

## ORIGINAL ARTICLE

# Criteria-led discharge for simple appendicitis in children: A pilot study

Bridget Roddis,<sup>1</sup> Nicholas Ensor<sup>1</sup>, Shona Williamson,<sup>2</sup> Hannah Funnell,<sup>2</sup> Sangeetha Murthi,<sup>3</sup> Maurizio Pacilli<sup>1,4,5</sup> and Ramesh M Nataraja<sup>1,4,5</sup>

Departments of <sup>1</sup>Paediatric Surgery and Surgical Simulation, <sup>2</sup>Nursing, <sup>3</sup>Anaesthetics, Monash Children's Hospital, Departments of <sup>4</sup>Paediatrics, School of Clinical Sciences, Faculty of Medicine, Nursing and Health Sciences, and <sup>5</sup>Surgery, School of Clinical Sciences, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia

**Aim:** Criteria-led discharge (CLD) protocols have been suggested to increase efficiency of discharge from hospital following surgical interventions. Our aim was to assess the feasibility, clinical outcomes and parental satisfaction following the introduction of a pilot CLD for simple appendicitis (SA) in children.

**Methods:** A prospective pilot cohort study was conducted including paediatric patients with SA who were managed with CLD and a control group who were managed with standard discharge procedures. A CLD *pro forma* was developed, standardising care guidelines and clinical criteria indicators to be met for children to be discharged post-operatively. A post-discharge parent survey was also utilised. The primary outcome measure was post-operative length of stay (pLOS), with secondary outcomes of post-operative complication rates and parental satisfaction.

**Results:** The control group consisted of 31 patients and CLD group 35 patients. There was no difference in the median pLOS (24 [16.7–44.6] vs. 25.3 [19.1–50.1] h,  $P = 0.3$ ). Furthermore, there were no significant differences on any of the secondary outcomes. Parental confidence with time of discharge was very high in both control (85.7%) and CLD (88.2%) groups ( $P = 1.0$ ).

**Conclusion:** The introduction of CLD is safe and feasible. Whilst this pilot has not demonstrated a reduction in pLOS, our data suggest that it is well accepted by the parents.

**Key words:** appendicitis; criteria led discharge; event led discharge; paediatric surgery.

## What is already known on this topic

- 1 Appendicitis is the most common surgical presentation in children.
- 2 Expedited discharge practices decrease pLOS without increasing complications.
- 3 Criteria-led discharge reduces post-operative length of stay compared to standard discharge, though has not been studied as extensively as (time-led) same-day discharge.

## What this paper adds

- 1 Criteria-led discharge can be safely and feasibly implemented without any risk of increased post-operative complications in children with simple appendicitis.
- 2 Criteria-led discharge did not reduce post-operative length of stay.
- 3 Parental satisfaction with discharge practice is equally as high for criteria-led discharge as it is for clinician-led standard practice.

Appendicitis is the most common indication for paediatric emergency surgical intervention in Australia.<sup>1–3</sup> Simple appendicitis (SA) is an acutely inflamed appendix without perforation.<sup>4</sup> It has low complications (e.g. wound infections, intrabdominal abscess, small bowel adhesion) and due to its prevalence, there are

established evidence-based guidelines for treatment, allowing interventions surrounding discharge to be safely explored.<sup>1</sup> Given the significant burden appendicitis places on hospital resources, any means of maximising the efficiency of its management is beneficial for both hospitals and patients.<sup>2</sup>

Discharge from hospital following appendicectomy for SA should be safe for patients, prevent complications and proceed in an efficient and timely manner. Several studies have previously investigated expediting discharge following appendicectomy for SA, often utilising a protocol to reduce post-operative length of stay (pLOS).<sup>5–18</sup> These studies have uniformly found that expedited discharge practices decrease pLOS without increasing complications.<sup>5–18</sup> Of these, only two paediatric studies

**Correspondence:** Associate Professor Ramesh M. Nataraja, Department of Paediatric Surgery, Monash Children's Hospital & Monash University, 246 Clayton Road, Clayton, Melbourne, Vic. 3168, Australia. Fax: +61 (0) 3 9594 6008; email: [ram.nataraja@monashhealth.org](mailto:ram.nataraja@monashhealth.org)

Conflict of interest: None declared.

Accepted for publication 21 March 2022.

specifically reported parent satisfaction following expedited discharge post-appendectomy.<sup>8,10</sup> Both reported positive responses, though neither made a direct comparison to satisfaction following standard discharge.

Benefits of expedited discharge include the ability for patients to recover at home, reduced absences from school or work, and less exposure to nosocomial infections.<sup>19,20</sup> Additionally, if the patient is contributing directly to their admission cost, their financial burden is reduced.<sup>15</sup> Expedited discharge practices benefit health services by increased bed availability and financial savings.<sup>17,21</sup>

Whilst time-focussed protocols such as same-day discharge (SDD) or 24-h discharge carry a potential risk of premature discharge in order to meet a deadline, criteria-led discharge (CLD) aims to facilitate efficient and safe discharge when patients are clinically ready.<sup>17,19</sup> CLD specifies criteria guided by standard post-operative clinical progression that must be met before discharge. As expectations for a patient's clinical condition on discharge are already established, they can therefore be discharged without medical review.<sup>19</sup>

CLD for paediatric appendicitis has been explored in one case-control study, as other studies examined SDD.<sup>17</sup> The study demonstrated a 29.2% reduction in median pLOS in the CLD group ( $n = 83$ ) compared to controls; 19.6 versus 27.7 h;  $P < 0.001$ . This study is limited by a retrospective control group and the absence of a systematic approach to assessing parental satisfaction.

A patient's comfort with the timing of their discharge can reduce unnecessary stress, maintain confidence in the health-care system and reduce unnecessary readmissions.<sup>22</sup> Therefore, we conducted a prospective pilot cohort study investigating the feasibility of CLD in paediatric SA, specifically assessing parental satisfaction in both control and CLD groups.

## Methods

### Participants

Our pilot cohort study was conducted at a tertiary paediatric hospital. The control (standard discharge) group were recruited over a four-month period from 1 March to 30 June 2019. Following this, CLD was introduced as routine practice for eligible patients. Recruitment for the CLD group ran from 1 July to 17 October 2019.

Patients were eligible for inclusion into their respective study arm if they:

- 1 Underwent laparoscopy and appendectomy for suspected acute appendicitis;
- 2 Had a diagnosis of simple or negative appendicitis at surgery;
- 3 Were >5 years old and treated by the paediatric surgical team;
- 4 Were not determined to be of higher anaesthetic or surgical risk due to medical comorbidities (ASA1);
- 5 Had experienced no unexpected anaesthetic events.

Both the CLD and standard discharge patients were formally invited to participate in the post-discharge survey when they attended their routine 4- to 8-week post-operative clinic appointment.

The primary study coordinator also contacted by telephone parents whose children did not attend their outpatient clinic appointment. This was to avoid potential bias in the trial as per the recommendations of the institutional HREC committee.

### Human research and ethics

Ethics approval was granted by the institutional Human Research Ethics Council (NMA HREC Ref Number: 48065).

### Data collection

A CLD *pro forma* (Appendix S1, Supporting Information) was developed through multidisciplinary (nursing, surgical and anaesthetic) collaboration. It was designed to be implemented by senior nurses on the surgical ward, enabling expedited discharge of patients when clinically ready.

The *pro forma* comprised three sections. The first section was completed by the surgical team identifying patients eligible for CLD. The second section comprises a set of standard post-operative measures/guidelines for patients, including specifying two post-operative doses of intravenous antibiotics. The final section was completed by ward nurses for eligible patients, detailing the clinical criteria that patients must meet before discharge. A senior nurse would sign the form to indicate the criteria had been met, and the patient could be discharged.

The parent and guardian survey described the study rationale, data collection process, and researchers' contact information. Further questions investigated the child's analgesia requirements, return to school, and if further medical attention was also sought following discharge. Parents were asked whether they were satisfied with the timing of their child's discharge and if they were confident their child was ready for discharge. Parents also had the opportunity to leave a general comment about their child's admission.

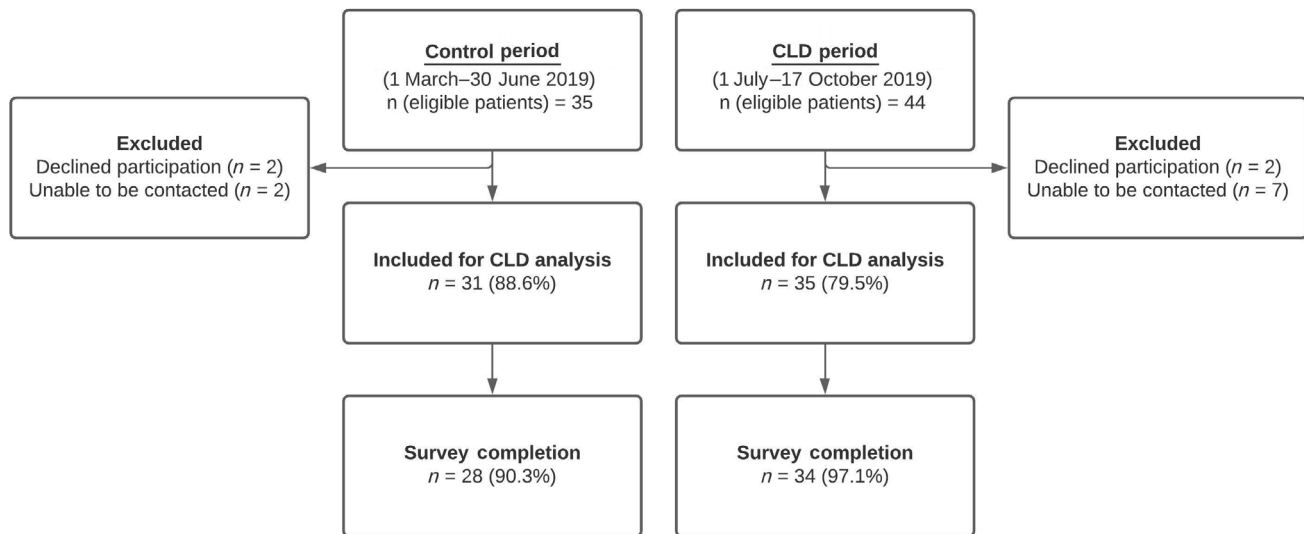
### Primary and secondary outcomes

The primary outcome was the pLOS. Operative time was defined as the child's in-theatre arrival time. Discharge was defined as when the patient left the hospital according to the institutional electronic patient management system.

Secondary outcomes included: time from admission to discharge, complications and self-reported return visits to health services, time to return to school, analgesia use, and parental satisfaction. The patients' electronic medical record and parent survey responses informed secondary outcomes. Complications were defined as patients who required readmission in hospital for further intervention or symptom management following appendectomy, or patients who required treatment with antibiotics for a suspected surgical site infection in the community or a hospital.

### Power calculation and statistical analysis

The sample size is based on the findings of Skarda *et al.*<sup>5</sup> who reported a decrease in total hospital stay after implementation of a CLD pathway from mean 40.1 ( $\pm 27.5$ ) h to 23.5 ( $\pm 20.8$ ) h (absolute difference of mean 16.6 h). A power calculation



**Fig. 1** Flowchart demonstrating participant recruitment and follow-up rates.

determined that 70 patients were required to have an 80% chance ( $1 - \beta = 0.80$ ) of detecting a reduction in post-operative nausea at the 5% significance level.

Statistical analyses were conducted in GraphPad Prism Version 8 (GraphPad Software, CA, USA). Continuous data were assessed for normality using the D'Agostino Pearson test. Normally-distributed data were analysed using the Student *T*-test. Non-normally distributed data were analysed with the Mann–Whitney *U* test. Categorical data were analysed with Fisher's test. A *P*-value <0.05 was considered significant.

## Results

The prospective control group consisted of 31 participants from 35 admissions (88.6%) and the CLD group consisted of

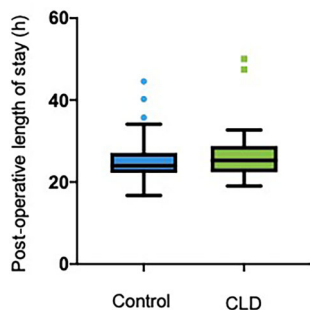
35 participants from 44 admissions (79.5%) (Fig. 1). There were no significant demographic differences or hospital outcomes between groups (Table 1), including the primary outcome, pLOS (Fig. 2). Although the median length of admission for the control group was slightly shorter, this difference was not significant (24.0 vs. 25.3 h, *P* = 0.3).

In the control group, 2/31 (6.5%) patients experienced complications, compared to 4/35 (11.4%) in the CLD group (*P* = 0.7) (Table 1). All complications were minor and classified as Clavien-Dindo Grade 1.<sup>23</sup> One patient was readmitted and treated for inability to tolerate oral fluids and another for ongoing post-operative pain. CLD group complications included one superficial surgical site infection requiring oral antibiotics, and three patients who re-attended an emergency department and were readmitted for symptom control (pain and nausea).

**Table 1** Key demographics and hospital outcomes of the control and CLD groups

	Control ( <i>n</i> = 31)	CLD ( <i>n</i> = 35)	<i>P</i> value
Sex (male) <sup>†</sup>	26/31 (83.9)	23/35 (65.7)	0.2
Mean age at operation (years) <sup>‡</sup>	10.8 ± 2.7	11.5 ± 2.3	0.3
			95% CI (−0.5 to 2.0)
Negative appendicectomy <sup>†</sup>	4/31 (12.9)	1/35 (2.9)	0.2
Laparoscopic surgery <sup>†</sup>	31/31 (100)	35/35 (100)	1
Complication <sup>†</sup>	2/31 (6.5)	4/35 (11.4)	0.7
Complication details ( <i>n</i> )	<ul style="list-style-type: none"> <li>Inability to tolerate oral fluids requiring re-admission (1)</li> <li>Ongoing post-operative pain (1)</li> </ul>	<ul style="list-style-type: none"> <li>Symptom management (pain and nausea) requiring re-admission (3)</li> <li>Superficial surgical site infection requiring oral antibiotics (1)</li> </ul>	
Median time from operation to discharge (h) <sup>‡</sup>	24 (27.9)	25.3 (31.1)	0.3
Median time from admission to discharge (h) <sup>‡</sup>	39.3 (64.3)	43.4 (67.9)	0.4

<sup>†</sup> Discrete data presented as *n/N* (%). <sup>‡</sup> Continuous data assessed for normality and analysed with Mann–Whitney *U* test [Median (range)] if nonparametric or Student's *t*-test [Mean ± SD] if normally distributed.



**Fig. 2** Post-operative length of stay box plot – control versus CLD (box and whiskers plot of pLOS for control and CLD groups; middle line showing median, box demonstrating IQR (25–75%), whiskers representing 1.5 times IQR and outliers plotted as individual points).

An intention to treat analysis was performed to assess the clinical impact of the CLD implementation. As per institutional practice, there is a daily consultant-led ward round. Therefore, at the discretion of the attending consultant, some patients in the CLD group were discharged via standard medical review prior to fulfilling all the CLD criteria. In total, 20 (20/35, 57.1%) patients were discharged using the CLD, whilst 15 (15/35, 42.9%) were discharged following early medical review. A sub-group analysis was therefore conducted within the CLD group. The difference in median pLOS between subgroups was not significant ( $P = 0.1$ ); 24.8 h (CLD) versus 27.3 h (medical review).

Overall, 62 (93.9%) of 66 parents completed the survey; 28/31 (90.3%) in the control group and 34/35 (97.1%) in the CLD group. Survey outcomes are presented in Table 2. More patients from the CLD group (12/34 [34.3%] vs. 4/28 [14.3%],  $P = 0.08$ ) returned to see a health professional after discharge, though this difference was not significant. These visits account for complications already discussed and the remainder were for check-up appointments without specific concerns.

Overall, parents were highly satisfied with the discharge process. In both control (24/28, 85.7%) and CLD (30/34, 88.2%) groups, parents were confident their child was ready for discharge ( $P = 1.0$ ).

### Discussion

This prospective pilot study investigated the implementation of a CLD for paediatric SA compared to standard discharge. The primary research question was whether CLD could safely and feasibly expedite discharge times following appendicectomy for SA. Our results revealed no significant difference in pLOS following CLD compared to standard discharge, nor any differences in secondary outcomes with maintained parent satisfaction ratings. Since this was a pilot feasibility study, we found that a CLD protocol could be safely implemented and, therefore, investigated further in a larger study.

Our study demonstrated no change to pLOS following CLD introduction, which remained approximately 24 h. These results were unexpected and at odds with previous evidence suggesting that introduction of discharge protocols following appendicectomy consistently reduced pLOS.<sup>5–18</sup> We do note that our result was statistically limited by the fact that many patients did not complete the CLD protocol. A lack of reduction in pLOS following CLD introduction may have been influenced by observing the early stages of a staff learning curve. In addition, during the control period, having a consultant paediatric surgeon on-call without elective clinical duties meant that early identification of patients suitable for discharge could be achieved by continuity of care with regular medical reviews. A final factor influencing >24-h pLOS is that our hospital has a large rural catchment, and if a patient meets CLD criteria late in the day, then they would often need to stay until morning in order to be discharged appropriately.

Whilst similar studies report pLOS <6 h,<sup>5,10,13,15</sup> our institutional policy is that children with SA receive two post-operative doses of intravenous antibiotics to prevent surgical site infection in accordance with the findings of Mennie *et al* which was

	Control (n = 28)	CLD (n = 34)	P value
Median time to return to school or normal activities (days) <sup>†</sup>	6 (13)	7 (26)	0.1
Median post-operative days of use; simple analgesia (days) <sup>†</sup>	2 (15)	2.5 (16)	0.9
Median post-operative days of use; opioid analgesia (days) <sup>†</sup>	0 (1)	0 (10)	0.9
Returned to see a health professional <sup>‡</sup>	4/28 (14.3)	12/34 (35.3)	0.08
Thought length of stay post-operatively was ‘Just right’ <sup>‡</sup>	21/28 (75)	24/34 (70.6)	0.8
Confident child was ready for home at time of discharge <sup>‡</sup>	24/28 (85.7)	30/34 (88.2)	1
Confident with the information provide regarding the discharge <sup>‡</sup>	23/28 (82.1)	30/34 (88.2)	0.7

<sup>†</sup> Continuous data assessed for normality and analysed with Mann–Whitney *U* test [Median (range)] if nonparametric. <sup>‡</sup> Discrete data presented as n/N (%).

conducted at our institution.<sup>24</sup> This is a possible additional limiting factor that prevents observing a pLOS reduction with CLD implementation.

We found that there was limited completion of the CLD protocol (43%) following implementation. Whilst positive uptake and buy-in was noted across professions, we believe that a possible explanation for this was that the daily morning consultant ward round would occur shortly after nursing handover. This potentially meant that in many cases the medical team would review the patient prior to when nurses would routinely assess the patient for CLD eligibility. There was commonly no medical indication for medical-led discharge, rather more often being a matter of opportunity and convenience on the ward. Despite education, it may have been viewed as safer and simpler for bedside nursing staff to let medical-led discharge occur rather than complete the CLD protocol. Anecdotally, it seemed that the CLD was beneficial for the medical team and ward Nurse in Charge, whilst still requiring further buy-in from bedside nursing staff. Formal staff feedback and qualitative analysis should be sought in further studies.

Consistent with previous studies, we found no difference in complication rates between groups. However, a marginally higher proportion of patients in the CLD group returned to visit a health practitioner post-discharge. This warrants further investigation, because if CLD leads to an increased requirement for general practitioner review, then this may decrease its effectiveness for the health system overall.

As non-comparative surveys of satisfaction for expedited discharge have had positive responses, we anticipated parental satisfaction would be maintained following the introduction of CLD. Our follow-up parental survey indicated that the majority believed that the time of their child's discharge was 'just right' in both groups. This shows that pre-existing satisfaction with the discharge process after appendectomy was high and, importantly, maintained after introducing CLD. In addition, the majority of parents in both groups were 'quite confident' or 'very confident' that their child was ready for discharge at time of discharge. As there is a paucity of evidence comparing expedited discharge to a control group of standard discharge patients, this is useful in demonstrating that CLD can be accepted by parents as standard practice.

A key strength of our study is the ability to collect parental satisfaction assessment information from both standard discharge and CLD groups. This is unique as this has not been assessed in previous studies exploring expedited discharge for paediatric appendicitis. This is a vital component of assessing any clinical change as hospital benefits are balanced with patient/parental experience. A final strength is that following the introduction of CLD both doctors and nurses could discharge patients, enabling efficient discharge for patients who were clinically ready whilst maintaining patient safety if there were any concerns during the post-operative period.

A limitation of our study relates to the rate of medical-led discharge during the CLD period, as previously discussed. In addition, completion of the satisfaction surveys at 4 weeks post-operatively may have led to a degree of recall bias. However, this was minimised as the follow-up period was the same for both groups and that survey completion rates were >90% in both groups. Patients who did not attend clinic and whose parents

were not contactable by phone could not be included in the study. The results are therefore potentially affected by attrition bias, but the recruitment rates were good in both the control (88.6%) and the CLD (79.5%) groups.

Future research should focus on how CLD can be incorporated into discharge care, specifically considering the requirement for post-operative antibiotics which are often a limiting factor in discharge time.<sup>24</sup> The comparative satisfaction of other expedited discharge protocols to standard discharge could also be explored in future studies.

## Conclusion

Our study demonstrates that a CLD protocol for discharge following SA is safe for patients and is equally accepted by parents when compared to standard discharge. Whilst not observing a significant difference in pLOS, further qualitative investigation is needed to determine potential barriers to implementation. Due to the prevalence of appendicitis, any potential improvements in the discharge process that are safe for patients and improve efficiency for hospitals should continue to be explored.

## Acknowledgements

The authors would like to acknowledge the medical and nursing staff at our tertiary hospital who contributed to the care of paediatric patients recruited into our study. Open access publishing facilitated by Monash University, as part of the Wiley – Monash University agreement via the Council of Australian University Librarians. [Correction added on May 13, 2022, after first online publication: CAUL funding statement has been added.]

## References

- 1 Arthur T, Gartrell R, Manoharan B, Parker D, Collaboration Q. Emergency appendectomy in Australia: Findings from a multicentre, prospective study. *ANZ J. Surg.* 2017; **87**: 656–60.
- 2 4.5 Appendectomy hospitalisations. Sydney; 2017 p. 292–304. (The Second Australian Atlas of Healthcare Variation). Available from: <https://www.safetyandquality.gov.au/sites/default/files/migrated/4.5-Appendectomy.pdf>
- 3 Rentea RM, SDSt P, Snyder CL. Pediatric appendicitis: State of the art review. *Pediatr. Surg. Int.* 2017; **33**: 269–83.
- 4 Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: Modern understanding of pathogenesis, diagnosis, and management. *Lancet* 2015; **386**: 1278–87.
- 5 Cheng O, Cheng L, Burjonrappa S. Facilitating factors in same-day discharge after pediatric laparoscopic appendectomy. *J. Surg. Res.* 2018; **229**: 145–9.
- 6 Putnam LR, Levy SM, Johnson E *et al.* Impact of a 24-hour discharge pathway on outcomes of pediatric appendectomy. *Surgery* 2014; **156**: 455–61.
- 7 Aguayo P, Alemayehu H, Desai AA, Fraser JD, St. Peter SD. Initial experience with same day discharge after laparoscopic appendectomy for nonperforated appendicitis. *J Surg. Res.* 2014; **190**: 93–7.
- 8 Ngo S, Gee K, Burkhalter L, Beres AL. Parental satisfaction with same-day discharge after laparoscopic appendectomy for uncomplicated appendicitis. *Paediatr. Child Health* 2019; **24**: 318–22.
- 9 Yu YR, Smith CM, Ceyanes KK *et al.* A prospective same day discharge protocol for pediatric appendicitis: Adding value to a common surgical condition. *J. Pediatr. Surg.* 2017; **S0022-3468**: 30633–4.

- 10 Alkhoury F, Burnweit C, Malvezzi L *et al.* A prospective study of safety and satisfaction with same-day discharge after laparoscopic appendectomy for acute appendicitis. *J. Pediatr. Surg.* 2012; **47**: 313–6.
- 11 Alkhoury F, Malvezzi L, Knight CG *et al.* Routine same-day discharge after acute or interval appendectomy in children: A prospective study. *Arch. Surg.* 2012; **147**: 443–6.
- 12 Gee K, Ngo S, Burkhalter L, Beres AL. Safety and feasibility of same-day discharge for uncomplicated appendicitis: A prospective cohort study. *J. Pediatr. Surg.* 2018; **53**: 988–90.
- 13 Farach SM, Danielson PD, Walford NE, Harmel RP, Chandler NM. Same-day discharge after appendectomy results in cost savings and improved efficiency. *Am. Surg.* 2014; **80**: 787–91.
- 14 Halter JM, Mallory B, Neilson IR, Langer M. Same-day discharge following laparoscopic appendectomy for uncomplicated acute appendicitis as a measure of quality in the pediatric population. *J. Laparoendosc. Adv Surg Tech* 2016; **26**: 309–13.
- 15 Benedict LA, Sujka J, Sobrino J, Aguayo P, St Peter SD, Oyetunji TA. Same-day discharge for nonperforated appendicitis in children: An updated institutional protocol. *J. Surg. Res.* 2018; **232**: 346–50.
- 16 Oyetunji TA, Gonzalez DO, Aguayo P, Nwomeh BC. Variability in same-day discharge for pediatric appendicitis. *J. Surg. Res.* 2015; **199**: 159–63.
- 17 Cundy TP, Sierakowski K, Manna A, Cooper CM, Burgoyne LL, Khurana S. Fast-track surgery for uncomplicated appendicitis in children: A matched case–control study. *ANZ J. Surg.* 2017; **87**: 271–6.
- 18 Skarda DE, Schall K, Rollins M *et al.* A dynamic postoperative protocol provides efficient care for pediatric patients with non-ruptured appendicitis. *J. Pediatr. Surg.* 2015; **50**: 149–52.
- 19 Lees-Deutsch L, Robinson J. A systematic review of criteria-led patient discharge. *J. Nurs. Care Qual.* 2019; **34**: 121–6.
- 20 Sibbern T, Bull Sellevold V, Steindal SA, Dale C, Watt-Watson J, Dihle A. Patients' experiences of enhanced recovery after surgery: A systematic review of qualitative studies. *J. Clin. Nurs.* 2017; **26**: 1172–88.
- 21 Gray C, Christensen M, Bakon S. Nurse-initiated and criteria-led discharge from hospital for children and young people. *Nurs. Child. Young People* 2016; **28**: 26.
- 22 Rathert C, Williams ES, McCaughey D, Ishqaidef G. Patient perceptions of patient-centred care: Empirical test of a theoretical model. *Health Expect.* 2015; **18**: 199–209.
- 23 Dindo D, Demartines N, Clavien P-A. Classification of surgical complications. *Ann. Surg.* 2004; **240**: 205–13.
- 24 Mennie N, Panabokke G, Chang A *et al.* Are postoperative intravenous antibiotics indicated after laparoscopic appendectomy for simple appendicitis? A prospective double-blinded randomized controlled trial. *Ann. Surg.* 2020; **272**: 248–52.

## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Appendix S1** Supporting Information.