PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Timmer, Allard; Wolfhagen, Niels; Pianka, Frank; Knebel, Phillip; Justinger, Christoph; Stravodimos, Christos; Ichida, Kosuke; Rikiyama, Toshiki; Baracs, József; Vereczkei, András; Gianotti, Luca; Ruiz-Tovar, Jaime; Marc-Hernández, Artur; Nakamura, T; Dijkgraaf, Marcel; Boermeester, Marja; de Jonge, Stijn

VERSION 1 – REVIEW

REVIEWER	Nelson, Richard University of Illinois at Chicago, Epidemiology/Biometry
REVIEW RETURNED	09-Aug-2021

GENERAL COMMENTS	Very thorough presentation. I have not reviewed a IPDMA before. Does secondry review of individual patient records require any additional ethics review from the individual contributors as well as your institution? Aside from that it seems ready to go.

REVIEWER	Smith, Margaret University of Oxford, Nuffield Dept of Primary Care Health Sciences
REVIEW RETURNED	19-Aug-2021

GENERAL COMMENTS	The paper does not contain any Discussion section, which should contain a more detailed description of the strengths and limitations of the proposed research. Otherwise, in general, the protocol is clear and detailed. I have some specific comment which are laid out below. Line 74 The Strengths and Limitation bulletin points could be made more specific to the study question. Line 84 Rationale. Can the authors provide a more detailed estimate of the number of studies/participants that are likely to have data on AWD. In other words, from preliminary investigations, do they assess that there are likely to be enough data to do an adequately powered IPDMA? Lines 141-145. Please can you make the Eligibility Criteria clearer. Do included studies have to have data on both the SSI and AWD outcomes, or just AWD? Is this criterion for aggregate or individual data ? Please check that this description is consistent with the last sentence in the Study Selection statement (line 173) (and make that statement clearer). Line 191 How will the risk of bias assessment be used in this IPDMA?

	Line 205 Please explain more clearly when and how aggregate data will be collected and used. For which outcomes? Also see the comment about Line 284-285. Line 243. The meaning of this sentence is unclear to me. "When needed, additional follow up to rectify any imbalances may be conducted by the collaborating authors" Line 256. It would be better to use a different term than "aggregated" for describing the database e.g. "combined". Line 272. Please explain briefly what is meant by van der Veeles principles of confounder selection. The authors might also want to consider whether the number of potential covariates is too many relative to the number of outcomes in each study, leading to overfitting and convergence issues. Line 277. "is able to more accurately estimate covariate interactions". Are the authors planning covariate interactions? Line 284. Is there a mistype here? "When IPD will or cannot not be made available" Lines 284-285. Please explain further about the use of aggregate data. As I understand it this is an IPDMA, so included studies will have IPD. Line 295 "type of incision". Is this another subgroup analysis? If so, could this be made clear? Line 309. Are all GRADE domains relevant to the present study? e.g. dose response?

REVIEWER	Sandblom, Gabriel Karolinska Institute, Center for Digestive Diseasee
REVIEW RETURNED	16-Oct-2021

GENERAL COMMENTS	The paper describes an intended meta-analysis of the effect of triclosan-coated sutures for abdominal wound closure. The design is interesting and has the potential to provide unique data on the effectiveness on the effectiveness of TCS for preventing wound dehiscence. As they have already contacted the authors from the original studies I suppose it is of no use to suggest modifications of the protocol. Nevertheless, I have some comments on the data the authors plan to assemble: 1. How will suspected wound dehiscences and confirmed dehischences in patients not undergoing re-operation be treated? The routines and threshold for deciding on re-operation or imaging diagnostics in case a vague suspicion of wound dehiscence is raised at clinical examination (e.g., moderate wound discharge or mild pain) could vary between the included centres. 2. Why is the suturing technique (interval between the stitches and the distance of the bites from the wound edges) not included? I suspect that this information has not been consistently recorded in all studies, yet it is crucial for the development of wound dehiscence. 3. I would assume that the heterogeneity will be substantially reduced without diminishing the sample size very much if only midline incisions are included.

VERSION 1 – AUTHOR RESPONSE

Comment from Reviewer 1

Reviewer: Dr. Richard Nelson, University of Illinois at Chicago Comments to the Author:
Very thorough presentation. I have not reviewed an IPDMA before. Does secondary review of individual patient records require any additional ethics review from the individual contributors as well as your institution? Aside from that it seems ready to go.

Author response: We would like to thank Dr. Nelson for taking the time to review our study protocol. Prior to the data sharing process, each collaborating centre signed a data transfer agreement (IPDMA study contract). This contract states that data should be pseudonymized, removing names, date of births and . All individual trials were approved by a medical ethics committee according to local legislation. As data transfer is necessary for a project that serves public interest (according to GDPR 6) re-consent of participants is not required. The Medical Ethics Committee of the Amsterdam UMC, location AMC in the Netherlands waived the necessity for a formal approval of this study. This statement of approval will be included in the publication of the manuscript. We hope this explanation is satisfactory to the reviewer.

Amended manuscript [lines 69-73]
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.

Comment from Reviewer 2
Dr. Margaret Smith, University of Oxford Comments to the Author:

2.0 Reviewer: The paper does not contain any Discussion section, which should contain a more detailed description of the strengths and limitations of the proposed research. Otherwise, in general, the protocol is clear and detailed. I have some specific comment which are laid out below.

2.0 Author response: We would like to express our sincere gratitude to dr. Smith for taking the time to review our manuscript and providing us with multiple valuable comments. As proposed by the reviewer we added a discussion section.

Amended manuscript [lines 340-381]
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.[34] 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.

2.1 Reviewer: Line 74 The Strengths and Limitation bulletin points could be made more specific to the study question.

2.1 Author response: We thank the reviewer for pointing out that the included strength and limitations are not study specific and have amended the manuscript accordingly.

Amended manuscript [lines 78-89]
- 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.

2.2 Reviewer: Line 84 Rationale. Can the authors provide a more detailed estimate of the number of studies/participants that are likely to have data on AWD. In other words, from preliminary investigations, do they assess that there are likely to be enough data to do an adequately powered IPDMA?

2.2 Author response: We are more than happy to elaborate on this. During preliminary investigations with the authors from the two largest trials, both confirmed that IPD on AWD could be made available. Assuming the differences measured in the latest trial to be true, their combined sample size will be sufficiently large to detect the expected risk difference. We amended the manuscript and added the description of this preliminary process.

Amended manuscript [lines 112-116]
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.

2.3 Reviewer: Lines 141-145. Please can you make the Eligibility Criteria clearer. Do included studies have to have data on both the SSI and AWD outcomes, or just AWD? Is this criterion for aggregate or individual data ? Please check that this description is consistent with the last sentence in the Study Selection statement (line 173) (and make that statement clearer).

2.3 Author response: We acknowledge that the eligibility criteria are not clear. We amended the inclusion criteria in both the section ‘eligibility criteria’ and the ‘Study selection’

Amended manuscript [lines 139-140]
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.

Amended manuscript [lines 144-145]
Trials will only be included if they can share either IPD or aggregated data on the incidence of AWD within 30 days after surgery.

2.4 Reviewer: Line 191 How will the risk of bias assessment be used in this IPDMA?

2.4 Author response: We thank the reviewer for pointing out the possibility for improvement of our manuscript. The outcome of the risk of bias assessment will be used to select studies for a sensitivity analysis in which trials at high risk of bias are excluded.

Amended manuscript [lines 308-310]
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.

2.5 Reviewer: Line 205 Please explain more clearly when and how aggregate data will be collected and used. For which outcomes? Also see the comment about Line 284-285.

2.5 Author response: We agree with the reviewer that this item is not clear and amended the manuscript.

Amended manuscript [lines 261-265]
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.

Amended manuscript [lines 278-281]
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.

2.6 Reviewer: Line 243. The meaning of this sentence is unclear to me. “When needed, additional follow up to rectify any imbalances may be conducted by the collaborating authors”

2.6 Author response: We thank the reviewer for this observation. This sentence was included before we performed the systematic review. At that period, we had not yet identified all potentially eligible trials, and thus were not aware if all trials used a similar study period to assess the primary outcome. To account for possible differences between trials we added the sentence. We now know that the primary outcome in all trials was assessed one months after surgery and additional follow-up will not be needed. Therefore, we removed the sentence.

2.7 Reviewer: Line 256. It would be better to use a different term than “aggregated” for describing the database e.g. “combined”.

2.6 Author response: We agree with the proposed modification.

Amended manuscript [lines 254-255]
The recoded IPD will then be combined into one IPD database containing the IPD from all studies

2.8 Reviewer: Line 272. Please explain briefly what is meant by vanderWeeles principles of confounder selection. The authors might also want to consider whether the number of potential covariates is too many relative to the number of outcomes in each study, leading to overfitting and convergence issues.

2.8 Author response: We thank the reviewer for pointing out that these principles are not common knowledge and added a brief explanation. Secondly, we will limit the number of variables included in the model by the number of observed events in a 1:10 ratio. Because this was not described clearly, we amended this sentence.

Amended manuscript [lines 272-278]
Variable selection will be based on VanderWeeles 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.

2.9 Reviewer: Line 277. “is able to more accurately estimate covariate interactions”. Are the authors planning covariate interactions?

2.9 Author response: We agree with the reviewer that this is not well explained. One of the main strengths of IPDMA is its ability to explore covariate interactions, in other words whether or not certain subgroups of patients benefit more from an intervention than others. This is now included in the discussion section.

Amended manuscript [lines 353-358]
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.

2.10 Reviewer: Line 284. Is there a mistype here? “When IPD will or cannot not be made available”

2.10 Author response:
We thank the reviewer for pointing out that this sentence does not belong in this paragraph. We meant to describe that aggregated data will be analysed in the two-step approach and have therefore amended the corresponding paragraph.

Amended manuscript [lines 278-281]
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.

2.11 Author response: Lines 284-285. Please explain further about the use of aggregate data. As I understand it this is an IPDMA, so included studies will have IPD.

2.11 Author response: We acknowledge that it is not well explained whether IPD or aggregate data will be used. We now explain this in more detail.

Amended manuscript [lines 261-265]
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.

2.12 Author response: Line 295 “type of incision”. Is this another subgroup analysis? If so, could this be made clear?

2.12 Author response: We agree with the reviewer that this is not explained clearly. There is no data indicating that use of TCS has a different effect on AWD for different incision types. Because patients undergoing a midline incision have a higher risk to develop an incisional hernia, it may be that the risk of AWD is also higher after a midline incision. Inclusion of patients with a non-midline incision could introduce clinical heterogeneity and affect the observed treatment effect. Therefore, a sensitivity analysis specifically investigating patients undergoing a midline incision will be performed.

Amended manuscript [lines 301-305]
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.

2.13 Author response: Line 309. Are all GRADE domains relevant to the present study? e.g. dose response?

2.13 Author response: We thank the reviewer for this sharp observation. Indeed, dose response relationship is not applicable in this situation as TCS with different dosages triclosan do not exist. We removed this domain.

Comment from Reviewer 3
Dr. Gabriel Sandblom, Karolinska Institute, Karolinska Institutet Department for Clinical Intervention and Technology Comments to the Author:

3.0 Reviewer: The paper describes an intended meta-analysis of the effect of triclosan-coated sutures for abdominal wound closure. The design is interesting and has the potential to provide unique data on the effectiveness of TCS for preventing wound dehiscence. As they have already contacted the authors from the original studies I suppose it is of no use to suggest modifications of the protocol. Nevertheless, I have some comments on the data the authors plan to assemble.

3.0 Author response: We would like to express our sincere gratitude to Dr. Sandblom for taking the time and effort to review our manuscript.

3.1 Reviewer: How will suspected wound dehiscence and confirmed dehiscence in patients not undergoing re-operation be treated? The routines and threshold for deciding on re-operation or imaging diagnostics in case a vague suspicion of wound dehiscence is raised at clinical examination (e.g., moderate wound discharge or mild pain) could vary between the included centers.

3.1 Author response: We thank the reviewer for this interesting point of discussion and we would like to elaborate on this. If AWD is clinically suspected this will be confirmed (or refuted) by physical examination or radiologic imaging. The vast majority of AWD require reoperation. Whether or not a reoperation is performed depends on the clinical status of the patient and final decision made by the treating physician. Variation between clinicians in their threshold to operate and nuances in their considerations are hard if not impossible to capture from trial databases or clinical charts because this consideration is seldom reported and collected during a trial.
During preliminary contact with the authors from potentially eligible trials, we found out that one trial was specifically designed to also detect asymptomatic AWD by the routine use of radiological imaging postoperatively. Because we aimed to define a primary outcome for which all studies would be able to uniformly provide data, and all other trials were not designed to detect asymptomatic AWD, we choose ‘AWD requiring reoperation’ as primary outcome. Being a universally available outcome definition, it remains limited by the absence of a strict criteria when to reoperate. One may argue that selective reoperation in doubtful cases by biased investigators could affect the results. Blinding - easily performed with identically looking sutures - would however make selective reoperation in either group unlikely. Moreover, none of the included trials was designed to assess AWD which makes selective reoperation even more unlikely.
Nonetheless, the issue raised by the reviewer is incredibly important to fully understand the data and we are grateful that it is brought to our attention. We will explore this hypothesis as follows; reoperation by itself is already a secondary outcome in our current protocol. We will inquire with the trialist for a substantiation of the reason for reoperation of each case. Potential differences in reoperation not explainable by chance alone should surface with this approach. To quantify a potential effect of such bias we will conduct an additional sensitivity analysis only including studies that blind participants and personnel and compare both the effect estimate as well as the proportion of re-operation between the two groups.

Amended manuscript [lines 370-376]
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.

Amended manuscript [lines 293-297]
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.

3.2 Reviewer: Why is the suturing technique (interval between the stitches and the distance of the bites from the wound edges) not included? I suspect that this information has not been consistently recorded in all studies, yet it is crucial for the development of wound dehiscence.

3.2 Author response: We thank the reviewer for pointing out another important issue. During preliminary consultation with the authors from eligible trials, we proposed to include data on the suturing technique. As the reviewer correctly suspects, IPD on stitch interval and distance is not available in the majority of the trials.

3.3 Reviewer: I would assume that the heterogeneity will be substantially reduced without diminishing the sample size very much if only midline incisions are included.

3.3 Author response: Because the incidence of AWD is expected to be very low we want to exclude as little participants as possible. There is no data indicating that use of TCS has a different effect on AWD for different incision types. Because patients undergoing a midline incision have a higher risk to develop an incisional hernia, it may be that the risk of AWD is also higher after a midline incision. Thus, inclusion of patients with a non-midline incision could introduce clinical heterogeneity and therewith have an effect on the observed treatment effect. Therefore, a sensitivity analysis specifically investigating patients undergoing a midline incision will be performed. We sincerely hope these explanations are satisfactory to the reviewer.

Amended manuscript [lines 301-305]
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.

VERSION 2 – REVIEW

REVIEWER	Smith, Margaret University of Oxford, Nuffield Dept of Primary Care Health Sciences
REVIEW RETURNED	21-Dec-2021

GENERAL COMMENTS	Thankyou for the clear and very thorough response to reviewer comments.

REVIEWER	Sandblom, Gabriel Karolinska Institute, Center for Digestive Diseasee

REVIEW RETURNED	25-Dec-2021

GENERAL COMMENTS	All my comments have been adequately addressed. I corroborate publishing the manuscript.