 3 stacks were acquired at each of these two table positions.

Supplemental Digital Content 4: Table 2

SUPPLEMENTAL TABLE 2. Individual participants' characteristics

Participant number	Patient or healthy control	Age	Gender	Weight (kg)	Height (m)	BMI (kg/m ²)
1	Healthy control	16	Female	63	1.65	23.0
2	Healthy control	17	Female	65	1.63	24.5
3	Patient	8	Male	60	1.30	35.5
4	Healthy control	11	Male	48	1.60	18.7
5	Healthy control	14	Male	52	1.60	20.3
6	Healthy control	16	Female	63	1.70	21.8
7	Patient	11	Male	99	1.67	35.5
8	Healthy control	17	Male	72	1.79	22.5
9	Healthy control	17	Female	70	1.70	24.2
10	Healthy control	15	Female	58	1.59	22.8
11	Patient	10	Female	41	1.05	37.1
12	Healthy control	18	Male	85	1.69	29.8
13	Healthy control	18	Male	91	1.75	29.7
14	Healthy control	17	Male	70	1.73	23.4
15	Healthy control	18	Male	106	1.67	38.0
16	Healthy control	16	Female	59	1.71	20.2
17	Patient	13	Female	60	1.64	22.3
18	Patient	7	Male	25	1.28	15.5
19	Healthy control	14	Female	55	1.60	21.4
20	Patient	8	Female	48	1.30	28.4
21	Healthy control	17	Female	57	1.52	24.7
22	Healthy control	17	Male	80	1.85	23.4
23	Healthy control	15	Female	97	1.79	30.3
24	Healthy control	18	Female	57	1.63	21.5
25	Patient	10	Male	34	1.20	23.6
26	Patient	16	Female	68	1.55	28.3
27	Patient	10	Female	22	1.28	13.2
28	Patient	12	Male	34	1.40	17.3
29	Patient	9	Female	35	1.20	24.3
30	Patient	18	Female	52	1.25	33.3
31	Patient	13	Male	60	1.54	25.3
32	Patient	13	Male	42	1.54	17.7
33	Patient	14	Female	63	1.64	23.4
34	Patient	7	Female	23	1.20	15.9
35	Healthy control	10	Female	42	1.45	20.0