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Establishing a core outcome set for treatment of uncomplicated appendicitis in children: study protocol for a systematic review and international Delphi survey

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1 Establishing a core outcome set for treatment of uncomplicated 2 appendicitis in children: study protocol for a systematic review and 3 international Delphi survey. 4

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39 ABSTRACT

40 Introduction

41 Appendicitis is a global disease affecting roughly one in every 12 people in the world, with
42 the highest incidence between ages 10 and 19 years. To date, a wide variety of health
43 outcomes have been reported in randomized controlled trials (RCTs) and meta-analyses
44 evaluating treatments for appendicitis. This is especially the case in studies comparing non-
45 operative treatment to operative treatment. A set of standard outcomes, to be reported in all
46 future trials, is needed to allow for adequate comparison and interpretation of clinical trial
47 results and to make data pooling possible. This protocol describes the development of such
48 a global core outcome set (COS) to allow unified reporting of treatment interventions in
49 children with acute uncomplicated appendicitis.

50 Methods and analysis

51 We use current international standard methodology for the development and reporting of this
52 COS. Its development consists of three phases: (1) Update the most recent systematic
53 review on outcomes reported in uncomplicated paediatric appendicitis research, to identify
54 additional outcomes, (2) Three-step global Delphi study to identify a set of core outcomes for
55 which there is consensus between parents and (paediatric) surgeons, and (3) Expert meeting
56 to finalize the COS and its definitions. Children and young people will be involved through
57 their parents during phase two and will be engaged directly using a customized face-to-face
58 approach.

59 Ethics and dissemination.

60 The medical research ethics committee of the Academic Medical Centre Amsterdam has
61 approved the study. Each participating country/research group will ascertain ethics board
62 approval. Electronic informed consent will be obtained from all participants. Results will be
63 presented in peer-reviewed academic journals and at (international) conferences.

64 Registration details

65 The COS development project was registered with the COMET initiative in February 2018
66 (<http://www.comet-initiative.org/studies/details/1119>).

67 Article Summary

68 Strengths and limitations of this study

- 70 1. Globally relevant set of outcomes to be assessed in prospective research
- 71 2. International steering committee including patient representation
- 72 3. Involvement of parents and their children in choosing what to measure
- 73 4. Direct face-to-face involvement of young people, however, only in selected countries
- 74 5. Limited face-to-face consensus

76 INTRODUCTION

77 Appendicitis is a common gastro-intestinal disease affecting roughly one in every 12 people
78 in the world, with the highest incidence between ages 10 and 19 years[1,2]. While the
79 incidence varies from country to country, appendicitis is a global disease[3]. In the last
80 decade, there have been several developments in the treatment of appendicitis in children,
81 with the most recent being non-operative treatment (NOT) for acute uncomplicated
82 appendicitis. Studies investigating the effectiveness of NOT in children show promising
83 results[4–7]. However, the selected primary (and secondary) outcomes vary widely, as
84 reflected in recent systematic reviews assessing the efficacy and safety of NOT, this may
85 contribute to their contradictory conclusions[4–8]. In the systematic review by Georgiou et
86 al.[4], the need for universal outcome selection and reporting in appendicitis studies is
87 emphasized. In general, it is recognized that clinical trials in children often lack outcomes that
88 are appropriately chosen for this particular population[9].

89 Inconsistent selection and reporting of outcomes limits the ability to adequately compare and
90 interpret clinical trial results. Furthermore, it hampers data pooling and subsequent meta-
91 analysis. It also increases the risk of selective outcome reporting, a form of publication bias.
92 This in turn jeopardizes the validity of results from individual trials, which feeds into
93 subsequent systematic reviews[10] and meta-analyses, which are by nature retrospective,
94 and therefore liable to various risks of bias[11,12].

95 As demonstrated by Hall et al. in 2015, a wide variety of outcomes has been reported in
96 randomized controlled trials (RCTs) and meta-analyses reporting on the treatment of
97 appendicitis in children[13]. In the 63 included studies, a total of 115 different outcomes were
98 reported[13]. Hall et al. proposed the development of a Core Outcome Set (COS), which is a
99 standardized collection of outcomes that should be measured and reported in all future
100 trials[14]. Recently a study protocol was published for developing such a COS in the United
101 Kingdom[15]. To overcome any limitations of a COS focused on UK-specific surgical
102 practice, the aim of this study is to develop an international COS to be used for trials
103 assessing the treatment of acute uncomplicated appendicitis in children. The development of
104 this protocol and the international COS is being performed in conjunction with the UK
105 research group. Outcomes considered important by patients and families are essential to a
106 meaningful and complete COS[16]. Parent and patient representation in the development of
107 this protocol was provided through the Dutch patient and parent Foundation: “Children and
108 Hospital”. Furthermore, parents and patients will play a central role in the consensus process
109 as a stakeholder group.

110 Scope

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3 111 We aim to reach a global consensus amongst patients, parents, researchers and physicians
4 112 on the minimal set of core outcomes that should be measured and reported in all future
5 113 clinical trials investigating any type of treatment for acute uncomplicated appendicitis in
6 114 children, including surgical treatment, non-operative treatment or other treatment aimed at
7 115 curing appendicitis.
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11 116 **METHODS**

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14 117 In the development of this protocol, we adhere to the COS-STAD (Core Outcome Set-
15 118 STAndards for Development) recommendations[17] and the COMET (Core Outcome
16 119 Measures in Effectiveness Trials) handbook[18]. The completed COS-STAD checklist can be
17 120 found in online supplement S1. The final core outcome set will be reported in accordance
18 121 with the COS-Standards for reporting (COS-STAR) statement[19]. Involvement of patients
19 122 and the public will be described using the GRIPP2 reporting checklist[20] (Guidance for
20 123 Reporting on Involvement of Patients and Public). This study was registered with the COMET
21 124 initiative (registration number: 1119) on February 11, 2018[21].
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29 126 **Study design**

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31 127 The paediatric appendicitis COS (PA-COS) development will consist of three phases: (1) An
32 128 update of the 2015 systematic review on outcomes reported in uncomplicated paediatric
33 129 appendicitis research[13], in order to identify any additional outcomes used in trials that were
34 130 published since the previous systematic review; (2) A three-step Delphi study to identify a set
35 131 of core outcomes from those selected in the literature review. Development of the Delphi is
36 132 performed according to the checklist by Sinha et al.[22] on the design and reporting of Delphi
37 133 studies concerning COS selection; and (3) An expert panel meeting to ratify the final COS,
38 134 including physicians, researchers and children/parent representatives. Children and young
39 135 people will be involved through their parents during phase two and will be engaged directly
40 136 using a customized approach.
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49 138 **Steering Committee**

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51 139 An international steering committee has been established and consists of the following; the
52 140 authors, a parent/patient representative of the Dutch Foundation: "Children and Hospital",
53 141 and the lead local investigator of each participating centre (paediatric appendicitis COS
54 142 development group). The steering committee will agree on the final version of the protocol at
55 143 the start of the project and will provide input throughout the duration of the project. The
56 144 steering committee members will also be involved in the development of the final COS.
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59 145 Within the steering committee, a smaller study management group has been appointed
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3 146 which will convene during regular (videoconference) meetings.
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6 147 **Systematic review: Treatment outcomes**
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8 148 Hall et al. performed a systematic review of RCTs and meta-analyses reporting treatment
9 149 outcomes in children with appendicitis up to April 2014[13]. The 115 unique outcomes were
10 150 collapsed into a total of 38 standardized outcome terms. We will update the systematic
11 151 review to identify any additional reported outcomes in clinical trials or systematic reviews. All
12 152 RCTs and systematic reviews/meta-analyses reporting treatment outcomes of acute
13 153 uncomplicated appendicitis in children (<18 years of age) published between January 1st
14 154 2014 and November 23th 2017 will be included. The final review will follow the PRISMA
15 155 reporting guideline[23]. We will search the Cochrane Central Register of Controlled Trials,
16 156 MEDLINE and EMBASE with the help of a clinical librarian. Additional information on the
17 157 search strategy/study selection and data extraction can be found in online supplement S2.
18 158 Studies only reporting outcomes of treatment in complex or complicated appendicitis (for
19 159 example - gangrenous or perforated appendicitis, appendiceal mass, appendiceal abscess)
20 160 will be excluded.
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29 161 After data extraction, a meeting of the study management group will be held to discuss
30 162 potential similarity between the outcomes in order to assign an appropriate standardized
31 163 outcome term for them. Outcome terms will be mapped to four core areas (death, life impact,
32 164 resource use, pathophysiological manifestations) in accordance with the methods from the
33 165 OMERACT FILTER 2.0[24]. Although Hall et al.[13] chose to list the adverse events as a
34 166 separate core area, we will reclassify these outcome terms to one of the four core areas
35 167 (Table 1.). We will however, label adverse events of treatment separately, as the OMERACT
36 168 filter suggests[24]. A meeting of the study management group will be held to discuss
37 169 potential similarity between outcomes and to assign an appropriate outcome term for similar
38 170 outcomes. Outcomes that are only found once and are not generalizable can be excluded
39 171 (e.g. the width of lateral thermal damage of the mesoappendix after appendectomy).
40 172 Grouping the outcomes under a common outcome term aims to arrive at a manageable and
41 173 cohesive list of outcomes that is appropriate as a basis for the Delphi questionnaire.
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174 **Table 1. Outcome Core Areas**

| Core Area | Example(s) |
|-----------------------------------|---|
| Life impact | <i>Quality of life, loss of ability to work</i> |
| Resource use | <i>Length of hospital stay, healthcare costs, societal cost</i> |
| Pathophysiological Manifestations | <i>Biochemical parameters, organ function, (ir)reversible manifestations (complications, pathology results)</i> |
| Death | <i>Death</i> |

175

176 **Stakeholders and recruitment**177 **1) Children and Young People**

178 Children and young people (5-18 years) who have been treated for acute
 179 uncomplicated appendicitis in the preceding 24 months, either with initial NOT or with
 180 surgery. Children less than 5 years old are excluded since different outcomes might
 181 be appropriate in this very young age group. Also, uncomplicated appendicitis is
 182 much less common in young children than in older children. Furthermore, there are
 183 no studies in which children below the age of 5 are treated non-operatively. Children
 184 will be engaged (indirectly) through their parents in the Delphi questionnaire, and
 185 directly through a customized face-to-face approach in selected countries. For the
 186 invited children, considering the complexity of the subject and methodology, age is
 187 limited to 12-18 years.

188

189 **2) Parents**

190 Parents of children and young people (5-18 years) treated for acute uncomplicated
 191 appendicitis either with initial NOT or with surgery in the preceding 24 months or
 192 during the initial phase of the study. Parents will be asked to discuss the answers
 193 they provide with their child whilst filling out the Delphi questionnaire. Parents will be
 194 invited to participate by their child's treating physician or their designate in each
 195 participating country/hospital. Participants will be identified retrospectively by

196 contacting patients that were treated in the past 24 months or prospectively by
197 inviting patients to participate directly after they have completed their treatment.

198

199 **3) (Paediatric) Surgeons**

200 General and/or paediatric surgeons who care for children in the specified age group
201 will be asked to participate. Surgeons will be identified and invited by the local
202 coordinators in each participating country. These local coordinators are research
203 groups that have previously registered a clinical trial on uncomplicated appendicitis in
204 children. This should allow for inclusion of physicians that also have experience in
205 research on the treatment of appendicitis.

206

207 **Participating countries and research groups**

208 It was decided to invite research groups that are currently conducting clinical trials on the
209 treatment of acute uncomplicated in children. Groups were identified through
210 www.clinicaltrials.gov by searching (January 2017) for 'appendicitis' with an age limitation of
211 5-18 years. Studies with a mixed population (children and adults) were excluded. Studies
212 that had been completed before 2014, had not been updated since 2015, or with incomplete
213 registrations, were excluded. We found 111 trials, of which 12 trials assessed the treatment
214 of uncomplicated appendicitis in children. Groups from the Netherlands, USA, Canada,
215 Australia, Sweden, Finland, UK, France, Italy, Israel, Japan, Singapore and Malaysia were
216 identified. Some trials included hospitals from multiple countries.

217 **Sample size**

218 There is no rationale for determining the number of respondents to invite for a Delphi
219 study[18]. A minimum of seven respondents per stakeholder group is suggested to have a
220 large enough group to allow for a consensus process[25]. Taking into account that only some
221 invited participants will register for the Delphi and that not all respondents will complete all
222 rounds of the Delphi (attrition), a minimum of 40 respondents per stakeholder group per
223 country will be invited. There will be no maximum. In case the number of respondents per
224 country is significantly higher than other countries, we will consider a weightage per country
225 in the analyses. We anticipate that this sample will be large enough to reflect all relevant
226 opinions.

227

228 **Delphi study**

229 International online Delphi study

230 The Delphi method is an effective tool for reaching consensus in a large group without the
231 need for face-to-face contact[26]. The use of sequential questionnaires which are answered

232 anonymously by stakeholders is an established method for reaching consensus in a group of
233 experts[22]. Questionnaires will be sent using DelphiManager[27], a web-based system
234 designed for Delphi studies. The questionnaires will be open simultaneously to all
235 respondents of the participating countries. After each round, the responses of all participants
236 are shared anonymously in accordance with the Delphi principle.

237 The list of outcomes from the systematic review will be formatted into questions with
238 extensive additional information per outcome. The Delphi questionnaire will originally be
239 formulated in English and will be translated if required. Translation will only be performed by
240 native speaking professionals.

241 Participants will be asked to score the importance of each outcome using a 1 to 9 Likert
242 scale as recommended by the Grading of Recommendations Assessment, Development and
243 Evaluation (GRADE) working group[28] and COMET initiative[18]. A score of 7-9 indicates a
244 critical outcome for assessing the effect of a treatment, 4-6 important but not critical, 1-3
245 indicates an outcome with low importance for assessing the treatment effect. It will also be
246 possible to select an “unable to score” option, which is especially of importance if parents do
247 not feel equipped to score certain outcomes. The questionnaires will be piloted by a group of
248 laypersons (n=10) to check for ambiguity and readability.

249 Delphi round one

250 Participants will be divided into two stakeholder groups: parents (with their children), and
251 surgeons. Parents will be asked to discuss the answers they provide with their child whilst
252 filling out the Delphi questionnaire. Baseline characteristics (age, country) will be
253 ascertained. Parents will be asked if their child was treated with non-operative or operative
254 treatment, time between registration and the first diagnosis of appendicitis and if their
255 treatment was with or without complications. Surgeons will be asked their speciality
256 (paediatric, general, abdominal, other), workplace (academic, teaching hospital, non-
257 teaching hospital), experience with non-operative treatment, experience in research
258 regarding appendicitis in children.

259 All participants will be asked to score all previously identified outcomes according to their
260 perceived importance for assessing the treatment effect. In the first round there will be an
261 option to suggest additional outcomes not yet listed.

262 Participants will have between four and eight weeks to complete each round, depending on
263 the response rate. In that time they will receive two reminder emails as long as they have not
264 yet replied to the questionnaire.

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266 Delphi round one: analysis

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3 267 Results will be analysed **by stakeholder group and for all participants** using descriptive
4 268 statistics. Outcomes will be analysed separately for each stakeholder group, as there is
5 269 evidence that patients are likely to assign importance to outcomes differently than
6 270 surgeons[29], which has the potential to influence eventual outcome selection.

9
10 271 “Consensus-in” will be defined as:

- 12 272 – Greater than 70% of participants in **both** stakeholder groups scoring the outcome as
14 273 7-9 and less than 15% in **both** stakeholder groups scoring the outcome as 1-3.
- 16 274 – Greater than 90% of participants within **one** stakeholder group scoring the outcome
18 275 as 7-9. This implies that these outcomes are highly regarded by an individual
20 276 stakeholder group, and should also be included[18].

22 277 “Consensus-out” will be defined as:

- 25 278 – Greater than 70% of participants in **both** stakeholder groups scoring the outcomes as
26 279 1-3 and less than 15% of participants in **both** stakeholder groups scoring the
28 280 outcome as 7–9. Consensus-out can only be reached when there is consensus
29 281 across **both** stakeholders groups.

31
32 282 Outcomes that do not meet any of these criteria will be defined as “no consensus”. A
33 283 stratified analysis will be performed to check for skewing as a result of divergent opinions
34 284 from a single country or surgeons with or without research experience.

37 285 At the end of round one, there will be a meeting of the study management group to assess
38 286 whether an alteration in the Delphi study is appropriate. If additional outcomes are suggested
39 287 by Delphi participants, each outcome will be assessed by the study management group to
40 288 determine whether it is indeed new and to which category it should be classified. Wording of
41 289 the Delphi questionnaire will be adjusted if misinterpretation is suspected.

45
46 290 Delphi rounds two and three

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48 291 All participants who have completed the previous round will be asked to participate in the
49 292 next round. Only outcomes that have not been defined as “consensus-in” or “consensus-out”
50 293 during the previous round will be presented in the following rounds to all participants.
51 294 Outcomes for which there was “consensus-in” only within a single stakeholder group, will still
52 295 be presented to the other stakeholder group to evaluate whether consensus can be achieved
53 296 in both stakeholder groups. An overview of included and excluded outcomes will be
54 297 available. The outcomes for which there is no consensus and the newly suggested outcomes
55 298 from the previous rounds will be presented with the participants’ individual score and the
56 299 median scores from each stakeholder group combined with a histogram showing the scoring

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3 300 distribution. Participants will be asked again to score all remaining outcomes in the same
4 301 manner as in round one.

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7 302 Delphi rounds two and three analysis

8 303 Results will be analysed per stakeholder group and for all participants, using descriptive
9 304 statistics with the same definitions for consensus in/out as in the first Delphi round, including
10 305 a stratified analysis. After the second round, there will be a meeting of the study
11 306 management group to assess the need for alteration in the Delphi study, and to decide
12 307 whether or not to proceed with a third Delphi round, assuming consensus between **both**
13 308 stakeholder groups on more than 80% of the outcomes, and more than five outcomes with
14 309 consensus in. To give an estimate of the degree of agreement between respondents, the
15 310 width of the interquartile range of the median ranking score will be calculated, potentially
16 311 ranging from 0.00, meaning complete agreement, to 8.00, meaning least possible
17 312 agreement. This will be calculated for both the individual stakeholder groups as well as the
18 313 entire group of respondents after the final round.

26 27 314 **Face-to-face engagement of young people**

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29 315 We wish to check for discrepancies of opinion between parents answering the Delphi
30 316 together with their child and children who are interviewed directly. For this, a form of in-
31 317 person interaction will be organised with young people (12-18 years) who have been treated
32 318 for appendicitis. They will be asked to comment on the preliminary COS selection
33 319 established at the end of the Delphi study, and to suggest additional outcomes and comment
34 320 on outcomes that did not make the preliminary COS selection. This will either be done by a
35 321 short, face-to-face, one round questionnaire involving only outcomes relevant to
36 322 children/young people, or in the form of a small consensus meeting (prioritization meeting)
37 323 before finalizing the definitive COS. Due to feasibility, the face-to-face engagement will take
38 324 place in selected countries and separate ethics board approval will be obtained as
39 325 appropriate in those countries.

46 47 326 **Consensus discussion**

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50 327 If adequate consensus (we aim to achieve consensus on at least one outcome per
51 328 OMERACT core area) is reached in the Delphi study, we will organise a face-to-face expert
52 329 panel meeting with selected individuals with the purpose to ratify a pragmatic and well-
53 330 defined set of outcomes. A secondary aim of this meeting is to enhance support and
54 331 implementation of the final COS.

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57 332 The meeting will be held at an international conference for paediatric surgery. Through
58 333 purposive sampling, approximately 30 "experts" from across all stakeholder groups, including

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3 334 physicians, researchers and children/parent representatives, will be invited to participate in a
4 335 face-to-face meeting with the Steering Committee. Journal editors and healthcare
5 336 commissioners will also be invited to attend in an observational capacity with the purpose of
6 337 promoting implementation and to provide comments on the final list of outcomes.
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10 338 In the event that adequate consensus cannot be reached in the Delphi process, we will
11 339 organise a formal face-to-face consensus meeting or teleconference. In that case, we will
12 340 select an appropriate representation of all stakeholder groups from the panel members that
13 341 participated in the Delphi study.
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17 342 **Final COS development**

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20 343 The goal is to achieve a pragmatic COS that is applicable and feasible for all future trials that
21 344 evaluate the treatment of uncomplicated appendicitis in children. To achieve the goal of a
22 345 pragmatic COS we aim to arrive at a maximum of 10 outcomes. As a minimum, we aim to
23 346 have at least one outcome per core area. If consensus is reached on more than 10
24 347 outcomes, the 10 outcomes with the highest level of consensus will be considered part of the
25 348 suggested COS. Highest level of consensus depends on whether there is consensus in both
26 349 stakeholder groups, the median score that was appointed to the outcome, and the
27 350 interquartile range of the median score as an estimate of the degree of consensus.
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33 351 Only outcomes for which consensus is reached internationally will be selected. To test for
34 352 country bias, stratified analyses of the Delphi results will be performed. The results from the
35 353 face-to-face engagement of young people will be taken into account for the final COS
36 354 selection and will be reported separately. If there is no consensus between patients, parents
37 355 and healthcare professionals, an outcome can still be selected if there is clear consensus
38 356 within a single stakeholder group. These will be reported separately. The final COS will be
39 357 categorised according to the four core areas.
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45 358 **Ethics and dissemination.**

46 359 **Ethics**

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48 360 The medical research ethics committee of the Academic Medical Centre Amsterdam
49 361 confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) does not
50 362 apply to this study and that complete approval of this study by the committee is not required.
51 363 Each participating country/research group will be asked to obtain ethics board approval or
52 364 confirm that ethics board approval is not required. Electronic informed consent will be
53 365 obtained from all participants. The face-to-face engagement of young people (12-18 years)
54 366 will take place in selected countries and separate ethics board approval will be obtained, as
55 367 appropriate.
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368 Data collection and confidentiality

369 All data will be handled confidentially and in accordance with the Dutch Personal Data
370 Protection Act and the European General Data Protection Regulation (GDPR).
371 DelphiManager[27] will be used for the online questionnaire. After informed consent from all
372 participants only limited identifying information (name, email) will be ascertained during
373 registration. This information will be stored separately from the answers given in the
374 questionnaire and will only be used for the purpose of direct feedback and reminder emails.
375 Access to personally identifiable data will be strictly limited.

376 Dissemination

377 Dissemination of the results will be accomplished by publication in an international peer-
378 reviewed scientific journal and by presentations at (international) conferences. By inviting as
379 many of the principal investigators who are currently involved in research on uncomplicated
380 appendicitis in children, we aim to optimize implementation of the final COS. By involving
381 journal editors and healthcare commissioners in the face-to-face consensus discussion, we
382 aim to ultimately have the COS introduced as a requirement in future outcome reporting on
383 the treatment of uncomplicated appendicitis in children.

384 **DISCUSSION**

385 **Strengths and limitations of this study**

386 **Outcomes selection**

387 The selection of potential outcomes will be done systematically and will provide a selection
388 for the first Delphi questionnaire that reflects most issues pertinent to the treatment of
389 uncomplicated appendicitis. By including systematic reviews/meta-analyses that also report
390 on non-comparative studies, we expect to identify all reported treatment outcomes, including
391 those from the relatively new field of NOT for uncomplicated appendicitis.

392 To be able to arrive at a manageable list of outcomes that is appropriate for a Delphi study,
393 the number of outcome terms needs to be somewhat limited. In order to achieve this, the
394 outcomes derived from our systematic review will be merged in case of similarity. If
395 outcomes are not generalizable and only reported once, they will be excluded. This will be
396 proposed and prepared by two independent reviewers and discussed in the study
397 management group. However, the merging of outcomes will inevitably lead to some loss of
398 detail.

399 **Global consensus**

400 In order to reflect the views of different stakeholders, a variety of groups will be part of the
401 development of this COS. This is not only the case on a national level, but also on an
402 international level, related to, for example, differences between countries in resources,

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3 403 treatment practises for acute uncomplicated appendicitis, and cultural differences. By also
4 404 involving patients and parents from the participating countries we hope to correct for these
5 405 differences[30]. Involving members from different countries will not only lead to the
6 406 development of a COS that reflects the opinions of the international community, it should
7 407 also lead to an internationally applicable “minimal” COS. However, selecting the participating
8 408 countries on the basis of their involvement in research on appendicitis in children is a
9 409 limitation. This choice was made on the basis of feasibility. Researchers in the field of
10 410 uncomplicated appendicitis have an interest in the development of a COS and have the
11 411 network to help carry out the Delphi study. With our current selection we will, however, have
12 412 participants from four different continents. Our means of selection has another advantage.
13 413 Since non-operative treatment is an important research subject in childhood appendicitis, we
14 414 aim to include surgeons and parents who have experience in that field. As non-operative
15 415 treatment is still experimental in most of the world, we need surgeons and patients who have
16 416 been involved in such research.

26 417 **Limited face-to-face consensus**

27 418 If consensus is reached in the Delphi study we will not be organising a formal consensus
28 419 meeting. The Delphi method can be used for reaching consensus in a group of respondents
29 420 without the need for face-to-face contact. There is a risk of bias if a face-to-face consensus
30 421 meeting leads to selection of only participants who are able to attend the meeting, which is
31 422 especially a problem in a global consensus procedure. There are also problems regarding
32 423 language barriers in an international consensus meeting. To check for interpretation errors in
33 424 the Delphi method and to ensure a pragmatic and well-defined set of outcomes the results of
34 425 the Delphi study will be discussed in an (international) expert meeting. The influence of this
35 426 meeting on which outcomes are selected for the final COS is however very limited, as this is
36 427 decided in the prior Delphi study.

44 428 **Involving parents and their children**

45 429 Involving patients in COS development has recently become common practice with 88%
46 430 (n=112 as of April 12th 2016) of ongoing COS development studies doing so[18]. Involving
47 431 patients as participants seems imperative as patients may identify different outcomes that
48 432 should be measured, compared with physicians[16]. Several recent COS development
49 433 projects have attempted to engage children/young people in developing their COS, either as
50 434 part of the advisory group or the steering committee, or as a stakeholder group in the
51 435 Delphi[15,22], focus groups[31], interviews[32] or as a part of the consensus meeting[33].
52 436 Attempts to engage children and young people in an online Delphi questionnaire have
53 437 proven to be difficult. In the UK COS for uncomplicated appendicitis, there were substantial
54 438 difficulties with retaining young people in the consecutive rounds of the Delphi questionnaire,

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3 439 despite extensive efforts to optimize the methodology to appeal to children and young
4 440 people, including: preliminary semi-structured interviews on the subject, pre-testing of the
5 441 Delphi survey by young people and children[15] and video animations explaining the need for
6 442 a COS. Parent participation however showed more promising results. Consequently, to
7 443 safeguard the input of children/young people, the Delphi questionnaire for this study will be
8 444 developed to be completed by parents with input from their children (5-18 years) whenever
9 445 possible. In order to ensure that there are no large discrepancies between the opinions of
10 446 parents with their children, and with children without their parents, we will organize a form of
11 447 in-person interaction with young people (12-18 years) who have been treated for
12 448 appendicitis. Involving children/young people in COS development is a subject of interest in
13 449 many ongoing COS development projects. If experience from these groups warrants a
14 450 change in our methodology, we will adjust our protocol accordingly during the course of the
15 451 development and publish the updated protocol on an online, open source format (via the
16 452 Open Science Framework).

17 453 A limitation is that due to the international nature of our study it will not be feasible to engage
18 454 children directly in all the participating countries. That is why the face-to-face engagement
19 455 will take place in selected countries.

31 456 **Other stakeholders**

32 457 After careful consideration and consultation with the participating countries, it was decided
33 458 not to include paediatricians, general practitioners, or emergency medicine physicians.
34 459 Although all these specialists play an intricate role in the diagnosis and care for children with
35 460 appendicitis, they do not make the final decision regarding treatment or its provision. We will
36 461 however, depending on the organisation of the healthcare system in each country, ask these
37 462 stakeholders to comment on the final COS in order to ensure that essential outcomes are not
38 463 missed. Since almost all research regarding treatment of paediatric uncomplicated
39 464 appendicitis is initiated by (paediatric) surgeons, it was decided that researchers will not be
40 465 included as a separate individual stakeholder group. However, involvement in research will
41 466 be registered. Whilst their opinion is vital to the development of a COS, it is likely researchers
42 467 will be well represented in the (paediatric) surgeon stakeholder group. A stratified analyses
43 468 will be performed to check for skewing of the results by surgeons involved in research. It was
44 469 also decided not to include journal editors or healthcare commissioners. Even though their
45 470 opinion is of great importance especially regarding implementation, it was determined that
46 471 their opinion is not essential in establishing the outcomes selected for the COS. There is
47 472 much variability between countries regarding the role of these stakeholders, which would
48 473 lead to major challenges regarding Delphi analyses of such a small stakeholder group.
49 474 However, to enhance implementation and because of their expertise on the use of COSs,

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3 475 representatives from these stakeholder groups will be asked to attend the final consensus
4 476 discussion.

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7 477 **Outcome measures**

8 478 This study will not answer the question on how to measure the outcomes that are included in
9 479 the final COS, or at what time point the outcomes should be measured. We will however
10 480 attempt to come to a clear definition of each outcome. We expect that further research will be
11 481 necessary to answer the question of timing and how to measure the outcomes. We will
12 482 advise on this subject in the final report.
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3 484 **FOOTNOTES**
4

5 485 **Collaborators:**

6 486 The pediatric surgery departments of following hospitals have initiated the COS project and will
7 487 contribute by recruiting participants. Nationwide Children's Hospital, Columbus, OH, USA. Hasbro
8 488 Children's Hospital and Alpert Medical School of Brown University, Providence, RI, USA. Children's
9 489 Mercy Hospital, Kansas City, MO, USA. Karolinska University Hospital, Stockholm, Sweden.
10 490 Southampton General Hospital, Southampton, UK. Hôpital des Enfants, Centre Hospitalier
11 491 Universitaire Toulouse, Toulouse, France. Hôpital Femme-Enfant, University Hospital, CHU Rennes,
12 492 Rennes, France. Sydney Children's Hospital, Randwick NSW, Australia. KK Women's and Children's
13 493 Hospital, Singapore. BC Children's Hospital, Vancouver, BC, Canada. The Hospital for Sick Children,
14 494 Toronto, ON, Canada. Montreal Children's Hospital, Montreal, QC, Canada. Children's Hospital of
15 495 Manitoba, Winnipeg, MB, Canada. Emma Children's Hospital, Amsterdam UMC, University of
16 496 Amsterdam, Vrije Universiteit, Amsterdam, Netherlands. Helsinki Children's Hospital, Helsinki, Finland.
17 497 Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, Malaysia.
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20 498
21 499 **Acknowledgments**

22 500 We acknowledge Hester Rippen as the representative of the Dutch Foundation Children and Hospital
23 501 for her advice and support in drafting the protocol.
24 502

25 503 **Author contributions:**

26 504 All authors have contributed to the design of this protocol. MK, NJH JHvdL, RB and RRG have
27 505 initiated the project. The protocol was drafted by MK which was refined by NJH, JHvdL, RB, MO, NJB,
28 506 LWEvH, and RRG. Statistical advice was provided by JHvdL. MK was responsible for drafting this
29 507 manuscript. All authors have contributed to the manuscript and read and approved the final
30 508 manuscript. The paediatric appendicitis COS development group consist of all local investigators who
31 509 are responsible for translation, ethical board approval, participant recruitment. They have all read and
32 510 approved the final manuscript.
33 511

34 512 **Data sharing statement:**

35 513 The project is registered on the comet-initiative.org which is open access. The study findings will be
36 514 presented in a report which will be submitted for publication in a relevant peer-reviewed journal to
37 515 ensure dissemination to relevant healthcare professionals. Findings may also be submitted for
38 516 presentation at local meetings or conferences. The protocol will be published on an open access
39 517 repository.
40 518

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42 520 commercial or not-for-profit sectors
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44 521 **Competing interests statement:** None to declare
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523 **REFERENCES**

524

- 525 1 Addiss DG, Shaffer N, Fowler BS, *et al.* the Epidemiology of Appendicitis and
526 Appendectomy in the United States. *Am J Epidemiol* 1990;**132**:910–25.
527 doi:10.1093/oxfordjournals.aje.a115734
- 528 2 Anderson JE, Bickler SW, Chang DC, *et al.* Examining a common disease with
529 unknown etiology: trends in epidemiology and surgical management of appendicitis in
530 California, 1995-2009. *World J Surg* 2012;**36**:2787–94. doi:10.1007/s00268-012-1749-
531 z
- 532 3 Ferris M, Quan S, Kaplan BS, *et al.* The Global Incidence of Appendicitis. *Ann Surg*
533 2017;**266**:237–41. doi:10.1097/SLA.0000000000002188
- 534 4 Georgiou R, Eaton S, Stanton MP, *et al.* Efficacy and Safety of Nonoperative
535 Treatment for Acute Appendicitis: A Meta-analysis. *Pediatrics* 2017;;e20163003.
536 doi:10.1542/peds.2016-3003
- 537 5 Huang L, Yin Y, Yang L, *et al.* Comparison of Antibiotic Therapy and Appendectomy
538 for Acute Uncomplicated Appendicitis in Children. *JAMA Pediatr* 2017;**171**:426.
539 doi:10.1001/jamapediatrics.2017.0057
- 540 6 Xu J, Adams S, Liu YC, *et al.* Nonoperative management in children with early acute
541 appendicitis: A systematic review. *J Pediatr Surg* Published Online First: May 2017.
542 doi:10.1016/j.jpedsurg.2017.05.003
- 543 7 Kessler U, Mosbahi S, Walker B, *et al.* Conservative treatment versus surgery for
544 uncomplicated appendicitis in children: a systematic review and meta-analysis. *Arch*
545 *Dis Child* 2017;;archdischild-2017-313127. doi:10.1136/archdischild-2017-313127
- 546 8 Gorter RR, The S-MML, Gorter-Stam MAW, *et al.* Systematic review of nonoperative
547 versus operative treatment of uncomplicated appendicitis. *J Pediatr Surg* 2017;**18 Apr**
548 **201**. doi:10.1016/j.jpedsurg.2017.04.005
- 549 9 Sinha I, Jones L, Smyth RL, *et al.* A Systematic Review of Studies That Aim to
550 Determine Which Outcomes to Measure in Clinical Trials in Children. *PLoS Med*
551 2008;**5**:e96. doi:10.1371/journal.pmed.0050096
- 552 10 Kirkham JJ, Dwan KM, Altman DG, *et al.* The impact of outcome reporting bias in
553 randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:c365.

- 1
2
3 554 11 Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised
4 555 controlled trials. *Lancet (London, England)* 1998;**351**:47–52. doi:10.1016/S0140-
5 556 6736(97)08461-4
6
7
8
9 557 12 Zanchetti A, Mancia G. Searching for information from unreported trials--amnesty for
10 558 the past and prospective meta-analyses for the future. *J Hypertens* 1998;**16**:125.
11
12
13 559 13 Hall NJ, Kapadia MZ, Eaton S, *et al*. Outcome reporting in randomised controlled trials
14 560 and meta-analyses of appendicitis treatments in children: a systematic review. *Trials*
15 561 2015;**16**:275. doi:10.1186/s13063-015-0783-1
16
17
18 562 14 Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials*
19 563 2007;**8**:39. doi:10.1186/1745-6215-8-39
20
21
22 564 15 Sherratt FC, Eaton S, Walker E, *et al*. Development of a core outcome set to
23 565 determine the overall treatment success of acute uncomplicated appendicitis in
24 566 children: a study protocol. *BMJ Paediatr Open* 2017;**1**:e000151. doi:10.1136/bmjpo-
25 567 2017-000151
26
27
28
29 568 16 Sanderson T, Morris M, Calnan M, *et al*. What outcomes from pharmacologic
30 569 treatments are important to people with rheumatoid arthritis? Creating the basis of a
31 570 patient core set. *Arthritis Care Res (Hoboken)* 2010;**62**:640–6. doi:10.1002/acr.20034
32
33
34
35 571 17 Kirkham JJ, Davis K, Altman DG, *et al*. Core Outcome Set-STAndards for
36 572 Development: The COS-STAD recommendations. *PLOS Med* 2017;**14**:e1002447.
37 573 doi:10.1371/journal.pmed.1002447
38
39
40
41 574 18 Williamson PR, Altman DG, Bagley H, *et al*. The COMET Handbook: version 1.0.
42 575 *Trials* 2017;**18**:280. doi:10.1186/s13063-017-1978-4
43
44
45 576 19 Kirkham JJ, Gorst S, Altman DG, *et al*. Core Outcome Set-STAndards for Reporting:
46 577 The COS-STAR Statement. *PLoS Med* 2016;**13**:e1002148.
47 578 doi:10.1371/journal.pmed.1002148
48
49
50 579 20 Staniszewska S, Brett J, Simera I, *et al*. GRIPP2 reporting checklists: tools to improve
51 580 reporting of patient and public involvement in research. *BMJ* 2017;**358**:j3453.
52
53
54 581 21 Protocol for the development of a global core outcome set for treatment of
55 582 uncomplicated appendicitis in children :: Core Outcome Measures in Effectiveness
56 583 Trials Initiative (COMET). <http://www.comet-initiative.org/studies/details/1119>
57 584 (accessed 5 Mar 2018).
58
59
60 585 22 Sinha IP, Smyth RL, Williamson PR. Using the Delphi Technique to Determine Which
18

- 1
2
3 586 Outcomes to Measure in Clinical Trials: Recommendations for the Future Based on a
4 587 Systematic Review of Existing Studies. *PLoS Med* 2011;**8**:e1000393.
5 588 doi:10.1371/journal.pmed.1000393
6
7
8
9 589 23 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting
10 590 systematic reviews and meta-analyses of studies that evaluate health care
11 591 interventions: explanation and elaboration. *J Clin Epidemiol* 2009;**62**:e1–34.
12 592 doi:10.1016/j.jclinepi.2009.06.006
13
14
15
16 593 24 Boers M, Kirwan JR, Gossec L, *et al*. How to choose core outcome measurement sets
17 594 for clinical trials: OMERACT 11 approves filter 2.0. *J Rheumatol* 2014;**41**:1025–30.
18 595 doi:10.3899/jrheum.131314
19
20
21 596 25 Mullen PM. Delphi: myths and reality. *J Health Organ Manag* 2003;**17**:37–52.
22 597 doi:10.1108/14777260310469319
23
24
25 598 26 Murphy MK, Black NA, Lamping DL, *et al*. Consensus development methods, and their
26 599 use in clinical guideline development. *Health Technol Assess* 1998;**2**:i–iv, 1–88.
27
28
29 600 27 COMET DelphiManager. 2017.<http://www.comet-initiative.org/delphimanager/>
30 601 (accessed 4 Dec 2018).
31
32
33 602 28 Guyatt GH, Oxman AD, Kunz R, *et al*. GRADE guidelines: 2. Framing the question
34 603 and deciding on important outcomes. *J Clin Epidemiol* 2011;**64**:395–400.
35 604 doi:10.1016/j.jclinepi.2010.09.012
36
37
38
39 605 29 Brookes ST, Macefield RC, Williamson PR, *et al*. Three nested randomized controlled
40 606 trials of peer-only or multiple stakeholder group feedback within Delphi surveys during
41 607 core outcome and information set development. *Trials* 2016;**17**:409.
42 608 doi:10.1186/s13063-016-1479-x
43
44
45
46 609 30 Biggane AM, Brading L, Ravaud P, *et al*. Survey indicated that core outcome set
47 610 development is increasingly including patients, being conducted internationally and
48 611 using Delphi surveys. *Trials* 2018;**19**:113. doi:10.1186/s13063-018-2493-y
49
50
51
52 612 31 Tsihchaki A, O'Brien K, Johal A, *et al*. Development of a core outcome set for
53 613 orthodontic trials using a mixed-methods approach: protocol for a multicentre study.
54 614 *Trials* 2017;**18**:366. doi:10.1186/s13063-017-2098-x
55
56
57 615 32 Allard A, Fellowes A, Shilling V, *et al*. Key health outcomes for children and young
58 616 people with neurodisability: qualitative research with young people and parents. *BMJ*
59 617 *Open* 2014;**4**:e004611. doi:10.1136/bmjopen-2013-004611

1
2
3 618 33 Morris C, Janssens A, Shilling V, *et al.* Meaningful health outcomes for paediatric
4 619 neurodisability: Stakeholder prioritisation and appropriateness of patient reported
5 620 outcome measures. *Health Qual Life Outcomes* 2015;**13**:87. doi:10.1186/s12955-015-
6 621 0284-7
7
8
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15
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Online supplement 1.

S1. Completed COS-STAD checklist for PA-COS project

| Domain | Methodology | Notes | Addressed on page number |
|-----------------------|--|---|--------------------------------|
| Scope specification | 1. The research or practice setting(s) in which the COS is to be applied | e.g., for application in research studies or for use in routine care | 4. |
| | 2. The health condition(s) covered by the COS | e.g., treatment of rheumatoid arthritis or screening for cancer | 4. |
| | 3. The population(s) covered by the COS | e.g., patients with advanced disease or children | 4. |
| | 4. The intervention(s) covered by the COS | e.g., all interventions, drug therapy, or surgical interventions | 4. |
| Stakeholders involved | 5. Those who will use the COS in research | e.g., clinical trialists or industry | 6. |
| | 6. Healthcare professionals with experience of patients with the condition | e.g., clinical experts, practitioners, and investigators with particular experience in the condition | 6. |
| | 7. Patients with the condition or their representatives | involve those who have experienced or who are affected by the condition (e.g., patients, family members, and carers). | 6. |
| Consensus process | 8. The initial list of outcomes considered both healthcare professionals' and patients' views. | consider the views of healthcare professionals and patients (most likely identified from literature reviews or interviews) when generating an initial list of outcomes for inclusion in the consensus process. | 5. (No patient involvement) |
| | 9. A scoring process and consensus definition were described a priori. | Although different consensus methods may be employed in different studies, to avoid any potential biases, COS developers should describe their consensus method a priori. | 7, 8, 9. |
| | 10. Criteria for including/dropping/adding | prespecify criteria for including, dropping, or adding new outcomes to avoid potential biases. | 7, 8, 9. |
| | 11. Care was taken to avoid ambiguity of language used in the list of outcomes. | consider the language used when describing outcomes in front of different stakeholder groups. An example of 1 approach taken is to include both lay and medical terms, with these previously piloted with the stakeholders. | 7,8. |

1 Online supplement 2.

2 S2. Search strategy for systematic review PA-COS

3 **Appendicitis**

4 "Appendix"[Mesh] OR appendix[tiab] OR appendix[ot] OR "Appendicitis"[Mesh] OR
5 "Appendectomy"[Mesh] OR appendicit*[tiab] OR appendicit*[ot] OR appendectom*[tiab] OR
6 appendectom*[ot] OR appendicectom*[tiab] OR appendicectom*[ot]

7 **Children**

8 child*[tw] OR schoolchild*[tw] OR infan*[tw] OR adolescen*[tw] OR pediatri*[tw] OR
9 paediatr*[tw] OR neonat*[tw] OR boy[tw] OR boys[tw] OR boyhood[tw] OR girl[tw] OR
10 girls[tw] OR girlhood[tw] OR youth[tw] OR youths[tw] OR baby[tw] OR babies[tw] OR
11 toddler*[tw] OR teen[tw] OR teens[tw] OR teenager*[tw] OR newborn*[tw] OR
12 postneonat*[tw] OR postnat*[tw] OR perinat*[tw] OR puberty[tw] OR preschool*[tw] OR
13 suckling*[tw] OR picu[tw] OR nicu[tw]

14 **3.2.2 Study selection**

15 Selection of studies will be performed by 2 independent reviewers (MK, JF) according to the
16 below mentioned in- and exclusion criteria. In case of disagreement between two reviewers,
17 a third independent reviewer (RG) will make the final decision.

18 *Inclusion/Exclusion Criteria:*

19 All RCTs and systematic reviews/meta-analyses reporting the outcome of treatment of acute
20 uncomplicated appendicitis will be included in this systematic review. By including systematic
21 reviews that also report on non-comparative studies we expect to identify all reported
22 treatment outcomes, including those from the relatively new field of non-operative
23 management of uncomplicated appendicitis. Publications before January 2014 will be
24 excluded. Only studies in children (<18 years of age) will be included. Studies only reporting
25 on the outcome of treatment in complex or complicated appendicitis (gangrenous
26 appendicitis, appendiceal mass, appendiceal abscess) will be excluded.

27 **3.2.3 Data extraction**

28 The two reviewers will extract the data independently using the predefined data extraction
29 form shown in Appendix A. In case of disagreement a third reviewer will make the final
30 decision. A risk of bias assessment of the individual studies is not applicable as we will not
31 be using individual study data but only the reported outcomes. As diversity in terminology will
32 be anticipated, we decided to initially report all outcome measure as mentioned in the original
33 study. Outcome measures will be mapped independently by two reviewers and in case of
34 disagreement a third reviewer will make the final decision. After data extraction of all studies
35 is completed, a meeting of the study management group will be held between to discuss
36 potential similarity between the outcome measures in order to assign an appropriate term for
37 them.

BMJ Open

Establishing a core outcome set for treatment of uncomplicated appendicitis in children: study protocol for an international Delphi survey.

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2018-028861.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 11-Mar-2019 |
| Complete List of Authors: | Knaapen, Max; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Paediatric Surgical Centre Hall, Nigel; University of Southampton Faculty of Medicine, University Surgery Unit van der Lee, Johanna H.; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Paediatric clinical Research Office Butcher, Nancy; Sick Kids, Child Health Evaluative Sciences Offringa, Martin; The Hospital for Sick Children, University of Toronto, Department of Paediatrics Van Heurn, Ernst; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Paediatric Surgical Centre Bakx, Roel; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Paediatric Surgical Centre Gorter, Ramon; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Paediatric Surgical Centre + On behalf of the paediatric , appendicitis COS development group |
| Primary Subject Heading: | Surgery |
| Secondary Subject Heading: | Emergency medicine, Gastroenterology and hepatology, Medical publishing and peer review, Paediatrics, Research methods |
| Keywords: | delphi, appendicitis, children, core outcome set, paediatric, Global |
| | |

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Manuscripts

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3 **1 Establishing a core outcome set for treatment of uncomplicated**
4 **2 appendicitis in children: study protocol for an international Delphi**
5 **3 survey.**

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8 4 Knaapen M, MD¹, Hall NJ, MD, PhD², Van der Lee JH, MD, PhD³, Butcher NJ, PhD⁴,
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45 30 Word count: 5753

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47 31 Funding statement: None

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49 32 Competing interests statement: None to declare

34 **ABSTRACT**

35 **Introduction**

36 Appendicitis is a global disease affecting roughly one in every 12 people in the world, with
37 the highest incidence between ages 10 and 19 years. To date, a wide variety of health
38 outcomes have been reported in randomized controlled trials (RCTs) and meta-analyses
39 evaluating treatments for appendicitis. This is especially the case in studies comparing non-
40 operative treatment to operative treatment. A set of standard outcomes, to be reported in all
41 future trials, is needed to allow for adequate comparison and interpretation of clinical trial
42 results and to make data pooling possible. This protocol describes the development of such
43 a global core outcome set (COS) to allow unified reporting of treatment interventions in
44 children with acute uncomplicated appendicitis.

45 **Methods and analysis**

46 We use current international standard methodology for the development and reporting of this
47 COS. Its development consists of three phases: (1) Update the most recent systematic
48 review on outcomes reported in uncomplicated paediatric appendicitis research, to identify
49 additional outcomes, (2) Three-step global Delphi study to identify a set of core outcomes for
50 which there is consensus between parents and (paediatric) surgeons, and (3) Expert meeting
51 to finalize the COS and its definitions. Children and young people will be involved through
52 their parents during phase two and will be engaged directly using a customized face-to-face
53 approach.

54 **Ethics and dissemination.**

55 The medical research ethics committee of the Academic Medical Centre Amsterdam has
56 approved the study. Each participating country/research group will ascertain ethics board
57 approval. Electronic informed consent will be obtained from all participants. Results will be
58 presented in peer-reviewed academic journals and at (international) conferences.

59 **Registration details**

60 The COS development project was registered with the COMET initiative in February 2018
61 (<http://www.comet-initiative.org/studies/details/1119>).

62 **Article Summary: Strengths and limitations of this study**

- 63 1. A globally relevant set of core outcomes for paediatric uncomplicated appendicitis
64 assessed in an international online Delhi study.
- 65 2. A that protocol was developed in conjunction with an international steering committee,
66 including patient representation.
- 67 3. Involvement of parents and their children in choosing what to measure in future
68 uncomplicated appendicitis research.
- 69 4. Direct face-to-face involvement of young people, however, only in selected countries.
- 70 5. A limited consensus discussion with only selected individuals.

72 INTRODUCTION

73 Appendicitis is a common gastro-intestinal disease affecting roughly one in every 12 people
74 in the world, with the highest incidence between ages 10 and 19 years[1,2]. While the
75 incidence varies from country to country, appendicitis is a global disease[3]. In the last
76 decade, there have been several developments in the treatment of appendicitis in children,
77 with the most recent being non-operative treatment (NOT) for acute uncomplicated
78 appendicitis. Studies investigating the effectiveness of NOT in children show promising
79 results[4–7]. However, the selected primary (and secondary) outcomes vary widely, as
80 reflected in recent systematic reviews assessing the efficacy and safety of NOT, this may
81 contribute to their contradictory conclusions[4–8]. In the systematic review by Georgiou et
82 al.[4], the need for universal outcome selection and reporting in appendicitis studies is
83 emphasized. In general, it is recognized that clinical trials in children often lack outcomes that
84 are appropriately chosen for this particular population[9].

85 Inconsistent selection and reporting of outcomes limits the ability to adequately compare and
86 interpret clinical trial results. Furthermore, it hampers data pooling and subsequent meta-
87 analysis. It also increases the risk of selective outcome reporting, a form of publication bias.
88 This in turn jeopardizes the validity of results from individual trials, which feeds into
89 subsequent systematic reviews[10] and meta-analyses, which are by nature retrospective,
90 and therefore liable to various risks of bias[11,12].

91 As demonstrated by Hall et al. in 2015, a wide variety of outcomes has been reported in
92 randomized controlled trials (RCTs) and meta-analyses reporting on the treatment of
93 appendicitis in children[13]. In the 63 included studies, a total of 115 different outcomes were
94 reported[13]. Hall et al. proposed the development of a Core Outcome Set (COS), which is a
95 standardized collection of outcomes that should be measured and reported in all future
96 trials[14]. Recently a study protocol was published for developing such a COS in the United
97 Kingdom[15]. To overcome any limitations of a COS focused on UK-specific surgical
98 practice, the aim of this study is to develop an international COS to be used for trials
99 assessing the treatment of acute uncomplicated appendicitis in children. The development of
100 this protocol and the international COS is being performed in conjunction with the UK
101 research group. The principal investigator of UK COS (NJ Hall) has been involved from the
102 beginning of the protocol development and is part of the study management group.
103 Outcomes considered important by patients and families are essential to a meaningful and
104 complete COS[16]. That is why parents and patients will play a central role in the consensus
105 process as a stakeholder group. Parent and patient representation was insured through
106 involvement of the Dutch patient and parent Foundation: “Children and Hospital”. A
107 representative from this group provided feedback from the perspective of parents and

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3 108 children in several stages of the protocol development. They will also be involved in the
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5 109 development of a face-to-face methodology for engaging children in this COS project.
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7 110 **Scope**

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9 111 We aim to reach a global consensus amongst patients, parents, researchers and physicians
10 112 on the minimal set of core outcomes that should be measured and reported in all future
11 113 clinical trials investigating any type of treatment for acute uncomplicated appendicitis in
12 114 children, including surgical treatment, non-operative treatment or other treatment aimed at
13 115 curing appendicitis.
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18 116 **METHODS**

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21 117 In the development of this protocol, we adhere to the COS-STAD (Core Outcome Set-
22 118 STAndards for Development) recommendations[17] and the COMET (Core Outcome
23 119 Measures in Effectiveness Trials) handbook[18]. The completed COS-STAD checklist can be
24 120 found in online supplement S1. The final core outcome set will be reported in accordance
25 121 with the COS-Standards for reporting (COS-STAR) statement[19]. Involvement of patients
26 122 and the public will be described using the GRIPP2 reporting checklist[20] (Guidance for
27 123 Reporting on Involvement of Patients and Public). This study was registered with the COMET
28 124 initiative (registration number: 1119) on February 11, 2018[21].
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36 126 **Study design**

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38 127 The paediatric appendicitis COS (PA-COS) development will consist of three phases: (1) An
39 128 update of the 2015 systematic review on outcomes reported in uncomplicated paediatric
40 129 appendicitis research[13], in order to identify any additional outcomes used in trials that were
41 130 published since the previous systematic review; (2) A three-step Delphi study to identify a set
42 131 of core outcomes from those selected in the literature review. Development of the Delphi is
43 132 performed according to the checklist by Sinha et al.[22] on the design and reporting of Delphi
44 133 studies concerning COS selection; and (3) An expert panel meeting to ratify the final COS,
45 134 including physicians, researchers and children/parent representatives. Children and young
46 135 people will be involved through their parents during phase two and will be engaged directly
47 136 using a customized approach.
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55 138 **Steering Committee**

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58 139 An international steering committee has been established and consists of the following; the
59 140 authors, a parent/patient representative of the Dutch Foundation: "Children and Hospital",
60 141 and the lead local investigator of each participating centre (paediatric appendicitis COS

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3 142 development group). The steering committee will agree on the final version of the protocol at
4 143 the start of the project and will provide input throughout the duration of the project. The
5 144 steering committee members will also be involved in the development of the final COS.
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7 145 Within the steering committee, a smaller study management group has been appointed
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9 146 which will convene during regular (videoconference) meetings.
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11 12 147 **Systematic review: Treatment outcomes**

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14 148 Hall et al. performed a systematic review of RCTs and meta-analyses reporting treatment
15 149 outcomes in children with appendicitis up to April 2014[13]. They found a 115 unique
16 150 outcomes which they collapsed into a total of 38 standardized outcome terms. We will update
17 151 the systematic review to identify any new unique outcomes in clinical trials or systematic
18 152 reviews. All RCTs and systematic reviews/meta-analyses reporting treatment outcomes of
19 153 acute uncomplicated appendicitis in children (<18 years of age) published between January
20 154 1st 2014 and November 23th 2017 will be included. The final review will follow the PRISMA
21 155 reporting guideline[23]. We will search the Cochrane Central Register of Controlled Trials,
22 156 MEDLINE and EMBASE with the help of a clinical librarian. Additional information on the
23 157 search strategy/study selection and data extraction can be found in online supplement S2.
24 158 Studies only reporting outcomes of treatment in complex or complicated appendicitis (for
25 159 example - gangrenous or perforated appendicitis, appendiceal mass, appendiceal abscess)
26 160 will be excluded.
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35 161 After data extraction, a meeting of the study management group (including NJ Hall) will be
36 162 held to discuss potential similarities between the outcomes from the 2015 systematic review
37 163 from Hall et al.[13]. New unique outcomes will be discussed within the group in order to
38 164 assign an appropriate standardized outcome term. If these outcomes do not match any of the
39 165 original 38 outcome terms a new term will be assigned, figure 1. illustrates this methodology.
40 166 The new and original outcome terms will be mapped to four core areas (death, life impact,
41 167 resource use, pathophysiological manifestations) in accordance with the methods from the
42 168 OMERACT FILTER 2.0[24]. Although Hall et al.[13] chose to list the adverse events as a
43 169 separate core area, we will reclassify these outcome terms to one of the four core areas
44 170 (Table 1.). We will however, label adverse events of treatment separately, as the OMERACT
45 171 filter suggests[24]. A meeting of the study management group will be held to discuss
46 172 potential similarity between outcomes and to assign an appropriate outcome term for similar
47 173 outcomes. Outcomes that are only found once and are not generalizable can be excluded
48 174 (e.g. the width of lateral thermal damage of the mesoappendix after appendectomy).
49 175 Grouping the outcomes under a common outcome term aims to arrive at a manageable and
50 176 cohesive list of outcomes that is appropriate as a basis for the Delphi questionnaire.
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177 **Table 1. Outcome Core Areas**

| Core Area | Example(s) |
|-----------------------------------|---|
| Life impact | <i>Quality of life, loss of ability to work</i> |
| Resource use | <i>Length of hospital stay, healthcare costs, societal cost</i> |
| Pathophysiological Manifestations | <i>Biochemical parameters, organ function, (ir)reversible manifestations (complications, pathology results)</i> |
| Death | <i>Death</i> |

178

179 **Stakeholders and recruitment**180 **1) Children and Young People**

181 Children and young people (5-18 years) who have been treated for acute
 182 uncomplicated appendicitis in the preceding 24 months, either with initial NOT or with
 183 surgery. Children less than 5 years old are excluded since different outcomes might
 184 be appropriate in this very young age group. Also, uncomplicated appendicitis is
 185 much less common in young children than in older children. Furthermore, there are
 186 no studies in which children below the age of 5 are treated non-operatively. Children
 187 will be engaged indirectly as we will urge parents to discuss the answers they provide
 188 with their child whilst filling out the Delphi questionnaire. Young people will be
 189 engaged directly through a customized face-to-face approach in selected countries.
 190 For the invited children, considering the complexity of the subject and methodology,
 191 age is limited to 12-18 years.

192

193 **2) Parents**

194 Parents of children and young people (5-18 years) treated for acute uncomplicated
 195 appendicitis either with initial NOT or with surgery in the preceding 24 months or
 196 during the initial phase of the study. Parents will be asked to discuss the answers
 197 they provide with their child whilst filling out the Delphi questionnaire. Parents will be
 198 invited to participate by their child's treating physician or their designate in each

199 participating country/hospital. Participants will be identified retrospectively by
200 contacting patients that were treated in the past 24 months or prospectively by
201 inviting patients to participate directly after they have completed their treatment.

202

203 **3) (Paediatric) Surgeons**

204 General and/or paediatric surgeons who care for children in the specified age group
205 will be asked to participate. Surgeons will be identified and invited by the local
206 coordinators in each participating country. These local coordinators are research
207 groups that have previously registered a clinical trial on uncomplicated appendicitis in
208 children. This should allow for inclusion of physicians that also have experience in
209 research on the treatment of appendicitis.

210

211 **Participating countries and research groups**

212 It was decided to invite research groups that are currently conducting clinical trials on the
213 treatment of acute uncomplicated in children. Groups were identified through
214 www.clinicaltrials.gov by searching (January 2017) for 'appendicitis' with an age limitation of
215 5-18 years. Studies with a mixed population (children and adults) were excluded. Studies
216 that had been completed before 2014, had not been updated since 2015, or with incomplete
217 registrations, were excluded. We found 111 trials, of which 12 trials assessed the treatment
218 of uncomplicated appendicitis in children. Groups from the Netherlands, USA, Canada,
219 Australia, Sweden, Finland, UK, France, Italy, Israel, Japan, Singapore and Malaysia were
220 identified. Some trials included hospitals from multiple countries.

221 **Sample size**

222 There is no rationale for determining the number of respondents to invite for a Delphi
223 study[18]. A minimum of seven respondents per stakeholder group is suggested to have a
224 large enough group to allow for a consensus process[25]. Taking into account that only some
225 invited participants will register for the Delphi and that not all respondents will complete all
226 rounds of the Delphi (attrition), a minimum of 40 respondents per stakeholder group per
227 country will be invited. There will be no maximum. In case the number of respondents per
228 country is significantly higher than other countries, we will consider a weightage per country
229 in the analyses. We anticipate that this sample will be large enough to reflect all relevant
230 opinions.

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232 **Delphi study**

233 International online Delphi study

234 The Delphi method is an effective tool for reaching consensus in a large group without the

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3 235 need for face-to-face contact[26]. The use of sequential questionnaires which are answered
4 236 anonymously by stakeholders is an established method for reaching consensus in a group of
5 237 experts[22]. Questionnaires will be sent using DelphiManager[27], a web-based system
6 238 designed for Delphi studies. The questionnaires will be open simultaneously to all
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8 239 respondents of the participating countries. After each round, the responses of all participants
9 240 are shared anonymously in accordance with the Delphi principle.
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13 241 The list of outcomes from the systematic review will be formatted into questions
14 242 accompanied by an extensive plain language summary per outcome, including figures if
15 243 appropriate. The Delphi questionnaire will originally be formulated in English and will be
16 244 translated if required. Translation will only be performed by native speaking professionals.
17
18 245 Participants will be asked to score the importance of each outcome using a 1 to 9 Likert
19 246 scale as recommended by the Grading of Recommendations Assessment, Development and
20 247 Evaluation (GRADE) working group[28] and COMET initiative[18]. A score of 7-9 indicates a
21 248 critical outcome for assessing the effect of a treatment, 4-6 important but not critical, 1-3
22 249 indicates an outcome with low importance for assessing the treatment effect. It will also be
23 250 possible to select an "unable to score" option, which is especially of importance if parents do
24 251 not feel equipped to score certain outcomes. The questionnaires including the plain language
25 252 summaries will be piloted by a group of laypersons (n=10) to check for ambiguity and
26 253 readability.
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34 254 Delphi round one

35 255 Participants will be divided into two stakeholder groups: parents (with their children), and
36 256 surgeons. Parents will be asked to discuss the answers they provide with their child whilst
37 257 filling out the Delphi questionnaire. Baseline characteristics (age, country) will be
38 258 ascertained. Parents will be asked if their child was treated with non-operative or operative
39 259 treatment, time between registration and the first diagnosis of appendicitis and if their
40 260 treatment was with or without complications. And also if they will be answering the Delphi
41 261 whilst consulting their child. Surgeons will be asked their speciality (paediatric, general,
42 262 abdominal, other), workplace (academic, teaching hospital, non-teaching hospital),
43 263 experience with non-operative treatment, experience in research regarding appendicitis in
44 264 children.
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53 265 All participants will be asked to score all previously identified outcomes according to their
54 266 perceived importance for assessing the treatment effect. In the first round there will be an
55 267 option to suggest additional outcomes not yet listed.
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58 268 Participants will have between four and eight weeks to complete each round, depending on
59 269 the response rate. In that time they will receive a reminder email every two weeks as long as

270 they have not replied to the questionnaire.

271

272 Delphi round one: analysis

273 Results will be analysed **by stakeholder group and for all participants** using descriptive
274 statistics. Outcomes will be analysed separately for each stakeholder group, as there is
275 evidence that patients are likely to assign importance to outcomes differently than
276 surgeons[29], which has the potential to influence eventual outcome selection.

277 “Consensus-in” will be defined as:

- 278 – Greater than 70% of participants in **both** stakeholder groups scoring the outcome as
279 7-9 and less than 15% in **both** stakeholder groups scoring the outcome as 1-3.
- 280 – Greater than 90% of participants within **one** stakeholder group scoring the outcome
281 as 7-9. This implies that these outcomes are highly regarded by an individual
282 stakeholder group, and should also be included[18].

283 “Consensus-out” will be defined as:

- 284 – Greater than 70% of participants in **both** stakeholder groups scoring the outcomes as
285 1-3 and less than 15% of participants in **both** stakeholder groups scoring the
286 outcome as 7–9. Consensus-out can only be reached when there is consensus
287 across **both** stakeholders groups.

288 Outcomes that do not meet any of these criteria will be defined as “no consensus”. A
289 stratified analysis will be performed to check for skewing as a result of divergent opinions
290 from a single country or surgeons with or without research experience.

291 At the end of round one, there will be a meeting of the study management group to assess
292 whether an alteration in the Delphi study is appropriate. If additional outcomes are suggested
293 by Delphi participants, each outcome will be assessed by the study management group to
294 determine whether it is indeed new and to which category it should be classified. Wording of
295 the Delphi questionnaire will be adjusted if misinterpretation is suspected.

296 Delphi rounds two and three

297 All participants who have completed the previous round will be asked to participate in the
298 next round. Only outcomes that have not been defined as “consensus-in” or “consensus-out”
299 during the previous round will be presented in the following rounds to all participants.

300 Outcomes for which there was “consensus-in” only within a single stakeholder group, will still
301 be presented to the other stakeholder group to evaluate whether consensus can be achieved
302 in both stakeholder groups. An overview of included and excluded outcomes will be

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3 303 available. The outcomes for which there is no consensus and the newly suggested outcomes
4 304 from the previous rounds will be presented with the participants' individual score and the
5 305 median scores from each stakeholder group combined with a histogram showing the scoring
6 306 distribution. Participants will be asked again to score all remaining outcomes in the same
7 307 manner as in round one.

11 308 Delphi rounds two and three analysis

12 309 Results will be analysed per stakeholder group and for all participants, using descriptive
13 310 statistics with the same definitions for consensus in/out as in the first Delphi round, including
14 311 a stratified analysis. After the second round, there will be a meeting of the study
15 312 management group to assess the need for alteration in the Delphi study, and to decide
16 313 whether or not to proceed with a third Delphi round, assuming consensus between **both**
17 314 stakeholder groups on more than 80% of the outcomes, and more than five outcomes with
18 315 consensus in. To give an estimate of the degree of agreement between respondents, the
19 316 width of the interquartile range of the median ranking score will be calculated, potentially
20 317 ranging from 0.00, meaning complete agreement, to 8.00, meaning least possible
21 318 agreement. This will be calculated for both the individual stakeholder groups as well as the
22 319 entire group of respondents after the final round.

31 320 **Face-to-face engagement of young people**

32 321 We wish to check for discrepancies of opinion between parents answering the Delphi
33 322 together with their child and children who are interviewed directly. For this, a form of in-
34 323 person interaction will be organised with young people (12-18 years) who have been treated
35 324 for appendicitis. They will be asked to comment on the preliminary COS selection
36 325 established at the end of the Delphi study, and to suggest additional outcomes and comment
37 326 on outcomes that did not make the preliminary COS selection. This will either be done by a
38 327 short, face-to-face, one round questionnaire involving only outcomes relevant to
39 328 children/young people, or in the form of a small consensus meeting (prioritization meeting)
40 329 before finalizing the definitive COS. Doing this type of research requires experienced
41 330 interviewers and resources. That is why the face-to-face engagement will only take place in
42 331 selected countries, however, we will aim to involve as many countries as feasible. Separate
43 332 ethical board approval will be obtained as appropriate.

53 333 **Consensus discussion**

54 334 If adequate consensus (we aim to achieve consensus on at least one outcome per
55 335 OMERACT core area) is reached in the Delphi study, we will organise a face-to-face expert
56 336 panel meeting with selected individuals with the purpose to ratify a pragmatic and well-
57 337 defined set of outcomes. A secondary aim of this meeting is to enhance support and
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3 338 implementation of the final COS.
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5 339 The meeting will be held at an international conference for paediatric surgery. Through
6
7 340 purposive sampling, approximately 30 “experts” from across all stakeholder groups, including
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9 341 physicians, researchers and children/parent representatives, will be invited to participate in a
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11 342 face-to-face meeting with the Steering Committee. Journal editors and healthcare
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13 343 commissioners will also be invited to attend in an observational capacity with the purpose of
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15 344 promoting implementation and to provide comments on the final list of outcomes.

16 345 In the event that adequate consensus cannot be reached in the Delphi process, we will
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18 346 organise a formal face-to-face consensus meeting or teleconference. In that case, we will
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20 347 select an appropriate representation of all stakeholder groups from the panel members that
21
22 348 participated in the Delphi study.

23 349 **Final COS development**

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25 350 The goal is to achieve a pragmatic COS that is applicable and feasible for all future trials that
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27 351 evaluate the treatment of uncomplicated appendicitis in children. There is no recommended
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29 352 maximum number of outcomes that should be included in a COS. However, if the final COS
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31 353 includes too many outcomes, the COS would not be feasible to use in practice. To achieve the
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33 354 goal of a pragmatic COS we aim to arrive at a maximum of 10 outcomes, the same
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35 355 maximum number as the UK COS protocol specifies[15]. As a minimum, we aim to have at
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37 356 least one outcome per core area. If the number of outcomes for which consensus is achieved
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39 357 greatly exceeds 10 outcomes, the outcomes with the highest level of consensus will be
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41 358 considered part of the suggested COS. We will however report all outcomes for which
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43 359 consensus is achieved. The highest level of consensus depends on whether there is
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45 360 consensus in both stakeholder groups, the median score that was appointed to the outcome,
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47 361 and the interquartile range of the median score as an estimate of the degree of consensus.

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49 362 Only outcomes for which consensus is reached internationally will be selected. To test for
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51 363 country bias, stratified analyses of the Delphi results will be performed. The results from the
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53 364 face-to-face engagement of young people will be taken into account for the final COS
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55 365 selection and will be reported separately. If there is no consensus between patients, parents
56
57 366 and healthcare professionals, an outcome can still be selected if there is clear consensus
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59 367 within a single stakeholder group. These will be reported separately. The final COS will be
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368 categorised according to the four core areas of the OMERACT filter[24]. We will also
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370 annotate the outcomes according to the recently published outcome taxonomy to maximise
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370 future data harmonisation[30].

371 **Patient and Public Involvement**

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3 372 Patient involvement is at the core of this study design. By asking parents and patients with
4 373 experience in having simple appendicitis what outcomes they feel should be part of future
5 374 research. To ensure our design is appropriate for parents and children we have involved the
6 375 Dutch child and parents representation group as part of our steering committee. In that
7 376 capacities they provide input on the protocol and study. To make sure the Delphi
8 377 questionnaire is understandable and has no ambiguities it is checked by a group of
9 378 laypersons before the start of the Delphi study. Part of the Delphi study is giving feedback to
10 379 all its participants after each round, this will also be done with the final study results.

16 380 **Ethics and dissemination.**

18 381 **Ethics**

19 382 The medical research ethics committee of the Academic Medical Centre Amsterdam
20 383 confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) does not
21 384 apply to this study and that complete approval of this study by the committee is not required.
22 385 Each participating country/research group will be asked to obtain ethics board approval or
23 386 confirm that ethics board approval is not required. Electronic informed consent will be
24 387 obtained from all participants. The face-to-face engagement of young people (12-18 years)
25 388 will take place in selected countries and separate ethics board approval will be obtained, as
26 389 appropriate.

33 390 **Data collection and confidentiality**

34 391 All data will be handled confidentially and in accordance with the Dutch Personal Data
35 392 Protection Act and the European General Data Protection Regulation (GDPR).
36 393 DelphiManager[27] will be used for the online questionnaire. After informed consent from all
37 394 participants only limited identifying information (name, email) will be ascertained during
38 395 registration. This information will be stored separately from the answers given in the
39 396 questionnaire and will only be used for the purpose of direct feedback and reminder emails.
40 397 Access to personally identifiable data will be strictly limited.

46 398 **Study status and dissemination**

47 399 In the first quarter (Q1) of 2018 the following 13 countries were invited to participate in the
48 400 project; Netherlands, USA, Canada, Australia, Sweden, Finland, UK, France, Italy, Israel,
49 401 Japan, Singapore and Malaysia. Ten countries replied, Italy, Israel and Japan did not. In Q1
50 402 2018 the systematic review was finished. In Q2 2018 the Delphi questionnaire was
51 403 developed and piloted. In Q3 2018 all materials were translated. Between Q4 2018 and Q1
52 404 2019 IRB applications were submitted in 10 countries and 15 participating centres. The
53 405 anticipated start of the online Delphi study is May 2019. We anticipate to have the final COS
54 406 ready by Q1 2020. Dissemination of the results will be accomplished by publication in an

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3 407 international peer-reviewed scientific journal and by presentations at (international)
4 408 conferences. By involving the majority of the principal investigators who are currently
5 409 involved in research on uncomplicated appendicitis in children, we aim to optimize uptake of
6 410 the final COS. By involving journal editors and healthcare commissioners in the face-to-face
7 411 consensus discussion, we aim to ultimately have the COS introduced as a requirement in
8 412 future outcome reporting on the treatment of uncomplicated appendicitis in children. We will
9 413 also actively send out the final COS to relevant journal editors and funding bodies to promote
10 414 uptake in future research.

16 415 **DISCUSSION**

17 416 **Strengths and limitations of this study**

20 417 **Outcomes selection**

21 418 The selection of potential outcomes will be done systematically and will provide a selection
22 419 for the first Delphi questionnaire that reflects most issues pertinent to the treatment of
23 420 uncomplicated appendicitis. By including systematic reviews/meta-analyses that also report
24 421 on non-comparative studies, we expect to identify all reported treatment outcomes, including
25 422 those from the relatively new field of NOT for uncomplicated appendicitis.

26 423 To be able to arrive at a manageable list of outcomes that is appropriate for a Delphi study,
27 424 the number of outcome terms needs to be somewhat limited. In order to achieve this, the
28 425 outcomes derived from our systematic review will be merged in case of similarity. If
29 426 outcomes are not generalizable and only reported once, they will be excluded. This will be
30 427 proposed and prepared by two independent reviewers and discussed in the study
31 428 management group. However, the merging of outcomes will inevitably lead to some loss of
32 429 detail.

33 430 **Global consensus**

34 431 In order to reflect the views of different stakeholders, a variety of groups will be part of the
35 432 development of this COS. This is not only the case on a national level, but also on an
36 433 international level, related to, for example, differences between countries in resources,
37 434 treatment practises for acute uncomplicated appendicitis, and cultural differences. For
38 435 example there is a large difference with regard to the standard length of hospital stay after an
39 436 appendectomy for simple appendicitis. In the USA much effort is devoted to reduce the
40 437 number of admission days, in the UK there is only limited attention for the duration of
41 438 admission and for instance in Japan an admission for 5 days is not uncommon. We can
42 439 expect that these kind of differences result in different opinions regarding the core outcomes
43 440 set. By also involving patients and parents from the participating countries we hope to correct
44 441 for these differences[31]. In conjunction with the UK paediatric appendicitis COS research

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3 442 group we decided that an international validation of the UK COS would not give the depth of
4 443 information and would not allow for consensus formation on all possible outcomes. Which we
5 444 feel is appropriate considering the before mentioned significant differences between
6 445 countries. Involving members from different countries will not only lead to the development of
7 446 a COS that reflects the opinions of the international community, it should also lead to an
8 447 internationally applicable “minimal” COS. However, selecting the participating countries on
9 448 the basis of their involvement in research on appendicitis in children is a limitation. This
10 449 choice was made on the basis of feasibility. Researchers in the field of uncomplicated
11 450 appendicitis have an interest in the development of a COS and have the network to help
12 451 carry out the Delphi study. With our current selection we will, however, have participants from
13 452 four different continents. Our means of selection has another advantage. Since non-
14 453 operative treatment is an important research subject in childhood appendicitis, we aim to
15 454 include surgeons and parents who have experience in that field. As non-operative treatment
16 455 is still experimental in most of the world, we need surgeons and patients who have been
17 456 involved in such research.

27 457 **Limited face-to-face consensus**

28 458 If consensus is reached in the Delphi study we will not be organising a formal consensus
29 459 meeting. The Delphi method can be used for reaching consensus in a group of respondents
30 460 without the need for face-to-face contact. There is a risk of bias if a face-to-face consensus
31 461 meeting leads to selection of only participants who are able to attend the meeting, which is
32 462 especially a problem in a global consensus procedure. There are also problems regarding
33 463 language barriers in an international consensus meeting. To check for interpretation errors in
34 464 the Delphi method and to ensure a pragmatic and well-defined set of outcomes the results of
35 465 the Delphi study will be discussed in an (international) expert meeting. The influence of this
36 466 meeting on which outcomes are selected for the final COS is however very limited, as this is
37 467 decided in the prior Delphi study.

46 468 **Involving parents and their children**

47 469 Involving patients in COS development has recently become common practice with 88%
48 470 (n=112 as of April 12th 2016) of ongoing COS development studies doing so[18]. Involving
49 471 patients as participants seems imperative as patients may identify different outcomes that
50 472 should be measured, compared with physicians[16]. For this protocol we performed a
51 473 scoping review [unpublished work] that found 12 studies that directly engaged children in
52 474 COS development. Either as part of the advisory group or the steering committee, or as a
53 475 stakeholder group in the Delphi[15,22], focus groups[32], interviews[33] or as a part of the
54 476 consensus meeting[34]. Attempts to engage children and young people in an online Delphi
55 477 questionnaire have proven to be difficult. In the UK COS for uncomplicated appendicitis,

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3 478 there were substantial difficulties with retaining young people in the consecutive rounds of
4 479 the Delphi questionnaire, despite extensive efforts to optimize the methodology to appeal to
5 480 children and young people, including: preliminary semi-structured interviews on the subject,
6 481 pre-testing of the Delphi survey by young people and children[15] and video animations
7 482 explaining the need for a COS. Parent participation however showed more promising results.
8 483 Consequently, to safeguard the input of children/young people, the Delphi questionnaire for
9 484 this study will be developed to be completed by parents with input from their children (5-18
10 485 years) whenever possible. In order to ensure that there are no large discrepancies between
11 486 the opinions of parents with their children, and with children without their parents, we will
12 487 organize a form of in-person interaction with young people (12-18 years) who have been
13 488 treated for appendicitis. Involving children/young people in COS development is a subject of
14 489 interest in many ongoing COS development projects. As the search for the optimal approach
15 490 to engage young people is ongoing we have not yet selected a final methodology. Two
16 491 members of the study management group are currently involved in group that is developing
17 492 such methodology in consultation with young people themselves. We will update our protocol
18 493 as soon as we settle on a methodology before starting the face-to-face engagement. The
19 494 updated protocol will be published on an online, open source format (via the Open Science
20 495 Framework).

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32 496 A limitation is that due to the international nature of our study it will not be feasible to engage
33 497 children directly in all the participating countries. That is why the face-to-face engagement
34 498 will take place in selected countries.

37 38 499 **Other stakeholders**

39 500 After careful consideration and consultation with the participating countries, it was decided
40 501 not to include paediatricians, general practitioners, nurses or emergency medicine
41 502 physicians. Although all these specialists play an intricate role in the diagnosis and care for
42 503 children with appendicitis, they do not make the final decision regarding treatment or its
43 504 provision. We will however, depending on the organisation of the healthcare system in each
44 505 country, ask these stakeholders to comment on the final COS in order to ensure that
45 506 essential outcomes are not missed. Since almost all research regarding treatment of
46 507 paediatric uncomplicated appendicitis is initiated by (paediatric) surgeons, it was decided that
47 508 researchers will not be included as a separate individual stakeholder group. However,
48 509 involvement in research will be registered. Whilst their opinion is vital to the development of a
49 510 COS, it is likely researchers will be well represented in the (paediatric) surgeon stakeholder
50 511 group. A stratified analyses will be performed to check for skewing of the results by surgeons
51 512 involved in research. It was also decided not to include journal editors or healthcare
52 513 commissioners. Even though their opinion is of great importance especially regarding

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3 514 implementation, it was determined that their opinion is not essential in establishing the
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5 515 outcomes selected for the COS. There is much variability between countries regarding the
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7 516 role of these stakeholders, which would lead to major challenges regarding Delphi analyses
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9 517 of such a small stakeholder group. However, to enhance implementation and because of
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11 518 their expertise on the use of COSs, representatives from these stakeholder groups will be
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13 519 asked to attend the final consensus discussion.

13 520 **Outcome measures**

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15 521 This study will not answer the question on how to measure the outcomes that are included in
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17 522 the final COS, or at what time point the outcomes should be measured. We will however
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19 523 attempt to come to a clear definition of each outcome. We expect that further research will be
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21 524 necessary to answer the question of timing and how to measure the outcomes. We will
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23 525 advise on this subject in the final report.
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527 FOOTNOTES**528 Paediatric appendicitis COS development group.**

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533 Collaborators:

534 The pediatric surgery departments of following hospitals have initiated the COS project and will
535 contribute by recruiting participants. Nationwide Children's Hospital, Columbus, OH, USA. Hasbro
536 Children's Hospital and Alpert Medical School of Brown University, Providence, RI, USA. Children's
537 Mercy Hospital, Kansas City, MO, USA. Karolinska University Hospital, Stockholm, Sweden.
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539 Universitaire Toulouse, Toulouse, France. Hôpital Femme-Enfant, University Hospital, CHU Rennes,
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541 Hospital, Singapore. BC Children's Hospital, Vancouver, BC, Canada. The Hospital for Sick Children,
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544 Helsinki Children's Hospital, Helsinki, Finland. Universiti Kebangsaan Malaysia Medical Centre
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551 Author contributions:

552 All authors have contributed to the design of this protocol. MK, NJH JHvdL, RB and RRG have
553 initiated the project. The protocol was drafted by MK which was refined by NJH, JHvdL, RB, MO, NJB,
554 LWEvH, and RRG. Statistical advice was provided by JHvdL. MK was responsible for drafting this
555 manuscript. All authors have contributed to the manuscript and read and approved the final
556 manuscript. The paediatric appendicitis COS development group consist of all local investigators who
557 are responsible for translation, ethical board approval, participant recruitment. They have all read,
558 refined and approved the final manuscript.

560 Data sharing statement:

561 The project is registered on the comet-initiative.org which is open access. The study findings will be
562 presented in a report which will be submitted for publication in a relevant peer-reviewed journal to
563 ensure dissemination to relevant healthcare professionals. Findings may also be submitted for
564 presentation at local meetings or conferences. The protocol will be published on an open access
565 repository.

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569 **Competing interests statement:** None to declare

571 **REFERENCES**

572

- 573 1 Addiss DG, Shaffer N, Fowler BS, *et al.* the Epidemiology of Appendicitis and
574 Appendectomy in the United States. *Am J Epidemiol* 1990;**132**:910–25.
575 doi:10.1093/oxfordjournals.aje.a115734
- 576 2 Anderson JE, Bickler SW, Chang DC, *et al.* Examining a common disease with
577 unknown etiology: trends in epidemiology and surgical management of appendicitis in
578 California, 1995-2009. *World J Surg* 2012;**36**:2787–94. doi:10.1007/s00268-012-1749-
579 z
- 580 3 Ferris M, Quan S, Kaplan BS, *et al.* The Global Incidence of Appendicitis. *Ann Surg*
581 2017;**266**:237–41. doi:10.1097/SLA.0000000000002188
- 582 4 Georgiou R, Eaton S, Stanton MP, *et al.* Efficacy and Safety of Nonoperative
583 Treatment for Acute Appendicitis: A Meta-analysis. *Pediatrics* 2017;;e20163003.
584 doi:10.1542/peds.2016-3003
- 585 5 Huang L, Yin Y, Yang L, *et al.* Comparison of Antibiotic Therapy and Appendectomy
586 for Acute Uncomplicated Appendicitis in Children. *JAMA Pediatr* 2017;**171**:426.
587 doi:10.1001/jamapediatrics.2017.0057
- 588 6 Xu J, Adams S, Liu YC, *et al.* Nonoperative management in children with early acute
589 appendicitis: A systematic review. *J Pediatr Surg* Published Online First: May 2017.
590 doi:10.1016/j.jpedsurg.2017.05.003
- 591 7 Kessler U, Mosbahi S, Walker B, *et al.* Conservative treatment versus surgery for
592 uncomplicated appendicitis in children: a systematic review and meta-analysis. *Arch*
593 *Dis Child* 2017;;archdischild-2017-313127. doi:10.1136/archdischild-2017-313127
- 594 8 Gorter RR, The S-MML, Gorter-Stam MAW, *et al.* Systematic review of nonoperative
595 versus operative treatment of uncomplicated appendicitis. *J Pediatr Surg* 2017;**18 Apr**
596 **201**. doi:10.1016/j.jpedsurg.2017.04.005
- 597 9 Sinha I, Jones L, Smyth RL, *et al.* A Systematic Review of Studies That Aim to
598 Determine Which Outcomes to Measure in Clinical Trials in Children. *PLoS Med*
599 2008;**5**:e96. doi:10.1371/journal.pmed.0050096
- 600 10 Kirkham JJ, Dwan KM, Altman DG, *et al.* The impact of outcome reporting bias in
601 randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:c365.

- 1
2
3 602 11 Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised
4 603 controlled trials. *Lancet (London, England)* 1998;**351**:47–52. doi:10.1016/S0140-
5 604 6736(97)08461-4
6
7
8
9 605 12 Zanchetti A, Mancia G. Searching for information from unreported trials--amnesty for
10 606 the past and prospective meta-analyses for the future. *J Hypertens* 1998;**16**:125.
11
12
13 607 13 Hall NJ, Kapadia MZ, Eaton S, *et al.* Outcome reporting in randomised controlled trials
14 608 and meta-analyses of appendicitis treatments in children: a systematic review. *Trials*
15 609 2015;**16**:275. doi:10.1186/s13063-015-0783-1
16
17
18 610 14 Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials*
19 611 2007;**8**:39. doi:10.1186/1745-6215-8-39
20
21
22 612 15 Sherratt FC, Eaton S, Walker E, *et al.* Development of a core outcome set to
23 613 determine the overall treatment success of acute uncomplicated appendicitis in
24 614 children: a study protocol. *BMJ Paediatr Open* 2017;**1**:e000151. doi:10.1136/bmjpo-
25 615 2017-000151
26
27
28
29 616 16 Sanderson T, Morris M, Calnan M, *et al.* What outcomes from pharmacologic
30 617 treatments are important to people with rheumatoid arthritis? Creating the basis of a
31 618 patient core set. *Arthritis Care Res (Hoboken)* 2010;**62**:640–6. doi:10.1002/acr.20034
32
33
34
35 619 17 Kirkham JJ, Davis K, Altman DG, *et al.* Core Outcome Set-STAndards for
36 620 Development: The COS-STAD recommendations. *PLOS Med* 2017;**14**:e1002447.
37 621 doi:10.1371/journal.pmed.1002447
38
39
40 622 18 Williamson PR, Altman DG, Bagley H, *et al.* The COMET Handbook: version 1.0.
41 623 *Trials* 2017;**18**:280. doi:10.1186/s13063-017-1978-4
42
43
44 624 19 Kirkham JJ, Gorst S, Altman DG, *et al.* Core Outcome Set-STAndards for Reporting:
45 625 The COS-STAR Statement. *PLoS Med* 2016;**13**:e1002148.
46 626 doi:10.1371/journal.pmed.1002148
47
48
49
50 627 20 Staniszewska S, Brett J, Simera I, *et al.* GRIPP2 reporting checklists: tools to improve
51 628 reporting of patient and public involvement in research. *BMJ* 2017;**358**:j3453.
52
53
54 629 21 Protocol for the development of a global core outcome set for treatment of
55 630 uncomplicated appendicitis in children :: Core Outcome Measures in Effectiveness
56 631 Trials Initiative (COMET). <http://www.comet-initiative.org/studies/details/1119>
57 632 (accessed 5 Mar 2018).
58
59
60 633 22 Sinha IP, Smyth RL, Williamson PR. Using the Delphi Technique to Determine Which
19

- 1
2
3 634 Outcomes to Measure in Clinical Trials: Recommendations for the Future Based on a
4 Systematic Review of Existing Studies. *PLoS Med* 2011;**8**:e1000393.
5 635
6 636 doi:10.1371/journal.pmed.1000393
7
- 8
9 637 23 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting
10 638 systematic reviews and meta-analyses of studies that evaluate health care
11 639 interventions: explanation and elaboration. *J Clin Epidemiol* 2009;**62**:e1–34.
12 640 doi:10.1016/j.jclinepi.2009.06.006
13
14
15
16 641 24 Boers M, Kirwan JR, Gossec L, *et al*. How to choose core outcome measurement sets
17 642 for clinical trials: OMERACT 11 approves filter 2.0. *J Rheumatol* 2014;**41**:1025–30.
18 643 doi:10.3899/jrheum.131314
19
20
21 644 25 Mullen PM. Delphi: myths and reality. *J Health Organ Manag* 2003;**17**:37–52.
22 645 doi:10.1108/14777260310469319
23
24
25 646 26 Murphy MK, Black NA, Lamping DL, *et al*. Consensus development methods, and their
26 647 use in clinical guideline development. *Health Technol Assess* 1998;**2**:i–iv, 1–88.
27
28
29 648 27 COMET DelphiManager. 2017.<http://www.comet-initiative.org/delphimanager/>
30 649 (accessed 4 Dec 2018).
31
32
33 650 28 Guyatt GH, Oxman AD, Kunz R, *et al*. GRADE guidelines: 2. Framing the question
34 651 and deciding on important outcomes. *J Clin Epidemiol* 2011;**64**:395–400.
35 652 doi:10.1016/j.jclinepi.2010.09.012
36
37
38
39 653 29 Brookes ST, Macefield RC, Williamson PR, *et al*. Three nested randomized controlled
40 654 trials of peer-only or multiple stakeholder group feedback within Delphi surveys during
41 655 core outcome and information set development. *Trials* 2016;**17**:409.
42 656 doi:10.1186/s13063-016-1479-x
43
44
45
46 657 30 Dodd S, Clarke M, Becker L, *et al*. A taxonomy has been developed for outcomes in
47 658 medical research to help improve knowledge discovery. *J Clin Epidemiol* 2018;**96**:84–
48 659 92. doi:10.1016/j.jclinepi.2017.12.020
49
50
51
52 660 31 Biggane AM, Brading L, Ravaud P, *et al*. Survey indicated that core outcome set
53 661 development is increasingly including patients, being conducted internationally and
54 662 using Delphi surveys. *Trials* 2018;**19**:113. doi:10.1186/s13063-018-2493-y
55
56
57 663 32 Tsihlaiki A, O'Brien K, Johal A, *et al*. Development of a core outcome set for
58 664 orthodontic trials using a mixed-methods approach: protocol for a multicentre study.
59 665 *Trials* 2017;**18**:366. doi:10.1186/s13063-017-2098-x
60

- 1
2
3 666 33 Allard A, Fellowes A, Shilling V, *et al.* Key health outcomes for children and young
4 667 people with neurodisability: qualitative research with young people and parents. *BMJ*
5 668 *Open* 2014;**4**:e004611. doi:10.1136/bmjopen-2013-004611
6
7
8
9 669 34 Morris C, Janssens A, Shilling V, *et al.* Meaningful health outcomes for paediatric
10 670 neurodisability: Stakeholder prioritisation and appropriateness of patient reported
11 671 outcome measures. *Health Qual Life Outcomes* 2015;**13**:87. doi:10.1186/s12955-015-
12 672 0284-7
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For peer review only

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3 675 **Figures**
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8 677 **Figure 1. Schematic depiction of outcome term selection from systematic reviews**

9 678 *RCTs= Randomized controlled trials. SRs= Systematic reviews*
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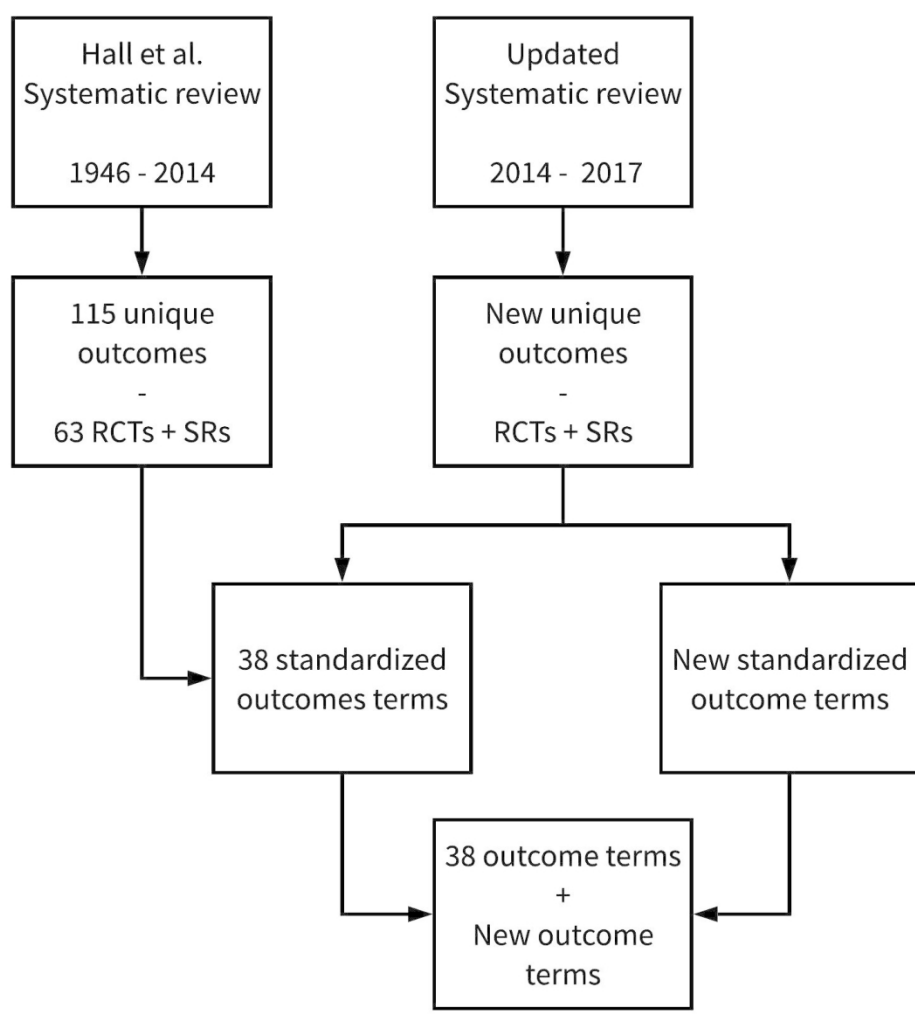


Figure 1. Schematic depiction of outcome term selection from systematic reviews
RCTs= Randomized controlled trials. SRs= Systematic reviews

134x146mm (300 x 300 DPI)

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3 **Online supplement 1.**
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6 **S1. Completed COS-STAD checklist for PA-COS project**
7

| Domain | Methodology | Notes | Addressed on page number |
|-----------------------|--|---|--------------------------------|
| Scope specification | 1. The research or practice setting(s) in which the COS is to be applied | e.g., for application in research studies or for use in routine care | 4. |
| | 2. The health condition(s) covered by the COS | e.g., treatment of rheumatoid arthritis or screening for cancer | 4. |
| | 3. The population(s) covered by the COS | e.g., patients with advanced disease or children | 4. |
| | 4. The intervention(s) covered by the COS | e.g., all interventions, drug therapy, or surgical interventions | 4. |
| Stakeholders involved | 5. Those who will use the COS in research | e.g., clinical trialists or industry | 6. |
| | 6. Healthcare professionals with experience of patients with the condition | e.g., clinical experts, practitioners, and investigators with particular experience in the condition | 6. |
| | 7. Patients with the condition or their representatives | involve those who have experienced or who are affected by the condition (e.g., patients, family members, and carers). | 6. |
| Consensus process | 8. The initial list of outcomes considered both healthcare professionals' and patients' views. | consider the views of healthcare professionals and patients (most likely identified from literature reviews or interviews) when generating an initial list of outcomes for inclusion in the consensus process. | 5. (No patient involvement) |
| | 9. A scoring process and consensus definition were described a priori. | Although different consensus methods may be employed in different studies, to avoid any potential biases, COS developers should describe their consensus method a priori. | 7, 8, 9. |
| | 10. Criteria for including/dropping/adding | prespecify criteria for including, dropping, or adding new outcomes to avoid potential biases. | 7, 8, 9. |
| | 11. Care was taken to avoid ambiguity of language used in the list of outcomes. | consider the language used when describing outcomes in front of different stakeholder groups. An example of 1 approach taken is to include both lay and medical terms, with these previously piloted with the stakeholders. | 7,8. |

1 Online supplement 2.

2 S2. Search strategy for systematic review PA-COS

3 **Appendicitis**

4 "Appendix"[Mesh] OR appendix[tiab] OR appendix[ot] OR "Appendicitis"[Mesh] OR
5 "Appendectomy"[Mesh] OR appendicit*[tiab] OR appendicit*[ot] OR appendectom*[tiab] OR
6 appendectom*[ot] OR appendicectom*[tiab] OR appendicectom*[ot]

7 **Children**

8 child*[tw] OR schoolchild*[tw] OR infan*[tw] OR adolescen*[tw] OR pediatri*[tw] OR
9 paediatr*[tw] OR neonat*[tw] OR boy[tw] OR boys[tw] OR boyhood[tw] OR girl[tw] OR
10 girls[tw] OR girlhood[tw] OR youth[tw] OR youths[tw] OR baby[tw] OR babies[tw] OR
11 toddler*[tw] OR teen[tw] OR teens[tw] OR teenager*[tw] OR newborn*[tw] OR
12 postneonat*[tw] OR postnat*[tw] OR perinat*[tw] OR puberty[tw] OR preschool*[tw] OR
13 suckling*[tw] OR picu[tw] OR nicu[tw]

14 **3.2.2 Study selection**

15 Selection of studies will be performed by 2 independent reviewers (MK, JF) according to the
16 below mentioned in- and exclusion criteria. In case of disagreement between two reviewers,
17 a third independent reviewer (RG) will make the final decision.

18 *Inclusion/Exclusion Criteria:*

19 All RCTs and systematic reviews/meta-analyses reporting the outcome of treatment of acute
20 uncomplicated appendicitis will be included in this systematic review. By including systematic
21 reviews that also report on non-comparative studies we expect to identify all reported
22 treatment outcomes, including those from the relatively new field of non-operative
23 management of uncomplicated appendicitis. Publications before January 2014 will be
24 excluded. Only studies in children (<18 years of age) will be included. Studies only reporting
25 on the outcome of treatment in complex or complicated appendicitis (gangrenous
26 appendicitis, appendiceal mass, appendiceal abscess) will be excluded.

27 **3.2.3 Data extraction**

28 The two reviewers will extract the data independently using the predefined data extraction
29 form shown in Appendix A. In case of disagreement a third reviewer will make the final
30 decision. A risk of bias assessment of the individual studies is not applicable as we will not
31 be using individual study data but only the reported outcomes. As diversity in terminology will
32 be anticipated, we decided to initially report all outcome measure as mentioned in the original
33 study. Outcome measures will be mapped independently by two reviewers and in case of
34 disagreement a third reviewer will make the final decision. After data extraction of all studies
35 is completed, a meeting of the study management group will be held between to discuss
36 potential similarity between the outcome measures in order to assign an appropriate term for
37 them.

BMJ Open

Establishing a core outcome set for treatment of uncomplicated appendicitis in children: study protocol for an international Delphi survey.

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2018-028861.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 17-Apr-2019 |
| Complete List of Authors: | Knaapen, Max; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Paediatric Surgical Centre Hall, Nigel; University of Southampton Faculty of Medicine, University Surgery Unit van der Lee, Johanna H.; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Paediatric clinical Research Office Butcher, Nancy; Sick Kids, Child Health Evaluative Sciences Offringa, Martin; The Hospital for Sick Children, University of Toronto, Department of Paediatrics Van Heurn, Ernst; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Paediatric Surgical Centre Bakx, Roel; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Paediatric Surgical Centre Gorter, Ramon; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Paediatric Surgical Centre + On behalf of the paediatric , appendicitis COS development group |
| Primary Subject Heading: | Surgery |
| Secondary Subject Heading: | Emergency medicine, Gastroenterology and hepatology, Medical publishing and peer review, Paediatrics, Research methods |
| Keywords: | delphi, appendicitis, children, core outcome set, paediatric, Global |
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Manuscripts

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1 Establishing a core outcome set for treatment of uncomplicated 2 appendicitis in children: study protocol for an international Delphi 3 survey.

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6 PhD¹ + On behalf of the paediatric appendicitis COS development group

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34 **ABSTRACT**

35 **Introduction**

36 Appendicitis is a global disease affecting roughly one in every 12 people in the world, with
37 the highest incidence between ages 10 and 19 years. To date, a wide variety of health
38 outcomes have been reported in randomized controlled trials (RCTs) and meta-analyses
39 evaluating treatments for appendicitis. This is especially the case in studies comparing non-
40 operative treatment to operative treatment. A set of standard outcomes, to be reported in all
41 future trials, is needed to allow for adequate comparison and interpretation of clinical trial
42 results and to make data pooling possible. This protocol describes the development of such
43 a global core outcome set (COS) to allow unified reporting of treatment interventions in
44 children with acute uncomplicated appendicitis.

45 **Methods and analysis**

46 We use current international standard methodology for the development and reporting of this
47 COS. Its development consists of three phases: (1) Update the most recent systematic
48 review on outcomes reported in uncomplicated paediatric appendicitis research, to identify
49 additional outcomes, (2) Three-step global Delphi study to identify a set of core outcomes for
50 which there is consensus between parents and (paediatric) surgeons, and (3) Expert meeting
51 to finalize the COS and its definitions. Children and young people will be involved through
52 their parents during phase two and will be engaged directly using a customized face-to-face
53 approach.

54 **Ethics and dissemination.**

55 The medical research ethics committee of the Academic Medical Centre Amsterdam has
56 approved the study. Each participating country/research group will ascertain ethics board
57 approval. Electronic informed consent will be obtained from all participants. Results will be
58 presented in peer-reviewed academic journals and at (international) conferences.

59 **Registration details**

60 The COS development project was registered with the COMET initiative in February 2018
61 (<http://www.comet-initiative.org/studies/details/1119>).

62 **Strengths and limitations of this study**

- 63 1. This protocol describes an international online Delhi study that should result in a globally
64 relevant set of core outcomes for paediatric uncomplicated appendicitis.
- 65 2. The protocol was developed in conjunction with an international steering committee, patient
66 representation and follows all relevant core outcomes set development guidelines and
67 standards.
- 68 3. This study involves parents and patients in deciding what to measure in future
69 uncomplicated appendicitis research.

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70 4. The involvement of young people in core outcome set development requires a customized
71 approach. This protocol addresses this issue and describes a direct face-to-face
72 involvement.
73 5. Because of the global and multilingual aspect of the study there will be a limited
74 consensus discussion with only selected individuals. Also, due to feasibility, the direct face-
75 to-face engagement of young people will only take place in selected countries.

For peer review only

77 INTRODUCTION

78 Appendicitis is a common gastro-intestinal disease affecting roughly one in every 12 people
79 in the world, with the highest incidence between ages 10 and 19 years[1,2]. While the
80 incidence varies from country to country, appendicitis is a global disease[3]. In the last
81 decade, there have been several developments in the treatment of appendicitis in children,
82 with the most recent being non-operative treatment (NOT) for acute uncomplicated
83 appendicitis. Studies investigating the effectiveness of NOT in children show promising
84 results[4–7]. However, the selected primary (and secondary) outcomes vary widely, as
85 reflected in recent systematic reviews assessing the efficacy and safety of NOT, which may
86 contribute to their contradictory conclusions[4–8]. In the systematic review by Georgiou et
87 al.[4], the need for universal outcome selection and reporting in appendicitis studies is
88 emphasized. In general, it is recognized that clinical trials in children often lack outcomes that
89 are appropriately chosen for this particular population[9].

90 Inconsistent selection and reporting of outcomes limits the ability to adequately compare and
91 interpret clinical trial results. Furthermore, it hampers data pooling and subsequent meta-
92 analysis. It also increases the risk of selective outcome reporting, a form of publication bias.
93 This in turn jeopardizes the validity of results from individual trials, which feeds into
94 subsequent systematic reviews[10] and meta-analyses, which are by nature retrospective,
95 and therefore liable to various risks of bias[11,12].

96 As demonstrated by Hall et al. in 2015, a wide variety of outcomes has been reported in
97 randomized controlled trials (RCTs) and meta-analyses reporting on the treatment of
98 appendicitis in children[13]. In the 63 included studies, a total of 115 different outcomes were
99 reported[13]. Hall et al. proposed the development of a Core Outcome Set (COS), which is a
100 standardized collection of outcomes that should be measured and reported in all future
101 trials[14]. Recently a study protocol was published for developing such a COS in the United
102 Kingdom[15]. Because of the differences between countries in treatment practises, resources
103 and cultural aspects it was decided, in conjunction with the UK COS research group, that
104 there is a need for an international COS, to be used in all trials assessing the treatment of
105 acute uncomplicated appendicitis in children. The development of the current international
106 protocol was performed in conjunction with the UK research group. Its principal investigator
107 (NJ Hall) has been involved in its development and is part of the study management group.

108 Outcomes considered important by patients and families are essential to a meaningful and
109 complete COS[16]. That is why parents and patients play a central role in the consensus
110 process as a stakeholder group. Parent and patient representation was ensured through
111 involvement of the Dutch patient and parent Foundation: “Children and Hospital”. A

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3 112 representative from this group provided feedback from the perspective of parents and
4 113 children in several stages of the protocol development. They are also involved in the
5 114 development of a face-to-face methodology for engaging children in this COS project.

8 9 115 **Scope**

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11 116 We aim to reach a global consensus amongst patients, parents, researchers and physicians
12 117 on a minimal set of core outcomes that should be measured and reported in all future clinical
13 118 trials investigating any type of treatment for acute uncomplicated appendicitis in children,
14 119 including surgical treatment, non-operative treatment or other treatments aimed at curing
15 120 appendicitis.

19 20 121 **METHODS**

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22 122 In the development of this protocol, we adhere to the COS-STAD (Core Outcome Set-
23 123 STAndards for Development) recommendations[17] and the COMET (Core Outcome
24 124 Measures in Effectiveness Trials) handbook[18]. The completed COS-STAD checklist can be
25 125 found in online supplement S1. The final core outcome set will be reported in accordance
26 126 with the COS-STAR (COS-STAndaRds for reporting) statement[19]. Involvement of patients
27 127 and the public will be described using the GRIPP2 reporting checklist[20] (Guidance for
28 128 Reporting on Involvement of Patients and Public). This study was registered with the COMET
29 129 initiative (registration number: 1119) on February 11, 2018[21].
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35 36 131 **Study design**

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38 132 The paediatric appendicitis COS (PA-COS) development will consist of three phases: (1) An
39 133 update of the 2015 systematic review on outcomes reported in uncomplicated paediatric
40 134 appendicitis research[13]. Aiming to identify any additional outcomes used in trials that were
41 135 published since the previous systematic review; (2) A three-step Delphi study to identify a set
42 136 of core outcomes from those selected in the literature review. Development of the Delphi is
43 137 performed according to the checklist by Sinha et al.[22] on the design and reporting of Delphi
44 138 studies concerning COS selection; and (3) An expert panel meeting including physicians,
45 139 researchers and children/parent representatives in order to ratify the final COS. Children and
46 140 young people will be involved through their parents during phase two and will be engaged
47 141 directly using a customized approach.
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55 56 143 **Steering Committee**

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58 144 An international steering committee has been established and consists of the following; the
59 145 authors, a parent/patient representative of the Dutch Foundation: "Children and Hospital",

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3 146 and the lead local investigator of each participating centre (paediatric appendicitis COS
4 147 development group). The steering committee will agree on the final version of the protocol at
5 148 the start of the project and will provide input throughout the duration of the project. The
6 149 steering committee members will also be involved in the development of the final COS.
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8 150 Within the steering committee, a smaller study management group has been appointed
9 151 which will convene during regular (videoconference) meetings.

13 152 **Systematic review: Treatment outcomes**

16 153 Hall et al. performed a systematic review of RCTs and meta-analyses reporting treatment
17 154 outcomes of children with appendicitis up to April 2014[13]. They reported 115 unique
18 155 outcomes which were collapsed into a total of 38 standardized outcome terms. We will
19 156 update the systematic review in order to identify any new unique outcomes in clinical trials or
20 157 systematic reviews. All RCTs and systematic reviews/meta-analyses reporting treatment
21 158 outcomes of acute uncomplicated appendicitis in children (<18 years of age) published
22 159 between January 1st 2014 and November 23th 2017 will be included. The final review will
23 160 follow the PRISMA reporting guideline[23]. We will search the Cochrane Central Register of
24 161 Controlled Trials, MEDLINE and EMBASE with the help of a clinical librarian. Additional
25 162 information on the search strategy/study selection and data extraction can be found in online
26 163 supplement S2. Studies only reporting outcomes of treatment in complex or complicated
27 164 appendicitis (for example - gangrenous or perforated appendicitis, appendiceal mass,
28 165 appendiceal abscess) will be excluded.

36 166 After data extraction, a meeting of the study management group (including NJ Hall) will be
37 167 held to discuss potential similarities between the outcomes from the 2015 systematic review
38 168 from Hall et al.[13]. New unique outcomes will be discussed within the group in order to
39 169 assign an appropriate standardized outcome term. If these outcomes do not match any of the
40 170 original 38 outcome terms a new term will be assigned, this methodology is illustrated in
41 171 figure 1. The new and original outcome terms will be mapped to four core areas (death, life
42 172 impact, resource use, pathophysiological manifestations) in accordance with the methods
43 173 from the OMERACT FILTER 2.0[24]. Although Hall et al.[13] chose to list the adverse events
44 174 as a separate core area, we will reclassify these outcome terms to one of the four core areas
45 175 (Table 1.). Adverse events of treatment will, however, be labelled separately, as the
46 176 OMERACT filter suggests[24]. A meeting of the study management group will be held to
47 177 discuss potential similarities between outcomes and to assign appropriate common outcome
48 178 terms for corresponding outcomes. Outcomes that are only found once and are not
49 179 generalizable can be excluded (e.g. the width of lateral thermal damage of the
50 180 mesoappendix after appendectomy). Grouping the outcomes under a common outcome term
51 181 aims to arrive at a manageable and cohesive list of outcomes that is appropriate as a basis

182 for the Delphi questionnaire.

183 **Table 1. Outcome Core Areas**

| Core Area | Example(s) |
|-----------------------------------|---|
| Life impact | <i>Quality of life, loss of ability to work</i> |
| Resource use | <i>Length of hospital stay, healthcare costs, societal cost</i> |
| Pathophysiological Manifestations | <i>Biochemical parameters, organ function, (ir)reversible manifestations (complications, pathology results)</i> |
| Death | <i>Death</i> |

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185 Stakeholders and recruitment

186 1) Children and Young People

187 Children and young people (5-18 years) who have been treated for acute
 188 uncomplicated appendicitis in the preceding 24 months, either with initial NOT or with
 189 surgery. Children less than 5 years old are excluded as different outcomes might be
 190 appropriate in this very young age group. Also, uncomplicated appendicitis is much
 191 less common in young children than in older children. Furthermore, there are no
 192 studies in which children below the age of 5 are treated non-operatively. Children will
 193 be engaged indirectly as we will urge parents to discuss the answers they provide
 194 with their child whilst filling out the Delphi questionnaire. Young people will be
 195 engaged directly through a customized face-to-face approach in selected countries.
 196 For the invited children, considering the complexity of the subject and methodology,
 197 age is limited to 12-18 years.

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199 2) Parents

200 Parents of children and young people (5-18 years) treated for acute uncomplicated
 201 appendicitis either with initial NOT or with surgery in the preceding 24 months or
 202 during the initial phase of the study. Parents will be asked to discuss the answers
 203 they provide with their child whilst filling out the Delphi questionnaire. Parents will be

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3 204 invited to participate by their child's treating physician or their designate in each
4 205 participating country/hospital. Participants will be identified retrospectively by
5 206 contacting patients that were treated in the past 24 months or prospectively by
6 207 inviting parents to participate after their child has completed its treatment.
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11 209 **3) (Paediatric) Surgeons**

12 210 General and/or paediatric surgeons who care for children in the specified age group
13 211 will be asked to participate. Surgeons will be identified and invited by the local
14 212 coordinators in each participating country. These local coordinators are research
15 213 groups that have previously registered a clinical trial on uncomplicated appendicitis in
16 214 children. This should allow for inclusion of physicians that also have experience in
17 215 research on the treatment of appendicitis.
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23 217 **Participating countries and research groups**

24 218 It was decided to invite research groups that are currently conducting clinical trials on the
25 219 treatment of acute uncomplicated in children. Groups were identified through
26 220 www.clinicaltrials.gov by searching (January 2017) for 'appendicitis' with an age limitation of
27 221 5-18 years. Studies with a mixed population (children and adults) were excluded. Studies
28 222 that had been completed before 2014, had not been updated since 2015, or with incomplete
29 223 registrations, were excluded. We found 111 trials, of which 12 trials assessed the treatment
30 224 of uncomplicated appendicitis in children. Groups from the Netherlands, USA, Canada,
31 225 Australia, Sweden, Finland, UK, France, Italy, Israel, Japan, Singapore and Malaysia were
32 226 identified. Some trials included hospitals from multiple countries.
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40 227 **Sample size**

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43 228 There is no rationale for determining the number of respondents to invite for a Delphi
44 229 study[18]. A minimum of seven respondents per stakeholder group is suggested to have a
45 230 large enough group to allow for a consensus process[25]. Taking into account that only some
46 231 invited participants will register for the Delphi and not all respondents will complete all rounds
47 232 of the Delphi study (attrition), a minimum of 40 respondents per stakeholder group, per
48 233 country will be invited. There will be no maximum. In case the number of respondents per
49 234 country is significantly higher than other countries, we will consider a weightage per country
50 235 in the analyses. We anticipate that this sample will be large enough to reflect all relevant
51 236 opinions.
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237 238 **Delphi study**

239 International online Delphi study

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3 240 The Delphi method is an effective tool for reaching consensus in a large group without the
4 241 need for face-to-face contact[26]. The use of sequential questionnaires which are answered
5 242 anonymously by stakeholders is an established method for reaching consensus in a group of
6 243 experts[22]. Questionnaires will be sent using DelphiManager[27], a web-based system
7 244 designed for Delphi studies. The questionnaires will be open simultaneously to all
8 245 respondents of the participating countries. After each round, the aggregated responses of all
9 246 participants are shared anonymously in accordance with the Delphi principle.

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15 247 The list of outcomes from the systematic review will be formatted into questions,
16 248 accompanied by an extensive plain language summary per outcome, including figures if
17 249 appropriate. The Delphi questionnaire will originally be formulated in English and will be
18 250 translated if required. Translation will only be performed by native speaking professionals.

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22 251 Participants will be asked to score the importance of each outcome using a 1 to 9 Likert
23 252 scale as recommended by the Grading of Recommendations Assessment, Development and
24 253 Evaluation (GRADE) working group[28] and COMET initiative[18]. A score of 7-9 indicates a
25 254 critical outcome for assessing the effect of a treatment, 4-6 important but not critical, 1-3
26 255 indicates an outcome with low importance for assessing the treatment effect. It will also be
27 256 possible to select an “unable to score” option, which is especially of importance in case
28 257 parents do not feel equipped to score certain outcomes. The questionnaires, including the
29 258 plain language summaries, will be piloted by a group of laypersons (n=10) to check for
30 259 ambiguity and readability.

36 260 Delphi round one

37 261 Participants will be divided into two stakeholder groups: parents (with their children), and
38 262 surgeons. Parents will be asked to discuss the answers they provide with their child whilst
39 263 filling out the Delphi questionnaire. Baseline characteristics (age, country) will be
40 264 ascertained. Parents will be asked if their child was treated with non-operative or operative
41 265 treatment, time between registration and the first diagnosis of appendicitis and if their
42 266 treatment was with or without complications. They will also be asked whether they will be
43 267 answering the Delphi together with their child. Surgeons will be asked their speciality
44 268 (paediatric, general, abdominal, other), workplace (academic, teaching hospital, non-
45 269 teaching hospital), experience with non-operative treatment and experience in research
46 270 regarding appendicitis in children.

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55 271 All participants will be asked to score all previously identified outcomes according to their
56 272 perceived importance for assessing the treatment effect. In the first round there will be an
57 273 option to suggest additional outcomes not yet listed.

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60 274 Participants will have between four and eight weeks to complete each round, depending on

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3 275 the response rate. In that time they will receive a reminder email every two weeks as long as
4 276 they have not replied to the questionnaire.

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8 278 Delphi round one: analysis

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10 279 Results will be analysed **by stakeholder group and for all participants** using descriptive
11 280 statistics. Outcomes will be analysed separately for each stakeholder group, as there is
12 281 evidence that patients are likely to assign importance to outcomes differently than
13 282 surgeons[29], which has the potential to influence eventual outcome selection.

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17 283 “Consensus-in” will be defined as:

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19 284 – Greater than 70% of participants in **both** stakeholder groups scoring the outcome as
20 285 7-9 and less than 15% in **both** stakeholder groups scoring the outcome as 1-3.
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23 286 – Greater than 90% of participants within **one** stakeholder group scoring the outcome
24 287 as 7-9. This implies that these outcomes are highly regarded by an individual
25 288 stakeholder group, and should also be included[18].

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29 289 “Consensus-out” will be defined as:

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31 290 – Greater than 70% of participants in **both** stakeholder groups scoring the outcomes as
32 291 1-3 and less than 15% of participants in **both** stakeholder groups scoring the
33 292 outcome as 7–9. Consensus-out can only be reached when there is consensus
34 293 across **both** stakeholder groups.

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38 294 Outcomes that do not meet any of these criteria will be defined as “no consensus”. A
39 295 stratified analysis will be performed to check for skewing as a result of divergent opinions
40 296 from a single country, or surgeons with or without research experience.

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44 297 At the end of round one, there will be a meeting of the study management group to assess
45 298 whether an alteration in the Delphi study is appropriate. If additional outcomes are suggested
46 299 by Delphi participants, each outcome will be assessed by the study management group to
47 300 determine whether it is indeed new and to which category it should be classified. Wording of
48 301 the Delphi questionnaire will be adjusted if misinterpretation is suspected.

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53 302 Delphi rounds two and three

54 303 All participants that complete the previous round will be asked to participate in the next
55 304 round. Only outcomes that have not yet been defined as “consensus-in” or “consensus-out”
56 305 during the previous round will be presented in the following rounds to **all** participants.
57 306 Outcomes for which there was only “consensus-in” within a single stakeholder group, will still
58 307 be presented to the other stakeholder group to evaluate whether consensus can be achieved

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3 308 in both stakeholder groups. An overview of included and excluded outcomes will be
4 309 available. The outcomes for which there is no consensus and the newly suggested outcomes
5 310 from the previous rounds will be presented with the participants' individual score and the
6 311 median scores from each stakeholder group combined with a histogram showing the scoring
7 312 distribution. Participants will be asked to score all remaining outcomes in the same manner
8 313 as in round one.

13 314 Delphi rounds two and three analysis

15 315 Results will be analysed per stakeholder group and for all participants, using descriptive
16 316 statistics, including a stratified analysis. The same definitions for consensus in/out as in the
17 317 first Delphi round are upheld. After the second round, there will be a meeting of the study
18 318 management group to assess the need for alterations in the Delphi study, and to decide
19 319 whether or not to proceed with a third Delphi round, assuming consensus between **both**
20 320 stakeholder groups on more than 80% of the outcomes, and more than five outcomes with
21 321 consensus in. To give an estimate of the degree of agreement between respondents, the
22 322 width of the interquartile range of the median ranking score will be calculated, potentially
23 323 ranging from 0.00, meaning complete agreement, to 8.00, meaning least possible
24 324 agreement. This will be calculated for both the individual stakeholder groups as well as the
25 325 entire group of respondents after the final round.

33 326 **Face-to-face engagement of young people**

35 327 We wish to check for discrepancies of opinion between parents answering the Delphi
36 328 together with their child and children who are interviewed directly. For this, a form of in-
37 329 person interaction will be organised with young people (12-18 years) who have been treated
38 330 for appendicitis. They will be asked to comment on the preliminary COS selection
39 331 established at the end of the Delphi study, and to suggest additional outcomes and comment
40 332 on outcomes that did not make the preliminary COS selection. This will either be done by a
41 333 short, face-to-face, one round questionnaire involving only outcomes relevant to
42 334 children/young people, or in the form of a small consensus meeting (prioritization meeting)
43 335 before finalizing the definitive COS. Doing this type of research requires experienced
44 336 interviewers and resources. That is why the face-to-face engagement will only take place in
45 337 selected countries, however, we will aim to involve as many countries as feasible. Separate
46 338 ethical board approval will be obtained as appropriate.

55 339 **Consensus discussion**

57 340 If adequate consensus (we aim to achieve consensus on at least one outcome per
58 341 OMERACT core area) is reached in the Delphi study, we will organise a face-to-face expert
59 342 panel meeting with selected individuals with the purpose to ratify a pragmatic and well-

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3 343 defined set of outcomes. A secondary aim of this meeting is to enhance support and
4 344 implementation of the final COS.

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7 345 The meeting will be held at an international conference for paediatric surgery. Through
8 346 purposive sampling, approximately 30 “experts” from across all stakeholder groups, including
9 347 physicians, researchers and children/parent representatives, will be invited to participate in a
11 348 face-to-face meeting with the Steering Committee. Journal editors and healthcare
12 349 commissioners will also be invited to attend in an observational capacity with the purpose of
13 350 promoting implementation and to provide comments on the final list of outcomes.

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17 351 In the event that adequate consensus cannot be reached in the Delphi process, we will
18 352 organise a formal face-to-face consensus meeting or teleconference. In that case, we will
19 353 select an appropriate representation of all stakeholder groups from the panel members that
20 354 participated in the Delphi study.

23 355 **Final COS development**

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27 356 The goal is to achieve a pragmatic COS that is applicable and feasible for all future trials that
28 357 evaluate the treatment of uncomplicated appendicitis in children. There is no recommended
29 358 maximum number of outcomes that should be included in a COS. However, if the final COS
30 359 includes too many outcomes, the COS would not be feasible to use in practice. To achieve the
31 360 goal of a pragmatic COS we aim to arrive at a maximum of 10 outcomes, the same
32 361 maximum number as the UK COS protocol specifies[15]. As a minimum, we aim to have at
33 362 least one outcome per core area. If the number of outcomes for which consensus is achieved
34 363 greatly exceeds 10 outcomes, the outcomes with the highest level of consensus will be
35 364 considered part of the suggested COS. However, we will report all outcomes for which
36 365 consensus is achieved. The highest level of consensus depends on whether there is
37 366 consensus in both stakeholder groups, the median score that was appointed to the outcome,
38 367 and the interquartile range of the median score as an estimate of the degree of consensus.

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47 368 Only outcomes for which consensus is reached internationally will be selected. To test for
48 369 country bias, stratified analyses of the Delphi results will be performed. The results from the
49 370 face-to-face engagement of young people will be taken into account for the final COS
50 371 selection and will be reported separately. If there is no consensus between patients, parents
51 372 and healthcare professionals, an outcome can still be selected if there is clear consensus
52 373 within a single stakeholder group. These will be reported separately. The final COS will be
53 374 categorised according to the four core areas of the OMERACT filter[24]. We will also
54 375 annotate the outcomes according to the recently published outcome taxonomy to maximise
55 376 future data harmonisation[30].

377 **Patient and Public Involvement**

378 Patient involvement is at the core of this study design. By asking parents and patients with
379 experience in having uncomplicated appendicitis what outcomes they feel should be part of
380 future research. To ensure our design is appropriate for parents and children we have
381 involved the Dutch child and parents representation group as part of the steering committee.
382 In that capacities they provide input on the protocol and the study. To make sure the Delphi
383 questionnaire is understandable and has no ambiguities it is checked by a group of
384 laypersons before the start of the Delphi study. Part of the Delphi study is giving feedback to
385 all its participants after each round, this will also be done with the final study results.

386 **Ethics and dissemination.**

387 Ethics

388 The medical research ethics committee of the Academic Medical Centre Amsterdam
389 confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) does not
390 apply to this study and that complete approval of this study by the committee is not required.
391 Each participating country/research group will be asked to obtain ethics board approval or
392 confirm that ethics board approval it not required. Electronic informed consent will be
393 obtained from all participants. The face-to-face engagement of young people (12-18 years)
394 will take place in selected countries and separate ethics board approval will be obtained, as
395 appropriate.

396 Data collection and confidentiality

397 All data will be handled confidentially and in accordance with the Dutch Personal Data
398 Protection Act and the European General Data Protection Regulation (GDPR).
399 DelphiManager[27] will be used for the online questionnaire. After informed consent from all
400 participants only limited identifying information (name, email) will be ascertained during
401 registration. This information will be stored separately from the answers given in the
402 questionnaire and will only be used for the purpose of direct feedback and reminder emails.
403 Access to personally identifiable data will be strictly limited.

404 Study status and dissemination

405 In the first quarter (Q1) of 2018 the following 13 countries were invited to participate in the
406 project; Netherlands, USA, Canada, Australia, Sweden, Finland, UK, France, Italy, Israel,
407 Japan, Singapore and Malaysia. Ten countries replied, Italy, Israel and Japan did not. In Q1
408 2018 the systematic review was finished. In Q2 2018 the Delphi questionnaire was
409 developed and piloted. In Q3 2018 all materials were translated. Between Q4 2018 and Q1
410 2019 IRB applications were submitted in 10 countries and 15 participating centres. The
411 anticipated start of the online Delphi study is May 2019. We anticipate to have the final COS

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3 412 ready by Q1 2020. Dissemination of the results will be accomplished by publication in an
4 413 international peer-reviewed scientific journal and by presentations at (international)
5 414 conferences. By involving the majority of the principal investigators who are currently
6 415 involved in research on uncomplicated appendicitis in children, we aim to optimize uptake of
7 416 the final COS. By involving journal editors and healthcare commissioners in the face-to-face
8 417 consensus discussion, we aim to ultimately have the COS introduced as a requirement in
9 418 future outcome reporting on the treatment of uncomplicated appendicitis in children. We will
10 419 also actively send out the final COS to relevant journal editors and funding bodies to promote
11 420 uptake in future research.

421 **DISCUSSION**

422 **Strengths and limitations of this study**

423 **Outcomes selection**

424 The selection of potential outcomes will be done systematically and will provide a selection
425 for the first Delphi questionnaire that reflects most issues pertinent to the treatment of
426 uncomplicated appendicitis. By including systematic reviews/meta-analyses that also report
427 on non-comparative studies, we expect to identify all reported treatment outcomes, including
428 those from the relatively new field of NOT for uncomplicated appendicitis.

429 To be able to arrive at a manageable list of outcomes that is appropriate for a Delphi study,
430 the number of outcome terms needs to be somewhat limited. In order to achieve this, the
431 outcomes derived from our systematic review will be merged in case of similarity. If
432 outcomes are not generalizable and only reported once, they will be excluded. This will be
433 proposed and prepared by two independent reviewers and discussed in the study
434 management group. However, the merging of outcomes will inevitably lead to some loss of
435 detail.

436 **Global consensus**

437 In order to reflect the views of different stakeholders, a variety of groups will be part of the
438 development of this COS. This is not only the case on a national level, but also on an
439 international level, related to, for example, differences between countries in resources,
440 treatment practises for acute uncomplicated appendicitis, and cultural differences. For
441 example there is a large difference with regard to the standard length of hospital stay after an
442 appendectomy for uncomplicated appendicitis. In the USA much effort is devoted to reduce
443 the number of admission days, in the UK there is only limited attention for the duration of
444 admission and for instance in Japan an admission for 5 days is not uncommon. We can
445 expect that these kind of differences result in different opinions regarding the core outcomes
446 set. By also involving patients and parents from the participating countries we hope to correct

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3 447 for these differences[31]. In conjunction with the UK paediatric appendicitis COS research
4 448 group we decided that an international validation of the UK COS would not give the depth of
5 449 information and would not allow for consensus formation on all possible outcomes. Which we
6 450 feel is appropriate considering the before mentioned significant differences between
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8 451 countries. Involving members from different countries will not only lead to the development of
9 452 a COS that reflects the opinions of the international community, it should also lead to an
10 453 internationally applicable “minimal” COS. However, selecting the participating countries on
11 454 the basis of their involvement in research on appendicitis in children is a limitation. This
12 455 choice was made on the basis of feasibility. Researchers in the field of uncomplicated
13 456 appendicitis have an interest in the development of a COS and have the network to help
14 457 carry out the Delphi study. With our current selection we will still have participants from four
15 458 different continents. Our method of country selection has another advantage. Since non-
16 459 operative treatment is an important research subject in childhood appendicitis, we aim to
17 460 include surgeons and parents who have experience in that field. As non-operative treatment
18 461 is still experimental in most of the world, we also need surgeons and patients who have been
19 462 involved in such research.

29 463 **Limited face-to-face consensus**

30 464 If consensus is reached in the Delphi study we will not be organising a formal consensus
31 465 meeting. The Delphi method can be used for reaching consensus in a group of respondents
32 466 without the need for face-to-face contact. There is a risk of bias if a face-to-face consensus
33 467 meeting leads to selection of only participants who are able to attend the meeting, which is
34 468 especially a problem in a global consensus procedure. There are also problems regarding
35 469 language barriers in an international consensus meeting. To check for interpretation errors in
36 470 the Delphi method and to ensure a pragmatic and well-defined set of outcomes the results of
37 471 the Delphi study will be discussed in an (international) expert meeting. The influence of this
38 472 meeting on which outcomes are selected for the final COS is however very limited, as this
39 473 selection is primarily made in the Delphi study.

47 474 **Involving parents and their children**

48 475 Involving patients in COS development has recently become common practice with 88%
49 476 (n=112 as of April 12th 2016) of ongoing COS development studies doing so[18]. Involving
50 477 patients as participants seems imperative as patients may select different outcomes,
51 478 compared to physicians[16]. For this protocol we performed a scoping review [unpublished
52 479 work] that found 12 studies that directly engaged children in COS development. Either as
53 480 part of the advisory group or the steering committee, or as a stakeholder group in the
54 481 Delphi[15,22], focus groups[32], interviews[33] or as a part of the consensus meeting[34].
55 482 Attempts to engage children and young people in an online Delphi questionnaire have

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3 483 proven to be difficult. In the UK COS for uncomplicated appendicitis, there were substantial
4 484 difficulties with retaining young people in the consecutive rounds of the Delphi questionnaire,
5 485 despite extensive efforts to optimize the methodology to appeal to children and young
6 486 people, including: preliminary semi-structured interviews on the subject, pre-testing of the
7 487 Delphi survey by young people and children[15] and video animations explaining the need for
8 488 a COS. Parent participation however showed more promising results. Consequently, to
9 489 safeguard the input of children/young people, the Delphi questionnaire for this study will be
10 490 developed to be completed by parents with input from their children (5-18 years) whenever
11 491 possible. In order to ensure that there are no large discrepancies between the opinions of
12 492 parents together with their child, and with children without their parents, we will organize a
13 493 form of in-person interaction with young people (12-18 years) who have been treated for
14 494 appendicitis. Involving children/young people in COS development is a subject of interest in
15 495 many ongoing COS development projects. As the search for the optimal approach to engage
16 496 young people is ongoing we have not yet selected a final methodology. Two members of the
17 497 study management group are currently involved in group that is developing such
18 498 methodology in consultation with young people themselves. We will update our protocol as
19 499 soon as we settle on a methodology before starting the face-to-face engagement. The
20 500 updated protocol will be published on an online, open source format (via the Open Science
21 501 Framework).

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34 502 A limitation is that due to the international nature of our study it will not be feasible to engage
35 503 children directly in all the participating countries. That is why the face-to-face engagement
36 504 will take place in selected countries.

37 38 39 505 **Other stakeholders**

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41 506 After careful consideration and consultation with the participating countries, it was decided
42 507 not to include paediatricians, general practitioners, nurses or emergency medicine
43 508 physicians. Although all these specialists play an intricate role in the diagnosis and care for
44 509 children with appendicitis, they do not make the final decision regarding treatment or its
45 510 provision. We will however, depending on the organisation of the healthcare system in each
46 511 country, ask these stakeholders to comment on the final COS in order to ensure that
47 512 essential outcomes are not missed. Since almost all research regarding treatment of
48 513 paediatric uncomplicated appendicitis is initiated by (paediatric) surgeons, it was decided that
49 514 researchers will not be included as a separate individual stakeholder group. However,
50 515 involvement in research will be registered. Whilst their opinion is vital to the development of a
51 516 COS, it is likely researchers will be well represented in the (paediatric) surgeon stakeholder
52 517 group. A stratified analyses will be performed to check for skewing of the results by surgeons
53 518 involved in research. It was also decided not to include journal editors or healthcare

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3 519 commissioners. Even though their opinion is of great importance especially regarding
4 520 implementation, it was determined that their opinion is not essential in establishing the
5 521 outcomes selected for the COS. Also there is much variability between countries regarding
6 522 the role of these stakeholders, which would lead to major challenges regarding Delphi
7 523 analyses of such a small stakeholder group. However, to enhance implementation and
8 524 because of their expertise on the use of COSs, representatives of these stakeholder groups
9 525 will be asked to attend the final consensus discussion.
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15 526 **Outcome measures**

16 527 This study will not answer the question on how to measure the outcomes that are included in
17 528 the final COS, or at what time point the outcomes should be measured. We will however
18 529 attempt to come to a clear definition of each outcome. We expect that further research will be
19 530 necessary to answer the question of timing and how to measure the outcomes. We will
20 531 advise on this subject in the final report.
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533 FOOTNOTES

534 **Paediatric appendicitis COS development group.**

535 Minneci PC, MD, Svensson JF, MD, PhD, Luks FI, MD, PhD, St. Peter SD, MD, Abbo O, MD, Arnaud
536 AP, MD, Adams S, MBBS, FRACS, Nah SA, MBBS, MRCS, Skarsgard ED, MD, Pierro A, MD, PhD,
537 Zani A, MD, PhD, Emil S, MD, CM, Keijzer R, MD, PhD, Suominen JS, MD, PhD, Aziz DA, MD, FRCS

539 **Collaborators:**

540 The pediatric surgery departments of following hospitals have initiated the COS project and will
541 contribute by recruiting participants. Nationwide Children's Hospital, Columbus, OH, USA. Hasbro
542 Children's Hospital and Alpert Medical School of Brown University, Providence, RI, USA. Children's
543 Mercy Hospital, Kansas City, MO, USA. Karolinska University Hospital, Stockholm, Sweden.
544 Southampton General Hospital, Southampton, UK. Hôpital des Enfants, Centre Hospitalier
545 Universitaire Toulouse, Toulouse, France. Hôpital Femme-Enfant, University Hospital, CHU Rennes,
546 Rennes, France. Sydney Children's Hospital, Randwick NSW, Australia. KK Women's and Children's
547 Hospital, Singapore. BC Children's Hospital, Vancouver, BC, Canada. The Hospital for Sick Children,
548 Toronto, ON, Canada. Montreal Children's Hospital, Montreal, QC, Canada. Emma Children's
549 Hospital, Amsterdam UMC, University of Amsterdam, Vrije Universiteit, Amsterdam, Netherlands.
550 Helsinki Children's Hospital, Helsinki, Finland. Universiti Kebangsaan Malaysia Medical Centre
551 (UKMMC), Kuala Lumpur, Malaysia.

553 **Study management group**

554 Knaapen M, Hall NJ, Van der Lee JH, Butcher NJ, Offringa M, Bakx R, Gorter RR

556 **Acknowledgments**

557 We acknowledge Hester Rippen as the representative of the Dutch Foundation Children and Hospital
558 for her advice and support in drafting the protocol.

560 **Author contributions:**

561 All authors have contributed to the design of this protocol. MK, NJH JHvdL, RB and RRG have
562 initiated the project. The protocol was drafted by MK which was refined by NJH, JHvdL, RB, MO, NJB,
563 EWEvH, and RRG. Statistical advice was provided by JHvdL. MK was responsible for drafting this
564 manuscript. All authors have contributed to the manuscript and read and approved the final
565 manuscript. The paediatric appendicitis COS development group consist of all local investigators who
566 are responsible for translation, ethical board approval, participant recruitment. They have all read,
567 refined and approved the final manuscript.

569 **Data sharing statement:**

570 The project is registered on the comet-initiative.org which is open access. The study findings will be
571 presented in a report which will be submitted for publication in a relevant peer-reviewed journal to
572 ensure dissemination to relevant healthcare professionals. Findings may also be submitted for
573 presentation at local meetings or conferences. The protocol will be published on an open access
574 repository.

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577 commercial or not-for-profit sectors

578 **Competing interests statement:** None to declare

580 **REFERENCES**

581

582 1 Addiss DG, Shaffer N, Fowler BS, *et al.* the Epidemiology of Appendicitis and
583 Appendectomy in the United States. *Am J Epidemiol* 1990;**132**:910–25.
584 doi:10.1093/oxfordjournals.aje.a115734

585 2 Anderson JE, Bickler SW, Chang DC, *et al.* Examining a common disease with
586 unknown etiology: trends in epidemiology and surgical management of appendicitis in
587 California, 1995-2009. *World J Surg* 2012;**36**:2787–94. doi:10.1007/s00268-012-1749-
588 z

589 3 Ferris M, Quan S, Kaplan BS, *et al.* The Global Incidence of Appendicitis. *Ann Surg*
590 2017;**266**:237–41. doi:10.1097/SLA.0000000000002188

591 4 Georgiou R, Eaton S, Stanton MP, *et al.* Efficacy and Safety of Nonoperative
592 Treatment for Acute Appendicitis: A Meta-analysis. *Pediatrics* 2017;;e20163003.
593 doi:10.1542/peds.2016-3003

594 5 Huang L, Yin Y, Yang L, *et al.* Comparison of Antibiotic Therapy and Appendectomy
595 for Acute Uncomplicated Appendicitis in Children. *JAMA Pediatr* 2017;**171**:426.
596 doi:10.1001/jamapediatrics.2017.0057

597 6 Xu J, Adams S, Liu YC, *et al.* Nonoperative management in children with early acute
598 appendicitis: A systematic review. *J Pediatr Surg* Published Online First: May 2017.
599 doi:10.1016/j.jpedsurg.2017.05.003

600 7 Kessler U, Mosbahi S, Walker B, *et al.* Conservative treatment versus surgery for
601 uncomplicated appendicitis in children: a systematic review and meta-analysis. *Arch*
602 *Dis Child* 2017;;archdischild-2017-313127. doi:10.1136/archdischild-2017-313127

603 8 Gorter RR, The S-MML, Gorter-Stam MAW, *et al.* Systematic review of nonoperative
604 versus operative treatment of uncomplicated appendicitis. *J Pediatr Surg* 2017;**18 Apr**
605 **201**. doi:10.1016/j.jpedsurg.2017.04.005

606 9 Sinha I, Jones L, Smyth RL, *et al.* A Systematic Review of Studies That Aim to
607 Determine Which Outcomes to Measure in Clinical Trials in Children. *PLoS Med*
608 2008;**5**:e96. doi:10.1371/journal.pmed.0050096

609 10 Kirkham JJ, Dwan KM, Altman DG, *et al.* The impact of outcome reporting bias in
610 randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:c365.

- 1
2
3 611 11 Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised
4 612 controlled trials. *Lancet (London, England)* 1998;**351**:47–52. doi:10.1016/S0140-
5 613 6736(97)08461-4
6
7
8
9 614 12 Zanchetti A, Mancia G. Searching for information from unreported trials--amnesty for
10 615 the past and prospective meta-analyses for the future. *J Hypertens* 1998;**16**:125.
11
12
13 616 13 Hall NJ, Kapadia MZ, Eaton S, *et al.* Outcome reporting in randomised controlled trials
14 617 and meta-analyses of appendicitis treatments in children: a systematic review. *Trials*
15 618 2015;**16**:275. doi:10.1186/s13063-015-0783-1
16
17
18 619 14 Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials*
19 620 2007;**8**:39. doi:10.1186/1745-6215-8-39
20
21
22 621 15 Sherratt FC, Eaton S, Walker E, *et al.* Development of a core outcome set to
23 622 determine the overall treatment success of acute uncomplicated appendicitis in
24 623 children: a study protocol. *BMJ Paediatr Open* 2017;**1**:e000151. doi:10.1136/bmjpo-
25 624 2017-000151
26
27
28
29 625 16 Sanderson T, Morris M, Calnan M, *et al.* What outcomes from pharmacologic
30 626 treatments are important to people with rheumatoid arthritis? Creating the basis of a
31 627 patient core set. *Arthritis Care Res (Hoboken)* 2010;**62**:640–6. doi:10.1002/acr.20034
32
33
34
35 628 17 Kirkham JJ, Davis K, Altman DG, *et al.* Core Outcome Set-STAndards for
36 629 Development: The COS-STAD recommendations. *PLOS Med* 2017;**14**:e1002447.
37 630 doi:10.1371/journal.pmed.1002447
38
39
40
41 631 18 Williamson PR, Altman DG, Bagley H, *et al.* The COMET Handbook: version 1.0.
42 632 *Trials* 2017;**18**:280. doi:10.1186/s13063-017-1978-4
43
44
45 633 19 Kirkham JJ, Gorst S, Altman DG, *et al.* Core Outcome Set-STAndards for Reporting:
46 634 The COS-STAR Statement. *PLoS Med* 2016;**13**:e1002148.
47 635 doi:10.1371/journal.pmed.1002148
48
49
50 636 20 Staniszewska S, Brett J, Simera I, *et al.* GRIPP2 reporting checklists: tools to improve
51 637 reporting of patient and public involvement in research. *BMJ* 2017;**358**:j3453.
52
53
54 638 21 Protocol for the development of a global core outcome set for treatment of
55 639 uncomplicated appendicitis in children :: Core Outcome Measures in Effectiveness
56 640 Trials Initiative (COMET). <http://www.comet-initiative.org/studies/details/1119>
57 641 (accessed 5 Mar 2018).
58
59
60 642 22 Sinha IP, Smyth RL, Williamson PR. Using the Delphi Technique to Determine Which
20

- 1
2
3 643 Outcomes to Measure in Clinical Trials: Recommendations for the Future Based on a
4 Systematic Review of Existing Studies. *PLoS Med* 2011;**8**:e1000393.
5 644
6 645 doi:10.1371/journal.pmed.1000393
7
8
9 646 23 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting
10 647 systematic reviews and meta-analyses of studies that evaluate health care
11 648 interventions: explanation and elaboration. *J Clin Epidemiol* 2009;**62**:e1–34.
12 649 doi:10.1016/j.jclinepi.2009.06.006
13
14
15
16 650 24 Boers M, Kirwan JR, Gossec L, *et al*. How to choose core outcome measurement sets
17 651 for clinical trials: OMERACT 11 approves filter 2.0. *J Rheumatol* 2014;**41**:1025–30.
18 652 doi:10.3899/jrheum.131314
19
20
21 653 25 Mullen PM. Delphi: myths and reality. *J Health Organ Manag* 2003;**17**:37–52.
22 654 doi:10.1108/14777260310469319
23
24
25 655 26 Murphy MK, Black NA, Lamping DL, *et al*. Consensus development methods, and their
26 656 use in clinical guideline development. *Health Technol Assess* 1998;**2**:i–iv, 1–88.
27
28
29 657 27 COMET DelphiManager. 2017.<http://www.comet-initiative.org/delphimanager/>
30 658 (accessed 4 Dec 2018).
31
32
33 659 28 Guyatt GH, Oxman AD, Kunz R, *et al*. GRADE guidelines: 2. Framing the question
34 660 and deciding on important outcomes. *J Clin Epidemiol* 2011;**64**:395–400.
35 661 doi:10.1016/j.jclinepi.2010.09.012
36
37
38
39 662 29 Brookes ST, Macefield RC, Williamson PR, *et al*. Three nested randomized controlled
40 663 trials of peer-only or multiple stakeholder group feedback within Delphi surveys during
41 664 core outcome and information set development. *Trials* 2016;**17**:409.
42 665 doi:10.1186/s13063-016-1479-x
43
44
45
46 666 30 Dodd S, Clarke M, Becker L, *et al*. A taxonomy has been developed for outcomes in
47 667 medical research to help improve knowledge discovery. *J Clin Epidemiol* 2018;**96**:84–
48 668 92. doi:10.1016/j.jclinepi.2017.12.020
49
50
51
52 669 31 Biggane AM, Brading L, Ravaud P, *et al*. Survey indicated that core outcome set
53 670 development is increasingly including patients, being conducted internationally and
54 671 using Delphi surveys. *Trials* 2018;**19**:113. doi:10.1186/s13063-018-2493-y
55
56
57 672 32 Tsihchaki A, O'Brien K, Johal A, *et al*. Development of a core outcome set for
58 673 orthodontic trials using a mixed-methods approach: protocol for a multicentre study.
59 674 *Trials* 2017;**18**:366. doi:10.1186/s13063-017-2098-x
60

- 1
2
3 675 33 Allard A, Fellowes A, Shilling V, *et al.* Key health outcomes for children and young
4 676 people with neurodisability: qualitative research with young people and parents. *BMJ*
5 677 *Open* 2014;**4**:e004611. doi:10.1136/bmjopen-2013-004611
6
7
8 678 34 Morris C, Janssens A, Shilling V, *et al.* Meaningful health outcomes for paediatric
9 679 neurodisability: Stakeholder prioritisation and appropriateness of patient reported
10 680 outcome measures. *Health Qual Life Outcomes* 2015;**13**:87. doi:10.1186/s12955-015-
11 681 0284-7
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684 **Figures**

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686 **Figure 1. Schematic depiction of outcome term selection from systematic reviews**

687 *RCTs= Randomized controlled trials. SRs= Systematic reviews*

For peer review only

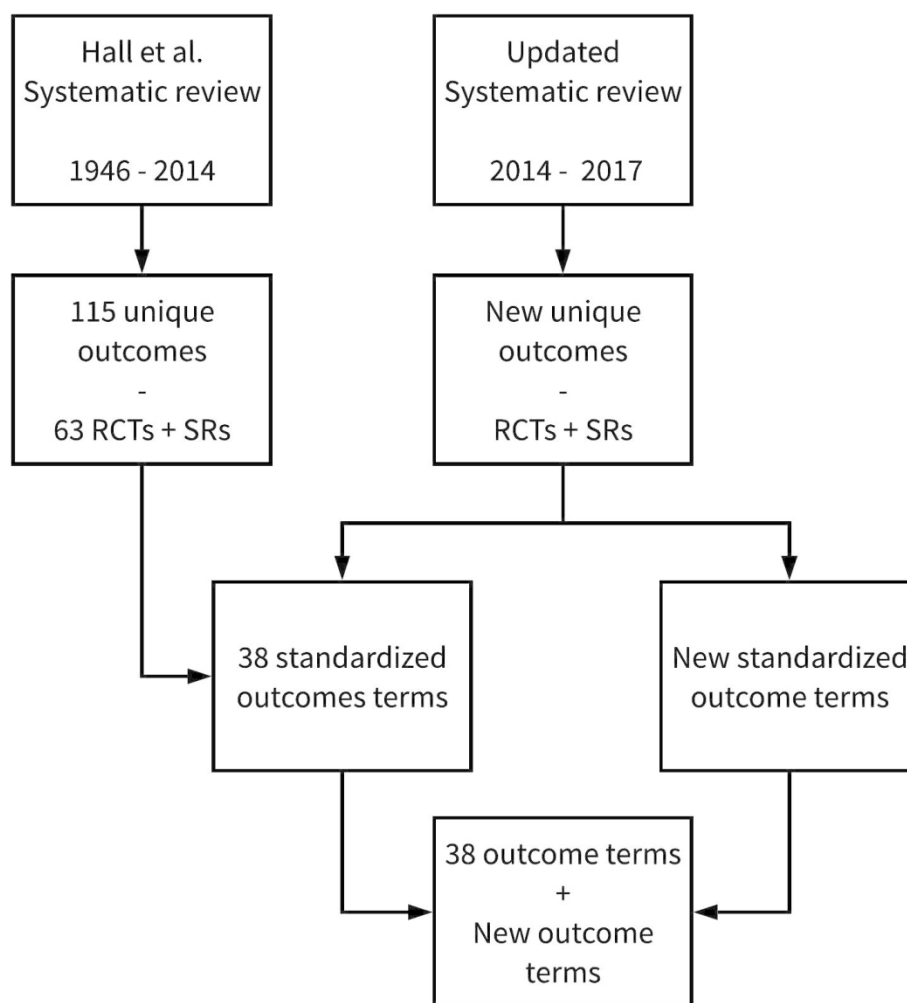


Figure 1. Schematic depiction of outcome term selection from systematic reviews
RCTs= Randomized controlled trials. SRs= Systematic reviews

134x146mm (300 x 300 DPI)

Online supplement 1.

S1. Completed COS-STAD checklist for PA-COS project

| Domain | Methodology | Notes | Addressed on page number |
|-----------------------|--|---|--------------------------------|
| Scope specification | 1. The research or practice setting(s) in which the COS is to be applied | e.g., for application in research studies or for use in routine care | 4. |
| | 2. The health condition(s) covered by the COS | e.g., treatment of rheumatoid arthritis or screening for cancer | 4. |
| | 3. The population(s) covered by the COS | e.g., patients with advanced disease or children | 4. |
| | 4. The intervention(s) covered by the COS | e.g., all interventions, drug therapy, or surgical interventions | 4. |
| Stakeholders involved | 5. Those who will use the COS in research | e.g., clinical trialists or industry | 6. |
| | 6. Healthcare professionals with experience of patients with the condition | e.g., clinical experts, practitioners, and investigators with particular experience in the condition | 6. |
| | 7. Patients with the condition or their representatives | involve those who have experienced or who are affected by the condition (e.g., patients, family members, and carers). | 6. |
| Consensus process | 8. The initial list of outcomes considered both healthcare professionals' and patients' views. | consider the views of healthcare professionals and patients (most likely identified from literature reviews or interviews) when generating an initial list of outcomes for inclusion in the consensus process. | 5. (No patient involvement) |
| | 9. A scoring process and consensus definition were described a priori. | Although different consensus methods may be employed in different studies, to avoid any potential biases, COS developers should describe their consensus method a priori. | 7, 8, 9. |
| | 10. Criteria for including/dropping/adding | prespecify criteria for including, dropping, or adding new outcomes to avoid potential biases. | 7, 8, 9. |
| | 11. Care was taken to avoid ambiguity of language used in the list of outcomes. | consider the language used when describing outcomes in front of different stakeholder groups. An example of 1 approach taken is to include both lay and medical terms, with these previously piloted with the stakeholders. | 7,8. |

1 Online supplement 2.

2 S2. Search strategy for systematic review PA-COS

3 **Appendicitis**

4 "Appendix"[Mesh] OR appendix[tiab] OR appendix[ot] OR "Appendicitis"[Mesh] OR
5 "Appendectomy"[Mesh] OR appendicit*[tiab] OR appendicit*[ot] OR appendectom*[tiab] OR
6 appendectom*[ot] OR appendicectom*[tiab] OR appendicectom*[ot]

7 **Children**

8 child*[tw] OR schoolchild*[tw] OR infan*[tw] OR adolescen*[tw] OR pediatri*[tw] OR
9 paediatr*[tw] OR neonat*[tw] OR boy[tw] OR boys[tw] OR boyhood[tw] OR girl[tw] OR
10 girls[tw] OR girlhood[tw] OR youth[tw] OR youths[tw] OR baby[tw] OR babies[tw] OR
11 toddler*[tw] OR teen[tw] OR teens[tw] OR teenager*[tw] OR newborn*[tw] OR
12 postneonat*[tw] OR postnat*[tw] OR perinat*[tw] OR puberty[tw] OR preschool*[tw] OR
13 suckling*[tw] OR picu[tw] OR nicu[tw]

14 **3.2.2 Study selection**

15 Selection of studies will be performed by 2 independent reviewers (MK, JF) according to the
16 below mentioned in- and exclusion criteria. In case of disagreement between two reviewers,
17 a third independent reviewer (RG) will make the final decision.

18 *Inclusion/Exclusion Criteria:*

19 All RCTs and systematic reviews/meta-analyses reporting the outcome of treatment of acute
20 uncomplicated appendicitis will be included in this systematic review. By including systematic
21 reviews that also report on non-comparative studies we expect to identify all reported
22 treatment outcomes, including those from the relatively new field of non-operative
23 management of uncomplicated appendicitis. Publications before January 2014 will be
24 excluded. Only studies in children (<18 years of age) will be included. Studies only reporting
25 on the outcome of treatment in complex or complicated appendicitis (gangrenous
26 appendicitis, appendiceal mass, appendiceal abscess) will be excluded.

27 **3.2.3 Data extraction**

28 The two reviewers will extract the data independently using the predefined data extraction
29 form shown in Appendix A. In case of disagreement a third reviewer will make the final
30 decision. A risk of bias assessment of the individual studies is not applicable as we will not
31 be using individual study data but only the reported outcomes. As diversity in terminology will
32 be anticipated, we decided to initially report all outcome measure as mentioned in the original
33 study. Outcome measures will be mapped independently by two reviewers and in case of
34 disagreement a third reviewer will make the final decision. After data extraction of all studies
35 is completed, a meeting of the study management group will be held between to discuss
36 potential similarity between the outcome measures in order to assign an appropriate term for
37 them.