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BMJ Paediatrics Open

Using laxatives and/or enemas to accelerate the diagnosis in children presenting with acute abdominal pain: a randomized controlled trial study protocol

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2018-000341
Article Type:	Protocol
Date Submitted by the Author:	14-Jul-2018
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Keywords:	Gastroenterology, Paediatric Surgery

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3 1 **Using laxatives and/or enemas to accelerate the diagnosis in children presenting with**
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5 2 **acute abdominal pain: a randomized controlled trial study protocol**
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24 ABSTRACT

25 **Introduction:** Many children with acute abdominal pain and suspicion of appendicitis are
26 diagnosed with constipation. Nevertheless, it can be difficult to differentiate between acute
27 constipation and acute appendicitis because of similar symptoms and lack of diagnostic
28 criteria. Consequently, constipation is often missed despite repeated consultations at the
29 emergency department. We hypothesize that the diagnostic process can be improved and
30 adequate treatment accelerated by supporting fecal evacuation in children with acute
31 abdominal pain.

32 **Methods and analysis:** An unblinded randomized controlled trial including children between
33 5 and 18 years old with acute abdominal pain and suspicion of acute appendicitis. Children
34 who do not receive a diagnosis after the first consultation and who need to return for a second
35 consultation will be randomized. The intervention group will receive laxatives and enemas,
36 while the control group will receive no medication. If, after the second consultation, still no
37 diagnosis is established and a third consultation is needed, then the intervention group will
38 receive only laxatives and the control group will again not receive medication. The primary
39 outcome will be the differences in abdominal pain scores obtained with FACES[®] Pain Rating
40 Scale and the Visual Analogue Scale at first, second, and possibly third consultation. The
41 secondary outcome will be the number of consultations needed to reach final diagnosis.

42 **Ethics and dissemination:** Laxatives and enemas have proven to be safe and effective
43 treatments for constipation in children. Adverse events are therefore not expect, however,
44 should they occur, then the child concerned shall be properly followed and treated until the
45 event is over. The local Medical Research Ethics Committee approved of this study and
46 waived the otherwise mandatory insurance for human test subjects.

47 **Trial registration:** Dutch trial register (CCMO): NL44710.042.12. European trial registration
48 (EudraCT): 2013-000498-56.

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Keywords: constipation; acute appendicitis; diagnostic method; randomized controlled trial

Confidential: For Review Only

75 INTRODUCTION

76 Acute abdominal pain is the third-leading cause of visits to emergency departments by
77 children under 15 years, and is associated with high costs, especially when hospitalization is
78 required [1]. For instance, in the United States of America, approximately 900.000 children
79 visit an emergency department with acute abdominal pain and suspicion of appendicitis
80 annually [2]. Nevertheless, only 30% of these children are eventually diagnosed with acute
81 appendicitis [3], while constipation is diagnosed in 21% of girls and 18% of boys with acute
82 abdominal pain [3].

83 It can be difficult to differentiate between constipation with an acute presentation and acute
84 appendicitis, because the symptoms of constipation sometimes mimic those of acute
85 appendicitis. Besides, there are no diagnostic criteria for acute constipation, unlike the Rome
86 IV criteria for diagnosing chronic constipation [4]. In clinical practice, in order to exclude or
87 confirm constipation, most physicians limit their questioning of patients presenting with acute
88 abdominal pain on whether their bowel habits have changed recently or whether they are
89 “normal”, even though it is known that many people pay scarce attention to their bowel habits
90 and/or are unaware of what “normal” stool frequencies or consistencies are [5,6]. In addition,
91 to diagnose constipation physicians often avoid performing digital rectal examinations in
92 children because of discomfort or fear on the part of the patients, and their own lack of
93 adequate training or experience [7]. Moreover, additional investigations, such as abdominal
94 X-rays to diagnose children with constipation, was strongly criticized in a number of studies
95 [8,9,10]. Because the abovementioned methods to diagnose constipation are often not
96 performed or carried out insufficiently, an extra consultation the following day can be
97 recommended to determine whether the symptoms improve or worsen. Nonetheless, even
98 after extra consultations many children are diagnosed with non-specific abdominal pain
99 instead of constipation [11]. These misdiagnoses could result in chronic abdominal pain,

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3 100 because the underlying cause, constipation, is left untreated [12,13]. We believe therefore that
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5 101 a better method is needed to either confirm or exclude constipation in children presenting with
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7 102 acute abdominal pain at the emergency department.
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9 103 Laxatives and/or enemas are standard treatment for fecal disimpaction in children with
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11 104 constipation [9]. This combination of medications can provide a rapid relief of symptoms and
12
13 105 has proven to be safe and adverse events rarely occur [9,14,15,16]. We hypothesize that by
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15 106 supporting fecal evacuation with laxatives and enemas in children suffering acute abdominal
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17 107 pain, but who were not diagnosed after first consultation, the diagnostic process could be
18
19 108 accelerated. In case a child does indeed suffer from constipation, laxatives and/or enemas lead
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21 109 to rapid reduction of pain. In addition to the positive effect this has on the child's condition,
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23 110 the reduction of pain also points towards constipation as the cause of the abdominal pain. If a
24
25 111 child does not suffer from constipation then laxatives and/or enemas will not provide
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27 112 significant relief of symptoms, indicating to the physician that constipation is less likely to be
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29 113 the cause of the abdominal pain.
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33 114 Our objective with this randomized controlled trial is to study whether supporting fecal
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35 115 evacuation in children with acute abdominal pain, but without a diagnosis after the first
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37 116 consultation at the emergency department, could accelerate and improve the diagnostic
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39 117 process.
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124 **METHODS AND ANALYSIS**

125 **Study design and setting**

126 An unblinded randomized controlled trial at the emergency department of an academic
127 hospital, the University Medical Center Groningen, in the Netherlands.

128

129 **Participants**

130 We intend to include children between 5 and 18 years who are referred to the emergency
131 department with acute abdominal pain and suspicion of acute appendicitis. Exclusion criteria
132 are pregnancy and severe co-morbidity like malignancy, recent abdominal surgery, or known
133 inflammatory bowel disease.

134

135 **Recruitment**

136 Children presenting at the emergency department with suspicion of acute appendicitis will be
137 approached to participate in the study. First, the researcher will explain the study protocol to
138 the parent(s)/legal guardian and the child. Subsequently, we will hand them the study
139 brochure that was adapted so as to be readily understood by children. If, after having had
140 some time to read the brochure and the opportunity to ask questions, the parent(s)/legal
141 guardian and/or the child agree to participate in the study, we will ask them to sign the
142 consent form. Dutch law requires that in case of children younger than 12 years old, only the
143 parent(s)/legal guardian need to sign the consent form. If children are between 12 and 16
144 years old, both children and their parent(s)/legal guardian are required to sign the consent
145 form. In case of children older than 16 years, only the children are obliged to sign the consent
146 form. The code of resistance of minors will also be taken into account.

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148 **Randomization**

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3 149 Children will be randomized using sealed envelopes without any stratification factors. The
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5 150 researcher will randomly pick a sealed envelope from a sealed box located in the emergency
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7 151 room and will open it in the presence of the child and parent(s)/legal guardian. The study is
8
9 152 not blinded for the children, parent(s)/legal guardian, or for the researcher.
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13 154 **Intervention**

15 155 If children do not receive a conclusive diagnosis after the first consultation at the emergency
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17 156 room and need to return for a second consultation, then they will be randomized. After
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19 157 randomization, the intervention group will receive both laxatives and enemas, while the
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21 158 control group receives no laxatives or enemas. If children need to return for a third
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23 159 consultation, the children in the intervention group will receive only laxatives without an
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25 160 enema, while the children in the control group will again receive no study medication. We
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27 161 decided against prescribing enemas to children in the intervention group twice, because we
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29 162 expect a reduced effect after a second time and adverse events may occur.
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33 163 The dosage of laxatives and enemas will be adjusted according to the children's ages.
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35 164 Children between 5 and 10 years will receive 4 g Macrogol 4000 twice, while children older
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37 165 than 10 years will receive 10 g Macrogol 4000 twice. In addition, children between 5 to 12
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39 166 years will receive a 10 mL sorbitol enema, while children older than 12 years will receive a
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41 167 133 mL sodium phosphate enema. As a safety precaution, children under the age of 12 years
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43 168 will receive the enema in hospital. The laxatives and sodium phosphate enemas for children
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45 169 older than 12 years can be administered at home.
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50 171 **Outcome measures**

51
52 172 The primary outcome of this study will be the differences in the pain scores for abdominal
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54 173 pain as indicated by the child during the first, second, and possibly third consultation. We will
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3 174 assess the pain scores by using a combination of the Wong-Baker FACES[®] Pain Rating Scale
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5 175 and the Visual Analogue Scale (VAS) for pain. The secondary outcome will be the time
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7 176 needed to reach the final diagnosis as expressed in the number of consultations. This involves
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9 177 the number of times a physician decides that an extra consultations is needed in combination
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11 178 with the number of times a child returns to hospital with persistent complaints of abdominal
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13 179 pain.

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15 180 Additional data we will collect are the patients' characteristics, such as age, sex, weight,
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17 181 height, comorbidities, and medication use. The dosage and type of painkillers will be
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19 182 analyzed and used to correct the pain scores. In addition, we will collect information on stool
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21 183 frequency, stool consistency, and other diagnostic criteria for constipation to evaluate the
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23 184 accuracy of the constipation diagnosis. Finally, we will collect information on whether the
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25 185 children took the study medication correctly and whether children produced stool after taking
26
27 186 the medication.
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32 33 188 **Study protocol**

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35 189 In Table 1 we provide an overview of the study schedule. After arrival at the emergency
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37 190 department, the child and parent(s)/legal guardian will be approached by the researcher and
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39 191 informed consent for the study will be obtained. During the standard clinical examination, the
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41 192 researcher will collect data on the outcome measures (e.g. the pain scores and patient
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43 193 characteristics). If a child receives a diagnosis after the first consultation at the emergency
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45 194 department, the study protocol ends and the child will receive standard care. The children who
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47 195 are not diagnosed after the first consultation and who need to return for a second consultation,
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49 196 will be randomly assigned to the intervention group or the control group. During the second
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51 197 consultation, we will again collect data on the outcome measures. If a child receives a
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53 198 diagnosis after the second consultation, the study protocol ends and the child will receive
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199 standard care. If, after the second consultation, the physician is still unable to establish a
200 diagnosis, and requires the child to return for a third consultation, then the child in the
201 intervention group will receive only laxatives to be administered at home. During the third
202 consultation, we will once again collect data on the outcome measures. After this
203 consultation, the study protocol will end for all children, even if they need to come back for
204 extra consultations. Between two to three months after the first consultation, the researcher
205 will check the electronic patient file to see whether the child had returned to the emergency
206 department with abdominal pain in the meanwhile.

207

208 **Sample size**

209 This trial will be a pilot study, because the necessary data to perform a sample size calculation
210 are not available in the literature. Nevertheless, we propose to set out by including 30 children
211 before possibly expanding the study.

212

213 **Statistical analyses**

214 All analyses will be conducted in SPSS 23.0 for Windows (IBM SPSS Statistics, IBM
215 Corporation, Armonk, NY) using a per-protocol analysis. The primary outcome, the pain
216 score, is an ordinal variable and will be reported as frequencies per points on the scale. The
217 secondary outcome, the number of consultations required to arrive at a final diagnosis, is a
218 non-parametric variable and will be presented as median with range. Other variables to be
219 analyzed include the patient characteristics and use of painkillers. Categorical data will be
220 reported as absolute numbers and percentages, parametric continuous data as means with SDs,
221 and non-parametric continuous data as medians with ranges.

222 For the primary outcome, the Mann Whitney test will be used to analyze the difference the
223 pain scores obtained between the first and second consultation by comparing the intervention

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3 224 group with the control group. An ordinal logistic regression will be used for this comparison
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5 225 to correct for confounding factors, as the use of painkillers. The secondary outcome, the
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7 226 number of consultations required to arrive at a final diagnosis, will also be analyzed using the
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9 227 Mann Whitney test. A *P* value below 0.05 will be considered statistically significant.
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3 249 **ETHICS AND DISSEMINATION**

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5 250 **Data management**

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7 251 All data will be anonymized directly after collection and stored on a secure part of the
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9 252 network drive of University Medical Center Groningen. The hard copies of the informed
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11 253 consent forms will also be stored securely. Only authorized persons will have access to the
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13 254 data. In accordance with Dutch law, the data will be stored for 15 years.
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18 256 **Patient safety**

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20 257 Laxatives and enemas have proven to be safe and effective treatments for constipation in
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22 258 children [9,14]. We therefore do not we expect any adverse events in this study. Nonetheless,
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24 259 should an adverse event occur, then the child concerned shall be followed until the event is
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26 260 over. Depending on the adverse event, follow-up may require additional tests or medical
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28 261 procedures and/or referral to the general physician or a medical specialist. In addition, an
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30 262 annual safety report will be sent to the local Medical Research Ethics Committee of
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32 263 University Medical Center Groningen. As a result of the expected safety level of this study
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34 264 protocol, our local ethics committee waived the otherwise mandatory insurance for human test
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36 265 subjects.
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42 267 **Ethics approval and consent to participate**

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44 268 All interventions discussed in this study protocol are in accordance with the 1964 Declaration
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46 269 of Helsinki. The study is also approved by the Medical Research Ethics Committee of
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48 270 University Medical Center Groningen (2012/393). A written informed consent will be
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50 271 obtained from the parents/legal guardian of eligible children and/or from the children
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52 272 themselves, depending on their age.
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DISCUSSION

Laxatives and enemas have proven to be effective and safe treatments for children with constipation [9,14]. Nevertheless, during the inclusion of participants, we noticed a negative attitude of Dutch parents towards such medication for their children, leading to a larger refusal rate on the part of parents than anticipated. In addition, not all children from the intervention group take their study medication according to protocol. Medication adherence is a familiar issue, also for chronic constipation in which case the adherence rate is around 38% for the first month [17]. We therefore decided in advance on a per-protocol analysis instead of an intention-to-treat analysis, so that a possible deviation from the study protocol would not influence the results. Nevertheless, as a result of these problems it is probably necessary to perform a larger multicenter study in the future. Perhaps even in another country where parents have a more positive attitude towards such medication for their children, so as to increase the power of the results. In that case, performing this study protocol with an intention-to-treat analysis could also provide the opportunity to investigate the effect of the new diagnostic method in practice.

Nonetheless, we have every confidence that this study protocol will prove that supporting fecal evacuation with laxatives and enemas will lead to a quicker diagnosis of constipation in children with abdominal pain and a more rapid relief of pain. We are of the opinion that this diagnostic method can reduce the number of misdiagnosed children with non-specific abdominal pain and who are left untreated for their constipation symptoms. In addition, if we were to recognize acute constipation more often in these children, we may prevent the development of chronic abdominal pain or chronic constipation [12,13], both conditions that are associated reduced quality of life [18,19].

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299 **REFERENCES**

- 300 1. National Center for Health Statistics. National Hospital Ambulatory Medical Care
301 Survey: 2009 Emergency Department Summary Tables. 2012: 1–37.
- 302 2. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United
303 States: 2012 update. *Gastroenterology*. 2012 Nov;143(5):1179-87.e1-3.
- 304 3. Buddingh KT, Wieselmann E, Heineman E, Broens PM. Constipation and nonspecific
305 abdominal pain in teenage girls referred for emergency surgical consultation. *J Pediatr*
306 *Gastroenterol Nutr*. 2012 May;54(5):672-6.
- 307 4. Hyams JS, Di Lorenzo C, Saps M, et al. Functional disorders: children and
308 Adolescents. *Gastroenterology*. 2016;150(6):1456–1468
- 309 5. Walter SA, Kjellström L, Nyhlin H, Talley NJ, Agréus L. Assessment of normal
310 bowel habits in the general adult population: the Popcol study. *Scand J Gastroenterol*. 2010
311 May;45(5):556-66.
- 312 6. Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ 3rd. Self-reported diarrhea: what
313 does it mean? *Am J Gastroenterol*. 1994 Aug;89(8):1160-4.
- 314 7. Orenstein SR, Wald A. Pediatric Rectal Exam: Why, When, and How. *Curr*
315 *Gastroenterol Rep*. 2016 Jan;18(1):4.
- 316 8. Beinvogl B, Sabharwal S, McSweeney M, Nurko S. Are We Using Abdominal
317 Radiographs Appropriately in the Management of Pediatric Constipation? *J Pediatr*. 2017
318 Dec;191:179-183.
- 319 9. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, Staiano
320 A, Vandenplas Y, Benninga MA; European Society for Pediatric Gastroenterology,
321 Hepatology, and Nutrition; North American Society for Pediatric Gastroenterology.
322 Evaluation and treatment of functional constipation in infants and children: evidence-based

- 1
2
3 323 recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr.* 2014
4
5 324 Feb;58(2):258-74.
6
7 325 10. Berger MY, Tabbers MM, Kurver MJ, Boluyt N, Benninga MA. Value of abdominal
8
9 326 radiography, colonic transit time, and rectal ultrasound scanning in the diagnosis of idiopathic
10
11 327 constipation in children: a systematic review. *J Pediatr.* 2012 Jul;161(1):44-50.e1-2.
12
13 328 11. Thornton GC, Goldacre MJ, Goldacre R, Howarth LJ. Diagnostic outcomes following
14
15 329 childhood non-specific abdominal pain: a record-linkage study. *Arch Dis Child.* 2016
16
17 330 Apr;101(4):305-9.
18
19 331 12. Rey E, Balboa A, Mearin F. Chronic constipation, irritable bowel syndrome with
20
21 332 constipation and constipation with pain/discomfort: similarities and differences. *Am J*
22
23 333 *Gastroenterol.* 2014 Jun;109(6):876-84.
24
25 334 13. Chang L, Lembo AJ, Lavins BJ, Shiff SJ, Hao X, Chickering JG, Jia XD, Currie MG,
26
27 335 Kurtz CB, Johnston JM. The impact of abdominal pain on global measures in patients with
28
29 336 chronic idiopathic constipation, before and after treatment with linaclotide: a pooled analysis
30
31 337 of two randomised, double-blind, placebo-controlled, phase 3 trials. *Aliment Pharmacol Ther.*
32
33 338 2014 Dec;40(11-12):1302-12.
34
35 339 14. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and
36
37 340 stimulant laxatives for the management of childhood constipation. *Cochrane Database Syst*
38
39 341 *Rev.* 2016 Aug 17;(8):CD009118.
40
41 342 15. Miller MK, Dowd MD, Friesen CA, Walsh-Kelly CM. A randomized trial of enema
42
43 343 versus polyethylene glycol 3350 for fecal disimpaction in children presenting to an
44
45 344 emergency department. *Pediatr Emerg Care.* 2012 Feb;28(2):115-9.
46
47 345 16. Bekkali NL, van den Berg MM, Dijkgraaf MG, van Wijk MP, Bongers ME, Liem O,
48
49 346 Benninga MA. Rectal fecal impaction treatment in childhood constipation: enemas versus
50
51 347 high doses oral PEG. *Pediatrics.* 2009 Dec;124(6):e1108-15.
52
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54
55
56
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- 1
2
3 348 17. Steiner SA, Torres MR, Penna FJ, Gazzinelli BF, Corradi CG, Costa AS, Ribeiro IG,
4
5 349 de Andrade EG, do Carmo Barros de Melo M. Chronic functional constipation in children:
6
7 350 adherence and factors associated with drug treatment. *J Pediatr Gastroenterol Nutr.* 2014
8
9 351 May;58(5):598-602.
- 10
11 352 18. Warschburger P, Hänig J, Friedt M, Posovszky C, Schier M, Calvano C. Health-
12
13 353 related quality of life in children with abdominal pain due to functional or organic
14
15 354 gastrointestinal disorders. *J Pediatr Psychol.* 2014 Jan-Feb;39(1):45-54.
- 16
17 355 19. Youssef NN, Langseder AL, Verga BJ, Mones RL, Rosh JR. Chronic childhood
18
19 356 constipation is associated with impaired quality of life: a case-controlled study. *J Pediatr*
20
21 357 *Gastroenterol Nutr.* 2005 Jul;41(1):56-60.
- 22
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3 373 **AUTHORS' CONTRIBUTIONS**

4 374 Marjolijn E.W. Timmerman conceptualized and designed the study protocol, acquires data,
5
6
7 375 and drafted the manuscript.

8
9 376 Monika Trzpis conceptualized and designed the study, and critically revised the manuscript
10
11 377 for important intellectual content.

12
13 378 Paul M.A. Broens conceptualized and designed the study, and critically revised the
14
15 379 manuscript for important intellectual content.

16
17 380 All the authors read and approved the final manuscript.

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23
24 383 **FUNDING STATEMENT**

25
26 384 The authors have no funding source, financial assistance, or relationships relevant to this
27
28 385 article to disclose.

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34 388 **COMPETING INTEREST STATEMENT**

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36 389 The authors declare that they have no competing interests.

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43 392 **ACKNOWLEDGEMENTS**

44
45 393 The authors would like to thank T. van Wulfften Palthe, PhD, for correcting the English
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47 394 manuscript.

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398 **Table 1.** Study schedule

	Time points			
	1 st consultation at ED	2 nd consultation at ED	3 th consultation at ED	Close-out
Enrolment	- Standard diagnostic procedures			
	- Eligibility screening			
	- Informed consent			
	- Allocation when diagnosis is unknown			
Intervention	- Intervention group: laxatives and enema	- Intervention group: only laxatives		
	- Control group: no study medication	- Control group: no study medication		
Assessments	- Patient characteristics			
	- Pain score, used medication, stool production	- Pain score, used medication, stool production	- Pain score, used medication, stool production	
				- Number of consultations

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400 ED: emergency department

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Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2018-000341.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Jul-2018
Complete List of Authors:	Timmerman, Marjolijn; University of Groningen, University Medical Center Groningen, Department of Surgery Trzpis, Monika; University of Groningen, University Medical Center Groningen, Department of Surgery Broens, Paul; University of Groningen, University Medical Center Groningen, Department of Surgery
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24 ABSTRACT

25 **Introduction:** Many children with acute abdominal pain and suspicion of appendicitis are
26 diagnosed with constipation. Nevertheless, it can be difficult to differentiate between acute
27 constipation and acute appendicitis because of similar symptoms and lack of diagnostic
28 criteria. Consequently, constipation is often missed despite repeated consultations at the
29 emergency department. We hypothesize that the diagnostic process can be improved and
30 adequate treatment accelerated by supporting fecal evacuation in children with acute
31 abdominal pain.

32 **Methods and analysis:** An unblinded randomized controlled trial including children between
33 5 and 18 years old with acute abdominal pain and suspicion of acute appendicitis. Children
34 who do not receive a diagnosis after the first consultation and who need to return for a second
35 consultation will be randomized. The intervention group will receive laxatives and enemas,
36 while the control group will receive no medication. If, after the second consultation, still no
37 diagnosis is established and a third consultation is needed, then the intervention group will
38 receive only laxatives and the control group will again not receive medication. The primary
39 outcome will be the differences in abdominal pain scores obtained with FACES[®] Pain Rating
40 Scale and the Visual Analogue Scale at first, second, and possibly third consultation. The
41 secondary outcome will be the number of consultations needed to reach final diagnosis.

42 **Ethics and dissemination:** Laxatives and enemas have proven to be safe and effective
43 treatments for constipation in children. Adverse events are therefore not expect, however,
44 should they occur, then the child concerned shall be properly followed and treated until the
45 event is over. The local Medical Research Ethics Committee approved of this study and
46 waived the otherwise mandatory insurance for human test subjects.

47 **Trial registration:** Dutch trial register (CCMO): NL44710.042.12. European trial registration
48 (EudraCT): 2013-000498-56.

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Keywords: constipation; acute appendicitis; diagnostic method; randomized controlled trial

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75 INTRODUCTION

76 Acute abdominal pain is the third-leading cause of visits to emergency departments by
77 children under 15 years, and is associated with high costs, especially when hospitalization is
78 required [1]. For instance, in the United States of America, approximately 900.000 children
79 visit an emergency department with acute abdominal pain and suspicion of appendicitis
80 annually [2]. Nevertheless, only 30% of these children are eventually diagnosed with acute
81 appendicitis [3], while constipation is diagnosed in 21% of girls and 18% of boys with acute
82 abdominal pain [3].

83 It can be difficult to differentiate between constipation with an acute presentation and acute
84 appendicitis, because the symptoms of constipation sometimes mimic those of acute
85 appendicitis. Besides, there are no diagnostic criteria for acute constipation, unlike the Rome
86 IV criteria for diagnosing chronic constipation [4]. In clinical practice, in order to exclude or
87 confirm constipation, most physicians limit their questioning of patients presenting with acute
88 abdominal pain on whether their bowel habits have changed recently or whether they are
89 “normal”, even though it is known that many people pay scarce attention to their bowel habits
90 and/or are unaware of what “normal” stool frequencies or consistencies are [5,6]. In addition,
91 to diagnose constipation physicians often avoid performing digital rectal examinations in
92 children because of discomfort or fear on the part of the patients, and their own lack of
93 adequate training or experience [7]. Moreover, additional investigations, such as abdominal
94 X-rays to diagnose children with constipation, was strongly criticized in a number of studies
95 [8,9,10]. Because the abovementioned methods to diagnose constipation are often not
96 performed or carried out insufficiently, an extra consultation the following day can be
97 recommended to determine whether the symptoms improve or worsen. Nonetheless, even
98 after extra consultations many children are diagnosed with non-specific abdominal pain
99 instead of constipation [11]. These misdiagnoses could result in chronic abdominal pain,

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3 100 because the underlying cause, constipation, is left untreated [12,13]. We believe therefore that
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5 101 a better method is needed to either confirm or exclude constipation in children presenting with
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7 102 acute abdominal pain at the emergency department.
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9 103 Laxatives and/or enemas are standard treatment for fecal disimpaction in children with
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11 104 constipation [9]. This combination of medications can provide a rapid relief of symptoms and
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13 105 has proven to be safe and adverse events rarely occur [9,14,15,16]. We hypothesize that by
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15 106 supporting fecal evacuation with laxatives and enemas in children suffering acute abdominal
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17 107 pain, but who were not diagnosed after first consultation, the diagnostic process could be
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19 108 accelerated. In case a child does indeed suffer from constipation, laxatives and/or enemas lead
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21 109 to rapid reduction of pain. In addition to the positive effect this has on the child's condition,
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23 110 the reduction of pain also points towards constipation as the cause of the abdominal pain. If a
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25 111 child does not suffer from constipation then laxatives and/or enemas will not provide
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27 112 significant relief of symptoms, indicating to the physician that constipation is less likely to be
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29 113 the cause of the abdominal pain.
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33 114 Our objective with this randomized controlled trial is to study whether supporting fecal
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35 115 evacuation in children with acute abdominal pain, but without a diagnosis after the first
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37 116 consultation at the emergency department, could accelerate and improve the diagnostic
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39 117 process.
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124 **METHODS AND ANALYSIS**

125 **Study design and setting**

126 An unblinded randomized controlled trial at the emergency department of an academic
127 hospital, the University Medical Center Groningen, in the Netherlands.

128

129 **Participants**

130 We intend to include children between 5 and 18 years who are referred to the emergency
131 department with acute abdominal pain and suspicion of acute appendicitis. Exclusion criteria
132 are pregnancy and severe co-morbidity like malignancy, recent abdominal surgery, or known
133 inflammatory bowel disease.

134

135 **Recruitment**

136 Children presenting at the emergency department with suspicion of acute appendicitis will be
137 approached to participate in the study. First, the researcher will explain the study protocol to
138 the parent(s)/legal guardian and the child. Subsequently, we will hand them the study
139 brochure that was adapted so as to be readily understood by children. If, after having had
140 some time to read the brochure and the opportunity to ask questions, the parent(s)/legal
141 guardian and/or the child agree to participate in the study, we will ask them to sign the
142 consent form. Dutch law requires that in case of children younger than 12 years old, only the
143 parent(s)/legal guardian need to sign the consent form. If children are between 12 and 16
144 years old, both children and their parent(s)/legal guardian are required to sign the consent
145 form. In case of children older than 16 years, only the children are obliged to sign the consent
146 form. The code of resistance of minors will also be taken into account.

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148 **Randomization**

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3 149 Children will be randomized using sealed envelopes without any stratification factors. The
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5 150 researcher will randomly pick a sealed envelope from a sealed box located in the emergency
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7 151 room and will open it in the presence of the child and parent(s)/legal guardian. The study is
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9 152 not blinded for the children, parent(s)/legal guardian, or for the researcher.
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13 154 **Intervention**

15 155 If children do not receive a conclusive diagnosis after the first consultation at the emergency
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17 156 room and need to return for a second consultation, then they will be randomized. After
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19 157 randomization, the intervention group will receive both laxatives and enemas, while the
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21 158 control group receives no laxatives or enemas. If children need to return for a third
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23 159 consultation, the children in the intervention group will receive only laxatives without an
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25 160 enema, while the children in the control group will again receive no study medication. We
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27 161 decided against prescribing enemas to children in the intervention group twice, because we
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29 162 expect a reduced effect after a second time and adverse events may occur.
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33 163 The dosage of laxatives and enemas will be adjusted according to the children's ages.
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35 164 Children between 5 and 10 years will receive 4 g Macrogol 4000 twice, while children older
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37 165 than 10 years will receive 10 g Macrogol 4000 twice. In addition, children between 5 to 12
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39 166 years will receive a 10 mL sorbitol enema, while children older than 12 years will receive a
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41 167 133 mL sodium phosphate enema. As a safety precaution, children under the age of 12 years
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43 168 will receive the enema in hospital. The laxatives and sodium phosphate enemas for children
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45 169 older than 12 years can be administered at home.
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50 171 **Outcome measures**

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52 172 The primary outcome of this study will be the differences in the pain scores for abdominal
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54 173 pain as indicated by the child during the first, second, and possibly third consultation. We will
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3 174 assess the pain scores by using a combination of the Wong-Baker FACES[®] Pain Rating Scale
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5 175 and the Visual Analogue Scale (VAS) for pain. The secondary outcome will be the time
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7 176 needed to reach the final diagnosis as expressed in the number of consultations. This involves
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9 177 the number of times a physician decides that an extra consultations is needed in combination
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11 178 with the number of times a child returns to hospital with persistent complaints of abdominal
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13 179 pain.

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15 180 Additional data we will collect are the patients' characteristics, such as age, sex, weight,
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17 181 height, comorbidities, and medication use. The dosage and type of painkillers will be
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19 182 analyzed and used to correct the pain scores. In addition, we will collect information on stool
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21 183 frequency, stool consistency, and other diagnostic criteria for constipation to evaluate the
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23 184 accuracy of the constipation diagnosis. Finally, we will collect information on whether the
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25 185 children took the study medication correctly and whether children produced stool after taking
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27 186 the medication.
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32 33 188 **Study protocol**

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35 189 In Table 1 we provide an overview of the study schedule. After arrival at the emergency
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37 190 department, the child and parent(s)/legal guardian will be approached by the researcher and
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39 191 informed consent for the study will be obtained. During the standard clinical examination, the
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41 192 researcher will collect data on the outcome measures (e.g. the pain scores and patient
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43 193 characteristics). If a child receives a diagnosis after the first consultation at the emergency
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45 194 department, the study protocol ends and the child will receive standard care. The children who
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47 195 are not diagnosed after the first consultation and who need to return for a second consultation,
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49 196 will be randomly assigned to the intervention group or the control group. During the second
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51 197 consultation, we will again collect data on the outcome measures. If a child receives a
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53 198 diagnosis after the second consultation, the study protocol ends and the child will receive
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199 standard care. If, after the second consultation, the physician is still unable to establish a
200 diagnosis, and requires the child to return for a third consultation, then the child in the
201 intervention group will receive only laxatives to be administered at home. During the third
202 consultation, we will once again collect data on the outcome measures. After this
203 consultation, the study protocol will end for all children, even if they need to come back for
204 extra consultations. Between two to three months after the first consultation, the researcher
205 will check the electronic patient file to see whether the child had returned to the emergency
206 department with abdominal pain in the meanwhile.

207

208 **Sample size**

209 This trial will be a pilot study, because the necessary data to perform a sample size calculation
210 are not available in the literature. Nevertheless, we propose to set out by including 30 children
211 before possibly expanding the study.

212

213 **Statistical analyses**

214 All analyses will be conducted in SPSS 23.0 for Windows (IBM SPSS Statistics, IBM
215 Corporation, Armonk, NY) using a per-protocol analysis. The primary outcome, the pain
216 score, is an ordinal variable and will be reported as frequencies per points on the scale. The
217 secondary outcome, the number of consultations required to arrive at a final diagnosis, is a
218 non-parametric variable and will be presented as median with range. Other variables to be
219 analyzed include the patient characteristics and use of painkillers. Categorical data will be
220 reported as absolute numbers and percentages, parametric continuous data as means with SDs,
221 and non-parametric continuous data as medians with ranges.

222 For the primary outcome, the Mann Whitney test will be used to analyze the difference the
223 pain scores obtained between the first and second consultation by comparing the intervention

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3 224 group with the control group. An ordinal logistic regression will be used for this comparison
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5 225 to correct for confounding factors, as the use of painkillers. The secondary outcome, the
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7 226 number of consultations required to arrive at a final diagnosis, will also be analyzed using the
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9 227 Mann Whitney test. A *P* value below 0.05 will be considered statistically significant.
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249 ETHICS AND DISSEMINATION

250 Data management

251 All data will be anonymized directly after collection and stored on a secure part of the
252 network drive of University Medical Center Groningen. The hard copies of the informed
253 consent forms will also be stored securely. Only authorized persons will have access to the
254 data. In accordance with Dutch law, the data will be stored for 15 years.

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256 Patient safety

257 Laxatives and enemas have proven to be safe and effective treatments for constipation in
258 children [9,14]. We therefore do not we expect any adverse events in this study. Nonetheless,
259 should an adverse event occur, then the child concerned shall be followed until the event is
260 over. Depending on the adverse event, follow-up may require additional tests or medical
261 procedures and/or referral to the general physician or a medical specialist. In addition, an
262 annual safety report will be sent to the local Medical Research Ethics Committee of
263 University Medical Center Groningen. As a result of the expected safety level of this study
264 protocol, our local ethics committee waived the otherwise mandatory insurance for human test
265 subjects.

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267 Ethics approval and consent to participate

268 All interventions discussed in this study protocol are in accordance with the 1964 Declaration
269 of Helsinki. The study is also approved by the Medical Research Ethics Committee of
270 University Medical Center Groningen (2012/393). A written informed consent will be
271 obtained from the parents/legal guardian of eligible children and/or from the children
272 themselves, depending on their age.

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DISCUSSION

Laxatives and enemas have proven to be effective and safe treatments for children with constipation [9,14]. Nevertheless, during the inclusion of participants, we noticed a negative attitude of Dutch parents towards such medication for their children, leading to a larger refusal rate (23%) on the part of parents than anticipated. In addition, there were some practical problems, especially during the evening and at night, in which many children (27%) had already left the hospital before randomization and/or receiving study medication because they did not want to wait any longer. Also, 37% of the children from the intervention group did not take their study medication according to protocol. Medication adherence is a familiar issue, also for chronic constipation in which case the adherence rate is around 38% for the first month [17]. We therefore decided in advance on a per-protocol analysis instead of an intention-to-treat analysis, so that a possible deviation from the study protocol would not influence the results. Nevertheless, as a result of the abovementioned problems we have only included 10 patients according to protocol since the start of the inclusion in February 2014, so it is necessary to perform a larger multicenter study in the future. Perhaps even in another country where parents have a more positive attitude towards such medication for their children, so as to increase the power of the results. In that case, performing this study protocol with an intention-to-treat analysis could also provide the opportunity to investigate the effect of the new diagnostic method in practice.

Nonetheless, we have every confidence that this study protocol will prove that supporting fecal evacuation with laxatives and enemas will lead to a quicker diagnosis of constipation in children with abdominal pain and a more rapid relief of pain. We are of the opinion that this diagnostic method can reduce the number of misdiagnosed children with non-specific abdominal pain and who are left untreated for their constipation symptoms. In addition, if we were to recognize acute constipation more often in these children, we may prevent the

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299 development of chronic abdominal pain or chronic constipation [12,13], both conditions that
300 are associated reduced quality of life [18,19].

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324 **REFERENCES**

- 325 1. National Center for Health Statistics. National Hospital Ambulatory Medical Care
326 Survey: 2009 Emergency Department Summary Tables. 2012: 1–37.
- 327 2. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United
328 States: 2012 update. *Gastroenterology*. 2012 Nov;143(5):1179-87.e1-3.
- 329 3. Buddingh KT, Wieselmann E, Heineman E, Broens PM. Constipation and nonspecific
330 abdominal pain in teenage girls referred for emergency surgical consultation. *J Pediatr*
331 *Gastroenterol Nutr*. 2012 May;54(5):672-6.
- 332 4. Hyams JS, Di Lorenzo C, Saps M, et al. Functional disorders: children and
333 Adolescents. *Gastroenterology*. 2016;150(6):1456–1468
- 334 5. Walter SA, Kjellström L, Nyhlin H, Talley NJ, Agréus L. Assessment of normal
335 bowel habits in the general adult population: the Popcol study. *Scand J Gastroenterol*. 2010
336 May;45(5):556-66.
- 337 6. Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ 3rd. Self-reported diarrhea: what
338 does it mean? *Am J Gastroenterol*. 1994 Aug;89(8):1160-4.
- 339 7. Orenstein SR, Wald A. Pediatric Rectal Exam: Why, When, and How. *Curr*
340 *Gastroenterol Rep*. 2016 Jan;18(1):4.
- 341 8. Beinvogl B, Sabharwal S, McSweeney M, Nurko S. Are We Using Abdominal
342 Radiographs Appropriately in the Management of Pediatric Constipation? *J Pediatr*. 2017
343 Dec;191:179-183.
- 344 9. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, Staiano
345 A, Vandenplas Y, Benninga MA; European Society for Pediatric Gastroenterology,
346 Hepatology, and Nutrition; North American Society for Pediatric Gastroenterology.
347 Evaluation and treatment of functional constipation in infants and children: evidence-based

- 1
2
3 348 recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr.* 2014
4
5 349 Feb;58(2):258-74.
- 6
7 350 10. Berger MY, Tabbers MM, Kurver MJ, Boluyt N, Benninga MA. Value of abdominal
8
9 351 radiography, colonic transit time, and rectal ultrasound scanning in the diagnosis of idiopathic
10
11 352 constipation in children: a systematic review. *J Pediatr.* 2012 Jul;161(1):44-50.e1-2.
- 12
13 353 11. Thornton GC, Goldacre MJ, Goldacre R, Howarth LJ. Diagnostic outcomes following
14
15 354 childhood non-specific abdominal pain: a record-linkage study. *Arch Dis Child.* 2016
16
17 355 Apr;101(4):305-9.
- 18
19 356 12. Rey E, Balboa A, Mearin F. Chronic constipation, irritable bowel syndrome with
20
21 357 constipation and constipation with pain/discomfort: similarities and differences. *Am J*
22
23 358 *Gastroenterol.* 2014 Jun;109(6):876-84.
- 24
25 359 13. Chang L, Lembo AJ, Lavins BJ, Shiff SJ, Hao X, Chickering JG, Jia XD, Currie MG,
26
27 360 Kurtz CB, Johnston JM. The impact of abdominal pain on global measures in patients with
28
29 361 chronic idiopathic constipation, before and after treatment with linaclotide: a pooled analysis
30
31 362 of two randomised, double-blind, placebo-controlled, phase 3 trials. *Aliment Pharmacol Ther.*
32
33 363 2014 Dec;40(11-12):1302-12.
- 34
35 364 14. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and
36
37 365 stimulant laxatives for the management of childhood constipation. *Cochrane Database Syst*
38
39 366 *Rev.* 2016 Aug 17;(8):CD009118.
- 40
41 367 15. Miller MK, Dowd MD, Friesen CA, Walsh-Kelly CM. A randomized trial of enema
42
43 368 versus polyethylene glycol 3350 for fecal disimpaction in children presenting to an
44
45 369 emergency department. *Pediatr Emerg Care.* 2012 Feb;28(2):115-9.
- 46
47 370 16. Bekkali NL, van den Berg MM, Dijkgraaf MG, van Wijk MP, Bongers ME, Liem O,
48
49 371 Benninga MA. Rectal fecal impaction treatment in childhood constipation: enemas versus
50
51 372 high doses oral PEG. *Pediatrics.* 2009 Dec;124(6):e1108-15.

- 1
2
3 373 17. Steiner SA, Torres MR, Penna FJ, Gazzinelli BF, Corradi CG, Costa AS, Ribeiro IG,
4
5 374 de Andrade EG, do Carmo Barros de Melo M. Chronic functional constipation in children:
6
7 375 adherence and factors associated with drug treatment. *J Pediatr Gastroenterol Nutr.* 2014
8
9 376 May;58(5):598-602.
- 11 377 18. Warschburger P, Hänig J, Friedt M, Posovszky C, Schier M, Calvano C. Health-
12
13 378 related quality of life in children with abdominal pain due to functional or organic
14
15 379 gastrointestinal disorders. *J Pediatr Psychol.* 2014 Jan-Feb;39(1):45-54.
- 18 380 19. Youssef NN, Langseder AL, Verga BJ, Mones RL, Rosh JR. Chronic childhood
19
20 381 constipation is associated with impaired quality of life: a case-controlled study. *J Pediatr*
21
22 382 *Gastroenterol Nutr.* 2005 Jul;41(1):56-60.
- 24 383
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3 398 **AUTHORS' CONTRIBUTIONS**

4 399 Marjolijn E.W. Timmerman conceptualized and designed the study protocol, acquires data,
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7 400 and drafted the manuscript.

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9 401 Monika Trzpis conceptualized and designed the study, and critically revised the manuscript
10
11 402 for important intellectual content.

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13 403 Paul M.A. Broens conceptualized and designed the study, and critically revised the
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15 404 manuscript for important intellectual content.

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17 405 All the authors read and approved the final manuscript.

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24 408 **FUNDING STATEMENT**

25
26 409 The authors have no funding source, financial assistance, or relationships relevant to this
27
28 410 article to disclose.

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34 413 **COMPETING INTEREST STATEMENT**

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36 414 The authors declare that they have no competing interests.

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42 417 **ACKNOWLEDGEMENTS**

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44 418 The authors would like to thank T. van Wulfften Palthe, PhD, for correcting the English
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46 419 manuscript.

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423 **Table 1.** Study schedule

	Time points			
	1 st consultation at ED	2 nd consultation at ED	3 th consultation at ED	Close-out
Enrolment	- Standard diagnostic procedures			
	- Eligibility screening			
	- Informed consent			
	- Allocation when diagnosis is unknown			
Intervention	- Intervention group: laxatives and enema	- Intervention group: only laxatives		
	- Control group: no study medication	- Control group: no study medication		
Assessments	- Patient characteristics			
	- Pain score, used medication, stool production	- Pain score, used medication, stool production	- Pain score, used medication, stool production	
				- Number of consultations

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425 ED: emergency department

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BMJ Paediatrics Open

Using laxatives and/or enemas to accelerate the diagnosis in children presenting with acute abdominal pain: a randomized controlled trial study protocol

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2018-000341.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Sep-2018
Complete List of Authors:	Timmerman, Marjolijn; University of Groningen, University Medical Center Groningen, Department of Surgery Trzpis, Monika; University of Groningen, University Medical Center Groningen, Department of Surgery Broens, Paul; University of Groningen, University Medical Center Groningen, Department of Surgery
Keywords:	Gastroenterology, Paediatric Surgery

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3 1 **Using laxatives and/or enemas to accelerate the diagnosis in children presenting with**
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5 2 **acute abdominal pain: a randomized controlled trial study protocol**
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3 24 **ABSTRACT**

4
5 25 **Introduction:** Many children with acute abdominal pain and suspicion of appendicitis are
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7 26 diagnosed with constipation. Nevertheless, it can be difficult to differentiate between acute
8
9 27 constipation and acute appendicitis because of similar symptoms and lack of diagnostic
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11 28 criteria. Consequently, constipation is often missed despite repeated consultations at the
12
13 29 emergency department. We hypothesize that the diagnostic process can be improved, and
14
15 30 adequate treatment accelerated by supporting fecal evacuation in children with acute
16
17 31 abdominal pain.

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20 32 **Methods and analysis:** An unblinded randomized controlled trial including children between
21
22 33 5 and 18 years old with acute abdominal pain and suspicion of acute appendicitis. Children
23
24 34 who do not have a definitive diagnosis after the first consultation and who need to return for a
25
26 35 second consultation will be randomized. The intervention group will receive laxatives and
27
28 36 enemas, while the control group will receive no medication. If, after the second consultation,
29
30 37 still no diagnosis is established, and a third consultation is needed, then the intervention group
31
32 38 will receive only laxatives and the control group will again not receive medication. The
33
34 39 primary outcome will be the differences in abdominal pain scores obtained with FACES[®]
35
36 40 Pain Rating Scale and the Visual Analogue Scale at first, second, and possibly third
37
38 41 consultation. The secondary outcome will be the number of consultations needed to reach
39
40 42 final diagnosis.

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43 43 **Ethics and dissemination:** Laxatives and enemas have proven to be safe and effective
44
45 44 treatments for constipation in children. Adverse events are therefore not expected, however,
46
47 45 should they occur, then the child concerned shall be properly followed and treated until the
48
49 46 event is over. The local Medical Research Ethics Committee approved of this study and
50
51 47 waived the otherwise mandatory insurance for human test subjects.
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3 48 **Trial registration:** Dutch trial register (CCMO): NL44710.042.12. European trial registration
4
5 49 (EudraCT): 2013-000498-56.
6
7 50

8
9 51 **Keywords:** constipation; acute appendicitis; diagnostic method; randomized controlled trial
10
11 52

12
13 53 **What is known:**

14
15 54 - Constipation is often missed in children with acute abdominal pain, despite repeated
16
17 55 consultations at the emergency department.
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20 56 - Differentiating between acute constipation and acute appendicitis in children with acute
21
22 57 abdominal pain is troublesome due to similar symptoms.
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24 58

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26 59 **What this study hopes to add:**

27
28 60 - We hope to show that supported fecal evacuation can accelerate relief from pain in children
29
30 61 whose acute abdominal pain results from constipation instead of appendicitis.
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33 62 - We hope to accelerate and improve the diagnostic process of acute constipation in these
34
35 63 children, resulting in less children misdiagnosed with non-specific abdominal pain.
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72 INTRODUCTION

73 Acute abdominal pain is the third-leading cause of visits to emergency departments by
74 children under 15 years, and is associated with high costs, especially when hospitalization is
75 required [1]. For instance, in the United States of America, approximately 900.000 children
76 visit an emergency department with acute abdominal pain and suspicion of appendicitis
77 annually [2]. Nevertheless, only 30% of these children are eventually diagnosed with acute
78 appendicitis [3], while constipation is diagnosed in 21% of girls and 18% of boys with acute
79 abdominal pain [3].

80 It can be difficult to differentiate between constipation with an acute presentation and acute
81 appendicitis, because the symptoms of constipation sometimes mimic those of acute
82 appendicitis. Besides, there are no diagnostic criteria for acute constipation, unlike the Rome
83 IV criteria for diagnosing chronic constipation [4]. In clinical practice, in order to exclude or
84 confirm constipation, most physicians limit their questioning of patients presenting with acute
85 abdominal pain on whether their bowel habits have changed recently or whether they are
86 “normal”, even though it is known that many people pay scarce attention to their bowel habits
87 and/or are unaware of what “normal” stool frequencies or consistencies are [5,6]. In addition,
88 to diagnose constipation physicians often avoid performing digital rectal examinations in
89 children because of discomfort or fear on the part of the patients, and their own lack of
90 adequate training or experience [7]. Moreover, additional investigations, such as abdominal
91 X-rays to diagnose children with constipation, was strongly criticized in a number of studies
92 [8,9,10]. Because the abovementioned methods to diagnose constipation are often not
93 performed or carried out insufficiently, an extra consultation the following day can be
94 recommended to determine whether the symptoms improve or worsen. Nonetheless, even
95 after extra consultations many children are diagnosed with non-specific abdominal pain
96 instead of constipation [11]. These misdiagnoses could result in chronic abdominal pain,

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3 97 because the underlying cause, constipation, is left untreated [12,13]. We believe therefore that
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5 98 a better method is needed to either confirm or exclude constipation in children presenting with
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7 99 acute abdominal pain at the emergency department.
8

9 100 Laxatives and/or enemas are standard treatment for fecal disimpaction in children with
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11 101 constipation [9]. This combination of medications can provide a rapid relief of symptoms and
12
13 102 has proven to be safe and adverse events rarely occur [9,14,15,16]. We hypothesize that by
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15 103 supporting fecal evacuation with laxatives and enemas in children suffering acute abdominal
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17 104 pain, but who were not diagnosed after first consultation, the diagnostic process could be
18
19 105 accelerated. In case a child does indeed suffer from constipation, laxatives and/or enemas lead
20
21 106 to rapid reduction of pain. In addition to the positive effect this has on the child's condition,
22
23 107 the reduction of pain also points towards constipation as the cause of the abdominal pain. If a
24
25 108 child does not suffer from constipation then laxatives and/or enemas will not provide
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27 109 significant relief of symptoms, indicating to the physician that constipation is less likely to be
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29 110 the cause of the abdominal pain.
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33 111 Our objective with this randomized controlled trial is to study whether supporting fecal
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35 112 evacuation in children with acute abdominal pain, but without a definitive diagnosis after the
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37 113 first consultation at the emergency department, could accelerate and improve the diagnostic
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39 114 process.
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121 **METHODS AND ANALYSIS**

122 **Study design and setting**

123 An unblinded randomized controlled trial at the emergency department of an academic
124 hospital, the University Medical Center Groningen, in the Netherlands. This protocol
125 describes a study which can be performed as a pilot study and as a final study with an
126 increased sample size. The pilot study will allow to gain data required to perform power
127 analysis, and in this way will allow the performance of adequately powered randomized
128 follow-up study. The final study is required to evaluate our hypothesis and reach the goal of
129 this study.

130

131 **Participants**

132 We intend to include children between 5 and 18 years who are referred to the emergency
133 department with acute abdominal pain and suspicion of acute appendicitis. If children do not
134 receive a definitive diagnosis after the first consultation, and need to return for a second
135 consultation, then they will be randomized. Exclusion criteria are pregnancy and severe co-
136 morbidity like malignancy, recent abdominal surgery, or known inflammatory bowel disease.

137

138 **Recruitment**

139 Children presenting at the emergency department with suspicion of acute appendicitis will be
140 approached to participate in the study. First, the researcher will explain the study protocol to
141 the parent(s)/legal guardian and the child. Subsequently, we will hand them the study
142 brochure that was adapted so as to be readily understood by children. If, after having had
143 some time to read the brochure and the opportunity to ask questions, the parent(s)/legal
144 guardian and/or the child agree to participate in the study, we will ask them to sign the
145 consent form. Dutch law requires that in case of children younger than 12 years old, only the

1
2
3 146 parent(s)/legal guardian need to sign the consent form. If children are between 12 and 16
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5 147 years old, both children and their parent(s)/legal guardian are required to sign the consent
6
7 148 form. In case of children older than 16 years, only the children are obliged to sign the consent
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9 149 form. Furthermore, if a child refuses to cooperate during the study, consent for further
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11 150 participation in the research will be withdrawn.
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15 152 **Randomization**

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18 153 Children will be randomized using sealed envelopes without any stratification factors. The
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20 154 researcher will randomly pick a sealed envelope from a sealed box located in the emergency
21
22 155 room and will open it in the presence of the child and parent(s)/legal guardian. The study is
23
24 156 not blinded for the children, parent(s)/legal guardian, or for the researcher.
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28 158 **Intervention**

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31 159 If children do not receive a conclusive diagnosis after the first consultation at the emergency
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33 160 room and need to return for a second consultation, then they will be randomized. After
34
35 161 randomization, the intervention group will receive both laxatives and enemas, while the
36
37 162 control group receives no laxatives or enemas. If children need to return for a third
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39 163 consultation, the children in the intervention group will receive only laxatives without an
40
41 164 enema, while the children in the control group will again receive no study medication. We
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43 165 decided against prescribing enemas to children in the intervention group twice, because we
44
45 166 expect a reduced effect after a second time and adverse events may occur.
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48 167 The dosage of laxatives and enemas will be adjusted according to the children's ages.
49
50 168 Children between 5 and 10 years will receive 4 g Macrogol 4000 twice, while children older
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52 169 than 10 years will receive 10 g Macrogol 4000 twice. In addition, children between 5 to 12
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54 170 years will receive a 10 mL sorbitol enema, while children older than 12 years will receive a
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3 171 133 mL sodium phosphate enema. As a safety precaution, children under the age of 12 years
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5 172 will receive the enema in hospital. The laxatives and sodium phosphate enemas for children
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7 173 older than 12 years can be administered at home.
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9 174

11 175 **Outcome measures**

12
13 176 The primary outcome of this study will be the differences in the pain scores for abdominal
14
15 177 pain as indicated by the child during the first, second, and possibly third consultation.
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17 178 Specifically for the pilot study with a small sample size, the primary outcome will be whether
18
19 179 or not there is a diminish in abdominal pain in the consecutive consultation, measured as a
20
21 180 binary variable. We will assess the pain scores by using a combination of the Wong-Baker
22
23 181 FACES[®] Pain Rating Scale and the Visual Analogue Scale (VAS) for pain. The secondary
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25 182 outcome will be the time needed to reach the final diagnosis as expressed in the number of
26
27 183 consultations. This involves the number of times a physician decides that an extra
28
29 184 consultation is needed in combination with the number of times a child returns to hospital
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31 185 with persistent complaints of abdominal pain.
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35 186 Additional data we will collect are the patients' characteristics, such as age, sex, weight,
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37 187 height, comorbidities, and medication use. The dosage and type of painkillers will be
38
39 188 analyzed and used to correct the pain scores. In addition, we will collect information on stool
40
41 189 frequency, stool consistency, and other diagnostic criteria for constipation to evaluate the
42
43 190 accuracy of the constipation diagnosis. Finally, we will collect information on whether the
44
45 191 children took the study medication correctly and whether children produced stool after taking
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47 192 the medication.
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52 194 **Study protocol**

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3 195 In Table 1 we provide an overview of the study schedule. After arrival at the emergency
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5 196 department, the child and parent(s)/legal guardian will be approached by the researcher and
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7 197 informed consent for the study will be obtained. During the standard clinical examination, the
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9 198 researcher will collect data on the outcome measures (e.g. the pain scores and patient
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11 199 characteristics). If a child receives a diagnosis after the first consultation at the emergency
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13 200 department, the study protocol ends, and the child will receive standard care. The children
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15 201 suffering from acute abdominal pain, without a definitive diagnosis after the first consultation
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17 202 and who need to return for a second consultation, will be randomly assigned to the
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19 203 intervention group or the control group. During the second consultation, we will again collect
20
21 204 data on the outcome measures. If a child receives a diagnosis after the second consultation,
22
23 205 the study protocol ends, and the child will receive standard care. If, after the second
24
25 206 consultation, the physician is still unable to establish a diagnosis, and requires the child to
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27 207 return for a third consultation, then the child in the intervention group will receive only
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29 208 laxatives to be administered at home. During the third consultation, we will once again collect
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31 209 data on the outcome measures. After this consultation, the study protocol will end for all
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33 210 children, even if they need to come back for extra consultations. Between two to three months
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35 211 after the first consultation, the researcher will check the electronic patient file to see whether
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37 212 the child had returned to the emergency department with abdominal pain in the meanwhile.
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214 **Sample size**

215 This trial will be a pilot study, because the necessary data to perform a sample size calculation
216 are not available in the literature. Nevertheless, we propose to set out by including 30 children
217 before possibly expanding the study.

218

219 **Statistical analyses**

220 All analyses will be conducted in SPSS 23.0 for Windows (IBM SPSS Statistics, IBM
221 Corporation, Armonk, NY) using a per-protocol analysis. The primary outcome, the pain
222 score, is an ordinal variable and will be reported as frequencies per points on the scale. The
223 secondary outcome, the number of consultations required to arrive at a final diagnosis, is a
224 non-parametric variable and will be presented as median with range. Other variables to be
225 analyzed include the patient characteristics and use of painkillers. Categorical data will be
226 reported as absolute numbers and percentages, parametric continuous data as means with SDs,
227 and non-parametric continuous data as medians with ranges.

228 For the primary outcome, the Mann Whitney test will be used to analyze the difference the
229 pain scores obtained between the first and second consultation by comparing the intervention
230 group with the control group. An ordinal logistic regression will be used for this comparison
231 to correct for confounding factors, as the use of painkillers. The secondary outcome, the
232 number of consultations required to arrive at a final diagnosis, will also be analyzed using the
233 Mann Whitney test. A *P* value below 0.05 will be considered statistically significant.

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245 ETHICS AND DISSEMINATION

246 Data management

247 All data will be anonymized directly after collection and stored on a secure part of the
248 network drive of University Medical Center Groningen. The hard copies of the informed
249 consent forms will also be stored securely. Only authorized persons will have access to the
250 data. In accordance with Dutch law, the data will be stored for 15 years.

251

252 Patient safety

253 Laxatives and enemas have proven to be safe and effective treatments for constipation in
254 children [9,14]. We therefore do not we expect any adverse events in this study. Nonetheless,
255 should an adverse event occur, then the child concerned shall be followed until the event is
256 over. Depending on the adverse event, follow-up may require additional tests or medical
257 procedures and/or referral to the general physician or a medical specialist. In addition, an
258 annual safety report will be sent to the local Medical Research Ethics Committee of
259 University Medical Center Groningen. As a result of the expected safety level of this study
260 protocol, our local ethics committee waived the otherwise mandatory insurance for human test
261 subjects.

262

263 Ethics approval and consent to participate

264 All interventions discussed in this study protocol are in accordance with the 1964 Declaration
265 of Helsinki. The study is also approved by the Medical Research Ethics Committee of
266 University Medical Center Groningen (2012/393). A written informed consent will be
267 obtained from the parents/legal guardian of eligible children and/or from the children
268 themselves, depending on their age.

269

270 DISCUSSION

271 Laxatives and enemas have proven to be effective and safe treatments for children with
272 constipation [9,14]. Nevertheless, during the inclusion of participants, we noticed a negative
273 attitude of Dutch parents towards such medication for their children, leading to a larger
274 refusal rate (23%) on the part of parents than anticipated. In addition, there were some
275 practical problems, especially during the evening and at night, in which many children (27%)
276 had already left the hospital before randomization and/or receiving study medication because
277 they did not want to wait any longer. Also, 37% of the children from the intervention group
278 did not take their study medication according to protocol. Medication adherence is a familiar
279 issue, also for chronic constipation in which case the adherence rate is around 38% for the
280 first month [17]. We therefore decided in advance on a per-protocol analysis instead of an
281 intention-to-treat analysis, so that a possible deviation from the study protocol would not
282 influence the results. We included the first patient in February 2014, however, as a result of
283 the abovementioned problems we have only included 10 patients, as originally described in
284 protocol. In the future however, it is necessary to perform this study in another country where
285 parents have a more positive attitude towards such medication for their children. One might
286 be surprised by the low number of patients presented in this protocol. We would therefore like
287 to emphasize that this protocol has a twofold application; it can be used firstly as a pilot study
288 in order to gain the data allowing power analysis, and secondly, it can be used for adequately
289 powered follow-up study. The only difference between these the pilot and the final phase of
290 this study will be the number of the included patients.

291 Nonetheless, we hope that final study performed according to our study protocol, will prove
292 that supporting fecal evacuation with laxatives and enemas can accelerate the relief from pain
293 in these children whose acute abdominal pain results from constipation. Moreover, such a
294 relief from pain, upon supported evacuation, would afterwards allow the confirmation of the

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3 295 diagnose of constipation in these children. Consequently, usage of our protocol may even
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5 296 reduce the number of misdiagnosed children with non-specific abdominal pain, who are left
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7 297 untreated for their constipation symptoms. In addition, if we were to recognize acute
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9 298 constipation more often in these children, we may prevent the development of chronic
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11 299 abdominal pain or chronic constipation [12,13], both conditions that are associated reduced
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13 300 quality of life [18,19].
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320 **REFERENCES**

- 321 1. National Center for Health Statistics. National Hospital Ambulatory Medical Care
322 Survey: 2009 Emergency Department Summary Tables. 2012: 1–37.
- 323 2. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United
324 States: 2012 update. *Gastroenterology*. 2012 Nov;143(5):1179-87.e1-3.
- 325 3. Buddingh KT, Wieselmann E, Heineman E, Broens PM. Constipation and nonspecific
326 abdominal pain in teenage girls referred for emergency surgical consultation. *J Pediatr*
327 *Gastroenterol Nutr*. 2012 May;54(5):672-6.
- 328 4. Hyams JS, Di Lorenzo C, Saps M, et al. Functional disorders: children and
329 Adolescents. *Gastroenterology*. 2016;150(6):1456–1468
- 330 5. Walter SA, Kjellström L, Nyhlin H, Talley NJ, Agréus L. Assessment of normal
331 bowel habits in the general adult population: the Popcol study. *Scand J Gastroenterol*. 2010
332 May;45(5):556-66.
- 333 6. Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ 3rd. Self-reported diarrhea: what
334 does it mean? *Am J Gastroenterol*. 1994 Aug;89(8):1160-4.
- 335 7. Orenstein SR, Wald A. Pediatric Rectal Exam: Why, When, and How. *Curr*
336 *Gastroenterol Rep*. 2016 Jan;18(1):4.
- 337 8. Beinvogl B, Sabharwal S, McSweeney M, Nurko S. Are We Using Abdominal
338 Radiographs Appropriately in the Management of Pediatric Constipation? *J Pediatr*. 2017
339 Dec;191:179-183.
- 340 9. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, Staiano
341 A, Vandenplas Y, Benninga MA; European Society for Pediatric Gastroenterology,
342 Hepatology, and Nutrition; North American Society for Pediatric Gastroenterology.
343 Evaluation and treatment of functional constipation in infants and children: evidence-based

- 1
2
3 344 recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr.* 2014
4
5 345 Feb;58(2):258-74.
6
7 346 10. Berger MY, Tabbers MM, Kurver MJ, Boluyt N, Benninga MA. Value of abdominal
8
9 347 radiography, colonic transit time, and rectal ultrasound scanning in the diagnosis of idiopathic
10
11 348 constipation in children: a systematic review. *J Pediatr.* 2012 Jul;161(1):44-50.e1-2.
12
13 349 11. Thornton GC, Goldacre MJ, Goldacre R, Howarth LJ. Diagnostic outcomes following
14
15 350 childhood non-specific abdominal pain: a record-linkage study. *Arch Dis Child.* 2016
16
17 351 Apr;101(4):305-9.
18
19
20 352 12. Rey E, Balboa A, Mearin F. Chronic constipation, irritable bowel syndrome with
21
22 353 constipation and constipation with pain/discomfort: similarities and differences. *Am J*
23
24 354 *Gastroenterol.* 2014 Jun;109(6):876-84.
25
26 355 13. Chang L, Lembo AJ, Lavins BJ, Shiff SJ, Hao X, Chickering JG, Jia XD, Currie MG,
27
28 356 Kurtz CB, Johnston JM. The impact of abdominal pain on global measures in patients with
29
30 357 chronic idiopathic constipation, before and after treatment with linaclotide: a pooled analysis
31
32 358 of two randomised, double-blind, placebo-controlled, phase 3 trials. *Aliment Pharmacol Ther.*
33
34 359 2014 Dec;40(11-12):1302-12.
35
36
37 360 14. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and
38
39 361 stimulant laxatives for the management of childhood constipation. *Cochrane Database Syst*
40
41 362 *Rev.* 2016 Aug 17;(8):CD009118.
42
43
44 363 15. Miller MK, Dowd MD, Friesen CA, Walsh-Kelly CM. A randomized trial of enema
45
46 364 versus polyethylene glycol 3350 for fecal disimpaction in children presenting to an
47
48 365 emergency department. *Pediatr Emerg Care.* 2012 Feb;28(2):115-9.
49
50 366 16. Bekkali NL, van den Berg MM, Dijkgraaf MG, van Wijk MP, Bongers ME, Liem O,
51
52 367 Benninga MA. Rectal fecal impaction treatment in childhood constipation: enemas versus
53
54 368 high doses oral PEG. *Pediatrics.* 2009 Dec;124(6):e1108-15.
55
56
57
58
59
60

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2
3 369 17. Steiner SA, Torres MR, Penna FJ, Gazzinelli BF, Corradi CG, Costa AS, Ribeiro IG,
4
5 370 de Andrade EG, do Carmo Barros de Melo M. Chronic functional constipation in children:
6
7 371 adherence and factors associated with drug treatment. *J Pediatr Gastroenterol Nutr.* 2014
8
9 372 May;58(5):598-602.
- 11 373 18. Warschburger P, Hänig J, Friedt M, Posovszky C, Schier M, Calvano C. Health-
12
13 374 related quality of life in children with abdominal pain due to functional or organic
14
15 375 gastrointestinal disorders. *J Pediatr Psychol.* 2014 Jan-Feb;39(1):45-54.
- 17 376 19. Youssef NN, Langseder AL, Verga BJ, Mones RL, Rosh JR. Chronic childhood
18
19 377 constipation is associated with impaired quality of life: a case-controlled study. *J Pediatr*
20
21 378 *Gastroenterol Nutr.* 2005 Jul;41(1):56-60.
22
23
24 379
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3 394 **AUTHORS' CONTRIBUTIONS**

4
5 395 Marjolijn E.W. Timmerman conceptualized and designed the study protocol, acquires data,
6
7 396 and drafted the manuscript.

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9 397 Monika Trzpis conceptualized and designed the study, and critically revised the manuscript
10
11 398 for important intellectual content.

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13 399 Paul M.A. Broens conceptualized and designed the study, and critically revised the
14
15 400 manuscript for important intellectual content.

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17 401 All the authors read and approved the final manuscript.

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24 404 **FUNDING STATEMENT**

25
26 405 The authors have no funding source, financial assistance, or relationships relevant to this
27
28 406 article to disclose.

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34 409 **COMPETING INTEREST STATEMENT**

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36 410 The authors declare that they have no competing interests.

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42 413 **ACKNOWLEDGEMENTS**

43
44 414 The authors would like to thank T. van Wulfften Palthe, PhD, for correcting the English
45
46 415 manuscript.

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419 **Table 1.** Study schedule

	Time points			
	1 st consultation at ED	2 nd consultation at ED	3 th consultation at ED	Close-out
Enrolment	- Standard diagnostic procedures			
	- Eligibility screening			
	- Informed consent			
	- Allocation when diagnosis is unknown			
Intervention	- Intervention group: laxatives and enema	- Intervention group: only laxatives		
	- Control group: no study medication	- Control group: no study medication		
Assessments	- Patient characteristics			
	- Pain score, used medication, stool production	- Pain score, used medication, stool production	- Pain score, used medication, stool production	
				- Number of consultations

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421 ED: emergency department

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