NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT507 Plus Sutures

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
1.	09/03/2021	Initial teleconference with the company, raising EAC queries on company submission of clinical evidence		EAC notes from call: Appendix 2
2.	11/03/2021	Ethicon supplied additional written responses to the questions on triclosan submitted in advance of the Company call		Additional responses: Appendix 3

3.	16/03/2021	Expert Engagement meeting	EAC questions for clinical experts shared in advance of the meeting (summarised as appendix to the notes)	Notes from Expert Engagement meeting: Appendix 4
4.	09/04/2021	Company Engagement meeting		Notes from Company Engagement meeting and additional information provided by the Company following the call Appendix 5
5.	09/04/2021	Additional paper provided by the Company		Company provided pdf of additional study: Dhom J, Bloes DA, Peschel A, Hofmann UK. Bacterial adhesion to suture material in a contaminated wound model: Comparison of monofilament, braided, and barbed sutures. J Orthop Res. 2017 Apr;35(4):925-933. doi: 10.1002/jor.23305. Epub 2016 Jun 14. PMID: 27208547.
6.	14/04/2021	Additional paper provided by the Company		Company provided pdf of additional study: 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 May;21(5):896-903. doi: 10.1007/s11605-017-3357-6. Epub 2017 Jan 18. PMID: 28101722.
7.	19/04/2021	Combined EAQs (MIB and MTG) received from NICE		Collated comments from EAQs Appendix 6
8.	19/04/2021	Query to Suzi Patel at Quidel	Good morning Suzi, Hope you had a lovely weekend.	Hi Kim, You are correct - the SE, alpha and beta parameters used in the subgroups analysis in the model were not correct and the base case values

<table>
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<td>We have an additional query regarding the number of sutures (and its modelled distribution) which is applied in the economic model.
There appears to be a difference between the SE, alpha and beta parameters used in the base-case and those used in the different scenarios (adults, children, clean, non-clean) – see below table.

<table>
<tr><th>Analysis</th><th>From economic submission (report)</th><th>From Excel model</th></tr>
<tr><td>Base case</td><td>Distribution Gamma
Standard error 1.53
Based on lower and upper bounds provided by independent clinical experts</td><td>Standard error 1.531
Alpha 10.67
Beta 0.47
[Data_store worksheet, cell C7, E7, F7]

[The 95% CI of this distribution would be from 2.4 to 8.4 sutures]</td></tr>
<tr><td>Adults
Children
Clean
Non-clean</td><td>Not reported</td><td>Standard error 1.020
Alpha 24.0
Beta 0.208
[e.g. Data_store worksheet, cell C19, E19, F19]</td></tr>
</table>
</td>
<td>should have been applied. The model has been updated accordingly, attached.

We do not believe this changes the results provided in the submission dossier itself.

I’ve cc’d our economic modeler, Thibaut, into my reply (who has confirmed this). Please let us know if any further queries?

Many thanks, Suzi</td>
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<table>
<tr><td></td><td></td><td>[The 95% CI of this distribution would be from 3.2 to 7.2 sutures]</td></tr>
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Can you provide some explanation as to why the distribution of number of sutures is different in the scenario analysis?
Many thanks</td>
<td></td>
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<td>9.</td>
<td>19/04/2021</td>
<td>Query sent to clinical experts:</td>
<td>The EAC is currently reviewing the economic model for Plus Sutures. We have been able to validate most of the data inputs used in the model, however, one parameter we have been unable to verify is the average number of unit sutures used (for reference, each unit costs around about £3 and £5 each). The company has made the following estimate which was derived from contacting the authors of an economic study and the company's own expert advisers:
Average number used per procedure: 5
Range (used in sensitivity analysis): 3 to 9

We appreciate this variable will be dependent on the patient (e.g. adult/child) and procedure complexity used, but do these estimates sound reasonable to you? If you have access to any audit data which might be informative this would also be useful.

Many thanks for your help
Best wishes
Emma</td>
<td>
<table>
<tr><th>Sent to</th><th>Replied</th><th>Response</th></tr>
<tr><td>Mike Reed</td><td></td><td></td></tr>
<tr><td>Melissa Rochon</td><td></td><td></td></tr>
<tr><td>Justin Wormald</td><td>26/04/2021</td><td>Briefly, I'd say those figures are reasonable for most operations. Some plastic surgery procedures, such as breast reconstruction, would use many more suture packs (15-20 perhaps), but for most I would say we</td></tr>
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						would use around 5 packs. Let me know if you'd like further info.
				Lillian Chiwera		
				Shafi Mussa	20/04/2021	In cardiac surgery these sutures are used mainly for wound closure. In adults, the average number of “vicryl” sutures used is 2, in paediatrics it is usually 1. Given that sutures occasionally snap, it would be reasonable to say the range in adults is 2-4, and paediatrics 1-2. I personally use vicryl sutures for sternal closure in smaller children (on average 3 sutures per case) but this is not

						routine for all surgeons. I hope this helps. I don't have any audit data to substantiate the numbers but this is based on clinical experience. Happy to discuss further.

Insert more rows as necessary

Appendix 1

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

File attachments/additional information from question X:

Insert

File attachments/additional information from question X:

Insert

File attachments/additional information from question X:

Insert

Appendix 2

Plus Sutures – post submission meeting [Zoom]

Tuesday 09 March 2021, 15:30 – 16:30

In attendance:
Company (Ethicon): Suzi Patel (SP), Gianluca Casali (GC), Stephen Murray (SM), Walt Danker (WD)
Newcastle EAC: Iain Willits (IW), Kim Keltie (KK), Emma Belilios (EB), Kathryn Fletcher (KF)
NICE: Victoria Fitton (VF), Kimberley Carter (KC), Rebecca Owens (RO), Samantha Baskerville (SB).

NOTES

1. **Introductions**

Suzi Patel – Health Economics and Market Access (UK)
Walt Danker - Health Economics and Market Access (Global)
Stephen Murray – Marketing (Europe, Middle East & Africa)
Gianluca Casali – Medical Director (UK & Ireland)

2. **Clinical evidence submission (Part 1): external assessment centre (EAC) questions**

IW thanked the Company for a comprehensive submission – the EAC has very few questions.

The list of questions was circulated in advance of the meeting. The Company's R&D department (based in the US) are working on the questions in parallel and will provide a full response. They will also be happy to answer any additional questions that arise as the assessment progresses, though due to the time difference there may be a slight delay.

ACTION: Company will submit written responses to the questions on triclosan

POST MEETING NOTE: Response received 11/03/2021

The technology

i) Can you confirm that the list of brand/trade names included in the submission (see below) is a comprehensive list of all the variants available? Can you also add any additional variants not included in this list please?

- PDS Plus

- PDS II Plus
- VICRYL Plus
- MONOCRYL Plus
- STRATAFIX Spiral MONOCRYL Plus
- STRATAFIX Spiral PDS Plus
- STRATAFIX SYM PDS Plus

Company Response:
Plus Sutures are all absorbable sutures – the first decision a surgeon will make is whether a permanent or absorbable suture is needed. There are 3 'traditional' Plus Sutures (containing triclosan), PDS, VICRYL and MONOCRYL. PDS II is a standard suture (does not contain triclosan), not a Plus Suture. Therefore the company requested that PDS II Plus be removed from the list.

Stratafix sutures were not included in the original scope, but the Company thought it was important to include them in the submission. There are 3 STRATAFIX Plus brands, 2 with PDS polymers and 1 with MONOCRYL polymer. Stratafix is a knotless technology.

Ethicon do produce Stratafix versions of permanent (non-Plus) sutures, but most (95-96%) Stratafix sutures are absorbable Plus Sutures

ii) Could you briefly describe what are the differences between these technologies and when they may be indicated (e.g. operation type, depth of incised layer), or direct us to information on this?

Company Response:
The difference between the polymers/ suture types is the length of time the suture takes to absorb, and therefore how long the suture will support the tissue. The 3 polymers are therefore suitable for different wound types – a surgeon will make a clinical judgement as to which is the most appropriate.

iii) Can you confirm that the suture polymers (polyglactin, poliglecaprone, polydioxanone) can be regarded as equivalent for purposes of analysis?

iv) Can you confirm whether polyglactin and poliglecaprone polymers are specific to Ethicon Plus Sutures?

Company Response:
PDS, VICRYL and MONOCRYL are all trademarked and unique to J&J/Ethicon. Polyglactin and poliglecaprone are the chemical polymer names (not trademarked and not specific to J&J/Ethicon).

v) Are Ethicon Plus Sutures the only available suture with triclosan coating? Is this a patented use of triclosan or are they otherwise a protected intellectual technology?

Company Response:

Plus Sutures are the only sutures with Triclosan available worldwide with antibacterial protection offered by IRGACARE®† MP (Triclosan)*. Ethicon Plus Sutures are also the only triclosan coated sutures with CE Mark and FDA approval.

Comparator

vi) *The comparator in the scope is "Sutures that do not contain an antibacterial agent". To be regarded as a fair comparator, would you agree the sutures should be otherwise equivalent (e.g. made of same polymer, same thread size etc)?*

Company Response:
[redacted]

vii) *We understand that* [redacted]*. Is this representative of sales of sutures in the UK NHS? What proportion of the UK NHS market is currently supplied by the equivalent non-Plus Ethicon sutures? Can you name some widely used brands in the NHS that would act as fair comparators?*

Company Response:
[redacted]

viii) *Are there any other anti-microbial coated or impregnated sutures on the market?*

Company Response:
The Company are aware of sutures containing chlorohexidine, but to the best of their knowledge, today they are not available in the UK. Ethicon Plus Sutures are the only anti-microbial sutures with FDA and CE mark approval

Contraindications

ix) *What are the contraindications to use of Plus Sutures other than known allergy to triclosan?*

Company Response:
No other contraindications. Plus Sutures are absorbable, so would not be used where a permanent suture is needed.

x) *Regarding triclosan allergy, how would a person know they had it? Is it likely healthcare professionals would be informed about such an allergy? What would be the likely consequence of a person with a triclosan allergy receiving Plus Sutures? Is the rate of triclosan allergy known?*

Company Response:
Triclosan is widely used in cosmetics and toiletries. Patients may well be aware if they have a triclosan allergy. Reactions at the wound site may be due to the suture or the surgery rather than

the triclosan – it would be very hard to differentiate. Some reaction (e.g. redness) is a normal part of the reabsorption process.

Adverse event rates are quoted in the submission – allergic reaction is extremely rare. Triclosan dosage on the sutures is very low compared to exposure from toiletries and cosmetic products.

xi) Other than cost and known contraindications (see below) are there any reason Plus Sutures would NOT be used?

Company Response:
No known issues. Would always recommend using a Plus Suture where an absorbable suture is appropriate and the patient does not have a known allergy to triclosan.

Antibiotic stewardship

xii) Would it be correct to consider triclosan to be a broad spectrum bacteriostatic antiseptic rather than an antibiotic per se?

Company Response:
Yes

POST MEETING NOTE: Company submitted written response to triclosan questions, received 11/03/2021

xiii) Whilst triclosan could potentially reduce antibiotic use, is there the possibility that it could directly contribute to antimicrobial resistance, especially if used indiscriminately?

Company Response:
No

Economic model

xiv) Could you give us any "heads up" information regarding the economic model, in terms of:

- *Software used (Excel, other).*
- *Model structure (decision tree, Markov)*
- *Population scenarios?*

Company Response:
The model has been built in Excel. It is a decision tree, cost consequence model, aligned to the NICE scope. The Company are currently working on specific sensitivity analyses.

The Company agreed to request the EndNote bibliography of search results from the York Health Economics Consortium (YHEC).

ACTION: Company to request EndNote bibliography from YHEC and share with the EAC

POST MEETING NOTE: 10/03/2021 SP updated that due to licencing restrictions, it would be challenging to share the library in its current format. The Company are happy to respond to specific questions relating to the search libraries.

3. **Future correspondence and the EAC correspondence log**

   Going forward the EAC will contact Company directly. RO will share contact details with the EAC and the Company. SP is the key Company contact, GC will be copied in to all correspondence. NICE should also be copied in to communications.

   All correspondence contributing to the development of the assessment report will be logged by EB in the external correspondence log which will be published in the public domain on NICE's website. All information highlighted by the Company as commercially sensitive or academic in confidence will be redacted before publication. The Company will have the opportunity to check the correspondence log before it is published.

4. **Handling confidential information and the confidential information checklist**

   The Company are asked to highlight all confidential information shared with the EAC and NICE so that it can be redacted. The Company's completion of the confidentiality checklist in the submission looks very thorough, but NICE are happy for any omissions to be redacted retrospectively. If any information currently redacted becomes publically available and redaction is therefore no longer necessary, the Company are asked to inform NICE/EAC.

5. **Next steps and any other business**

   - **16/03/2021 - Expert Engagement meeting**: 8 experts from a range of specialities will be present at the meeting – RO will follow up with details of specialities represented. The Company are not invited to the Expert Engagement meeting, but notes from the meeting will be published in the correspondence log.

     ACTION: RO to share details of expert specialities.

   - **30/03/2021 - Economic submission**
   - **09/04/2021 - Company engagement meeting**
   - **29/04/2021 - Final report and correspondence log submitted to NICE**

Appendix 3

10.03.21 J&J Ethicon reply to Newcastle EAC

Contraindications

9. What are the contraindications to use of Plus Sutures other than known allergy to triclosan?

Plus Antibacterial sutures and the equivalent non Plus version share the same base polymer. The only difference is the addition of the triclosan antibacterial agent. The contraindications are the same as the base polymer. The only additional contraindication for Plus Antibacterial sutures is it should not be used in patients with a known allergic reaction to Irgacare MP (triclosan).

Please also refer to the IFUs shared alongside our submission part 1.

10. Regarding triclosan allergy, how would a person know they had it? Is it likely healthcare professionals would be informed about such an allergy? What would be the likely consequence of a person with a triclosan allergy receiving Plus Sutures? Is the rate of triclosan allergy known?

Allergenicity

The substances that trigger allergies are a particular type of antigen called “allergens.” Allergens are typically proteins that in some people, for reasons that are not clear, fool the immune system into thinking that they are harmful and trigger the production of antibodies (usually IgE immunoglobulins). The antibodies then trigger mast cells to release chemicals, including histamine, into the bloodstream to defend against the allergen "invaders." There are some non-protein allergens that in certain circumstances low-molecular-weight sugars, metals and isocyanates act as substances called “haptens.” Haptens are small molecules that by themselves, are not antigenic (not capable of making allergens.) But if a hapten binds to a protein, the complex becomes capable of triggering antibody formation. The proteins that they bind to are called the carriers.

Allergenicity of Plus Sutures

Triclosan is an antimicrobial active substance that has been used for over 40 years. According to BASF (the supplier of triclosan used in Plus sutures) , triclosan does not contain protein, heavy metals, isocyanates or molecules that can act as haptens and as a result is considered non-allergenic. This position is further validated with the support of numerous studies investigating the skin sensitization potential of triclosan, submitted to the authorities for review[4] with subsequent expert opinions[3] affirming that triclosan is not classifiable as a skin contact allergen. As with any substance there are always some individuals with unique responses. While the existence of triclosan-related acute contact dermatitis (ACD) can occur, the rate at which this happens is relatively low compared to the higher incidence seen for other substances. Such as fragrance mix with a reactivity rate of 14.0% and nickel sulfate, with a 14.3% reactivity rate, according to the North American Contact Dermatitis Group.[2]

Triclosan coated sutures have been evaluated in standard preclinical biocompatibility assays and were found to be noncytotoxic, nonirritating, and not a chemical pyrogen. The tissue reaction, healing response, and absorption profile of the suture were not affected by the presence of triclosan[1]. Ford et al 2005, compared the intraoperative handling and wound healing characteristics of coated polyglactin 910 suture with triclosan and traditional coated polyglactin 910 suture in pediatric patients undergoing various general surgical procedures. In this randomized controlled trial, coated polyglactin 910 suture with triclosan performed as well or better than traditional coated polyglactin 910 suture in pediatric patients. Significantly fewer patients treated with coated polyglactin 910 suture reported pain at post-operative day 1. There were no significant differences in wound healing parameters and adverse events between the two groups.[5] A review of our post marketing safety and surveillance data did not show any trends of increased allergic reactions or skin reactions with Plus sutures compared to the non Plus suture.

Allergenicity of Triclosan in general

In a 1989, the Swiss Contact Dermatitis Research Group conducted a 1-year study to evaluate the frequency of sensitization to common preservatives. Triclosan was shown to have a low sensitizing potential as only 0.8% of the 2,295 patients tested had positive reactions.[4] Schena et al 2008, evaluated the sensitizing potential of triclosan and triclosan based skin care products in patients with eczematous dermatitis. Two hundred and seventy-five patients were patch tested with standard patch test series as well as triclosan and triclosan based products. Only two patients developed positive reactions to triclosan (0.7%) and four (1.4%) to triclosan-based products.[2] Several cases of patients who developed allergic contact dermatitis secondary to triclosan-containing products, none of which were triclosan coated sutures, have been reported, including one case of a health care worker whose contact dermatitis from triclosan was confirmed by patch testing. [6,10,11,12,13] Wahlberg published a large series in 1976 that showed negative test results for 902 patients tested with 0.5% and 1.0% triclosan concentrations for 16 months but reported three cases of allergic contact dermatitis from triclosan at a 2.0% concentration among 1,100 patients tested for 17 months.[12]

Triclosan is generally patch-tested at a concentration of 2% in petrolatum. Overall, it appears that the frequency of positive patch-test reactions to triclosan is low and that the prevalence of allergic and irritant contact dermatitis due to triclosan is very low, especially considering its widespread use in consumer and health care products.

It should be noted that a patient's exposure to triclosan from suture is minimal and is less than typical daily exposure from personal care products. Triclosan is rapidly metabolized before being excreted in a neutralized form; therefore, it does not accumulate in the body and has minimal impact on the environment.

References:

1. Barbolt, T. A. (2002). Chemistry and safety of triclosan, and its use as an antimicrobial coating on coated VICRYL. plus antibacterial suture (coated polyglactin 910 suture with triclosan). Surgical Infections, 3(SUPPL. 1), S-45-S-53.
2. Brown L. and Brancaccio R. (2002). Cosmetics and Allergies. Skin and Aging, 10(6), www.skinandaging.com.
3. European Scientific Committee on Consumer Products, Opinion on Triclosan, 21 January 2009 (SCCP/1192/08); Priority Existing Chemical Assessment Report No. 30, Triclosan, January 2009, Australian Government, NICNAS
4. Evaluation of the sensitization potential of triclosan. A comprehensive review containing predictive tests in animals and humans as well as clinical data. March 2003. Ciba Specialty Chemicals, Basel, Switzerland
5. Ford, H. R., Jones, P., Gaines, B., Reblock, K., & Simpkins, D. L. (2005). Intraoperative handling and wound healing: controlled clinical trial comparing coated VICRYL® Plus antibacterial suture (coated polyglactin 910 suture with triclosan) with Coated VICRYL® suture (coated polyglactin 910 suture). Surgical infections, 6(3), 313-321.
6. Lachapelle, J. M. (2014). A comparison of the irritant and allergenic properties of antiseptics. European Journal of Dermatology, 24(1), 3-9.
7. Leaper, D. J., Edmiston Jr, C. E., & Holy, C. E. (2017). Meta-analysis of the potential economic impact following introduction of absorbable antimicrobial sutures. Journal of British Surgery, 104(2), e134-e144.
8. Perrenoud, D., Bircher, A., Hunziker, T., Sutter, H., Bruckner-Tuderman, L., Stäger, J., ... & Swiss Contact Dermatitis Research Group. (1994). Frequency of sensitization to 13 common preservatives in Switzerland. Contact Dermatitis, 30(5), 276-279.
9. Schena, D., Papagrigoraki, A., & Girolomoni, G. (2008). Sensitizing potential of triclosan and triclosan-based skin care products in patients with chronic eczema. Dermatologic therapy, 21, S35-S38.
10. Steinkjer, B., & Braathen, L. R. (1988). Contact dermatitis from triclosan (Irgasan DP 300). Contact Dermatitis, 18(4), 243-244.
11. Veronesi, S., De Padova, S. M. P., Vanni, D., & Melino, M. (1986). Contact dermatitis to triclosan. Contact Dermatitis, 15(4), 257-258.
12. Wahlberg, J. E. (1976). Routine patch testing with Irgasan DP 300®. Contact Dermatitis, 2(5), 292-292.
13. Zaugg, T., & Hunziker, T. (1987). Germall II and triclosan. Contact dermatitis, 17(4), 262-262.

Antibiotic stewardship

12. Would it be correct to consider triclosan to be a broad spectrum bacteriostatic antiseptic rather than an antibiotic per se?

Yes. Triclosan (TCS), or 5-chloro-2-(2,4-dichlorophenoxy)phenol, is a synthetic broad-spectrum antiseptic developed in the 1960s. The product has activity against gram-negative and gram-positive bacteria as well as yeast and fungi. It achieves its antimicrobial effect by inhibiting the activity of the enzyme enoyl-acyl carrier-protein reductase, which catalyzes an essential step in membrane synthesis of many bacteria and fungi. Triclosan has been widely employed for over 40 years in a variety of personal care and human hygiene applications as well as professional medical applications. Irgacare MP is a medical grade of triclosan employed in Plus Sutures.

13. Whilst triclosan could potentially reduce antibiotic use, is there the possibility that it could directly contribute to antimicrobial resistance, especially if used indiscriminately?

Sutures, while necessary to close the incision and provide external support to maintain wound edge apposition during the critical wound healing period; do act as a foreign body (even absorbable sutures). Small numbers of bacteria in the wound can colonize the suture surface and develop into a biofilm which is resistant to phagocytic immune cells as well as to antibiotics. In this way, the suture although ubiquitous and necessary for surgical wound closure, also presents a risk factor for the development of surgical site infection. This risk factor can be addressed by coating the suture surface with an antibacterial agent that inhibits bacterial colonization of the suture surface and prevents biofilm formation.

While laboratory studies have value in evaluating mechanisms of action of and resistance to biocides, including triclosan, wherever possible, findings from laboratory studies should be correlated to the actual clinical uses of these agents. Existing clinical surveys on the use of biocides, including triclosan have typically failed to support such correlation from laboratory studies. In a 10-year clinical survey, it was found that there was no relationship between triclosan usage and antibiotic resistance in MRSA and P. aeruginosa (Lambert 2002). Another clinical survey found no significant differences in overall titers of bacteria, potential pathogens or frequencies of antibiotic resistance in a single-time analysis of homes that did or did not use surface antibacterial agents including triclosan (Marshall 2003). A third comprehensive clinical survey could find no relationship between the use of triclosan and other biocides and antibiotic resistance in homes where biocidal products were or were not being used (Cole 2003). A review of the literature does not support the conclusion medical grade triclosan has a clinical connection with antibiotic resistance. Given the short-term nature of suture use, it is highly unlikely that such use would do other than reduce the risks of postoperative infection (Gilbert and McBain 2002).

Overall, there is no convincing evidence to support the contention that triclosan usage has resulted in the clinical development of antibiotic-resistant bacteria. Nevertheless, it would be wise to restrict the use of triclosan to areas where it has been shown to be effective in order to retain its important and valuable application. One such area of importance is the use of triclosan as an antibacterial coating on sutures.

There is an abundance of clinical data examining the use of triclosan coated sutures and their effects on reducing the risk of surgical site infection for patients. Prospective randomized controlled trials, as well as prospective and retrospective comparative cohort studies and case series have been conducted since 2002 to present, in over 23 countries, and in surgical procedures encompassing all four CDC surgical wound classifications. Multiple prospective meta-analyses of the higher-level studies over the past 6 years have consistently demonstrated a statistically significant clinical benefit associated with triclosan coated sutures versus non-coated sutures for the outcome of reducing the risk for surgical site infection. The most recent such meta-analysis also included a trial sequential analysis concluding that the outcome of the meta-analysis was robust with additional data unlikely to change the summary effect (De Jonge 2017).

In discussing the treatment controversy involving triclosan resistance, it is important to distinguish between the expansion of the scientific literature describing the modes of action and mechanisms of resistance of triclosan versus risk assessment and/or demonstration of actual clinical effect or failure. The argument that the use of triclosan in

medical devices, and in particular Plus sutures, poses some peculiar risk relative to fostering triclosan or antibiotic resistance fails to consider the following:

- All antimicrobials that are safe for human use exhibit limits in their spectrum of activity.
- Bacteria have various and ever-changing susceptibility (or resistance) to antibacterial chemistry as they respond to the selective pressures placed on them.
- The selection and isolation of bacterial mutants resistant to all sorts of antimicrobials is common practice in microbiology and molecular biology labs worldwide.
- The fact that bacteria can become resistant to antimicrobials does not change the fact that antimicrobials are useful and necessary components of infection control practice.
- The argument against indiscriminate and non-value-added use of antimicrobials is well recognized.
- The predominant cause of antibiotic resistance is the abundant and often poorly managed use of antibiotics, including agricultural uses and uncontrolled exposure through wastewater and other environmental sources. Medical devices and their packaging are managed very closely as medical waste, and their potential to contribute to environmental exposure is small.
- The literature on triclosan resistance continues to focus on the issues of environmental exposure from triclosan use in consumer and industrial products and the hypothesis of triclosan resistance leading to or co-existing with antibiotic resistance.
- The significant reduction in consumer product use of triclosan, including toothpaste and hand soaps, can only improve the risk of resistance.

The Scientific Committee on Consumer Safety (SCCS) conducted a comprehensive review. The SCCS approved this opinion at the 7th plenary of 22 June 2010 after public consultation.

There is so far no epidemiological data linking outbreaks of antimicrobial resistant human and zoonotic pathogens following exposure to triclosan from cosmetics and other products. When used appropriately, biocides, including triclosan, have an important role to play in disinfection, antisepsis and preservation. To preserve the role of triclosan in infection control and hygiene, SCCS can only recommend its prudent use, for instance limited to applications where a health benefit can be demonstrated.

References

1. Cole, E. C., Addison, R. M., Rubino, J. R., Leese, K. E., Dulaney, P. D., Newell, M. S., ... & Criger, D. A. (2003). Investigation of antibiotic and antibacterial agent cross-resistance in target bacteria from homes of antibacterial product users and nonusers. Journal of Applied microbiology, 95(4), 664-676.
2. De Jonge, S. W., Atema, J. J., Solomkin, J. S., & Boermeester, M. A. (2017). Meta-analysis and trial sequential analysis of triclosan-coated sutures for the prevention of surgical-site infection. Journal of British Surgery, 104(2), e118-e133. Gilbert P, and McBain AJ. Literature-Based Evaluation of the Potential Risks Associated With Impregnation of Medical Devices and Implants With Triclosan. Surg Infect J. 2002;3(suppl 1):S55-S64.
3. Gilbert, P., & McBain, A. J. (2002). Literature-based evaluation of the potential risks associated with impregnation of medical devices and implants with triclosan. Surgical infections, 3(S1), s55-s63.
4. Lambert, R. J. W., Graf, J. F., & Sedlak, R. I. (2002). Antimicrobial resistance and cross-resistance in several bacterial species between 1989 and 2000. Program and Abstracts of the Forty-Second Interscience.
5. Marshall, B. M., Robleto, E., Dumont, T., Billhim, W., Wiandt, K., Keswick, B., & Levy, S. B. (2003, May). The frequency of bacteria and antibiotic resistance in homes that use and do not use surface antibacterial agents. In Proceedings of the 103rd General Meeting of the American Society for Microbiology, Washington, DC, USA (pp. 18-22).
6. SCCS (Scientific Committee on Consumer Safety), Opinion on triclosan (antimicrobial resistance), 22 June 2010

What is the amount of triclosan is in the sutures and how is it excreted?

To provide further detail to support part 1 of our submission on triclosan, a patient's exposure to triclosan from a suture is minimal, and is less than typical daily exposure from personal care products. Triclosan is rapidly metabolized before

being excreted in a neutralized form; therefore, it does not accumulate in the body and has minimal impact on the environment.

Numerous pharmacokinetic studies have been conducted, specifically oral and dermal routes of exposure. Absorption of triclosan from the gastrointestinal tract is rapid and estimated to be 50-100% of the administered dose across species. It is well distributed in the body, binding to serum albumin and is present as the sulfate and or glucuronide conjugate. Only a small amount of free triclosan is detected in the blood with the majority found in its conjugated form. There is no indication that triclosan accumulates in the plasma or in the tissues over time.

Coated VICRYL™ Plus suture has a coating of copolymer and calcium stearate and contains no more than 275 micrograms/m Triclosan. MONOCRYL™ Plus and PDS™ Plus Sutures contain no more than 2,360 micrograms/m Triclosan.

References

Builee, G. T., Chen, K., Johns, L., Savidge, S., & Oldham, J. (2013, January). An In Vivo Subcutaneous Model in Rat to Evaluate Triclosan Dissipation from a Combination Product and a Triclosan Risk Assessment K. In INTERNATIONAL JOURNAL OF TOXICOLOGY (Vol. 32, No. 1, pp. 84-85). 2455 TELLER RD, THOUSAND OAKS, CA 91320 USA: SAGE PUBLICATIONS INC

Ford, H. R., Jones, P., Gaines, B., Reblock, K., & Simpkins, D. L. (2005). Intraoperative handling and wound healing: controlled clinical trial comparing coated VICRYL® Plus antibacterial suture (coated polyglactin 910 suture with triclosan) with Coated VICRYL® suture (coated polyglactin 910 suture). Surgical infections, 6(3), 313-321.

Rodricks, J. V., Swenberg, J. A., Borzelleca, J. F., Maronpot, R. R., & Shipp, A. M. (2010). Triclosan: a critical review of the experimental data and development of margins of safety for consumer products. Critical reviews in toxicology, 40(5), 422-484.

Appendix 4

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Expert Engagement Meeting

MT507 Plus Sutures for preventing surgical site infection

Date: **16/03/2021**

Time: **09:30 – 11:00**

Documents

MIB: **MIB 204 Plus Sutures for preventing surgical site infection**

MTG Scope: **Plus sutures for preventing surgical site infection - final scope**

NOTES

In attendance:

NICE: Victoria Fitton (VF), Rebecca Owens (RO), Kim Carter (KC), Louisa Regan (LR), Helen Crosbie (HC), Chris Chesters (CC), Sam Baskerville (SB)

Newcastle EAC: Iain Willits (IW), Kim Keltie (KK), Emma Belilios (EB)

Experts:

- **MTG**
  - Mike Reed (MR) - Consultant Orthopaedic Surgeon, Northumbria Healthcare
  - Melissa Rochon (MRo) - Quality and Safety lead for Surveillance, Royal Brompton and Harefield Hospitals, part of Guy's and St Thomas' NHS FT
  - Justin Wormald, DPhil Candidate and Specialty Trainee/ Registrar in Plastic and Reconstructive Surgery (ST6), Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford
  - Lillian Chiwera, Infection control surveillance team leader, Guy's & St Thomas' NHS Foundation Trust

- Shafi Mussa (SM), Consultant Congenital Cardiac Surgeon, University Hospitals Bristol and Weston NHS FT

- **MIB**
  - Giles Bond-Smith (GBS), Consultant Surgeon, Clinical Lead for Emergency General Surgery, Clinical Lead for SSI Reduction, Oxford University Hospitals NHS Foundation Trust

Welcome and introductions

Declarations of interest: MR gave a talk for Ethicon last year (already declared).

No additional conflicts of interest were declared.

Questions for the professional experts by theme: (see below)

Technology and indication

Despite some initial scepticism (one expert co-authored an earlier RCT which showed no evidence of effectiveness of triclosan in reducing SSI) all the experts are now confident that Plus Sutures are effective in reducing SSI rates (same expert co-authored a more recent meta-analysis which demonstrated significant reduction in SSI at 30 days from the use of Plus Sutures). Sutures are a known risk area for biofilm formation, and there is an established evidence base supporting the use of Plus Sutures to minimise this risk. The experts were not aware of any safety concerns. One expert reported that the evidence for Plus Sutures is stronger for some wound types than for others and that the sutures are likely to be more effective for some wound types than others.

Choice of suture should be considered as part of a package of measures to reduce the risk of SSI.

The experts agreed that because STRATAFIX sutures differ in mechanism from standard Plus Sutures it would not be possible to isolate the additional effect of triclosan when making comparisons with standard sutures. Would need to compare Stratafix Plus Suture with an equivalent barbed suture without triclosan for the same indication for fair comparison. Barbed sutures are used for different indications to standard sutures.

Triclosan allergy

None of the experts had experience of triclosan allergy in practice. Triclosan is very widely used in toiletries and cosmetics. Patch testing is available for triclosan allergy, but this would not be carried out routinely before using Plus Sutures. The Company may have more information on prevalence of triclosan allergy, or, might be useful to speak with an allergy specialist.

Symptoms of triclosan allergy are likely to be blistering, redness and discharge at the wound site, and would be difficult to differentiate from symptoms of an SSI.

Surgical site infection

Definition

PHE's definition of an SSI is based on the US National Healthcare Safety Network's Centre for Disease Control (CDC) definition, and works well, although it is important that Trusts ensure that all staff are using the same definition. The CDC criteria changed in 2019 - length of follow up reduced to 3 months. PHE's SSI surveillance protocol still requires 1 year follow up for some surgeries.

Assessment and treatment

The experts were aware of the ASEPSIS wound scoring method, but found it difficult as many of the categories are hard to quantify. It also requires sight of the wound which is problematic for wounds that need a dressing. The experts felt there was generally a lack of consistency in SSI assessment and treatment (particularly, when antibiotics would be prescribed) between clinicians, specialities and Trusts, although some Trusts have done a lot of work to standardise their approach.

Patients with larger/deeper wounds would usually receive prophylactic antibiotics initially and their wounds would be well managed in hospital. There is less consistency once they are discharged to primary/community care. One expert reported that their Trust has developed an app so that patients can share pictures of their wound with their surgical team if they are concerned. For minor procedures, patients go home on the day of their surgery and are expected to self-manage their wound care, meaning that issues may not be picked up in good time. The Bluebelle wound healing questionnaire (14 questions to patients) gives a score which helps to guide patients on when they should seek medical attention.

The experts agreed that although it is usually impossible to identify a single factor that caused an SSI, factors that increase the risk are well known. Clinicians should follow SSI 'care bundle' of measures to reduce risk of SSI. One expert reported that for a laparotomy wound, if no measures are taken to prevent infection, there is a 40% SSI rate. With strict adherence to SSI bundle, this goes down to 4%.

One expert reported that their Trust has an SSI investigation protocol based on NG125 Surgical Site Infections: prevention and treatment to see if any elements were missed.

Classification

Studies in the company meta-analyses have been grouped into clean and contaminated wounds. The experts agreed that this was appropriate as the categorisation is well recognised amongst medical professionals.

Other useful sub-groups for analysis suggested:

- Paeds/adults
- By speciality - this would be relatable to clinicians (unclear if there are enough studies to facilitate this subgroup analysis)
- Emergency c/w elective procedures

The experts agreed that attempting to classify by comorbidities should be avoided.

It is unclear at this stage whether the evidence will support a positive recommendation for use of Plus Sutures for all procedures where absorbable sutures are used, or for specific procedures only. The evidence seems strongest for emergency procedures and contaminated wounds, and one expert reported that their Trust is mandating use of Plus Sutures for emergency procedures only.

Management and cost of surgical site infection

Management of superficial/deep SSI

Management of an SSI depends on the location of the wound and what the procedure was.

Generally, superficial infections would be treated with antibiotics. The experts recommended that the wound should be swabbed for confirmation of infection before prescribing antibiotics as the redness that occurs as a normal part of suture reabsorption can be confused with superficial SSI. Deeper infections may require further surgical interventions.

For joint replacement procedures, a deep SSI would require at least one surgical debridement at a cost of c.£10K, and failure of this could potentially lead to a revision procedure costing c.£30K.

For day case procedures, patients would usually present to primary care with superficial SSIs so it is difficult to estimate cost or prevalence.

Length of stay (LoS)

One expert reported that their Trust had reduced their LoS considerably through a focussed reduction in SSIs.

One expert reported that their Trust prospectively collects data on LoS related to SSI.

One expert reported that in their speciality, SSI would usually result in a readmission rather than an extension to the LoS of the primary admission.

Discharge to primary/community care

The experts agreed SSIs could be safely treated in primary/community care provided a care plan was in place.

Incidence of SSI

The experts agreed that incidence of SSI varied greatly between specialities, surgery-types, emergency/elective surgery, patient populations. Pre-procedure risk assessment is important.

Emergency/contaminated surgeries represent the highest risk. One expert reported that Hepato-Pancreato-Biliary (HPB) procedures were a particular concern in their speciality, as they often involve open surgery and large wounds in immunocompromised patients with co-morbidities. There are sub-groups within all specialities that are at higher risk, e.g., cardiac procedures usually classed as 'clean' but procedures involving neonates are higher risk (immunocompromised, hypoxic, desaturated, cooled), diabetic adults with ischaemic heart disease also high risk. Open surgery is higher risk than laparoscopic surgery.

Range of Costs and known studies

Huge range, very difficult to estimate. There will also be significant costs to primary care (GP time, district nurse costs etc.) which will not be reflected in HES, also social costs (patients need time off work etc.)

Prof Leaper's US-based study calculates additional cost of colorectal SSI as c. $100,000. Hard to compare with UK/NHS costs, but the experts thought that the overall cost is likely to be underestimated.

The experts did not know of any additional studies on cost of SSI.

MR might have some information on SSI costs in joint replacement for grant applications which he can share.

Next steps

The experts agreed that the evidence suggests that Plus Sutures appear to be effective. They noted that surgeons value having a choice of suture, and many have strong personal preferences that work well for them. If the choice is likely to be limited, that change will have to be carefully managed.

Draft guidance will go to Committee in May. A positive recommendation is needed to meet the requirements of the MedTech Funding Mandate. The technology will also have to be shown to meet the cost saving criteria.

Questions for discussion

Technology and Indication

1. *What are the indications for using the three Ethicon sutures that were included in the original scope? These were PDS Plus, VICRYL Plus, MONOCRYL Plus. What information guides choice of suture?*

2. *We understand that Plus Sutures are equivalent to their non-Plus counterparts in every way except for the addition of the antiseptic triclosan. Are there any specific indications where you would:*

   - *Specifically want to use Plus Sutures rather than their non-triclosan alternatives?*
   - *Specifically not want to use them (other than documented allergy)?*

   If there are no reasons not to use Plus Sutures over their counterparts, would you have any concerns about this technology being adopted as the standard of care? What are the potential drawbacks, if any, of non-discriminatory use?

3. *The company added STRATAFIX Plus to the scope in their submission. This is a barbed/knotless suture. Would you agree that because this suture differs in mechanism, it is not possible to isolate the additional effect of triclosan when making comparisons with standard sutures?*

Triclosan allergy

4. *Triclosan allergy is the only contraindication for use of Plus Sutures we are aware of. Do you know:*

   - *What proportion of patients have a known allergy to triclosan? If not, have you ever encountered this in clinical practice?*
   - *Would an allergy to triclosan be documented in the clinical record? Would patients be prompted on this prior to having an operation involving Plus Sutures?*
   - *If a person was allergic to triclosan, but this was missed and they were operated on with Plus Sutures, how would this clinically manifest itself?*

Surgical site infections (SSI)

5. *Many studies have adopted the US National Healthcare Safety Network's Centre for Disease Control (CDC) definition of SSI. Is this an accepted definition used in the UK? Are there any other definitions or diagnostic criteria we should be aware of?*

6. *In practice, how are SSIs identified and their severity graded? We are aware of the ASEPSIS wound scoring method, but this was developed in 1986. Is it used routinely across the NHS, and if not, what other methods (if any) are used?*

7. *Is there consistency in assessment of SSI between surgeons/specialities/centres*?

8. *SSI risk factors are multifactorial and the aetiology is complex. Given this, in practice is it ever possible to attribute the cause of an individual SSI (e.g. SSI due to suture use) or to make assumptions on this?*

9. *Relating to the above, studies in meta-analyses have been grouped into clean and contaminated wounds. In practice, how are could these groupings be determined and do you think this grouping is reflective of NHS practice? What other classifications of SSI type might be useful for subgroup analysis (e.g. procedure/specialty type, comorbidities etc)?*

Management and cost of SSIs

10. *Although we appreciate every case will be different, can you briefly describe how an SSI is managed:*
    - *Presenting in superficial tissue?*
    - *Presenting in deep tissue?*
11. *What are the typical consequences of an SSI on hospital length of stay (LoS)? Do you think this could be accurately measured, or would involvement of other factors mean this is essentially not measurable (we are aware that no studies have reported statistically significant differences in LoS between treatment arms).*

12. *Can patients with SSIs be safely discharged and treated in primary/community care? What are the typical barriers to discharge?*

13. *Incidence of SSI appears to vary greatly between surgery types, populations etc. Is this in line with your experience in the NHS?*

14. *Which types of surgery give rise to the highest SSI incidence rate and are these qualitatively different to SSIs from other surgery types?*

15. *Finally, we anticipate putting an average cost on an SSI will be one of the most challenging aspects of economic modelling. With this in mind:*

- *Could you make a reasonable estimate on how costly it is to treat an SSI and what the range of costs might be?*
- *Are you aware of any source or study that have investigated the costs of SSIs previously?*

Appendix 5

Company Engagement Meeting
09/04/2021 @ 14:00

Attendees:

NICE: Kim Carter, Chris Chesters, Rebecca Owens, Sam Baskerville,
EAC: Iain Willits, Kim Keltie
Company (J&J, Ethicon):

- Suzi Patel, UK HEMA (Health Economics and Market Access)
- Gianluca Casali, UK Medical Director
- Stephen Murray, EMEA Marketing
- Walt Danker, Global HEMA
- Liza Ovington, Global Medical Director
- Meagen Hicks, UK/EMEA HEMA

1. **Question from EAC:**

- We note that the device costs included in the submission are based on weighted average volumes (assuming this represents sales volume of each VICRYL Plus, MONOCRYL Plus, and PDS Plus). The economic submission also states that Stratafix costs were included in the intervention and comparator arm costs.

  However as your main meta-analysis of the clinical submission excluded STRATAFIX, could you please send us the intervention and comparator costs without STRATAFIX (i.e. representing the weighted average of VICRYL Plus, MONOCRYL Plus, and PDS Plus alone) please?

  Company response:
  This is an evaluation of "Plus technology", not suture characteristic. As barbed sutures were referenced in the description of the technology section of the final scope, we took the decision to present it within a subgroup analysis rather than our main meta-analysis simply to minimise heterogeneity. Inclusion of STRATAFIX did not change the results of our meta-analysis. However, looking to our economic submission, because the use of barbed sutures is well established as part of clinical practice in the NHS, its inclusion ensures completeness and is more reflective of NHS clinical practice.

  For the purposes of the economic model, it is the price differential between Plus and non-Plus that is most relevant. And the economic submission was intentionally presented with as conservative estimates as possible. The company explained that the technology price would reduce if STRATAFIX was removed. However all scenarios were showing a cost saving.

  With regards to STRATAFIX, the company highlighted Ruiz-Tovar 2020 from the clinical submission, that compared STRATAFIX PDS Plus, PDS Plus and uncoated PDS, and reiterated that it is the Plus technology that is the focus for this evaluation. The company explained how it is relevant to note that the suture itself – whether monofilament, braid, or barbed represents a foreign body with surface area for bacteria to colonize, form a biofilm and pose a risk for SSI (e.g. its base polymer or its morphology is less important than its physical presence).

  Clarification from EAC: Evidence on STRATAFIX sutures has been excluded from the assessment of the clinical submission as out of scope. The clinical experts consulted had

advised that it was not possible to attribute better outcomes to the triclosan coating or the barbed nature of the suture, and that barbed sutures would be used in different procedures and used in a different way by surgeons. Therefore STRATAFIX has been excluded, as there are no uncoated equivalent absorbable STRATAFIX sutures, and therefore no direct comparator. The EAC appreciated the approach taken in the clinical submission (i.e. main analysis without STRATAFIX, but a scenario analysis included STRATAFIX). Therefore anticipated the same approach to the economics (i.e. STRATAFIX not included in basecase, however included in scenario analysis).

2. AOB

Assessment report is completed by EAC on 29th April. The company will have until COP (UK time) 5th May to return comments.

Additional information provided by the company post-meeting

Removing cost of STRATAFIX falls within the 20% variance modelled within the pricing sensitivity analysis presented within the submission.

Barbed sutures have a greater surface area than a monofilament and are subject to bacteria hiding in the barb cleft (Dhom 2016 Bacterial Adhesion of Suture Material in a Contaminated Wound Model: Comparison of Monofilament, Braided, and Barbed Sutures, Journal of Orthopedic Research).

Company explained that the specific outcome of SSI would only be attributable to the triclosan coating as barbed closure has not previously been suggested or clinically associated with a decreased risk of infection versus triclosan coating of a suture which has been associated with a decreased risk of SSI.

To provide additional supporting information on this topic, several meta-analyses of Plus Sutures and SSI risk reduction have performed meta regressions (De Jonge 2017) or subgroup analyses (Elsohl 2017) on suture type (e.g., monofilament versus braid) and found no differential association of effect with suture morphology. While barbed suture studies were indeed not part of the included data in these meta-analyses, one can surmise that the effect on SSI is due to the antibacterial coating alone and extrapolate to a similar effect on barbed sutures.

Appendix 6

MTG Medtech Guidance: MT507 Plus Sutures

Expert contact details and declarations of interest:

Expert #1	ANDREW MILLER, **CONSULTANT COLORECTAL SURGEON,** UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST, [redacted]
	DOI: YES Travel reimbursement and honorarium For travel and involvement on the consensus meeting held at Royal College of Surgeons on 16th July 2016 July 2016 July 2016 Co-author of paper reporting a consensus meeting looking at triclosan coated sutures – paper published June 2017 July 2016 June 2017
Expert #2	ANNE PULLYBLANK, **CONSULTANT SURGEON/MEDICAL DIRECTOR,** NORTH BRISTOL NHS TRUST/WEST OF ENGALND ACADEMIC HEALTH SCIENCE NETWORK, [redacted]
	DOI: No
Expert #3	Giles Bond-Smith, **Consultant Surgeon, Clinical Lead for Emergency General Surgery, Clinical Lead for SSI Reduction,** Oxford University Hospitals NHS Foundation Trust, [redacted]
	DOI: YES Spoke at Ethicon event about SSI Reduction 27/11/2019 27/11/2019 Spoke at Ethicon event about SSI Reduction 21/11/2019 22/11/2019 Spoke at Ethicon event about SSI Reduction 10/09/2019 11/09/2019
Expert #4	Melissa Rochon, Quality & Safety Lead for Surveillance, Royal Brompton and Harefield Hospitals, part of Guy's and St Thomas' NHS FT[redacted]
	Nominated by: IPS
	DOI: NONE
Expert #5	Mike Reed, Consultant Orthopaedic Surgeon, Northumbria Healthcare NHS FT, [redacted]

	Nominated by: Company
	DOI: yes – I gave paid talk at a webinar they funded recently. I have previously run a very large RCT that advised against its use on the basis of efficacy. Recently did a meta-analysis which supported it use. Hence they wanted me on the podium to discuss that.
Expert #6	Justin Wormald, DPhil Candidate and Specialty Trainee/ Registrar in Plastic and Reconstructive Surgery (ST6), Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, [redacted]
	Nominated by : NICE
	DOI: NONE
Expert #7	Lilian Chiwera, Infection control surveillance team leader, Guy's & St Thomas' NHS Foundation Trust, [redacted]
	Nominated by: Company
	DOI: NONE
Expert #8	Mohamedshafi Mussa, Consultant Congenital Cardiac Surgeon, University Hospitals Bristol and Weston NHS Foundation Trust [redacted]
	Nominated by: Company
	DOI-NONE
Expert #9	

1		Expert #1: Please describe your level of experience with the technology, for example: − Are you familiar with the technology?

	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	− − Are you currently using it? Are you familiar with the technology? YES Have you used it? YES Are you currently using it? NO Have you been involved in any research or development on this technology? NO Do you know how widely used this technology is in the NHS?NO
		Expert #2 I have used Plus sutures since 2013 as part of a bundle in a quality improvement project to reduce surgical site infection (SSI) after elective colorectal surgery. This halved patient-reported 30 day surgical site infection from approximately 16% to 8%. Our current rate is 6% this year I have not been involved in any R&D I am currently leading a region wide project in the West of England Academic Health Science Network to reduce SSI after colorectal surgery. The role of the AHSN is to improve uptake of new technology. As a result of this I know that in my region of 6 hospitals, 5 were not using Plus sutures for colorectal surgery prior to the start of this project
		Expert #3 I am familiar with the technology We are about to trial these sutures in Orthopaedics, HPB and Emergency Surgery. No involvement in the research or development of this technology

		Plus Sutures are slowly being adopted in centres around the UK as evidence and awareness increases about them.
	–	Expert #4: I am familiar with the Plus Sutures for preventing surgical site infection. One of our hospital sites routinely uses Plus Sutures in surgery. Our second hospital site offers the technology (based on operator preference). I am aware that the agent Tricolsan lasts longer in Moncryl and PDS (monofilaments) because they are impregnated, vs Vicryl which is braided and coated. I am aware that NHS Improvement announced that as part of their Innovations, the ITP would support the introduction of triclosan sutures, paying the differences between products (if the hospital rates qualified for the re-imbursement, >4%) and that it was a one-off (not continuous) discount.
	–	Expert #5 Very familiar. This is a suture I use for almost every operation I do. Yes No sure how commonly it is used compared to competitor products. Yes

		No
	–	Expert #6 I am a plastic surgery registrar and the majority of my clinical practice involves the use of sutures with different types of wounds. I have used Plus sutures in my practice on an ad hoc basis. I am currently doing full-time research (DPhil) at the Univeristy of Oxford. As part of my DPhil I am conducting a Cochrane review of antimicrobial sutures to prevent surgical site infection. I am also conducting a multi-centre feasibility RCT of antimicrobial sutures vs. standard sutures in upper limb trauma (n=116, three sites). I am therefore familiar with the literature on Plus sutures and have practical experience of using them in surgical procedures.
	–	Expert #7 The technology has been used in my organisation as an SSI prevention intervention. My organisation is currently using it for various surgical procedures.
	–	Expert #8 I used PLUS Antibacterial sutures for wound closure on a daily basis at a previous institution. I was actually unaware that these sutures were in use, as they handled exactly like standard sutures.

		I am not using the sutures at my current institution as they are not part of the current stock. I am not sure how widely the sutures are used in the NHS. I would imagine that the sutures would be used across all surgical specialties.
2	Has the technology been superseded or replaced?	Expert #1: No
		Expert #2 Not yet. There is another company who have just developed antibacterial sutures but to my knowledge, do not have appropriate sutures for colorectal surgery
		Expert #3 No
	–	Expert #4 – not asked
	–	Expert #5 – not asked
	–	Expert #6 – not asked
	–	Expert #7 – not asked
	–	Expert #8 – not asked

3	Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 - not asked
		Expert #4: I have done bibliographic research on this procedure. Other (please comment) I was a NICE NG125 2019 committee member I am a co-author of Cochrane protocol reviewing SSI preventions in cardiac surgery https://www.cochrane.org/CD013332/VASC_interventions-prevent-surgical-site-infection-adults-undergoing-cardiac-surgery
		Expert #5 I have done bibliographic research on this procedure. Yes I have done clinical research on this procedure involving patients or healthy volunteers. Yes I have published this research. Yes .
		Expert #6 **I have done bibliographic research on this procedure. YES**

		I have done clinical research on this procedure involving patients or healthy volunteers. PLANNED **I have published this research. PLANNED** Expert #7 X I have had no involvement in research on this procedure
		Expert #8 I have done bibliographic research on this procedure.

Current management

4	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design?	Expert #1: Innovative – it has the potential to address the huge issue of surgical site infections. It is novel design and concept
	Which of the following best describes the procedure (please choose one):	Expert #2 This is a minor variation. The sutures look and feel exactly the same as non antibacterial sutures
		Expert #3 It is a novel adaptation of a standard piece of surgical equipment to aid in the reduction of SSI.

		Expert #4: In adult cardiac surgery in the UK, I don't believe that it is standard practice to use the antimicrobial tricolosan-coated sutures (estimate <25%).
		Expert #5 Monir variation with subtle but important reduction in infection rates.
		Expert #6 **A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.**
		Expert #7 X Established practice and no longer new.
		Expert #8 A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy
5	Does this procedure/technology have the potential to replace current standard care or	Expert #1: It would be in addition to current care because some patients may not be eligible for this technology and so will need standard care as exists at this time

	would it be used as an addition to existing standard care?	Expert #2 It would replace existing sutures. Currently the focus is on using these sutures for muscle and skin only. In theory they could be used for everything but this would probably not be cost effective
		Expert #3 It would replace standard sutures.
		Expert #4 - At the moment it is in addition to existing standard of care although the potential to replace exists
		Expert #5 - **Replace**
		Expert #6 - May replace standard care if effectiveness and cost-effectiveness are demonstrable.
		Expert #7 - Potential to replace, however if there are cost implications then it can be used for procedures considered to be high risk.
		Expert #8 - Has the potential to replace current standard of care.

Potential patient benefits

6	Please describe the current standard of care that is used in the NHS.	Expert #1 – not asked
		Expert #2 - not asked
		Expert #3 – not asked
		Expert #4 I am not from a theatre background but uncoated Vicryl may be used for deep soft tissue, Monocryl for skin layers

		Expert #5 Same sutures, often with the same Brand of suture but without the antibacterial coating.
		Expert #6 There appears to be substantial variability in the use of Plus sutures. Some specialties within the same trust will use them, others are unaware of their existence. There are between-trust and within-trust differences in practice.
		Expert 7 - Currently used for different surgeries
		Expert 8 - Non-antibacterial sutures.
7	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #1: No I am unaware of any competing technology
		Expert #2 No
		Expert #3 No. There are currently no comparative sutures with antimicrobial properties.
		Expert #4: No
		Expert #5 No
		Expert #6 No I am not aware.
		Expert #7

		Not aware, need to research
		Expert #8 I am unaware of a competing product.
8	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1: This has the potential to reduce length of stay for patients, to reduce their need for antimicrobial therapy (both in primary and secondary care) to reduce the need for re-operative surgery
		Expert #2 Firstly, many hospitals do not know their SSI rates. There is a wealth of evidence from RCTs and systematic reviews that anti-bacterial sutures reduce SSI and they have been recommended by NICE and WHO. I am confident that wider use of these sutures would reduce SSI
		Expert #3 A reduction in SSI rates.
		Expert #4: Fewer patients may suffer an SSI. This complication can have devastating impact to patient and families
		Expert #5 Reduced infection rates
		Expert #6 They may reduce surgical site infection
		Expert #7

		In line with already published literature, the product is an evidence based SSI prevention intervention, therefore would reduce the risk of wound infections.
		Expert #8 Potential reduced rate of surgical site infection, with reduced requirement for antibiotic treatment, reduction in prolonged hospital stay, and further wound review in the primary care and hospital settings.

Potential system impact

9	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: Anyone undergoing surgery that requires skin incision – that is applying the exclusions listed in this document – elderly , and those who are at risk of prolonged wound problems
		Expert #2 Patients in whom SSI is more common eg after colorectal surgery or emergency laparotomy or in areas where a SSI has serious consequences eg spinal or orthopaedic surgery
		Expert #3 Patients with high risk wounds. Patients who are in need of getting chemotherapy on time – an SSI would reduce the chance of this happening.
		Expert #4: NICE guidance suggests paediatric surgery

		Expert #5 Possibly those patients with triclosan allergy. I haven't met any patients with that though.
		Expert #6 Potentially those at higher risk of infection (e.g. immunosuppression, diabetes)
		Expert #7 Current NICE guidance suggests a benefit in paediatric surgery
		Expert #8 All patients could benefit.
10	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1: It will not really change the pathway but will alter certain components eg length of stay and need for antimicrobial therapy in some individuals Outcomes may improve in terms of length of stay, re-operative rates and readmission rates
		Expert #2 Yes. For patients who have an SSI in hospital we know length of stay (LOS) is increased and SSI is a cause of readmission. In my own data of over 1300 patients undergoing colorectal surgery, 60% of SSI presented in the community so this is a significant burden on GPs in terms of time, dressing changes, cost of dressings and antibiotics. For patients this means pain and discomfort, increased scarring, slower recovery and slower return to work
		Expert #3 Yes. A reduction in SSI rates would mean a shorted length of stay, less morbidity, fewer returns to hospital, increase the percentage of patients hitting " optimal post-operative time to chemotherapy", less pressure on community services and an improved patient experience.

		Expert #4: Improve outcomes
		Expert #5 Yes
		Expert #6 Yes, by preventing SSI which leads to significant additional morbidity and mortality
		Expert #7 If surgical site infections are avoided, then yes there will be patient, organisation & economic benefits
		Expert #8 See my answer to Q7.
11	What do you consider to be the potential benefits to the health or care system from using this technology?	Expert #1: Potentially huge considering the huge burden that SSI places on the NHS at the present time
		Expert #2 Reduced LOS and emergency readmissions. Reduced GP/district nurse visits and reduced cost of treating SSI
		Expert #3 A reduction in overall cost in the surgical management of patients. SSI are expensive.

		Expert #4 – not asked
		Expert #5 – not asked
		Expert #6 – not asked
		Expert #7 – not asked
		Expert # 8 – not asked
12	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1: Initial increase in cost to fund the technology but this should soon be offset by the reduced need for antimicrobial therapy, time in hospital and management of SSI – if the potential impact is fully realised
		Expert #2 The technology is estimated to cost about £1 more per suture which means approximately £3:00 per patient for colorectal surgery or emergency laparotomy (this will vary depending on site of surgery and type of closure). However, a SSI is estimated to cost on average £3000. The number needed to treat quoted in the literature is 28
		Expert #3 It will cost a “small” amount more but the price is likely to come down with increased use.
		Expert #4: Prevention of SSI = costs avoided
		Expert #5 Cheaper. We including a basic cost analysis in one of our papers
		Expert #6 Plus sutures are more expensive. This needs to be weighed against the cost of SSI.

		Expert #7 There is potential for a return in investment if surgical site infections are avoided
		Expert #8 I believe that PLUS antibacterial sutures cost more than standard sutures.
13	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1: The obvious resource impact will be in purchasing the technology initially. The biggest resource impact may be seen in terms of nursing time during shifts. The nurses will need to commit less time to the management of infected wounds and this should allow them to focus on other aspects of patient care. There will be no change in the number of staff required. If there are less SSI s in surgical patients this should also have an impact on the need for primary care nursing – eg District Nurse time – many SSIs occur in primary care after discharge
		Expert #2 This technology will reduce complications. It should reduce emergency readmissions to secondary care and emergency attendances in primary care.
		Expert #3 It will reduce the need for community services to deal with complex wound problems. It will reduce re-admission and length of stay in hospital.
		Expert #4: Costs more than standard care
		Expert #5 The actual suture costs slightly more than standard care. This risk is that the manufacturer will put the cost up if it becomes standard of care, as I believe it holds the patent, and other companies cannot compete

		Expert #6 It will cost more, but only in relation to the cost of the sutures themselves. There shouldn't be any additional costs.
		Expert #7 The product will probably cost more than standard care but if infections are avoided, then it may be cost neutral
		Expert #8 Potential reduction in antibiotic treatment for surgical site infection, reduction in prolonged hospital stay, reduction in follow-up requirements. These could lead to potential cost savings.
14	Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology? Or What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: No
		Expert #2 None. The suture is used exactly the same way as existing sutures
		Expert #3 No
		Expert #4: Potential storage, if stocked in addition to standard
		Expert #5 None over existing

		Expert #6 None
		Expert #7 No changes to facilities
		Expert #8 No changes required.
15	Are you aware of any safety concerns or regulatory issues surrounding this technology?	Expert #1: None other than sensitivity to Triclosan
		Expert #2 There has been anxiety about antimicrobial resistance but the sutures are antibacterial, not antibiotic. In theory, there is a risk of allergy however since 2013 I have not seen an incident of allergy.
		Expert #3 No
		Expert #4 – not asked
		Expert #5 – not asked
		Expert #6 – not asked
		Expert #7 – not asked

		Expert # 8 – not asked

General advice

16	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1:
		Expert #2 My expertise comes from my own experience in over 1300 patients. However, the sutures were part of a bundle of care so all improvements cannot be attributed solely to antibacterial sutures
		Expert #3 In the small groups where PLUS sutures have been implemented alongside an SSI reduction bundle we have seen a significant reduction in SSI rates across a wide spectrum of surgical procedures.
		Expert #4: Not that I am aware
		Expert #5 No
		Expert #6 No

		Expert #7 Perhaps just raising awareness of upcoming change then support for clinicians should they have queries or concerns
		Expert #8 None required.

Other considerations

17	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4 CDC has suggested use is considered, with no evidence of harm Theoretical increased resistance to triclosan
		Expert #5 Possible allergy. I havent seen this

		Expert #6 There are some reports of allergy to Triclosan, the active ingredient There are also some reports of distant organ pathology (e.g. thyroid disease) from exposure to Triclosan
		Expert #7 Not aware, unless contraindicated
		Expert #8 Potential allergic reaction to PLUS antibacterial sutures, although my anecdotal experience is that this is no more likely than standard sutures.
18	Please list the key efficacy outcomes for this procedure/technology?	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4 Prevention of superficial SSI Prevention of deep SSI Prevention of SSI across different wound classes
		Expert #5 Infection rates
		Expert #6 Reduction of surgical site infection
		Expert #7

		SSI reduction & improved patient outcomes
		Expert #8 Surgical site infection rate, rate of sterile wound dehiscence, antibiotic treatment for surgical site infection.
19	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4: Evidence based on smaller, less robust studies
		Expert #5
		Expert #6
		Expert #7 Not aware
		Expert #8

		None.
20	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 – not asked
		Expert #4: Cost-effectiveness to detail economic benefit is needed Antimicrobial resistance Does targeted intervention make sense (eg. high risk patients)
		Expert #5
		Expert #6 Plus sutures may only be effective in certain populations or certain wound types. Just because they may be effective in laparotomy wounds, does not mean they are effective in traumatic wounds, or elective surgery
		Expert #7 Not aware
		Expert #8 None.
21		Expert #1 – not asked

	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one): Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. Fewer than 10 specialist centres in the UK Cannot predict at present.	Expert #2 – not asked
		Expert #3 – not asked
		Expert #4
		Expert #5 **Most or all district general hospitals.**
		Expert #6 **Most or all district general hospitals.**
		Expert #7 X Most or all district general hospitals.
		Expert #8 Most or all district general hospitals.
22	Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology? Please indicate if you would be able/willing to share this data with NICE. Any	Expert #1: No
		Expert #2 I would be willing to share my local data from 2013 to date. I am currently trying to get it published

	information you provide will be considered in confidence within the NICE process and will not be shared or published. (Experts 1 to 3) Or Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important. (Experts 4-8)	
		Expert #3 YES. Locally we are assessing the impact of PLUS sutures on our already implemented SSI reduction bundle.
		Expert #4: Conferences have been suspended due to COVID-19
		Expert #5 None recent. My last paper in BMJ open in ? 2019
		Expert #6 Not aware of any
		Expert #7 Product used as part of an SSI prevention bundle for our adult cardiac surgery patients. Check publications: https://pubmed.ncbi.nlm.nih.gov/29604297/. https://bmjopenquality.bmj.com/content/9/3/e000976.

		Expert #8 None
23	Are you aware of any further evidence for the technology that is not included in this briefing? (experts 1 to 3) Or Are there any major trials or registries of this procedure/technology currently in progress? If so, please list. (Expert 4 to 8)	Expert #1: No
		Expert #2 no
		Expert #3 Not that out performs the attached studies.
		Expert #4: I am not aware
		Expert #5 Not aware but check ISRCTRN
		Expert #6
		Expert #7 Not aware
		Expert #84Not that I know of.
24	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as	Expert #1: There are over 10 million operations undertaken in the NHS each year. Allowing for the exclusions listed in the document then several million patients per year will potentially be eligible

	an estimated number, or a proportion of the target population)?	
		Expert #2 It depends on whether the sutures are used for all surgeries or just high risk patients. There is no reason why the sutures could not be used for all patients undergoing surgery but there would need to be a cost benefit analysis
		Expert #3 ALL surgical procedures could utilise PLUS sutures.
		Expert #4: I am not aware
		Expert #5 Not aware but check ISRCTRN
		Expert #6
		Expert #7 Not aware
		Expert #8 Not that I know of.

25	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert #1: No
		Expert #2 no
		Expert #3 No
		Expert#4 Surgeon preference
		Expert#5 No
		Expert#6 No
		Expert #7 Not aware
		Expert #8 None.
26	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert #1: No – only issue would be the usual spectre of financial constraint initially
		Expert #2 Only cost. They are more expensive. Most hospitals do not know their SSI rates and so they cannot see the benefit of the technology. As most SSI occurs in the community

		in some specialties eg colorectal, the hospital has to pay extra but the gains are mainly in primary care
		Expert #3 Price. Procurement feel they are more expensive than standard sutures. However, procurement are failing to see the overall reduction in the cost to the NHS through the reduction in SSI rates.
		Expert#4 Cost -and lack of data- if there is no 'issue' with SSI rates, theatres would be unlikely to change
		Expert#5 No – our organisation has just adopted for all surgery
		Expert#6 Additional cost, lack of evidence of effectiveness
		Expert #7 Not aware
		Expert #8 The only issue I can foresee is cost versus benefit.
27	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert #1: The research is all based around studies that look at skin closure. Particularly in the area of abdominal surgery many SSIs are not caused by skin bacteria but by enteric bacteria and as such the SSI involves the subcutaneous tissues and deeper layers of a wound.

		Work looking at using the triclosan sutures in all layers of wound closure would be very useful in abdominal surgery This should probably be made clear in the guidance
		Expert #2 I am only familiar with the evidence in the field of general surgery. It would be necessary to look at the evidence for all specialties before making final recommendations. Recommending Plus sutures for surgery where SSI rate is very low eg after excision of skin lesions, scrotal surgery etc might not be cost effective, especially where SSI is not being measured. Ideally linking of data between primary and secondary care would allow robust SSI measurement or else using technology to measure patient reported SSI would be less labour intensive than using postal questionnaire. Currently accurate measurement of SSI is hard and requires investment in manpower but large scale investment in antibacterial sutures would occur with a focus on measurement of SSI. The current GIRFT audit has flawed methodology. Data needs to be collected continuously and accurately
		Expert #3 No
		Expert#4 Antimicrobial resistance, target high risk
		Expert#5 No
		Expert#6 A Cochrane review is essential. RCTs in populations that have not currently been studied (as mentioned above).
		Expert #7

		Expert #8 None. There meta-analyses available that support the use of these sutures.
28	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert #1 – not asked
		Expert #2 – not asked
		Expert #3 - not asked
		Expert#1 Beneficial outcome measures: Generally, superficial SSI up to 30 days, deep SSI 90 days Adverse outcome measures:

		Allergy/Sensitivity Surgical wound dehiscence
		Expert#2 Beneficial outcome measures: Very tricky infection is a rare complication that could only be detected in huge trials Adverse outcome measures:
		Expert#3 Beneficial outcome measures: Surgical site infection measured at 30/90 days and defined according to the CDC criteria Measured by patient reported outcome measure and/or hospital records Adverse outcome measures: Incidence of allergy

		Expert #4 Beneficial outcome measures: Need a robust surgical site infection surveillance programme in place to monitor surgical site infection rates locally Adverse outcome measures: Not anticipated
		Expert #5 Beneficial outcome measures: Surgical site infection rates – already being measured in all UK paediatric cardiac surgery units Reduction in antibiotic use for surgical site infection Hospital length of stay solely for antibiotic administration / surgical site infection treatment. All should be measured over a 30-day post-operative period. Adverse outcome measures: Wound dehiscence Allergic reaction to sutures Both should be measured over a 90-day post-operative period, as the sutures would be completely absorbed by this time.

29	How useful would NICE guidance on this particular technology be to you or other NHS colleagues?	Expert #1: Very, particularly when producing business cases for the finance departments within the varying NHS organisations
		Expert #2 Very
		Expert #3 Very useful.
		Expert #4 – not asked
		Expert #5 – not asked
		Expert #6 – not asked
		Expert #7 – not asked
		Expert #8 – not asked
30	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert #1 – not asked
		Expert #2 - not asked

		Expert #3 - not asked
		Expert#4
		Expert# 5
		Expert#6
		Expert #7 n/a
		Expert #8 No further comment.