

1 **A randomized, parallel-group, 30-day, difference analysis study to investigate**
2 **the efficacy of the transanal drainage tube (TDT) for anastomotic leakage (AL)**
3 **prevention following the laparoscopic low anterior resection for rectal cancer**

Clinical Study Protocol

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17 University

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72 **Protocol Synopsis**

Study Title	Use of the TDT for Prevention of Anastomotic Leakage After Laparoscopic Anterior Resection for Rectal Cancer
Scientific Title	A randomized, parallel-group, 30-day, difference analysis study to compare the efficacy of the transanal drainage tube (TDT) for anastomotic leakage (AL) prevention following the laparoscopic low anterior resection for rectal cancer
Contact Investigator	Prof. Weidong Tong
Primary sponsor	Army Medical Center (Daping Hospital), Army Medical University
Secondary sponsor(s)	Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine Department of Gastrointestinal Surgery, The First Affiliated Hospital of Air Force Medical University Department of Colorectal and Anal Surgery, The 940th Hospital of Joint Logistics Support Force of The Chinese People's Liberation Army Department of gastrointestinal and hernia surgery, Second People's Hospital of Yibin Department of Gastrointestinal Surgery, Yongchuan Hospital of Chongqing Medical University Department of Epidemiology, College of Preventive Medicine, Army Medical University (Third Military Medical University) Department of Gastrointestinal and breast surgery, The People's Hospital of Kaizhou District
Primary Registry and Trial Identifying Number	ClinicalTrials.gov NCT02686567

Date of Registration In Primary Registry	02/19/2016
Funding Support	None
Study Objective	To evaluate whether the TDTs can reduce the incidence of anastomotic leakage after laparoscopic anterior resection for rectal cancer
Intervention(s)	For patients who were assigned to the TDT group, a silicone tube (28Fr, Sumitomo Bakelite Co, Japan) is inserted through the anus and the tip of the tube is placed approximately 5 cm above the anastomosis under laparoscopy at the end of the surgery.
Groups	<ul style="list-style-type: none"> ● TDT group: application of TDT after laparoscopic low anterior resection for rectal cancer ● Non-TDT group (control): without TDT application
Key Inclusion And Exclusion Criteria	<p>Ages Eligible for Study: ≥ 18 years Sexes Eligible for Study: both Accepts healthy volunteers: no</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> ● age from 18 to 80 years old ● primary rectal adenocarcinoma ● tumor location ≤ 10 cm ● ASA I, II, or III ● laparoscopic LAR + DST ● patients and their families can understand and are willing to participate in this study and provide written informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> ● emergency operation

	<ul style="list-style-type: none"> ● patients with preoperative radiotherapy ● patients with IBD, FAP, recurrent rectal cancer, or synchronous cancer, other types of surgeries for rectal cancer ● patients with serious mental illness or uncontrolled infections before surgery ● pregnant or breastfeeding women ● patients with other clinical and laboratory conditions considered by the investigator should not participate in the trial
Study Type	<ul style="list-style-type: none"> ● Interventional ● Allocation: randomized ● Intervention model: the parallel assignment ● Masking: no ● Primary purpose: comparison
Target Sample Size	560
Recruitment Status	Recruiting
Primary Outcome(s)	AL rate within 30 days after surgery in 2 groups
Key Secondary Outcomes	<ul style="list-style-type: none"> ● Grades of AL ● Postoperative anal pain score ● TDT-related adverse events: bleeding ● TDT-related adverse events: iatrogenic colonic perforations(ICP)
Sample Size Estimation	Based on the synthesis of information from multiple published studies with large sample sizes, we assume that the AL rate will be reduced from 10.5% to the expected 4% due to the TDT intervention. With an 80% power and a 5% significance level, and an expected crossover rate of 1%, and a dropout rate of 10%, we needed to recruit 560 patients overall

<p>Study Method</p>	<ol style="list-style-type: none"> 1. Eligible patients are randomly assigned to two groups with a 1:1 allocation ratio (TDT and non-TDT group) after the laparoscopic LAR and DST procedures are chosen during the operation 2. Simple randomization was obtained through computer-generated random number sequence allocation by the <i>Quality Control Committee</i>. 3. Allocation concealment was performed: After completion of the anastomosis and further DS construction if necessary, the surgeon was notified to implement the intervention based on the randomization results by the circulating nurse 4. Quality requirements: All perioperative treatments must comply with relevant guidelines. The preservation of the left colonic artery was assessed by the surgeon according to his or her own experiences and assessment of the patient's conditions 5. The decision regarding DS construction was made by the surgeon 6. A silicone tube (28Fr, Sumitomo Bakelite Co, Japan) is inserted through the anus and the tip of the tube is placed approximately 5 cm above the anastomosis under laparoscopy at the end of the surgery in patients of TDT group 7. The tube is fixed with a skin suture and connected to a drainage bag 8. TDT is planned to remove 3-7 days after surgery according to the surgeon's discretion when the discharge of feces or flatus was clearly and repeatedly observed and/or when surgeons confirmed the absence of signs of AL 9. Early removal is allowed if the patient experienced intolerable pain 10. AL will be recorded within 30 days after surgery (the definition of AL is detailed in the following text ,see 8.1)
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	<p>11. Grades of AL will be identified and recorded</p> <p>12. The numerical rating scale (NRS) is used to assess the anal postoperative pain score of patients in the TDT group. The assessment will be performed every day postoperatively until the TDT is removed</p> <p>13. TDT-related adverse events such as bleeding and ICPs will be identified and recorded</p>
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73

74 **1 Background**

75 Anastomotic leakage (AL) is one of the most dreadful complications after LAR
76 and is associated with increased medical costs, longer hospital stay, higher
77 postoperative morbidity, and mortality for patients, even higher rate of recurrence(1).
78 Diverting stoma (DS) is still one of the most common methods used in AL prevention,
79 despite the clinical benefit of reducing morbidity from anastomotic leaks, DS remains
80 a large source of morbidity for patients, with increased postoperative stay,
81 readmission, dehydration, etc(2-4). It has been reported that the transanal drainage
82 tube (TDT) is valuable and safe to prevent AL after LAR, but doubts about this never
83 ceased. The potential role of applying a TDT is supposed to be beneficial for
84 endoluminal pressure reduction as well as fecal diversion, resulting in a protective
85 effect on anastomotic healing (5). Several meta-analytical studies have reported that
86 the TDT is effective in AL prevention (6). However, the majority of previous studies
87 have the limitation of retrospective observation, a small sample size or utilization of a
88 nonrandomized control group. Moreover, inconsistent results have also been reported,
89 failing to prove the effectiveness of the implementation (7-9). Cong and his
90 colleagues reported that the AL rate in the TDT group was unexpectedly higher than
91 that in the non-TDT group (15.1% vs. 4.9%, $P = 0.008$)(9). Zhao supposed that the
92 TDT would reduce anastomotic complications but found that the AL rate was not
93 significantly different between the two groups (2.5% vs. 7.8%, $P = 0.160$)(8). In a
94 study using propensity score matching (PSM), Yang reported no significant difference
95 in the overall AL rate between the two groups (9.8% vs. 11.8%, $P = 0.652$). A similar
96 result was concluded by Lee in their retrospective study, both before and after PSM
97 (5.8% vs. 10.7%, $P = 0.652$; 5.8% vs. 9.1%, $P = 0.278$, respectively)(7). Therefore,

98 due to the lack of a high level of evidence, the role of TDTs in AL prevention after
99 LAR is still unclear.

100 **2 Study Title**

101 Use of the TDT for Prevention of Anastomotic Leakage After Laparoscopic
102 Anterior Resection for Rectal Cancer.

103 **3 Objective**

104 **3.1 Research Hypothesis**

105 The null hypothesis is that the AL rate of patients with TDT is the same as that
106 without TDT within 30 days following laparoscopic LAR. (H0)

107 The alternative hypothesis is that the AL rate of patients with TDT is different
108 from that without TDT within 30 days following laparoscopic LAR. (H1)

109 **3.2 Study Objective**

110 To evaluate whether the TDTs can reduce the incidence of anastomotic leakage
111 after laparoscopic anterior resection for rectal cancer.

112 **4 Intervention(s)**

113 A silicone tube (28Fr, Sumitomo Bakelite Co, Japan) is inserted through the anus and the tip
114 of the tube is placed approximately 5 cm above the anastomosis under laparoscopy at the end of
115 the surgery in patients from the TDT group.

116 **5 Trial Design**

117 This trial is designed as a randomized, controlled, open-label, multicenter,
118 difference analysis study with two parallel groups and a primary endpoint of
119 anastomotic leakage within 30 days after laparoscopic low anterior resection for rectal
120 cancer.

121 **5.1 Groups:**

122 Randomization will be performed with a 1:1 allocation ratio.

- 123 ● TDT group: application of TDTs after laparoscopic low anterior resection
- 124 for rectal cancer.
- 125 ● Non-TDT group (control): without TDT application.

126 **6 Eligibility Criteria**

127 Patients (or a representative) must provide written, informed consent before any
128 study procedures occur.

129 **6.1 Inclusion criteria**

130 All patients should meet the surgical conditions under the Chinese guideline for the
131 diagnosis and treatment of colorectal cancer. Besides, patients eligible for the trial
132 must comply with all of the following at randomization:

- 133 ● Age from 18 to 80 years old
- 134 ● Primary rectal adenocarcinoma
- 135 ● Tumor location ≤ 10 cm
- 136 ● ASA I, II, or III
- 137 ● Laparoscopic LAR + DST

138 **6.2 Exclusion criteria**

- 139 ● Emergency operation
- 140 ● Patients with preoperative radiotherapy
- 141 ● Patients with IBD, FAP, recurrent rectal cancer, or synchronous cancer, other
142 types of surgeries for rectal cancer
- 143 ● Patients with serious mental illness or uncontrolled infections before surgery
- 144 ● Pregnant or breastfeeding women
- 145 ● Patients with other clinical and laboratory conditions considered by the
146 investigator should not participate in the trial

147 **7 Sample Size Estimation**

148 Based on the synthesis of information from multiple published studies with large
149 sample sizes (5, 10-15), we assume that the AL rate will be reduced from 10.5% to the
150 expected 4% due to the TDT intervention. With an 80% power and a 5% significance
151 level, and an expected crossover rate of 1%, and a dropout rate of 10%, we needed to
152 recruit 560 patients overall

153 **8 Standard operating procedures (SOP)**

154 8.1 All patients should meet the surgical conditions under the Chinese guideline
155 for the diagnosis and treatment of colorectal cancer

156 8.2 Perioperative management should comply with relevant guidelines. For
157 example, routinely implement mechanical bowel preparation combined
158 with antibiotics before surgery, nutritional risk assessment and support;
159 postoperative antibiotics and nutritional support treatment must strictly
160 comply with the requirements of the local health department; pay attention
161 to pain management.

162 8.3 After reporting relevant information to the *Quality Control Committee*,
163 eligible patients are randomly assigned to two groups with a 1:1 allocation
164 ratio (TDT and non-TDT group) after the laparoscopic LAR and DST
165 procedures are chosen during the operation.

166 8.4 Simple randomization was obtained through computer-generated random
167 number sequence allocation by the *Quality Control Committee*.

168 8.5 Allocation concealment was performed: After completion of the
169 anastomosis and further DS construction if necessary, the surgeon was
170 notified to implement the intervention based on the randomization results
171 by the circulating nurse.

172 8.6 Quality requirements: All procedures must be performed by experienced
173 surgeons who had performed at least 300 laparoscopic LARs before the
174 study. All perioperative treatments must comply with relevant guidelines.
175 The preservation of the left colonic artery was assessed by the surgeon

176 according to his or her own experiences and assessment of the patient's
177 conditions.

178 8.7 The decision regarding DS construction was made by the surgeon.

179 8.8 A silicone tube (28Fr, Sumitomo Bakelite Co, Japan) is inserted through the
180 anus and the tip of the tube is placed approximately 5 cm above the
181 anastomosis under laparoscopy at the end of the surgery in patients from
182 the TDT group.

183 8.9 The tube is fixed with a skin suture and connected to a drainage bag.

184 8.10 TDT is planned to remove 3-7 days after surgery according to the surgeon's
185 discretion when the discharge of feces or flatus was clearly and repeatedly
186 observed and/or when surgeons confirmed the absence of signs of AL.

187 8.11 Early removal is allowed if the patient experienced intolerable pain.

188 8.12 Record whether the patient has AL-related symptoms and signs, collect
189 blood routine, albumin, prealbumin and other laboratory test results on the
190 day after the operation, postoperative day (POD) 1, 3, 5, and so on. Record
191 the pelvic drainage volume and fluid properties every day after the
192 operation, and combine the above inspection results as an important
193 supporting result for evaluating the presence or absence of AL and the
194 grades.

195 8.13 AL will be recorded within 30 days after surgery (the definition of AL is
196 detailed in the following text)

197 8.14 Grades of AL will be identified and recorded

198 8.15 The numerical rating scale (NRS) is used to assess the anal postoperative
199 pain score of patients in the TDT group.

200 8.16 TDT-related adverse events such as bleeding and ICPs will be identified
201 and recorded.

202 8.17 Discharge criteria: able to take a liquid or semi-liquid diet; there are signs
203 of recovery of intestinal function; normal body temperature; no positive
204 signs in abdominal examination; able to go to the ground and have a certain
205 ability to take care of themselves.

206 **9 Follow-up plan**

207 9.1 Follow-up period: within 30 days after surgery;

208 9.2 Designate a investigator to keep in touch with discharged patients, and
209 instruct patients to return to the hospital for follow-up treatment if they feel
210 unwell;

211 9.3 The follow-up content focuses on the presence or absence of AL-related
212 symptoms or signs such as abdominal pain, chills, fever, and acute
213 abdomen after discharge, as well as other symptoms that observers believe
214 are related to AL (this can be determined by discussion with lead
215 observers).

216 **10 Outcomes Measures**

217 **10.1 Primary Outcome Measures**

218 The primary endpoint is the AL rate within 30 days after surgery.

219 AL was defined when the following symptoms were noticed: abdominal pain;
220 fever; peritonitis; leukocytosis; increased procalcitonin (PCT) or C-reactive protein
221 (CRP); discharge of feces, pus, or gas from the drainage tube or the vagina; and
222 septicemia with pelvic abscess. All clinically suspicious symptoms were confirmed by
223 digital rectal examination, computed tomography (CT) scan, or surgery when
224 necessary(5, 7-9, 16-20).

225 **10.2 Secondary Outcome Measures**

- 226 ● The grades of AL. The severity grading of AL was defined according to the
227 International Study Group of Rectal Cancer(21). In the present study, AL was
228 referred to as grades B and C, and asymptomatic AL (grade A) was not
229 considered because no active therapeutic intervention was required.
- 230 ● Anal postoperative pain score. The numerical rating scale (NRS) is used to assess
231 the anal postoperative pain score of patients in the TDT group. The assessment
232 will be performed every day postoperatively until the TDT is removed.
- 233 ● TDT-related adverse events such as bleeding and ICPs. Only 2 cases of iatrogenic
234 colonic perforations (ICPs) were reported in all cases of previous studies. The
235 underline benefit will be a significant reduction of AL rate in patients with TDTs
236 while the underline harms may be bleeding, ICP, or discomfort caused by TDTs.

237 **11 Data Collection Methods**

238 The data to be collected includes but is not limited to the following: preoperative
239 information including gender, age, contact information; basic hospitalization
240 information of the patient; related examination results including colonoscopy, CT,
241 MRI, etc.; surgery related including operation methods, operation time, blood loss, etc.
242 The postoperative related information includes laboratory results such as blood
243 routine, albumin, patient symptoms, signs, pelvic drainage and traits, and related
244 measurement results of TDT. See the Case Report Forms (CRFs) for details.

245 **11.1 Case report form (CRF)**

246 In this trial, the required observation or inspection items need to be recorded in
247 the case report form. The contents of the case report form must be completely
248 consistent with the original data. For the results calculated from the original data, the
249 calculation basis should be traceable.

250 **11.2 Original data record**

251 All information should be recorded in the CRFs in a timely, truthful and detailed
252 manner. The *Data Manager* will check the completeness and accuracy of the CRF
253 and make necessary modifications or additions.

254 **11.3 Quality control**

255 Perform corresponding inspections and evaluations as required and record them in
256 the CRFs. All forms must be completed, signed, and dated by the investigators. The
257 *lead investigators* check every 6 months, supervise the completion of the CRF forms,
258 and conduct a review and signature. All items should have a corresponding objective
259 basis, be prepared for review and use, and should not be fabricated. The *Data*
260 *Manager* should carefully check each CRF and sign it after confirming that it is
261 complete and correct. The medical records required to be recorded are true and
262 reliable, properly kept, and subject to random inspections at any time. If you make

263 any mistakes and modify them, you should sign and date them, and the original
264 modification can be identified.

265 **12 Statistical Analysis Plan**

- 266 ● Public health statisticians and *lead investigators* formulate statistical analysis
267 plans based on the research plan; *Data Manager* will perform statistical
268 analysis according to the statistical plan.
- 269 ● Sample size estimation was performed using PASS, version 11 (NCSS, LLC,
270 Kaysville, UT, USA).
- 271 ● Statistical analysis will be performed using SPSS, version 25.0 (Statistical
272 Package for the Social Sciences, IBM Corporation, Armonk, NY, USA).
- 273 ● All analyses are two-sided, and a $P < 0.05$ is considered statistically
274 significant.
- 275 ● Analyses of the primary and secondary endpoints are based on the
276 intention-to-treat (ITT) principles. Per-protocol (PP) analysis is restricted to
277 the participants who fulfilled the protocol in the terms of eligibility,
278 interventions, and outcome assessment.
- 279 ● A chi-square test or Fisher's exact test is used for the comparison of
280 categorical variables, as appropriate. This mainly involves the baseline data,
281 the primary outcomes (AL rate) and the grades of AL of the two groups of
282 patients.
- 283 ● Continuous variables are expressed as the median and interquartile range
284 (IQR) and are analyzed using a Mann -Whitney U test if not normally
285 distributed, or are expressed as mean \pm standard deviation (SD) and analyzed
286 using Student's t-test if normally distributed. This mainly involves the
287 baseline data of the two groups of patients.
- 288 ● The comparison of the AL rate in two arms is performed using a chi-square
289 test and is present as relative risk (RR) with a 95% confidence interval (CI).
- 290 ● Subgroup analysis is not considered at this stage, post hoc subgroup analysis
291 will be planning to perform when suitable.
- 292 ● Univariate and multivariate logistic regression analysis can be performed to
293 identify the factors which would facilitate the surgeon's decision of DS
294 construction or the factors of high risk of AL.

- 295 ● Missing values handling: This study does not fill in missing values

296 **13 Research Ethics Approval**

297 **13.1 Ethical Committees Approval**

298 This protocol and the template informed consent forms will be reviewed and
299 approved by the sponsor and the applicable *ethical committees* concerning scientific
300 content and compliance with applicable research and human subjects regulations.

301 The protocol, site-specific consent forms, participant education, and recruitment
302 materials, and other requested documents - and any subsequent modifications - also
303 will be reviewed and approved by the ethical review bodies.

304 **13.2 Informed Consent**

305 Trained residents will introduce the trial to patients. Patients will also receive
306 information sheets. Research residents will discuss the trial with patients in light of
307 the information provided in the information sheets. Patients will then be able to have
308 an informed discussion with the participating consultant. Research residents will
309 obtain written consent from patients willing to participate in the trial.

310 **13.3 Participant confidentiality**

311 All study-related information will be stored securely at the study site. All
312 participant information will be stored in locked file cabinets in areas with limited
313 access. All laboratory specimens, reports, data collection, process, and administrative
314 forms will be identified by a coded ID [identification] number only to maintain
315 participant confidentiality. All records that contain names or other personal identifiers,
316 such as locator forms and informed consent forms, will be stored separately from
317 study records identified by code number. All local databases will be secured with
318 password-protected access systems. Forms, lists, logbooks, appointment books, and
319 any other listings that link participant ID numbers to other identifying information

320 will be stored in a separate, locked file in an area with limited access. Participants’
 321 study information will not be released outside of the study without the written
 322 permission of the participant.

323 **13.4 Protocol Amendments**

324 After this protocol has been approved by the *ethical committees*, if there are
 325 major changes during the implementation process, the contact investigator will draft
 326 an instruction about the amendments and sign it, and report to the *ethical committees*
 327 for approval before implementation. The *Quality Control Committee* will discuss
 328 with methodologists and sign together. Administrative changes to the protocol are
 329 minor corrections and/or clarifications that do not affect the way the study is to be
 330 conducted. These administrative changes will be agreed upon by the *Quality Control*
 331 *Committee* and will be documented in a memorandum.

332 Revision Chronology:

Date	Version	Overview of the Amendment
2016-Feb-20	version 1.0	Original
2016-Dec-26	version 2.0	Seven additional secondary sponsors are mentioned on page 3

333 **14 Committee**

334 Before the start of the trial, organize project team members to study this clinical
 335 research plan to fully understand and master the requirements and content of this
 336 research.

337 **14.1 Lead Investigators**

338 In each participating center, a lead investigator will be identified, to be
 339 responsible for the identification, recruitment, data collection, and completion of
 340 CRFs, along with follow-up of study patients and adherence to study protocol and

341 investigators brochure. Lead investigators will be quality control committee members.

342 The *lead investigators* check every 6 months, supervise the completion of the
343 CRF form, and conduct a review and signature. All items should have a
344 corresponding objective basis, be prepared for review and use, and should not be
345 fabricated. The original data related to this experiment include: 1) Medical records:
346 case registration form, case registration confirmation form, informed consent, patient
347 background investigation, symptoms and signs, treatment and treatment content;2)
348 Inspection report (pathological examination, imaging diagnosis result; 3) Laboratory
349 test data (blood biochemical test, etc.). The investigator must save the relevant data of
350 the clinical trial for five years after the end of the clinical trial.

351 **14.2 Data Manager**

352 Be responsible for data collection and verification. He or She will check the
353 completeness and accuracy of the CRF and make necessary modifications or
354 additions.

355 **14.3 Quality control committee (QCC)**

356 It consists of lead investigators and the data manager. They are responsible for
357 agreement of final protocol; reviewing the progress of the study and if necessary
358 agreeing to changes of the protocol and/or investigator brochure to facilitate the
359 smooth running of the study; study planning; responsible for trial master file and
360 randomization.

361 **15 Adverse Events**

362 ICPs were the adverse event reported by previous studies. In this study, the
363 height of most anastomoses is expected to be less than 6cm. Theoretically, the
364 possibility of perforation is small, but we still need to be alert. The investigator will
365 be trained to voluntarily report from time to time when an adverse event occurs to the
366 subject. In addition, the investigators should check the occurrence of the adverse

367 events through consultation and interviews at regular visits during the study period.
368 The situation of patients with adverse events should be discussed and reported to the
369 *Quality Control Committee* to analyze the reasons. After discussion, if the actual
370 existence is directly related to the research design, the plan should be modified.

371 **15.1 Classification of adverse events**

372 For the evaluation of adverse events in this research, please refer to the Chinese
373 version of CTCAE v4.02 and [Accordion Severity Grading System]. Grade refers to
374 the severity of the adverse event. CTCAE provides a specific clinical description of
375 the severity of each adverse event (grades 1 to 5) according to the following general
376 guidelines:

377 Grade 1: Mild; asymptomatic or mild; only clinically or diagnostically seen; no
378 treatment is required.

379 Grade 2: Moderate; requires minor, topical, or non-invasive treatment;
380 age-appropriate instrumental limitation of activities of daily living*.

381 Grade 3: Severe or medically significant but not immediately life-threatening;
382 leading to hospitalization or prolonging the hospital stay; disabled; personal activities
383 of daily living are restricted**.

384 Level 4: Life-threatening; urgent treatment is required.

385 Level 5: Death related to it.

386 Activities of Daily Living (ADL)

387 *Instrumental activities of daily living refer to cooking, buying clothes, using the
388 phone, managing finances, etc.

389 **Personal activities of daily living refer to bathing, dressing, and undressing,
390 eating, washing, taking medicine, etc., who are not bedridden.

391 **15.2 Records of Adverse Events**

392 All adverse events must be recorded on the adverse event report form, attached
393 to the case report form. For each adverse event, the lead investigator must evaluate

394 and record its severity, duration, relationship with surgery or TDTs, measures, and the
395 outcome of the event.

396 **15.3 Report of Adverse Events**

397 If any "serious adverse event" or "unexpected adverse event" occurs, the
398 researcher must report the adverse event to the *Quality Control Committee* within 24
399 hours after learning of the adverse event, the *Quality Control Committee* responsible
400 for handling serious adverse events, regardless of whether the event is related to
401 treatment. The results of all reported serious adverse events (death, etc.) will be
402 followed up and recorded. Reporting to relevant authorities by national regulations
403 will be done by the responsible unit; in any case, all participants must comply with
404 local legal regulations and requirements.

405

406 **Appendix 1**

407 **Current Definitions and ASA-Approved Examples**

ASA Classification	PS	Definition	Adult Examples, Including, but not Limited to:	Pediatric Examples, Including but not Limited to:	Obstetric Examples, Including but not Limited to:
ASA I		A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use	Healthy (no acute or chronic disease), normal BMI percentile for age	
ASA II		A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease	Asymptomatic congenital cardiac disease, well controlled dysrhythmias, asthma without exacerbation, well controlled epilepsy, non-insulin dependent diabetes mellitus, abnormal BMI percentile for age, mild/moderate OSA, oncologic state in remission, autism with mild limitations	Normal pregnancy*, well controlled gestational HTN, controlled preeclampsia without severe features, diet-controlled gestational DM.
ASA III		A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents.	Uncorrected stable congenital cardiac abnormality, asthma with exacerbation, poorly controlled epilepsy, insulin dependent diabetes mellitus, morbid obesity, malnutrition, severe OSA, oncologic state, renal failure, muscular dystrophy, cystic fibrosis, history of organ transplantation, brain/spinal cord malformation, symptomatic hydrocephalus, premature infant PCA <60 weeks, autism with severe limitations, metabolic disease, difficult airway, long term parenteral nutrition. Full term infants <6 weeks of age.	Preeclampsia with severe features, gestational DM with complications or high insulin requirements, a thrombophilic disease requiring anticoagulation.
ASA IV		A patient with severe systemic disease that is a constant threat to life	Recent (<3 months) MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis	Symptomatic congenital cardiac abnormality, congestive heart failure, active sequelae of prematurity, acute hypoxic-ischemic encephalopathy, shock, sepsis, disseminated intravascular coagulation, automatic implantable cardioverter-defibrillator, ventilator dependence, endocrinopathy, severe trauma, severe respiratory distress, advanced	Preeclampsia with severe features complicated by HELLP or other adverse event, peripartum cardiomyopathy with EF <40,

			oncologic state.	uncorrected/decompensated heart disease, acquired or congenital.
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction	Massive trauma, intracranial hemorrhage with mass effect, patient requiring ECMO, respiratory failure or arrest, malignant hypertension, decompensated congestive heart failure, hepatic encephalopathy, ischemic bowel or multiple organ/system dysfunction.	Uterine rupture.
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes			

408

409 * Although pregnancy is not a disease, the parturient's physiologic state is significantly altered from when the woman is not pregnant, hence the assignment of ASA 2 for a woman with uncomplicated pregnancy.

410 **The addition of "E" denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

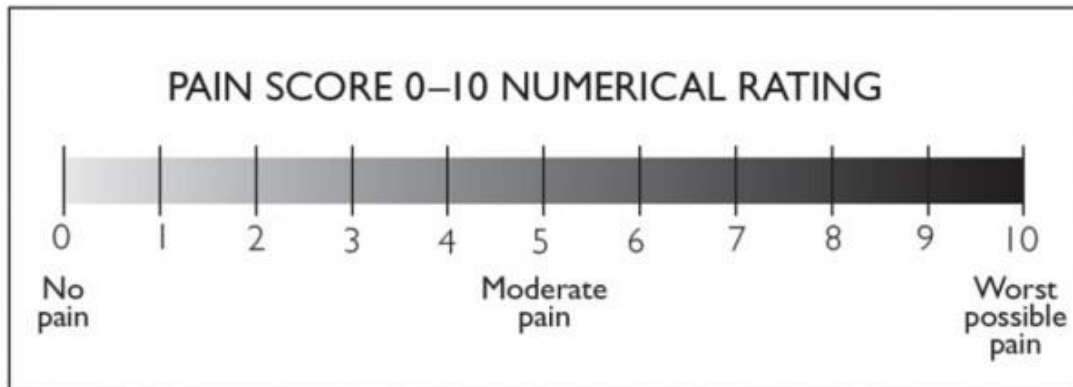
411 **Appendix 2**

412 **Pain Scales**

413 The (NPRS-11) is an 11-point scale for self-report of pain. It is the most commonly
 414 used unidimensional pain scale. The respondent selects a whole number (integers
 415 0–10) that best reflects the intensity (or other quality if requested of his/her pain. The
 416 anchors are 0 = no pain and 10 = extreme pain/worst possible pain (there are various
 417 wordings of the upper anchor). It is often categorized into: no pain = 0, mild pain =
 418 1-3, moderate pain = 4-6, severe pain = 7-10, but these categories do not necessarily
 419 reflect patient meanings, and are poor for any assessment of change. The categories
 420 might be used to set targets for intervention outcomes. The NPRS can be administered
 421 verbally (therefore also by telephone) or graphically for self-completion.

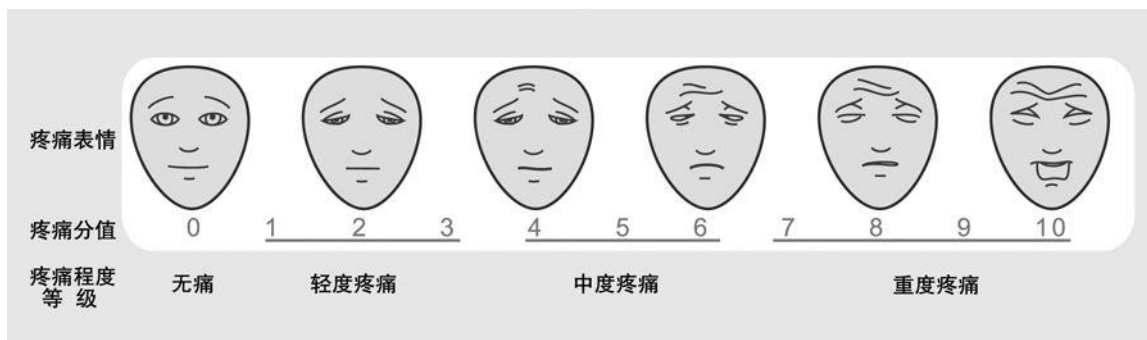
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425 Pain scales (visual analog scale method):



426

427

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