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Complex And Simple Appendicitis: REstrictive or Liberal postoperative Antibiotic eXposure (CASA RELAX) using Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR): study protocol for a randomized controlled trial

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ABSTRACT

Objectives After appendectomy for simple or complicated appendicitis, the optimal duration of postoperative antibiotics (postop abx) is unclear and great practice variability exists. We propose to compare restrictive versus liberal postop abx using a hierarchical composite endpoint which includes patient-centered outcomes and accounts for duration of antibiotic exposure.

Methods/Design Participants with simple or complicated appendicitis undergoing appendectomy are randomly assigned to either restricted or liberal strategy. Eligible subjects declining randomization will be recruited to enroll in an observation only cohort. The primary endpoint is an ordinal scale of mutually exclusive clinical outcomes with within-category rankings determined by duration of antibiotic exposure. Subjects in both randomized and observation only cohorts will be analyzed as intention-to-treat, per-protocol, and as-treated. Exploratory Bayesian analyses will be performed.

Conclusion The complex and simple appendicitis: restrictive or liberal postoperative antibiotic exposure multicenter randomized controlled trial will enroll surgical appendectomy patients and seeks to analyze if a strategy of restricted (compared with liberal) postoperative antibiotics results in similar clinical outcomes with the benefit of reduced antibiotic exposure.

Trial registration number NCT05002829.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antibiotics are often given preoperatively and perioperatively for appendectomy for simple and complicated appendicitis, but the optimal duration of postoperative antibiotics is currently unknown and wide treatment variability exists.

WHAT THIS STUDY ADDS

⇒ Herein, we describe a study protocol for a randomized trial to compare restricted versus liberal postoperative antibiotic treatment for simple and complicated appendicitis using a novel study design that incorporates duration of antibiotic exposure in a hierarchical scale primary endpoint.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ When completed, the complex and simple appendicitis: restrictive or liberal postoperative antibiotic exposure trial will help inform clinicians about postoperative antibiotic treatment duration and will also help inform trialists about the feasibility and utility of the desirability of outcome ranking and response adjusted for duration of antibiotic risk study design.

BACKGROUND

The treatment of acute appendicitis in the USA is primarily surgical, with the vast majority undergoing a laparoscopic approach to appendectomy. Although the postoperative treatment of simple acute (non-perforated, non-gangrenous) appendicitis is relatively straightforward, the same cannot be said for complicated (eg, perforated or gangrenous) appendicitis. In the presence of an established complicated intra-abdominal infection (cIAI), a more prolonged duration of postoperative antibiotic treatment may be warranted as a therapeutic measure, though the overall clinical benefit of prolonged antibiotic treatment after achieving definitive source control remains uncertain.

In 2015, Sawyer *et al* published the STOP-IT trial comparing outcomes of two treatment strategies after source control of cIAI: a short-course (4 days) versus a standard-course (8 days).[1] There were no significant differences detected in the primary composite endpoint of surgical-site infection, recurrent intra-abdominal infection, or death within 30 days, leading the investigators to conclude that 4 days was noninferior to a longer course of postoperative antibiotic treatment. However, enrollment of appendiceal disease was limited to no more than 10% of the study population in the STOP-IT trial. The MUSTANG (Multicenter Study of the Treatment of Appendicitis in North America: Acute,

Perforated, and Gangrenous) study was an observational study of 28 centers in the USA, enrolling 3597 subjects from January 2017 through June 2018.[2] Posthoc analyses revealed wide practice variation in the postoperative prescription of antibiotics for both simple and complicated appendicitis.[3 4] Subsequently, a hypothesis-generating posthoc analysis was performed using a novel study design (Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR), see below) which demonstrated that restricted postoperative antibiotic use after both simple and complicated appendicitis was a dominant strategy when considering treatment effectiveness and antibiotic exposure.[5] The Complex And Simple Appendicitis: REstrictive or Liberal postoperative Antibiotic eXposure (CASA RELAX) trial will therefore test this hypothesis in a prospective fashion.

STUDY OBJECTIVES

The primary objective of the CASA RELAX trial is to compare two different strategies of postoperative adjunctive antibiotics after appendectomy. We hypothesize that a restrictive strategy of postoperative antibiotics after simple and complicated appendicitis results in a higher DOOR-RADAR compared with a liberal strategy of postoperative antibiotics.

METHODS

General

The CASA RELAX is a multicenter, prospective, open-label, randomized controlled trial (RCT) and institutional review board (IRB) approval was obtained at the primary coordinating site, Denver Health (IRB #21–4816). Each additional enrolling site must obtain approval from their local IRB. Informed consent will be obtained either prior to appendectomy or in the early postoperative period.

Eligibility criteria

Eligible patients are age ≥18 years undergoing appendectomy for simple or complicated (perforated or gangrenous) appendicitis who have a working telephone number of other reliable method for patient contact after hospital discharge. The diagnosis of appendicitis is determined by the surgeon according to local standards. Exclusion criteria include pregnancy, prisoner, immunocompromised (as determined by clinical team or patients actively receiving steroids, chemotherapy, or immunosuppressing medications (eg, tacrolimus), or patients with active hematologic malignancy affecting the immune system, leukopenia, or end-stage AIDS), heart failure, allergy to bupivacaine, patient unlikely to comply with treatment or follow-up, inpatient consultation for appendicitis, clinically suspected of sepsis based on Sepsis-3 definition, current use of antibiotics for other indications, type 1 diabetes mellitus or uncontrolled hyperglycemia, surgeon preference, patient preference, and research team unavailable.

Site recruitment

Eligible patients will be approached for consent either preoperatively or in the early postoperative period. Patients who decline to enroll in the randomized trial will be requested to enroll in an *observation only* arm and analyzed in an as-treated (AT) fashion (see below).

Randomization

A 1:1 allocation ratio using permuted block sizes of four to six and stratified according to center and age (< or ≥65 years) was constructed by an independent statistician. Allocation concealment will be ensured using sealed, opaque, sequentially numbered envelopes. Blinding will not be performed due to practical limitations.

Interventions

Subjects with simple appendicitis (as determined by the surgeon at the time of operation) randomized to the restrictive strategy will not receive any postoperative antibiotics and those randomized to the liberal strategy will receive up to 24 hours of postoperative antibiotics. Antibiotic agent and route (oral or intravenous) will be according to local standards. Subjects with complicated appendicitis (as determined by the surgeon at the time of operation) randomized to the restrictive strategy will receive 24 hours of postoperative antibiotics and those randomized to the liberal strategy will receive 4 days of postoperative antibiotics. As with simple appendicitis, for patients with complicated appendicitis, antibiotic agent and route (oral or intravenous) will be according to local standards.

Demographics, imaging, operative details, and protocol compliance

Data fields to be collected include: age, gender, weight, height, body mass index, race (American Indian or Alaska Native; Arab, Middle Eastern, or North African; Asian; Black or African-American; Hispanic, Latino, or of Spanish Origin; Native Hawaiian or Other Pacific Islander; White or Caucasian; Not Listed; or Prefer not to answer), comorbid medical conditions, tobacco use, Charlson Comorbidity Index (CCI),[6] duration of symptoms (from onset to emergency department (ED) triage), symptoms, Alvarado score,[7] temperature, heart rate, systolic blood pressure, physical examination findings, white blood cell count, American Association for the Surgery of Trauma (AAST) appendicitis severity grade,[8] imaging modality, imaging findings, operative approach, operative findings, operative duration, antibiotics given in ED, antibiotics given in the operating room (OR), intraoperative adverse events,[9] and postoperative antibiotic use.

Complications

Selected complications during index hospitalization and up to 30-days after appendectomy will be assessed and graded according to the National Institutes of Health/National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) V.5.0: surgical site infection, intra-abdominal abscess, wound dehiscence, bleeding, sepsis, catheter-associated urinary tract infection, ileus, C. difficile infection, pneumonia, acute kidney injury, deep vein thrombosis/pulmonary embolism, supraventricular tachyarrhythmia, and ventricular arrhythmia. Intraoperative complications will be assessed and graded using a validated scoring tool[9 10] and all postoperative complications will be graded according to the Clavien-Dindo complication schema[11] and the Comprehensive Complication Index will be calculated.[12]

Primary endpoint

All subjects will be contacted 30 days after appendectomy by telephone and assigned to seven mutually exclusive hierarchical (ie, ordinal) categories in decreasing order of desirability:

1. Cure; no adverse effects.
2. Infectious/antibiotic complication requiring antibiotic treatment only or no specific treatment.
3. Infectious/antibiotic complication requiring ED visit.

4. Infectious/antibiotic complication requiring hospital readmission.
5. Infectious/antibiotic complication requiring percutaneous drainage.
6. Infectious/antibiotic complication requiring operative intervention.
7. Death.

The *DOOR* ranking system analyzes trial participants according to the desirability of their overall outcome and distributions of DOOR are compared between strategies.[13] Within categories, subjects have similar overall clinical outcomes, whereas subjects in different categories have clinically relevant differences in patient-centered outcomes. Additionally, the subjects will be ranked according to the *RADAR*, a version of DOOR designed for trials comparing strategies to optimize antibiotic use. The underlying principle of RADAR is that less antibiotic exposure is better but must not come at the expense of clinical outcomes. Thus, within DOOR categories, subjects are ranked according to duration of antibiotic exposure, with shorter durations receiving a higher rank when comparing patients with similar overall clinical outcomes. Within this system, a subject with a worse clinical outcome cannot have a higher rank than a subject with a better clinical outcome, no matter how short the antibiotic exposure. This novel analysis is pragmatic and compares two strategies in a way similar to how clinicians and patients actually weigh treatment decisions, by considering all clinical consequences, incorporating competing risks, and accounting for patient outcome preferences. Once the DOOR distributions for the two strategies have been determined, then the probability of a randomly selected control (liberal strategy) patient will have a better DOOR (if assigned to the experimental/restrictive strategy) is calculated with confidence intervals. Assuming no difference (*null hypothesis*) in strategies, then the probability will be approximately 50%. However, if the experimental strategy has a benefit in clinical outcome, shorter antibiotic exposure, or both, then the probability will be proportionally and significantly higher than 50%.

Secondary outcomes

Several a priori secondary analyses will be performed. Simple and complicated appendicitis will be analyzed separately; furthermore, complicated appendicitis will be further divided into gangrenous and perforated and subgroup analyses will be performed. Protocol violations and crossover rates will be calculated and, in addition to the intention-to-treat (ITT) primary analysis, per-protocol and AT analyses will also be performed.[14] Additional secondary outcomes to be assessed include the need for secondary outcomes (eg, percutaneous intervention or operation) and discharge disposition.

Previous appendicitis studies have demonstrated that the majority of patients decline to be randomized (eg, 63% in the CODA trial),[15] thereby indicating a treatment preference. To discern if patients declining randomization differ from those who enroll, the observation only cohort will be compared with the enrolled cohort across all demographic and baseline features. If these features are not significantly different, then the observation only cohort will be combined with the enrolled randomized cohort for the AT analysis. If significant differences are observed between patients in the randomization and observational groups, then the analysis will include propensity score matching to adjust for differences in baseline covariates.

Sample size

We used the MUSTANG database to help inform our estimates of event rates for complicated appendicitis.[2] To attempt to retrieve the expected rates of DOOR outcomes from an RCT, propensity score matching via the MatchIt algorithm was utilized. AAST clinical appendicitis grade, body mass index, age, CCI, and prior operations were used in the matching. 1:1 matching was utilized resulting in 479 match pairs from the MUSTANG dataset and diagnostics for matches were explored and it suggested that good matches were obtained. Table 1 displays the rates from the matched set, one observation was added to every cell to ensure that there were no zero rates in the assumptions.

Table 1 Complicated appendicitis 1:1 propensity score matched MUSTANG dataset assigned to primary endpoint ordinal scale

DOOR	Matched population	
Treatment	<24	>24
1	88.7%	70.8%
2	1.4%	11.1%
3	4.2%	1.4%
4	2.8%	8.3%
5	4.2%	4.2%
6	1.4%	2.8%
7	1.4%	1.4%

MUSTANG, Multicenter Study of the Treatment of Appendicitis in North America: Acute, Perforated, and Gangrenous.

We conducted Monte Carlo simulations to calculate power using the derived DOOR distributions. The number of clusters and events (ie, infectious complications) per cluster were varied between 3 and 30 and 5 and 40, respectively. This process was replicated 1000 times at a 5% significance level to determine power. Powering was based on a signed rank test for clustered data to take into consideration correlation within clusters. Number of patients expected per cluster is taken from the rate of complicated cases in the MUSTANG dataset of 31.8%.

We will recruit patients until we see a sufficient number of complicated cases to be sufficiently powered for our comparison on treatment within the complicated strata. Since we expect fewer than 50% to be complicated cases, we expect a larger sample size to be available for analysis in the acute (simple) arm. Thus, we will be powered for an even larger effect size for simple appendicitis and if we do not find a statistically significant difference, it is very likely that if there is a difference it would not be clinically meaningful. Also, since each analysis will depend on a mutually exclusive set of patients, we can consider these to be independent samples for which no adjustment for multiple testing is required.

This will be an 'event-driven' power analysis, meaning that we will enroll subjects until the minimum number of primary endpoints necessary for clinically meaningful comparisons have occurred. This approach will guard against type 2 error if the actual incident rate is lower than expected. Because this is a multicenter trial, the effect of enrollment site must be taken into account, and we have constructed a table with varying combinations of enrollment sites and subjects per site (table 2). Total events range from 300 to 625, and we will add 15% to account for loss-to-follow-up. Given that MUSTANG had an event rate of 31.8%, we expect to recruit up to 2275 patients.

Statistical analysis

Difference in DOOR score will be tested between restrictive versus liberal strategies via proportional odds regression, accounting for enrollment site and age strata. The primary endpoint will be analyzed using an ITT analysis. In case a

Table 2 Combinations of enrollment sites (cluster) and subjects per site

Clusters	Events per cluster	Total events	Patients per cluster	Patients per cluster+15% attrition	Power
30	15	300	48	55	0.84
20	20	400	63	72	0.804
25	20	500	63	72	0.876
30	20	600	63	72	0.906
15	25	375	79	91	0.809
20	25	200	79	91	0.842
25	25	625	79	91	0.927
15	30	450	95	109	0.857
10	35	350	111	128	0.818
15	35	525	111	128	0.916
10	40	400	126	145	0.836

significant difference is discovered, we plan to calculate the Fragility Index to analyze the fragility of the study results.[16 17] Statistical significance will be determined at an alpha of 0.05. All analyses will be performed in R V.3.6.1.

Bayesian analysis

Bayesian analyses will be used to assess the probability of benefit with restrictive antibiotic use for appendicitis. Both primary and secondary outcomes will be assessed. Bayesian analyses combine prior beliefs (priors) and data obtained from the study (likelihood) to generate posterior distributions that reflect the updated evidence. Posterior probabilities calculated from these distributions indicate the probability of an effect of interest (eg, reduced mortality; 10% or more reduced mortality), when considering both prior knowledge and the observed study data. The minimum clinically important difference in the primary outcome will be considered any increase in DOOR score (OR>1.0). To assess the primary outcome, data-derived, skeptical, and neutral priors will be utilized.

Uncomplicated

Our informed prior was generated by Bayesian ordinal regression models using data from the MUSTANG study and a vague, neutral prior. The median OR was 1.11 (95% credible interval 0.75 to 1.71), with a 69% posterior probability that a restrictive antibiotic treatment will increase (worsen) DOOR scores in patients with uncomplicated appendicitis. This will be applied as our informed prior. Our skeptical prior will assume that the opposite effect is true, or that the DOOR score will decrease (improve) with restrictive antibiotic strategy compared with a liberal strategy (OR 0.90, 95% CI 0.58 to 1.34). Finally, our neutral prior was based on a prior belief that antibiotic administration does not affect DOOR score (OR 1.0, 95% CI 0.25 to 4.)

Complicated

Again, our informed prior for the Complicated arm of the CASA RELAX trial was generated from Bayesian ordinal regression models using data from the MUSTANG study under a vague, neutral prior. The median OR was 0.48 (95% credible interval 0.27 to 0.90), with a 99% posterior probability that a restrictive antibiotic treatment will decrease (improve) DOOR scores in patients with complicated appendicitis. This will be applied as our informed prior. Our skeptical prior will assume that the opposite effect is true, or that the DOOR score will increase (worsen) with restrictive antibiotic strategy (OR 2.06, 95% CI 1.11 to 3.73). Finally, our neutral prior was based on a prior belief that antibiotic administration does not affect DOOR score (OR 1.0, 95% CI 0.25 to 4.)

Bayesian models will be built using the aforementioned criteria and will be adjusted for stratification variables which include clinical site and age group. Secondary outcomes will be assessed with vague, neutral priors only. All Bayesian analyses will use R[18] with rstanarm package.[19]

A priori interim analyses

Interim analyses will be conducted annually and presented to an independent data safety monitoring board comprised of members of the Surgical Infection Society Multicenter Trials committee at the annual meeting. A Bayesian interim analysis will be conducted as outlined above. The two arms (uncomplicated and complicated) will be analyzed separately and considered for early termination separately. Our stopping rule for safety will be a >95% posterior probability that a restrictive antibiotic strategy increases DOOR scores in either group. Our efficacy rule will be a >98% posterior probability that a restrictive antibiotic strategy decreases DOOR scores in either group. Finally, our stopping rule for futility will be a posterior probability between 45% and 55% that restrictive antibiotic strategy increased DOOR scores in either group after half the target sample size has been enrolled.

DISCUSSION

Herein, we describe the study protocol for a multicenter, open label, randomized trial comparing a restrictive versus liberal strategy of postoperative antibiotic therapy after appendectomy for simple and complicated appendicitis.

Acute

In a posthoc analysis of the MUSTANG study, 28% of patients with simple acute appendicitis received postoperative antibiotics.[3] Those receiving postoperative antibiotics did not have improved clinical outcomes in terms of 30-day ED visits, hospital readmission, surgical site infections, intra-abdominal abscess, or need for secondary interventions. Mui *et al* performed a randomized trial of 269 adults with non-perforated appendicitis undergoing open appendectomy. Subjects were assigned to a single preoperative dose of cefuroxime/metronidazole, three doses, or 5 days of perioperative antibiotics and there were no significant differences between groups in the primary endpoint of postoperative infective complication.[20]

Complicated

In a posthoc analysis of the MUSTANG study, the majority (86%) of patients with complicated appendicitis received postoperative antibiotics, though the duration was highly variable. Regression analysis did not demonstrate any association between duration of postoperative antibiotics and rates of surgical site infection, ED visits, hospital readmission, or secondary interventions at 30 days.[4] Indeed, all trends seemed to favor short-course (<24 hours) antibiotic treatment, though a selection bias is highly likely. Kim *et al* examined 410 patients with complicated appendicitis, of whom 274 (67%) received postoperative antibiotics and reported the absence of clinical benefit (regarding wound complications or readmissions) associated with postoperative antibiotics.[21] Similarly, Kimbrell *et al* reviewed 52 complicated appendicitis patients from their institution and were unable to demonstrate that those receiving greater than 24 hours of postoperative antibiotics had improved outcomes regarding

intra-abdominal abscess formation.[22] A large observational study in the Netherlands similarly reported that a longer course of postoperative antibiotics (5 days) was not associated with reduced infectious complications compared with a shorter course (3 days).[23]

The APPIC (Antibiotics following aPPendectomy in Complex appendicitis, Dutch Trial Register NTR6128) recently completed enrollment, though results have not yet been published.[24] The APPIC trial differs from the CASA RELAX trial in that APPIC enrolled pediatric patients (age above 8) and employed a traditional non-inferiority trial design. Additionally, the comparator durations were 2 days vs 5 days of postoperative antibiotics, with intravenous antibiotics (cefuroxime or ceftriaxone and metronidazole with an optional daily dose of gentamicin) mandated for the first 2 days of both arms. These stringent protocols will strengthen internal validity at the expense of external validity (generalizability).

The aforementioned studies support the notion that longer postoperative antibiotics after appendectomy for simple and complicated appendicitis are not necessarily better.

There are several features of the CASA RELAX which are unique. First, the event-driven power calculation and adjustments for variable numbers of enrollment sites (clusters) helps guard against type 2 error from an inadequately powered study. We have also defined rigorous stopping rules for futility and efficacy to minimize risk of type 1 error encountered during preplanned interim analyses. Second, the use of a hierarchical ordinal ranking scale as the primary endpoint is novel in the appendicitis research field. Based on encouraging experience with recent large-scale COVID-19 trials, we selected this endpoint to provide a more nuanced understanding of patient outcomes than typical binary outcomes such as mortality or abscess formation. Furthermore, the inclusion of exposure to antibiotic risk introduces the further dimension of antibiotic stewardship as a desirable outcome assuming equality in patient clinical outcome.

CONCLUSION

The CASA RELAX multicenter RCT will enroll surgical appendectomy patients and seeks to analyze if a strategy of restricted (compared with liberal) postoperative antibiotics results in similar clinical outcomes with the benefit of reduced antibiotic exposure.

Trial status

Actively recruiting; accepting new enrollment sites.

Contributors DDY conceived the study. DDY and GEH drafted the article. DDY, GEH, CP, GP, AM, NN, and LSK all provided critical revision of the article and approve the final draft. DDY accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Denver Health IRB: 21-4816. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Not applicable, as this article describes only the study protocol. Data collection is currently ongoing.

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REFERENCES

1 Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, Cook CH, O'Neill PJ, Mazuski JE, Askari R, *et al*. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* 2015;372:1996–2005.
2 Yeh DD, Eid AI, Young KA, Wild J, Kaafarani HMA, Ray-Zack M, Kana'an T, Lawless R, Cralley AL, Crandall M, *et al*. Multicenter study of the treatment of appendicitis in America: acute, perforated, and gangrenous (MUSTANG), an East multicenter study. *Ann Surg* 2021;273:548–56.
3 Lawless RA, Cralley A, Qian S, Vasileiou G, Yeh DD, Allmond SL, Alouidor R, Barth N, Behrens B, Bradley M, Group EAS, *et al*. Antibiotics after simple (acute) appendicitis are not associated with better clinical outcomes: a Post-Hoc analysis of an East multicenter study. *Surg Infect* 2021;22:504–8.
4 Bou Zein Eddine S, Dodgion CM, Qian S, Trevino C, De Moya MA, Yeh DD, . EAST Appendicitis Research Group. Complicated Appendicitis: Are Extended Antibiotics Necessary? A Post Hoc Analysis of the EAST Appendicitis "MUSTANG" Study. *J Surg Res* 2020;247:508–13.
5 Chammas M, Pust GD, Hatton G, Pedroza C, Kao L, Rattan R, Namias N, Yeh DD, . EAST Appendicitis Study Group. Outcomes of restricted versus liberal post-operative antibiotic use in patients undergoing appendectomy: a DOOR/RADAR post hoc analysis of the East appendicitis MUSTANG study. *Surg Infect* 2022;23:489–94.
6 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
7 Alvarado A. A practical score for the early diagnosis of acute appendicitis. *Ann Emerg Med* 1986;15:557–64.
8 Tominaga GT, Staudenmayer KL, Shafi S, Schuster KM, Savage SA, Ross S, Muskat P, Mowery NT, Miller P, Inaba K, *et al*. The American association for the surgery of trauma grading scale for 16 emergency general surgery conditions: disease-specific criteria characterizing anatomic severity grading. *J Trauma Acute Care Surg* 2016;81:593–602.
9 Kaafarani HMA, Mavros MN, Hwabejire J, Fagenholz P, Yeh DD, Demoya M, King DR, Alam HB, Chang Y, Hutter M, *et al*. Derivation and validation of a novel severity classification for intraoperative adverse events. *J Am Coll Surg* 2014;218:1120–8.
10 Mavros MN, Velmahos GC, Larentzakis A, Yeh DD, Fagenholz P, de Moya M, King DR, Lee J, Kaafarani HMA. Opening Pandora's box: understanding the nature, patterns, and 30-day outcomes of intraoperative adverse events. *Am J Surg* 2014;208:626–31.
11 Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery* 1992;111:518–26.
12 Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien P-A. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg* 2013;258:1–7.
13 Evans SR, Rubin D, Follmann D, Pennello G, Huskins WC, Powers JH, Schoenfeld D, Chuang-Stein C, Cosgrove SE, Fowler VG, *et al*. Desirability of outcome ranking (door) and response adjusted for duration of antibiotic risk (radar). *Clin Infect Dis* 2015;61:800–6.
14 Smith VA, Coffman CJ, Hudgens MG. Interpreting the results of intention-to-treat, Per-Protocol, and As-Treated analyses of clinical trials. *JAMA* 2021;326:433–4.
15 , Flum DR, Davidson GH, Monsell SE, Shapiro NI, Odom SR, Sanchez SE, Drake FT, Fischkoff K, Johnson J, *et al*. CODA Collaborative. A randomized trial comparing antibiotics with appendectomy for appendicitis. *N Engl J Med* 2020;383:1907–19.
16 Walsh M, Srinathan SK, McAuley DF, Mrkobrada M, Levine O, Ribic C, Molnar AO, Dattani ND, Burke A, Guyatt G, *et al*. The statistical significance of randomized controlled trial results is frequently fragile: a case for a fragility index. *J Clin Epidemiol* 2014;67:622–8.
17 Tignanelli CJ, Napolitano LM. The fragility index in randomized clinical trials as a means of optimizing patient care. *JAMA Surg* 2019;154:74–9.
18 Team RC. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2017. https://www.R-project.org/.
19 Goodrich BG J, Ali I, Brilleman Srstanarm. Bayesian applied regression modeling via Stan. 2020 [R package version 2.21.1. https://mc-stan.org/rstanarm.
20 Mui LM, Ng CSH, Wong SKH, Lam Y-H, Fung TMK, Fok K-L, Chung SSC, Ng EKW. Optimum duration of prophylactic antibiotics in acute non-perforated appendicitis. *ANZ J Surg* 2005;75:425–8.
21 Kim DY, Nassiri N, Saltzman DJ, Ferebee MP, Macqueen IT, Hamilton C, Alipour H, Kaji AH, Moazzez A, Plurad DS, *et al*. Postoperative antibiotics are not associated with decreased wound complications among patients undergoing appendectomy for complicated appendicitis. *Am J Surg* 2015;210:983–9.
22 Kimbrell AR, Novosel TJ, Collins JN, Weireter LJ, Terzian HWT, Adams RT, Beydoun HA. Do postoperative antibiotics prevent abscess formation in complicated appendicitis? *Am Surg* 2014;80:878–83.
23 van Rossem CC, Schreinemacher MHF, van Geloven AAW, Bemelman WA, . Snapshot Appendicitis Collaborative Study Group. Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. *JAMA Surg* 2016;151:323–9.
24 van den Boom AL, de Wijkerslooth EML, van Rosmalen J, Beverdam FH, Boerma E-JG, Boermeester MA, Bosmans JWAM, Burghgraef TA, Consten ECJ, Dawson I, *et al*. Two versus five days of antibiotics after appendectomy for complex acute appendicitis (APPIC): study protocol for a randomized controlled trial. *Trials* 2018;19:263.