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:	*BMJ Open*
Manuscript ID	bmjopen-2021-054534
Article Type:	Protocol
Date Submitted by the Author:	15-Jun-2021
Complete List of Authors:	Timmer, Allard; Amsterdam UMC Locatie AMC, Department of Surgery Pianka, Frank; UniversitatsKlinikum Heidelberg, Department of General, Visceral and Transplantation Surgery Justinger, Christoph; Städtisches Klinikum Karlsruhe gGmbH, Department of surgery Stravodimos, Christos; Stadtisches Klinikum Karlsruhe gGmbH, Department of surgery Ichida, Kosuke; Jichi Medical University, Department of Surgery Baracs, József; University of Pecs, Department of Surgery Vereczkei, András; University of Pecs, Department of Surgery Marc-Hernández, Artur; University Isabel I, Department of Humanities and Social Sciences Boermeester, Marja; Amsterdam UMC Locatie AMC, Department of Surgery Wolfhagen, Niels; Amsterdam UMC Locatie AMC, Department of Surgery Knebel, Phillip; UniversitatsKlinikum Heidelberg, Department of General, Visceral and Transplantation Surgery Rikiyama, Toshiki; Jichi Medical University, Department of Surgery Gianotti, Luca ; San Gerardo Hospital, Department of Surgery Ruiz-Tovar, Jaime; Rey Juan Carlos University, Department of Surgery Nakamura, T; Hokkaido University, Department of Surgery Dijkgraaf, Marcel; Amsterdam UMC - Locatie AMC, Clinical Epidemiology, Biostatistics and Bioinformatics de Jonge, Stijn; Amsterdam UMC Locatie AMC, Department of Surgery
Keywords:	Infection control < INFECTIOUS DISEASES, SURGERY, WOUND MANAGEMENT

TITLE PAGE

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

Allard S. Timmer[1]*, Niels Wolfhagen[1]*, Frank Pianka[2], Phillip Knebel[2], Christoph Justinger[3], Christos Stravodimos[3], Kosuke Ichida[4], Toshiki Rikiyama[4], József Baracs[5], András Vereczkei[5], Luca Gianotti[6], Jaime Ruiz-Tovar[7], Artur Marc-Hernández[8], Toru Nakamura[9], Marcel G.W. Dijkgraaf[10]**, Marja A. Boermeester[1]**, Stijn W. de Jonge[1]**

* These authors share first authorship

** These authors share senior authorship

[1] Department of Surgery, Amsterdam UMC, location AMC, Amsterdam Gastroenterology & Metabolism, University of Amsterdam, Amsterdam, The Netherlands

[2] Department of General, Visceral and Transplantation Surgery, University Hospital Heidelberg, Heidelberg, Germany

[3] Department of surgery, Städtisches Klinikum Karlsruhe and Albert-Ludwigs University, Freiburg i.Br., Germany, Karlsruhe, Germany and Freiburg i.Br., Germany

[4] Department of Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

[5] Department of Surgery, University of Pécs, Clinical Center, Pécs, Hungary.

[6] School of Medicine and Surgery and Department of Surgery, Milano-Bicocca University and San Gerardo Hospital, Monza, Italy

[7] Department of Surgery, Rey Juan Carlos University, Madrid, Spain

[8] Department of Humanities and Social Sciences, University Isabel I, Burgos, Spain.

[9] Department of Gastroenterological Surgery II, Hokkaido University Faculty of Medicine, Sapporo, Japan

[10] Department of Epidemiology and Data Science, Amsterdam UMC, Amsterdam Public Health, University of Amsterdam, Amsterdam, The Netherlands

Corresponding author

Professor M.A. Boermeester, Department of Surgery (suite G4-132.1), Amsterdam UMC, location AMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: m.a.boermeester@amsterdamumc.nl

Word count

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

Key words

Triclosan

Wound dehiscence

Surgical Site Infection

APPENDICES

Appendix 1: Search strategy

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: Ethics approval is not required. Collaborating investigators will de-identify data before sharing. The results will be submitted to a peer-reviewed journal.

Trial Registration Number: PROSPERO CRD42019121173

ARTICLE SUMMARY

Strengths and limitations of this study

- Current available RCTs that investigate the effect of TCS for abdominal wound closure provide insufficiently detailed information regarding acute abdominal wound dehiscence to perform aggregate data meta-analysis.
- IPDMA has the advantages over aggregate meta-analysis that it uses uniform inclusion and exclusion criteria, study data can be checked at participant level, statistical analysis can be standardised and baseline effect modifiers can be identified.
- The strength of this review is depending on the data that is (made) available by the authors of the original studies.

INTRODUCTION

Rationale

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

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

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

exclusion criteria, check the raw data for integrity and missing data, standardise statistical analysis and identify baseline effect modifiers.[22 23]

Objectives

The purpose of this IPDMA is to evaluate the effect of using TCS for abdominal wound closure on the incidence of AWD within 30 days after surgery in patients undergoing open abdominal surgery. A subgroup analysis will be performed according to the specific type of suture that is used for wound closure (polyglactin 910 or polydioxanone). We hypothesise that wound closure with TCS reduces the risk of AWD.

METHODS

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

Systematic Review

Eligibility criteria

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

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

Literature search

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

studies. In addition, meta-analyses investigating the effect of TCS on the incidence of SSI will be searched for possibly missed eligible studies. The corresponding authors from the collaborating studies will be contacted to review the list of identified studies for omission of potentially relevant studies.

A professional clinical librarian will be consulted to develop the search strategy. The search includes the free text and index terms: sutures, polyglactin 910, vicryl, polydioxanone, PDS, triclosan, wound infection, surgical wound dehiscence, fascial dehiscence and burst abdomen. These terms will be combined with the Cochrane highly sensitive search strategy for identifying randomised trials.[25] The final search strategy is presented in appendix 1.

Study selection

All studies, identified by the search strategy, will be handled through Rayyan (QCRI)[26]. Duplicates will be removed. Two reviewers (AST and NW) will independently assess the studies based on previously described eligibility criteria. After screening title and abstract, full text of potentially eligible studies will be retrieved and assessed. When it is not possible to retrieve the manuscript or study eligibility is not clear, the authors will be contacted to provide further information. Any discrepancies in study selection will be resolved through discussion or, when necessary, by consultation with the principle investigator. We will keep a list with reasons for exclusions for all articles that pass title and abstract screening but are deemed ineligible for inclusion. Only studies that provide aggregate data and/or IPD on AWD incidence will meet the criteria for final inclusion in the IPDMA.

Individual Patient Data Meta-Analysis

Study collaboration invitation

Authors from potentially eligible studies will be contacted and invited to contribute to the IPDMA if their study indeed meets the inclusion criteria. An email invitation letter will be sent to the corresponding authors, outlining the IPMDA goals. If no reply is received within two weeks, a second email request will be sent to both the corresponding and first author. If again no response is received, we will try to contact all individual authors by email and/or telephone. IPD and/or aggregate data on AWD will be considered unavailable if numerous times (at least five) no reply is received, if authors no longer have access to the study data or

authors do not consent for collaboration. Collaborating investigators will be asked to critically appraise the study protocol, provide feedback, approve the finalised version, and will be offered co-authorship on the publication of the study protocol. By sharing their IPD, collaborators will be offered one co-authorship on the IPDMA manuscript, with one additional co-authorship if data of more than 300 participants is shared.

Risk of bias

Two reviewers (AST and NW) will independently assess the quality of the included studies using the revised tool for assessing Risk of Bias in randomised trials (Rob 2).[27] Studies will be judged as " *low risk", "some concerns" or "high risk* of bias". Only data from the original manuscripts and study protocols will be used to ensure consistent and uniform assessments of studies that do and studies that do not provide IPD. Presence of publication bias will be assessed with the construction of a contour enhanced funnel plot.[28]

Data collection process

The collaborating investigators will be requested to sign a data transfer agreement before de-identified IPD is shared. The agreement describes the purposes of the IPDMA, the ownership of the IPD and confirms that the IPD is stored on a secure location. A researcher (AST) will conduct data collection, an interview on the study protocol and a formal handoff of the data codebook, if possible, in person. In the event that IPD will not be made available, the reason will be recorded and, if possible, the aggregate data of the particular study will be used instead.

Aggregate data will be collected as appropriate by two independent researchers (AST and NW) according to a predefined data extraction sheet and overseen by the principle investigator to settle potential discrepancies.

Data items

We will propose a selection of data items of interest (with definitions and measures). All collaborating investigators will be asked to criticise and supplement this list. To ease the process of data handover, collaborating investigators can opt to share the complete data set of

their study. We will select and clean only those data items that were selected collaboratively. After repeated consultation with the collaborating investigators we selected data items on study-level and data items on participant-level. The list of data items with definitions is presented in appendix 2. Study-level data includes: study design (number of participating centers, blinding, randomised tissue layer, TCS specification, sample size), inclusion- and exclusion criteria, and primary- and secondary outcomes. Participant-level data includes: baseline characteristics (age, gender, ASA score, BMI, COPD, smoking status, and previous midline incisions), and procedural characteristics (received suture, procedural status, target organ, wound classification, duration of surgery, and incision type).

Outcomes

The primary outcome is the incidence of AWD requiring reoperation. AWD is defined as spontaneous dehiscence of the abdominal fascia within 30 days postoperatively. Reoperation, for any indication other than AWD, is not regarded as AWD.

Secondary outcomes are SSI within 30 days after surgery according to the CDC criteria (specified as superficial, deep, organ/space), skin wound dehiscence, length of hospital stay, all-cause reoperations within 30 days after surgery, and all-cause mortality within 30 days after surgery.

Data integrity

IPD will be checked for missing, invalid, out-of-range and inconsistent outcomes and for discrepancies with the published aggregate data. When detected, we will seek to resolve the issues with the collaborating investigators to improve data quality and ensure that trials are represented accurately. To ensure all randomised patients are included, IPD will be compared with the aggregate data from the original studies. In the case of any concerns on IPD integrity that cannot be resolved with the collaborating investigators, the data of the concerning study will not be included in the analysis. Checking baseline imbalances will be used to assess randomisation and allocation concealment. Pattern and extent of follow-up will be checked. When needed, additional follow up to rectify any imbalances may be conducted by the collaborating authors.

Missing data

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

level will be assumed to be at random. Multivariate imputation by chained equations (MICE) will be used to handle missing data. Multiple rounds of imputation will be used to estimate the missing value. Percentage of missing data will determine the number of imputation sets. MICE will be done for each individual trial before merged in the aggregate database.

Data synthesis

The raw data from each study will be copied to a separate database and recoded according to the predefined IPDMA settings. The recoded IPD databases will then be aggregated into one IPD database containing all studies.

Both one and two-step approaches will be used for each outcome separately. Dichotomous data will be expressed using risk ratios (RR) with corresponding 95% confidence intervals (CI). Continuous data will be expressed using weighted mean differences with corresponding 95% CI. Data will be analysed according to the intention-to treat-principle, meaning that the original randomisation allocation is used to define treatment groups, regardless of the treatment that is actually received.

The primary analysis will be performed using the one-step approach, in which IPD from all studies will be analysed using the generalised linear mixed model framework and an appropriate statistical model for the type of outcome. We will use a linear regression model for continuous outcome data and a log-binomial model for binary outcome data. If the log-binomial model fails to converge we will use a log-binomial generalised estimating equation (GEE) or a log Poisson GEE model.[29] A random intercept and, if appropriate, a random slope will be added to account for clustering of patients within studies. Potential confounding variables that, despite randomisation, show baseline imbalances across treatment arms will be added to the appropriate model. Variable selection will be based on VanderWeeles[30] principles of confounder selection. The collaborating investigators will be asked to critically appraise the list of potential confounders and to suggest additional variables if indicated (appendix 2). Confounders available in all datasets will be added to the model. The one step approach can be statistically challenging, but has the advantage that it – compared to the two-step approach - is able to more accurately estimate covariate interactions.

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

study will then be summarised in a second step, synthesising an overall estimate using DerSimonian and Laird method assuming random effects.

Statistical heterogeneity among studies will be evaluated using the Chi² test and expressed using the I^2 statistic. The between-study variance will be assessed using the Tau² statistic. When IPD will or cannot not be made available, aggregate study data provided by the collaborating investigators or from the study manuscript will be included in the two step analyses. As all tests are pre-specified and effects follow from our hypothesis no correction for multiple testing will be performed.

Additional analysis

Additional analyses will be performed using the one-step approach. A subgroup analysis will be performed according to the specific type of suture that is used for wound closure (polyglactin 910 or polydioxanone).

The risk of incisional hernia after a midline incision is higher than for a non-midline incision.[31] Although there is currently no evidence that this holds for AWD, we will investigate if the type of incision influences the risk of AWD (midline versus non-midline). Sensitivity analysis will be used to determine if the effect is influenced by the additional use of TCS for skin wound closure. A series of sensitivity analyses will be performed on combinations of confounders that pass criteria for confounder selection but are not included in the former model as the variables are not reported in all included studies. Besides the intention-to-treat analysis we will perform, if feasible, an adjusted per protocol analysis. If the results of the one-step and two-step approaches differ greatly, we will perform the additional analysis also for the two-step approach. Furthermore, we will investigate if adding aggregate data to the IPDMA has an effect on study outcome and perform a sensitivity analysis with trials assessed as low risk of bias.

Confidence in cumulative estimate

The quality of evidence will be judged using the Grading of Recommendations Assessment Development and Evaluation (GRADE) working group methodology for the following domains: risk of bias, unexplained inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose-response relationship, and residual confounding.[32] The level of

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

Software

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

Patient and public involvement

No patients or patient federations are involved in the design of this study protocol nor the IPDMA. Yet, the disastrous consequences of AWD are well described, underlining the need for (surgical) interventions that reduce the risk of AWD.[1]

Study status

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

ETHICS AND DISSEMINATION

Ethical approval

Ethical approval is not deemed necessary for this study protocol.

Dissemination:

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

Author and collaborative statement

MB is guarantor of the study. MB & SWJ conceived the study. AST, NW and SWJ drafted the study protocol. AST will provide input for the literature search. AST and NW will perform the screening, inclusion and assessment of risk of bias. AST will coordinate the assembly of the data set. AST, NW, SWJ, MGWD, MAB will provide statistical expertise. AST, NW and SWJ will draft the final manuscript under supervision of all co-authors. All authors compliant with their responsibilities according to the research protocol, meet authorship criteria as defined by the international committee of medical journal editors, and contributed to the study protocol, provided critical feedback and approved the final manuscript. All co-authors of the original studies that supplied IPD or additional aggregate data, will be mentioned as non-authorship collaborators to the IPD meta-analysis.

Sponsor

This is an investigator-initiated study. The sponsor of this study is the Amsterdam UMC, location Amsterdam, the Netherlands. The study protocol is written solely by members of the steering committee and the industry had no say in study design, data items, data collection, data analysis and data reporting.

Funding

This study is supported by a grant from Johnson & Johnson.

Competing interest

AST, NW, FP, PK, CS, KI, TR, JB, AV, LG, JRT, AMH, TN, MGWD and SWJ declare no conflict of interest. CJ is an advisory board member of Johnson & Johnson/Ethicon. MAB reports receiving institutional grants from J&J/Ethicon, KCI/3M, and New Compliance; and is an advisory board member and/or speaker and/or instructor for KCI/3M, Johnson & Johnson/Ethicon, LifeCell/Allergan, Bard, Gore, TelaBio, Medtronic, GD Medical, and Smith & Nephew.

Acknowledgement

The authors would like to thanks F.S. van Etten - Jamaludin, clinical librarian for the help with the literature search.

References

1. van Ramshorst GH, Eker HH, van der Voet JA, et al. Long-term outcome study in patients with abdominal wound dehiscence: a comparative study on quality of life, body image, and incisional hernia. *J Gastrointest Surg* 2013;17(8):1477-84. doi: 10.1007/s11605-013-2233-2 [published Online First: 2013/05/30]

2. Mazilu O, Grigoras D, Cnejevici S, et al. Postoperative complete abdominal dehiscence: risk factors and clinical corelations. *Chirurgia-Bucharest* 2009;104(4):419-23.

3. Carlson MA. Acute wound failure. *Surg Clin North Am* 1997;77(3):607-36. doi: 10.1016/s0039-6109(05)70571-5 [published Online First: 1997/06/01]

4. Fleischer GM, Rennert A, Ruhmer M. [Infected abdominal wall and burst abdomen]. *Chirurg* 2000;71(7):754-62. doi: 10.1007/s001040051134 [published Online First: 2000/09/15]

5. Shanmugam VK, Fernandez SJ, Evans KK, et al. Postoperative wound dehiscence: Predictors and associations. *Wound Repair Regen* 2015;23(2):184-90. doi: 10.1111/wrr.12268 [published Online First: 2015/02/17]

6. van Ramshorst GH, Nieuwenhuizen J, Hop WC, et al. Abdominal wound dehiscence in adults: development and validation of a risk model. *World J Surg* 2010;34(1):20-7. doi: 10.1007/s00268-009-0277-y [published Online First: 2009/11/10]

7. de Jonge SW, Atema JJ, Solomkin JS, et al. Meta-analysis and trial sequential analysis of triclosan-coated sutures for the prevention of surgical-site infection. *Br J Surg* 2017;104(2):e118-e33. doi: 10.1002/bjs.10445 [published Online First: 2017/01/18]

8. Diener MK, Knebel P, Kieser M, et al. Effectiveness of triclosan-coated PDS Plus versus uncoated PDS II sutures for prevention of surgical site infection after abdominal wall closure: the randomised controlled PROUD trial. *Lancet* 2014;384(9938):142-52. doi: 10.1016/S0140-6736(14)60238-5 [published Online First: 2014/04/11]

9. Ruiz-Tovar J, Llavero C, Jimenez-Fuertes M, et al. Incisional Surgical Site Infection after Abdominal Fascial Closure with Triclosan-Coated Barbed Suture vs Triclosan-Coated Polydioxanone Loop Suture vs Polydioxanone Loop Suture in Emergent Abdominal Surgery: A Randomized Clinical Trial. *J Am Coll Surg* 2020;230(5):766-74. doi: 10.1016/j.jamcollsurg.2020.02.031 [published Online First: 2020/03/01]

10. Baracs J, Huszar O, Sajjadi SG, et al. Surgical site infections after abdominal closure in colorectal surgery using triclosan-coated absorbable suture (PDS Plus) vs. uncoated

sutures (PDS II): a randomized multicenter study. *Surg Infect (Larchmt)* 2011;12(6):483-9. doi: 10.1089/sur.2011.001 [published Online First: 2011/12/07]

11. Galal I, El-Hindawy K. Impact of using triclosan-antibacterial sutures on incidence of surgical site infection. *Am J Surg* 2011;202(2):133-8. doi: 10.1016/j.amjsurg.2010.06.011 [published Online First: 2011/05/24]
12. Huszar O, Baracs J, Toth M, et al. [Comparison of wound infection rates after colon and rectal surgeries using triclosan-coated or bare sutures -- a multi-center, randomized clinical study]. *Magy Seb* 2012;65(3):83-91. doi: 10.1556/MaSeb.65.2012.3.1 [published Online First: 2012/06/22]
13. Ichida K, Noda H, Kikugawa R, et al. Effect of triclosan-coated sutures on the incidence of surgical site infection after abdominal wall closure in gastroenterological surgery: a double-blind, randomized controlled trial in a single center. *Surgery* 2018 doi: 10.1016/j.surg.2017.12.020 [published Online First: 2018/02/07]
14. Justinger C, Slotta JE, Ningel S, et al. Surgical-site infection after abdominal wall closure with triclosan-impregnated polydioxanone sutures: results of a randomized clinical pathway facilitated trial (NCT00998907). *Surgery* 2013;154(3):589-95. doi: 10.1016/j.surg.2013.04.011 [published Online First: 2013/07/19]
15. Mattavelli I, Rebora P, Doglietto G, et al. Multi-Center Randomized Controlled Trial on the Effect of Triclosan-Coated Sutures on Surgical Site Infection after Colorectal Surgery. *Surg Infect (Larchmt)* 2015;16(3):226-35. doi: 10.1089/sur.2014.005 [published Online First: 2015/03/27]
16. Nakamura T, Kashimura N, Noji T, et al. Triclosan-coated sutures reduce the incidence of wound infections and the costs after colorectal surgery: a randomized controlled trial. *Surgery* 2013;153(4):576-83. doi: 10.1016/j.surg.2012.11.018 [published Online First: 2012/12/25]
17. Olmez T, Berkesoglu M, Turkmenoglu O, et al. Effect of Triclosan-Coated Suture on Surgical Site Infection of Abdominal Fascial Closures. *Surg Infect (Larchmt)* 2019;20(8):658-64. doi: 10.1089/sur.2019.052 [published Online First: 2019/04/23]
18. Rasic Z, Schwarz D, Adam VN, et al. Efficacy of antimicrobial triclosan-coated polyglactin 910 (Vicryl* Plus) suture for closure of the abdominal wall after colorectal surgery. *Coll Antropol* 2011;35(2):439-43. [published Online First: 2011/07/16]
19. Ruiz-Tovar J, Alonso N, Morales V, et al. Association between Triclosan-Coated Sutures for Abdominal Wall Closure and Incisional Surgical Site Infection after Open Surgery in Patients Presenting with Fecal Peritonitis: A Randomized Clinical Trial. *Surg Infect*

(Larchmt) 2015;16(5):588-94. doi: 10.1089/sur.2014.072 [published Online First: 2015/07/15]

20. Tae BS, Park JH, Kim JK, et al. Comparison of intraoperative handling and wound healing between (NEOSORB(R) plus) and coated polyglactin 910 suture (NEOSORB(R)): a prospective, single-blind, randomized controlled trial. *BMC Surg* 2018;18(1):45. doi: 10.1186/s12893-018-0377-4 [published Online First: 2018/07/08]
21. Preventing Surgical Site Infection (SSI) [online] Available at: https://www.jnjmedicaldevices.com/sites/default/files/2020-10/134427-200310%20Global%20Plus%20WHO.pdf (Accessed: 19 March 2021).
22. Riley RD, Lambert PC, Staessen JA, et al. Meta-analysis of continuous outcomes combining individual patient data and aggregate data. *Stat Med* 2008;27(11):1870-93. doi: 10.1002/sim.3165 [published Online First: 2007/12/12]
23. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA* 2015;313(16):1657-65. doi: 10.1001/jama.2015.3656 [published Online First: 2015/04/29]
24. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1. doi: 10.1186/2046-4053-4-1 [published Online First: 2015/01/03]
25. Higgins JP, Green Se. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: https://training.cochrane.org/handbook, 2011
26. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4 [published Online First: 2016/12/07]
27. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi: 10.1136/bmj.l4898 [published Online First: 2019/08/30]
28. Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61(10):991-6. doi: 10.1016/j.jclinepi.2007.11.010 [published Online First: 2008/06/10]

29. Pedroza C, Truong VTT. Estimating relative risks in multicenter studies with a small number of centers - which methods to use? A simulation study. *Trials* 2017;18(1):512. doi: 10.1186/s13063-017-2248-1 [published Online First: 2017/11/04]

30. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol* 2019;34(3):211-19. doi: 10.1007/s10654-019-00494-6 [published Online First: 2019/03/07]

31. Halm JA, Lip H, Schmitz PI, et al. Incisional hernia after upper abdominal surgery: a randomised controlled trial of midline versus transverse incision. *Hernia* 2009;13(3):275-80. doi: 10.1007/s10029-008-0469-7 [published Online First: 2009/03/05]

32. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD [published Online First: 2008/04/26]

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

Appendix 2: Data items

Study-level data		
Study design	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		
Baseline	Age	Year
	Gender	Male or female
	ASA Physical Status score	Number
	Body mass index	Kg/m²
	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)
Procedural	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
Outcome	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

521

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	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	✓	☐	2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	✓	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	✓	☐	72
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓	☐	30-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓	☐	340-350
Amendments	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	✓	☐	130
Support					
Sources	5a	Indicate sources of financial or other support for the review	✓	☐	358-359
Sponsor	5b	Provide name for the review funder and/or sponsor	✓	☐	352-356
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	✓	☐	352-356
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	✓	☐	85-116
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓	☐	117-122
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	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	✓	☐	135-147
Information sources	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	✓	☐	150-157
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓	☐	158-162
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	☐	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)	✓	☐	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	✓	☐	177-189 + 200-207
Data items	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	✓	☐	211-223
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	☐	225-232
Risk of bias in individual studies	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	✓	☐	191-197
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	✓	☐	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)	✓	☐	254-287
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	✓	☐	289-304
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	✓	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	✓	☐	196-197
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	✓	☐	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:	*BMJ Open*
Manuscript ID	bmjopen-2021-054534.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Dec-2021
Complete List of Authors:	Timmer, Allard; Amsterdam UMC Locatie AMC, Department of Surgery Wolfhagen, Niels; Amsterdam UMC Locatie AMC, Department of Surgery Pianka, Frank; UniversitatsKlinikum Heidelberg, Department of General, Visceral and Transplantation Surgery Knebel, Phillip; UniversitatsKlinikum Heidelberg, Department of General, Visceral and Transplantation Surgery Justinger, Christoph; Städtisches Klinikum Karlsruhe gGmbH, Department of surgery Stravodimos, Christos; Stadtisches Klinikum Karlsruhe gGmbH, Department of surgery Ichida, Kosuke; Jichi Medical University, Department of Surgery Rikiyama, Toshiki; Jichi Medical University, Department of Surgery Baracs, József; University of Pecs, Department of Surgery Vereczkei, András; University of Pecs, Department of Surgery Gianotti, Luca ; San Gerardo Hospital, Department of Surgery Ruiz-Tovar, Jaime; Rey Juan Carlos University, Department of Surgery Marc-Hernández, Artur; University Isabel I, Department of Humanities and Social Sciences Nakamura, T; Hokkaido University, Department of Surgery Dijkgraaf, Marcel; Amsterdam UMC - Locatie AMC, Clinical Epidemiology, Biostatistics and Bioinformatics Boermeester, Marja; Amsterdam UMC Locatie AMC, Department of Surgery de Jonge, Stijn; Amsterdam UMC Locatie AMC, Department of Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Medical management
Keywords:	Infection control < INFECTIOUS DISEASES, SURGERY, WOUND MANAGEMENT

TITLE PAGE

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

Allard S. Timmer[1]*, Niels Wolfhagen[1]*, Frank Pianka[2], Phillip Knebel[2], Christoph Justinger[3], Christos Stravodimos[3], Kosuke Ichida[4], Toshiki Rikiyama[4], József Baracs[5], András Vereczkei[5], Luca Gianotti[6], Jaime Ruiz-Tovar[7], Artur Marc-Hernández[8], Toru Nakamura[9], Marcel G.W. Dijkgraaf[10]**, Marja A. Boermeester[1]**, Stijn W. de Jonge[1]**

* These authors share first authorship

** These authors share senior authorship

[1] Department of Surgery, Amsterdam UMC, location AMC, Amsterdam Gastroenterology & Metabolism, University of Amsterdam, Amsterdam, The Netherlands

[2] Department of General, Visceral and Transplantation Surgery, University Hospital Heidelberg, Heidelberg, Germany

[3] Department of surgery, Städtisches Klinikum Karlsruhe and Albert-Ludwigs University, Freiburg i.Br., Germany, Karlsruhe, Germany and Freiburg i.Br., Germany

[4] Department of Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

[5] Department of Surgery, University of Pécs, Clinical Center, Pécs, Hungary.

[6] School of Medicine and Surgery and Department of Surgery, Milano-Bicocca University and San Gerardo Hospital, Monza, Italy

[7] Department of Surgery, Rey Juan Carlos University, Madrid, Spain

[8] Department of Humanities and Social Sciences, University Isabel I, Burgos, Spain.

[9] Department of Gastroenterological Surgery II, Hokkaido University Faculty of Medicine, Sapporo, Japan

[10] Department of Epidemiology and Data Science, Amsterdam UMC, Amsterdam Public Health, University of Amsterdam, Amsterdam, The Netherlands

Corresponding author

Professor M.A. Boermeester, Department of Surgery (suite G4-132.1), Amsterdam UMC, location AMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: m.a.boermeester@amsterdamumc.nl

Word count

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

Key words

Triclosan

Wound dehiscence

Surgical Site Infection

APPENDICES

Appendix 1: Search strategy

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

ARTICLE SUMMARY

Strengths and limitations of this study

- Our individual participant data meta-analysis (IPDMA) allows inclusion and analysis of original trial data - including unpublished data on abdominal wall dehiscence (AWD) – and thereby provides detailed information on the effect of triclosan-coated sutures on AWD.
- By this IPDMA we will be able to check trial data at participant level, standardise inclusion criteria and standardise statistical analysis to minimise heterogeneity, reduce bias and strengthen the conclusion.
- A study limitation is that we aim to collect and analyse trial data of an outcome that was not specified in most of the original studies and individual patient data on this outcome may thus not be available in some trials.
- An IPDMA is statistically challenging and relies on collaboration and input of participating trials.

INTRODUCTION

Rationale

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

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

Objectives

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

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

METHODS

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

Systematic Review

Eligibility criteria

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

Literature search

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

collaborating studies will be contacted to review the list of identified studies for omission of potentially relevant studies.

A professional clinical librarian will be consulted to develop the search strategy. The search includes the free text and index terms: sutures, polyglactin 910, vicryl, polydioxanone, PDS, triclosan, wound infection, surgical wound dehiscence, fascial dehiscence and burst abdomen. These terms will be combined with the Cochrane highly sensitive search strategy for identifying randomised trials.[26] The final search strategy is presented in supplementary appendix 1.

Study selection

All studies, identified by the search strategy, will be handled through Rayyan (QCRI)[27]. Duplicates will be removed. Two reviewers (AST and NW) will independently assess the studies based on previously described eligibility criteria. After screening title and abstract, full text of potentially eligible studies will be retrieved and assessed. When it is not possible to retrieve the manuscript or study eligibility is not clear, the authors will be contacted to provide further information. Any discrepancies in study selection will be resolved through discussion or, when necessary, by consultation with the principle investigator. We will keep a list with reasons for exclusions for all articles that pass title and abstract screening but are deemed ineligible for inclusion. Only trials that can provide either IPD or aggregated data on AWD incidence will meet the criteria for final inclusion in the IPDMA.

Individual Patient Data Meta-Analysis

Study collaboration invitation

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

appraise the study protocol, provide feedback, approve the finalised version, and will be offered co-authorship on the publication of the study protocol. By sharing their IPD, collaborators will be offered one co-authorship on the IPDMA manuscript, with one additional co-authorship if data of more than 300 participants is shared.

Risk of bias

Two reviewers (AST and NW) will independently assess the quality of the included studies using the revised tool for assessing Risk of Bias in randomised trials (Rob 2).[28] Studies will be judged as " low risk", "some concerns" or "high risk of bias". Only data from the original manuscripts and study protocols will be used to ensure consistent and uniform assessments of studies that do and studies that do not provide IPD. Presence of publication bias will be assessed with the construction of a contour enhanced funnel plot.[29]

Data collection process

The collaborating investigators will be requested to sign a data transfer agreement before de-identified IPD is shared. The agreement describes the purposes of the IPDMA, the ownership of the IPD and confirms that the IPD is stored on a secure location. A researcher (AST) will conduct data collection, an interview on the study protocol and a formal handoff of the data codebook, if possible, in person. The primary objective will be to collect IPD for all outcomes. Aggregated data will only be collected if IPD is not available. If aggregated study data are not reported in the publication, this will be requested from the study authors.

Data items

We will propose a selection of data items of interest (with definitions and measures). All collaborating investigators will be asked to criticise and supplement this list. To ease the process of data handover, collaborating investigators can opt to share the complete data set of their study. We will select and clean only those data items that were selected collaboratively. After repeated consultation with the collaborating investigators we selected data items on study-level and data items on participant-level. The list of data items with definitions is presented in supplementary appendix 2. Study-level data includes: study design (number of participating centers, blinding, randomised tissue layer, TCS specification, sample size),

inclusion- and exclusion criteria, and primary- and secondary outcomes. Participant-level data includes: baseline characteristics (age, gender, ASA score, BMI, COPD, smoking status, and previous midline incisions), and procedural characteristics (received suture, procedural status, target organ, wound classification, duration of surgery, and incision type).

Outcomes

The primary outcome is the incidence of AWD requiring reoperation. AWD is defined as spontaneous dehiscence of the abdominal fascia within 30 days postoperatively. Reoperation, for any indication other than AWD, is not regarded as AWD.

Secondary outcomes are incisional SSI within 30 days after surgery according to the CDC criteria (specified as superficial and/or deep)[30], skin wound dehiscence, length of hospital stay, all-cause reoperations within 30 days after surgery, and all-cause mortality within 30 days after surgery.

Data integrity

IPD will be checked for missing, invalid, out-of-range and inconsistent outcomes and for discrepancies with the published aggregated data. When detected, we will seek to resolve the issues with the collaborating investigators to improve data quality and ensure that trials are represented accurately. To ensure all randomised patients are included, IPD will be compared with the aggregated data from the original studies. In the case of any concerns on IPD integrity that cannot be resolved with the collaborating investigators, the data of the concerning study will not be included in the analysis. Checking baseline imbalances will be used to assess randomisation and allocation concealment. Pattern and extent of follow-up will be checked.

Missing data

For the primary analysis, we will not perform imputation of the complete variable for a study if variables are systematically missing in one or multiple trials. Missing data at participant level will be assumed to be at random. Multivariate imputation by chained equations (MICE) will be used to handle missing data. Multiple rounds of imputation will be used to estimate the missing value. Percentage of missing data will determine the number of imputation sets. MICE will be done for each individual trial before merged in the aggregated database.

Data synthesis

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

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

Statistical heterogeneity among studies will be evaluated using the Chi² test and expressed using the I² statistic. The between-study variance will be assessed using the Tau² statistic. As all tests are pre-specified and effects follow from our hypothesis no correction for multiple testing will be performed.

Additional analysis

All additional analyses will be performed using the one-step approach. Besides the intention-to-treat analysis we will perform an as-treated analysis in which participants are analyzed according to the type of suture that was actually used rather than the randomization allocation. When a patient is reoperated, the study-suture is removed and the effect of the used suture on future AWD is diminished if not completely absent. As a result, inclusion of patients that underwent a reoperation might affect the observed treatment effect. We will investigate this in a per-protocol analysis in which patient that underwent a reoperation for any indication other than AWD are excluded. This analysis was added during the peer review process.

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

The risk to develop and incisional hernia is higher after a midline incision than after a non-midline incision.[33] As such, different incision types may also have different risks for AWD. Inclusion of patients with a non-midline incision introduces some degree of clinical heterogeneity and may affect the observed treatment effect. Therefore, we will perform a sensitivity analysis specifically investigating midline incisions. Additional sensitivity analyses will be performed to assess the effect of the additional use of TCS for skin closure and the effect of adding confounders that pass criteria for confounder selection but are not included in the former model as the variables are not reported in all included studies. Potential bias will further be explored in sensitivity analyses specifically investigating trials that blinded participants and personnel and through exclusion of trials assessed at high risk of bias. A complete case analysis will be performed to investigate the effect of imputation of missing data.

Confidence in cumulative estimate

The quality of evidence will be judged using the Grading of Recommendations Assessment Development and Evaluation (GRADE) working group methodology for the following domains: risk of bias, unexplained inconsistency, indirectness, imprecision, publication bias, magnitude of effect, and residual confounding.[34] The level of evidence will be downgraded for imprecision based the optimal information size and the confidence interval. If the optimal information size is met and the confidence interval fails to excluded important benefit or harm, we will rate down for imprecision. We set a default threshold for appreciable benefit and harm that warrants rating down (relative risk reduction (RRR) or RR of 25% or more). The level of evidence will be upgraded for a large magnitude of effect (RR >2 or <0.5) or very large magnitude of effect (RR >5 or <0.02). The overall quality will be classified using four levels: high, moderate, low and very low.

Software

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

Patient and public involvement

No patients or patient federations are involved in the design of this study protocol nor the IPDMA. Yet, the disastrous consequences of AWD are well described, underlining the need for (surgical) interventions that reduce the risk of AWD.[1]

Study status

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

DISCUSSION

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

Based on the observed risk difference in the largest published trial, a new RCT investigating the effect TCS on AWD should include around 1500 participants. Such trial would be very time consuming and expose numerous patients to random assignment of two treatments while sufficient information to assess comparative effectiveness may already be available. Moreover, the effect of TCS for wound closure on the risk of SSI is well-documented, and SSI and subsequent AWD risk are closely related. A new RCT is therefore not ethical before the already available information has been optimally analysed.

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

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

reoperate. Variation between clinicians exist and the consideration on whether or not to re-operate are hard if not impossible to retrieve. As selective reoperation by biased investigators may affect the results, we will perform a sensitivity analysis only including trials that blinded both participants and personnel making selective reoperation near impossible. Blinding for allocation is easily performed because the sutures look identical.

In conclusion, this study protocol describes an individual participant data meta-analysis in which we aim to investigate if the use of TCS for abdominal wound closure reduces the risk of AWD. If a lower incidence of AWD is observed, this may have considerable consequences for daily practice.

ETHICS AND DISSEMINATION

Ethical approval

All individual trials were approved by a medical ethics committee according to national legislation. 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.

Dissemination:

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

Contributorship statement

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

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

AST and NW contributed equally to this paper.

MGWD, MAB and SWJ contributed equally to this paper.

Sponsor

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

steering committee and the industry had no say in study design, data items, data collection, data analysis and data reporting.

Funding

This study is supported by a grant from Johnson & Johnson.

Competing interest

AST, NW, FP, PK, CS, KI, TR, JB, AV, LG, JRT, AMH, TN, MGWD and SWJ declare no conflict of interest. CJ is an advisory board member of Johnson & Johnson/Ethicon. MAB reports receiving institutional grants from J&J/Ethicon, KCI/3M, and New Compliance; and is an advisory board member and/or speaker and/or instructor for KCI/3M, Johnson & Johnson/Ethicon, LifeCell/Allergan, Bard, Gore, TelaBio, Medtronic, GD Medical, and Smith & Nephew.

Acknowledgement

The authors would like to thanks F.S. van Etten - Jamaludin, clinical librarian for the help with the literature search.

References

1. van Ramshorst GH, Eker HH, van der Voet JA, et al. Long-term outcome study in patients with abdominal wound dehiscence: a comparative study on quality of life, body image, and incisional hernia. *J Gastrointest Surg* 2013;17(8):1477-84. doi: 10.1007/s11605-013-2233-2 [published Online First: 2013/05/30]
2. Mazilu O, Grigoras D, Cnejevici S, et al. Postoperative complete abdominal dehiscence: risk factors and clinical corelations. *Chirurgia-Bucharest* 2009;104(4):419-23.
3. Carlson MA. Acute wound failure. *Surg Clin North Am* 1997;77(3):607-36. doi: 10.1016/s0039-6109(05)70571-5 [published Online First: 1997/06/01]
4. Fleischer GM, Rennert A, Ruhmer M. [Infected abdominal wall and burst abdomen]. *Chirurg* 2000;71(7):754-62. doi: 10.1007/s001040051134 [published Online First: 2000/09/15]
5. Shanmugam VK, Fernandez SJ, Evans KK, et al. Postoperative wound dehiscence: Predictors and associations. *Wound Repair Regen* 2015;23(2):184-90. doi: 10.1111/wrr.12268 [published Online First: 2015/02/17]
6. van Ramshorst GH, Nieuwenhuizen J, Hop WC, et al. Abdominal wound dehiscence in adults: development and validation of a risk model. *World J Surg* 2010;34(1):20-7. doi: 10.1007/s00268-009-0277-y [published Online First: 2009/11/10]
7. Ahmed I, Boulton AJ, Rizvi S, et al. The use of triclosan-coated sutures to prevent surgical site infections: a systematic review and meta-analysis of the literature. *BMJ Open* 2019;9(9):e029727. doi: 10.1136/bmjopen-2019-029727 [published Online First: 2019/09/05]
8. de Jonge SW, Atema JJ, Solomkin JS, et al. Meta-analysis and trial sequential analysis of triclosan-coated sutures for the prevention of surgical-site infection. *Br J Surg* 2017;104(2):e118-e33. doi: 10.1002/bjs.10445 [published Online First: 2017/01/18]
9. Henriksen NA, Deerenberg EB, Venclauskas L, et al. Triclosan-coated sutures and surgical site infection in abdominal surgery: the TRISTAN review, meta-analysis and trial sequential analysis. *Hernia* 2017;21(6):833-41. doi: 10.1007/s10029-017-1681-0 [published Online First: 2017/10/19]
10. Uchino M, Mizuguchi T, Ohge H, et al. The Efficacy of Antimicrobial-Coated Sutures for Preventing Incisional Surgical Site Infections in Digestive Surgery: a Systematic Review and Meta-analysis. *J Gastrointest Surg* 2018;22(10):1832-41. doi: 10.1007/s11605-018-3832-8 [published Online First: 2018/06/22]
11. Elsolh B, Zhang L, Patel SV. The Effect of Antibiotic-Coated Sutures on the Incidence of Surgical Site Infections in Abdominal Closures: a Meta-Analysis. *J Gastrointest Surg* 2017;21(5):896-903. doi: 10.1007/s11605-017-3357-6 [published Online First: 2017/01/20]
12. Baracs J, Huszar O, Sajjadi SG, et al. Surgical site infections after abdominal closure in colorectal surgery using triclosan-coated absorbable suture (PDS Plus) vs. uncoated sutures (PDS II): a randomized multicenter study. *Surg Infect (Larchmt)* 2011;12(6):483-9. doi: 10.1089/sur.2011.001 [published Online First: 2011/12/07]
13. Diener MK, Knebel P, Kieser M, et al. Effectiveness of triclosan-coated PDS Plus versus uncoated PDS II sutures for prevention of surgical site infection after abdominal wall closure: the randomised controlled PROUD trial. *Lancet* 2014;384(9938):142-52. doi: 10.1016/S0140-6736(14)60238-5 [published Online First: 2014/04/11]
14. Galal I, El-Hindawy K. Impact of using triclosan-antibacterial sutures on incidence of surgical site infection. *Am J Surg* 2011;202(2):133-8. doi: 10.1016/j.amjsurg.2010.06.011 [published Online First: 2011/05/24]
15. Ichida K, Noda H, Kikugawa R, et al. Effect of triclosan-coated sutures on the incidence of surgical site infection after abdominal wall closure in gastroenterological surgery: a double-blind, randomized controlled trial in a single center. *Surgery* 2018 doi: 10.1016/j.surg.2017.12.020 [published Online First: 2018/02/07]

16. Justinger C, Slotta JE, Ningel S, et al. Surgical-site infection after abdominal wall closure with triclosan-impregnated polydioxanone sutures: results of a randomized clinical pathway facilitated trial (NCT00998907). *Surgery* 2013;154(3):589-95. doi: 10.1016/j.surg.2013.04.011 [published Online First: 2013/07/19]
17. Mattavelli I, Rebora P, Doglietto G, et al. Multi-Center Randomized Controlled Trial on the Effect of Triclosan-Coated Sutures on Surgical Site Infection after Colorectal Surgery. *Surg Infect (Larchmt)* 2015;16(3):226-35. doi: 10.1089/sur.2014.005 [published Online First: 2015/03/27]
18. Nakamura T, Kashimura N, Noji T, et al. Triclosan-coated sutures reduce the incidence of wound infections and the costs after colorectal surgery: a randomized controlled trial. *Surgery* 2013;153(4):576-83. doi: 10.1016/j.surg.2012.11.018 [published Online First: 2012/12/25]
19. Olmez T, Berkesoglu M, Turkmenoglu O, et al. Effect of Triclosan-Coated Suture on Surgical Site Infection of Abdominal Fascial Closures. *Surg Infect (Larchmt)* 2019;20(8):658-64. doi: 10.1089/sur.2019.052 [published Online First: 2019/04/23]
20. Rasic Z, Schwarz D, Adam VN, et al. Efficacy of antimicrobial triclosan-coated polyglactin 910 (Vicryl* Plus) suture for closure of the abdominal wall after colorectal surgery. *Coll Antropol* 2011;35(2):439-43. [published Online First: 2011/07/16]
21. Ruiz-Tovar J, Alonso N, Morales V, et al. Association between Triclosan-Coated Sutures for Abdominal Wall Closure and Incisional Surgical Site Infection after Open Surgery in Patients Presenting with Fecal Peritonitis: A Randomized Clinical Trial. *Surg Infect (Larchmt)* 2015;16(5):588-94. doi: 10.1089/sur.2014.072 [published Online First: 2015/07/15]
22. Ruiz-Tovar J, Llavero C, Jimenez-Fuertes M, et al. Incisional Surgical Site Infection after Abdominal Fascial Closure with Triclosan-Coated Barbed Suture vs Triclosan-Coated Polydioxanone Loop Suture vs Polydioxanone Loop Suture in Emergent Abdominal Surgery: A Randomized Clinical Trial. *J Am Coll Surg* 2020;230(5):766-74. doi: 10.1016/j.jamcollsurg.2020.02.031 [published Online First: 2020/03/01]
23. Riley RD, Lambert PC, Staessen JA, et al. Meta-analysis of continuous outcomes combining individual patient data and aggregate data. *Stat Med* 2008;27(11):1870-93. doi: 10.1002/sim.3165 [published Online First: 2007/12/12]
24. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA* 2015;313(16):1657-65. doi: 10.1001/jama.2015.3656 [published Online First: 2015/04/29]
25. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1. doi: 10.1186/2046-4053-4-1 [published Online First: 2015/01/03]
26. Higgins JP, Green Se. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. 2011
27. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210. doi: 10.1186/s13643-016-0384-4 [published Online First: 2016/12/07]
28. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi: 10.1136/bmj.l4898 [published Online First: 2019/08/30]
29. Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61(10):991-6. doi: 10.1016/j.jclinepi.2007.11.010 [published Online First: 2008/06/10]
30. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1999;20(4):250-78; quiz 79-80. doi: 10.1086/501620 [published Online First: 1999/04/29]
31. Pedroza C, Truong VTT. Estimating relative risks in multicenter studies with a small number of centers - which methods to use? A simulation study. *Trials* 2017;18(1):512. doi: 10.1186/s13063-017-2248-1 [published Online First: 2017/11/04]

32. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol* 2019;34(3):211-19. doi: 10.1007/s10654-019-00494-6 [published Online First: 2019/03/07]
33. Halm JA, Lip H, Schmitz PI, et al. Incisional hernia after upper abdominal surgery: a randomised controlled trial of midline versus transverse incision. *Hernia* 2009;13(3):275-80. doi: 10.1007/s10029-008-0469-7 [published Online First: 2009/03/05]
34. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD [published Online First: 2008/04/26]
35. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010;340:c221. doi: 10.1136/bmj.c221 [published Online First: 2010/02/09]

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		
Study design	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		
Baseline	Age	Year
	Gender	Male or female
	ASA Physical Status score	Number
	Body mass index	Kg/m²
	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)
Procedural	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
Outcome	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	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	✓	☐	2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	✓	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	✓	☐	75
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	✓	☐	13-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	✓	☐	395-405
Amendments	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	✓	☐	133
Support					
Sources	5a	Indicate sources of financial or other support for the review	✓	☐	413-414
Sponsor	5b	Provide name for the review funder and/or sponsor	✓	☐	408-409
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	✓	☐	409-411
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	✓	☐	91-116
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	✓	☐	117-125
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	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	✓	☐	138-149
Information sources	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	✓	☐	152-159
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	✓	☐	160-165
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	✓	☐	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)	✓	☐	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	✓	☐	202-209
Data items	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	✓	☐	211-223
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	✓	☐	225-232
Risk of bias in individual studies	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	✓	☐	194-200
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	✓	☐	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)	✓	☐	253-288
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	✓	☐	290-313
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	✓	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	✓	☐	199-200
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	✓	☐	315-326