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2 Uncomplicated Pediatric Appendicitis

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67 **ABBREVIATIONS AND DEFINITIONS OF TERMS**

68	CA	Complex appendicitis (ruptured or gangrenous)
69	CI	Confidence Interval
70	CIPP	Center for Innovation in Pediatric Practice
71	CSOR	Center for Surgical Outcomes Research
72	ED	Emergency Department
73	NCH	Nationwide Children’s Hospital
74	OR	Operating Room
75	PEDSQL	The Pediatric Quality of Life Inventory Measurement Model, a validated
76		pediatric model for measuring quality of life
77	QOL	Quality of Life
78	REDCap	The Research Electronic Data Capture System, an electronic system for
79		storing and managing research data in an encrypted form appropriate for
80		clinical information
81	RINCH	The Research Institute at Nationwide Children’s Hospital
82	SA	Simple appendicitis
83		
84		

85 **ABSTRACT**

86 Traditionally, children presenting with appendicitis are referred for urgent appendectomy. Recent
87 improvements in both the quality and availability of diagnostic imaging now allow for better pre-
88 operative characterization of appendicitis, including the severity of inflammation; size of the
89 appendix; and presence of extra-luminal inflammation, phlegmon, or abscess [1-3]. These
90 imaging advances, in conjunction with the availability of broad spectrum oral antibiotics, allow
91 for the identification of a subset of patients with uncomplicated appendicitis that can be
92 successfully treated with antibiotics alone.

93 Several recent European randomized controlled trials demonstrated that therapy with antibiotics
94 alone is an effective treatment option for adults with appendicitis, with no increase in the rate of
95 complicated appendicitis. A study from Nationwide Children’s Hospital (NCH) in Columbus,
96 Ohio, demonstrated the effectiveness of a non-operative treatment strategy in children with
97 suspected uncomplicated appendicitis [4]. At interim analysis with a median follow-up of nine
98 months, non-operative management had a 78% success rate with no increase in the rate of
99 complicated appendicitis (non-operative management group 3% vs. surgery group 11%).

100 The objective of this study is to perform a multi-institutional trial across the ten hospitals of the
101 Midwest Pediatric Surgical Research Consortium to investigate the effectiveness of non-
102 operative management for uncomplicated acute appendicitis as an alternative first line therapy in
103 children across a group of large children’s hospitals. Patients diagnosed with uncomplicated
104 appendicitis without a fecalith at participating institutions between September 2014 and October
105 2018 will be offered a choice of non-operative management or appendectomy. Outcomes will
106 include determining the success rate of non-operative management and comparing differences in
107 disability days, complication rates, cost of care, and quality of life between patients choosing
108 non-operative management and those choosing appendectomy.

109 Patients diagnosed with uncomplicated appendicitis without a fecalith between September 2014
110 and October 2018 will choose between non-operative management and appendectomy. Data to be
111 collected include patient demographics, clinical information related to the diagnosis and hospital
112 admission, and patient-centered quality of life measures. In addition, we will collect detailed cost
113 information related to the treatment and care for appendicitis and post-surgery care, reported by
114 participating institutions and self-reported by patients. For those subjects who have consented, a
115 one year follow-up phone call or letter (with survey) with the patient’s PCP will be performed .
116 Long-term follow-up will be conducted by phone or email to collect information on post-
117 treatment morbidity, including disability days, and healthcare satisfaction. All data will be
118 collected in a central Research Electronic Data Capture (REDCap) database housed at NCH.

119

120

121

122 **1 BACKGROUND INFORMATION AND RATIONALE**

123 **1.1 Introduction**

124 Over 70,000 appendectomies are performed on children annually in the United States for the
125 diagnosis of appendicitis. Irrespective of the severity of the inflammation and the presence or
126 absence of extraluminal extension of disease, appendicitis has been traditionally treated with an
127 operation, hospital admission, and a variable course of antibiotics. However, operative
128 management exposes children to the risks of anesthesia and surgery, and is associated with
129 inherent post-operative pain and stress.

130 Several recent European randomized controlled trials demonstrated that therapy with antibiotics
131 alone is an effective treatment option for adults with appendicitis [1-3, 5-7] with no increase in
132 the rate of complicated appendicitis [8]. An ongoing prospective clinical trial from NCH
133 confirmed the effectiveness of a non-operative treatment strategy in children with suspected
134 uncomplicated appendicitis [4]. At 1 year, non-operative management has a 76% success rate
135 with no increase in the rate of complicated appendicitis (non-operative management group 3%
136 vs. surgery group 11%).

137 Our objective is to validate these findings at multiple institutions to determine the success rate of
138 non-operative management and compare differences in disability days, complication rates, cost
139 of care, and quality of life between patients choosing non-operative management and those
140 choosing appendectomy.

141 **1.2 Relevant literature and data**

142 The management of appendicitis has evolved to incorporate alternative treatment strategies based
143 on severity of illness, in part because of substantial improvements in imaging modalities. In
144 patients with perforated appendicitis, treatment algorithms now utilize radiographic catheter-
145 guided procedures for intra-abdominal abscesses, and non-operative management with prolonged
146 antibiotics for patients with intra-abdominal phlegmons and prolonged symptoms for whom a
147 surgical resection may incur greater peri-operative morbidity [9-11]. Currently, investigators are
148 also re-evaluating the need to perform an interval appendectomy after the child recovers from
149 their acute illness in these severe cases. [12-15]

150 To date, uncomplicated appendicitis in the United States is treated with appendectomy, brief
151 peri-operative antibiotics, and a short hospital stay for post-operative observation. Operative
152 management is curative in these cases, but overall complication rates are reported between 5-
153 15% and with serious complications occurring in 1.5-2% of patients [16-19]. In addition,
154 operative management exposes children to the risks of anesthesia and is associated with inherent
155 post-operative pain [20] and stress. Furthermore, the median total cost of an uncomplicated
156 appendectomy in children is around \$6,355 [21]. With the rate of negative appendectomies at
157 approximately 6.7% [22] this indicates that over \$29 million of the above costs are unnecessary.
158 A successful non-operative treatment strategy for the management of uncomplicated appendicitis
159 would decrease the number of children requiring appendectomy.

160 There have been several randomized controlled studies comparing appendectomy to antibiotics
161 in patients with appendicitis (in non-U.S. countries) [1-3, 5-7]. A meta-analysis of 4 of these
162 studies reveals that antibiotic use is a safe initial treatment for appendicitis and that non-

163 operative management of appendicitis is associated with a significantly lower risk of
164 complications with no difference in risk of developing complicated appendicitis [8]. However, in
165 the pooled analysis, 37% of patients initially managed non-operatively underwent appendectomy
166 within one year for either primary failure of non-operative management or subsequent recurrence
167 of appendicitis. Based on careful examination of this meta-analysis and its associated studies, the
168 results of these studies need to be carefully extrapolated to pediatric practice because they
169 included very few children. Data on non-operative management in children was limited to one
170 retrospective study, conducted outside the United States, which demonstrated an 81% success
171 rate of non-operative management in patients with suspected uncomplicated appendicitis at one
172 year follow-up [1].

173 In addition, most of the adult studies did not select for patients with suspected uncomplicated
174 appendicitis; these studies enrolled all patients with appendicitis regardless of duration of
175 symptoms, imaging findings or suspicion of more advanced or complicated disease. Based on
176 these studies, specific clinical factors associated with a higher likelihood of failure of non-
177 operative management include the presence of a fecalith or fluid collection on imaging and the
178 presence of symptoms for >48 hours.

179 A prospective clinical trial from NCH has to date confirmed the effectiveness of a non-operative
180 treatment strategy in children with suspected uncomplicated appendicitis ([4]). In this
181 prospective non-randomized clinical trial, patients diagnosed with suspected uncomplicated
182 appendicitis are allowed to choose between non-operative management and appendectomy. This
183 study has enrolled 102 patients, 37 of whom selected non-operative management. The overall
184 success rate of non-operative management is 76% at a 1 year follow-up. In addition, patients in
185 the non-operative group have demonstrated significantly faster return to normal activity and
186 reported higher quality of life scores. Also, consistent with the adult studies, there has been no
187 increase in the rates of complicated appendicitis (non-operative management group 3% vs.
188 surgery group 11%) or overall complication in patients choosing non-operative management
189 compared to patients choosing appendectomy. The results of this study confirm that non-
190 operative management is a reasonable treatment strategy for children with uncomplicated
191 appendicitis. At NCH, non-operative management has been incorporated into the standard
192 treatment protocol for uncomplicated acute appendicitis (See Appendix).

193 This proposed study will expand upon the previous NCH study to perform a multi-institutional
194 study to determine the generalizability of a non-operative management strategy for
195 uncomplicated appendicitis across ten Children's Hospitals that comprise the Midwest Pediatric
196 Surgical Consortium. This multi-intuitional study will allow us to: 1) determine the success rate
197 of non-operative management; 2) compare differences in disability days, complication rates, and
198 quality of life between patients choosing non-operative management and those choosing
199 appendectomy; and 3) determine the cost-effectiveness of a non-operative management strategy
200 for suspected uncomplicated appendicitis. Successful completion of this study may result in a
201 paradigm shift away from operation, thereby decreasing the number of appendectomies
202 performed and reducing the overall costs and risks associated with pediatric appendicitis.

203 **1.3 Compliance Statement**

204 This study will be conducted in full accordance of all applicable institution's Research Policies
205 and Procedures, the bylaws of the Midwest Pediatric Surgical Consortium, and all applicable

206 federal and state laws and regulations including the HIPAA Privacy Rule. Any episode of non-
207 compliance will be documented.

208 The investigators will perform the study in accordance with this protocol and will report
209 unexpected problems in accordance with each institution's IRB Policies and Procedures and all
210 federal requirements. Collection, recording, and reporting of data will be accurate and will
211 ensure the privacy, health, and welfare of research subjects during and after the study. In
212 addition, site principal investigators will report all unexpected problems and adverse events to
213 the study principal investigator (PI) and research team at NCH (overall study PI and data
214 coordinating center). Finally, all events will be reviewed by the study Data Safety and
215 Monitoring Committee (DSMC) every six months throughout the period.

216 **2 STUDY OBJECTIVES**

217 **2.1 Primary Objectives**

218

- 219 1) To compare differences in treatment-related disability days at 1 year between non-
220 operative management and surgery in children with uncomplicated appendicitis across 10
221 children's hospitals.
- 222 2) To determine the 1 year success rate of non-operative management of uncomplicated
223 appendicitis at 10 children's hospitals

224

225 **2.2 Secondary Objectives**

- 226 1) To compare rates of complicated appendicitis between groups at 30 days, and at one, two,
227 and three years.
- 228 2) To determine differences in disability days at 30 days which includes the inpatient days,
229 days of missed school, days until return to normal activities, days until guardian returns
230 to normal schedule, and days for doctor or ER visits.
- 231 3) To compare quality of life measures at 30 days and at one year between the treatment
232 groups.
- 233 4) To determine cost-effectiveness of non-operative management at one year, including
234 initial admission, subsequent emergency department (ED) visits or physician visits,
235 subsequent readmissions and reoperations and additional imaging related to appendicitis
236 or complications of appendectomy.
- 237 5) To compare rates of treatment-related complications at 30 days, 6 months and at one,
238 two, and three years.

239 **3 INVESTIGATIONAL PLAN**

240 **3.1 Study Design**

241 This is a prospective, non-randomized multi-institutional trial investigating a non-operative
242 management strategy for children (7-17 years old) with uncomplicated appendicitis across
243 children's hospitals. In this trial, patients and their families will choose between two treatment
244 options: non-operative management with antibiotics alone or urgent appendectomy. There will
245 be two groups: those choosing non-operative management (Non-Operative group) and those

246 choosing appendectomy (Surgery group). Outcomes will include determining the success rate of
247 non-operative management and comparing differences in disability days, complication rates, cost
248 of care, and quality of life between the two groups.

249 This is a patient choice trial rather than a randomized trial because we believe that the success of
250 each treatment option depends on which outcomes are most important to the patient and their
251 family [23-27]. For example, although initial non-operative management of early appendicitis
252 may be safe for most patients, appendectomy may be a better treatment option for patients who
253 live in remote areas or for families who are so fearful of a recurrence that they are likely to return
254 to the ED every time their child develops abdominal pain. For these patients, the risk of post-
255 operative complications may be perceived as minor compared to the benefit of a curative
256 appendectomy. In contrast, for families who are averse to surgery, initial non-operative therapy
257 may be the least stressful and most appealing choice because it may eliminate the need for an
258 operation and its inherent risks while expediting return to activities. For these reasons, we opted
259 to allow eligible patients and their families to choose between surgery and non-operative
260 management rather than randomize patients to one of the two treatment groups.

261 **3.2 Study Duration and Enrollment**

262 **3.2.1 Duration of Study and Enrollment**

263 Enrollment for this study will be conducted through October 2018 with annual follow-up phone
264 calls for subjects who choose antibiotic treatment until age 18 years and three years for subjects
265 who choose surgery. A minimum of one year of data will be necessary to collect to assess our
266 primary outcome.

267 **3.2.2 Total Number of Subjects Projected and Site**

268 The study will be coordinated through the Center for Surgical Outcomes Research (CSOR)
269 within the Center for Innovation in Pediatric Practice (CIPP) at the Research Institute at
270 Nationwide Children's Hospital (RINCH) in Columbus, OH. A total of 300 children are
271 projected to be enrolled from our institution as part of a broader cohort of 1100 children with
272 approximately 40% choosing non-operative management. We plan for 91 patients to be enrolled
273 at each site but with larger sites (such as NCH) potentially enrolling more patients as needed to
274 meet the necessary enrollment numbers (up to a maximum of 300 patients). Study participants
275 will be recruited after surgical consultation has been performed in the ED and will be consented
276 either in the ED or surgical inpatient units of each institution.

277 Follow-up research phone calls and surveys will be conducted (see schedule below) by study
278 coordinators at each site through the first two weeks and then by a study coordinator at NCH for
279 all subsequent phone calls through three years for those subject choosing surgery and annually
280 for those who choose antibiotics. Patients will also follow up on an outpatient basis with each
281 institution's department of surgery in accordance with standard of care.

282 **3.3 Study Population**

283 Children between the ages of 7-17 who are diagnosed with early appendicitis will be screened
284 for eligibility.

285 **3.3.1 Inclusion Criteria**

- 286 - English and non-English speaking patients
- 287 - Age : 7-17 years
- 288 - US, CT, or MRI-confirmed early appendicitis:
 - 289 ○ US: hyperemia, ≤ 1.1 cm in diameter, compressible or non-compressible, no
 - 290 abscess, no fecalith, no phlegmon
 - 291 ○ CT or MRI: hyperemia, fat stranding, ≤ 1.1 cm in diameter, no abscess, no
 - 292 fecalith, no phlegmon
- 293 - WBC count $> 5,000/\mu\text{L}$ and $\leq 18,000/\mu\text{L}$
- 294 - Abdominal pain ≤ 48 hours prior to receiving antibiotics

295 **3.3.2 Exclusion Criteria**

- 296 - History of chronic intermittent abdominal pain
- 297 - Pain > 48 hours prior to first antibiotic dose
- 298 - Diffuse peritonitis
- 299 - Positive urine pregnancy test
- 300 - WBC $\leq 5,000/\mu\text{L}$ or $\geq 18,000/\mu\text{L}$
- 301 - Presence of a fecalith on imaging
- 302 - Evidence on imaging studies for evolving perforated appendicitis, including abscess or
- 303 phlegmon
- 304 - Communication difficulties (e.g. severe developmental delay)

305 **4 STUDY PROCEDURES**

306 **4.1 Screening and Enrollment**

307 During initial contact with a potential subject, a physician-member of the surgical consult team
308 will assess their eligibility through satisfaction of both inclusion and exclusion criteria. If all
309 eligibility criteria are met, a physician-member of the research team will invite the child and
310 legal guardian to enroll. The physician-member of the research team will then review the written
311 information about the study and answer any questions. The patient and family will then choose
312 between non-operative management with antibiotics alone (Non-Operative group) and urgent
313 appendectomy (Surgery group).

314 Upon enrollment, study staff at each institution will be contacted by the physician-member of the
315 research team who obtained consent/assent. The study staff will conduct all data collection
316 throughout the study, with study staff at each institution conducting data collection during the
317 inpatient admission and through two weeks post-discharge. Study staff at NCH will conduct data
318 collection after the two-week period. A research team call schedule will be maintained that
319 assigns a physician-member of the NCH research team to be available for consultation with each
320 institution's clinical team. The clinical team will also be able to contact a physician-member of
321 the research team by pager 24 hours per day. This information will be provided to the clinicians
322 caring for the patients and will be posted in pre-specified areas within the surgical wards. Study
323 staff will also contact families with visit reminders via phone and letter, if necessary. Families in
324 the non-operative group who do not respond to our follow-ups at six months, one year and/or the
325 yearly follow-up will be considered lost to follow-up.

326 **4.2 Study Procedures: Non-Operative Group**

327 **4.2.1 Hospital Course**

328 **4.2.1.1 Treatment Intervention**

329 Upon enrollment, the subject will receive IV Zosyn (piperacillin-tazobactam 2 g/0.25 g)¹. This is
330 the standard therapy given to every patient diagnosed with appendicitis at NCH. Dispensation of
331 the drug is based on weight. Participants <40 kg will be prescribed a dose of 300 mg piperacillin
332 component/kg/day divided every eight hours and those >40 kg will receive Zosyn at a dose of
333 3.375 g piperacillin-tazobactam every six hours². Patients with penicillin allergies will receive IV
334 Cipro (ciprofloxacin) at a dose of 30 mg/kg/day divided every eight hours up to 1200 mg per day
335 and IV Flagyl (metronidazole) at a dose of 30 mg/kg/day divided every six hours up to 500 mg
336 per dose³.

337 **4.2.1.2 Treatment Algorithm**

338 Vital signs and pain score will be assessed per standard nursing protocol⁴ (please see appendix
339 for sample pain scores used) for each institution. If the pain improves, then the child will be
340 offered food.

341 Cross-over to appendectomy will occur in 2 situations:

- 342 1. Failure to improve after 24 hours of IV antibiotics: Patients who do not exhibit clinical
343 improvement (decreased tenderness, resolution of fever) or do not report symptomatic
344 relief (decreased pain, resolution of nausea/vomiting, advancement of diet) after
345 receiving 24 hours of intravenous antibiotics will be recommended for appendectomy. If
346 there is either objective or subjective improvement, then the child can continue on IV
347 antibiotics for up to another 24 hours.
- 348 2. If clinical status worsens: If a patient's symptoms worsen (increased abdominal pain) or
349 there is evolving objective evidence of systemic signs of infection (increasing
350 tachycardia, hypotension, persistent fever, or decreased mental status), then he/she will
351 be recommended for appendectomy.

352 Failure to improve or worsening of clinical status that leads to an appendectomy is considered
353 treatment failure of non-operative management. This is different from an independent request
354 from the parent or legal guardian for the patient to undergo surgery, despite clinical improvement
355 and/or symptom relief, which is considered conversion to the surgery group or elective
356 withdrawal from the study and not a treatment failure of non-operative management.

357 Patients whose symptoms begin to resolve (decreased abdominal pain, no nausea or vomiting, or
358 fever resolution) and who tolerate regular food will be discharged. Patients will be sent home on

¹ IV Zosyn is the standard regimen for our institution. You may change this and the following directions on dosing to a different antibiotic based on your institutional policies and standard of care.

² IV Zosyn is the standard regimen for our institution. You may change this and the following directions on dosing to a different antibiotic based on your institutional policies and standard of care.

³ IV Cipro and Flagyl is the standard regimen for our institution for patients with penicillin allergies. You may change this antibiotic selection and these directions on dosing based on your institutional policies and standard of care.

⁴ We have included a sample of NCH nursing protocol in the appendix. Your nursing protocol may be different.

359 standard oral Augmentin (<14 years will receive 45 mg amoxicillin component/kg/day divided
360 every 12 hours and 14 years and older will receive 875 mg amoxicillin component every 12
361 hours, using the 400 mg/5mL suspension or 875 mg tablet depending on patient preference for
362 liquid or tablets) for a total antibiotic course of seven days. For those children who have
363 penicillin allergies, the alternative will be oral Cipro (30 mg/kg/day divided every 12 hours to a
364 maximum of 1.5 g/day) and Flagyl (30 mg/kg/day divided every six hours up to 500 mg per
365 dose).

366 Before discharge, the patient and legal guardian will complete a quality of life (QOL) survey
367 (PEDSQL Quality of Life Inventory: Child and Parent Report) that asks about the child's health,
368 feelings, and social functioning in and out of school and Decisional Regret, Decisional Self
369 Efficacy, Decisional Conflict Scale and HealthCare Satisfaction surveys. Additionally, the family
370 will be informed that while on antibiotics, if the child is on oral contraceptives, the efficacy of oral
371 contraceptives may be impaired. The child's primary care physician will be notified via direct mail
372 and a letter placed within the electronic medical record.

373 In addition, at the Nationwide Children's Hospital site only, legal guardians will be asked to
374 complete questionnaires to assess decision making processes and satisfaction with their chosen
375 treatment course; surgical management or nonoperative (antibiotic) management of appendicitis.
376 Furthermore, legal guardians will also be asked to complete the PEDSQL HealthCare Satisfaction-
377 Generic Module to assess their satisfaction with the healthcare provided.

378 In addition, we will collect information from the medical record to document procedures and
379 treatments received during the initial hospital stay. We will record the costs directly from
380 hospital departments that provide patient services, including inpatient (e.g., ICU) and outpatient
381 nursing departments, diagnostic departments (e.g., labs, imaging), and pharmacies. We will also
382 document payments received from all payers regarding each relevant procedure (by reviewing
383 medical charts and searching claims data) and track the time spent by surgeons and nurses spent
384 on non-operative management.

385 When patients undergo a surgical or interventional radiology procedure related to treatment of
386 appendicitis, such as an appendectomy or intra-abdominal drain placement, study staff will collect
387 information from medical records and clinical interview with the patient and family to document
388 procedures and treatments received during that additional clinical visit or hospital stay and any
389 complications related to that procedure. Please see the form in the appendix (Data collection form
390 for additional procedures) for data points to be collected as part of this process. Chart reviews will
391 be conducted by each site at 1 year, 6 months to 6 weeks prior to the first analysis, and 3 years to
392 validate patient outcomes.

393 We will also collect the demographic and socioeconomic information of both the patient and the
394 legal guardian including: age, race, ethnicity, and gender of the patient; annual parent/guardian
395 income range; guardian occupations; and specific insurance coverage status for the patient.

396 **4.2.2 Follow-Up**

397 **4.2.2.1 2-5 days and 10-14 days**

398 A member of each institution's research team will call the family for a follow-up. Any concerns,
399 issues or complications regarding the oral antibiotics or the study will be discussed. In addition,
400 how many days the child missed from normal activities, including school, gym, recess, sports, and

401 other after school activities, will be recorded. Similarly, the number of days that the legal guardian
402 spent without a normal schedule will also be assessed. Please see the form in the appendix (Survey
403 at 2-5 days and 10-14 days for Non-Operative group) for data points to be collected during this
404 phone call. The family will also be asked if they have any comments regarding the study.

405 **4.2.2.2 30 days (± 10 days)**

406 A member of the central research team from NCH will call or email the family for a follow-up.
407 Please see the form in the appendix (Survey at 30 days, 6 months, 1 year, and annually for Non-
408 Operative group) for data points to be collected during this phone call. The child and legal
409 guardian will complete the same QOL survey (PEDSQL Quality of Life Inventory: Child and
410 Parent Report) completed before hospital discharge either in person or over the phone.

411 The legal guardian will also complete a health satisfaction survey (PEDSQL Healthcare
412 Satisfaction Generic Module: Parent Report) regarding their satisfaction with the care the child
413 received at the hospital. We will also ask questions about any problems the child has had with
414 their appendix since discharge, any other issues, and how many days the child missed their
415 normal activities and the legal guardian could not engage in their normal schedule. We will ask
416 specifically about subsequent ED visits or physician visits, readmissions and operations and
417 additional imaging related to appendicitis. We will also ask about the out-of-pocket expenditures
418 directly spent on post-treatment medical care and returning visits (e.g. insurance copayments;
419 costs of drugs) and other expenditures related to the visits within 30 days. The family will also
420 be asked if they have any comments regarding the study.

421

422 A VISA® ClinCard, preloaded with \$25.00 and will be mailed to the legal guardian's address at
423 the completion of the 30 day follow-up.

424 **4.2.2.3 6 months (± 20 days)**

425 A member of the central research team from NCH will call or email the family and ask questions
426 about any problems the child has had with their appendix since their 30-day follow-up.
427 Specifically, we will ask about subsequent ED visits or physician visits, readmissions and
428 operations, additional imaging, and missed days from normal activities by the patient and legal
429 guardian that were related to appendicitis. We will also ask about the out-of-pocket expenditures
430 directly spent on post-treatment medical care and returning visits (e.g. insurance copayments;
431 costs of drugs) and other expenditures related to the visits within six months. Please see the form
432 in the appendix (Survey at 30 days, six months, one year, and annually for Non-Operative group)
433 for data points to be collected during this phone call. The family will also be asked if they have
434 any comments regarding the study, \$25.00 will be loaded onto the participant's VISA® Clincard
435 upon completion of the 6 month follow-up.

436 **4.2.2.4 1 year (± 30 days)**

437 A member of the central research team from NCH will call or email the family and ask questions
438 about any problems the child has had with their appendix since their six-month follow-up.
439 Specifically, the research team will ask about subsequent ED visits or physician visits,
440 readmissions and operations, additional imaging, and missed days from normal activities by the
441 patient and legal guardian that were related to appendicitis.

442 If previously consented to at the time of enrollment, a team member will contact the subject's
443 PCP by phone or letter (with accompanying survey) as part of the 1 year follow-up to assess for
444 events related to the diagnosis, treatment, and health care services provided for the subject's
445 appendicitis treatment during the past year. A specific section of the consent form asks the
446 patient's legal guardian to either accept or decline this part of the study.

447 Subjects who will turn 18 before their one-year follow-up will be asked to sign the informed
448 consent used for the study. Consent will either be obtained by a member of the local research
449 team or the NCH research team. After speaking with the subject and explaining the study, an
450 informed consent will be mailed to the subjects to sign so that the research team may continue to
451 collect data up to one year after their initial hospital discharge.

452 We will also ask about the out-of-pocket expenditures directly spent on post-treatment medical
453 care and returning visits (e.g. insurance copayments; costs of drugs) and other expenditures
454 related to the visits within one year. Please see the form in the appendix (Survey at 30 days, six
455 months, one year, and annually for Non-Operative group) for data points to be collected during
456 this phone call. The family will also be asked if they have any comments regarding the study.

457 \$50.00 will be loaded onto the participant's VISA® Clincard upon completion of the 1 year
458 follow-up.

459 For those 1 year follow-ups that are not completed, we will conduct one final phone call and
460 send a letter outside the window in an attempt to obtain data for final follow-up. If we are unable
461 to reach the patient, then the local site will also try one final phone call

462 **4.2.2.5 Annually (± 30 days) through the age of 18**

463 A member of the central research team from NCH will call or email the family once a year until
464 three years after initial treatment. The same follow-up questions as those asked during the one year
465 follow-up will be asked. Please see the form in the appendix (Survey at 30 days, six months, one
466 year, and annually for Non-Operative Group) for data points to be collected during this phone
467 call. In addition, we will call all patients and families for their consent to follow them with an
468 annual phone call or email until their child turns 18 years of age. The family will also be asked if
469 they have any comments regarding the study.

470 **4.3 Study Procedures: Surgery Group**

471 **4.3.1 Hospital Course**

472 **4.3.1.1 Treatment Intervention**

473 Each institution's standard of care for managing appendicitis will be applied.

474 Before discharge, the patient and legal guardian will complete a QOL survey (PEDSQL Quality
475 of Life Inventory: Child and Parent Report) that asks about the child's health, feelings, and social
476 functioning in and out of school.

477 In addition, we will collect information from the medical record to document procedures and
478 treatments received during the initial hospital stay. We will record the costs directly from
479 hospital departments that provide patient services, including inpatient (e.g., ICU) and outpatient
480 nursing departments, diagnostic departments (e.g., labs, imaging), and pharmacies. We will also

481 document payments received from all payers regarding each relevant procedure (by reviewing
482 medical charts and searching claims data) and track the time spent by surgeons and nurses spent
483 on non-operative management.

484 We will also collect the demographic and socioeconomic information of both the patient and the
485 legal guardian including: age, race, ethnicity, gender, annual parent/guardian income range,
486 guardian occupations and specific insurance coverage status.

487 **4.3.2 Follow-Up**

488 **4.3.2.1 30 days (± 10 days)**

489 A member of the central research team from NCH will call or email the family for a follow-up.
490 The child and legal guardian will complete the same QOL survey (PEDSQL Quality of Life
491 Inventory: Child and Parent Report) completed before hospital discharge either in person or over
492 the phone. Please see the form in the appendix (Survey at 30 days, six months, one year, and
493 annually for Surgery group) for data points to be collected during this phone call.

494 The legal guardian will also complete a healthcare satisfaction survey (PEDSQL Healthcare
495 Satisfaction Generic Module: Parent Report) regarding their satisfaction with the care the child
496 received at the hospital. We will also ask questions about any problems the child has had with
497 their appendix since discharge, any other issues, and how many days the child missed normal
498 activities including school, gym, recess, sports, and other after school activities will be recorded.
499 Similarly, the number of days the legal guardian could not engage in their normal schedule will
500 be recorded. We will ask specifically about subsequent ED visits or physician visits,
501 readmissions and operations and additional imaging related to their appendectomy. We will also
502 ask the out-of-pocket expenditures directly spent on post-treatment medical care and returning
503 visits (e.g. insurance copayments; costs of drugs) and other expenditures related to the visits
504 within 30 days. The family will also be asked if they have any comments regarding the study.

505 A VISA® ClinCard, preloaded with \$25.00 and will be mailed to the legal guardian's address at
506 the completion of the 30 day follow-up.

507 **4.3.2.2 6 months (± 20 days)**

508 A member of the central research team from NCH will call the family and ask questions about any
509 problems the child has had with their appendix since their 30-day follow-up. Specifically, we will
510 ask about subsequent ED visits or physician visits, readmissions and operations, additional
511 imaging, and missed days from normal activities by the patient and legal guardian that were
512 related to their appendectomy. We will also ask about the out-of-pocket expenditures directly
513 spent on post-treatment medical care and returning visits (e.g. insurance copayments; costs of
514 drugs) and other expenditures related to the visits (e.g. transportation costs) within one year.
515 Please see the form in the appendix (Survey at 30 days, six months, one year, and annually for
516 Surgery group) for data points to be collected during this phone call. The family will also be
517 asked if they have any comments regarding the study.

518 \$25.00 will be loaded onto the participant's VISA® Clincard upon completion of the 6 month
519 follow-up.

520 **4.3.2.3 1 year (30 days)**

521 A member of the central research team from NCH will call or email the family and ask questions
522 about any problems the child has had with their appendix since their six-month follow-up.
523 Specifically, we will ask about subsequent ED visits or physician visits, readmissions and
524 operations, additional imaging, and missed days from normal activities by the patient and legal
525 guardian that were related to their appendectomy. We will also ask about the out-of-pocket
526 expenditures directly spent on post-treatment medical care and returning visits (e.g. insurance
527 copayments; costs of drugs) and other expenditures related to the visits (e.g. transportation costs)
528 within one year. Please see the form in the appendix (Survey at 30 days, six months, one year,
529 and annually for Surgery Group) for data points to be collected during this phone call.

530 For subjects who will turn 18 before their one-year follow-up, they will be asked to sign the
531 informed consent used for the study. After speaking with the subject and explaining the study, an
532 informed consent will be mailed to the subjects to sign so that we may continue to collect data up
533 to 1 year after their initial hospital discharge. The family will also be asked if they have any
534 comments regarding the study.

535 \$50.00 will be loaded onto the participant's VISA® Clincard upon completion of the 1 year
536 follow-up.

537 For those 1 year follow-ups that are not completed, we will conduct one final phone call and
538 send a letter outside the window in an attempt to obtain data for final follow-up . If we are unable
539 to reach the patient, then the local site will also try one final phone call.

540

541 **4.3.2.4 Annually (± 30 days) through age of 18**

542 A member of the research team will call the family once a year until three years after initial
543 treatment. The same follow-up questions as those asked during the one year follow-up will be
544 asked. Please see the form in the appendix (Survey at 30 days, six months, one year, and annually
545 for Surgery Group) for data points to be collected during this phone call. In addition, we will call
546 all patients and families for their consent to follow them with an annual phone call or until their
547 child turns 18 years of age. The family will also be asked if they have any comments regarding
548 the study.

549 **5 STATISTICAL CONSIDERATIONS**

550 **5.1 Primary and Secondary Endpoints**

551 The primary endpoints are: 1) to compare differences in treatment-related disability days at 1
552 year between non-operative management and surgery in children with uncomplicated
553 appendicitis across 10 children's hospitals; and 2) to determine the 1 year success rate of
554 non-operative management of uncomplicated appendicitis at 10 children's hospitals.
555 Secondary endpoints that will be compared between groups are: rates of complicated
556 appendicitis between groups at 30 days, one year, two years and three years; differences in
557 disability days at 30 days and one year (which includes the inpatient days, days of missed
558 school, days until return to normal activities, and days until guardian returns to normal
559 schedule and days for doctor or ER visits); quality of life measures at discharge, 30 days, and

560 one year; cost-effectiveness of non-operative management at one year (including initial
 561 admission, subsequent ED visits or physician visits, subsequent readmissions and
 562 reoperations and additional imaging related to appendicitis or complications of
 563 appendectomy); and rates of treatment related complications at 30 days, one year, two years,
 564 and three years. A summary of the outcomes that will be assessed are listed in the table
 565 below.

566
 567

Table: Outcomes to be assessed

Outcome	Time points
<u>In all patients</u> <u>Decisional Regret***</u> <u>Decisional Self Efficacy***</u> <u>Decisional Conflict Scale ***</u> <u>HealthCare Satisfaction ***</u> Disability Days Length of Stay Emergency Department Visits Readmissions Complicated Appendicitis Post-treatment Related Complications Satisfaction with Health Care Health Related Quality of Life Satisfaction with Decision Health Care Associated Costs Incremental Cost Effectiveness Additional surgical or interventional procedures	Index hospitalization Index hospitalization Index hospitalization Index hospitalization 30 days, 1 year Index hospitalization 30 days, 1 year, 2 year, 3 year 30 days, 1 year, 2 year, 3 year 30 days, 1 year, 2 year, 3 year 30 days, 1 year, 2 year, 3 year 30 days Index hospitalization, 30 days, 1 year 30 days, 1 year 30 days, 1 year 1 year 30 days, 1 year, 2 year, 3 year
<u>In Operative Subgroup only</u> Postoperative Infections Re-operation	30 days 30 days, 1 year, 2 year, 3 year
<u>In Non-operative Subgroup only</u> Success rate Need for appendectomy during initial admission Recurrence Antibiotic complications	30 days, 1 year, 2 year, 3 year Index hospitalization 30 days, annually 30 days

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 569

570 **5.2 Statistical Methods**

571

572 All patient baseline demographics and clinical characteristics will be described and summarized
 573 overall and between treatment groups. The balance/imbalance of these characteristics will be
 574 studied and reported, particularly for analyses comparing the two treatment groups. Balance in
 575 all pre-treatment characteristics between groups will be measured through the standardized
 576 difference of each covariate. All of these covariates (including demographics, race, ethnicity,
 577 socioeconomic variables, clinical and imaging characteristics, laboratory values and patient
 578 recruitment site) will be collected from the patient, caregiver and medical record at the time of
 579 enrollment; this will allow robust data capture with minimal missing data. All measured pre-

580 treatment covariates considered to potentially confound the relationship between treatment and
581 outcome or those considered to be highly associated with outcome will be included in the
582 development of the propensity score/probability of treatment model.

583 Missing Data: Missing data will be minimized in several ways. First, data on all
584 demographics and clinical characteristics will be collected at the time of enrollment which
585 should minimize missing data for covariates necessary for stratification and sensitivity analyses.
586 Data management will be monitored weekly by central study staff to ensure complete data entry
587 on all enrolled patients within the REDCap database. Missing elements will be identified and
588 relayed to each site weekly to allow for remediation and prevention of future instances of
589 missing data. Patient incentives will be used to minimize missing outcome data due to patient
590 dropout and short, simple language follow-up questions and surveys have been chosen to
591 minimize the chances that patients will fail to provide data due to the time burden of the surveys
592 or not understanding the questions.

593 If a participant drops out, we will document the reason for dropping out, whose decision
594 it was (patient, family member, physician), drop out date, and whether it was a complete or
595 partial drop out. We will attempt to collect information on success rate of non-operative
596 management using medical records unless consent is withdrawn. All participants'
597 information/data will be used in all the study analyses. Patients who are lost to follow-up or
598 withdraw from the study will be censored from longitudinal analyses after the date in which they
599 were lost to follow-up or withdrew.

600 Any outliers and/or missing data will be carefully revised and addressed by going back to
601 the original sources to double check for potential errors. The amount of missing data will be
602 reported and if patterns of missing data are detected, the statisticians will carefully evaluate
603 them. Sensitivity analyses will be performed to address the effect of missing data on the primary
604 and secondary endpoints. The amount of missing data could be indicative of problems with the
605 design or feasibility of the study. Therefore, if more than 15% of data are missing, the
606 generalizability of the study will be limited and study outcomes may be inconclusive. We will
607 report differences between groups with and without missing data as part of these analyses
608 including examining differences across sites, by treatment choice, by race, ethnicity, gender, SES
609 status, and distance from the treating institution. We will consider multiple imputation
610 exclusively for the purpose of sensitivity analyses.

611 Analysis Methods: Analysis of the primary endpoint of disability days of the child will
612 employ propensity score methods as a means to quantify differences in baseline characteristic
613 between groups and to balance them in final analysis. We will utilize inverse probability
614 weighting with the estimated propensity score and will consider further adjustment through
615 regression models for any covariate that does not appear to be adequately balanced following
616 estimation of the propensity score (incorporating the inverse probability weights). The
617 distribution of the propensity scores (and inverse probability weights) will be described and
618 graphically displayed. Stabilized inverse probability weights will be considered to mitigate the
619 influence of very small estimated probabilities from the propensity score model. Regression
620 models will be utilized to make inference, taking into account the estimated inverse probability
621 of treatment weight and potential covariates, and will estimate standard errors either as robust
622 standard errors or through bootstrap procedures. Inverse probability weighting was chosen
623 instead of propensity score matching because it enables us to estimate the average treatment
624 effect (ATE), rather than the average treatment effect in the treated (ATT), on all outcomes,
625 including success of non-operative management. Propensity score weighting has been shown to

626 balance measured covariates and reduce bias in estimated treatment effects to a similar degree as
627 propensity score matching in both empirical and simulation studies. Where possible, we will
628 estimate effects stratified by institution and will examine the sensitivity of results to varying
629 methods of analysis. Heterogeneity of effects due to three main factors of interest: age group
630 (≤ 10 vs. > 10 yrs), household income ($< \$50,000$, $\geq \$50,000$), transfer status, will be explored by
631 evaluating these factors as potential effect modifiers by including each in a model to include the
632 main treatment effect, the main factor effect and the interaction term for the treatment by factor.
633 Treatment effects will be estimated for each level of factor and compared across these groups.
634 Identification of effect modification will be made through tests of interaction in these models,
635 which control the family-wise error rate of each of these 6 comparisons at the 2% level
636 (translating to a maximum family wise error rate of 12%)

637 Analysis of the primary endpoint of success rate of non-operative management, defined
638 as the success rate of non-operative management at 1 year, will be estimated and reported along
639 with the 95% confidence interval. This rate will be examined overall and by treatment
640 institution. The standardized success rate (to the overall population) will also be estimated and
641 reported (along with the associated 95% CI). Success rate of non-operative management at 30
642 days and the rate of complicated appendicitis at 1 year (both secondary endpoints) will be
643 estimated along with their 95% CI. These analyses are all hypothesis driven with an expected 1-
644 year success rate of non-operative management of $> 75\%$ across all 10 institutions with a range
645 between 70-80% with no increase in the rate of complicated appendicitis. Both primary and
646 secondary endpoint points will be examined stratified by various socio-economic (SES) and
647 patient demographic characteristics, including race, ethnicity, household annual income and
648 number of household residents. These are exploratory analyses.

649 Secondary outcomes that involve the comparison of treatment groups will employ
650 propensity score methods, as a means to quantify differences in baseline characteristic between
651 groups and to balance them in final analysis. Analysis will mimic that of the primary endpoint
652 comparison above for disability days, including inverse probability weighting by the estimated
653 propensity score and will consider further adjustment in regression models for any covariate that
654 does not appear to be adequately balanced following estimation of the propensity score. Where
655 possible, we will estimate effects stratified by institution and will examine the sensitivity of
656 results to varying methods of analysis. These are hypothesis driven analyses (See “Primary and
657 Secondary Endpoints” section above for specific definitions of each outcome) with expected:
658 rates of complicated appendicitis to be similar; rates of treatment related complications to be
659 lower in the non-operative group; lower caregiver disability days at 30 days and 1 year in non-
660 operative group; higher HRQOL scores in non-operative group at 30 days, and similar HRQOL,
661 health care satisfaction, satisfaction with decision scores at 1 year; longer hospital length of stay
662 in the non-operative group; similar antibiotic associated complications; and similar rates of
663 imaging related to appendicitis. We will pay specific consideration to the potential of varying
664 effects of treatment by treatment site, SES and patient characteristics including age, household
665 income and transfer status; these are exploratory analyses which will be carried through
666 including interaction effects in the models and by fully stratifying analyses as described above.

667 We will explore the candidate instrumental variables of transfer status and distance from
668 treating hospital. It is hypothesized that each of these impacts the treatment choice but does not
669 directly influence the outcomes of interest. Sensitivity of results to model assumptions and bias
670 in analytic methods, including un-measured confounding, will be explored for each endpoint of
671 interest to assess the potential impact on inferences. An interim analysis will be performed to

672 asses for futility after 25% (n=91) of the total number of non-operative patients (n=363) to be
673 enrolled has reached their one-year follow-up. Based on the first 227 participants (25% of 908),
674 an initial set of inverse probability weights will be developed in order to assess initial futility of
675 treatment. We will review participant balance following development of the initial selection into
676 treatment model by IPW. Using IPW methods, we will assess the adjusted comparison of
677 disability days between treatment groups. Further we will assess the success rate of the non-
678 operative management group on these first 91 participants. At the interim analysis we will
679 evaluate futility (Rejection of H1) of both primary endpoints through Lan-Demets spending
680 function approach with O'Brien-Fleming boundary for each primary endpoint.

681 Throughout the trial, the success rate of non-operative management at 30 days and
682 disability days of the child and the rate of complicated appendicitis at 1 year will be monitored
683 for safety. These rates will be regularly reported to the Data and Safety Monitoring Committee
684 (DSMC) and will be formally examined during the interim analysis assessment. The overall 30
685 day success rate is expected to be no lower than 80%. Further, if the rate of complicated
686 appendicitis exceeds 30% in the patients who fail non-operative treatment and undergo
687 appendectomy, this will be considered unacceptable. In the event that these rates (both primary
688 and secondary) appear to be unacceptable, we will investigate if they vary by institution or
689 patient characteristics.

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Cost Effectiveness Analyses

693 The cost-effectiveness analysis is taken from a hospital perspective as well as from societal
694 perspective. We will consider both the direct medical costs and indirect medical costs associated
695 with informal care provided by parents. The direct medical costs are defined by the one year total
696 health care expenditures per patient in our study, including that of initial admission, subsequent
697 ED visits or physician visits, subsequent readmissions and reoperations, and additional
698 pharmaceutical, imaging or laboratory procedures related to appendicitis or complications of
699 appendectomy. The institutional claims data is augmented by that of the parental survey to obtain
700 the cost information of patients who go to a separate hospital for subsequent care after the initial
701 discharge. The follow-up surveys will also document the number of days the parents were absent
702 from work due to the chosen appendicitis-related care for their child. The indirect medical costs
703 associated with informal care are represented by the wage lost due to the absent days from work
704 (even though parents may not have a real reduction in salaries). For parents that do not work, we
705 will estimate the indirect costs based on the average income for their zip code and age groups.
706 We will conduct both cost-saving analysis and cost-effectiveness analysis. The end point is
707 whether a patient developed a complication related to their chosen treatment at 1 year follow-up;
708 multiple complications may occur during the year. To analyze the cost-saving from non-
709 operative management, the total costs (direct plus indirect) will be compared between the Non-
710 operative and Surgery groups. For the cost effectiveness analysis, we will estimate the
711 incremental cost-effectiveness ratios (ICERs), in terms of the marginal cost of an additional
712 patient managed non-operatively who does not develop complications at 1 year. In addition, we
713 will compute the marginal costs of an incremental unit of quality-of-life outcomes over 12
714 months derived from PEDSQL Quality of Life Inventory: Child and Parent Report. The health
715 states used in this study are complication free or with complications at discharge, 30 days, 6
716 months or 12 months. The types of complications differ based on the chosen treatment with some
717 specific to each treatment and some common to both. Common complications to both groups

718 include return to the ED or hospital readmission. Complications unique to non-operative
719 management include a failure of non-operative management requiring appendectomy either in
720 the hospital or after discharge and antibiotic associated side effects. Complications unique to
721 appendectomy include complications associated with general anesthesia, bleeding or other intra-
722 operative complications including inadvertent organ damage, wound complications, post-
723 operative intra-abdominal infections, and repeat admission or operation for post-operative bowel
724 obstruction due to scar tissue. Patients who fail non-operative management and undergo
725 appendectomy are subsequently at risk for the complications related to appendectomy listed
726 above. All analyses will be performed using decision tree analysis, with Data Pro HealthCare
727 software (TreeAge Software, Inc., Williamstown, Massachusetts). In addition to the static
728 probabilities and utilities (costs) derived from our clinical trial, we will also perform Monte
729 Carlo sensitivity analysis using simulations at 10,000 trials each.

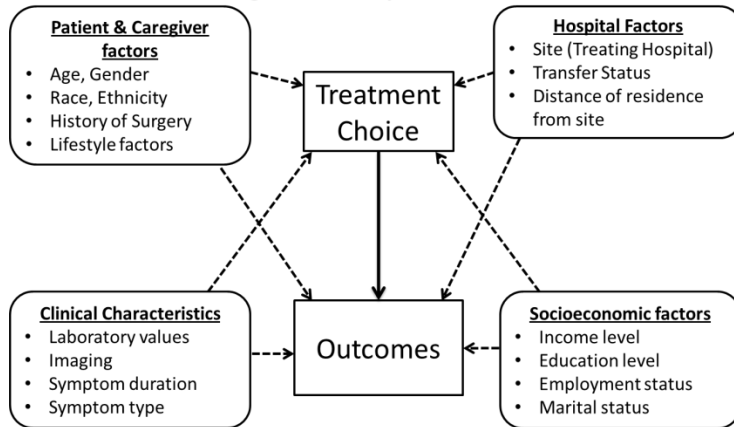
730 **5.3 Sample Size and Power**

731 The sample size needed to assess the primary outcome of the 1-year success rate of non-
732 operative management is based on preliminary data that the expected point estimate is between
733 76-78%. Based on previous studies and input from our stakeholders and participating surgeons,
734 the lowest acceptable success rate of non-operative management required for it to be considered
735 as part of routine clinical practice would be 70% (p_0) at 1 year follow-up. It is expected that the
736 study success rate (p_1) will be higher, ranging from 76-78%. Under a group sequential design,
737 with one interim and one final analysis, overall type I error (two-sided) of 5 % (adjusted for the 2
738 primary endpoints), the maximum sample sizes required are listed below.

739 Given these estimates, the expected rates of patient choice of non-operative management
740 (40%) or surgery (60%), and an approximately 10% expected rate of loss to follow up, we will
741 enroll 908 patients. This sample size will provide more than adequate power to assess the other
742 primary endpoint of disability days between groups. Based on previous data, we expect children
743 who undergo non-operative management to have at least five fewer disability days in the year
744 following treatment (assuming 10 days ($sd=9.8$) on average) than children who have initial
745 surgery (assuming 15 ($sd=7.7$) on average). With the proposed sample sizes in each group, we
746 will have >90% power to detect these differences, assuming an adjusted overall type I error of
747 5% (adjusted to account for the two primary endpoints).

748 Stratification by institution will be pursued to examine both primary and secondary
749 endpoints and will be detailed descriptively. Heterogeneity of treatment effects will be formally
750 explored for three patient demographic characteristics (age, household income, and transfer
751 status). Comparison between groups will employ propensity score methods to quantify and
752 adjust for differences in baseline characteristics and to balance them in final analyses, focusing
753 on inverse probability weighting (marginal structural models).[28-30] We will consider further
754 adjustment through regression models for any covariate that does not appear to be adequately
755 balanced following propensity score model development and to assess potential effect
756 modification (See Figure: Conceptual Model).

Figure: Conceptual Model



757

758 **Table: Estimated required sample sizes of the**
759 **non-operative group**

Success rate	Power	Sample Size Non-operative group *
0.78	80%	250
0.77	80%	330

760 *Accounts for 1 interim analysis to determine
761 fertility with overall two-sided type I error rate of 5%.

762

763 6 STUDY ADMINISTRATION

764 6.1 Data Collection and Management

765 All clinical monitoring performed as standard procedure in the hospital, such as vital signs, pain
766 scoring, dietary advancement, and other pertinent variables for the purposes of the study, will be
767 recorded by local study staff in the study’s central REDCap database maintained at NCH. NCH
768 study staff will collect, compile and manage follow-up data. This data will be compiled on
769 REDCap, a network software suite that provides encryption and password protection for health
770 information, to which only study staff will have access.

771 Privacy and security will be maintained by minimizing the amount of identifiable data as much
772 as possible. All information will be stored and managed on REDCap, and identifiable patient
773 information not necessary for data analysis will not be exported from REDCap. Local data will
774 be maintained on computers located at each institution’s facilities that are maintained on a secure
775 network. All necessary identifiers will be used only to identify the relevant source documents.
776 Identified data will be shared with investigators at NCH (Principal Investigator: Dr. Peter
777 Minneci, Site PI: Katherine Deans), and study staff at NCH that contact the patients at all sites
778 by phone for follow-up phone interviews as detailed in our study design. Following completion
779 of follow-up, the information will be de-identified once all of the data has been collected.

780 **6.2 Confidentiality**

781 All data and records generated during this study will remain confidential. All documents will be
782 used solely for the use of this study by approved personnel. Consent forms and written surveys
783 will be maintained at each institution in locked cabinets and all other data will be maintained in a
784 central REDcap database that would be housed at NCH for the duration of the study. De-
785 identified data exported from REDCap for statistical analysis will be maintained in password-
786 protected files and on password-protected computers at NCH.

787 **6.3 Regulatory and Ethical Considerations**

788 **6.3.1 Risk Assessment**

789 The Division of Surgery at each participating institution has reviewed the results of the trials of
790 non-operative management of appendicitis, including the recent pediatric study from NCH, and
791 has determined that the evidence supports offering non-operative management as an alternative
792 therapy to appendectomy as part of the routine care of patients with suspected uncomplicated
793 appendicitis without a fecalith on imaging. Therefore, the following discussion of risks and
794 benefits are divided into two sections: the risks associated with participating in the study to allow
795 for data collection for research purposes, and the risks associated with each treatment option they
796 will be offered as part of routine care for uncomplicated appendicitis and not directly related to
797 study participation.

798 **6.3.1.1 Risks associated with study participation**

799 The quality of life surveys may make the subjects feel uncomfortable due to questions that ask
800 about their emotional and social functioning. In addition, loss of confidentiality could be a risk.

801 **6.3.1.2 Risks Associated with each treatment option (independent of study participation)**

802 **Non-Operative Group**

803 Potential risks may include:

- 804 - No relief of symptoms (ex: persistent/prolonged pain) thereby requiring appendectomy,
805 which will involve the inherent risks of surgery
- 806 - Possibility of experiencing interval progression of appendicitis, requiring appendectomy
807 and may endure a prolonged hospital stay
- 808 - Recurrence of appendicitis at a later time
- 809 - Antibiotic associated side effects (see below)

810 Those who choose non-operative management will receive oral antibiotics (Augmentin⁵, or if
811 they have a penicillin allergy, Cipro and Flagyl⁶) on discharge. These antibiotics are no different
812 than what is commonly used for pediatric intra-abdominal infections such as perforated
813 appendicitis, Crohn's disease, and intra-abdominal abscesses. Some common side effects of

⁵ PO Augmentin is the antibiotic we have selected as a department for this trial. It is the antibiotic we use for patients with ruptured appendicitis. You may change this based on your institutional and departmental policies.

⁶ PO Cipro and Flagyl is the antibiotic we have selected as a department for this trial. It is the antibiotic we use for patients with ruptured appendicitis and a penicillin allergy. You may change this based on your institutional and departmental policies.

814 antibiotics⁷ include: nausea, vomiting and diarrhea. Other rare side effects can include dizziness,
815 skin rashes, drowsiness, metallic taste, difficulty breathing, and joint pain. While on antibiotics,
816 the efficacy of oral contraceptives may be impaired.

817 **Surgery Group**

818 Potential risks may include:

- 819 - Side effects and rare complications associated with general anesthesia
- 820 - Wound complications including infections
- 821 - Bleeding or other intra-operative complication including inadvertent organ damage
- 822 - Post-operative intra-abdominal infections
- 823 - Repeat admission or operation for post-operative bowel obstruction due to scar tissue

824

825 **6.3.2 Potential Benefits of Trial Participation**

826 **6.3.2.1 Benefits associated with study participation**

827 Beyond the \$25 and \$50 Visa gift card incentives, there is no personal benefit to participating in
828 the study, but information obtained may help others.

829 **6.3.2.2 Benefits associated with each treatment option (independent of study participation)**

830 **Non-Operative Group**

831 Potential benefits may include:

- 832 - Faster relief of symptoms (ex: resolution of pain),
- 833 - Shorter recovery period
- 834 - Avoiding risks of surgical complications

835 **Surgery Group**

836 Potential benefits may include:

- 837 - Appendicitis will never comeback
- 838 - No antibiotics after surgery

839 **6.3.3 Risk-Benefit Assessment/Risk Minimization**

840 **6.3.3.1 Related to study participation**

841 Regarding the quality of life surveys, participants have the option of skipping questions they find
842 to be uncomfortable or simply wish to refuse answering. This will be stated on the informed
843 consent.

844 Risk of loss of confidentiality will be minimized by using study ID numbers, limiting the number
845 of team members with access to data with PHI and using a password protected database
846 (REDCap) and password protected files.

⁷ If you select different antibiotics, do note that they may have different side effects which should be noted here.

847 **6.3.3.2 Related to Clinical care and specific treatment choice**

848 **Non-Operative Group**

849 As part of routine care, patients will be closely monitored throughout their hospital stay by
850 physicians and clinical staff to assess any adverse events and clinical symptoms. Patients who do
851 not exhibit clinical improvement or report symptomatic relief as defined in our study procedure
852 after receiving 24 hours of intravenous antibiotics will be recommended for appendectomy. Also,
853 if a patient's symptoms worsen or there is evolving objective evidence of systemic signs of
854 infection as defined in our study procedure, then he/she will be recommended for appendectomy.

855 Before discharge, patients and their caregivers will be given clear instructions on taking oral
856 antibiotics and for reporting any concerns while on antibiotics. A research phone number for
857 study staff at NCH will be provided in the informed consent should they have any questions or
858 concerns relating to the study, and local contact information for medical questions will be
859 provided consistent with the standard of care in surgical discharges. A magnetic reminder card
860 with times for follow-up phones calls will be provided to each patient at discharge.

861 Regarding the quality of life surveys, participants have the option of skipping questions they find
862 to be uncomfortable or simply wish to refuse answering. This will be stated on the informed
863 consent.

864 **6.3.3.3 Surgery Group**

865 Patients will receive and be monitored according to the standard of care. Any adverse events will
866 be handled according to hospital procedure. A magnetic reminder card with times for follow-up
867 phones calls will be provided to each patient at discharge.

868 Regarding the quality of life surveys, participants have the option of skipping questions they find
869 to be uncomfortable or simply wish to refuse answering. This will be stated on the informed
870 consent.

871 **6.3.4 Data Safety and Monitoring**

872 The principal investigators, attending surgeons or fellows and clinical staff on the floor will be
873 monitoring the data of participants including clinical symptoms and disposition at time of
874 initiation onto the study and throughout their hospital stay. Vital signs, physical exam and pain
875 scores will be assessed per each institution's nursing protocol and surgical service standards. An
876 attending level surgeon will round on all patients every day to ensure that the child's clinical
877 status is assessed. A research team call schedule will be maintained that assigns a member of the
878 local research team to be available to check in with the clinical team daily. This person is also
879 available by pager 24 hours per day. This information will be provided to the clinicians caring
880 for the patients and will be posted in pre-specified areas within the surgical wards. Any
881 suggestion of an adverse event identified by this person will be discussed with the principal
882 investigator immediately.

883 Data will be monitored by research team members once a week. Research team members will
884 ensure that all data (clinical data and questionnaires) collected are correctly completed. In
885 addition, a Data Safety and Monitoring Committee (DSMC) has been formed and will meet
886 every six months throughout the period during which patients are being recruited and

887 experiencing their first year of follow-up. The DSMC will review data provided by the primary
888 study statisticians (Drs. Erinn Hade and Soledad Fernandez) and other study staff involved in
889 data management and analysis. Dr. Martin Blakely (pediatric surgeon, Vanderbilt) will act as the
890 chairman of the DSMB alongside Dr. William Garner, PhD (Statistician/Researcher, Children's
891 Hospital of Eastern Ontario) and Dr. Adam Goldin (pediatric surgeon, Seattle Children's
892 Hospital). In addition, the principal investigator and research team at NCH (overall study PI and
893 data coordinating center) will be made aware of all adverse events as they occur and a quarterly
894 conference call with all site PIs and the NCH PI and team will be held to review and discuss all
895 AEs that occur in the trial. As mentioned above, all unexpected non-serious adverse events and
896 serious adverse events relating to participation in the study will be reported verbally and in
897 writing to the local IRB and the study PI and NCH IRB. The verbal report will occur within 48
898 hours of the occurrence. The written report of the serious adverse event (e.g., death or life-
899 threatening adverse event) will be reported within seven days.

900 **6.3.5 Adverse events (AE) and Serious adverse events (SAEs)**

901 In the event that a child treated non-operatively should exhibit progression of their disease
902 process to perforated appendicitis, which will be determined at the time of surgery, this will be
903 considered an anticipated AE with an expected rate of 5% in the entire group of patients
904 managed non-operatively and less than 30% in the subgroup of patients managed non-
905 operatively who undergo appendectomy. In addition, patients treated non-operatively may
906 experience an anticipated AE following discharge such as an unfavorable, non-life threatening
907 reaction to the antibiotics. These include nausea, vomiting, diarrhea, dizziness, drowsiness,
908 metallic taste, difficulty breathing, joint pain and also possible cutaneous reactions such as
909 urticaria (skin rashes).

910 Patients who fail non-operative management are not expected to have an increased rate or
911 severity of AEs following surgery. In essence, the patient who fails non-operative management
912 initially will receive the same treatment as those patients in the Surgery Group.

913 For those patients in the Surgery Group, their potential anticipated adverse events will not differ
914 from those of a patient who undergoes routine treatment for acute appendicitis. Specifically, the
915 patient might experience an allergic reaction to the perioperative antibiotics given, discomfort
916 and pain prior to and after the procedure, and standard complications associated with
917 appendectomy. These complications include: bleeding; infection manifesting as either a
918 superficial (cutaneous) or deep (intra-abdominal or pelvic) process; injury to adjacent structures
919 including the small bowel, cecum, and right ureter; anesthesia-related complications; post-
920 operative urinary tract infections and pneumonia; adhesive small bowel obstruction; and
921 appendiceal stump leaks.

922 It is also possible that AEs might occur that are not directly related to the study. As such, all
923 AEs will be classified as not related (clearly unrelated to study participation), possibly related
924 (temporally related to study participation but could have been caused by other factors), or
925 probably related (temporally related to study participation and cannot be reasonably explained by
926 other factors) to study participation. The clinical study team will review all AEs as they occur
927 and determine the seriousness and relatedness of them.

928 We do not expect any severe AE in either study group. The clinical study team will review SAE
929 as they occur. All SAE deemed probably related to the study (and all deaths) will be reported to
930 the local IRB and to the NCH IRB within 72 hours⁸ of discovery and will be reviewed by the
931 DSMC.

932 **6.4 Recruitment Strategy**

933 No active recruitment will take place. Subjects will be screened for eligibility once a diagnosis of
934 suspected uncomplicated appendicitis has been determined and the surgical consult team has
935 been contacted.

936 **6.5 Informed Consent and Assent**

937 All informed consents and assents will be performed by a physician-member of the research
938 team.

939 If the child and legal guardian (for subjects < 18 years) are interested in participating in the
940 study, a physician-member of the research team will guide the child and legal guardian through
941 the informed consent/assent process. A one page decision aid will be made available if they seek
942 extra information (see appendix). Written informed consent will be obtained from one legal
943 guardian of subjects < 18 years of age. Written informed assent will be obtained from subjects ≥
944 9 and < 18 years of age⁹.

945 An informed consent and pros and cons script will be available to all consenting physician-
946 members of the research team should they need it (see appendix).

947 Refusal to participate in the study will not affect the child's clinical care. Participants and their
948 legal guardian have the right to switch to the standard treatment and/or withdraw from the study
949 at any time. Withdrawal from the study will not affect receipt of clinical care.

950 **6.6 Payment to Subjects and Families**

951 The parent/legal guardian of all participants will be paid a \$25 VISA® gift card after completion
952 of their 30 day and 6 month follow-up. A \$50 VISA® gift card will be paid after completion of
953 their 1 year follow-up. This will be mailed to the legal guardian's address.

954 **6.7 Confidentiality**

955 Privacy and security will be maintained by minimizing the amount of identifiable data as much
956 as possible. Only study identifications (IDs) will be used to identify patients on all data forms
957 and all datasets used for analysis. The REDCap form linking study IDs to patient names and
958 medical record numbers (MRNs) will be made available only to local study staff and will never
959 be exported from REDCap or used during data analysis. All information will be compiled in
960 REDCap, to which only study staff will have access.

⁸ This is based on practice at NCH. Your institutional practice and IRB requirements may be different.

⁹ This is based on our institutional requirements. Your institutional requirements may differ, but the trial should maintain this range for obtaining assent at a minimum. Note that at NCH, we are not required to secure assent for patients who are 8 years old; therefore, although patients may participate in this study if they are 8 years old, they do not have to sign assent forms.

961 **APPENDIX: Example of Standard Nursing Protocol for Pain Assessment**

962 **Vital Signs & Pain Score**

- 963 - Ordered Q4 hours as a standard on admission.
- 964 - Recorded by the RN or by the LPN/PCA if one is assigned – patients on any surgical
- 965 service should have a pain score recorded Q4 hrs. and PRN.
- 966 - The score is documented by the RN or LPN.
- 967 - If an intervention is provided, its effectiveness should be reassessed within one hour with
- 968 another pain score.

969 **Vital Sign Protocol:**

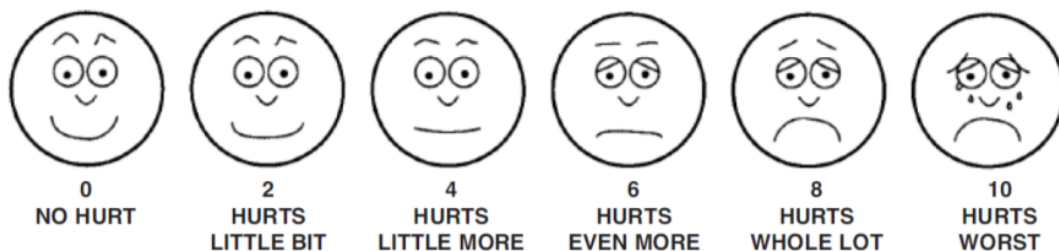
- 970 - You may skip ordered Q4hr vital signs at 4am when the following criteria are met:
 - 971 - Patient has been admitted for longer than 24 hours and is more than 24 hours past any
 - 972 surgical procedure
 - 973 - Patient has had stable vital signs for 24 hours (including being afebrile)
 - 974 - Patient must have had a complete set of midnight vitals including BP
- 975 - If the patient is on a pulse ox and/or cardiac monitor this data still needs to be
- 976 documented at 4am.

977 Pain Scales used include FACES and VAS, demonstrated below:

SUBJECTIVE PAIN SCALES

FACES (3 years of Age and Older)

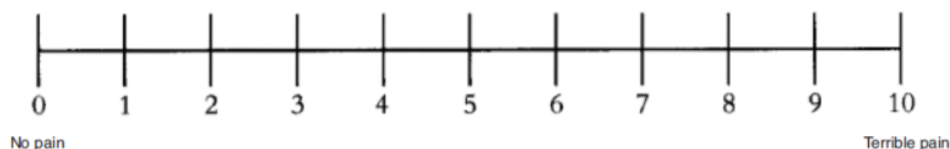
Show me how you feel by POINTING to the face.



From Wong D.L., Hockenberry-Eaton M., Wilson D., Winkelstein M.L., Schwartz P.: *Wong's Essentials of Pediatric Nursing*, ed. 6, St. Louis, 2001, p. 1301. Copyrighted by Mosby, Inc. Reprinted by permission.

Visual Analog Scale (VAS) (8 years of Age and Older)

On this chart the "0" means no pain, each number means a little more pain, and "10" means the most pain possible.



978

979 **APPENDIX: Physician Informed Consent/Assent Script**

980 Hi Mr./Mrs./Ms. _____, my name is Dr. _____. There is a research study
981 in our department which involves treating appendicitis without surgery. Are you interested in
982 learning more about it?

983 **If “yes”:**

984 This study is being performed to determine if using antibiotics alone to treat appendicitis is as
985 effective as performing surgery. The care and procedures performed here in the hospital would
986 be the same as if you would be having surgery, without the surgical part. In addition, we would
987 like you and (child’s name) to fill out a quick survey before you leave the hospital, and over the
988 phone at around 30 days after discharge. A member of the research team would also call you
989 throughout the year and once a year after that to see how (child’s name) is doing.

990 Are you interested in going through the informed consent?

991 You don’t have to be in the study if you don’t want to.

- 992 - Discuss informed consent and assent with legal guardian and patient.
- 993 - Show decision aid to legal guardian and patient.
- 994 - Leave room so that legal guardian and patient can privately discuss study and their
995 decision.
- 996 - Come back and answer questions they may have.
- 997 - Remember to give the legal guardian a signed and dated copy of the Informed Consent
998 and Assent

999 **If “no” at any point:**

1000 Is it ok if you give us permission to track (child’s name) treatment course and call you so that we
1001 may compare the surgical course to the non-operative course?

1002 **If “yes”:**

1003 Like the non-operative group, we would like you and (child’s name) to fill out a quick survey
1004 before you leave the hospital and by phone around 30 days after discharge. We will need to go
1005 through a different informed consent so that we can follow (child’s name) treatment.

1006 **If “no”:**

1007 Ok. Thank you for your time.

1008 **APPENDIX: Physician Pros and Cons Script**

1009 Hi Mr./Mrs./Ms. __, my name is Dr. __. There is a research study in our department which
1010 involves treating appendicitis without the need for surgery. Are you interested in learning more
1011 about it?

1012 *Discuss informed consent and assent with legal guardian and patient.*
1013 *Show decision aid/informational sheet to legal guardian and patient, then also say:*

1014

1015 The pros of non-operative management with antibiotics only include:

- 1016 - Previous research studies show that it works in most adults and children with
- 1017 uncomplicated appendicitis
- 1018 - Your pain may go away faster and you may recover sooner
- 1019 - You may not need surgery – about 8 of 10 patients will not need an appendectomy

1020

1021 The possible cons of non-operative management with antibiotics only include:

- 1022 - Your symptoms will not get better and you will need an appendectomy while in the
- 1023 hospital - this happens in 1 out of 10 patients
- 1024 - Your appendicitis may come back in the future – this happens in another 1 out of ten
- 1025 patients
- 1026 - Side effects of antibiotics
 - 1027 ○ Most common: nausea (feeling sick), vomiting and diarrhea
 - 1028 ○ Oral contraceptives may not work as well

1029

1030 The pros of surgery may include:

- 1031 - Your child will never have appendicitis again.
- 1032 - This is the most common way to treat appendicitis
- 1033 - You can usually go home within 1 day after surgery

1034

1035 The possible cons of surgery may include:

- 1036 - Your child will have some pain after surgery
- 1037 - Most kids need several days of rest before going back to school and up to 2 weeks before
- 1038 returning to sports activities
- 1039 - It will leave small scars on your belly
- 1040 - There are risks associated with surgery - about 1 out of 10 kids will have some
- 1041 complication of surgery
- 1042 - The most common are minor and include infections or problems with the wounds.
- 1043 - Less common but more serious complications include
 - 1044 ○ Infections inside the belly
 - 1045 ○ Bleeding during surgery...
 - 1046 ○ Injury to other organs near the appendix...
 - 1047 ○ Scar tissue in the belly causing future blockage.

1048

1049 *Remember to give the legal guardian a signed and dated copy of the Informed Consent and*
1050 *Assent*

1051 **APPENDIX: Standardized Treatment Protocol for Uncomplicated Acute Appendicitis at**
1052 **Nationwide Children’s Hospital**

1053 **Standardized Treatment Protocol for Uncomplicated Acute Appendicitis at Nationwide Children’s**
1054 **Hospital**

1055 Patients who meet the following criteria will be offered two treatment options: Appendectomy or
1056 antibiotics alone (Non-operative Management)

- 1057 - Abdominal pain \leq 48 hours
- 1058 - Absence of peritonitis
- 1059 - WBC <18k, >5k
- 1060 - Ultrasound, CT, or MRI positive for appendicitis and
 - 1061 o Diameter \leq 1.1cm
 - 1062 o No appendicolith
 - 1063 o No evidence of perforation, abscess, or phlegmon

1064 Treatment Protocols:

1065 Appendectomy:

- 1066 1. Admission, NPO, IV fluids
- 1067 2. IV Zosyn (or Clinda/Gent)
- 1068 3. To OR for urgent laparoscopic appendectomy
- 1069 4. Post-operative management as per current protocols depending on intra-operative findings
1070 (simple vs. complicated)

1071 Antibiotics Alone (Non-operative management):

- 1072 1. Admission, IV fluids, NPO for minimum 12 hours and until improving
- 1073 2. Serial observation and physical exams
 - 1074 a) No improvement within first 24 hours or acute worsening triggers crossover to Surgery
 - 1075 a) After 12 hour minimum NPO status, may advance diet (starting with clears) once improving
- 1076 3. Antibiotic management:
 - 1077 a) IV Zosyn (or Cipro/Flagyl) for minimum 24 hours
 - 1078 b) Transition to PO Augmentin (or Cipro/Flagyl) once tolerating regular diet
 - 1079 c) Discharge home to complete total course of 7 days of antibiotics with recommendation for
1080 yogurt intake
- 1081 4. Please use standardized discharge instructions in Epic (.dinonopappendicitis)
- 1082 5. Nurse phone follow up at 5-7 days and one month post-discharge:
1083 PLEASE EMAIL the following to Kim Welch at kimberly.welch@nationwidechildrens.org:
1084 Patient name
1085 MRN
1086 Date of discharge to

1087

1088 **APPENDIX: Decision Aid: Pros and Cons of Choosing Surgery or Antibiotics-Only to**
1089 **Treat Appendicitis**

1090

Pros and Cons of Choosing Surgery or Antibiotics-Only to Treat Appendicitis

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1092
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What is appendicitis?

When your appendix swells up, it's called appendicitis. Your appendix is a small pouch connected to your large intestine and has no known function. Anyone can get appendicitis. There isn't always a reason why appendicitis happens. Sometimes it happens after there is an infection in the intestine or something causes it to be blocked, then it gets swollen.

Appendectomy (Surgery for Appendicitis)

Pros:

- This is the usual way to treat appendicitis
- You will never have appendicitis again
- You can go home 1 to 2 days after surgery
- About 9 out of 10 children will not have a complication

Cons:

- You will be in some pain after surgery
- Most kids need a few days rest before going back to school and 1-2 weeks before returning to full activities
- It will leave 1-3 small scars on your belly
- There are some risks during surgery, such as bleeding or problems from the anesthesia
- Other possible risks include:
 - infection on the skin where you are cut, or inside your belly
 - staying longer at the hospital and needing more medicines like antibiotics
 - Needing additional surgery due to scars (adhesions) that can cause future blockage in your belly
- Side effects of antibiotics
 - Most common: nausea (feeling sick), vomiting and diarrhea

Antibiotics Only

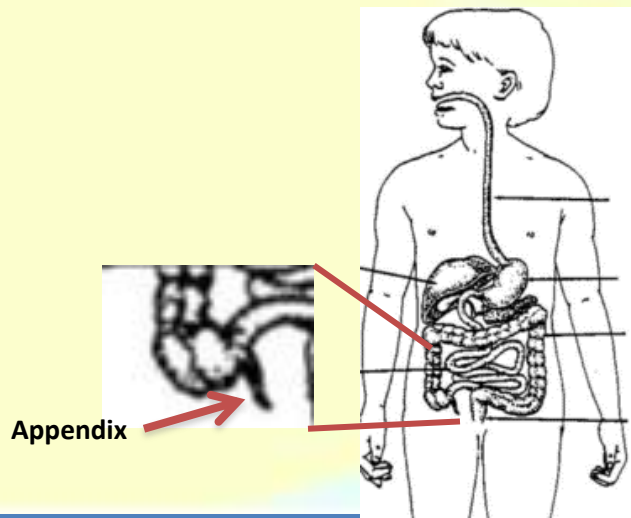
Pros:

- Research studies show that it works in most adults and children
- Your pain may go away faster
- About 8 out of 10 children will not need surgery
 - No risks of surgery
- You may recover sooner

Cons:

- Your symptoms might not go away (ex: you are still in pain) and you will need an appendectomy which involve the risks of surgery
- Your appendicitis could come back in the future
- Side effects of antibiotics
 - Most common: nausea (feeling sick), vomiting and diarrhea
 - Oral contraceptives may not work as well

1100
1101



- 1102 **APPENDIX: Survey at 2-5 days and 10-14 days for Non-Operative Group**
- 1103 **APPENDIX: Survey at 30 days, 6 months, 1 year, and annually for Non-Operative Group**
- 1104 **APPENDIX: Survey at 30 days, 6 months, and 1 year for Surgery Group**
- 1105 **APPENDIX: Data collection form for patients undergoing surgery or IR procedures**
- 1106 Attached as separate documents

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