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## **Biomarker-guided antibiotic duration for hospitalized patients with suspected sepsis. The ADAPT-Sepsis Randomized Clinical Trial**

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1 **Biomarker-guided antibiotic duration for hospitalized patients with suspected sepsis: The ADAPT-**  
2 **Sepsis Randomized Clinical Trial**

3

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13

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47

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71 **KEY POINTS**

72 **Question:** Do critically ill adult patients hospitalized for suspected sepsis and treated with intravenous  
73 antibiotics based on procalcitonin (PCT) or C-reactive protein (CRP) protocols, have a safe reduction in  
74 treatment duration compared to standard care?

75 **Findings:** In this multi-center, randomized trial of 2,760 patients, the daily PCT-guided protocol reduced  
76 total antibiotic duration and had non-inferior all-cause mortality compared to standard care. No  
77 difference was found in total antibiotic duration between standard care and daily CRP-guided protocol,  
78 and CRP showed inconclusive results for all-cause mortality.

79 **Meaning:** In hospitalised adults, daily PCT-guided protocol reduces antibiotic duration safely  
80 compared to standard care, while daily CRP-guided protocol does not.

81

82 **ABSTRACT**

83 **IMPORTANCE:** For hospitalized critically ill adults with suspected sepsis, procalcitonin (PCT) and C-  
84 reactive protein (CRP) monitoring protocols can guide the duration of antibiotic therapy, but the  
85 evidence of the effect and safety of these protocols remains uncertain.

86 **OBJECTIVES:** To determine whether CRP or PCT safely results in a reduction in the duration of  
87 antibiotic therapy.

88 **DESIGN, SETTING, AND PARTICIPANTS:** A multi-center, intervention-concealed randomized controlled  
89 trial, involving 2, 760 adults ( $\geq 18$  years), in 41 UK NHS intensive care units, requiring critical care within  
90 24 hours of initiating intravenous antibiotics for suspected sepsis and likely to remain on antibiotics  
91 for at least 72 hours.

92 **INTERVENTION:** From January 2018 to June 2024, 918 patients were assigned to the daily PCT-guided  
93 protocol, 924 to the daily CRP-guided protocol and 918 assigned to standard care.

94 **MAIN OUTCOMES AND MEASURES:** The primary outcomes were total duration of antibiotics  
95 (effectiveness) and all-cause mortality (safety) to 28 days. Secondary outcomes included critical care  
96 unit data and hospital stay data. Ninety-day all-cause mortality was also collected.

97 **RESULTS:** Among the randomized patients (mean age 60.2 [SD, 15.4] years; 60% males), there was a  
98 significant reduction in antibiotic duration from randomization to 28 days for those on the daily PCT-  
99 guided protocol compared to standard care (mean duration 10.7 [7.6] days for standard care and 9.8  
100 [7.2] days for PCT; mean difference [MD], 0.88 days; 95% Confidence Interval [CI], 0.19 to 1.58,  
101  $P=0.01$ ). For all-cause mortality up to 28 days, the daily PCT-guided protocol was non-inferior to  
102 standard care, where the non-inferiority margin was set at 5.4% (19.4% [170 of 878] on standard  
103 care, 20.9% [184 of 879] on PCT; absolute difference, 1.5 [95% CI, -2.18 to 5.32],  $P=0.02$ ). No  
104 difference was found in antibiotic duration for standard care versus daily CRP-guided protocol (mean  
105 duration 10.6 [7.7] days for CRP; MD 0.09; 95% CI, -0.60 to 0.79,  $P=0.79$ ). For all-cause mortality, the  
106 daily CRP-guided protocol was inconclusive compared to standard care (21.1% [184/874] on CRP;  
107 absolute difference, 1.7; [95% CI, -2.07 to 5.45],  $P=0.03$ ).

108 **CONCLUSIONS AND RELEVANCE:** PCT reduces antibiotic duration safely compared to standard care,  
109 while CRP does not. All-cause mortality for CRP was inconclusive.

110

111 **TRIAL REGISTRATION:** ISRCTN47473244

112 **INTRODUCTION**

113 Delivering timely, appropriate antimicrobial therapy is an international care standard to help provide  
114 the best outcomes for patients with sepsis.<sup>1</sup> The optimum duration of antibiotic treatment for sepsis  
115 is uncertain, with decisions to stop therapy guided by clinical progress and serum inflammatory  
116 biomarkers such as serum C-reactive protein (CRP) and procalcitonin (PCT).<sup>2</sup> Optimizing antibiotics  
117 duration helps reduce overtreatment , limits unwanted effects and preserves antibiotic effectiveness  
118 by minimizing resistance.<sup>3</sup> Biomarker-guided discontinuation, especially with PCT, has shown safe  
119 reductions in antibiotic duration.<sup>4</sup> However, the body of clinical trial evidence has been judged to be  
120 low quality<sup>1,5,6</sup> leading to a weak recommendation for routine sepsis care adoption of PCT-guided  
121 antibiotic discontinuation<sup>1</sup> and with no consensus guidance for CRP.<sup>1</sup>

122

123 A three-group multi-center, intervention-concealed randomized controlled trial was performed to  
124 determine whether treatment protocols for monitoring CRP or PCT safely resulted in a reduction in  
125 the duration of antibiotic therapy for critically ill hospitalized adults with suspected sepsis. The primary  
126 aim was to assess reduction in antibiotic duration (clinical effectiveness) while maintaining treatment  
127 safety (non-inferiority) as measured by 28-day all-cause mortality.

128

129 **METHODS**

130 **Trial Design and Oversight**

131 The ADAPT-Sepsis trial was an investigator initiated, randomized clinical trial conducted in 41 National  
132 Health Service (NHS) intensive care units in UK. The trial protocol and amendments (Supplement 1)  
133 were approved by the South-Central Oxford and Scotland Research Ethics Committees (17/SC/0434) and  
134 the protocol has been published previously.<sup>7</sup> The statistical analysis plan was approved by the independent  
135 Data Monitoring and Ethics Committee (Supplement 2). The independent Trial Steering and Data  
136 Monitoring Committees oversaw the operational processes and statistical rigor of this study. All

137 patients or their legal representatives provided signed informed consent. Enrollment was paused during  
138 the UK lockdown (March-August 2020) due to the SARS-CoV-2 pandemic.

139

#### 140 **Patient Population**

141 Eligible patients were hospitalized adults ( $\geq 18$  years old) treated in ICU (i.e. admission to a Critical  
142 Care/Intensive Care Unit), within 24 hours of initiating intravenous antibiotics for suspected sepsis and  
143 likely to remain on antibiotics for at least 72 hours. ‘Suspected sepsis’ was defined as ‘acute organ  
144 dysfunction associated with suspected infection’.<sup>8</sup> We did not mandate a definition for ‘acute organ  
145 dysfunction’ and patient information underpinning local clinical decisions were captured which  
146 included the Sequential Organ Failure Assessment (SOFA) score. A 24-hour recruitment window was  
147 required to determine baseline biomarkers for treatment guidance.<sup>2,9</sup> Patients were ineligible if they:  
148 (i) required prolonged antibiotic therapy (i.e.  $>21$  days); (ii) were severely immunocompromised from  
149 a cause other than sepsis (e.g. neutropenia less than 500 neutrophils/ $\mu\text{l}$ ); (iii) were expected to receive  
150 an IL-6 receptor inhibitors (e.g. tocilizumab or sarilumab) during their acute hospital admission; (iv)  
151 had sepsis treatments likely to stop within 24 hours because of futility; (v) declined consent; or (vi)  
152 were previously enrolled into this trial. Full inclusion and exclusion criteria are provided in Supplement  
153 3.

154

#### 155 **Randomization**

156 Patients were randomly assigned to standard care, PCT, or CRP groups in a 1:1:1 ratio using a computer-  
157 generated sequence (minimization method). Stratification factors were sepsis severity (shock or not)<sup>8</sup>,  
158 recruitment site, and recent surgery (within 72 hours). Allocation was concealed by a centralized 24-  
159 hour web-based system (located at Warwick Clinical Trials Unit), with randomization conducted by site  
160 research staff.



161

162 **Interventions**

163 Blood was drawn daily in trial patients from randomization until antibiotic discontinuation for the  
164 sepsis episode or hospital discharge. Clinicians responsible for managing patients received daily  
165 standardized written advice from the local research team on either standard care or on biomarker-  
166 guided antibiotic discontinuation. Advice was based on daily serum testing of either (a) PCT or (b) CRP  
167 or (c) 'no test' (standard care group). Patients received standard NHS care for sepsis and antibiotic  
168 stewardship which followed national service standards.<sup>10,11</sup> The intervention phase consisted of daily  
169 research blood sampling and local NHS quality assured laboratory biomarker testing. Reporting of  
170 laboratory results was via a trial-specific centralized web-based system, leading to automated  
171 production of written treatment advice for the local clinical research team. The intervention phase  
172 continued until antibiotics were discontinued, or the patient died or withdrew. Follow-up phase began  
173 when daily blood collection stopped. Research blood sampling did not resume if antibiotics were re-  
174 introduced within 28 days. If a patient was discharged from hospital on a course of antibiotics for the  
175 initial sepsis episode, the trial intervention ceased at the time of discharge. Phlebotomy and samples  
176 followed local standard care practice. The antibiotic discontinuation protocols and advice are  
177 described in eTable 1.

178 *Procalcitonin and C-reactive protein*

179 For those assigned to the intervention arms, blood collection and serum biomarker laboratory testing  
180 (PCT or CRP) commenced within the first 24 hours of initiating intravenous antibiotics for sepsis. Based  
181 on evidence from national pre-trial surveys of standard critical care in the UK, described in our trial  
182 protocol<sup>7</sup>, CRP, but not PCT, could be measured outside of the study protocol if deemed necessary by  
183 the clinician, but not used for protocolized antibiotic duration guidance. Daily patient reviews by the  
184 treating clinical team included documented decisions on antibiotic treatment guided by standard  
185 clinical assessment and review of microbiological culture results. Daily clinical reviews of patients also

186 allowed incorporation of the intervention protocols for daily assessment of antibiotic discontinuation  
187 described in eTable 1.

#### 188 *Standard care group*

189 For the standard care group, daily research blood samples were collected and transported to the  
190 laboratory. No CRP or PCT biomarker testing was performed but there was standardized computer-  
191 generated treatment advice for the local clinical research team (eTable 1), time-delayed by the  
192 centralized web-based system to assure maintenance of group concealment.

193 Routinely available laboratory data, such as white blood cell counts remained part of standard care for  
194 each group.<sup>10</sup>

#### 195 *Intervention concealment*

196 Group assignment was available to the local laboratory service only through the trial-specific web-  
197 based system, concealed from patients, their relatives, clinical teams and research staff. Research  
198 blood samples were allocated a unique research study number and were transported to the local  
199 hospital laboratory, until the antibiotics were discontinued. The research number did not reveal the  
200 identity of the patient and biomarker measurement results were not recorded in the patient's care  
201 record form or shared with the clinical team.

#### 202 **Procedure**

203 The schedule of delivery and data collection are detailed in Supplement 3. Data were collected daily  
204 using a local paper clinical record form and a web-based data capture system. Ninety- day all-cause  
205 mortality status was collected from sites and validated against available linked NHS England mortality  
206 data. For patients discharged to another hospital or the community before day 28, the local site  
207 research team assured data completeness.<sup>7</sup> Disease severity was collected using the ICNARC (Intensive  
208 Care National Audit and Research Centre) Case Mix Program (England, Northern Ireland and Wales)  
209 and Scottish equivalent (Scottish Intensive Care Society Audit Group).

210

211 **Outcomes**

212 *Primary outcomes*

213 The primary clinical effectiveness outcome was the total antibiotic duration (days), from randomization  
214 to 28 days. The primary safety outcome was the 28-day all-cause mortality.

215 *Secondary outcomes*

216 Several secondary outcomes were evaluated and these included: (i) antibiotic duration for initial sepsis  
217 period; (ii) total antibiotic dose (Defined Daily Dose); (iii) antibiotic dose for initial sepsis period; (iv)  
218 unscheduled escalation care/re-admission; (v) infection relapse/recurrence requiring further antibiotic  
219 treatment; (vi) super-infection defined as new infection at a different anatomical site; (vii) suspected  
220 antibiotic adverse reactions; (viii) time to 'fit for hospital discharge'; (ix) critical care unit length of stay;  
221 (x) hospital length of stay; (xi) all-cause mortality at 90 days. Adverse events (see Supplement 3) and  
222 trial process data were also obtained. This manuscript reports clinical effectiveness outcomes; health  
223 economics and process evaluation will be detailed in subsequent publications.

224

225 **Statistical Analysis**

226 This study, using a sample size of 2,760 patients, aimed to detect a 1-day reduction in total antibiotic  
227 duration (standard care mean: 7 days, standard deviation (SD) 6 days, 90% power, 5% significance level,  
228 5% withdrawal rate). The primary outcome focused on effectiveness, but safety was equally critical.  
229 For this reason this study aimed to show non-inferiority with a 5.4% safety margin (1-sided significance  
230 level: 2.5%<sup>12,13</sup>) assuming 28-day all-cause mortality of 15% in both arms (Supplement 1 details the  
231 justification of the choice in these parameter estimates). Analyses followed an 'intention-to-treat (ITT)  
232 approach.<sup>14</sup> Each intervention arm was compared with standard care and no adjustments were made

233 for multiple comparisons for the primary effectiveness outcome. All statistical analyses were  
234 conducted in Stata SE version 18.0.<sup>15</sup>

235

236 The statistical analysis plan is provided in Supplement 2. For the primary outcome, linear mixed effect  
237 regression models were fitted, adjusted for age, sex and stratification factors (where recruiting site was  
238 a random effect). Several sensitivity analyses were carried out: (a) a per protocol analysis, where major  
239 protocol violations were excluded from the sample; (b) a complier average causal effect (CACE)  
240 analysis<sup>16</sup> adjusted for patients who withdrew from the intervention phase but remained in the study  
241 for follow-up ; (c) imputation analysis which accommodated for missing antibiotic treatment duration  
242 (Supplement 2); and (d) the Pocock's win ratio test<sup>17</sup> used to assess the competing risks of death, with  
243 death as the first event and duration of antibiotics as the second event, in the hierarchy of outcomes.  
244 Total duration of antibiotic therapy was displayed using Kaplan-Meier curves and Bayesian  
245 probabilities were also reported using an uninformative prior distribution.

246

247 The primary safety outcome was assessed using a mixed effect logistic regression model. From this  
248 model, 95% CIs in proportions between the treatments were obtained. For the adjusted models, the  
249 standard error was obtained using bootstrapping methods.<sup>18,19</sup> As per guidance for non-inferiority  
250 trials<sup>20</sup>, inferiority was declared if  $P < 0.025$  and the lower bound of the 95% confidence interval  
251 exceeded the margin.<sup>12,13</sup> A post-hoc per protocol analysis was also conducted (where per protocol  
252 was defined as for the primary analysis).

253

254 Secondary outcomes were analyzed using mixed effects linear and logistic regression models, with  
255 additional analyses for SARS-CoV-2 impact and serious adverse events. For the categorical outcomes,  
256 where absolute and relative differences were reported, bootstrapping methods<sup>18,19</sup> were used to

257 obtain the standard errors for the confidence intervals. Prespecified sub-group analyses included: (i)  
258 community-acquired pneumonia (yes/no) (ii) hospital-acquired pneumonia (yes/no) (iii) urinary tract  
259 infection (yes/no) (iv) intra-abdominal infection (yes/no) (v) positive blood culture infection (yes/no)  
260 (vi) community-acquired and hospital acquired infections (vii) SARS-CoV-2 (yes/no); (viii) sepsis and  
261 septic shock (ix) ward and critical care unit (intervention stopped); (x) surgery and non-surgery  
262 previous 72 hours. These sub-groups were carried out using the duration of antibiotics (i) up to 28 days  
263 and (ii) the initial sepsis period (post-hoc analysis). Sub-group analyses were conducted using linear  
264 regression models with interaction terms and 99% CIs.

265

## 266 **RESULTS**

### 267 **Patient Characteristics**

268 From January 2018 to June 2024 a total of 16,109 patients were screened for eligibility for the trial in  
269 41 UK critical care units. Of these, 2,761 (17.1%) patients were enrolled into the study; one patient  
270 was removed due to an error in randomization. Of the remaining, 918 (33.3%) were assigned to  
271 standard care, 918 (33.3%) to the daily PCT-guided protocol and 924 (33.4%) to the daily CRP-guided  
272 protocol. 127 (4.6%) patients completely withdrew from the study prior to 28 days, and these were  
273 similar across the interventions (Figure 1 and eTables 9 & 12). In total, 364 (13.2%) patients withdrew  
274 from the intervention phase but remained in the study for follow-up (eTable 12).

275

276 Patients in the three groups had similar demographic and baseline characteristics (Table 1). The overall  
277 mean age was 60.2 [SD, 15.4] years, with 1,657 (60.3%) males. The mean APACHE (Acute Physiology  
278 and Chronic Health Evaluation) II score was 17.3 [SD, 6.5] and virtually all the patients would have met  
279 the Sepsis-3 criteria for the diagnosis of sepsis (SOFA score 7 [IQR 5-9])<sup>8</sup>. There were 1,397 (50.8%)  
280 sepsis and 1,352 (49.2%) septic shock patients.

281

282 **Implementation of intervention protocols**

283 Site monitoring revealed very low use of open PCT measurements (eTable 27) and there was no  
284 evidence of open protocolized daily CRP-guided antibiotic duration decisions in this intervention  
285 concealed trial. The daily PCT and CRP protocols were implemented into routine sepsis care, with  
286 concealed non-mandated advice on standard care and antibiotic discontinuation produced as  
287 summarized in Figure 3 (with additional data in eTable 29 & 30 and eFigures 6). No stop or strong stop  
288 advice was produced for the standard care group. Stop advice production was similar for both  
289 biomarker intervention groups. However, strong stop advice was more common and produced earlier  
290 for the PCT-protocol compared with the CRP-protocol.

291

292 **Primary And Secondary Efficacy Outcomes**

293 Primary outcome data were available on 898 (97.8%) patients for the daily PCT-guided protocol, 892  
294 (96.5%) for the daily CRP-guided protocol, and 905 (98.6%) for standard care. Compared with standard  
295 care, there was a significant reduction in the total duration of antibiotic treatment from randomization  
296 to 28 days for the daily PCT-guided protocol (mean total duration was 10.7 (7.6) days for standard care  
297 and 9.8 (7.2) days for daily PCT-guided protocol; MD, 0.88 days; 95% CI, 0.19 to 1.58, P=0.01). No  
298 difference was seen between standard care and daily CRP-guided protocol (mean total duration was  
299 10.6 (7.7) days for daily CRP-guided protocol; MD, 0.09 days; 95% CI, -0.60 to 0.79, P=0.79 (see Table  
300 2 and Figure 2(a)). Results were similar in the adjusted analyses (eTable 18) and for all sensitivity  
301 analyses, including accounting for those who died within 28 days (Table 2). The Bayesian analyses  
302 illustrated that the probability of a mean difference in favor of the daily PCT-guided protocol of > 0.5  
303 days was 0.85 and for daily CRP-guided protocol being >0.5 days was 0.13 respectively (see eTables 19  
304 and 20 for further estimates).

305

306 There was also a significant reduction in the duration of antibiotics for the initial sepsis period, with  
307 the difference favoring the biomarker protocols as opposed to standard care (daily PCT-guided  
308 protocol: MD, 1.13 days; 95% CI, 0.58 to 1.68 and daily CRP-guided protocol: MD, 0.71 days; 95% CI,  
309 0.16 to 1.26). For the other secondary outcomes, there was no statistical evidence in intervention  
310 effects when compared with standard care. Regarding additional analyses, the summary statistics for  
311 patients recruited pre-SARS-CoV-2 and post-SARS-CoV-2 are presented in eTable 22 and eTable 23. It is  
312 worth noting that there were only 19 trial patients included with a SARS-CoV-2 virus infection during  
313 the study.

314

### 315 **Safety Outcomes**

316 The 28-day all-cause mortality for the daily PCT-guided protocol was non-inferior to standard care  
317 (mortality: 19.4% (170 of 878) for standard care, 20.9% (184 of 879) for PCT; absolute difference, 1.57;  
318 95% CI, -2.18 to 5.32 P=0.02; comparisons are made with P=0.025). However, the treatment difference  
319 for the daily CRP-guided protocol was inconclusive with regards to non-inferiority (mortality: 19.4%  
320 (170 of 878) for standard care, 21.1% (184 of 874) for CRP; absolute difference, 1.69; 95% CI, -2.07 to  
321 5.45; P=0.03) (Table 2 & eFigure 1). Results were supported by the per protocol (Table 2) and the  
322 adjusted analyses (eTable 18 & eFigure 1). There were nine serious adverse events equally distributed  
323 across the treatment and standard care arms (eTables 25 & 26). There were no differences in all-cause  
324 mortality at 90-days when comparing each intervention group with control (Table 2).

325

### 326 **Pre-Specified Sub-Group Analyses**

327 The effect of the two protocols on the duration of antibiotic treatment was not significantly modified  
328 by any of the baseline characteristics defining the prespecified subgroups (eFigures 2 and 3) and for

329 the initial sepsis period (eFigures 4 and 5). Similar results were produced for unadjusted and adjusted  
330 sub-group analyses.

331

## 332 **DISCUSSION**

333 In hospitalized critically ill adult patients with suspected sepsis, a daily PCT biomarker-guided antibiotic  
334 discontinuation protocol, but not CRP-guided, resulted in safe reductions in total antibiotic duration  
335 when compared with standard care. Non-inferiority for 28-day all-cause mortality, our primary safety  
336 outcome, was met for the daily PCT-guided protocol.

337

338 Secondary outcomes suggest that antibiotic duration for the initial sepsis period was significantly  
339 reduced by both daily PCT-guided and daily CRP-guided protocols, with greater reductions for PCT.  
340 According to our primary outcomes, these initial antibiotic duration reductions are not present by the  
341 end of the trial period (28-days from randomization) for the daily CRP-guided protocol group, but there  
342 remain significant total antibiotic duration reductions for the daily PCT-guided protocol group, when  
343 compared with standard care. Supported by data on the implementation of our protocols, it is likely  
344 that these differential clinical effectiveness findings for daily PCT-guided and daily CRP-guided  
345 protocols are explained by the differences in the utility of these biomarkers to track inflammation  
346 caused by bacterial infection in the setting of critical illness, where PCT concentrations are known to  
347 increase earlier and normalize more rapidly than CRP in response to treatment.<sup>21</sup>

348

349 There are several important strengths to our study. This multi-center trial was designed to inform  
350 international guidance<sup>1</sup> for both daily PCT and CRP-guided antibiotic discontinuation protocols for  
351 sepsis. We successfully delivered an intervention concealment strategy to minimize risk of bias,  
352 rigorously testing biomarker-guided protocols within standard sepsis care and antibiotic stewardship.



353 The vast majority of enrolled study patients would have met the Sepsis-3 criteria for the diagnosis of  
354 sepsis<sup>8</sup>. This trial addressed two important areas: 1. the use of total antibiotic duration from  
355 randomization to 28-days to embrace the possibility that biomarker-guided reductions in initial  
356 antibiotic duration for sepsis may result in later antibiotic use; and 2. the use of primary outcomes that  
357 embraced total antibiotic duration (effectiveness) and all-cause mortality (safety). The design of the  
358 biomarker protocols was informed by the best available evidence published in advance of the trial.<sup>7</sup>

359

360 The daily PCT-guided protocol's safe reductions in antibiotic duration, though seemingly modest, are  
361 equivalent to the current synthesized evidence for PCT-guided duration effects from open-label clinical  
362 trials using PCT.<sup>4</sup> The duration reduction is of the order of 10% in antibiotic use for sepsis, which could  
363 provide significant cost and labor savings, and might also reduce the development of antimicrobial  
364 resistance.

365

366 Our trial protocol and concealed interventions provided high-quality evidence required to confidently  
367 assess biomarker-guided antibiotic protocols in standard sepsis care. However, there are a number of  
368 potential limitations to our study design. 1. It is possible that our concealment strategy could have led  
369 clinicians to stop antibiotics later in the standard care group while awaiting the return of stop advice.  
370 Reassuringly, our measured standard care antibiotic duration for the initial sepsis period was less than  
371 the synthesized standard care mean reported from current open label biomarker-guided trials<sup>4</sup>. 2.  
372 Patient-level randomization in this study could have led to contamination as treatment protocols and  
373 standard care were carried out in a shared environment. The complete elimination of these effects  
374 would be challenging and not pragmatic in this care setting. A cluster-randomized trial design was  
375 considered initially, which resulted in a much larger sample size and other care process challenges,  
376 making the study infeasible and therefore this was not adopted. It is anticipated that, in this trial, a  
377 strategy to conceal group assignment and daily biomarker results, and the use of remote centralized

378 hospital laboratories at each site, has gone to some way to eliminate the bias created by a potential  
379 for contamination. 3. It remains unclear whether allowing clinicians to monitor CRP as part of standard  
380 care, outside of the trial concealed daily biomarker protocols, impacted trial results. Any effects would  
381 have been mitigated by the intervention concealed nature of our trial and across all three randomized  
382 groups. Further analysis of this potential limitation is planned as part of a subsequent trial process  
383 evaluation. 4. For the pairwise comparisons, where treatment arms were compared to standard care,  
384 no statistical adjustments were applied to the results for multiple comparisons. Had we applied the  
385 correction retrospectively, where each pairwise comparison was based on a p-value of 0.025 (using a  
386 Bonferroni correction, for two tests), the conclusions of the study would not have altered.

387

388

389

390 The ADAPT-Sepsis trial strengthens substantially international recommendations for the routine use of  
391 protocolized daily PCT-guided antibiotic discontinuation in critically ill adults with sepsis.<sup>1</sup> and we found  
392 no evidence to recommend protocolized daily CRP-guided antibiotic discontinuation. We emphasize  
393 that critically ill patients recruited to this trial had already commenced antibiotics for sepsis, so this  
394 study does not provide evidence for biomarker use in initiating antibiotic therapy. In addition, this  
395 clinical research evidence was generated within a high-income country, therefore it is unclear if this  
396 evidence is generalizable to low-resource settings.

397

## 398 **CONCLUSION**

399 In critically ill hospitalized adults with sepsis, there is a significant safe reduction in the total antibiotic  
400 days when a daily PCT-guided protocol is administered compared with standard care. A daily CRP-  
401 guided protocol does not reduce the total duration of antibiotics.

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412

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417 Drs Lall and Hossain have full access to all the data in the study and take responsibility for the integrity  
418 of the data and the accuracy of the data analysis.

419 *Concept and design:* Dark, Lall, Perkins, McAuley, Carlson, Clayton, Felton, Gordon, Lone, McCullagh,  
420 McMullan, Singer, Stevenson, Walsh, Wilson.

421 *Acquisition, analysis or interpretation of data:* Dark, Hossain, Lall, Perkins, McAuley, Carlson, Clayton,  
422 Felton, Gordon, Lone, McCullagh, McMullan, Singer, Stevenson, Walsh, Wilson.

423 *Drafting of the manuscript:* Dark, Hossain, Lall

424 *Critical review of the manuscript for important intellectual content:* Dark, Hossain, Lall, Perkins,  
425 McAuley, Brealey, Carlson, Clayton, Felton, Ghuman, Gordon, Hellyer, Lone, Manazar, McCullagh,  
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429 McMullan, Singer, Stevenson, Walsh, Wilson.

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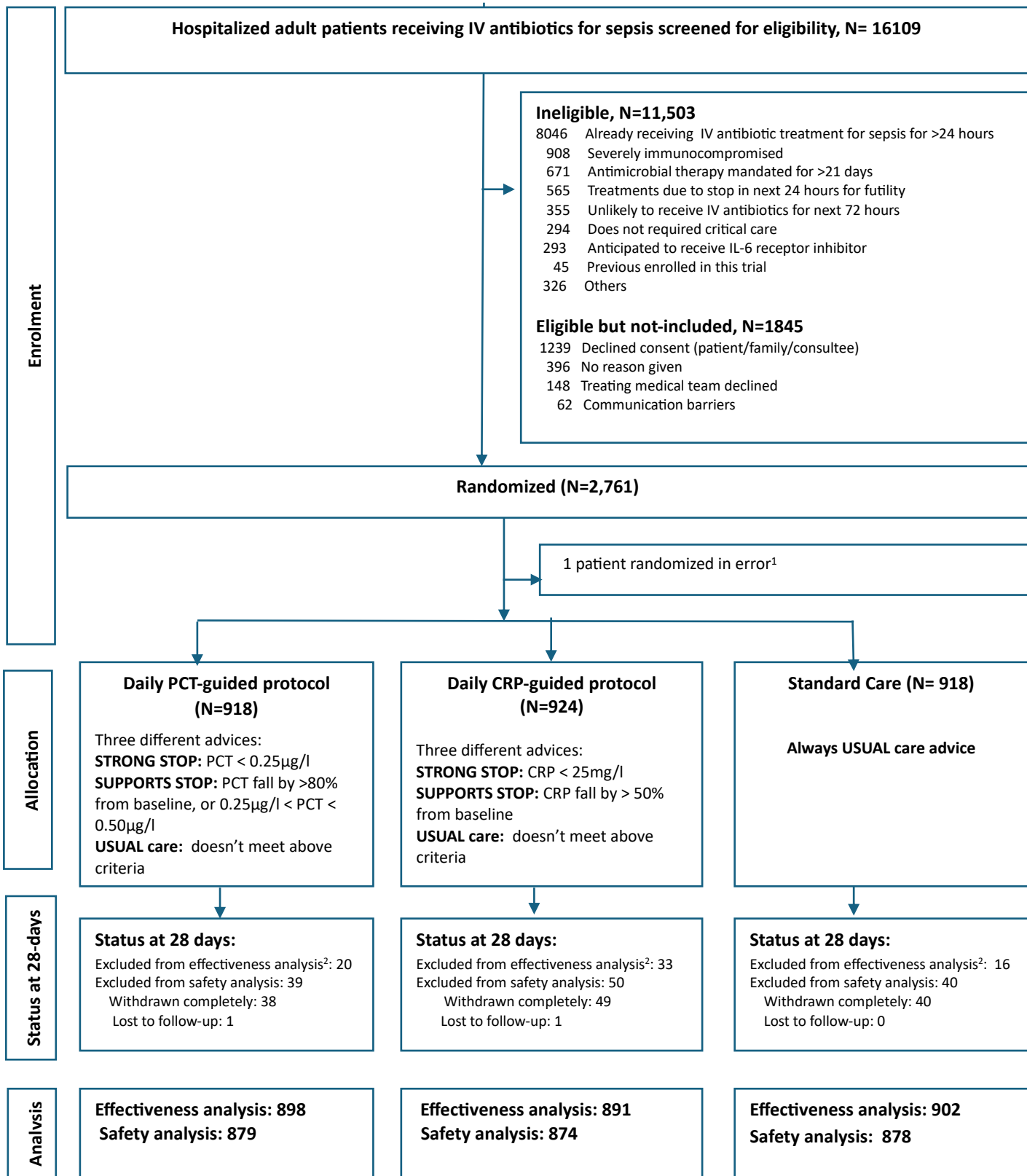
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486

487 **Figure 1: Recruitment, randomization and follow-up in the ADAPT-Sepsis trial.**



488 <sup>1</sup>No data was collected for this patient. <sup>2</sup>11 patients withdrew completely from the trial by day 28 and requested removal of  
 489 their data. In addition, data were missing and unobtainable from 54 patients.



490 **Table 1: Demographics and clinical characteristics of the randomized patients<sup>1</sup>**

<b>Characteristics</b>	<b>Daily PCT-guided protocol (N=918)</b>	<b>Daily CRP-guided protocol (N=924)</b>	<b>Standard Care (N=918)</b>
Age, mean (SD) [N], year	60.6 (15.2) [914]	60.3 (15.6) [918]	59.8 (15.3) [915]
<b>Sex - n (%)</b>			
N	915	918	915
Female	354 (38.7)	366 (39.9)	371 (40.6)
Male	561 (61.3)	552 (60.1)	544 (59.5)
<b>Critical Admission care category - n (%)</b>			
N	908	912	913
Medical	563 (62.0)	558 (61.2)	552 (60.5)
Emergency surgical	245 (27.0)	251 (27.5)	253 (27.7)
Elective surgical	73 (8.0)	73 (8.0)	73 (8.0)
Other	27 (3.0)	30 (3.3)	35 (3.8)
<b>Origin - n (%)</b>			
N	907	911	913
Emergency department	542 (59.8)	525 (57.6)	556 (60.9)
Surgical ward	106 (11.7)	110 (12.1)	97 (10.6)
Medical ward	99 (10.9)	92 (10.1)	83 (9.1)
Operating department	66 (7.3)	78 (8.6)	77 (8.4)
Emergency Assessment Unit (EAU) <sup>2</sup>	21 (2.3)	39 (4.3)	35 (3.8)
Another critical care unit	30 (3.3)	27 (3.0)	28 (3.1)
Other <sup>3</sup>	43 (4.7)	40 (4.4)	37 (4.1)
<b>Place of acquired infection causing sepsis - n (%)</b>			
N	904	904	907
Community acquired	612 (67.7)	616 (68.1)	618 (68.1)

<b>Characteristics</b>	<b>Daily PCT-guided protocol (N=918)</b>	<b>Daily CRP-guided protocol (N=924)</b>	<b>Standard Care (N=918)</b>
Hospital acquired	292 (32.3)	288 (31.9)	289 (31.9)
<b>Presumed site of infection causing sepsis - n (%)<sup>4</sup></b>			
Respiratory tract	437 (48.3)	447 (49.5)	451 (49.6)
Intra-abdominal	230 (25.5)	208 (23.0)	198 (21.8)
Urinary tract	124 (13.7)	109 (12.1)	118 (13.0)
Unknown focus	98 (10.9)	104 (11.5)	96 (10.6)
Blood stream	84 (9.3)	90 (10.0)	84 (9.3)
Skin and soft tissue	69 (7.6)	73 (8.1)	88 (9.7)
Central nervous system	31 (3.4)	32 (3.5)	20 (2.2)
Ear, nose and throat	19 (2.1)	19 (2.1)	29 (3.2)
Central line related infection	15 (1.7)	9 (1.0)	15 (1.7)
Not categorized	42 (4.7)	45 (5.0)	42 (4.6)
<b>Causative microorganism identified for the infection causing sepsis – n/N (%)</b>	422/901 (46.8)	411/901 (45.6)	428/904 (47.4)
<b>Baseline Core body temperature, mean (SD) [N], °C</b>	37.2 (1.4) [904]	37.2 (1.4) [904]	37.2 (1.4) [906]
<b>Baseline White Cell count, mean (SD) [N], x10<sup>9</sup>/L</b>	15.7 (9.3) [907]	15.9 (9.8) [909]	15.7 (9.8) [911]
<b>Sepsis Severity – n (%)</b>			
N	915	918	916
Sepsis	465 (50.8)	466 (50.8)	466 (50.9)
Septic Shock	450 (49.2)	452 (49.2)	450 (49.1)
<b>Surgery within last 72 hours – n/N (%)</b>	256/915 (28.0)	258/918 (28.1)	256/916 (28.0)
<b>SOFA score (5 items)<sup>5</sup>, median (IQR) [N]</b>	7.0 (5.0, 9.0) [836]	7.0 (5.0, 9.0) [839]	7.0 (5.0, 9.0) [841]
<b>APACHE II<sup>5</sup>, mean (SD) [N]</b>	17.5 (6.5) [811]	17.3 (6.4) [825]	17.2 (6.5) [810]
<sup>1</sup> The column percentage sums may not be exactly 100 because of rounding.			

Characteristics	Daily PCT-guided protocol (N=918)	Daily CRP-guided protocol (N=924)	Standard Care (N=918)
<p><sup>2</sup>EAU provides short stay hospital care for up to 72 hours to allow for early assessment and treatment to adult patients, who are referred by their family doctor directly from the community or by an emergency physician from the Emergency Department (ED).</p> <p><sup>3</sup>Others includes transfer from another hospital (N=49), hospital ward (N=49), ambulatory care clinic (N=8) and interventional radiology (N=14).</p> <p><sup>4</sup>Multiple response per patient, so the sum of column percentages is more than 100. SD: Standard Deviation, IQR: Interquartile Range.</p> <p><sup>5</sup>The Sequential Organ Failure Assessment (SOFA) score ranges from 0 (best) to 20 (worst). The Acute Physiology and Chronic Health Evaluation (APACHE) score ranges from 0 (best) to 71 (worst). The SOFA score assesses organ function failure, and the APACHE II score evaluates disease severity and predicts outcomes in critically ill patients. A SOFA score of 7 and/or APACHE II score of 17 indicates severe organ dysfunction and a high mortality risk, with potential respiratory failure, cardiovascular instability, acute kidney injury, liver dysfunction, altered consciousness, and severe coagulopathy. Patients with these scores require intensive care and close monitoring.</p>			

491

<b>Table 2: Primary and secondary outcomes</b>					
<b>Outcomes</b>	<b>Daily PCT-guided protocol (N=918)</b>	<b>Daily CRP-guided protocol (N=924)</b>	<b>Standard Care (N=918)</b>	<b>Unadjusted Treatment effect (95% CI), [P-value]<sup>1</sup></b>	
				<b>Standard care vs. daily PCT-guided protocol</b>	<b>Standard care vs. daily CRP-guided protocol</b>
<b>Primary outcomes</b>					
<b>Effectiveness:</b> Total antibiotic treatment duration to 28 days post randomization, mean (SD) [N], days	9.8 (7.2) [898]	10.6 (7.7) [892]	10.7 (7.6) [905]	MD: 0.88 (0.19 to 1.58), [0.01]	MD: 0.09 (-0.60 to 0.79), [0.79]
<b>Safety:</b> 28-days all-cause mortality <sup>2</sup> , n/N (%)	184/879 (20.9)	184/874 (21.1)	170/878 (19.4)	AD : 1.57 (-2.18 to 5.32), [0.02] <sup>3</sup>	AD: 1.69 (-2.07 to 5.45), [0.03] <sup>3</sup>
<b>Sensitivity Analysis</b>					
<b><i>Per protocol analysis for both effectiveness and safety outcomes</i></b>					
<b>Effectiveness:</b> Total antibiotic treatment duration to 28 days post randomization, mean (SD) [N], days	9.8 (7.2) [880]	10.6 (7.7) [874]	10.7 (7.6) [891]	MD: 0.86 (0.16 to 1.56), [0.02]	MD: 0.05 (- 0.65 to 0.75), [0.88]
<b>Safety:</b> 28-days all-cause mortality – n/N (%)	176/860 (20.5)	182/854 (21.3)	166/864 (19.2)	AD: 1.25 (-2.51 to 5.02) [0.02] <sup>3</sup>	AD: 2.10 (-1.70 to 5.90) [0.04] <sup>3</sup>
<b><i>CACE Analysis for the effectiveness outcome</i></b>				MD: 1.00 (0.22 to 1.77), [0.01]	0.10 (-0.70 to 0.91), [0.81]
<b><i>Imputation analysis</i></b> , mean (SD) [N]	9.8 (7.3) [915]	10.6 (7.9) [918]	10.8 (7.7) [916]	MD: 0.99 (0.29 to 1.69), [0.005]	MD: 0.15 (-0.55 to 0.85), [0.67]
<b><i>Pocock's Win Ratio</i></b> <sup>4</sup> : Using 28-days all-cause mortality status and total antibiotic duration to 28-days post randomization				Odds: 1.12 (1.00 to 1.25), [0.04]	Odds: 0.98 (0.88 to 1.10), [0.77]

<b>Secondary outcomes</b>					
<b>Antibiotic treatment duration for initial sepsis period, mean (SD) [N], days</b>	7.0 (5.7) [893]	7.4 (6.0) [889]	8.1 (6.1) [902]	MD: 1.13 (0.58 to 1.68)	MD: 0.71 (0.16 to 1.26)
<b>Antibiotic dose from randomization until 28-days, median (IQR), DDD</b>	11.5 (6.0, 19.1) [797]	12.0 (6.0, 20.1) [773]	11.0 (5.8, 19.8) [760]		
<b>Antibiotic dose for sepsis period, median (IQR)[N], DDD</b>	8.0 (4.0, 14.0) [851]	8.0 (4.2, 15.0) [830]	9.0 (4.8, 17.0) [823]		
<b>Unscheduled care escalation/re-admission</b>					
Number of events	314	349	365	AD: 2.80 (-1.16 to 6.76)	AD: 0.05 (-3.91 to 4.03)
No. of patients with at least one event – n/N (%)	208/888 (23.4)	234/894 (26.2)	236/900 (26.2)	RD: 10.67 (-3.77 to 25.95) OR: 1.16 (0.94 to 1.44)	RD: 0.18 (-14.26 to 15.46) OR: 1.00 (0.81 to 1.24)
<b>Time to first deemed fit for Hospital discharge, mean (SD) [N], days</b>	12.5 (7.9) [190]	13.0 (6.9) [215]	12.4 (7.2) [194]	MD: -0.09(-1.56 to 1.38)	MD: -0.59(-2.02 to 0.83)
<b>Time to hospital discharge (survivors), mean (SD) [N], days</b>	12.6 (6.8) [439]	12.6 (6.9) [441]	12.7 (6.8) [436]	MD: 0.10 (-0.81 to 1.01)	MD: 0.11 (-0.80 to 1.02)
<b>Length of ICU stay, median (IQR) [N], days</b>	6.2 (3.1, 12.3) [763]	6.0 (3.1, 11.9) [771]	5.8 (3.0, 12.4) [762]		
<b>Infection relapse/recurrence requiring further antibiotic treatment</b>					
Number of events	15	8	5	AD: -0.66 (-1.51 to 0.01)	AD: -0.003 (-0.85 to 0.67)
No. of patients with at least one event – n/N (%)	11/908 (1.2)	5/908 (0.6)	5/913 (0.5)	RD <sup>5</sup> : -121.21 (-565.01 to 101.41)	RD <sup>5</sup> : -0.55 (-444.35 to 222.08)

				OR: 0.45 (0.16 to 1.30)	OR: 0.99 (0.29 to 3.44)
<b>New infection/superinfection at a different anatomical site</b>					
Number of events	41	39	32	AD: -0.57 (-2.13 to 0.93)	AD: -0.34 (-1.90 to 1.15)
No. of patients with at least one event – n/N (%)	29/908 (3.2)	27/908 (3.0)	24/913 (2.6)	RD: -21.50 (-92.76 to 45.02)	RD: -13.12 (-84.38 to 53.40)
				OR: 0.82 (0.47 to 1.42)	OR: 0.88 (0.50 to 1.54)
<b>Suspected clinically relevant antibiotic related events</b>					
Number of events	118	137	118	AD: -0.21 (-2.81 to 2.30)	AD: -0.84 (3.43 to 9.44)
No. of patients with at least one event – n/N (%)	71/888 (8.0)	77/894 (8.6)	70/900 (7.8)	RD: -2.80 (-38.18 to 32.80)	RD: -10.74 (-46.12 to 24.86)
				OR: 0.97 (0.69 to 1.37)	OR: 0.89 (0.64 to 1.25)
<b>90-days all-cause mortality – n/N (%)</b>	217/847 (25.6)	223/846 (26.4)	215/842 (25.5)	AD: -0.09 (-4.29 to 4.08)	AD: -0.82 (-5.03 to 3.34)
				RD: -0.33 (-17.04 to 16.40)	RD: -3.23 (-19.94 to 13.51)
				OR: 1.00 (0.80 to 1.24)	OR: 0.96 (0.77 to 1.19)

SD: Standard Deviation, MD: Mean Difference, AD: Absolute Difference, RD: Relative Difference, OR: Odds Ratio, DDD: Defined Daily Dose.

<sup>1</sup>P-values for primary outcomes analyses only.

<sup>2</sup>For 28-days all-cause mortality, the comparisons are made as Daily PCT-guided protocol vs. Standard care, and Daily CRP-guided protocol vs. Standard care

<sup>3</sup>P-values of the test if the RD is less than or equal to the pre-specified margin 5.4% (significance level = 0.025).

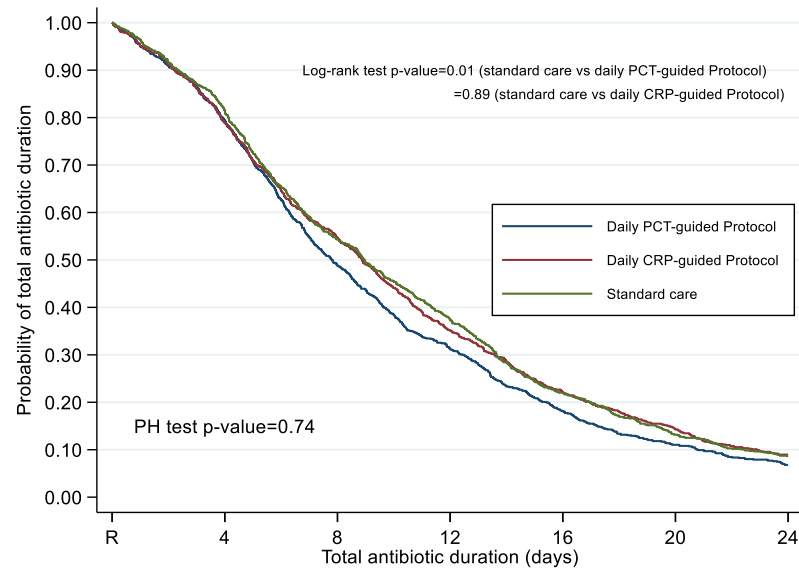
<sup>4</sup> The win-ratio is the odds that the intervention treatment wins for any randomly chosen patients' pair (intervention vs control).

<sup>5</sup>The RD value is very high because the proportions are very small.

492 **Figure 2: Kaplan-Meier curves for (a) probability of total antibiotic duration (primary effectiveness outcome),<sup>1,2</sup> and (b) all-cause mortality up to 28 days**

493 **(safety outcome)**

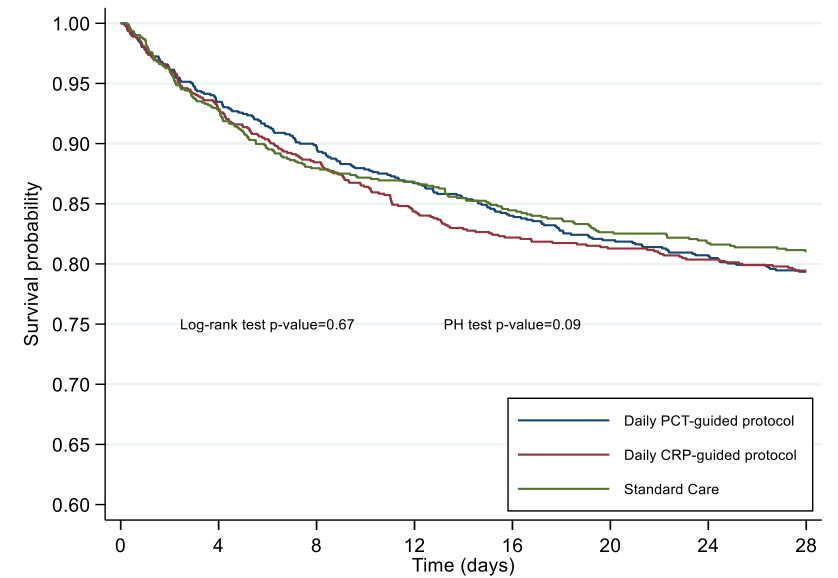
(a)



Number at risk

Daily PCT-guided protocol	897	713	438	280	163	99	61
Daily CRP-guided protocol	891	703	488	313	197	128	80
Standard care	904	737	491	339	199	119	78

(b)



Number at risk

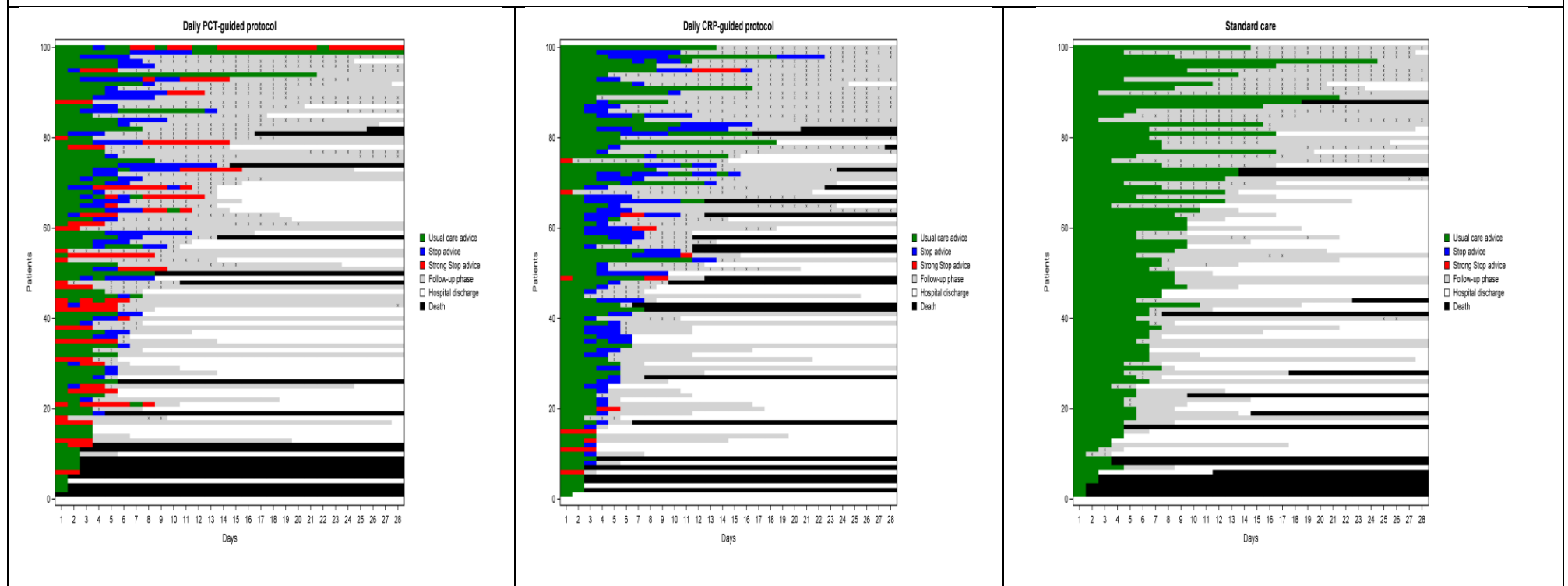
Daily PCT-guided protocol	917	837	797	768	742	722	709	695
Daily CRP-guided protocol	923	831	783	742	720	710	701	691
Standard care	918	838	784	769	744	728	715	708

<sup>1</sup>R=time of randomization.

<sup>2</sup> The median and inter-quartile range (IQR) of the total antibiotic treatment duration up to 28 days for each of the three arms are Daily PCT-guided protocol: 7.8 (4.5, 13.6), Daily CRP-guided protocol: 8.9 (4.5, 14.9), and Standard care: 9.0 (4.7, 14.6).

494

**Figure 3: Indicative maps of patient care pathways**



Trial patients were drawn at random (N = 100 per group) and tabulated to indicate their care pathways from randomization to day-28. The trial intervention periods (where patients were receiving antibiotics for sepsis and daily protocolized advice) are indicated by colors (standard care advice (green); stop advice (blue) and strong stop advice (red)). When antibiotics for sepsis are stopped and protocol advice ends, the patient enters the trial follow up phase in hospital (grey) and discharged from hospital (white). Any antibiotics commenced and delivered during follow up are indicated by black crosses. Patients in each group are ordered by length of total antibiotics from randomization to day-28, with the longest duration at the top. Death is indicated in black.