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# BMJ Open

## The effect of triclosan-coated sutures for abdominal wound closure on the incidence of abdominal wound dehiscence: a protocol for an individual participant data meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054534
Article Type:	Protocol
Date Submitted by the Author:	15-Jun-2021
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Keywords:	Infection control < INFECTIOUS DISEASES, SURGERY, WOUND MANAGEMENT

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Manuscripts

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3 **1 TITLE PAGE**  
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5 2 The effect of triclosan-coated sutures for abdominal wound closure on the incidence of  
6 3 abdominal wound dehiscence: a protocol for an individual participant data meta-analysis  
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36 **Word count**

37 3093 (excluding title page, abstract, article summary, figures and tables)  
38  
39

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41 **Key words**

42 Triclosan

43 Wound dehiscence

44 Surgical Site Infection  
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47 **APPENDICES**

48 Appendix 1: Search strategy

49 Appendix 2: Data items

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3 46 **ABSTRACT**  
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6 47 **Introduction:** Acute abdominal wound dehiscence (AWD) or burst abdomen is a severe  
7 48 complication after abdominal surgery with an incidence up to 3.8%. Surgical site infection  
8 49 (SSI) is the biggest risk factor for the development of AWD. It is strongly suggested that the  
9 50 use of triclosan-coated sutures (TCS) for wound closure, reduces the risk of SSI. We  
10 51 hypothesize that the use of TCS for abdominal wound closure may reduce the risk of AWD.  
11 52 Current randomised controlled trials (RCTs) lack power to investigate this. Therefore, the  
12 53 purpose of this individual participant data meta-analysis is to evaluate the effect of TCS for  
13 54 abdominal wound closure on the incidence of AWD.  
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22 56 **Methods and analysis:** We will conduct a systematic review of MEDLINE, EMBASE and  
23 57 CENTRAL for RCTs investigating the effect of TCS compared to non-coated sutures for  
24 58 abdominal wound closure in adult participants scheduled for open abdominal surgery. Two  
25 59 independent reviewers will assess eligible studies for inclusion and methodological quality.  
26 60 Authors of eligible studies will be invited to collaborate and share individual participant data.  
27 61 The primary outcome will be AWD within 30 days after surgery requiring reoperation.  
28 62 Secondary outcomes include SSI, all-cause reoperations, length of hospital stay, and all-cause  
29 63 mortality within 30 days after surgery. Data will be analysed with a one-step approach,  
30 64 followed by a two-step approach. In the one-step approach, treatment effects will be estimated  
31 65 as a risk ratio with corresponding 95% confidence interval in a generalised linear mixed  
32 66 model framework with a log link and binomial distribution assumption. The quality of  
33 67 evidence will be judged using the GRADE methodology.  
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46 69 **Ethics and dissemination:** Ethics approval is not required. Collaborating investigators will  
47 70 de-identify data before sharing. The results will be submitted to a peer-reviewed journal.  
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52 72 **Trial Registration Number:** PROSPERO CRD42019121173  
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3 74 **ARTICLE SUMMARY**  
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5 75 **Strengths and limitations of this study**  
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- 8 76 • Current available RCTs that investigate the effect of TCS for abdominal wound  
9 closure provide insufficiently detailed information regarding acute abdominal wound  
10 77 dehiscence to perform aggregate data meta-analysis.  
11 78  
12 79 • IPDMA has the advantages over aggregate meta-analysis that it uses uniform inclusion  
13 and exclusion criteria, study data can be checked at participant level, statistical  
14 80 analysis can be standardised and baseline effect modifiers can be identified.  
15 81  
16 82 • The strength of this review is depending on the data that is (made) available by the  
17 83 authors of the original studies.  
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## 84 **INTRODUCTION**

### 85 **Rationale**

86 Abdominal wound dehiscence (AWD), also known as acute fascial dehiscence or burst  
87 abdomen, is a severe complication after abdominal surgery with a reported incidence of up to  
88 3.8%.<sup>1 2</sup> AWD frequently requires reoperation and is associated with prolonged hospital stay,  
89 lower quality of life, increased healthcare costs and mortality rates as high as 45%.<sup>1 3 4</sup> In the  
90 US, the Nationwide Inpatient Sample demonstrated that AWD results in \$40,323 additional  
91 hospital costs per patient.<sup>5</sup> The most important risk factor for the development of AWD is  
92 surgical site infection (SSI), increasing the odds by 6.43 times.<sup>6</sup> The use of triclosan-coated  
93 sutures (TCS) for wound closure reduces the incidence of SSI.<sup>7</sup> As such, we hypothesise that  
94 the use of TCS for abdominal wound closure may reduce the incidence of AWD. This may  
95 occur through reduction of deep SSI by the use of TCS at the fascial level, or by the use of  
96 TCS at more superficial tissue layers reducing superficial SSI and its potential spread to the  
97 fascia.

98 Only a handful of studies investigating the effect of TCS for abdominal wound closure  
99 on SSI describe its effect on the incidence of AWD. Two studies report a decrease in AWD  
100 after using TCS for fascial closure.<sup>8 9</sup> One of these reports a statistically significant difference,  
101 but concludes this to be clinically irrelevant as rates of deep SSI are comparable among  
102 treatment arms.<sup>8</sup> Furthermore, the study was not powered to detect a difference in AWD.  
103 Using their reported observed risk difference, the study has a 72% power and is just 132  
104 participants per treatment arm short of the conventional 80% power to detect the described  
105 difference in AWD. There are multiple other RCTs that investigate the effect of TCS for  
106 abdominal wound closure on the incidence of SSI, that may have data on AWD in their  
107 database.<sup>9-20</sup> A pooled analysis will increase the power and provide a more definitive answer  
108 on the effect of TCS for abdominal wound closure for the development of AWD. Considering  
109 the disastrous consequences of AWD, even a very small risk reduction may be clinically  
110 relevant.

111 The published studies provide insufficient information on AWD to conduct a valid  
112 meta-analysis on this outcome. An Individual Participant Data Meta-Analysis (IPDMA) is a  
113 meta-analysis of the original study data and offers the possibility to overcome this limitation.  
114 Individual participant data (IPD) provides the opportunity to standardise inclusion and

1  
2  
3 115 exclusion criteria, check the raw data for integrity and missing data, standardise statistical  
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5 116 analysis and identify baseline effect modifiers.<sup>22 23</sup>  
6

7 **117 Objectives**  
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9  
10 118 The purpose of this IPDMA is to evaluate the effect of using TCS for abdominal wound  
11 119 closure on the incidence of AWD within 30 days after surgery in patients undergoing open  
12  
13 120 abdominal surgery. A subgroup analysis will be performed according to the specific type of  
14  
15 121 suture that is used for wound closure (polyglactin 910 or polydioxanone). We hypothesise that  
16  
17 122 wound closure with TCS reduces the risk of AWD.  
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For peer review only



## 124 **METHODS**

125 This study consists of a systematic review and a consecutive IPDMA. We will contact authors  
126 of studies that meet the inclusion criteria and invite them to contribute to the IPDMA. This  
127 study is registered with the International prospective register of systematic reviews  
128 (PROSPERO) (registration number CRD42019121173). This protocol is reported according  
129 to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols  
130 (PRISMA-P) statement.<sup>24</sup> Description and date of all amendments will be reported. The final  
131 manuscript will be reported according to PRISMA-Individual Participant Data (PRISMA-  
132 IPD) Statement.<sup>23</sup>

### 134 **Systematic Review**

#### 135 **Eligibility criteria**

136 RCTs that investigate the effect of TCS, compared to the exact same but non-coated sutures,  
137 on the incidence of spontaneous AWD and/or incidence of SSI within 30 days postoperative  
138 in patients that underwent open abdominal surgery are eligible. Studies investigating the  
139 effect of TCS for abdominal wound closure, and/or abdominal fascia closure will both be  
140 eligible.

141 If studies report only the SSI incidence and not the AWD incidence, authors will be asked if  
142 AWD incidence is registered (either for the trial or in the medical record for regular care) and  
143 available. Only RCTs that are able to provide prospectively registered data on both SSI and  
144 AWD incidence will be included in the IPDMA. If AWD incidence is not available, the study  
145 will not be included. We will exclude studies if TCS are part of a bundle of interventions, and  
146 studies that investigate the use of TCS after right lower quadrant incision for appendectomy.  
147 There will be no restrictions on publication date, language or publication status.

#### 149 **Literature search**

150 The PubMed (MEDLINE), EMBASE online databases (Ovid) and Cochrane Central Register  
151 of Controlled Trials (CENTRAL) will be searched. To identify potential unpublished  
152 evidence or any on-going trials, the International Clinical Trials Registry Platform will be  
153 searched. References of included studies will be hand searched for any additional relevant

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2  
3 154 studies. In addition, meta-analyses investigating the effect of TCS on the incidence of SSI will  
4  
5 155 be searched for possibly missed eligible studies. The corresponding authors from the  
6  
7 156 collaborating studies will be contacted to review the list of identified studies for omission of  
8  
9 157 potentially relevant studies.

10  
11 158 A professional clinical librarian will be consulted to develop the search strategy. The  
12  
13 159 search includes the free text and index terms: sutures, polyglactin 910, vicryl, polydioxanone,  
14  
15 160 PDS, triclosan, wound infection, surgical wound dehiscence, fascial dehiscence and burst  
16  
17 161 abdomen. These terms will be combined with the Cochrane highly sensitive search strategy  
18  
19 162 for identifying randomised trials.<sup>25</sup> The final search strategy is presented in appendix 1.

20 163

## 21 22 164 **Study selection**

23  
24  
25 165 All studies, identified by the search strategy, will be handled through Rayyan (QCRI)<sup>26</sup>.  
26  
27 166 Duplicates will be removed. Two reviewers (AST and NW) will independently assess the  
28  
29 167 studies based on previously described eligibility criteria. After screening title and abstract, full  
30  
31 168 text of potentially eligible studies will be retrieved and assessed. When it is not possible to  
32  
33 169 retrieve the manuscript or study eligibility is not clear, the authors will be contacted to  
34  
35 170 provide further information. Any discrepancies in study selection will be resolved through  
36  
37 171 discussion or, when necessary, by consultation with the principle investigator. We will keep a  
38  
39 172 list with reasons for exclusions for all articles that pass title and abstract screening but are  
40  
41 173 deemed ineligible for inclusion. Only studies that provide aggregate data and/or IPD on AWD  
42  
43 174 incidence will meet the criteria for final inclusion in the IPDMA.

44 175

## 45 176 **Individual Patient Data Meta-Analysis**

### 46 47 177 **Study collaboration invitation**

48  
49  
50 178 Authors from potentially eligible studies will be contacted and invited to contribute to the  
51  
52 179 IPDMA if their study indeed meets the inclusion criteria. An email invitation letter will be  
53  
54 180 sent to the corresponding authors, outlining the IPMDA goals. If no reply is received within  
55  
56 181 two weeks, a second email request will be sent to both the corresponding and first author. If  
57  
58 182 again no response is received, we will try to contact all individual authors by email and/or  
59  
60 183 telephone. IPD and/or aggregate data on AWD will be considered unavailable if numerous  
184 184 times (at least five) no reply is received, if authors no longer have access to the study data or

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3 185 authors do not consent for collaboration. Collaborating investigators will be asked to critically  
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5 186 appraise the study protocol, provide feedback, approve the finalised version, and will be  
6  
7 187 offered co-authorship on the publication of the study protocol. By sharing their IPD,  
8  
9 188 collaborators will be offered one co-authorship on the IPDMA manuscript, with one  
10  
11 189 additional co-authorship if data of more than 300 participants is shared.  
12  
13

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### 191 **Risk of bias**

16 192 Two reviewers (AST and NW) will independently assess the quality of the included studies  
17  
18 193 using the revised tool for assessing Risk of Bias in randomised trials (Rob 2).<sup>27</sup> Studies will  
19  
20 194 be judged as “*low risk*”, “*some concerns*” or “*high risk of bias*”. Only data from the original  
21  
22 195 manuscripts and study protocols will be used to ensure consistent and uniform assessments of  
23  
24 196 studies that do and studies that do not provide IPD. Presence of publication bias will be  
25  
26 197 assessed with the construction of a contour enhanced funnel plot.<sup>28</sup>  
27  
28

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### 199 **Data collection process**

30  
31  
32 200 The collaborating investigators will be requested to sign a data transfer agreement before de-  
33  
34 201 identified IPD is shared. The agreement describes the purposes of the IPDMA, the ownership  
35  
36 202 of the IPD and confirms that the IPD is stored on a secure location. A researcher (AST) will  
37  
38 203 conduct data collection, an interview on the study protocol and a formal handoff of the data  
39  
40 204 codebook, if possible, in person. In the event that IPD will not be made available, the reason  
41  
42 205 will be recorded and, if possible, the aggregate data of the particular study will be used  
43  
44 206 instead.

45 207 Aggregate data will be collected as appropriate by two independent researchers (AST and  
46  
47 208 NW) according to a predefined data extraction sheet and overseen by the principle  
48  
49 209 investigator to settle potential discrepancies.  
50

210

### 211 **Data items**

52  
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54  
55 212 We will propose a selection of data items of interest (with definitions and measures). All  
56  
57 213 collaborating investigators will be asked to criticise and supplement this list. To ease the  
58  
59 214 process of data handover, collaborating investigators can opt to share the complete data set of  
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1  
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3 215 their study. We will select and clean only those data items that were selected collaboratively.  
4  
5 216 After repeated consultation with the collaborating investigators we selected data items on  
6  
7 217 study-level and data items on participant-level. The list of data items with definitions is  
8  
9 218 presented in appendix 2. Study-level data includes: study design (number of participating  
10  
11 219 centers, blinding, randomised tissue layer, TCS specification, sample size), inclusion- and  
12  
13 220 exclusion criteria, and primary- and secondary outcomes. Participant-level data includes:  
14  
15 221 baseline characteristics (age, gender, ASA score, BMI, COPD, smoking status, and previous  
16  
17 222 midline incisions), and procedural characteristics (received suture, procedural status, target  
18  
19 223 organ, wound classification, duration of surgery, and incision type).  
20  
21 224

### 225 **Outcomes**

22 226 The primary outcome is the incidence of AWD requiring reoperation. AWD is defined as  
23  
24 227 spontaneous dehiscence of the abdominal fascia within 30 days postoperatively. Reoperation,  
25  
26 228 for any indication other than AWD, is not regarded as AWD.

27 229 Secondary outcomes are SSI within 30 days after surgery according to the CDC criteria  
28  
29 230 (specified as superficial, deep, organ/space), skin wound dehiscence, length of hospital stay,  
30  
31 231 all-cause reoperations within 30 days after surgery, and all-cause mortality within 30 days  
32  
33 232 after surgery.  
34  
35 233

### 36 234 **Data integrity**

37 235 IPD will be checked for missing, invalid, out-of-range and inconsistent outcomes and for  
38  
39 236 discrepancies with the published aggregate data. When detected, we will seek to resolve the  
40  
41 237 issues with the collaborating investigators to improve data quality and ensure that trials are  
42  
43 238 represented accurately. To ensure all randomised patients are included, IPD will be compared  
44  
45 239 with the aggregate data from the original studies. In the case of any concerns on IPD integrity  
46  
47 240 that cannot be resolved with the collaborating investigators, the data of the concerning study  
48  
49 241 will not be included in the analysis. Checking baseline imbalances will be used to assess  
50  
51 242 randomisation and allocation concealment. Pattern and extent of follow-up will be checked.  
52  
53 243 When needed, additional follow up to rectify any imbalances may be conducted by the  
54  
55 244 collaborating authors.  
56  
57 245

### 58 246 **Missing data**

59 247 For the primary analysis, we will not perform imputation of the complete variable for a study  
60 248 if variables are systematically missing in one or multiple trials. Missing data at participant

1  
2  
3 249 level will be assumed to be at random. Multivariate imputation by chained equations (MICE)  
4 250 will be used to handle missing data. Multiple rounds of imputation will be used to estimate the  
5 251 missing value. Percentage of missing data will determine the number of imputation sets.  
6  
7  
8 252 MICE will be done for each individual trial before merged in the aggregate database.  
9

10 253

## 11 12 254 **Data synthesis**

13  
14  
15 255 The raw data from each study will be copied to a separate database and recoded according to  
16 256 the predefined IPDMA settings. The recoded IPD databases will then be aggregated into one  
17  
18 257 IPD database containing all studies.  
19

20  
21 258 Both one and two-step approaches will be used for each outcome separately. Dichotomous  
22 259 data will be expressed using risk ratios (RR) with corresponding 95% confidence intervals  
23  
24 260 (CI). Continuous data will be expressed using weighted mean differences with corresponding  
25  
26 261 95% CI. Data will be analysed according to the intention-to treat-principle, meaning that the  
27  
28 262 original randomisation allocation is used to define treatment groups, regardless of the  
29  
30 263 treatment that is actually received.

31  
32 264 The primary analysis will be performed using the one-step approach, in which IPD from all  
33  
34 265 studies will be analysed using the generalised linear mixed model framework and an  
35  
36 266 appropriate statistical model for the type of outcome. We will use a linear regression model  
37  
38 267 for continuous outcome data and a log-binomial model for binary outcome data. If the log-  
39  
40 268 binomial model fails to converge we will use a log-binomial generalised estimating equation  
41  
42 269 (GEE) or a log Poisson GEE model.<sup>29</sup> A random intercept and, if appropriate, a random slope  
43  
44 270 will be added to account for clustering of patients within studies. Potential confounding  
45  
46 271 variables that, despite randomisation, show baseline imbalances across treatment arms will be  
47  
48 272 added to the appropriate model. Variable selection will be based on VanderWeeles<sup>30</sup>  
49  
50 273 principles of confounder selection. The collaborating investigators will be asked to critically  
51  
52 274 appraise the list of potential confounders and to suggest additional variables if indicated  
53  
54 275 (appendix 2). Confounders available in all datasets will be added to the model. The one step  
55  
56 276 approach can be statistically challenging, but has the advantage that it – compared to the two-  
57  
58 277 step approach - is able to more accurately estimate covariate interactions.

59  
60 278 In the two-step approach, all studies will be reanalysed separately in a similar fashion as the  
279 one step approach but without the term for trial clustering. The new aggregate data of each

1  
2  
3 280 study will then be summarised in a second step, synthesising an overall estimate using  
4  
5 281 DerSimonian and Laird method assuming random effects.

6  
7 282 Statistical heterogeneity among studies will be evaluated using the  $\text{Chi}^2$  test and expressed  
8  
9 283 using the  $I^2$  statistic. The between-study variance will be assessed using the  $\text{Tau}^2$  statistic.  
10  
11 284 When IPD will or cannot not be made available, aggregate study data provided by the  
12  
13 285 collaborating investigators or from the study manuscript will be included in the two step  
14  
15 286 analyses. As all tests are pre-specified and effects follow from our hypothesis no correction  
16  
17 287 for multiple testing will be performed.

18 288

### 20 289 **Additional analysis**

21  
22  
23 290 Additional analyses will be performed using the one-step approach. A subgroup analysis will  
24  
25 291 be performed according to the specific type of suture that is used for wound closure  
26  
27 292 (polyglactin 910 or polydioxanone).

28  
29 293 The risk of incisional hernia after a midline incision is higher than for a non-midline  
30  
31 294 incision.<sup>31</sup> Although there is currently no evidence that this holds for AWD, we will  
32  
33 295 investigate if the type of incision influences the risk of AWD (midline versus non-midline).  
34  
35 296 Sensitivity analysis will be used to determine if the effect is influenced by the additional use  
36  
37 297 of TCS for skin wound closure. A series of sensitivity analyses will be performed on  
38  
39 298 combinations of confounders that pass criteria for confounder selection but are not included in  
40  
41 299 the former model as the variables are not reported in all included studies. Besides the  
42  
43 300 intention-to-treat analysis we will perform, if feasible, an adjusted per protocol analysis. If the  
44  
45 301 results of the one-step and two-step approaches differ greatly, we will perform the additional  
46  
47 302 analysis also for the two-step approach. Furthermore, we will investigate if adding aggregate  
48  
49 303 data to the IPDMA has an effect on study outcome and perform a sensitivity analysis with  
50  
51 304 trials assessed as low risk of bias.

52 305

### 53 306 **Confidence in cumulative estimate**

54  
55 307 The quality of evidence will be judged using the Grading of Recommendations Assessment  
56  
57 308 Development and Evaluation (GRADE) working group methodology for the following  
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59 309 domains: risk of bias, unexplained inconsistency, indirectness, imprecision, publication bias,  
60  
310 magnitude of effect, dose-response relationship, and residual confounding.<sup>32</sup> The level of

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3 311 evidence will be downgraded for imprecision based the optimal information size and the  
4 312 confidence interval. If the optimal information size is met and the confidence interval fails to  
5 313 excluded important benefit or harm, we will rate down for imprecision. We set a default  
6 314 threshold for appreciable benefit and harm that warrants rating down (relative risk reduction  
7 315 (RRR) or RR of 25% or more). The level of evidence will be upgraded for a large magnitude  
8 316 of effect (RR >2 or <0.5) or very large magnitude of effect (RR >5 or <0.02). The overall  
9 317 quality will be classified using four levels: high, moderate, low and very low.  
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### 319 **Software**

320 Statistical analysis will be done using R 4.0.4., and/or SPSS, and/or STATA.  
321

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### 322 **Patient and public involvement**

323 No patients or patient federations are involved in the design of this study protocol nor the  
324 IPDMA. Yet, the disastrous consequences of AWD are well described, underlining the need  
325 for (surgical) interventions that reduce the risk of AWD.<sup>1</sup>  
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### 327 **Study status**

328 Currently we have executed the systematic review. We are in contact with the authors from  
329 the original studies. We have not collected any data from the original manuscripts nor  
330 received IPD from any of the collaborators.  
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3 332 **ETHICS AND DISSEMINATION**  
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5 333 **Ethical approval**  
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8 334 Ethical approval is not deemed necessary for this study protocol.  
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12 336 **Dissemination:**  
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14  
15 337 The results of this study will be submitted to peer-reviewed journals regardless of the  
16 338 outcome. The protocol will be submitted before the data is gathered and analysed.  
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19 339  
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21 340 **Author and collaborative statement**  
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23  
24 341 MB is guarantor of the study. MB & SWJ conceived the study. AST, NW and SWJ drafted  
25 342 the study protocol. AST will provide input for the literature search. AST and NW will  
26 343 perform the screening, inclusion and assessment of risk of bias. AST will coordinate the  
27 344 assembly of the data set. AST, NW, SWJ, MGWD, MAB will provide statistical expertise.  
28 345 AST, NW and SWJ will draft the final manuscript under supervision of all co-authors. All  
29 346 authors compliant with their responsibilities according to the research protocol, meet  
30 347 authorship criteria as defined by the international committee of medical journal editors, and  
31 348 contributed to the study protocol, provided critical feedback and approved the final  
32 349 manuscript. All co-authors of the original studies that supplied IPD or additional aggregate  
33 350 data, will be mentioned as non-authorship collaborators to the IPD meta-analysis.  
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44 352 **Sponsor**  
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46 353 This is an investigator-initiated study. The sponsor of this study is the Amsterdam UMC,  
47 354 location Amsterdam, the Netherlands. The study protocol is written solely by members of the  
48 355 steering committee and the industry had no say in study design, data items, data collection,  
49 356 data analysis and data reporting.  
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55 358 **Funding**  
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57 359 This study is supported by a grant from Johnson & Johnson.  
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3 360  
45 361 **Competing interest**

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7  
8 362 AST, NW, FP, PK, CS, KI, TR, JB, AV, LG, JRT, AMH, TN, MGWD and SWJ declare no  
9  
10 363 conflict of interest. CJ is an advisory board member of Johnson & Johnson/Ethicon. MAB  
11  
12 364 reports receiving institutional grants from J&J/Ethicon, KCI/3M, and New Compliance; and is  
13  
14 365 an advisory board member and/or speaker and/or instructor for KCI/3M, Johnson &  
15  
16 366 Johnson/Ethicon, LifeCell/Allergan, Bard, Gore, TelaBio, Medtronic, GD Medical, and Smith  
17  
18 367 & Nephew.

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21 369 **Acknowledgement**

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23  
24 370 The authors would like to thanks F.S. van Etten - Jamaludin, clinical librarian for the help  
25  
26 371 with the literature search.

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3 484 **Appendix 1: Search strategy**  
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5 485 PubMed:  
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8 486 ("Triclosan"[Mesh] OR "Anti-Infective Agents, Local"[Mesh] OR triclosan\*[tiab] OR  
9 487 antimicrobial\*[tiab] OR antibacterial\*[tiab] OR antiseptic\*[tiab] OR antibiotic\*[tiab]) AND  
10 488 ("Sutures"[Mesh] OR "Polyglactin 910"[Mesh] OR "Polydioxanone"[Mesh] OR suture\*[tiab]  
11 489 OR vicryl\*[tiab] OR polyglactin\*[tiab] OR PDS II[tiab] OR polydioxanone\*[tiab]) AND  
12 490 ("Surgical Wound Infection"[Mesh] OR "Surgical Wound Dehiscence"[Mesh] OR surgical  
13 491 wound infection\*[tiab] OR surgical site infection\*[tiab] OR postoperative infection\*[tiab] OR  
14 492 surgical infection\*[tiab] OR wound infection\*[tiab] OR SSI[tiab] OR SSIs[tiab] OR  
15 493 abdominal wound dehiscence\*[tiab] OR abdominal wall dehiscence\*[tiab] OR fascial  
16 494 dehiscence\*[tiab] OR burst abdomen\*[tiab]) AND ("Randomized Controlled Trial"  
17 495 [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "drug therapy"  
18 496 [Subheading] OR randomized [tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR  
19 497 groups[tiab]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])  
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24 499 EMBASE:  
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26 500 (1) triclosan/ or exp topical antiinfective agent/ or (triclosan\* or antimicrobial\* or  
27 501 antibacterial\* or antiseptic\* or antibiotic\*).ti,ab,kw. (2) exp suture/ or polyglactin/ or  
28 502 polydioxanone/ or absorbable suture/ or poliglecaprone suture/ or polydioxanone suture/ or  
29 503 polyglactin suture/ or (suture\* or vicryl\* or polyglactin\* or PDS\*).ti,ab,kw. (3) wound  
30 504 infection/ or surgical infection/ or wound dehiscence/ or (surgical wound infection\* or  
31 505 surgical site infection\* or postoperative infection\* or surgical infection\* or wound infection\*  
32 506 or SSI or SSIs or abdominal wound dehiscence\* or abdominal wall dehiscence\* or fascial  
33 507 dehiscence\* or burst abdomen\*).ti,ab,kw. (4) randomized controlled trial/ or controlled  
34 508 clinical trial/ or drug therapy.fs. or (randomized or placebo or randomly or trial or  
35 509 groups).ti,ab,kw. (5) 1 and 2 and 3 and 4 (6) exp animal/ not human/ (7) 5 not 6 (8) limit 7 to  
36 510 conference abstract status (9) 7 not 8  
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41 512 Cochrane Central Register of Controlled Trials:  
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43 513 (1) (triclosan\* or antimicrobial\* or antibacterial\* or antiseptic\* or antibiotic\*):ti,ab,kw (2)  
44 514 MeSH descriptor: [Anti-Infective Agents, Local] explode all trees (3) #1 or #2 (4) (suture\* or  
45 515 vicryl\* or polyglactin\* or polydioxanone or PDS\*):ti,ab,kw (5) (surgical wound infection\* or  
46 516 surgical site infection\* or postoperative infection\* or surgical infection\* or wound infection\*  
47 517 or SSI or SSIs or abdominal wound dehiscence\* or abdominal wall dehiscence\* or fascial  
48 518 dehiscence\* or burst abdomen\*):ti,ab,kw (6) #3 and #4 and #5 in Trial  
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519 **Appendix 2: Data items**

<b>Study-level data</b>		
<b>Study design</b>	Inclusion- and exclusion criteria	Text
	Inclusion period	Month/year – Month/year
	Number of participating centers	Number
	Blinding	Open label / single / double / triple blind
	Randomised tissue layer	Fascia and / or skin wound
	TCS specification	Polydioxanone / polyglactin 910
	Sample size	Number
	Follow up	(days)
	Primary and secondary outcomes	Text
	Standardised use of prophylactic antibiotics	Yes / no
<b>Participant-level data</b>		
<b>Baseline</b>	Age	Year
	Gender	Male or female
	ASA Physical Status score	Number
	Body mass index	Kg/m <sup>2</sup>
	Active cigarette smoking	Yes / no
	Diabetes mellitus (any type)	Yes / no
	Chronic obstructive pulmonary disease	Yes / no
	Previous midline incision	Yes / no (if yes: number)
<b>Procedural</b>	Randomisation allocation	Intervention / control
	Received suture	TCS / non-TCS
	Status	Elective / emergent
	Target organ	Upper gastrointestinal / small intestine / colorectal / hepato-pancreato-biliary / other
	Wound classification	According to the Center for Disease Control and Prevention classification
	Duration of surgery	According to hospital definition (min)
	Incision type	Midline (at least partly) / non-midline
<b>Outcome</b>	Spontaneous abdominal wound dehiscence, within 30 days after operation, requiring reoperation	Yes / no
	Abdominal skin wound dehiscence	Yes / no
	Surgical Site Infection	According to the Center for Disease Control and Prevention classification into superficial, deep and organ space
	Postoperative length of hospital stay	(days)
	All cause reoperation within 30 days after surgery	Yes / no
	All cause 30 days mortality	Yes / no

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For peer review only



## PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	✓	<input type="checkbox"/>	2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	✓	Not applicable
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	✓	<input type="checkbox"/>	72
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓	<input type="checkbox"/>	30-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓	<input type="checkbox"/>	340-350
<b>Amendments</b>	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	✓	<input type="checkbox"/>	130
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	✓	<input type="checkbox"/>	358-359
Sponsor	5b	Provide name for the review funder and/or sponsor	✓	<input type="checkbox"/>	352-356
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	✓	<input type="checkbox"/>	352-356
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	✓	<input type="checkbox"/>	85-116
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓	<input type="checkbox"/>	117-122
<b>METHODS</b>					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	✓	<input type="checkbox"/>	135-147
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	✓	<input type="checkbox"/>	150-157
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓	<input type="checkbox"/>	158-162
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	<input type="checkbox"/>	165
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	✓	<input type="checkbox"/>	164-174
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓	<input type="checkbox"/>	177-189 + 200-207
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	✓	<input type="checkbox"/>	211-223
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	<input type="checkbox"/>	225-232
<b>Risk of bias in individual studies</b>	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	✓	<input type="checkbox"/>	191-197
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	✓	<input type="checkbox"/>	234-252
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau)	✓	<input type="checkbox"/>	254-287
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	✓	<input type="checkbox"/>	289-304
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	✓	
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	✓	<input type="checkbox"/>	196-197
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	✓	<input type="checkbox"/>	306-317

# BMJ Open

## The effect of triclosan-coated sutures for abdominal wound closure on the incidence of abdominal wound dehiscence: a protocol for an individual participant data meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054534.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Dec-2021
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<b>Primary Subject Heading</b>:	Surgery
Secondary Subject Heading:	Medical management
Keywords:	Infection control < INFECTIOUS DISEASES, SURGERY, WOUND MANAGEMENT

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3 1 **TITLE PAGE**  
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5 2 The effect of triclosan-coated sutures for abdominal wound closure on the incidence of  
6 3 abdominal wound dehiscence: a protocol for an individual participant data meta-analysis  
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15  
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19  
20 35 **Word count**

21  
22 36 3318 (excluding title page, abstract, article summary, figures and tables)

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27 38 **Key words**

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29 39 Triclosan

30 40 Wound dehiscence

31 41 Surgical Site Infection

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37 43 **APPENDICES**

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39 44 Appendix 1: Search strategy

40 45 Appendix 2: Data items

## **ABSTRACT**

**Introduction:** Acute abdominal wound dehiscence (AWD) or burst abdomen is a severe complication after abdominal surgery with an incidence up to 3.8%. Surgical site infection (SSI) is the biggest risk factor for the development of AWD. It is strongly suggested that the use of triclosan-coated sutures (TCS) for wound closure, reduces the risk of SSI. We hypothesize that the use of TCS for abdominal wound closure may reduce the risk of AWD. Current randomised controlled trials (RCTs) lack power to investigate this. Therefore, the purpose of this individual participant data meta-analysis is to evaluate the effect of TCS for abdominal wound closure on the incidence of AWD.

**Methods and analysis:** We will conduct a systematic review of MEDLINE, EMBASE and CENTRAL for RCTs investigating the effect of TCS compared to non-coated sutures for abdominal wound closure in adult participants scheduled for open abdominal surgery. Two independent reviewers will assess eligible studies for inclusion and methodological quality. Authors of eligible studies will be invited to collaborate and share individual participant data. The primary outcome will be AWD within 30 days after surgery requiring reoperation. Secondary outcomes include SSI, all-cause reoperations, length of hospital stay, and all-cause mortality within 30 days after surgery. Data will be analysed with a one-step approach, followed by a two-step approach. In the one-step approach, treatment effects will be estimated as a risk ratio with corresponding 95% confidence interval in a generalised linear mixed model framework with a log link and binomial distribution assumption. The quality of evidence will be judged using the GRADE methodology.

**Ethics and dissemination:** The medical ethics committee of the Amsterdam UMC, location AMC in the Netherlands waived the necessity for a formal approval of this study, as this research does not fall under the Medical Research involving Human Subjects Act. Collaborating investigators will de-identify data before sharing. The results will be submitted to a peer-reviewed journal.

**Trial Registration Number:** PROSPERO CRD42019121173

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3 76 **ARTICLE SUMMARY**  
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5 77 **Strengths and limitations of this study**  
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- 8 78 • Our individual participant data meta-analysis (IPDMA) allows inclusion and analysis  
9 of original trial data - including unpublished data on abdominal wall dehiscence  
10 79 (AWD) – and thereby provides detailed information on the effect of triclosan-coated  
11 80 sutures on AWD.  
12 81  
13 82 • By this IPDMA we will be able to check trial data at participant level, standardise  
14 83 inclusion criteria and standardise statistical analysis to minimise heterogeneity, reduce  
15 84 bias and strengthen the conclusion.  
16 85 • A study limitation is that we aim to collect and analyse trial data of an outcome that  
17 86 was not specified in most of the original studies and individual patient data on this  
18 87 outcome may thus not be available in some trials.  
19 88 • An IPDMA is statistically challenging and relies on collaboration and input of  
20 89 participating trials.  
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## 90 **INTRODUCTION**

### 91 **Rationale**

92 Abdominal wound dehiscence (AWD), also known as acute fascial dehiscence or burst  
93 abdomen, is a severe complication after abdominal surgery with a reported incidence of up to  
94 3.8%.<sup>1 2</sup> AWD frequently requires reoperation and is associated with prolonged hospital stay,  
95 lower quality of life, increased healthcare costs and mortality rates as high as 45%.<sup>1 3 4</sup> In the  
96 US, the Nationwide Inpatient Sample demonstrated that AWD results in \$40,323 additional  
97 hospital costs per patient.<sup>5</sup> The most important risk factor for the development of AWD is  
98 surgical site infection (SSI), increasing the odds more than 6 times.<sup>6</sup> Several recently  
99 published meta-analyses investigate the effect of the use of TCS for wound closure; they all  
100 report that TCS reduces the risk of SSI.<sup>7-10</sup> One meta-analysis investigates the effect of TCS  
101 on the risk of AWD as a secondary aim, but found that current published trial data provide  
102 insufficient information to draw conclusions.<sup>11</sup> To date, cumulative information of the effect  
103 of TCS on the risk of AWD is lacking. Although there are multiple randomized controlled  
104 trials (RCTs) investigating the use of TCS for abdominal wound closure, only two describe its  
105 effect on the incidence of AWD.<sup>12-22</sup> The largest trial reports a statistically significant  
106 decrease in AWD, but concludes this to be clinically irrelevant as rates of deep SSI are  
107 comparable among treatment arms.<sup>13</sup> Also, the study was not powered to detect a difference in  
108 AWD. In the second largest trial AWD was an exclusion criteria.<sup>16</sup>

109 An individual participant data meta-analysis (IPDMA) is a meta-analysis of the original trial  
110 data and provides the opportunity to include unpublished trial data, standardise inclusion  
111 criteria and statistical analysis, check the raw data for integrity and missing data, and identify  
112 baseline effect modifiers.<sup>23 24</sup> To be able to detect the relative risk that is found in the largest  
113 trial (RR 0.42), a study would need 1436 participants. Prior the start of this study, the  
114 principle investigators of the two largest trials confirmed that IPD could be made available. A  
115 pooled analysis of just these two trials would contain 2152 participants and therewith easily  
116 be able to detect the expected risk difference.

### 117 **Objectives**

118 The purpose of this IPDMA is to evaluate the effect of using TCS for abdominal wound  
119 closure on the incidence of AWD within 30 days after surgery in patients undergoing open  
120 abdominal surgery. Subgroup analyses will be performed according to the specific type of  
121 suture that is used for wound closure (polyglactin 910 or polydioxanone) and the level of

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122 contamination. We hypothesise that wound closure with TCS reduces the risk of AWD. This  
123 may occur through reduction of deep SSI by the use of TCS at the fascial level, or by the use  
124 of TCS at more superficial tissue layers reducing superficial SSI and its potential spread to the  
125 fascia.

For peer review only

## 127 **METHODS**

128 This study consists of a systematic review and a consecutive IPDMA. We will contact authors  
129 of studies that meet the inclusion criteria and invite them to contribute to the IPDMA. This  
130 study is registered with the International prospective register of systematic reviews  
131 (PROSPERO) (registration number CRD42019121173). This protocol is reported according  
132 to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols  
133 (PRISMA-P) statement.<sup>25</sup> Description and date of all amendments will be reported. The final  
134 manuscript will be reported according to PRISMA-Individual Participant Data (PRISMA-  
135 IPD) Statement.<sup>24</sup>

### 137 **Systematic Review**

#### 138 **Eligibility criteria**

139 Randomized trials that investigate the use of TCS, compared to the exact same but non-coated  
140 sutures, in patients that underwent open abdominal surgery are potentially eligible. Studies  
141 investigating the effect of TCS for abdominal skin closure, and/or abdominal fascia closure  
142 will both be eligible. If studies only report the SSI incidence but not the AWD incidence,  
143 authors will be asked if AWD incidence is registered (either for the trial or in the medical  
144 record for regular care) and available. Trials will only be included if they can share either IPD  
145 or aggregated data on the incidence of AWD within 30 days after surgery. If AWD incidence  
146 is not available, the study will not be included. We will exclude studies if TCS are part of a  
147 bundle of interventions, and studies that investigate the use of TCS after right lower quadrant  
148 incision for appendectomy. There will be no restrictions on publication date, language or  
149 publication status.

#### 151 **Literature search**

152 The PubMed (MEDLINE), EMBASE online databases (Ovid) and Cochrane Central Register  
153 of Controlled Trials (CENTRAL) will be searched. To identify potential unpublished  
154 evidence or any on-going trials, the International Clinical Trials Registry Platform will be  
155 searched. References of included studies will be hand searched for any additional relevant  
156 studies. In addition, meta-analyses investigating the effect of TCS on the incidence of SSI will  
157 be searched for possibly missed eligible studies. The corresponding authors from the

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3 158 collaborating studies will be contacted to review the list of identified studies for omission of  
4  
5 159 potentially relevant studies.

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7 160 A professional clinical librarian will be consulted to develop the search strategy. The search  
8  
9 161 includes the free text and index terms: sutures, polyglactin 910, vicryl, polydioxanone, PDS,  
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11 162 triclosan, wound infection, surgical wound dehiscence, fascial dehiscence and burst abdomen.  
12  
13 163 These terms will be combined with the Cochrane highly sensitive search strategy for  
14  
15 164 identifying randomised trials.<sup>26</sup> The final search strategy is presented in supplementary  
16  
17 165 appendix 1.

18 166

## 19 20 21 167 **Study selection**

22  
23 168 All studies, identified by the search strategy, will be handled through Rayyan (QCRI)<sup>27</sup>.  
24  
25 169 Duplicates will be removed. Two reviewers (AST and NW) will independently assess the  
26  
27 170 studies based on previously described eligibility criteria. After screening title and abstract, full  
28  
29 171 text of potentially eligible studies will be retrieved and assessed. When it is not possible to  
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31 172 retrieve the manuscript or study eligibility is not clear, the authors will be contacted to  
32  
33 173 provide further information. Any discrepancies in study selection will be resolved through  
34  
35 174 discussion or, when necessary, by consultation with the principle investigator. We will keep a  
36  
37 175 list with reasons for exclusions for all articles that pass title and abstract screening but are  
38  
39 176 deemed ineligible for inclusion. Only trials that can provide either IPD or aggregated data on  
40  
41 177 AWD incidence will meet the criteria for final inclusion in the IPDMA.

42 178

## 43 179 **Individual Patient Data Meta-Analysis**

### 44 45 180 **Study collaboration invitation**

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48 181 Authors from potentially eligible studies will be contacted and invited to contribute to the  
49  
50 182 IPDMA if their study indeed meets the inclusion criteria. An email invitation letter will be  
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52 183 sent to the corresponding authors, outlining the IPMDA goals. If no reply is received within  
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54 184 two weeks, a second email request will be sent to both the corresponding and first author. If  
55  
56 185 again no response is received, we will try to contact all individual authors by email and/or  
57  
58 186 telephone. IPD and/or aggregated data on AWD will be considered unavailable if numerous  
59  
60 187 times (at least five) no reply is received, if authors no longer have access to the study data or  
188 188 authors do not consent for collaboration. Collaborating investigators will be asked to critically

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3 189 appraise the study protocol, provide feedback, approve the finalised version, and will be  
4 190 offered co-authorship on the publication of the study protocol. By sharing their IPD,  
5 191 collaborators will be offered one co-authorship on the IPDMA manuscript, with one  
6 192 additional co-authorship if data of more than 300 participants is shared.  
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10 193

### 11 194 **Risk of bias**

12  
13  
14 195 Two reviewers (AST and NW) will independently assess the quality of the included studies  
15 196 using the revised tool for assessing Risk of Bias in randomised trials (Rob 2).<sup>28</sup> Studies will  
16 197 be judged as “low risk”, “some concerns” or “high risk of bias”. Only data from the original  
17 198 manuscripts and study protocols will be used to ensure consistent and uniform assessments of  
18 199 studies that do and studies that do not provide IPD. Presence of publication bias will be  
19 200 assessed with the construction of a contour enhanced funnel plot.<sup>29</sup>  
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### 27 202 **Data collection process**

28  
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30 203 The collaborating investigators will be requested to sign a data transfer agreement before de-  
31 204 identified IPD is shared. The agreement describes the purposes of the IPDMA, the ownership  
32 205 of the IPD and confirms that the IPD is stored on a secure location. A researcher (AST) will  
33 206 conduct data collection, an interview on the study protocol and a formal handoff of the data  
34 207 codebook, if possible, in person. The primary objective will be to collect IPD for all  
35 208 outcomes. Aggregated data will only be collected if IPD is not available. If aggregated study  
36 209 data are not reported in the publication, this will be requested from the study authors.  
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### 44 211 **Data items**

45  
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47 212 We will propose a selection of data items of interest (with definitions and measures). All  
48 213 collaborating investigators will be asked to criticise and supplement this list. To ease the  
49 214 process of data handover, collaborating investigators can opt to share the complete data set of  
50 215 their study. We will select and clean only those data items that were selected collaboratively.  
51 216 After repeated consultation with the collaborating investigators we selected data items on  
52 217 study-level and data items on participant-level. The list of data items with definitions is  
53 218 presented in supplementary appendix 2. Study-level data includes: study design (number of  
54 219 participating centers, blinding, randomised tissue layer, TCS specification, sample size),  
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3 220 inclusion- and exclusion criteria, and primary- and secondary outcomes. Participant-level data  
4  
5 221 includes: baseline characteristics (age, gender, ASA score, BMI, COPD, smoking status, and  
6  
7 222 previous midline incisions), and procedural characteristics (received suture, procedural status,  
8  
9 223 target organ, wound classification, duration of surgery, and incision type).

10 224

### 11 225 **Outcomes**

12  
13 226 The primary outcome is the incidence of AWD requiring reoperation. AWD is defined as  
14  
15 227 spontaneous dehiscence of the abdominal fascia within 30 days postoperatively. Reoperation,  
16  
17 228 for any indication other than AWD, is not regarded as AWD.

18  
19 229 Secondary outcomes are incisional SSI within 30 days after surgery according to the CDC  
20  
21 230 criteria (specified as superficial and/or deep)<sup>30</sup>, skin wound dehiscence, length of hospital  
22  
23 231 stay, all-cause reoperations within 30 days after surgery, and all-cause mortality within 30  
24  
25 232 days after surgery.

26 233

### 27 234 **Data integrity**

28  
29 235 IPD will be checked for missing, invalid, out-of-range and inconsistent outcomes and for  
30  
31 236 discrepancies with the published aggregated data. When detected, we will seek to resolve the  
32  
33 237 issues with the collaborating investigators to improve data quality and ensure that trials are  
34  
35 238 represented accurately. To ensure all randomised patients are included, IPD will be compared  
36  
37 239 with the aggregated data from the original studies. In the case of any concerns on IPD  
38  
39 240 integrity that cannot be resolved with the collaborating investigators, the data of the  
40  
41 241 concerning study will not be included in the analysis. Checking baseline imbalances will be  
42  
43 242 used to assess randomisation and allocation concealment. Pattern and extent of follow-up will  
44  
45 243 be checked.

244

### 46 245 **Missing data**

47  
48 246 For the primary analysis, we will not perform imputation of the complete variable for a study  
49  
50 247 if variables are systematically missing in one or multiple trials. Missing data at participant  
51  
52 248 level will be assumed to be at random. Multivariate imputation by chained equations (MICE)  
53  
54 249 will be used to handle missing data. Multiple rounds of imputation will be used to estimate the  
55  
56 250 missing value. Percentage of missing data will determine the number of imputation sets.  
57  
58 251 MICE will be done for each individual trial before merged in the aggregated database.

59 252

## 253 **Data synthesis**

254 The raw IPD from each study will be copied to a separate database and recoded according to  
255 the predefined IPDMA settings. The recoded IPD will then be combined into one IPD  
256 database containing the IPD from all studies. Dichotomous data will be expressed using risk  
257 ratios (RR) with corresponding 95% confidence intervals (CI). Continuous data will be  
258 expressed using weighted mean differences with corresponding 95% CI. Data will be  
259 analysed according to the intention-to-treat-principle, meaning that the original randomisation  
260 allocation is used to define treatment groups, regardless of the treatment that is actually  
261 received.

262 The primary analysis will be performed in a one-step approach using only individual patient  
263 data (IPD). Because the availability of IPD is not an inclusion criterion, it might occur that  
264 some trials can only share aggregated data for one or more outcomes. In the additional two-  
265 step analysis, aggregated data of outcomes for which IPD is not available, will be added and  
266 analysed. For the one-step approach we will use a generalised linear mixed model framework  
267 and an appropriate statistical model for the type of outcome. We will use a linear regression  
268 model for continuous outcome data and a log-binomial model for binary outcome data. If the  
269 log-binomial model fails to converge we will use a log-binomial generalised estimating  
270 equation (GEE) or a log Poisson GEE model.<sup>31</sup> A random intercept and, if appropriate, a  
271 random slope will be added to account for clustering of patients within studies. Potential  
272 confounding variables that, despite randomisation, show baseline imbalances across treatment  
273 arms will be added to the appropriate model. Variable selection will be based on  
274 VanderWeeles<sup>32</sup> principles of confounder selection. In short; we will control for each variable  
275 that is considered a cause of the intervention, the outcome, or both and for any proxy of  
276 unmeasured variable that is considered a cause of the intervention and outcome. We will limit  
277 the number of variables included in the model by the number of observed events in the dataset  
278 with a factor of 1:10. Only variables that are available in all trials are eligible for confounder  
279 selection. Additionally, we will perform a two-step approach. In this analysis, IPD from all  
280 studies will be reanalysed separately in a similar fashion as the one-step approach but without  
281 the term for trial clustering. Aggregated study data of outcomes for which no IPD is available  
282 will be added in the two-step approach. The aggregated data of each study will then be  
283 summarised, synthesising an overall estimate using DerSimonian and Laird method assuming  
284 random effects.

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3 285 Statistical heterogeneity among studies will be evaluated using the Chi<sup>2</sup> test and expressed  
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5 286 using the I<sup>2</sup> statistic. The between-study variance will be assessed using the Tau<sup>2</sup> statistic. As  
6  
7 287 all tests are pre-specified and effects follow from our hypothesis no correction for multiple  
8  
9 288 testing will be performed.

10 289

### 11 12 13 290 **Additional analysis**

14  
15 291 All additional analyses will be performed using the one-step approach. Besides the intention-  
16  
17 292 to-treat analysis we will perform an as-treated analysis in which participants are analyzed  
18  
19 293 according to the type of suture that was actually used rather than the randomization allocation.  
20  
21 294 When a patient is reoperated, the study-suture is removed and the effect of the used suture on  
22  
23 295 future AWD is diminished if not completely absent. As a result, inclusion of patients that  
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25 296 underwent a reoperation might affect the observed treatment effect. We will investigate this in  
26  
27 297 a per-protocol analysis in which patient that underwent a reoperation for any indication other  
28  
29 298 than AWD are excluded. This analysis was added during the peer review process.

30 299 Subgroup analyses will be performed according to the specific type of suture that is used for  
31  
32 300 wound closure (polyglactin 910 or polydioxanone), and the level of contamination (according  
33  
34 301 to the Center for Disease Control and Prevention).

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36 302 The risk to develop and incisional hernia is higher after a midline incision than after a non-  
37  
38 303 midline incision.<sup>33</sup> As such, different incision types may also have different risks for AWD.  
39  
40 304 Inclusion of patients with a non-midline incision introduces some degree of clinical  
41  
42 305 heterogeneity and may affect the observed treatment effect. Therefore, we will perform a  
43  
44 306 sensitivity analysis specifically investigating midline incisions. Additional sensitivity analyses  
45  
46 307 will be performed to assess the effect of the additional use of TCS for skin closure and the  
47  
48 308 effect of adding confounders that pass criteria for confounder selection but are not included in  
49  
50 309 the former model as the variables are not reported in all included studies. Potential bias will  
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52 310 further be explored in sensitivity analyses specifically investigating trials that blinded  
53  
54 311 participants and personnel and through exclusion of trials assessed at high risk of bias. A  
55  
56 312 complete case analysis will be performed to investigate the effect of imputation of missing  
57  
58 313 data.

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### 60 315 **Confidence in cumulative estimate**



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2  
3 316 The quality of evidence will be judged using the Grading of Recommendations Assessment  
4 317 Development and Evaluation (GRADE) working group methodology for the following  
5 318 domains: risk of bias, unexplained inconsistency, indirectness, imprecision, publication bias,  
6 319 magnitude of effect, and residual confounding.<sup>34</sup> The level of evidence will be downgraded  
7 320 for imprecision based the optimal information size and the confidence interval. If the optimal  
8 321 information size is met and the confidence interval fails to excluded important benefit or  
9 322 harm, we will rate down for imprecision. We set a default threshold for appreciable benefit  
10 323 and harm that warrants rating down (relative risk reduction (RRR) or RR of 25% or more).  
11 324 The level of evidence will be upgraded for a large magnitude of effect (RR >2 or <0.5) or  
12 325 very large magnitude of effect (RR >5 or <0.02). The overall quality will be classified using  
13 326 four levels: high, moderate, low and very low.

327

### 328 **Software**

329 Statistical analysis will be done using R 4.0.4., and/or SPSS, and/or STATA.

330

### 331 **Patient and public involvement**

332 No patients or patient federations are involved in the design of this study protocol nor the  
333 IPDMA. Yet, the disastrous consequences of AWD are well described, underlining the need  
334 for (surgical) interventions that reduce the risk of AWD.<sup>1</sup>

335

### 336 **Study status**

337 Currently we have executed the systematic review. We are in contact with the authors from  
338 the original studies. We have not collected any data from the original manuscripts nor  
339 received IPD from any of the collaborators.

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## 340 DISCUSSION

341 We designed an individual participant data meta-analysis with the aim to evaluate the effect  
342 of using TCS for abdominal wound closure on the incidence of AWD. This protocol describes  
343 intended methodology and statistical analysis ahead of analysis to provide transparency and  
344 receive timely feedback.

345  
346 Based on the observed risk difference in the largest published trial, a new RCT investigating  
347 the effect TCS on AWD should include around 1500 participants. Such trial would be very  
348 time consuming and expose numerous patients to random assignment of two treatments while  
349 sufficient information to assess comparative effectiveness may already be available.

350 Moreover, the effect of TCS for wound closure on the risk of SSI is well-documented, and  
351 SSI and subsequent AWD risk are closely related. A new RCT is therefore not ethical before  
352 the already available information has been optimally analysed.

353  
354 IPDMA is considered the ‘gold standard’ in meta-analysis.<sup>35</sup> At the core of its strength is the  
355 use of individual participant data of available trials that allows standardisation of inclusion  
356 criteria, definitions, and statistical methods to reduce both clinical and statistical  
357 heterogeneity. Individual participant data also allows testing of interaction effects to assess  
358 subgroup differences and permits exploration of data that was not included in the original  
359 publications. Importantly, IPDMA requires intensive collaboration with all trialists on a  
360 certain topic, and consequently contributes to consensus on the interpretation of the available  
361 data among subject matter experts.

362  
363 Despite these advantages, an IPDMA has some potential limitations. Its quality depends on  
364 the quality, size and number of available studies, the number of included participants, the  
365 availability of high-quality data and, most importantly, the willingness to collaborate among  
366 the original trialists. We have been incredibly fortunate to find so many of the original  
367 researchers willing to collaborate and contribute to the project. The expert input of all  
368 involved trialist has greatly contributed to the completion of the study protocol. In consensus  
369 meetings, we discussed the differences in data collection and variable definition between the  
370 studies. Consequently, we selected a primary outcome for which all studies would be able to  
371 uniformly provide data, being AWD requiring reoperation. Despite being a universally  
372 available outcome definition, it remains limited by the absence of a strict criteria on when to

1  
2  
3 373 reoperate. Variation between clinicians exist and the consideration on whether or not to re-  
4  
5 374 operate are hard if not impossible to retrieve. As selective reoperation by biased investigators  
6  
7 375 may affect the results, we will perform a sensitivity analysis only including trials that blinded  
8  
9 376 both participants and personnel making selective reoperation near impossible. Blinding for  
10  
11 377 allocation is easily performed because the sutures look identical.  
12

13 378

14 379 In conclusion, this study protocol describes an individual participant data meta-analysis in  
15  
16 380 which we aim to investigate if the use of TCS for abdominal wound closure reduces the risk  
17  
18 381 of AWD. If a lower incidence of AWD is observed, this may have considerable consequences  
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20 382 for daily practice.  
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## 383 **ETHICS AND DISSEMINATION**

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### 385 **Ethical approval**

386 All individual trials were approved by a medical ethics committee according to national  
387 legislation. The medical ethics committee of the Amsterdam UMC, location AMC in the  
388 Netherlands waived the necessity for a formal approval of this study, as this research does not  
389 fall under the Medical Research involving Human Subjects Act.

390

### 391 **Dissemination:**

392 The results of this study will be submitted to peer-reviewed journals regardless of the  
393 outcome. The protocol will be submitted before the data is gathered and analysed.

394

### 395 **Contributorship statement**

396 MAB is guarantor of the study. SWJ and MAB conceived the study. AST, NW, SWJ, MGWD  
397 and MAB designed the study, drafted the study protocol and provided statistical expertise.  
398 AST and NW provided input for the literature search and will coordinate the assembly of the  
399 data and perform the screening, inclusion and assessment of risk of bias.

400 FP, PK, CJ, CS, KI, TR, JB, AV, LG, JRT, AMH and TN provided substantial contributions  
401 to the study design, provided critical feedback and approved the final version of the study  
402 protocol. All authors compliant with their responsibilities according to the research protocol,  
403 meet authorship criteria as defined by the international committee of medical journal editors.

404 AST and NW contributed equally to this paper.

405 MGWD, MAB and SWJ contributed equally to this paper.

406

### 407 **Sponsor**

408 This is an investigator-initiated study. The sponsor of this study is the Amsterdam UMC,  
409 location Amsterdam, the Netherlands. The study protocol is written solely by members of the

1  
2  
3 410 steering committee and the industry had no say in study design, data items, data collection,  
4  
5 411 data analysis and data reporting.  
6

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10 413 **Funding**

11  
12 414 This study is supported by a grant from Johnson & Johnson.  
13

14 415

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17 416 **Competing interest**

18  
19 417 AST, NW, FP, PK, CS, KI, TR, JB, AV, LG, JRT, AMH, TN, MGWD and SWJ declare no  
20  
21 418 conflict of interest. CJ is an advisory board member of Johnson & Johnson/Ethicon. MAB  
22  
23 419 reports receiving institutional grants from J&J/Ethicon, KCI/3M, and New Compliance; and is  
24  
25 420 an advisory board member and/or speaker and/or instructor for KCI/3M, Johnson &  
26  
27 421 Johnson/Ethicon, LifeCell/Allergan, Bard, Gore, TelaBio, Medtronic, GD Medical, and Smith  
28  
29 422 & Nephew.  
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32  
33 424 **Acknowledgement**

34  
35 425 The authors would like to thanks F.S. van Etten - Jamaludin, clinical librarian for the help  
36  
37 426 with the literature search.  
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## Supplementary appendix 1: Search strategy

### PubMed:

("Triclosan"[Mesh] OR "Anti-Infective Agents, Local"[Mesh] OR triclosan\*[tiab] OR antimicrobial\*[tiab] OR antibacterial\*[tiab] OR antiseptic\*[tiab] OR antibiotic\*[tiab]) AND ("Sutures"[Mesh] OR "Polyglactin 910"[Mesh] OR "Polydioxanone"[Mesh] OR suture\*[tiab] OR vicryl\*[tiab] OR polyglactin\*[tiab] OR PDS II[tiab] OR polydioxanone\*[tiab]) AND ("Surgical Wound Infection"[Mesh] OR "Surgical Wound Dehiscence"[Mesh] OR surgical wound infection\*[tiab] OR surgical site infection\*[tiab] OR postoperative infection\*[tiab] OR surgical infection\*[tiab] OR wound infection\*[tiab] OR SSI[tiab] OR SSIs[tiab] OR abdominal wound dehiscence\*[tiab] OR abdominal wall dehiscence\*[tiab] OR fascial dehiscence\*[tiab] OR burst abdomen\*[tiab]) AND ("Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "drug therapy" [Subheading] OR randomized [tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

### EMBASE:

(1) triclosan/ or exp topical antiinfective agent/ or (triclosan\* or antimicrobial\* or antibacterial\* or antiseptic\* or antibiotic\*).ti,ab,kw. (2) exp suture/ or polyglactin/ or polydioxanone/ or absorbable suture/ or poliglecaprone suture/ or polydioxanone suture/ or polyglactin suture/ or (suture\* or vicryl\* or polyglactin\* or PDS\*).ti,ab,kw. (3) wound infection/ or surgical infection/ or wound dehiscence/ or (surgical wound infection\* or surgical site infection\* or postoperative infection\* or surgical infection\* or wound infection\* or SSI or SSIs or abdominal wound dehiscence\* or abdominal wall dehiscence\* or fascial dehiscence\* or burst abdomen\*).ti,ab,kw. (4) randomized controlled trial/ or controlled clinical trial/ or drug therapy.fs. or (randomized or placebo or randomly or trial or groups).ti,ab,kw. (5) 1 and 2 and 3 and 4 (6) exp animal/ not human/ (7) 5 not 6 (8) limit 7 to conference abstract status (9) 7 not 8

### Cochrane Central Register of Controlled Trials:

(1) (triclosan\* or antimicrobial\* or antibacterial\* or antiseptic\* or antibiotic\*):ti,ab,kw (2) MeSH descriptor: [Anti-Infective Agents, Local] explode all trees (3) #1 or #2 (4) (suture\* or vicryl\* or polyglactin\* or polydioxanone or PDS\*):ti,ab,kw (5) (surgical wound infection\* or surgical site infection\* or postoperative infection\* or surgical infection\* or wound infection\* or SSI or SSIs or abdominal wound dehiscence\* or abdominal wall dehiscence\* or fascial dehiscence\* or burst abdomen\*):ti,ab,kw (6) #3 and #4 and #5 in Trial

## Supplementary appendix 2: Data items

Study-level data		
<b>Study design</b>	Inclusion- and exclusion criteria	Text
	Inclusion period	Month/year – Month/year
	Number of participating centers	Number
	Blinding	Open label / single / double / triple blind
	Randomised tissue layer	Fascia and / or skin wound
	TCS specification	Polydioxanone / polyglactin 910
	Sample size	Number
	Follow up	(days)
	Primary and secondary outcomes	Text
	Standardised use of prophylactic antibiotics	Yes / no
Participant-level data		
<b>Baseline</b>	Age	Year
	Gender	Male or female
	ASA Physical Status score	Number
	Body mass index	Kg/m <sup>2</sup>
	Active cigarette smoking	Yes / no
	Diabetes mellitus (any type)	Yes / no
	Chronic obstructive pulmonary disease	Yes / no
	Previous midline incision	Yes / no (if yes: number)
<b>Procedural</b>	Randomisation allocation	Intervention / control
	Received suture	TCS / non-TCS
	Status	Elective / emergent
	Target organ	Upper gastrointestinal / small intestine / colorectal / hepato-pancreato-biliary / other
	Wound classification	According to the Center for Disease Control and Prevention classification
	Duration of surgery	According to hospital definition (min)
	Incision type	Midline (at least partly) / non-midline
<b>Outcome</b>	Spontaneous abdominal wound dehiscence, within 30 days after operation, requiring reoperation	Yes / no
	Abdominal skin wound dehiscence	Yes / no
	Surgical Site Infection	According to the Center for Disease Control and Prevention classification into superficial, deep and organ space
	Postoperative length of hospital stay	(days)
	All cause reoperation within 30 days after surgery	Yes / no
	All cause 30 days mortality	Yes / no

## PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>ADMINISTRATIVE INFORMATION</b>					
<b>Title</b>					
Identification	1a	Identify the report as a protocol of a systematic review	✓	<input type="checkbox"/>	2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	✓	Not applicable
<b>Registration</b>	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	✓	<input type="checkbox"/>	75
<b>Authors</b>					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓	<input type="checkbox"/>	13-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓	<input type="checkbox"/>	395-405
<b>Amendments</b>	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	✓	<input type="checkbox"/>	133
<b>Support</b>					
Sources	5a	Indicate sources of financial or other support for the review	✓	<input type="checkbox"/>	413-414
Sponsor	5b	Provide name for the review funder and/or sponsor	✓	<input type="checkbox"/>	408-409
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	✓	<input type="checkbox"/>	409-411
<b>INTRODUCTION</b>					
<b>Rationale</b>	6	Describe the rationale for the review in the context of what is already known	✓	<input type="checkbox"/>	91-116
<b>Objectives</b>	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓	<input type="checkbox"/>	117-125
<b>METHODS</b>					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
<b>Eligibility criteria</b>	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	✓	<input type="checkbox"/>	138-149
<b>Information sources</b>	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	✓	<input type="checkbox"/>	152-159
<b>Search strategy</b>	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓	<input type="checkbox"/>	160-165
<b>STUDY RECORDS</b>					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	<input type="checkbox"/>	168
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	✓	<input type="checkbox"/>	169-177
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	✓	<input type="checkbox"/>	202-209
<b>Data items</b>	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	✓	<input type="checkbox"/>	211-223
<b>Outcomes and prioritization</b>	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	<input type="checkbox"/>	225-232
<b>Risk of bias in individual studies</b>	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	✓	<input type="checkbox"/>	194-200
<b>DATA</b>					
<b>Synthesis</b>	15a	Describe criteria under which study data will be quantitatively synthesized	✓	<input type="checkbox"/>	253-288
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau)	✓	<input type="checkbox"/>	253-288
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	✓	<input type="checkbox"/>	290-313
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	✓	
<b>Meta-bias(es)</b>	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	✓	<input type="checkbox"/>	199-200
<b>Confidence in cumulative evidence</b>	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	✓	<input type="checkbox"/>	315-326