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Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in children: protocol of a randomized controlled trial

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6 3 **Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in**
7 4 **children: protocol of a randomized controlled trial**
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37 32

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39 34 to the design of the study. DM and MK developed the first draft of the manuscript
40 35 and contributed equally. All authors approved the final draft of the manuscript.
41 36

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43 38 Warsaw.
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3 45 **ABSTRACT**

4 46 **Introduction**

5 47 Worldwide, acute gastroenteritis in children, usually caused by viruses, leads to
6 48 considerable morbidity and mortality. The treatment is aimed at preventing and
7 49 treating dehydration, promoting weight gain after rehydration, and reducing the
8 50 duration and severity of diarrhea. Effective and inexpensive interventions that could
9 51 add to the effect of oral rehydration therapy are of interest. Recently, in many
10 52 European countries, gelatin tannate is being widely marketed for treating acute
11 53 gastroenteritis. Gelatin tannate is a complex of tannic acid, which possesses
12 54 astringent and anti-inflammatory properties, and a protective gelatin. Currently,
13 55 there is no evidence to support the use of gelatin tannate for treating acute
14 56 gastroenteritis in children and only scant evidence to support the use of gelatin
15 57 tannate in adults. We aim to assess the efficacy of gelatin tannate for the treatment of
16 58 acute gastroenteritis in children.
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21 60 **Methods and analysis**

22 61 This will be a blind, placebo-controlled, randomized trial. Children younger than 5
23 62 years of age with acute gastroenteritis defined as a change in stool consistency to
24 63 loose or liquid form (according to the Bristol Stool Form scale or Amsterdam Stool
25 64 Form scale) and/or an increase in the frequency of evacuations (typically ≥ 3 in 24
26 65 hours), lasting for no longer than 5 days, will be recruited. A total of 158 children will
27 66 be randomized to receive either gelatin tannate (children younger than 3 years of age
28 67 will receive 250 mg 4 times per day and those older than 3 years of age will receive
29 68 500 mg 4 times per day) or matching placebo for 5 days. The primary outcome
30 69 measure is the duration of diarrhea.
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34 71 **Ethics and dissemination**

35 72 The Bioethics Committee approved the study protocol. The findings of this trial will
36 73 be submitted to a peer-reviewed pediatric journal. Abstracts will be submitted to
37 74 relevant national and international conferences.
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40 76 **Registration**

41 77 www.clinicaltrials.gov (NCT02280759)
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3 81 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 5 82 • The study design (randomized controlled trial, RCT) is the most robust
6 methodology to assess the effectiveness of therapeutic interventions.
7
8 84 • A precise clinical question has been posed to fill a gap in knowledge as to
9 whether gelatin tannate is safe and effective in the treatment of acute
10 gastroenteritis in children.
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12 86 • The findings of this RCT, whether positive or negative, will contribute to the
13 formulation of recommendations on the use of gelatin tannate for the treatment of
14 acute gastroenteritis.
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16 88 • Due to practicalities, stool volume, which is one of the objective ways of assessing
17 the efficacy of antidiarrheal drugs, will not be assessed.
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96 INTRODUCTION

97 Worldwide, acute gastroenteritis in children, usually caused by rotaviruses, leads to
98 considerable morbidity and mortality.¹ It is also the most common cause of primary
99 care consultations among children younger than 5 years of age.² According to current
100 European guidelines,³ the mainstay of treatment for acute gastroenteritis is oral
101 rehydration with a hypoosmolar solution. Breastfeeding should not be interrupted.
102 Regular feeding should continue with no dietary changes including milk.
103 Considering the burden of acute gastroenteritis both to children and the healthcare
104 system, effective and inexpensive interventions that could add to the effect of oral
105 rehydration therapy are of interest. Currently, effective interventions that may
106 reduce the duration and severity of diarrhea include administration of specific
107 probiotics such as *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*, diosmectite,
108 or racecadotril.³

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110 Recently, in many European countries, gelatin tannate is being marketed for treating
111 acute gastroenteritis. Gelatin tannate consists of tannic acid suspended in a gelatin
112 solution. Gelatin tannate has a stable structure both in the acidic environment of the
113 stomach as well as in a basic and neutral environment such as in the small intestine
114 and colon.⁴ Little is known about the specific mechanisms by which gelatin tannate
115 may act against gastrointestinal infection. It is known, however, that it forms a
116 biofilm, which mechanically protects the gastrointestinal mucosa and causes
117 precipitation of pro-inflammatory proteins such as mucoproteins in the intestinal
118 mucosa.⁵ In addition, it inhibits the growth of bacteria such as *Bacteroides fragilis*,
119 *Clostridium perfringens*, *Escherichia coli*, *Enterobacter cloacae*, *Salmonella typhimurium*,
120 *Helicobacter pylori*, *Listeria monocytogenes*, and in vitro mycobacterial *Vibrio cholerae*.^{5 6 7}
121 The action of anti-inflammatory tannate also involves blocking inflammatory agents
122 in the gastrointestinal mucosa.⁸

123
124 Only limited evidence is available on the effectiveness of gelatin tannate. In 2009,
125 Esteban Carretero et al. published a study (n=211, mean age 2.5 ± 2.4 years, no
126 randomization, no blinding, unbalanced baseline characteristics) that evaluated the

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3 127 effectiveness of gelatin tannate in the treatment of acute gastroenteritis in children.
4 128 Children received oral rehydration solution (ORS) alone or ORS in combination with
5 129 gelatin tannate (dose was not specified). During the 12-h observation period, a
6 130 significant reduction in the number of loose stools was found in the group receiving
7 131 ORS and gelatin tannate versus the group receiving ORS alone. Both groups had
8 132 similar weight gains, stool consistency, comparative risks of diarrhea with blood,
9 133 peritonitis, and sepsis, vomiting intensity, and degrees of dehydration in the 12 h of
10 134 observation.⁹ In 2012, Allegrini and Costantini performed a blinded, randomized,
11 135 placebo-controlled trial in the adult population (n = 40, mean age 43 ± 13 years). In
12 136 the group receiving gelatin tannate (500 mg, 6 times per day, for 2 consecutive days)
13 137 compared with the placebo group, a statistically significant decrease in both the daily
14 138 number of watery stools and severity of abdominal pain for the first 48 h of the
15 139 intervention was found. There were no clinically relevant adverse events.¹⁰
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28 141 A 2014 systematic review evaluated the efficacy of gelatin tannate in treating acute
29 142 gastroenteritis in children and adults.¹¹ The two above-described studies were
30 143 included. None of the included studies evaluated the effect of gelatin tannate on the
31 144 primary outcome measures for the review, such as stool output, duration of diarrhea,
32 145 need for admission to the hospital, duration of hospital stay, and (in children) weight
33 146 gain after rehydration. The review concluded that there is no evidence to support the
34 147 use of gelatin tannate for treating acute gastroenteritis in children and only sparse
35 148 evidence to support the use of gelatin tannate in adults.
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44 150 Taken together, currently, the evidence to support the use of gelatin tannate for
45 151 treating acute gastroenteritis in children or adults is very limited. According to the
46 152 current (2014) European guidelines,³ gelatin tannate is not recommended for the
47 153 management of acute gastroenteritis in children.
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53 155 **Trial objectives and hypotheses**

54 156 The main objective of this trial is to assess the effectiveness and safety of gelatin
55 157 tannate in the treatment of acute gastroenteritis in children. We aim to conduct a
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3 158 well-designed and executed study, with sufficient power, an adequate follow-up
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5 159 period, and relevant clinical endpoints. In our trial, we choose to use placebo for a
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7 160 comparator as it is widely regarded as the gold standard for testing the efficacy of
8
9 161 new treatments.¹²

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11 163 **METHODS AND ANALYSIS**

12 164 The trial is registered at www.clinicaltrials.gov (NCT02280759) and any important
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14 165 changes in the protocol will be implemented there.
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17 167 **Study design**

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19 168 This study is designed as a randomized, blinded, placebo-controlled trial, with
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21 169 allocation 1:1, and is described in more detail in subsequent sections.
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24 171 **Setting and participants**

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26 172 The recruitment will take place primarily in the emergency room of the pediatric
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28 173 hospital of the Medical University of Warsaw. However, other recruiting sites are
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30 174 under consideration provided that the personnel are adequately trained and
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32 175 competent in conducting clinical trials. Participants will be randomized after their
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34 176 first visit to the emergency room or after admission to the clinic. Caregivers will
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36 177 receive oral and written information on the study. Written informed consent will by
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38 178 obtained by physicians involved in the study.
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41 180 **Inclusion criteria**

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43 181 Children eligible for the trial must fulfill all of the following criteria:

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45 182 • Acute gastroenteritis defined as a change in stool consistency to loose or liquid
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47 183 form (according to the Bristol Stool Form, BSF, scale or Amsterdam Stool Form,
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49 184 ASF, scale) and/or an increase in the frequency of evacuations (typically ≥ 3 in 24
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51 185 hours), lasting for no longer than 5 days
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53 186 • Age younger than 5 years
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55 187 • A caregiver must provide written informed consent.
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3 189 **Exclusion criteria**

- 4 190 • Use of antibiotics, gelatin tannate, diosmectite, probiotics, or racecadotril within a
5 191 week prior to enrollment.
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8 192 • Exclusive or predominant (>50%) breastfeeding.
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10 193 • Chronic diarrheal gastrointestinal disease (e.g., inflammatory bowel diseases,
11 194 cystic fibrosis, celiac disease, food allergy).
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14 195 • Immunodeficiencies.
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16 196 • Malnutrition (weight/height/length under 3rd percentile) (WHO Childgrowth
17 197 Standards will be used).¹³
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19 198 • If needed, discontinuation or modification of the treatment may be considered at
20 199 the discretion of the physician.
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24 201 **Randomization criteria**

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26 202 After re-checking the inclusion and exclusion criteria, participants will be assigned
27 203 into one of two groups (experimental or control). After determination of eligibility,
28 204 caregivers will receive a diary of symptoms to record the number of stools and their
29 205 consistency during the intervention. BSF and ASF scales will be provided.
30 206 Additionally, caregivers will be asked to write down any adverse events during the
31 207 intervention period.
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39 209 **Interventions**

40 210 The intervention under investigation is gelatin tannate manufactured by ICN Polfa
41 211 Rzeszów/Valeant. The manufacturer does not have and will not have a role in the
42 212 design or conduct of the study. The placebo will contain maltodextrine, which is an
43 213 almost flavorless, easily digestible polysaccharide commonly used as a food additive.
44 214 The dose of the active product or placebo will be age dependent (i.e., in children
45 215 younger than 3 years of age the dose is 250 mg and in children older than 3 year of
46 216 age - 500 mg). Both the gelatin tannate and placebo will be taken orally, 4 times per
47 217 day, for 5 days. Caregivers will be instructed to administer the daily dose at the same
48 218 time of a day, after mixing the contents of the sachet with a small amount of water.
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51 219 The study products used in this trial will be prepared by the hospital pharmacy at
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3 220 the Medical University of Warsaw as identically appearing sachets.

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6 222 For initial rehydration, all children will be treated according to 2014 European
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8 223 recommendations (fast oral rehydration over 3–4 hours by mouth or via nasogastric
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10 224 tube with the recommended hypotonic solution). After all signs of dehydration have
11
12 225 disappeared, oral rehydration solution will be given for ongoing losses until the
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14 226 diarrhea stops. Rapid reintroduction of the previous diet after successful rehydration
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16 227 will be recommended. At all times, breastfeeding will be allowed.

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19 229 At any time, caregivers will have the right to withdraw the participating child from
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21 230 the study; they will be not obliged to give reasons for this decision, and there will be
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23 231 no effect on subsequent physician and/or institutional medical care.

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26 233 **Concomitant medications**

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28 234 The concomitant administration of any other medication, including antipyretics and
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30 235 antiemetics, will be at the discretion of the physician to provide adequate care.
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32 236 However, it is recommended that no unnecessary concomitant medication be used.

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35 238 **Follow up**

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37 239 All study participants will be followed-up for the duration of the intervention (5
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39 240 days) and then for an additional 48 h.

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42 242 **Allocation concealment and blinding**

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44 243 A computer-generated randomization list prepared by a person unrelated to the trial
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46 244 will be used to allocate subjects to the study groups in blocks of eight. Consecutive
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48 245 randomization numbers will be given to participants at enrollment. This procedure
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50 246 will be performed by one of two physicians involved. The study product will be
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52 247 weighed, packaged, and signed by consecutive numbers according to the
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54 248 randomization list by the hospital pharmacy at the Medical University of Warsaw by
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56 249 independent personnel not involved in the conduct of the study. The study products
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58 250 will be delivered to the physicians in small envelopes labeled with the consecutive

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3 251 numbers and dose (with the meaning of numbers blinded and information deposited
4 252 in a sealed envelope in a safe place in the administrative part of the department). The
5 253 active product and placebo will be packaged in identical sachets. Contents will look
6 254 and taste the same. Researchers, caregivers, outcome assessors, and a person
7 255 responsible for the statistical analysis will be blinded to the intervention until the
8 256 completion of the study. The information on intervention assignments will be stored
9 257 in a sealed envelope in a safe in the administrative part of the department. The
10 258 personal information about potential and enrolled participants will be stored in a
11 259 locker within the study site, accessible for the involved researchers only.
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21 **Compliance**

22 262 The caregivers will be asked to bring the remaining study product and diary to the
23 263 study site at the end of the intervention period. Compliance with the study protocol
24 264 will be checked by counting the number of sachets left unused. Based on previously
25 265 published trials, it seems to be appropriate to consider those subjects receiving less
26 266 than 75% of the recommended doses as noncompliant.
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33 268 **Primary outcome**

34 269 The primary outcome will be the duration of diarrhea, defined as the time until the
35 270 normalization of stool consistency according to the BSF or ASF scale (in BSF Scale,
36 271 numbers 2, 3, 4 and 5, and in ASF Scale, letters B or C), or the time until the
37 272 normalization of the number of stools (compared with the period before the onset of
38 273 diarrhea), and the presence of normal stools for 48 h.
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46 275 **Secondary outcomes**

- 47 276 • need for intravenous rehydration
- 48 277 • need for hospitalization in outpatients
- 49 278 • number of watery stools per day
- 50 279 • vomiting
- 51 280 • weight gain
- 52 281 • adverse events
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- 282 • recurrence of diarrhea (48 h after intervention)
- 283 • severity of diarrhea according to Vesikari scale.¹⁴

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285 **Table 1.** Timetable of activities planned during the study.

Days \ Activity	1	2	3	4	5	6	7
Enrollment	+						
Randomization	+						
Intervention	+	+	+	+	+		
Return of diary					+		
Follow up						+	+
Adverse events	+	+	+	+	+	+	+

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287 **Power calculation**

288 The primary outcome of the study is the duration of diarrhea. Based on available
 289 data in the literature, the average duration of gastroenteritis in children is 5-7 days.³
 290 We assume that a clinically significant difference in the effectiveness of gelatin
 291 tannate versus placebo will shorten the duration of symptoms by 12 hours. To detect
 292 such a difference in the duration of diarrhea between the study groups with a power
 293 of 80% and $\alpha = 0.05$, a sample of 126 infants is needed in each study group. Assuming
 294 about a 20% loss to follow up, we aim to recruit a total of 158 children for this study.

295

296 In the Department of Paediatrics of The Medical University of Warsaw, there are 200
 297 admissions of children with diarrhea per year and the same number of such patients
 298 who present to the emergency room. Assuming that 20% of these children will be
 299 eligible for the study, we will achieve adequate participant enrollment to reach the
 300 target sample size after 2 years of recruiting.

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302 **Statistical analysis**

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3 303 All analysis will be conducted on an intention-to-treat basis, including all patients in
4 304 the groups to which they are randomized for whom outcomes will be available
5 305 (including dropouts and withdrawals). Descriptive statistics will be used to
6 306 summarize baseline characteristics. The Student t test will be used to compare mean
7 307 values of continuous variables approximating a normal distribution. For non-
8 308 normally distributed variables, the Mann-Whitney U test will be used. The χ^2 test or
9 309 Fisher exact test will be used, as appropriate, to compare percentages. For continuous
10 310 outcomes, differences in means or differences in medians (depending on the
11 311 distribution of the data), and for dichotomous outcomes, the relative risk (RR) and
12 312 number needed to treat, all with a 95% confidence interval, will be calculated. The
13 313 difference between study groups will be considered significant when the p value is
14 314 <0.05 , when the 95% CI for RR does not include 1.0, or when the 95% CI for MD does
15 315 not include 0. All statistical tests will be two tailed and performed at the 5% level of
16 316 significance.

17 317

18 318 ETHICS AND DISSEMINATION

19 319 The Bioethical Committee of The Medical University of Warsaw issued approval for
20 320 the study before recruitment commenced. Verbal and written information regarding
21 321 informed consent will be presented to the caregivers. Any modifications to the
22 322 protocol that may affect the conduct of the study will be presented to the Committee.
23 323 The full protocol will be available freely due to open access publication. The findings
24 324 of this RCT will be submitted to a peer-reviewed journal. Abstracts will be submitted
25 325 to relevant national and international conferences.

26 326

27 327 FUNDING STATEMENT

28 328 This trial will be funded by The Medical University of Warsaw. At the time of
29 329 submission of this protocol for publication, no specific grant from any funding
30 330 agency in the public, commercial, or not-for-profit sectors has been awarded to this
31 331 project.

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33 333 AUTHORS' CONTRIBUTIONS

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3 334 HS conceptualized the study. All authors contributed to the design of the study and
4
5 335 read and approved the manuscript. DM and MK developed the first draft of the
6
7 336 manuscript. All authors contributed to the development of the study protocol and
8
9 337 approved the final draft of the manuscript.

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For peer review only

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ✓
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ✓
	2b	All items from the World Health Organization Trial Registration Data Set []
Protocol version	3	Date and version identifier ✓
Funding	4	Sources and types of financial, material, and other support ✓
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ✓
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) XXX
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ✓
	6b	Explanation for choice of comparators ✓
Objectives	7	Specific objectives or hypotheses ✓
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) ✓

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained ✓
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ✓
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ✓
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) ✓
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ✓
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial ✓
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended ✓
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) ✓
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations ✓
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ✓

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions ✓
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1			
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned ✓
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions ✓
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how ✓
13			
14		17b	If blinded, circumstances under which unblinding is permissible, and
15			procedure for revealing a participant's allocated intervention during
16			the trial ✓
17			
18			

Methods: Data collection, management, and analysis

20			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol ✓
27			
28		18b	Plans to promote participant retention and complete follow-up,
29			including list of any outcome data to be collected for participants who
30			discontinue or deviate from intervention protocols
31			
32			
33	Data	19	Plans for data entry, coding, security, and storage, including any
34	management		related processes to promote data quality (eg, double data entry;
35			range checks for data values). Reference to where details of data
36			management procedures can be found, if not in the protocol
37			
38	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
39	methods		Reference to where other details of the statistical analysis plan can be
40			found, if not in the protocol ✓
41			
42		20b	Methods for any additional analyses (eg, subgroup and adjusted
43			analyses) ✓
44			
45		20c	Definition of analysis population relating to protocol non-adherence
46			(eg, as randomised analysis), and any statistical methods to handle
47			missing data (eg, multiple imputation)
48			
49			

Methods: Monitoring

50			
51			
52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
53			and reporting structure; statement of whether it is independent from
54			the sponsor and competing interests; and reference to where further
55			details about its charter can be found, if not in the protocol.
56			Alternatively, an explanation of why a DMC is not needed ??
57			
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1		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ✓
2			
3			
4			
5			
6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ✓
7			
8			
9			
10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ✓
11			
12			
13			

Ethics and dissemination

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15			
16			
17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ✓
18			
19			
20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ✓
21			
22			
23			
24			
25			
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ✓
27			
28			
29		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable X
30			
31	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ✓
32			
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34			
35			
36	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ✓
37			
38			
39	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ✓
40			
41			
42			
43	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation ✓
44			
45			
46	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions ✓
47			
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51			
52		31b	Authorship eligibility guidelines and any intended use of professional writers ?
53			
54			
55		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code ✓
56			
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable ✓

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.



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

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6,8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

1			
2		assessing outcomes) and how	
3			
4		11b If relevant, description of the similarity of interventions	7
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	10
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
7			
8	Results		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	-
10	diagram is strongly	were analysed for the primary outcome	
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	-
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	-
13		14b Why the trial ended or was stopped	-
14			
15	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	-
16	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	-
17		by original assigned groups	
18			
19	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	-
20	estimation	precision (such as 95% confidence interval)	
21		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
22	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	-
23		pre-specified from exploratory	
24			
25	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
26			
27	Discussion		
28	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
29	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	-
30	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
31			
32	Other information		
33	Registration	23 Registration number and name of trial registry	2
34	Protocol	24 Where the full trial protocol can be accessed, if available	-
35	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	1
36			

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

BMJ Open

Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in children: protocol of a randomized controlled trial

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	children, antidiarrheal drugs, diarrhea, RCT

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Manuscripts

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6 3 **Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in**
7 4 **children: protocol of a randomized controlled trial**
8
9 5

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12 8

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25 20

26 21 **Key words:** antidiarrheal drugs, gastrointestinal infection, diarrhea, RCT
27 22

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3 37 **ABSTRACT**

4 38 **Introduction**

5 39 Worldwide, acute gastroenteritis in children, usually caused by viruses, leads to
6 40 considerable morbidity and mortality. The treatment is aimed at preventing and
7 41 treating dehydration, promoting weight gain after rehydration, and reducing the
8 42 duration and severity of diarrhea. Effective and inexpensive interventions that could
9 43 add to the effect of oral rehydration therapy are of interest. Recently, in many
10 44 European countries, gelatin tannate is being widely marketed for treating acute
11 45 gastroenteritis. Gelatin tannate is a complex of tannic acid, which possesses
12 46 astringent and anti-inflammatory properties, and a protective gelatin. Currently,
13 47 there is no evidence to support the use of gelatin tannate for treating acute
14 48 gastroenteritis in children and only scant evidence to support the use of gelatin
15 49 tannate in adults. We aim to assess the efficacy of gelatin tannate for the treatment of
16 50 acute gastroenteritis in children.
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21 51
22 52 **Methods and analysis**

23 53 This will be a blind, placebo-controlled, randomized trial. Children younger than 5
24 54 years of age with acute gastroenteritis defined as a change in stool consistency to
25 55 loose or liquid form (according to the Bristol Stool Form scale or Amsterdam Stool
26 56 Form scale) and/or an increase in the frequency of evacuations (typically ≥ 3 in 24
27 57 hours), lasting for no longer than 5 days, will be recruited. A total of 158 children will
28 58 be randomized to receive either gelatin tannate (children younger than 3 years of age
29 59 will receive 250 mg 4 times per day and those older than 3 years of age will receive
30 60 500 mg 4 times per day) or matching placebo for 5 days. The primary outcome
31 61 measure is the duration of diarrhea.
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33

34 62
35 63 **Ethics and dissemination**

36 64 The Bioethics Committee approved the study protocol. The findings of this trial will
37 65 be submitted to a peer-reviewed pediatric journal. Abstracts will be submitted to
38 66 relevant national and international conferences.
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40 67
41 68 **Registration**

42 69 www.clinicaltrials.gov (NCT02280759)
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3 73 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 4 74 • The study design (randomized controlled trial, RCT) is the most robust
5 methodology to assess the effectiveness of therapeutic interventions.
6
7
8 76 • A precise clinical question has been posed to fill a gap in knowledge as to
9 whether gelatin tannate is safe and effective in the treatment of acute
10 gastroenteritis in children.
11
12 78
13
14 79 • The findings of this RCT, whether positive or negative, will contribute to the
15 formulation of recommendations on the use of gelatin tannate for the treatment of
16 acute gastroenteritis.
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18 81
19 82 • Due to practicalities, stool volume, which is one of the objective ways of assessing
20 the efficacy of antidiarrheal drugs, will not be assessed.
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88 INTRODUCTION

89 Worldwide, acute gastroenteritis in children, usually caused by rotaviruses, leads to
90 considerable morbidity and mortality.¹ It is also the most common cause of primary
91 care consultations among children younger than 5 years of age.² According to current
92 European guidelines,³ the mainstay of treatment for acute gastroenteritis is oral
93 rehydration with a hypoosmolar solution. Breastfeeding should not be interrupted.
94 Regular feeding should continue with no dietary changes including milk.
95 Considering the burden of acute gastroenteritis both to children and the healthcare
96 system, effective and inexpensive interventions that could add to the effect of oral
97 rehydration therapy are of interest. Currently, effective interventions that may
98 reduce the duration and severity of diarrhea include administration of specific
99 probiotics such as *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*, diosmectite,
100 or racecadotril.³

101
102 Recently, in many European countries, gelatin tannate is being marketed for treating
103 acute gastroenteritis. Gelatin tannate consists of tannic acid suspended in a gelatin
104 solution. Gelatin tannate has a stable structure both in the acidic environment of the
105 stomach as well as in a basic and neutral environment such as in the small intestine
106 and colon.⁴ Little is known about the specific mechanisms by which gelatin tannate
107 may act against gastrointestinal infection. It is known, however, that it forms a
108 biofilm, which mechanically protects the gastrointestinal mucosa and causes
109 precipitation of pro-inflammatory proteins such as mucoproteins in the intestinal
110 mucosa.⁵ In addition, it inhibits the growth of bacteria such as *Bacteroides fragilis*,
111 *Clostridium perfringens*, *Escherichia coli*, *Enterobacter cloacae*, *Salmonella typhimurium*,
112 *Helicobacter pylori*, *Listeria monocytogenes*, and in vitro mycobacterial *Vibrio cholerae*.^{5 6 7}
113 The action of anti-inflammatory tannate also involves blocking inflammatory agents
114 in the gastrointestinal mucosa.⁸

115
116 Only limited evidence is available on the effectiveness of gelatin tannate. In 2009,
117 Esteban Carretero et al. published a study (n=211, mean age 2.5 ± 2.4 years, no
118 randomization, no blinding, unbalanced baseline characteristics) that evaluated the

1
2
3 119 effectiveness of gelatin tannate in the treatment of acute gastroenteritis in children.
4 120 Children received oral rehydration solution (ORS) alone or ORS in combination with
5 121 gelatin tannate (dose was not specified). During the 12-h observation period, a
6 122 significant reduction in the number of loose stools was found in the group receiving
7 123 ORS and gelatin tannate versus the group receiving ORS alone. Both groups had
8 124 similar weight gains, stool consistency, comparative risks of diarrhea with blood,
9 125 peritonitis, and sepsis, vomiting intensity, and degrees of dehydration in the 12 h of
10 126 observation.⁹ In 2012, Allegrini and Costantini performed a blinded, randomized,
11 127 placebo-controlled trial in the adult population (n = 40, mean age 43 ± 13 years). In
12 128 the group receiving gelatin tannate (500 mg, 6 times per day, for 2 consecutive days)
13 129 compared with the placebo group, a statistically significant decrease in both the daily
14 130 number of watery stools and severity of abdominal pain for the first 48 h of the
15 131 intervention was found. There were no clinically relevant adverse events.¹⁰
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28 133 A 2014 systematic review evaluated the efficacy of gelatin tannate in treating acute
29 134 gastroenteritis in children and adults.¹¹ The two above-described studies were
30 135 included. None of the included studies evaluated the effect of gelatin tannate on the
31 136 primary outcome measures for the review, such as stool output, duration of diarrhea,
32 137 need for admission to the hospital, duration of hospital stay, and (in children) weight
33 138 gain after rehydration. The review concluded that there is no evidence to support the
34 139 use of gelatin tannate for treating acute gastroenteritis in children and only sparse
35 140 evidence to support the use of gelatin tannate in adults.
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44 142 Taken together, currently, the evidence to support the use of gelatin tannate for
45 143 treating acute gastroenteritis in children or adults is very limited. According to the
46 144 current (2014) European guidelines,³ gelatin tannate is not recommended for the
47 145 management of acute gastroenteritis in children.
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53 147 **Trial objectives and hypotheses**

54 148 The main objective of this trial is to assess the effectiveness and safety of gelatin
55 149 tannate in the treatment of acute gastroenteritis in children. We aim to conduct a
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3 150 well-designed and executed study, with sufficient power, an adequate follow-up
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5 151 period, and relevant clinical endpoints. In our trial, we choose to use placebo for a
6
7 152 comparator as it is widely regarded as the gold standard for testing the efficacy of
8
9 153 new treatments.¹²

10 154

11 155 **METHODS AND ANALYSIS**

12
13 156 The trial is registered at www.clinicaltrials.gov (NCT02280759) and any important
14
15 157 changes in the protocol will be implemented there.

16 158

17 159 **Study design**

18
19 160 This study is designed as a randomized, blinded, placebo-controlled trial, with
20
21 161 allocation 1:1, and is described in more detail in subsequent sections.

22 162

23 163 **Setting and participants**

24
25 164 The recruitment will take place primarily in the emergency room of the pediatric
26
27 165 hospital of the Medical University of Warsaw. However, other recruiting sites are
28
29 166 under consideration provided that the personnel are adequately trained and
30
31 167 competent in conducting clinical trials. Participants will be randomized after their
32
33 168 first visit to the emergency room or after admission to the clinic. Caregivers will
34
35 169 receive oral and written information on the study. Written informed consent will by
36
37 170 obtained by physicians involved in the study.

38 171

39 172 **Inclusion criteria**

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41 173 Children eligible for the trial must fulfill all of the following criteria:

- 42
43 174 • Acute gastroenteritis defined as a change in stool consistency to loose or liquid
44
45 175 form (according to the Bristol Stool Form, BSF, scale or, in case of infants,
46
47 176 Amsterdam Stool Form, ASF, scale) and/or an increase in the frequency of
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49 177 evacuations (typically ≥ 3 in 24 hours), lasting for no longer than 5 days
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51 178 • Age younger than 5 years
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53 179 • A caregiver must provide written informed consent.
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181 Exclusion criteria

- 182 • Use of antibiotics, gelatin tannate, diosmectite, probiotics, racecadotril, or zinc
183 (including zinc containing oral rehydration solution) within a week prior to
184 enrollment.
- 185 • Exclusive breastfeeding.
- 186 • Chronic diarrheal gastrointestinal disease (e.g., inflammatory bowel diseases,
187 cystic fibrosis, celiac disease, food allergy).
- 188 • Immunodeficiencies.
- 189 • Malnutrition (weight/height/length under 3rd percentile) (WHO Childgrowth
190 Standards will be used).¹³
- 191 • If needed, discontinuation or modification of the treatment may be considered at
192 the discretion of the physician.

194 Randomization criteria

195 After re-checking the inclusion and exclusion criteria, participants will be assigned
196 into one of two groups (experimental or control). After determination of eligibility,
197 caregivers will receive a diary of symptoms to record the number of stools and their
198 consistency during the intervention (including recording of the timing of stools) BSF
199 and ASF scales will be provided. Additionally, caregivers will be asked to write
200 down any adverse events during the intervention period.

202 Interventions

203 The intervention under investigation is gelatin tannate manufactured by ICN Polfa
204 Rzeszów/Valeant. The manufacturer does not have and will not have a role in the
205 design or conduct of the study. The placebo will contain maltodextrine, which is an
206 almost flavorless, easily digestible polysaccharide commonly used as a food additive.
207 The dose of the active product or placebo will be age dependent (i.e., in children
208 younger than 3 years of age the dose is 250 mg and in children older than 3 year of
209 age – 500 mg). Both the gelatin tannate and placebo will be taken orally, 4 times per
210 day, for 5 days. Caregivers will be instructed to administer the daily dose at the same
211 time of a day, after mixing the contents of the sachet with a small amount of water.

212 The study products used in this trial will be prepared by the hospital pharmacy at
 213 the Medical University of Warsaw as identically appearing sachets. See **Table 1** for
 214 timetable of activities planned during the study.

215

216 **Table 1.** Timetable of activities planned during the study.

Days Activity	1	2	3	4	5	6	7
Enrollment	+						
Randomization	+						
Intervention	+	+	+	+	+		
Return of diary					+		
Follow up						+	+
Adverse events	+	+	+	+	+	+	+

217

218 For initial rehydration, all children will be treated according to 2014 European
 219 recommendations (fast oral rehydration over 3–4 hours by mouth or via nasogastric
 220 tube with the recommended hypotonic solution). After all signs of dehydration have
 221 disappeared, oral rehydration solution will be given for ongoing losses until the
 222 diarrhea stops. Rapid reintroduction of the previous diet after successful rehydration
 223 will be recommended. At all times, breastfeeding will be allowed.

224

225 At any time, caregivers will have the right to withdraw the participating child from
 226 the study; they will be not obliged to give reasons for this decision, and there will be
 227 no effect on subsequent physician and/or institutional medical care.

228

229 **Concomitant medications**

230 The concomitant administration of any other medication, including antipyretics and
 231 antiemetics, will be at the discretion of the physician to provide adequate care.

232 However, it is recommended that no unnecessary concomitant medication be used.

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3 233 In particular, the use of antibiotics, diosmectite, probiotics, or racecadotril (all
4 234 included in the exclusion criteria), should be avoided.

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6 235

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8 236 **Follow up**

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10 237 All study participants will be followed-up for the duration of the intervention (5
11 238 days) and then for an additional 48 h.

12
13 239

14 240 **Allocation concealment and blinding**

15
16 241 A computer-generated randomization list prepared by a person unrelated to the trial
17 242 will be used to allocate subjects to the study groups in blocks of eight. Consecutive
18 243 randomization numbers will be given to participants at enrollment. This procedure
19 244 will be performed by one of two physicians involved. The study product will be
20 245 weighed, packaged, and signed by consecutive numbers according to the
21 246 randomization list by the hospital pharmacy at the Medical University of Warsaw by
22 247 independent personnel not involved in the conduct of the study. The study products
23 248 will be delivered to the physicians in small envelopes labeled with the consecutive
24 249 numbers and dose (with the meaning of numbers blinded and information deposited
25 250 in a sealed envelope in a safe place in the administrative part of the department). The
26 251 active product and placebo will be packaged in identical sachets. Contents will look
27 252 and taste the same. Researchers, caregivers, outcome assessors, and a person
28 253 responsible for the statistical analysis will be blinded to the intervention until the
29 254 completion of the study. The information on intervention assignments will be stored
30 255 in a sealed envelope in a safe in the administrative part of the department. The
31 256 personal information about potential and enrolled participants will be stored in a
32 257 locker within the study site, accessible for the involved researchers only.

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34 258

35 259 **Compliance**

36
37 260 The caregivers will be asked to bring the remaining study product and diary to the
38 261 study site at the end of the intervention period. Compliance with the study protocol
39 262 will be checked by counting the number of sachets left unused. Based on previously

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3 263 published trials, it seems to be appropriate to consider those subjects receiving less
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5 264 than 75% of the recommended doses as noncompliant.
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7 265

8 266 **Primary outcome**

9
10 267 The primary outcome will be the duration of diarrhea, defined as the time until the
11
12 268 normalization of stool consistency according to the BSF or ASF scale (in BSF Scale,
13
14 269 numbers 2, 3, 4 and 5, and in ASF Scale, letters B or C), or the time until the
15
16 270 normalization of the number of stools (compared with the period before the onset of
17
18 271 diarrhea), and the presence of normal stools for 48 h.
19

20 272

21 273 **Secondary outcomes**

- 22 274 • need for intravenous rehydration
23
24 275 • need for hospitalization in outpatients
25
26 276 • number of watery stools per day
27
28 277 • vomiting
29
30 278 • weight gain
31
32 279 • adverse events
33
34 280 • recurrence of diarrhea (48 h after intervention)
35
36 281 • severity of diarrhea according to Vesikari scale.¹⁴
37

38 282

39 283 **Power calculation**

40 284 The primary outcome of the study is the duration of diarrhea. Based on available
41
42 285 data in the literature, the average duration of gastroenteritis in children is 5-7 days.³
43
44 286 We assume that a clinically significant difference in the effectiveness of gelatin
45
46 287 tannate versus placebo will shorten the duration of symptoms by 24. To detect such a
47
48 288 difference in the duration of diarrhea between the study groups with a power of 90%
49
50 289 and $\alpha = 0.01$, a sample of 60 children is needed. Assuming about a 20% loss to follow
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52 290 up, we aim to recruit a total of 72 children for this study. In the Department of
53
54 291 Paediatrics of The Medical University of Warsaw, there are 200 admissions of
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56 292 children with diarrhea per year and the same number of such patients who present
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58 293 to the emergency room. Assuming that 20% of these children will be eligible for the
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3 294 study, we will achieve adequate participant enrollment to reach the target sample
4 295 size after 2 years of recruiting.
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8 297 **Statistical analysis**

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10 298 All analysis will be conducted on an intention-to-treat basis, including all patients in
11 299 the groups to which they are randomized for whom outcomes will be available
12 300 (including dropouts and withdrawals). Descriptive statistics will be used to
13 301 summarize baseline characteristics. The Student t test will be used to compare mean
14 302 values of continuous variables approximating a normal distribution. For non-
15 303 normally distributed variables, the Mann-Whitney U test will be used. The χ^2 test or
16 304 Fisher exact test will be used, as appropriate, to compare percentages. For continuous
17 305 outcomes, differences in means or differences in medians (depending on the
18 306 distribution of the data), and for dichotomous outcomes, the relative risk (RR) and
19 307 number needed to treat, all with a 95% confidence interval, will be calculated. The
20 308 difference between study groups will be considered significant when the p value is
21 309 <0.05 , when the 95% CI for RR does not include 1.0, or when the 95% CI for MD does
22 310 not include 0. All statistical tests will be two tailed and performed at the 5% level of
23 311 significance.
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36 313 **ETHICS AND DISSEMINATION**

37 314 The Bioethical Committee of The Medical University of Warsaw issued approval for
38 315 the study before recruitment commenced. Verbal and written information regarding
39 316 informed consent will be presented to the caregivers. Any modifications to the
40 317 protocol that may affect the conduct of the study will be presented to the Committee.
41 318 The full protocol will be available freely due to open access publication. The findings
42 319 of this RCT will be submitted to a peer-reviewed journal. Abstracts will be submitted
43 320 to relevant national and international conferences.
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52 322 **FUNDING STATEMENT**

53 323 This trial will be funded by The Medical University of Warsaw. At the time of
54 324 submission of this protocol for publication, no specific grant from any funding
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3 325 agency in the public, commercial, or not-for-profit sectors has been awarded to this
4
5 326 project.

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7 327

8 328 Competing interest statement: None declared.

9 329

10 330 Contributorship statement: HS conceptualized the study. All authors contributed
11 to the design of the study. DM and MK developed the first draft of the manuscript
12 and contributed equally. All authors approved the final draft of the manuscript.
13 332

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15 334 Funding statement: This study will be fully funded by The Medical University of
16 Warsaw.
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¹² Benson H, Friedman R. Harnessing the power of the placebo effect and renaming it "remembered wellness". *Annu Rev Med* 1996;47:193-9.

¹³ The WHO Child Growth Standards <http://www.who.int/childgrowth/en/>

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

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6,8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	-
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	-
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	-
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	-
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	-
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	-
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

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



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ✓
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ✓
	2b	All items from the World Health Organization Trial Registration Data Set []
	3	Date and version identifier ✓
Funding	4	Sources and types of financial, material, and other support ✓
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ✓
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) XXX
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ✓
	6b	Explanation for choice of comparators ✓
Objectives	7	Specific objectives or hypotheses ✓
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) ✓

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained ✓
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ✓
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ✓
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) ✓
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ✓
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial ✓
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended ✓
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) ✓
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations ✓
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ✓

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions ✓
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2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned ✓
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions ✓
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how ✓
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14		17b	If blinded, circumstances under which unblinding is permissible, and
15			procedure for revealing a participant's allocated intervention during
16			the trial ✓
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Methods: Data collection, management, and analysis

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21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol ✓
27			
28		18b	Plans to promote participant retention and complete follow-up,
29			including list of any outcome data to be collected for participants who
30			discontinue or deviate from intervention protocols
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33	Data	19	Plans for data entry, coding, security, and storage, including any
34	management		related processes to promote data quality (eg, double data entry;
35			range checks for data values). Reference to where details of data
36			management procedures can be found, if not in the protocol
37			
38	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
39	methods		Reference to where other details of the statistical analysis plan can be
40			found, if not in the protocol ✓
41			
42		20b	Methods for any additional analyses (eg, subgroup and adjusted
43			analyses) ✓
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45		20c	Definition of analysis population relating to protocol non-adherence
46			(eg, as randomised analysis), and any statistical methods to handle
47			missing data (eg, multiple imputation)
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Methods: Monitoring

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52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
53			and reporting structure; statement of whether it is independent from
54			the sponsor and competing interests; and reference to where further
55			details about its charter can be found, if not in the protocol.
56			Alternatively, an explanation of why a DMC is not needed ??
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1		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ✓
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6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ✓
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10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ✓
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Ethics and dissemination

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17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ✓
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20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ✓
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26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ✓
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29		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable X
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31	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ✓
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36	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ✓
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39	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ✓
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43	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation ✓
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46	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions ✓
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52		31b	Authorship eligibility guidelines and any intended use of professional writers ?
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55		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code ✓
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable ✓

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

For peer review only

BMJ Open

Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in children: protocol of a randomized controlled trial

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	children, antidiarrheal drugs, diarrhea, RCT

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Manuscripts

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6 3 **Efficacy and safety of gelatin tannate for the treatment of acute gastroenteritis in**
7 4 **children: protocol of a randomized controlled trial**
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12 8

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24 19 **Date and protocol version identifier:** 10.11.2015 ver. 1.0
25 20

26 21 **Key words:** antidiarrheal drugs, gastrointestinal infection, diarrhea, RCT
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28 23 **Word count:** 3246
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30 25 Number of figures: 0
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32 27 Number of tables: 1
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34 29 Number of references: 14.
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3 37 **ABSTRACT**

4 38 **Introduction**

5 39 Worldwide, acute gastroenteritis in children, usually caused by viruses, leads to
6 40 considerable morbidity and mortality. The treatment is aimed at preventing and
7 41 treating dehydration, promoting weight gain after rehydration, and reducing the
8 42 duration and severity of diarrhea. Effective and inexpensive interventions that could
9 43 add to the effect of oral rehydration therapy are of interest. Recently, in many
10 44 European countries, gelatin tannate is being widely marketed for treating acute
11 45 gastroenteritis. Gelatin tannate is a complex of tannic acid, which possesses
12 46 astringent and anti-inflammatory properties, and a protective gelatin. Currently,
13 47 there is no evidence to support the use of gelatin tannate for treating acute
14 48 gastroenteritis in children and only scant evidence to support the use of gelatin
15 49 tannate in adults. We aim to assess the efficacy of gelatin tannate for the treatment of
16 50 acute gastroenteritis in children.
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21 51
22 52 **Methods and analysis**

23 53 This will be a blind, placebo-controlled, randomized trial. Children younger than 5
24 54 years of age with acute gastroenteritis defined as a change in stool consistency to
25 55 loose or liquid form (according to the Bristol Stool Form scale or Amsterdam Stool
26 56 Form scale) and/or an increase in the frequency of evacuations (typically ≥ 3 in 24
27 57 hours), lasting for no longer than 5 days, will be recruited. A total of 158 children will
28 58 be randomized to receive either gelatin tannate (children younger than 3 years of age
29 59 will receive 250 mg 4 times per day and those older than 3 years of age will receive
30 60 500 mg 4 times per day) or matching placebo for 5 days. The primary outcome
31 61 measure is the duration of diarrhea.
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35 63 **Ethics and dissemination**

36 64 The Bioethics Committee approved the study protocol. The findings of this trial will
37 65 be submitted to a peer-reviewed pediatric journal. Abstracts will be submitted to
38 66 relevant national and international conferences.
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41 68 **Registration**

42 69 www.clinicaltrials.gov (NCT02280759)
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3 73 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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5 74 • The study design (randomized controlled trial, RCT) is the most robust
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7 75 methodology to assess the effectiveness of therapeutic interventions.
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9 76 • A precise clinical question has been posed to fill a gap in knowledge as to
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11 77 whether gelatin tannate is safe and effective in the treatment of acute
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13 78 gastroenteritis in children.
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15 79 • The findings of this RCT, whether positive or negative, will contribute to the
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17 80 formulation of recommendations on the use of gelatin tannate for the treatment of
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19 81 acute gastroenteritis.
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21 82 • Due to practicalities, stool volume, which is one of the objective ways of assessing
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23 83 the efficacy of antidiarrheal drugs, will not be assessed.
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88 INTRODUCTION

89 Worldwide, acute gastroenteritis in children, usually caused by rotaviruses, leads to
90 considerable morbidity and mortality.¹ It is also the most common cause of primary
91 care consultations among children younger than 5 years of age.² According to current
92 European guidelines,³ the mainstay of treatment for acute gastroenteritis is oral
93 rehydration with a hypoosmolar solution. Breastfeeding should not be interrupted.
94 Regular feeding should continue with no dietary changes including milk.
95 Considering the burden of acute gastroenteritis both to children and the healthcare
96 system, effective and inexpensive interventions that could add to the effect of oral
97 rehydration therapy are of interest. Currently, effective interventions that may
98 reduce the duration and severity of diarrhea include administration of specific
99 probiotics such as *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*, diosmectite,
100 or racecadotril.³

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102 Recently, in many European countries, gelatin tannate is being marketed for treating
103 acute gastroenteritis. Gelatin tannate consists of tannic acid suspended in a gelatin
104 solution. Gelatin tannate has a stable structure both in the acidic environment of the
105 stomach as well as in a basic and neutral environment such as in the small intestine
106 and colon.⁴ Little is known about the specific mechanisms by which gelatin tannate
107 may act against gastrointestinal infection. It is known, however, that it forms a
108 biofilm, which mechanically protects the gastrointestinal mucosa and causes
109 precipitation of pro-inflammatory proteins such as mucoproteins in the intestinal
110 mucosa.⁵ In addition, it inhibits the growth of bacteria such as *Bacteroides fragilis*,
111 *Clostridium perfringens*, *Escherichia coli*, *Enterobacter cloacae*, *Salmonella typhimurium*,
112 *Helicobacter pylori*, *Listeria monocytogenes*, and in vitro mycobacterial *Vibrio cholerae*.^{5 6 7}
113 The action of anti-inflammatory tannate also involves blocking inflammatory agents
114 in the gastrointestinal mucosa.⁸

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116 Only limited evidence is available on the effectiveness of gelatin tannate. In 2009,
117 Esteban Carretero et al. published a study (n=211, mean age 2.5 ± 2.4 years, no
118 randomization, no blinding, unbalanced baseline characteristics) that evaluated the

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3 119 effectiveness of gelatin tannate in the treatment of acute gastroenteritis in children.
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5 120 Children received oral rehydration solution (ORS) alone or ORS in combination with
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7 121 gelatin tannate (dose was not specified). During the 12-h observation period, a
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9 122 significant reduction in the number of loose stools was found in the group receiving
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11 123 ORS and gelatin tannate versus the group receiving ORS alone. Both groups had
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13 124 similar weight gains, stool consistency, comparative risks of diarrhea with blood,
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15 125 peritonitis, and sepsis, vomiting intensity, and degrees of dehydration in the 12 h of
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17 126 observation.⁹ In 2012, Allegrini and Costantini performed a blinded, randomized,
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19 127 placebo-controlled trial in the adult population (n = 40, mean age 43 ± 13 years). In
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21 128 the group receiving gelatin tannate (500 mg, 6 times per day, for 2 consecutive days)
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23 129 compared with the placebo group, a statistically significant decrease in both the daily
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25 130 number of watery stools and severity of abdominal pain for the first 48 h of the
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27 131 intervention was found. There were no clinically relevant adverse events.¹⁰
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31 133 A 2014 systematic review evaluated the efficacy of gelatin tannate in treating acute
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33 134 gastroenteritis in children and adults.¹¹ The two above-described studies were
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35 135 included. None of the included studies evaluated the effect of gelatin tannate on the
36
37 136 primary outcome measures for the review, such as stool output, duration of diarrhea,
38
39 137 need for admission to the hospital, duration of hospital stay, and (in children) weight
40
41 138 gain after rehydration. The review concluded that there is no evidence to support the
42
43 139 use of gelatin tannate for treating acute gastroenteritis in children and only sparse
44
45 140 evidence to support the use of gelatin tannate in adults.
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47 141

48
49 142 Taken together, currently, the evidence to support the use of gelatin tannate for
50
51 143 treating acute gastroenteritis in children or adults is very limited. According to the
52
53 144 current (2014) European guidelines,³ gelatin tannate is not recommended for the
54
55 145 management of acute gastroenteritis in children.
56
57 146

58 147 **Trial objectives and hypotheses**

59 148 The main objective of this trial is to assess the effectiveness and safety of gelatin
60 149 tannate in the treatment of acute gastroenteritis in children. We aim to conduct a

1
2
3 150 well-designed and executed study, with sufficient power, an adequate follow-up
4
5 151 period, and relevant clinical endpoints. In our trial, we choose to use placebo for a
6
7 152 comparator as it is widely regarded as the gold standard for testing the efficacy of
8
9 153 new treatments.¹²

10 154

11 155 **METHODS AND ANALYSIS**

12
13 156 The trial is registered at www.clinicaltrials.gov (NCT02280759) and any important
14
15 157 changes in the protocol will be implemented there.

16 158

17 159 **Study design**

18
19 160 This study is designed as a randomized, blinded, placebo-controlled trial, with
20
21 161 allocation 1:1, and is described in more detail in subsequent sections.

22 162

23 163 **Setting and participants**

24
25 164 The recruitment will take place primarily in the emergency room of the pediatric
26
27 165 hospital of the Medical University of Warsaw. However, other recruiting sites are
28
29 166 under consideration provided that the personnel are adequately trained and
30
31 167 competent in conducting clinical trials. Participants will be randomized after their
32
33 168 first visit to the emergency room or after admission to the clinic. Caregivers will
34
35 169 receive oral and written information on the study. Written informed consent will by
36
37 170 obtained by physicians involved in the study.

38 171

39 172 **Inclusion criteria**

40
41 173 Children eligible for the trial must fulfill all of the following criteria:

- 42
43 174 • Acute gastroenteritis defined as a change in stool consistency to loose or liquid
44
45 175 form (according to the Bristol Stool Form, BSF, scale or, in case of infants,
46
47 176 Amsterdam Stool Form, ASF, scale) and/or an increase in the frequency of
48
49 177 evacuations (typically ≥ 3 in 24 hours), lasting for no longer than 5 days
50
51 178 • Age younger than 5 years
52
53 179 • A caregiver must provide written informed consent.
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181 Exclusion criteria

- 182 • Use of antibiotics, gelatin tannate, diosmectite, probiotics, racecadotril, or zinc
183 (including zinc containing oral rehydration solution) within a week prior to
184 enrollment.
- 185 • Exclusive breastfeeding.
- 186 • Chronic diarrheal gastrointestinal disease (e.g., inflammatory bowel diseases,
187 cystic fibrosis, celiac disease, food allergy).
- 188 • Immunodeficiencies.
- 189 • Malnutrition (weight/height/length under 3rd percentile) (WHO Childgrowth
190 Standards will be used).¹³
- 191 • If needed, discontinuation or modification of the treatment may be considered at
192 the discretion of the physician.

194 Randomization criteria

195 After re-checking the inclusion and exclusion criteria, participants will be assigned
196 into one of two groups (experimental or control). After determination of eligibility,
197 caregivers will receive a diary of symptoms to record the number of stools and their
198 consistency during the intervention (including recording of the timing of stools) BSF
199 and ASF scales will be provided. Additionally, caregivers will be asked to write
200 down any adverse events during the intervention period.

202 Interventions

203 The intervention under investigation is gelatin tannate manufactured by ICN Polfa
204 Rzeszów/Valeant. The manufacturer does not have and will not have a role in the
205 design or conduct of the study. The placebo will contain maltodextrine, which is an
206 almost flavorless, easily digestible polysaccharide commonly used as a food additive.
207 The dose of the active product or placebo will be age dependent (i.e., in children
208 younger than 3 years of age the dose is 250 mg and in children older than 3 year of
209 age – 500 mg). Both the gelatin tannate and placebo will be taken orally, 4 times per
210 day, for 5 days. Caregivers will be instructed to administer the daily dose at the same
211 time of a day, after mixing the contents of the sachet with a small amount of water.

212 The study products used in this trial will be prepared by the hospital pharmacy at
 213 the Medical University of Warsaw as identically appearing sachets. See **Table 1** for
 214 timetable of activities planned during the study.

215

216 **Table 1.** Timetable of activities planned during the study.

Days Activity	1	2	3	4	5	6	7
Enrollment	+						
Randomization	+						
Intervention	+	+	+	+	+		
Return of diary					+		
Follow up						+	+
Adverse events	+	+	+	+	+	+	+

217

218 For initial rehydration, all children will be treated according to 2014 European
 219 recommendations (fast oral rehydration over 3–4 hours by mouth or via nasogastric
 220 tube with the recommended hypotonic solution). After all signs of dehydration have
 221 disappeared, oral rehydration solution will be given for ongoing losses until the
 222 diarrhea stops. Rapid reintroduction of the previous diet after successful rehydration
 223 will be recommended. At all times, breastfeeding will be allowed.

224

225 At any time, caregivers will have the right to withdraw the participating child from
 226 the study; they will be not obliged to give reasons for this decision, and there will be
 227 no effect on subsequent physician and/or institutional medical care.

228

229 **Concomitant medications**

230 The concomitant administration of any other medication, including antipyretics and
 231 antiemetics, will be at the discretion of the physician to provide adequate care.

232 However, it is recommended that no unnecessary concomitant medication be used.

1
2
3 233 In particular, the use of antibiotics, diosmectite, probiotics, or racecadotril (all
4 234 included in the exclusion criteria), should be avoided.

5
6 235
7

8 236 **Follow up**

9
10 237 All study participants will be followed-up for the duration of the intervention (5
11 238 days) and then for an additional 48 h.

12
13 239

14 240 **Allocation concealment and blinding**

15
16
17 241 A computer-generated randomization list prepared by a person unrelated to the trial
18 242 will be used to allocate subjects to the study groups in blocks of eight. Consecutive
19 243 randomization numbers will be given to participants at enrollment. This procedure
20 244 will be performed by one of two physicians involved. The study product will be
21 245 weighed, packaged, and signed by consecutive numbers according to the
22 246 randomization list by the hospital pharmacy at the Medical University of Warsaw by
23 247 independent personnel not involved in the conduct of the study. The study products
24 248 will be delivered to the physicians in small envelopes labeled with the consecutive
25 249 numbers and dose (with the meaning of numbers blinded and information deposited
26 250 in a sealed envelope in a safe place in the administrative part of the department). The
27 251 active product and placebo will be packaged in identical sachets. Contents will look
28 252 and taste the same. Researchers, caregivers, outcome assessors, and a person
29 253 responsible for the statistical analysis will be blinded to the intervention until the
30 254 completion of the study. The information on intervention assignments will be stored
31 255 in a sealed envelope in a safe in the administrative part of the department. The
32 256 personal information about potential and enrolled participants will be stored in a
33 257 locker within the study site, accessible for the involved researchers only.

34
35 258

36 259 **Compliance**

37
38 260 The caregivers will be asked to bring the remaining study product and diary to the
39 261 study site at the end of the intervention period. Compliance with the study protocol
40 262 will be checked by counting the number of sachets left unused. Based on previously
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263 published trials, it seems to be appropriate to consider those subjects receiving less
264 than 75% of the recommended doses as noncompliant.

265

266 **Primary outcome**

267 The primary outcome will be the duration of diarrhea, defined as the time until the
268 normalization of stool consistency according to the BSF or ASF scale (in BSF Scale,
269 numbers 2, 3, 4 and 5, and in ASF Scale, letters B or C), or the time until the
270 normalization of the number of stools (compared with the period before the onset of
271 diarrhea), and the presence of normal stools for 48 h.

272

273 **Secondary outcomes**

- 274 • need for intravenous rehydration
- 275 • need for hospitalization in outpatients
- 276 • number of watery stools per day
- 277 • vomiting
- 278 • weight gain
- 279 • adverse events
- 280 • recurrence of diarrhea (48 h after intervention)
- 281 • severity of diarrhea according to Vesikari scale¹⁴
- 282 • use of concomitant medications.

283

284 **Power calculation**

285 The primary outcome of the study is the duration of diarrhea. Based on available
286 data in the literature, the average duration of gastroenteritis in children is 5-7 days.³
287 We assume that a clinically significant difference in the effectiveness of gelatin
288 tannate versus placebo will shorten the duration of symptoms by 24. To detect such a
289 difference in the duration of diarrhea between the study groups with a power of 90%
290 and $\alpha = 0.01$, a sample of 60 children is needed. Assuming about a 20% loss to follow
291 up, we aim to recruit a total of 72 children for this study. In the Department of
292 Paediatrics of The Medical University of Warsaw, there are 200 admissions of
293 children with diarrhea per year and the same number of such patients who present

1
2
3 294 to the emergency room. Assuming that 20% of these children will be eligible for the
4 295 study, we will achieve adequate participant enrollment to reach the target sample
5 296 size after 2 years of recruiting.
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9 10 298 **Statistical analysis**

11 299 All analysis will be conducted on an intention-to-treat basis, including all patients in
12 300 the groups to which they are randomized for whom outcomes will be available
13 301 (including dropouts and withdrawals). Descriptive statistics will be used to
14 302 summarize baseline characteristics. The Student t test will be used to compare mean
15 303 values of continuous variables approximating a normal distribution. For non-
16 304 normally distributed variables, the Mann-Whitney U test will be used. The χ^2 test or
17 305 Fisher exact test will be used, as appropriate, to compare percentages. For continuous
18 306 outcomes, differences in means or differences in medians (depending on the
19 307 distribution of the data), and for dichotomous outcomes, the relative risk (RR) and
20 308 number needed to treat, all with a 95% confidence interval, will be calculated. The
21 309 difference between study groups will be considered significant when the p value is
22 310 <0.05 , when the 95% CI for RR does not include 1.0, or when the 95% CI for MD does
23 311 not include 0. All statistical tests will be two tailed and performed at the 5% level of
24 312 significance.
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39 314 **ETHICS AND DISSEMINATION**

40 315 The Bioethical Committee of The Medical University of Warsaw issued approval for
41 316 the study before recruitment commenced. Verbal and written information regarding
42 317 informed consent will be presented to the caregivers. Any modifications to the
43 318 protocol that may affect the conduct of the study will be presented to the Committee.
44 319 The full protocol will be available freely due to open access publication. The findings
45 320 of this RCT will be submitted to a peer-reviewed journal. Abstracts will be submitted
46 321 to relevant national and international conferences.
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53 322 54 323 **FUNDING STATEMENT**

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3 324 This trial will be funded by The Medical University of Warsaw. At the time of
4
5 325 submission of this protocol for publication, no specific grant from any funding
6
7 326 agency in the public, commercial, or not-for-profit sectors has been awarded to this
8
9 327 project.

10 328

11 329 Competing interest statement: None declared.

12 330

13
14 331 Contributorship statement: HS conceptualized the study. All authors contributed
15 332 to the design of the study. DM and MK developed the first draft of the manuscript
16 333 and contributed equally. All authors approved the final draft of the manuscript.

17 334

18
19 335 Funding statement: This study will be fully funded by The Medical University of
20 336 Warsaw.

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¹² Benson H, Friedman R. Harnessing the power of the placebo effect and renaming it "remembered wellness". *Annu Rev Med* 1996;47:193-9.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ✓
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ✓
	2b	All items from the World Health Organization Trial Registration Data Set []
Protocol version	3	Date and version identifier ✓
Funding	4	Sources and types of financial, material, and other support ✓
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ✓
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) XXX
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ✓
	6b	Explanation for choice of comparators ✓
Objectives	7	Specific objectives or hypotheses ✓
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) ✓

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained ✓
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ✓
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ✓
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) ✓
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ✓
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial ✓
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended ✓
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) ✓
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations ✓
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ✓

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions ✓
---------------------	-----	--

1			
2	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
3	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
4	mechanism		describing any steps to conceal the sequence until interventions are
5			assigned ✓
6			
7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
8			and who will assign participants to interventions ✓
9			
10	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
11	(masking)		participants, care providers, outcome assessors, data analysts), and
12			how ✓
13			
14		17b	If blinded, circumstances under which unblinding is permissible, and
15			procedure for revealing a participant's allocated intervention during
16			the trial ✓
17			
18			

Methods: Data collection, management, and analysis

20			
21	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
22	methods		trial data, including any related processes to promote data quality (eg,
23			duplicate measurements, training of assessors) and a description of
24			study instruments (eg, questionnaires, laboratory tests) along with
25			their reliability and validity, if known. Reference to where data
26			collection forms can be found, if not in the protocol ✓
27			
28		18b	Plans to promote participant retention and complete follow-up,
29			including list of any outcome data to be collected for participants who
30			discontinue or deviate from intervention protocols
31			
32			
33	Data	19	Plans for data entry, coding, security, and storage, including any
34	management		related processes to promote data quality (eg, double data entry;
35			range checks for data values). Reference to where details of data
36			management procedures can be found, if not in the protocol
37			
38	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
39	methods		Reference to where other details of the statistical analysis plan can be
40			found, if not in the protocol ✓
41			
42		20b	Methods for any additional analyses (eg, subgroup and adjusted
43			analyses) ✓
44			
45		20c	Definition of analysis population relating to protocol non-adherence
46			(eg, as randomised analysis), and any statistical methods to handle
47			missing data (eg, multiple imputation)
48			
49			

Methods: Monitoring

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52	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
53			and reporting structure; statement of whether it is independent from
54			the sponsor and competing interests; and reference to where further
55			details about its charter can be found, if not in the protocol.
56			Alternatively, an explanation of why a DMC is not needed ??
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1		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ✓
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6	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ✓
7			
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10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ✓
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Ethics and dissemination

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17	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ✓
18			
19			
20	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ✓
21			
22			
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25			
26	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ✓
27			
28			
29		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable X
30			
31	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ✓
32			
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36	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ✓
37			
38			
39	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ✓
40			
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43	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation ✓
44			
45			
46	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions ✓
47			
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52		31b	Authorship eligibility guidelines and any intended use of professional writers ?
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56		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code ✓
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Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ✓
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable ✓

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

For peer review only



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

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6,8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

1			
2		assessing outcomes) and how	
3			
4		11b If relevant, description of the similarity of interventions	7
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	10
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
7			
8	Results		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	-
10	diagram is strongly	were analysed for the primary outcome	
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	-
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	-
13		14b Why the trial ended or was stopped	-
14			
15	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	-
16	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	-
17		by original assigned groups	
18			
19	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	-
20	estimation	precision (such as 95% confidence interval)	
21		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
22	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	-
23		pre-specified from exploratory	
24			
25	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
26			
27	Discussion		
28	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	-
29	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	-
30	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	-
31			
32	Other information		
33	Registration	23 Registration number and name of trial registry	2
34	Protocol	24 Where the full trial protocol can be accessed, if available	-
35	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	1
36			

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

Correction: Efficacy and safety of gelatine tannate for the treatment of acute gastroenteritis in children: protocol of a randomised controlled trial

Michałek D, Kołodziej M, Konarska Z, *et al.* Efficacy and safety of gelatine tannate for the treatment of acute gastroenteritis in children: protocol of a randomised controlled trial. *BMJ Open* 2016;**6**:e010530. doi: 10.1136/bmjopen-2015-010530

In the *Abstract*, the number of children to be recruited should be 72 (as shown under *Power calculation*).

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