



# Constipation in children and young people: Evidence Update June 2012

A summary of selected new evidence relevant to NICE clinical guideline 99 'Diagnosis and management of idiopathic childhood constipation in primary and secondary care' (2010)



Evidence Update 20

Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant guidance, available from the NHS Evidence topic page for constipation.

# Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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# Introduction

This Evidence Update identifies new evidence that is relevant to and may have a potential impact on the following reference guidance:

# **O** <sup>1</sup><u>Constipation in children and young people</u>. NICE clinical guideline 99 (2010)

A search was conducted for new evidence published between 21 July 2009 and 3 February 2012. A total of 674 pieces of evidence were identified and assessed, of which eight were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence which will be considered when guidance is reviewed.

## Feedback

If you have any comments you would like to make on this Evidence Update, please email <u>contactus@evidence.nhs.uk</u>

<sup>&</sup>lt;sup>1</sup> NICE-accredited guidance is denoted by the Accreditation Mark 9

# **Key points**

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the reference guidance.

	Potential impact on guidance	
Key point	Yes	No
History taking and physical examination		
<ul> <li>Limited recent evidence is consistent with the message in current guidance that early identification and treatment can improve outcomes.</li> </ul>		$\checkmark$
Clinical management		
<ul> <li>Evidence suggests similar efficacy with polyethylene glycol (PEG) 3350 plus electrolytes<sup>2</sup> versus rectal enemas in faecal disimpaction.</li> </ul>		$\checkmark$
• Evidence suggests similar efficacy with PEG (unspecified) versus rectal enemas in maintenance therapy for constipation, although enemas were negatively perceived by some children.		$\checkmark$
• Evidence suggests that PEG 4000 <sup>3</sup> is more effective than milk of magnesia in maintenance therapy for constipation.		$\checkmark$
Diet and lifestyle		
<ul> <li>A limited and heterogeneous evidence base currently prevents firm conclusions being made about the role of probiotics in constipation management.</li> </ul>		$\checkmark$
• Limited recent evidence for dietary interventions suggests that fibre can improve constipation but raising fluid intake above normal has no effect.		$\checkmark$
Psychological interventions		
• Limited recent evidence suggests no benefit of interventions involving a child psychiatrist or psychologist in constipation.		$\checkmark$

<sup>&</sup>lt;sup>2</sup> At the time of publication of this Evidence Update, Movicol Paediatric Plain is the only macrogol licensed for children under 12 years that includes electrolytes. It does not have UK marketing authorisation for use in faecal impaction in children under 5 years, or for chronic constipation in children under 2 years. Informed consent should be obtained and documented. Movicol Paediatric Plain is the only macrogol licensed for children under 12 years that is also unflavoured.

<sup>&</sup>lt;sup>3</sup> PEG 4000 is not recommended by current guidance and at the time of publication of this Evidence Update, did not have UK marketing authorisation for use in constipation in children under 8 years.

## 1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Section headings are taken from the reference guidance.

## 1.1 History-taking and physical examination

### Prognosis and prognostic factors

Recommendations in NICE clinical guideline (CG) 99 do not currently discuss prognosis.

A systematic review by **Pijpers et al. (2010)** of 14 prospective, observational studies (six in a general paediatric department, seven in a paediatric gastroenterology department, one setting not stated; 1752 patients in total) examined prognosis and prognostic factors of childhood constipation. The age of participants was provided as a mean in nine studies (72.2 months, range 21.0–188.8 months) and a median in five studies (66.0 months, range 3.5–100.8 months). The primary outcomes at the end of follow-up used by the review authors were: recovery from or no constipation (as defined by individual studies) with no laxative use; and successful outcome or no constipation (as defined by individual studies) regardless of laxative use.

For prognosis data, although the authors acknowledged substantial heterogeneity among the included studies (for example, differing populations, definitions of constipation, and outcomes) a pooled analysis was conducted using stratification. After 6–12 months follow-up, a mean of 49.3% (standard deviation [SD] 11.8%) of children had recovered and been taken off laxatives (n = 1253, eight studies) and 60.6% (SD 19.2%) of children were free from complaints regardless of laxative use (n = 1535, 11 studies). A non-significant difference (p = 0.11) in mean successful outcome regardless of laxative use was observed between studies conducted in paediatric gastroenterology departments (74.2% [SD 14.5%] success, n = 979, seven studies; mean follow-up 28.8 months) and those performed in general paediatric departments (57.8% [SD 19.5%] success, n = 643, six studies; mean follow-up 13.0 months).

Data on prognostic factors could not be pooled therefore a best evidence synthesis was conducted. 'Strong evidence' (consistent findings in at least two high quality studies) indicated that recovery from constipation was not associated with either a family history of childhood constipation (two studies, n = 465; numerical data not stated) or defecation frequency (two studies, n = 216; numerical data not stated). 'Limited evidence' (findings of one high quality cohort) suggested that recovery was associated with both symptom duration of less than 3 months before presentation and treatment duration of less than 2 months before presentation (n=47; numerical data not stated). Many other potential indicators of prognosis were examined by the review but evidence was conflicting, non-significant or low quality.

Conclusions from the prognosis evidence are limited by the heterogeneity and quality of the included studies (only three studies included in the review were deemed by the authors to be of high quality), and the absence of any information about the interventions used in the studies. Any potential association of improved prognosis with care in specialist versus general paediatric settings would require further investigation.

With regard to prognostic factors, the limited evidence found for an association between early intervention and improved recovery is consistent with the statement in the introduction to <u>NICE CG99</u> that early identification and effective treatment can improve outcomes; however overall, this evidence is unlikely to affect current guidance.

**Key reference** 

Pijpers MAM, Bongers MEJ, Benninga MA et al. (2010) <u>Functional constipation in children: a systematic</u> review on prognosis and predictive factors. Journal of Pediatric Gastroenterology and Nutrition 50: 256– 268

## 1.2 Digital rectal examination

No new key evidence was found for this section.

### 1.3 Clinical investigations

No new key evidence was found for this section.

## 1.4 Clinical management

### **Polyethylene glycol**

#### Faecal disimpaction

For faecal disimpaction, <u>NICE CG99</u> currently recommends first-line laxative treatment with polyethylene glycol (PEG) 3350 plus electrolytes, with subsequent addition of stimulant and osmotic laxatives if required, and only advises enemas if all oral medications have failed.

A randomised controlled trial (RCT) by <u>Bekkali et al. (2009)</u> compared disimpaction with rectal enemas versus oral laxatives in children aged 4–16 years (mean age 7.5 years, n = 90) with severe rectal faecal impaction in a tertiary care hospital in the Netherlands. Children were randomised to daily rectal enemas (dioctylsulfosuccinate sodium 60 ml for children < 6 years, 120 ml for children  $\ge$  6 years), or oral PEG 3350 plus electrolytes (1.5 g/kg), for 6 consecutive days. Maintenance treatment with oral PEG 3350 plus electrolytes 0.5 g/kg/day was then commenced in both groups.

No difference in the primary outcome of successful disimpaction was observed between the enema (80%) and PEG (68%; p = 0.28) groups at follow-up 2 weeks after disimpaction. These data are unlikely to affect current recommendations in <u>NICE CG99</u> for first-line treatment of impaction with PEG 3350 plus electrolytes.

The PEG used in the study was Movicol Paediatric Plain (also recommended in NICE CG99) which is the only macrogol licensed for children under 12 years that includes electrolytes. It does not have UK marketing authorisation for use in faecal impaction in children under 5 years, or for chronic constipation in children under 2 years. Informed consent should be obtained and documented. Movicol Paediatric Plain is the only macrogol licensed for children under 12 years that is also unflavoured.

#### **Key reference**

Bekkali NLH, van den Berg MM, Dijkgraaf MGW et al. (2009) <u>Rectal fecal impaction treatment in</u> <u>childhood constipation: enemas versus high doses oral PEG</u>. Pediatrics 124: e1108-e1115

#### Maintenance therapy

For ongoing treatment or maintenance therapy following disimpaction, <u>NICE CG99</u> currently recommends a regimen of oral laxatives, beginning with PEG 3350 plus electrolytes with subsequent addition of stimulant and osmotic laxatives if required. Enemas are not recommended for maintenance.

An RCT by **Bongers et al. (2009)** examined maintenance treatment with rectal enemas compared with oral laxatives in children aged 8–18 years (mean age 11 years, n = 100) in a tertiary care out-patient clinic in the Netherlands. Children entering the study had a history of functional constipation for at least 2 years that was refractory to conventional treatment with oral laxatives. Participants were first disimpacted by enema prior to starting the trial and were

then randomised to oral PEG (0.5 g/kg, increased if required to a maximum of 1.5 g/kg; type of PEG not specified), or oral PEG plus three enemas per week (which after 3 months was reduced by one enema per week every 3 months).

A primary outcome of overall treatment success (defined as greater than or equal to three bowel movements per week and less than one faecal incontinence episode per week, irrespective of laxative use) was no different between the enema group (47.1% success) and the PEG-only group (36.1% success; p = 0.67) after 52 weeks. A questionnaire filled out by children in the enema group after 1 year indicated that 15% perceived an enema as 'very to extremely terrible' and 11% as 'quite terrible' (although the authors stated that the remaining 74% 'found it no problem at all'). The PEG group were not asked to complete a questionnaire.

It should be noted that during the study, initial disimpaction was performed with enemas, and PEG was administered without electrolytes; neither of these practices are recommended in <u>NICE CG99</u>. Although the evidence suggests a similar efficacy of enemas and laxatives, the negative perception of enemas by some children and the additional burden of enema treatment mean that current recommendations in NICE CG99 for maintenance therapy with PEG are unlikely to be affected.

Movicol Paediatric Plain is the only macrogol licensed for children under 12 years that includes electrolytes. It does not have UK marketing authorisation for use in faecal impaction in children under 5 years, or for chronic constipation in children under 2 years. Informed consent should be obtained and documented. Movicol Paediatric Plain is the only macrogol licensed for children under 12 years that is also unflavoured.

An RCT by <u>Ratanamongkol et al. (2009)</u> compared maintenance treatment with PEG 4000 without electrolytes versus milk of magnesia (MOM) in children aged 1–4 years (mean age 2.6 years, n = 94) with at least one month of functional constipation attending a paediatric outpatient clinic in Thailand. PEG 4000 is not recommended by current guidance and at the time of publication of this Evidence Update, did not have UK marketing authorisation for use in constipation in children under 8 years.

All children were subject to a run-in phase of 1 week during which any faecal impaction was treated with a daily phosphate enema for 3 days. During the 4-week treatment phase children were randomised to PEG 4000 without electrolytes (0.5 g/kg/day) or a MOM suspension (0.5 ml/kg/day; dosages in both arms could be adjusted by parents with the aim of one or two soft stools per day).

The primary outcome of improvement rate (defined as the proportion of patients with three or more bowel movements per week, two or fewer episodes of faecal incontinence per month, and no painful defecation, with or without laxatives) after 4 weeks was significantly higher in the PEG group (89%) than in the MOM group (60%, p = 0.001).

Limitations of the study included the difference between intervention formulations preventing full blinding, the short follow-up period, a significant difference in compliance rates between the PEG and MOM groups (89% vs 72% respectively, p = 0.041; the authors noted that unpleasant taste was frequently reported with MOM), and the non-Western setting that may limit external validity to the UK. It should also be noted that during the study, initial disimpaction was performed with enemas, and electrolytes were not co-administered with PEG, both of which deviate from recommendations in <u>NICE CG99</u>.

This evidence reinforces current recommendations in NICE CG99 for maintenance therapy with PEG. The success with PEG in a young age group suggests the value of early intervention, but the short follow-up may give a misleading indication that medication can be stopped early in these patients.

#### **Key references**

Bongers MEJ, van den Berg MM, Reitsma JB et al. (2009) <u>A randomized controlled trial of enemas in</u> <u>combination with oral laxative therapy for children with chronic constipation</u>. Clinical Gastroenterology and Hepatology: the official clinical practice journal of the American Gastroenterological Association 7: 1069–1074

Ratanamongkol P, Lertmaharit S, Jongpiputvanich S (2009) <u>Polyethylene glycol 4000 without</u> <u>electrolytes versus milk of magnesia for the treatment of functional constipation in infants and young</u> <u>children: a randomized controlled trial</u>. Asian Biomedicine 3: 391–399

## 1.5 Diet and lifestyle

### **Probiotics**

<u>NICE CG99</u> does not currently recommend probiotics for idiopathic constipation. A systematic review and two RCTs recently examined probiotics in childhood constipation.

<u>Chmielewska and Szajewska (2010)</u> conducted a systematic review (following Cochrane methodology) to investigate probiotics for functional constipation in adults and children. The review analysed a total of five RCTs; three in adults (n = 266) and two in children (n = 111). The first of the RCTs in children aged 2–16 years (n = 84) found no effect of twice daily oral administration of  $2 \times 10^9$  colony-forming units (CFU) of *Lactobacillus rhamnosus* GG plus lactulose versus lactulose alone. The second RCT in children below the age of 10 years (n = 27) found some evidence of a treatment effect with *Lactobacillus casei rhamnosus* Lcr35 (8 x  $10^8$  CFU) versus placebo (treatment success as defined by the study of 78% vs 11% respectively, relative risk = 7, 95% confidence interval 1.1 to 45), although the sample size and wide confidence interval prevent firm conclusions being drawn.

The review authors stated that limitations of the data (such as potential publication bias, methodological issues with the included trials, small sample sizes and varying probiotic strains) prevented conclusions about the comparative efficacy of the probiotic strains. The authors concluded that published data do not currently support probiotics in the treatment of constipation and their use should be considered investigational.

Two RCTs published after the search dates of the above review also examined probiotics in constipation.

A double-blind RCT by <u>Coccorullo et al. (2010)</u> investigated *Lactobacillus reuteri* in infants at least 6 months old (mean age 8 months, n = 44) with functional chronic constipation referred to a paediatric gastrointestinal unit in Italy. Infants were randomised to a probiotic supplement containing  $10^8$  CFUs of *L reuteri* once a day for 8 weeks, or an identical placebo without probiotic. No laxatives were allowed during the study, but a glycerine suppository could be given in the absence of defecation for more than 5 days. There was no difference identified in diet between the two groups.

Primary outcomes were defecation frequency, stool consistency, and inconsolable crying episodes. Infants receiving probiotic had more bowel movements at week 2 (p = 0.042), week 4 (p = 0.008) and week 8 (p = 0.027) versus the placebo group (actual defecation frequency values not stated). However no differences between the groups were seen at any follow-up for stool consistency or inconsolable crying.

The study was conducted in a small number of very young infants with a short follow-up, which limits conclusions. The authors summarised that possible links between constipation and changes in intestinal flora need further evaluation.

A double-blind, multi-centre RCT by <u>Tabbers et al. (2011)</u> examined a fermented milk product containing *Bifidobacterium lactis* in constipated children aged 3–16 years (mean age 7 years; n = 159) in three academic hospitals in the Netherlands and Poland, and 12 Dutch non-academic hospitals. The first week of the study was used to obtain baseline values and all patients were then given enemas over a 3-day run-in period before randomisation to receive pots of a fermented milk product (Activia) containing  $4.25 \times 10^9$  CFU of *B lactis*, or an identical control pot without probiotic. The pots were consumed in the morning and evening for 3 weeks and no other fermented dairy products or yoghurts were allowed during the study. Patients could take 5 mg bisacodyl if they had not defecated for 3 or more days.

The primary endpoint of change in stool frequency from baseline to the end of the 3-week intervention period showed no statistical difference between the probiotic and control groups (increase of 2.9 vs 2.6 episodes per week respectively, p = 0.35).

Limitations of the evidence included the use of enemas immediately prior to the treatment phase which may have affected results, not analysing the diet of participants, the short followup, and conducting the study in secondary and tertiary centres which may see more severe cases of constipation. Additionally, the pots containing probiotic also contained a number of other bacterial strains which could confound results. There was also more rescue laxative use in the control group but this was non-significant. It should be noted that this study was sponsored by the manufacturer of the probiotic product.

Overall, evidence is limited and a robust assessment of probiotics in the management of constipation is currently not possible; these data therefore are unlikely to affect <u>NICE CG99</u>. Studies published to date exhibit considerable heterogeneity in terms of setting, population, interventions (type and quantity of probiotic), outcomes and design. Larger, well-designed studies with consistent interventions and outcomes, and longer follow-up periods, are needed.

#### **Key references**

Chmielewska A, Szajewska H (2010) <u>Systematic review of randomised controlled trials: probiotics for</u> <u>functional constipation</u>. World Journal of Gastroenterology 16: 69–75

Coccorullo P, Strisciuglio C, Martinelli M et al. (2010) <u>Lactobacillus reuteri (DSM 17938) in infants with</u> <u>functional chronic constipation: a double-blind, randomized, placebo-controlled study</u>. The Journal of Pediatrics 157: 598-602

Tabbers MM, Chmielewska A, Roseboom MG et al. (2011) <u>Fermented milk containing Bifidobacterium</u> <u>lactis DN-173 010 in childhood constipation: a randomized, double-blind, controlled trial</u>. Pediatrics 127: e1392–e1399

#### Non-pharmacological treatments

<u>NICE CG99</u> currently states that dietary interventions alone should not be used as first-line treatment for idiopathic constipation and that a balanced diet should include adequate fluid intake and adequate fibre (from high-fibre foods such as fruit, vegetables and wholegrain cereals; unprocessed bran is not recommended).

A systematic review of nine RCTs by <u>Tabbers et al. (2011)</u> examined non-pharmacological treatments for childhood constipation including fibre (three RCTs, n = 184), prebiotics and probiotics (three RCTs, n = 167), and fluid (one RCT, n = 108). Two RCTs of behavioural therapy were also assessed in this review (see section 1.6 for discussion of this evidence). Although part of the initial search, no studies were found that examined the effect of physical movement, multidisciplinary treatment or alternative medicine.

All trials were hospital-based; three were performed in a general paediatric department and six in a paediatric gastroenterology department. Heterogeneity among the included studies prevented pooling of data.

Of the three studies of fibre, one (n = 31) showed a significant effect with glucomannan compared with placebo for a number of outcome measures (for example, 19% of patients with defecation frequency < 3 times per week vs 52% in the control group; p < 0.05), although the small number of patients prevents firm conclusions. There were limited or no significant

differences from control in the other two studies of fibre. No effect was seen with raised fluid intake above normal, prebiotics or probiotics.

An inclusion criterion of the review stated only that 'a definition of constipation was provided' by each study, therefore interpreting the efficacy of these treatments in the context of the wide spectrum of severity seen with constipation is difficult. Further limitations included the authors' assessment that four of the included studies were of low quality, and that the studies were 'mainly underpowered'.

The review highlights an absence of large, good-quality studies for non-pharmacological interventions for childhood constipation, including a lack of data in primary care. The limited evidence from this review is consistent with current recommendations in <u>NICE CG99</u> for diet. It should be noted that although there was no evidence for raising fluid intake above normal, children with poor fluid intake should be encouraged to raise their intake of water to an adequate level (in line with the table of recommended water intake from food and drinks in current guidance). Inadequate fluid intake is one of the most frequent causes of chronic constipation (<u>Arnaud 2003</u>) and additional water intake can increase stool frequency when a child's voluntary fluid consumption is lower-than-normal for their age and activity level (<u>Young et al. 1998</u>).

#### **Key reference**

Tabbers MM, Boluyt N, Berger MY et al. (2011) <u>Nonpharmacologic treatments for childhood</u> <u>constipation: systematic review</u>. Pediatrics 128: 753-761

#### **Supporting references**

Arnaud MJ (2003) <u>Mild dehydration: a risk factor of constipation?</u> European Journal of Clinical Nutrition 57: S88–95

Young RJ, Beerman LE, Vanderhoof JA (1998) <u>Increasing oral fluid in chronic constipation in children</u>. Gastroenterology Nursing 21: 156–61

## 1.6 Psychological interventions

The systematic review by <u>Tabbers et al. (2011)</u> (see 'Non-pharmacological treatments' in section 1.5 for details) included two RCTs assessing behavioural interventions. A study in 47 children of psychotherapy with a child psychiatrist versus behaviour modification techniques did not include sufficient details for evaluation of the results. A second study of 134 children, considered to be high quality by the authors, showed no significant difference in success rate (as defined by the study) between behavioural therapy with a child psychologist versus conventional treatment. These findings are consistent with the recommendation in <u>NICE CG99</u> not to routinely refer children and young people to a psychologist or child and adolescent mental health services unless the child or young person has been specifically identified as likely to benefit from receiving a psychological intervention. The <u>full version of NICE CG99</u> states that interventions of this type may be beneficial where there is psychological distress related to the symptoms of constipation and/or family difficulties that maintain or exacerbate the constipation.

## 1.7 Antegrade colonic enema procedure

No new key evidence was found for this section.

### 1.8 Information and support

No new key evidence was found for this section.

# 2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

### **Diet and lifestyle**

- Probiotics for idiopathic constipation in children
- Non-pharmacological treatments for constipation in children

Further evidence uncertainties for constipation in children and young people can be found in the <u>UK DUETs database</u> and in the <u>NICE research recommendations database</u>.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

# **Appendix A: Methodology**

## Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

• <u>Constipation in children and young people</u>. NICE clinical guideline 99 (2010)

### Searches

The literature was searched to identify systematic reviews and RCTs relevant to the scope. Searches were conducted of the following databases, covering the dates 21 July 2009 (the end of the search period of the most recent Annual Evidence Update) to 3 February 2012:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)
- PsycINFO

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network <u>search filters for RCTs</u>, <u>systematic reviews and diagnostic studies</u>.

Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from <u>contactus@evidence.nhs.uk</u>

### Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp INFANT/
2	infant?.tw.
3	(newborn\$ or neonate\$).tw.
4	(baby or babies).tw.
5	exp Child/
6	(child? or children?).tw.
7	ADOLESCENT/
8	(adolescen\$ or teenager\$).tw.
9	or/1-8
10	CONSTIPATION/
11	constipat\$.tw.
12	((difficult\$ or delay\$ or irregular\$ or infrequen\$ or pain\$) adj3 (defecat\$ or stool\$ or faeces or feces or bowel movement\$)).tw.
13	Fecal Impaction/
14	((feces or faeces or fecal or faecal) adj3 (impaction or impacted)).tw.

15	(f?ecalith? or coprolith? or stercolith?).tw.
16	coprostasis.tw.
17	obstipation.tw.
18	Fecal incontinence/
19	Encopresis/
20	(f?ecal incontinence or soiling or encopresis).tw.
21	Megacolon/
22	(megacolon or megarectum).tw.
23	or/10-22
24	and/9,23
25	(2009072\$ or 200908\$ or 200909\$ or 20091\$ or 2010\$ or 2011\$ or 2012\$).dc.
26	24 and 25
27	limit 26 to english language

#### Figure 1 Flow chart of the evidence selection process



EUAG - Evidence Update Advisory Group

# Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

## Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

## Dr Graham Clayden – Chair

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