

# Medical Services Advisory Committee (MSAC) Public Summary Document

## *Application No. 1629 – Defensive Antibacterial Coating (DAC) 5ml Kit*

**Applicant:** Novagenit Australia Pty Ltd

**Date of MSAC consideration:** 24-25 November 2022

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

### **1. Purpose of application**

An application seeking MSAC's advice to inform the Prostheses List Advisory Committee (PLAC) on the comparative safety, effectiveness, cost-effectiveness and total cost of Defensive Antibacterial Coating 5ml kit (DAC) for patients at risk of periprosthetic deep surgical site infection (SSI) when undergoing surgery with orthopaedic implant procedure(s) was received from Novagenit Australia Pty Ltd by the Department of Health and Aged Care.

### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC will advise the PLAC that it did not support listing of DAC for patients at risk of periprosthetic SSI when undergoing surgery with orthopaedic implant procedure(s). MSAC noted that DAC is reconstituted with an antibiotic solution and considered the comparative evidence for DAC+antibiotics was limited, of low quality and did not demonstrate the comparative effectiveness and cost-effectiveness of surgery with DAC+antibiotics compared to surgery without DAC+antibiotics. MSAC considered the cost of DAC to be high and unjustified. MSAC was concerned that there was a real risk that DAC+antibiotics would be used outside the proposed populations and therefore considered the estimated utilisation and financial impacts to be highly uncertain and likely underestimated.

MSAC's consideration, rationale and advice to the Minister outlined in this Public Summary Document (PSD) is based on the evidence available at the time of consideration (i.e. November 2022), at which time the evaluation of DAC for inclusion on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA) was ongoing. The Department of Health and Aged Care acknowledges that since MSAC's consideration, DAC has been included on the Australian Register of Therapeutic Goods (ARTG, [ARTG 427290](#)), and this may be relevant context for any future resubmission to seek MSAC's reconsideration of its advice.

<b>Consumer summary</b>
Novagenit Australia Pty Ltd submitted an application requesting MSAC's advice on the comparative safety, effectiveness, cost-effectiveness and total costs of Defensive Antibacterial Coating 5ml kit (DAC) to prevent infection in patients who are at risk of developing an infection following surgery involving an orthopaedic implant (eg. joint replacement). MSAC's advice is

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intended to inform the Prostheses List Advisory Committee (PLAC) consideration of whether to list DAC on the Prostheses List.

Orthopaedic implants are used to replace bones and joints (e.g., a hip replacement or the insertion of plates and screws to fix fractured bones). With any surgery, there is a risk of infection, and, in orthopaedic surgery, there is a risk of infection at the site of the orthopaedic implant also known as a periprosthetic surgical site infection (SSI). These infections are difficult to treat and can have debilitating consequences for patients. As a preventative measure, it is routine practice for all patients to be provided antibiotics that circulate throughout the whole body (i.e., prophylactic systemic antibiotics). If a patient develops a periprosthetic SSI, it can be treated in several ways. Some periprosthetic SSI are successfully treated with additional systemic antibiotics. In some cases, the periprosthetic SSI may be treated with additional systemic antibiotics in addition to surgery to thoroughly clean the surgical site to remove any infected/dead tissue and to replace exchangeable components while retaining the fixed orthopaedic implants. In other cases, the periprosthetic SSI may be treated with additional systemic antibiotics and a revision surgery to clean the surgical site and replace the orthopaedic implants.

The exact number of patients who develop a periprosthetic SSI in Australia is difficult to determine as a central point for recording all periprosthetic SSI is not available. The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) collects information on joint replacement surgery including when a surgery is performed to replace orthopaedic implants due to infection at the surgical site. Based on the AOANJRR, hip or knee replacement surgery due to periprosthetic SSI is approximately 1-2% in Australia. The AOANJRR does not include information on patients with periprosthetic SSI that do not require additional surgery to replace orthopaedic implants. Research using multiple sources of information, reports that the AOANJRR may underestimate the risk of periprosthetic SSI, but these reports still suggest that the rate of periprosthetic SSI is under 2% in Australia.

DAC is a sterile, single-use powder that is mixed with an antibiotic solution (DAC+antibiotics) to form a hydrogel that is then applied to the surface of orthopaedic implants. The application suggested that coating the orthopaedic implant with DAC+antibiotics (in addition to the systemic antibiotics) stops bacteria from sticking to the surface of the implant and therefore further reduces the risk of developing an infection at the surgery site. MSAC noted that irrespective of whether patients do or do not receive DAC+antibiotics, all patients would continue to receive routine preventative systemic antibiotics at the time of surgery.

MSAC noted that the available evidence comparing the risk of periprosthetic SSI developing following surgery using DAC+antibiotics versus surgery without using DAC+antibiotics was limited and of low to very low quality. MSAC considered that while the poor-quality evidence indicated there may be a trend for DAC+antibiotics to reduce periprosthetic infections in some patients, the potential reduction was small and highly uncertain. Therefore, MSAC considered that surgery using DAC+antibiotics was no better (i.e., noninferior) than surgery without DAC+antibiotics. MSAC also considered that the proposed price for DAC is very high and was not justified. MSAC was also concerned that the high cost of DAC may be perceived by consumers as being directly related to high benefits even though this is not supported by the evidence, and this may result in additional out of pocket expense to patients. Overall, MSAC did not consider using DAC+antibiotics during orthopaedic surgery would provide good value

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for money given it is more expensive than surgery without DAC+antibiotics, yet has similar effectiveness and safety.

### MSAC's advice to the Prostheses List Advisory Committee (PLAC)

MSAC did not support the listing of DAC for patients at risk of periprosthetic SSI when undergoing surgery with orthopaedic implant procedures. MSAC considered the evidence did not demonstrate that DAC+antibiotics was superior to surgery without DAC+antibiotics and therefore, the high cost of DAC was not good value for money.

## 3. Summary of consideration and rationale for MSAC's advice

MSAC noted this application from Novagenit Australia Pty Ltd requested MSAC's advice to inform the PLAC on the comparative safety, effectiveness, cost-effectiveness and total cost of DAC for patients at risk of periprosthetic deep SSI when undergoing surgery with orthopaedic implant procedure(s).

MSAC noted that DAC is not included on the Australian Register of Therapeutic Goods (ARTG) but is currently under evaluation by the Therapeutic Goods Administration (TGA). MSAC noted that, per the intended use being evaluated by the TGA, DAC (a dry powder containing hyaluronic acid and polylactic acid) is rehydrated using an antibiotic solution (vancomycin or gentamicin, supplied separately). MSAC noted there is no clinical evidence on the use of DAC alone for reducing periprosthetic SSI therefore, consistent with the intended use submitted to the TGA, the evaluation pertains to DAC+antibiotics.

MSAC noted that DAC is applied to the whole of an uncemented prosthesis, or the surface of a cemented prosthesis not in contact with antibiotic-loaded cement during orthopaedic surgery where a prosthesis is implanted, for which appropriate MBS items already exist. Therefore, the application does not seek to create a new or amend an existing MBS item.

MSAC noted that while the rate of periprosthetic SSI is low in Australia (approximately 1-2%), periprosthetic SSI can have catastrophic consequences for patients including leading to serious morbidity and death. MSAC noted that joint replacement surgery is a common procedure and that the number of joint replacement surgeries is increasing each year. Therefore, while the rate of periprosthetic SSI is low in Australia, there is a clinical need to reduce the risk of periprosthetic SSI and subsequent consequences.

MSAC noted that DAC+antibiotics was proposed for use in four patient populations that are considered high risk for periprosthetic SSI: 1) patients undergoing elective joint replacement surgery with an ASA<sup>1</sup> score  $\geq 3$  and a BMI<sup>2</sup>  $>30$  kg/m<sup>2</sup>; 2) patients undergoing elective megaprotheses or revision surgery (not for infection); 3) patients undergoing revision surgery (implant replacement) due to periprosthetic SSI; and 4) patients undergoing open reduction and internal fixation for a) closed fracture (ASA score  $\geq 3$  and BMI  $>30$  kg/m<sup>2</sup>) or b) open fracture. MSAC noted that the ASA score is a subjective assessment that may not be a robust restriction criterion to prospectively assess risk for periprosthetic SSI and restrict the use of

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<sup>1</sup> ASA score - American Society of Anaesthesiologists score

<sup>2</sup> BMI - body mass index

DAC+antibiotics. MSAC noted the applicant's pre-MSAC response attempted to allay concerns raised by ESC regarding the potential for DAC+antibiotics to be used outside the four proposed populations. However, MSAC disagreed with the applicant's pre-MSAC response as MSAC considered there is a definite potential for DAC+antibiotics to be used outside of the proposed populations, noting there are other comorbidities that increase the risk of periprosthetic SSI and other orthopaedic surgeries (hemi-arthroplasties, anchors on tendon repairs, etc) where patients may be at a high risk of infection. MSAC also noted the applicant's pre-MSAC response presented company sales data illustrating the international utilisation of DAC. However, there was no information available to understand the patient population where DAC was used internationally. It was unclear whether clinical discretion was applied to reserve DAC+antibiotics for high-risk patients as defined in this application. Further, the data showed significant international variation in the utilisation with the highest utilisation in countries where the studies were performed. MSAC noted that this could suggest that the use of DAC+antibiotics was based on proponents who had adopted the use of DAC+antibiotics.

MSAC noted that the comparator was standard surgery without DAC+antibiotics. MSAC noted that the available clinical evidence, comparing surgery with DAC+antibiotics versus surgery without DAC+antibiotics, consisted of two randomised controlled trials (RCTs) and four case control studies. MSAC noted that the Department Contracted Assessment Report (DCAR) assessed the overall risk of bias in both RCTs as having "some concerns" regarding the blinding of participants, carers and people delivering the interventions. MSAC also noted the concerns raised by ESC and in the DCAR regarding potential measurement bias in both RCTs as the studies assumed a 6% periprosthetic SSI incidence in the control group. This conflicts with data from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) report that, using the rate of revision procedures for infection, the estimated incidence of SSI is around 1-2% in the Australian population. MSAC noted the applicant's pre-MSAC response reiterated its criticism of the AOANJRR data, claiming the AOANJRR underestimates the rate of periprosthetic SSI in Australia and cited two supporting studies<sup>3, 4</sup>. However, MSAC noted that while the two studies did indicate that the AOANJRR underestimates periprosthetic SSI, the studies still report that the rate of periprosthetic SSI is under 2% in Australia. For the case control studies, the overall risk of bias was assessed to be "serious" in three studies and "moderate" in one.

Regarding comparative safety, MSAC noted there was no difference in safety outcomes for surgery with DAC+antibiotics versus surgery without DAC+antibiotics. MSAC noted in response to concerns raised by ESC regarding the lack of long term safety data, the applicant's pre-MSAC response stated there is a large evidence base supporting the long term safety of hyaluronic acid and polylactic acid (components of DAC) used in other products in other clinical settings (e.g. wound dressings, dermal tissue fillers, drug-delivery vehicles). The applicant's pre-MSAC response claimed this data can be used as evidence for the long term safety of DAC. However, MSAC noted that no data were presented to support this claim and MSAC did not consider it appropriate to extrapolate the long-term safety of other products (that are not the same as DAC+antibiotics even though they contain hyaluronic acid and polylactic acid) used in other clinical settings to assume the long-term safety of DAC+antibiotics in an orthopaedic implant surgery setting.

Regarding comparative effectiveness, MSAC noted the applicant claimed that surgery with DAC+antibiotics was superior to surgery without DAC+antibiotics with regards to the risk of

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<sup>3</sup> Jin X, Luxan BG, Hanly M, et al. (2022) *Bone Joint J.* 104-B(9):1060-1066

<sup>4</sup> Sinagra ZP, Davis JS, Lorimer M, et al. (2022) *Bone Jt Open.* 3(5):367-373

periprosthetic SSI. MSAC noted that the evidence indicated a trend for DAC+antibiotics to reduce the risk of periprosthetic SSI, but that the trend was small and highly uncertain due to wide confidence intervals (see Figure 1 in Section 12). The uncertainty in the benefit was further impacted by the low to very low quality of the data as discussed above. MSAC concluded that the claim of superior effectiveness for surgery with DAC+antibiotics, relative to surgery without DAC+antibiotics, was not supported by the evidence.

MSAC noted that the ability to model the cost-effectiveness of DAC+antibiotics was limited by the paucity of data and the limitations/uncertainties in the clinical evidence base. MSAC noted that a stepped cost-utility analysis was presented for populations 1 and 3. MSAC noted the treatment effect of DAC+antibiotics was a key driver of the model. That is, DAC+antibiotics was dominated when the upper 95% confidence interval (CI) was used and as discussed above, based on the clinical evidence, surgery with DAC+antibiotics was considered noninferior to surgery without DAC+antibiotics.

MSAC noted that the rate of periprosthetic SSI was also a key driver. That is, the rate of periprosthetic SSI in the control arm in the trial evidence is different to the rate of periprosthetic SSI in Australia. Using the SSI rate from the AOANJRR, the ICER for Population 1 substantially increased to >\$1,000,000 (Step 2 over 1 year, but reduced to >\$100,000 when modelled over 20 years in Step 3) whereas for Population 3 the ICER flipped and became dominant (see Table 6). MSAC noted the applicant's pre-MSAC response criticised using the AOANJRR data in the CUA, claiming the AOANJRR underestimates the rate of periprosthetic SSI in Australia. However, MSAC considered application of the AOANJRR data appropriate and noted that the DCAR conducted sensitivity analysis on the SSI rate, including increasing the rate by 20% (see Table 8 [hips] and Table 9 [knee] for population 1; and Table 10 [hips] and Table 11 [knee] for population 3) which MSAC considered addressed the concern that the AOANJRR data underestimates the rate of periprosthetic SSI. MSAC also noted the cost of DAC and the number of kits used were also key drivers. In addition, MSAC noted that the proposed Protheses List benefit for DAC was high and not justified.

MSAC noted cost-consequence analyses were presented for populations 2 and 4a (closed fractures). MSAC noted that the estimated incremental cost of surgery with DAC+antibiotics versus surgery without DAC+antibiotics was approximately \$4,000 for Population 2 and approximately \$3,300 for Population 4b. However, MSAC did not consider these estimates meaningful given the clinical evidence indicates that surgery with DAC+antibiotics is noninferior to surgery without DAC+antibiotics.

In terms of the financial impact, MSAC noted the applicant had previously estimated that less than **redacted** patients would utilise DAC+antibiotics in the first year based on international sales data (**redacted**). In contrast, MSAC noted the DCAR estimated **redacted** patients may utilise DAC+antibiotics in the first year based on projections from the stated eligible population and assumed uptake rate of DAC. MSAC noted the applicant's pre-MSAC response criticised the DCAR estimates, highlighted an error in the assumption regarding private/public patient utilisation and provided international sales data to argue the uptake would be lower. MSAC noted that correcting the private/public patient assumption error would in fact increase the utilisation estimates and as discussed earlier, MSAC considered it highly likely that DAC+antibiotics could be used outside the proposed populations creating further uncertainty in the estimated utilisation which MSAC considered to be underestimated. MSAC queried whether there was any utilisation data from New Zealand that could help inform assumptions when estimating the potential utilisation in Australia. MSAC noted, based on the DCAR estimated utilisation (underestimated), that if DAC was listed on the Protheses List, the estimated annual cost to private health insurers would be more than **\$redacted**. MSAC considered that the additional estimated annual cost to the MBS (~\$100,000 for each population) was likely overestimated due

to over-estimating the costs associated with preparing the DAC+antibiotics. MSAC also noted the other concerns raised in the applicant's pre-MSAC response that the analysis did not include costs for mortality, amputation etc. MSAC was not convinced that these would have a consequential effect noting most periprosthetic SSI are treated without replacing the joint or amputating the limb.

MSAC noted antimicrobial resistance and stewardship had been raised as an 'other relevant factor' for MSAC consideration. MSAC acknowledged that these are important public health issues. MSAC noted the applicant's pre-MSAC response to this issue which amongst other things stated that antibiotics use with bone cement is common practice. After deliberating, MSAC considered the relevance of antimicrobial resistance and stewardship to DAC should not be dismissed given the potential for DAC (if listed on the PL) to increase antibiotic use when there is very uncertain evidence of clinical benefit.

Overall, MSAC will advise PLAC that MSAC did not support listing of DAC on the Protheses list. MSAC considered the evidence did not demonstrate that surgery with DAC+antibiotics has superior effectiveness relative to surgery without DAC+antibiotics (i.e., DAC+antibiotics has noninferior effectiveness) with regards to the risk of periprosthetic SSI. Given the high (and unjustified) cost of DAC and the noninferior effectiveness of DAC+antibiotics, MSAC concluded that DAC is not cost-effective. MSAC noted concerns that the high cost of DAC may influence consumers to assume DAC+antibiotics is of high benefit even though the evidence did not demonstrate this and considered this was important for consumers to understand (as it could lead to the high cost of DAC being borne as an additional out-of-pocket expense by patients). Further, MSAC considered the estimated utilisation and financial impacts to be highly uncertain and likely underestimated.

MSAC considered that any resubmission would need to present high quality RCT evidence that demonstrates the superior effectiveness of surgery with DAC+antibiotics over surgery without DAC+antibiotics where the periprosthetic SSI rate in the control arm is applicable to the Australian population. MSAC noted that as DAC+antibiotics is reabsorbed after 72hrs, it is more likely to have an impact on early (perioperative) SSI as opposed to late SSI therefore, it would be beneficial for the clinical evidence to clearly show the time points at which infection is reduced with DAC+antibiotics. The proposed population in any resubmission should be carefully reviewed and only include populations at high-risk of periprosthetic SSI that are supported by high quality evidence. The resubmission should also present a justification for the cost of DAC along with a revised economic and financial analysis.

## **4. Background**

MSAC has not previously considered the comparative safety, effectiveness, cost-effectiveness, and total cost to DAC+antibiotics.

## **5. Prerequisites to implementation of any funding advice**

DAC is a Class III medical device. At the time of MSAC consideration, DAC was not included on the ARTG but was under evaluation by TGA<sup>5</sup>. The TGA application for DAC states that DAC is indicated

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<sup>5</sup> Since MSAC's consideration, DAC has been included on the Australian Register of Therapeutic Goods (ARTG, [ARTG 427290](#)).

together with an antibiotic substance (vancomycin or gentamicin) to be loaded at the point of care by surgeons and prepared just before use in the operative field.

The antibiotics to be used with DAC are not supplied as part of the DAC kit. Vancomycin and gentamicin are included on the ARTG and listed on the Pharmaceutical Benefits Scheme (PBS). Note there are restrictions on the PBS listing of Vancomycin (i.e., prophylaxis for endocarditis, in hospital treatment of endophthalmitis/infection).

The application form and PICO Confirmation for MSAC application 1629 indicated that DAC could be used with or without antibiotics (p.14, para.3 of [MSAC 1629 PICO Confirmation](#)). However, the option to use DAC without antibiotics does not align with the current TGA application. Further, no clinical evidence was identified, for any population of interest, that used DAC without antibiotics (see Section 8 – Characteristics of the evidence base). Therefore, the intervention assessed in the Department Contracted Assessment Report (DCAR) was DAC loaded with antibiotics (DAC+antibiotics).

## 6. Proposal for funding

MSAC application 1629 for DAC does not seek to create or amend an MBS item(s) as there are existing MBS items that can accommodate the delivery of DAC+antibiotics.

MSAC application 1629 seeks MSAC's advice on the comparative safety, effectiveness, cost-effectiveness and total cost of DAC+antibiotics to inform PLAC's consideration of whether to list DAC on the Prostheses List for funding by private health insurers. The applicant has stated the price of DAC is \$redacted (redacted).

## 7. Population

As outlined in the [PICO Confirmation](#), DAC+antibiotics is proposed for use in four populations based on the type and indication of the surgical arthroplasty procedure(s):

- Population 1: Patients undergoing an elective primary joint implant at increased risk of infection due to the presence of comorbidities (American Society of Anaesthesiologists (ASA) score  $\geq 3$ ; and Body Mass Index (BMI)  $>30$  kg/m<sup>2</sup>; and receiving cementless components),
- Population 2: Patients undergoing elective megaprosthesis implantation or elective major revision of joint implants for indications other than periprosthetic infection, including total joint revision, tumour removal, and reconstruction,
- Population 3: Patients undergoing surgery for periprosthetic deep SSI with implant replacement,
- Population 4: Patients undergoing open reduction and internal fixation:
  - Subgroup 1: Closed fracture with comorbidities (ASA score  $\geq 3$  and BMI  $>30$  kg/m<sup>2</sup>).
  - Subgroup 2: Open fracture.

In all populations, the DAC+antibiotic hydrogel coating is applied to the orthopaedic implant in addition to the current standard of care (i.e., all other elements of the orthopaedic surgery and peri/post-operative care such as systemic antibiotic prophylaxis remain unchanged).

## 8. Comparator

The comparator is standard (orthopaedic implant) surgery without DAC+antibiotics. The choice of surgical intervention (including perioperative management) is individualised for each patient within the proposed populations.

The main difference between the delivery of standard surgery with DAC+antibiotics (intervention) and standard surgery without DAC+antibiotics (comparator) is that standard surgery with DAC+antibiotics requires additional resource use: DAC; antibiotics to load the hydrogel, surgeon/theatre time to prepare and apply the hydrogel, sterile water, sterile syringe needles. Antibiotics for loading the hydrogel are not supplied with the DAC.

## 9. Summary of public consultation input

Consultation feedback was received from two organisations (a specialist society and a patient advocacy group), both of which were supportive of the application:

- Orthopaedic oncology subgroup collective of the Australia and New Zealand Sarcoma Association (ANZSA)
- Musculoskeletal Australia (MSK).

The main benefits of the service considered in the consultation feedback included:

- Reduced risk of infection for the patient.
- Reduced pain and distress experienced by the patient.

The main disadvantages of the service considered in the consultation feedback considered the high cost of the product is likely to prohibit access for some patients.

Other comments provided in the consultation feedback included:

- Lower infection rates could reduce overall health costs due to reduced hospital stay and ongoing treatment management (due to less need for revision of a prosthesis or the removal of a prosthesis or antibiotic washouts, etc.).
- The reduction in burden of infection has a benefit to the patient as they (and their families) will experience less distress, pain and may be able to return to work sooner.

## 10. Characteristics of the evidence base

A total of six studies were included in the evidence base, comprising two RCTs (Romanò et al. 2016<sup>6</sup>, Populations 1 and 3 and Malizos et al. 2017<sup>7</sup>, Population 4) and four case-control studies (De Meo et al. 2020<sup>8</sup> and Zoccali et al. 2021<sup>9</sup>, Population 2; and Capuano et al. 2018<sup>10</sup>

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<sup>6</sup> Romanò CL, Malizos K, Capuano N, et al. (2016) *J Bone Jt Infect*, 1:34

<sup>7</sup> Malizos K, Blauth M, Danita A, et al. (2017) *J Orthopaedics & Traumatology*. 18(2):159-69

<sup>8</sup> De Meo D, Calogero V, Are L, et al. (2020) *Microorganisms*. 8(4):571

<sup>9</sup> Zoccali C, Scoccianti G, Biagini R, et al. (2021) *Eur J Orthop Surg Traumatol*. 31(8):1647-1655

<sup>10</sup> Capuano N, Logoluso N, Gallazzi E, et al. (2018) *Knee Surg Sports Traumatol Arthrosc*. 26(11):3362-7



and Zagra et al. 2019<sup>11</sup>, Population 3). The key features of the six studies are presented in Table 1.

The primary cohort in the RCT reported by Romanò et al. (2016) included both primary and revision total hip or knee joint replacement (i.e., population 1 and 3 combined). The primary outcome (SSI incidence) was reported for the whole cohort and by primary or revision subgroup. Secondary outcomes were only reported for the whole cohort. The subgroup analysis for primary hip and knee joint replacement surgery is the only comparative evidence available for Population 1.

The overall risk of bias in both RCTs (Romanò et al. 2016, Malizos et al. 2017) was assessed<sup>12</sup> to have 'some concerns' due to concerns regarding the blinding of participants, carers and people delivering the interventions. In addition, there were concerns that the outcome assessment was possibly influenced by knowledge of the intervention received. Further, there is also potential measurement bias in both RCTs as they assumed a 6% periprosthetic deep SSI incidence in the control group. However, data from the AOANJRR reports, using the rate of revision procedures for infection, the estimated incidence of SSI is around 1-2% for primary hip/knee joint arthroplasty. Thus, it is not clear if studies were sufficiently powered to detect the reported treatment effect.

The study design of all non-randomised studies was retrospective with an inherently high risk of bias. The overall risk of bias was assessed<sup>13</sup> to be 'serious' in three studies (Capuano et al. 2018, Zagra et al. 2019, and Zoccali et al. 2021), and 'moderate' in one (De Meo et al. 2020). De Meo et al. (2020) reduced confounding bias by collecting all pre-operative clinical, laboratory, and radiographic data, the Charlson Comorbidity Index (CCI), and the periprosthetic joint infection (PJI) risk score. Further, it also adopted a comparatively rigorous econometric technique (propensity score matching) to match cases and controls, which likely reduced selection bias to a certain extent.

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<sup>11</sup> Zagra L, Gallazzi E, Romanò D, et al. (2019) *Int Orthop*. 43(1):111-5

<sup>12</sup> Assessed using the Revised Cochrane Risk of Bias Tool for Randomised Trials (RoB 2)

<sup>13</sup> Assessed using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I)

**Table 1 Key features of the included evidence of the use of DAC+antibiotics to prevent periprosthetic deep SSI**

Trial/Study	N	Design/ duration	Risk of bias	Population characteristics	Key outcome(s)	Results used in modelled evaluation
Population 1						
Romanò 2016	Whole study cohort (primary and revision): 373 Hip: 78.8% (294/373) Knee: 21.2% (79/373)  Primary: 71.6% (267/373) Revision: 28.4% (106/373)	R, Mean±SD follow-up of 14.5 ± 5.5 months (range 6 to 24 months)	Some concerns	Intervention: Aged>18 yrs [Whole study cohort (primary, revision): mean 70.0 yrs (range 36 to 96 yrs)] Gender (Female): 57.1% Comorbidities <sup>1</sup> : diabetes and BMI>40: 0.37% (1/267) [only 1 patient] Control: Data specific to primary TJA subgroup not reported [Whole study cohort (primary, revision): mean±SD (range): 71±10.6 yrs (range 36-96 yrs)] Gender (Female): 59.8%  Comorbidities (primary): diabetes <sup>2</sup> 1.12% (3/267); nicotine abuse: 0.37% (1/267); previous PJI: 0.37% (1/267); previous surgeries: 0.37% (1/267)	Post-operative data at the latest follow-up: Early SSI <sup>3</sup> (overall/ overall (minimal 12 months follow-up), delayed wound healing <sup>4</sup> , other complications, unplanned antibiotic treatment during hospital stay for reasons other than SSI (mainly urinary or respiratory tract infections)  Continuous outcomes: Time to early wound healing <sup>5</sup> (mean ASEPSIS score at 7 and 14 days)  Serum laboratory values at 6 months after index surgery: Erythrocyte Sedimentation Rate (mm/h), C-reactive Protein (mg/L)  Postoperative data at the latest follow-up SF-12 score (physical, mental and total), HHS, KSS	SSI rates, follow-up, starting age, and number of DAC kits
Population 2						
De Meo 2020	34 (hip)	CC, NR, Mean±SD follow-up of 12.4±5.7 months in the treatment group and 34.3 ± 21.3 months in the control group	Moderate	Intervention (Mean±SD): Age: 74.9 ± 11.5 Gender (Female): 65% (11/17)  Control: Age (Mean±SD): 75.9 ±9.6 Gender (Female): 59% (10/17)  Intervention and control groups matched for the age, BMI, PJI risk score, CCI, length of stay, and operative time as response variables.	Early (3-6 months) infection  Functional outcomes: HOOS (only post), HHS (pre/post)  Others: Surgery duration, LOS, total complications, prolonged wound discharge, dislocation, nerve deficit, systemics, death	Not applicable

Trial/Study	N	Design/ duration	Risk of bias	Population characteristics	Key outcome(s)	Results used in modelled evaluation
Zoccali 2021	86 (bone tumors, severe trauma or infection)	CC, NR, Mean±SD follow-up of 24.3 ± 11.7 months in the treatment group and 24.2 ± 11.5 months in the control group	Serious	Intervention (Mean±SD): Age: 45.6 ± 21.3 Gender (Female): 44% (19/43)  Control: Age (Mean±SD): 47.4 ± 19.5 Gender (Female): 44% (19/43) Intervention and control groups matched for age, sex, pre-operative diagnosis and host type.	'Post-surgical infection' at follow-up, surgery duration  Post-operative complications: Intraoperative fracture, haematoma and surgical revision, aseptic implant revision, intraoperative femoral fissure, oncological disease progression, hip implant dislocation, transient femoral nerve palsy	Not applicable
Population 3						
Romanò 2016 <sup>6</sup>	106 (hip and knee)	R, MC, Mean±SD follow-up of 14.5 ± 5.5 months (range 6 to 24 months)	Some concerns	Intervention: Aged > 18 yrs [Whole study cohort (primary, revision): mean: 69 ± 12.6 yrs (range 36 to 96 yrs)] Gender (Female): 57.1% (108/189)  Control: Data specific to primary TJA subgroup not reported [Whole study cohort (primary, revision): mean±SD (range): 71±10.6 yrs (range 36-96 yrs)] Gender (Female): 59.8% (110/184)  Comorbidities: diabetes: 1.12% (3/267); nicotine abuse: 0.37% (1/267); previous PJI: 0.37% (1/267); previous surgeries: 0.37% (1/267)	Categorical: SSI, delayed wound healing, other complications, unplanned antibiotic treatment during hospital stay for other reasons than SSI  Continuous: time to early wound healing (mean ASEPSIS score at 7/14 days), serum laboratory values at six months after index surgery  Postoperative data at the latest follow-up: SF-12 (physical, mental, total), HHS, KSS	SSI rates, follow-up, starting age, and number of DAC kits
Capuano 2018	44 (hip and knee)	CC, NR, Mean±SD follow-up of 29.3 ± 5.0 months	Serious	Mean age: 71.3 ± 13.6 Gender (Female): 59.1% in both cases and controls Intervention and control groups matched for age, sex, site of infection and host type according to McPherson's classification	Categorical: delayed or late periprosthetic hip/knee infection  Continuous: SF-12 score (total), HHS, KSS, hospital LOS, duration of systemic antibiotic therapy	SSI rates, and number of DAC kits

Trial/Study	N	Design/ duration	Risk of bias	Population characteristics	Key outcome(s)	Results used in modelled evaluation
Zagra 2019	54 (hip)	CC, NR, Mean±SD follow-up of 2.7 ± 0.6 years (min: 2, max: 3.5 years)	Serious	Intervention (mean age): 63.9 ± 11.7 years; Control group: 64.8 ± 10.1 years Gender (Female): Treatment: 59.3% (16/27) Control: 48.1% (13/27) Intervention and control groups matched for age and host type	Categorical: delayed or later periprosthetic hip infection, delayed wound healing, dislocation  Continuous: HHS, hospital LOS	SSI rates, and number of DAC kits
Population 4						
Malizos 2017 (Closed fractures)	253 (fresh fractures)	R, MC, Mean±SD follow-up of 18.1 ± 4.5 months (range 12–30 months); results presented for minimum of 12-month follow-up	Some concerns	Age (>18 years), Mean±SD: Intervention: 62.5 ± 21.2 Control: 58.6 ± 17.6 Gender (Female): Intervention: 57.9% (73/126) Control: 55.1% (70/127) Comorbidities <sup>7</sup> : Nicotine abuse: 0.79% (2/253); alcohol abuse: 0.40% (1/253); diabetes: 0.79% (2/253); vasculopathy: 0.40% (1/253)	Complications: SSI, delayed wound healing, delayed union  Follow-up: SF-12 (physical, mental and total)	Not applicable

Source: Table 1, p 24 of MSAC 1629 DCAR, adapted from Capuano et al. 2018, De Meo et al. 2020, Malizos 2017, Romanò et al. 2016, Zagra et al. 2019; Zoccali et al. 2021

Abbreviations: ASEPSIS=Additional treatment, the presence of Serous discharge, Erythema, Purulent exudate, and Separation of the deep tissues, the Isolation of bacteria, and the duration of inpatient Stay; CC= Case-control; HHS= Harris Hip Score; HOOS= Hip disability osteoarthritis outcome score; ; KSS= Knee Society Scores LOS= Length of Stay; MC= Multi-centre; NR= Not randomised, R= Randomised; PJI= Periprosthetic Joint Infection; SD= Standard Deviation; SF-12= Short-form 12, SSI= Surgical Site Infection; THA= Total Hip Arthroplasty

Note: Intervention and control in the table refer to surgery with DAC+antibiotics and without DAC+antibiotics, respectively.

Note: No evidence was available for Population 4 - Subgroup 2 (Patients undergoing open reduction and internal fixation: open fracture).

<sup>1</sup> Comorbidities reported only for patients with SSIs

<sup>2</sup> 3 out of 4 patients (Population 1) with SSIs had diabetes

<sup>3</sup> SSIs were defined as the presence of positive local clinical signs of acute inflammation and/or a draining sinus requiring further surgery, including early debridement or implant removal and/or unplanned antibiotic treatment with or without a positive cultural examination.

<sup>4</sup> Delayed wound healing was defined as an incomplete healing of the wound at 4 weeks after surgery, including the presence of wound dehiscence, necrosis or serum leakage, that may need further medication, but that did not require any additional surgical treatment.

<sup>5</sup> The authors reported using the ASEPSIS scoring method to assess wound healing. Category of infection: total ASEPSIS score 0-10 = satisfactory healing; 11-20= disturbance of healing; 21-30= minor wound infection; 31-40= moderate wound infection; >40= severe wound infection.

<sup>6</sup> Elective TJA, both primary and revision and both hip and knee

<sup>7</sup> Reported among patients with SSIs

## 11. Comparative safety

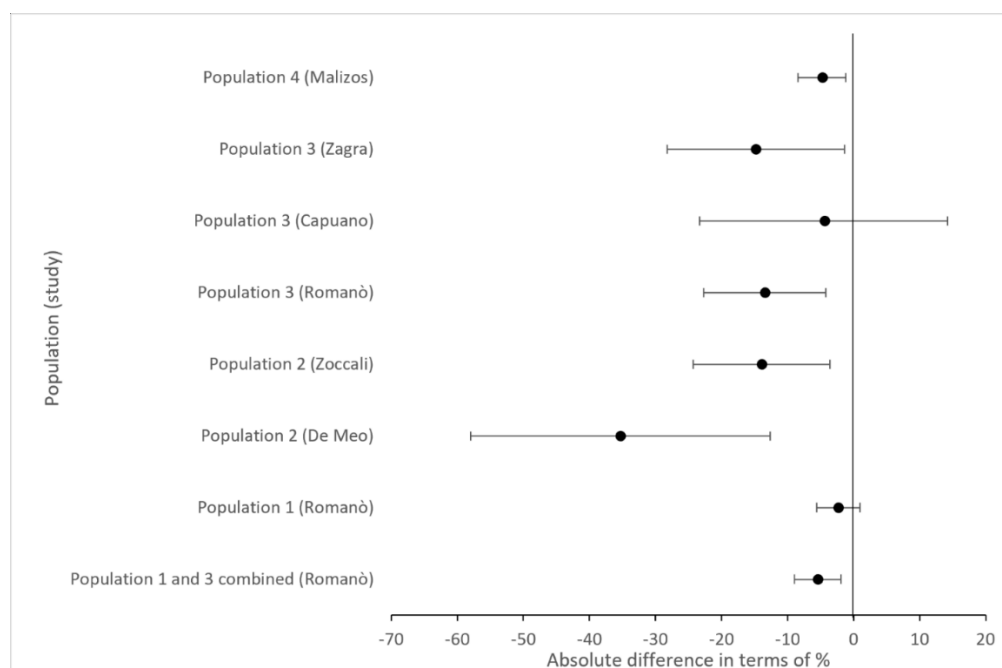
All six studies included in the DCAR reported that there were no detectable adverse events or side effects directly attributable to the DAC+antibiotic hydrogel coating across all populations. Further, no allergies associated with DAC+antibiotics were noted in the studies.

The studies indicated similar incidence of safety outcomes or complications for surgery with and without DAC+antibiotics across all populations.

## 12. Comparative effectiveness

The effectiveness of surgery with DAC+antibiotics versus no DAC+antibiotics, in terms of risk difference and relative risk of SSI/PJI are illustrated in Figure 1 and Figure 2, respectively. For all four populations, there is a trend in favour of surgery with DAC+antibiotics versus no DAC+antibiotics. This is evident from the fact that the point estimates for risk difference and relative risk lie on the left of zero and one, respectively.

**Figure 1 Risk difference of PJI/SSI among surgery with DAC+antibiotics vs no DAC+antibiotics in all populations**



Source: Figure 1, p27 of MSAC 1629 DCAR

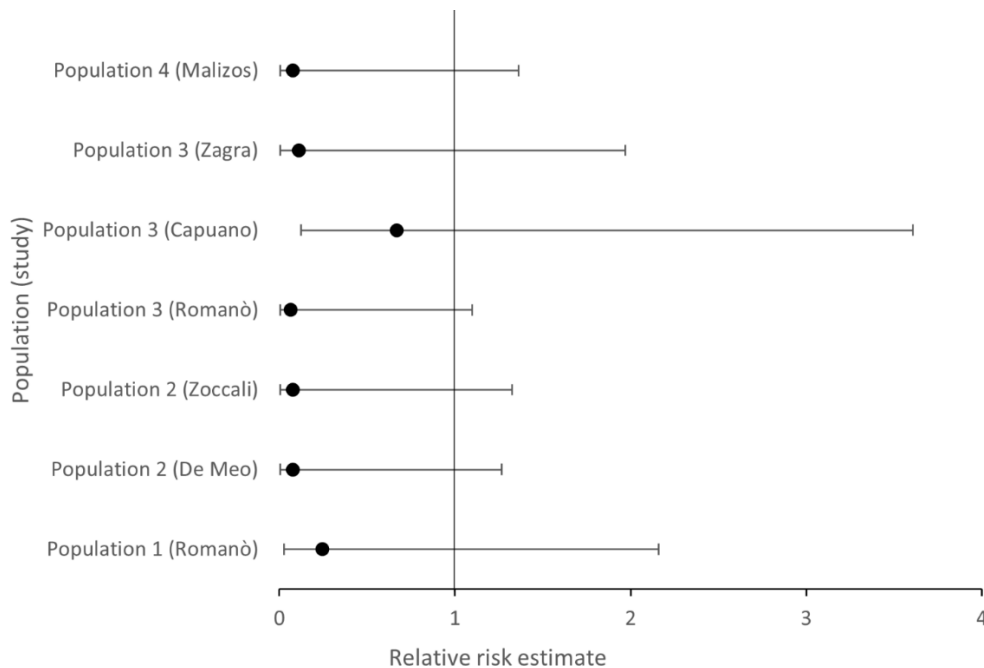
Note: Black dots represent risk difference

The risk of PJI/SSI was expressed in % terms by dividing total PJI/SSIs by the total number of patients in the group, where group= either surgery with DAC+antibiotics or surgery without DAC+antibiotics

Risk difference= Risk of PJI/SSI among patients in surgery with DAC+antibiotics - Risk of PJI/SSI among patients in surgery without DAC+antibiotics

Risk difference < 0% favours surgery with DAC, while relative risk >0% favours surgery without DAC.

**Figure 2 Relative risk of PJI/SSI among surgery with DAC+antibiotics vs no DAC+antibiotics in all populations**



Source: Figure 2, pg 28 of MSAC 1629 DCAR

Note: Black dots represent relative risk values

Relative risk < 1 favours surgery with DAC+antibiotics, while relative risk > 1 favours surgery without DAC+antibiotics.

### POPULATION 1+3

Romanò et al. (2016) reported for the whole cohort (primary [Population 1] and revision [Population 3] joint replacement), the overall incidence of SSI was lower for surgery with DAC+antibiotics compared to surgery without DAC+antibiotics ( $p=0.0196$ ; Table 2). It is noted that the statistical significance in the observed treatment effect is driven by the SSI rate in the revision subpopulation (Population 3), that is the point estimates in the SSI rate shift towards null for Population 1 but the converse is observed for Population 3 (see Figure 1 above).

Regarding secondary outcomes, SF-12 Health Survey total scores were higher at follow-up for surgery with DAC+antibiotics versus surgery without DAC+antibiotics ( $p=0.006$ , Table 2). Although it is noted that the SF-12 scores were very high for both with and without DAC+antibiotics (99.9/100 versus 94.7/100, respectively). However, surgery with and without DAC+antibiotics were similar in terms of delayed wound healing, other complications, unplanned antibiotic treatment during the hospital stay (other than SSI), Harris Hip Score (HHS) and Knee Society Score (KSS; Table 2). Romanò et al. (2016) also reported no difference between the study arms for early wound healing (assessed using the ASEPSIS<sup>14</sup> scoring method) and serum laboratory values.

### POPULATION 1

Romanò et al. (2016) reported, for the subgroup analysis of patients who underwent primary hip or knee replacement, that there was no difference in the incidence of SSI between surgery with DAC+antibiotics compared with surgery without DAC+antibiotics. That is there was a trend for

<sup>14</sup> Additional treatment, the presence of Serous discharge, Erythema, Purulent exudate, and Separation of the deep tissues, the Isolation of bacteria, and the duration of inpatient Stay (ASEPSIS)

lower incidence and relative risk for surgery with DAC+antibiotics but this was not statistically significant and the wide confidence intervals create uncertainty in the observed treatment effect (Table 2). No secondary outcomes were reported for this subpopulation.

The relevance of the trial evidence from Romanò et al. (2016) was limited in that it did not specify ASA score  $\geq 3$  and BMI  $\geq 30$ , a requirement for Population 1. It also had a relatively short follow-up. Further, randomisation had to be broken to estimate treatment effects separately for the subgroup analysis of primary joint replacement surgeries (Population 1).

## POPULATION 2

Both De Meo et al. (2020) and Zoccali et al (2021) reported the incidence of PJIs was lower for surgery with DAC+antibiotics compared with surgery without DAC+antibiotics ( $p=0.018$  and  $p=0.026$ , respectively). The relative risk of PJI favoured surgery with DAC+antibiotics but was not statistically significant (Table 2).

Regarding secondary outcomes, De Meo et al. (2020) reported the mean HHS and Hip Disability and Osteoarthritis Outcome Score (HOOS) favoured surgery with DAC+antibiotics but were not statistically significant. In De Meo et al. (2020), the rate of total complications was lower for surgery with DAC+antibiotics than without DAC+antibiotics ( $p=0.0134$ ; Table 2).

De Meo et al. (2020) reported one death (6%) due to sequelae of prolonged immobilisation in bed in the surgery with DAC+antibiotics group and 4 (23.5%) deaths due to periprosthetic infection complications ( $n=3$ ) and myocardial infection ( $n=1$ ) in the surgery without DAC+antibiotics group. Zoccali et al. (2021) reported one death (2%) due to underlying malignancy (Ewing's sarcoma) in the surgery with DAC+antibiotics group and two deaths (5%) due to tumour recurrence in the surgery without DAC+antibiotics group.

The confidence in the favourable outcomes reported for surgery with DAC+antibiotics group in De Meo et al. (2020) and Zoccali et al. (2021) are limited by their weak study designs and small sample sizes. Further, De Meo et al. (2020) considered hips only, and it is unclear if the results apply to other joints.

## POPULATION 3

Romanò et al. (2016) reported, for the subgroup analysis of patients who underwent revision hip or knee replacement for periprosthetic SSI, that the SSI incidence (recurrence) was lower for surgery with DAC+antibiotics versus without DAC+antibiotics ( $p=0.006$ ; Table 2). However, although the relative risk favoured surgery with DAC+antibiotics, it was not statistically significant ( $p=0.058$ ). In contrast, Capuano et al. (2018) and Zagara et al. (2019) reported, for both PJI recurrence and relative risk of PJI occurrence, that there was no statistically significant difference between surgery with and without DAC+antibiotics (Table 2).

Regarding secondary outcomes, Capuano et al. (2018) and Zagra et al. (2019) reported no difference in patient-reported outcomes measures (i.e. SF-12, HHS, KSS). Hospital length of stay and duration of systemic antibiotic therapy was statistically significantly less in the DAC+antibiotics group (Table 2).

All studies (Romanò et al. 2016, Capuano et al. 2018 and Zagra et al. 2019) exhibited several limitations. The subgroup in Romanò et al. (2016) included a relatively small sample size ( $n=106$ ), a short follow-up and randomisation had to be broken to estimate treatment effects for the subgroup. Both Capuano et al. (2018) and Zagra et al. (2019) had weak study designs (i.e., case-control studies) and small sample sizes. In addition, Capuano et al. (2018) compared single-stage revision with DAC+antibiotics (cases) to two-stage revisions without DAC+antibiotics

(controls), where the latter could be more prone to SSI. Further, Zagra et al. (2019) included hip revisions only and whether the treatment effect results apply to other joints is uncertain.

#### **POPULATION 4**

For patients with closed fractures (Population 4a), Malizos et al. (2017) reported the incidence of deep SSI was lower for surgery with DAC+antibiotics versus surgery without DAC+antibiotics ( $p=0.029$ , Table 2). However, there was no statistically significant difference between surgery with and without DAC+antibiotics in terms of relative risk for SSI ( $p= 0.08$ ).

Regarding secondary outcomes, Malizos et al. (2017) reported that there was no statistically significant difference between the groups for SF-12 Health Survey total score, delayed wound healing, delayed union or unplanned antibiotic treatment during hospital stay (for other reasons than SSI).

The relevance of the trial evidence from Malizos et al. (2017) is also limited as the study did not impose inclusion criteria for ASA score  $\geq 3$  and BMI  $\geq 30$ , required for Population 4 (closed fractures). Further, the study had a relatively short follow-up.

No evidence for the comparative safety of DAC+antibiotics for patients with open fractures (Population 4b) was identified.



**Table 2 Balance of clinical benefits of DAC, relative to no DAC, and as measured by the critical patient-relevant outcomes in the key studies**

Outcomes Follow-up	Participants (studies)	Quality of evidence (GRADE)	Event counts	P-value <sup>b</sup>	Relative Risk (95% CI)	Risk difference with DAC+abs (95% CI)	Number needed to treat (95% CI)
Populations 1 & 3 combined							
SSI	373 (1 RCT, whole cohort analysis of primary and revision joint replacement with or without DAC+antibiotics, Romanò 2016)	⊕⊕⊙⊙	DAC+abs: 0.53% (1/189); No DAC+abs: 6.0% (11/184)	0.003	0.09 (0.01, 0.68), p= 0.0196	-5.4% (-9.0%, -1.9%)	18 (11, 53)
SSI (minimal 12 mths follow-up)		⊕⊕⊙⊙	DAC+abs: 0.0% (0/126); No DAC+abs: 6.4% (8/125)	0.019	0.12 (0.016, 0.98), p= 0.0475	-6.4% (-10.59%, -2.11%)	18 (10, 94)
SF-12 total score (only follow-up)		⊕⊕⊕⊙	Mean±SD DAC+abs: 99.9 ± 18.4; No DAC+abs: 94.7 ± 18.3	0.006	NA	Absolute difference (95% CI): 5.2 (1.5, 8.9)	NA
Delayed wound healing <sup>15</sup>		⊕⊕⊕⊙	DAC+abs: 1.1% (2/189); No DAC+abs: 3.8% (7/184)	0.101	0.28 (0.06, 1.32), p= 0.1075	-2.7% (-5.9%, 0.4%)	36 (-281 to infinity to 17)
Other complications than SSI		⊕⊕⊕⊙	DAC+abs: 2.1% (4/189); No DAC+abs: 2.7% (5/184)	0.748	0.78 (0.21, 2.86); p= 0.377	-0.6% (-3.7%, 2.5%)	166 (-40 to infinity to 27)
Unplanned antibiotic treatment during hospital stay, for reasons other than SSI (mainly urinary or respiratory tract infections)		⊕⊕⊕⊙	DAC+abs: 4.8% (9/189); No DAC+abs: 4.3% (8/184)	1.000	1.10 (0.43, 2.80); p= 0.8480	0.41% (-3.8%, 4.6%)	241 (-22 to infinity to 26)
Harris Hip Score		⊕⊕⊕⊙	Mean±SD DAC+abs: 86.4 ± 16; No DAC+abs: 83.4 ± 16.7	0.08	NA	Absolute difference (95% CI): 3.0 (-0.3, 6.3)	NA
Knee Society Score		⊕⊕⊕⊙	Mean±SD DAC+abs: 75.8 ± 21.7; No DAC+abs: 79.4 ± 20.5	0.10	NA	Absolute difference (95% CI): -3.6 (-7.9, 0.7)	NA

<sup>15</sup> Delayed wound healing was defined as an incomplete healing of the wound at 4 weeks after surgery, including the presence of wound dehiscence, necrosis or serum leakage, that may need further medication, but that did not require any additional surgical treatment.

Outcomes Follow-up	Participants (studies)	Quality of evidence (GRADE)	Event counts	P-value <sup>b</sup>	Relative Risk (95% CI)	Risk difference with DAC+abs (95% CI)	Number needed to treat (95% CI)
Population 1							
SSI Mean±SD follow-up <sup>a</sup> of 14.5 ± 5.5 months (range 6 to 24 months)	267 (1 RCT, subgroup analysis of primary joint replacement surgery with or without DAC+antibiotics, Romanò 2016)	⊕⊕⊖⊖	DAC+abs: 0.7% (1/135); No DAC+abs: 3% (4/132)	0.210	0.24 (0.0277, 2.16); p= 0.205	-2.30% (-5.60%, 1.00%)	44 (-105 to infinity to 18)
Population 2							
Onset of short-term PJI 12.4±5.7 months in treatment group, 34.3 ± 21.3 months control group (range 6 to 24 months) [revision]	34 (1 case-control study, De Meo 2020)	⊕⊖⊖⊖	DAC+abs: 0.00% (0/17); No DAC+abs: 35.29% (6/17)	0.018	0.08 (0.0047, 1.27); p= 0.073	-35.29% (-58.00%, - 12.60%)	3 (2, 10)
Harris Hip Score -pre		⊕⊖⊖⊖	Mean±SD DAC+abs: 34.1 ± 29.8; No DAC+abs: 38.4 ± 13.7	0.7291	NA	Absolute difference (95% CI): -4.3 (-20.5, 11.9)	NA
Harris Hip Score -post		⊕⊖⊖⊖	Mean±SD DAC+abs: 72.9 ± 12.9; No DAC+abs: 57.6 ± 23.8	0.0687	NA	Absolute difference (95% CI): 15.3 (1.9, 28.7)	NA
Deaths		⊕⊖⊖⊖	DAC+abs: 5.9% (1/17); No DAC+abs: 23.5% (4/17)	0.34	0.25 (0.03, 2.01), p= 0.193	-17.6% (-40.7%, 5.4%)	6 (-19 to infinity to 2)
Total complications		⊕⊖⊖⊖	DAC+abs: 17.6% (3/17); No DAC+abs: 4.7% (11/17)	0.0134	0.08 (0.0047, 1.27); p= 0.0727	-35.3 (-58.0, -12.6)	2 (1, 6)
PJI 24.3 ± 11.7 months treatment group, 24.2 ± 11.5 months control group [megaprosthesis]	86 (1 case-control study, Zoccali 2021)	⊕⊖⊖⊖	DAC+abs: 0% (0/43); No DAC+abs: 13.90% (6/43)	0.026	0.08 (0.0045, 1.32); p= 0.077	-13.90% (-24.32%, - 3.60%)	7 (4, 37)
Deaths		⊕⊖⊖⊖	DAC+abs: 2.33% (1/43); No DAC+abs: 4.65% (2/43)		0.50 (0.047, 5.30), p= 0.565	-2.33% (-5.41%, 10.07%)	43 (-18 to infinity <sup>c</sup> to 10)
Population 3							

Outcomes Follow-up	Participants (studies)	Quality of evidence (GRADE)	Event counts	P-value <sup>b</sup>	Relative Risk (95% CI)	Risk difference with DAC+abs (95% CI)	Number needed to treat (95% CI)
SSI Mean±SD follow-up <sup>a</sup> of 14.5 ± 5.5 months (range 6 to 24 months)	106 (1 RCT, subgroup analysis of revision joint replacement surgery with or without DAC+antibiotics, Romanò 2016)	⊕⊕⊙⊙	DAC+abs: 0.00% (0/54) No DAC+abs: 13.4% (7/52)	0.006	0.064 (0.004, 1.097); p= 0.058	-13.4% (-22.70%, - 4.20%)	8 (4, 28)
Recurrence of PJI ( )	44 (1 case-control study, one-stage- DAC+antibiotics vs two-stage-no	⊕⊙⊙⊙	DAC+abs: 9.1% (2/22); No DAC+abs: 13.5% (3/22)	0.672	0.67 (0.12 to 3.60); p= 0.638	-4.4% (-23.3%, 14.2%)	22 (-7 to infinity to 4)
Hospital length of stay, days		⊕⊙⊙⊙	Mean±SD DAC+abs: 18.9 ± 2.9 No DAC+abs: 35.8 ± 3.4	0.0000	NA	Absolute difference (95% CI): <b>-16.9</b> <b>(-18.8, -15.0)</b>	NA
Duration of systemic antibiotic therapy, days		⊕⊙⊙⊙	Mean±SD DAC+abs: 23.5 ± 3.3 No DAC+abs: 53.7 ± 5.6	0.0000	NA	Absolute difference (95% CI): <b>-30.2</b> <b>(-33.0, -27.4)</b>	NA
SF-12 total score	DAC+antibiotics, Capuano 2018)	⊕⊙⊙⊙	Mean±SD DAC+abs: 84.4 ± 7.4; No DAC+abs: 84.3 ± 7.4	0.964	NA	Absolute difference (95% CI): 0.1 (-4.3, 4.5)	NA
Harris Hip Score		⊕⊙⊙⊙	Mean±SD DAC+abs: 85.4 ± 3.6; No DAC+abs: 83.6 ± 7.4	0.638	NA	Absolute difference (95% CI): 1.8 (-6.7, 10.3)	NA
Knee Society Score		⊕⊙⊙⊙	Mean±SD DAC+abs: 78.0 ± 6.1; No DAC+abs: 77.3 ± 6.4	0.746	NA	Absolute difference (95% CI): 0.7 (-3.7, 5.1)	NA
Recurrence of PJI	54 (1 case-control study, Zagra 2019)	⊕⊙⊙⊙	DAC+abs: 0% (0/27) No DAC+abs: 14.8% (4/27)	0.110	0.11 (0.006 to 1.968); p= 0.134	-14.8% (-28.2%, - 1.4%)	7 (-570 to infinity to 3)
Hospital length of stay, days		⊕⊙⊙⊙	Mean±SD DAC+abs: 28.2 ± 3.9 No DAC+abs: 33.8 ± 5.4	0.0001	NA	Absolute difference (95% CI): <b>-5.6 (-8.17, -3.03)</b>	NA

Outcomes Follow-up	Participants (studies)	Quality of evidence (GRADE)	Event counts	P-value <sup>b</sup>	Relative Risk (95% CI)	Risk difference with DAC+abs (95% CI)	Number needed to treat (95% CI)
Harris Hip score		⊕⊕○○	Mean±SD DAC+abs: 84.6 ± 15.8; No DAC+abs: 81.6 ± 15.2	0.480	NA	Absolute difference (95% CI): 3.0 (-5.5, 11.5)	NA
Population 4 (closed fractures only)							
SSI Mean±SD follow-up of 18.1 ± 4.5 months (range 12–30)	253 (1 RCT, Malizos 2017)	⊕⊕○○	DAC+abs: 0.0% (0/126) No DAC+abs: 4.7% (6/127)	0.029	0.08 (0.004 to 1.36); p= 0.080	<b>-4.70%</b> (-8.40%, -- 1.20%)	21 (12, 140)
SF-12 total score		⊕⊕⊕○	Mean±SD DAC+abs: 100.5 ± 14.2; No DAC+abs: 101.7 ± 15.4	0.51	NA	-1.2 (-9.3, 6.9)	NA
Delayed wound healing		⊕⊕⊕○	DAC+abs: 3.9% (5/126); No DAC+abs: 5.5% (7/127)	0.76	0.72 (0.23, 2.21), p= 0.5656	-1.5 (-6.8, 3.7)	65 (-27 to infinity to 15)
Delayed union		⊕⊕⊕○	DAC+abs: 1.6% (2/126); No DAC+abs: 3.9% (5/127)	0.44	0.40 (0.08, 2.04), p= 0.2721	-2.3 (-6.4, 1.7)	43 (-59 to infinity to 16)
Unplanned antibiotic treatment during hospital stay for other reasons than SSI		⊕⊕⊕○	DAC+abs: 8% (10/126); No DAC+abs: 9.4% (12/127)	0.80	0.84 (0.38, 1.87), p=0.6700	1.51 (-5.43, 8.45)	66 (-18 to infinity to12)

Source: Table 2, pg 31 of MSAC 1629 DCAR; GRADE Working Group grades of evidence (Guyatt, Oxman 2013)

Abbreviations: CI= Confidence Interval; DAC+abs=Defensive Antibacterial Coating loaded antibiotics; PJI= Periprosthetic Joint Infection; RCT= Randomised Controlled Trial; SD: Standard Deviation; SSI= Surgical Site Infection

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕○ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕○○ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕○○○ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

<sup>a</sup> For both primary and revision populations, while Population 3 is solely concerned with revisions.

<sup>b</sup> P-values for categorical items were based on Fisher exact test.

<sup>c</sup> A Number Needed to Treat (NNT) approaches infinity if there is no treatment, resulting in zero absolute risk difference.

Note: Relative risk was estimated using an online calculator based on [https://www.medcalc.org/calc/relative\\_risk.php](https://www.medcalc.org/calc/relative_risk.php)

Note: The outcomes based on RCTs were downgraded to 'low quality' because true treatment effect could be affected by several limitations observed in those studies, including a relatively short follow-up period, issues with the sample size calculation as the incidence of SSI was assumed to be 6% for the control group which was considered higher than the one in the Australian context, and non-fulfilment of the criteria of ASA≥ 3 and BMI> 30 (which is a requirement for Populations 1 and 4).

Number need to treat (NNT) denotes a sample size required to show a significant difference between the treatment arms. In the table above, NNT was estimated using an online calculator (<https://www.neoweb.org.uk/Additions/compare.htm>). The negative NNT denotes the number needed to harm (i.e., denotes a scenario where surgery with DAC+abs is harmful than surgery without DAC+abs).

Safety outcomes were not included in Table 2 as the frequency of reported safety outcomes was too low.

None of the outcomes based on RCTs was rated to be of 'high quality' as they were deemed to be underpowered in the Australian context (based on the clinical expert's opinion)

## CLINICAL CLAIM

The applicant claimed that the use of DAC+antibiotics to reduce peri-prosthetic deep SSI is likely to be superior compared with the current standard of care, i.e. standard surgery without DAC+antibiotics (p25, [MSAC 1629 PICO Confirmation](#)). No claim was made regarding comparative safety.

Numerically, a similar incidence of adverse events was observed in treatment (DAC+antibiotics) and control (no DAC+antibiotics) groups across all populations. On the basis of the benefits reported in the evidence base (summarised in Table 2), relative to surgery without DAC+antibiotics:

- there is low-quality evidence that surgery with DAC+antibiotics has uncertain effectiveness for Population 1
- there is very low-quality evidence that surgery with DAC+antibiotics may have superior effectiveness for Population 2
- there is low to very low-quality evidence that surgery with DAC+antibiotics may have superior effectiveness for Population 3
- there is very low-quality evidence that surgery with DAC+antibiotics may have superior effectiveness for Population 4.

However, this should be interpreted with caution in the light of the following limitations in the evidence base:

- DAC+antibiotics hydrogel is bio-resorbed within 72 hours and there were no reported adverse events or side effects directly attributable to the DAC+antibiotics reported across study follow up (trial mean follow up:  $14.5 \pm 5.5$  to  $18.1 \pm 4.5$  months) across all populations. However, the evidence base does not allow an assessment of the long-term safety or effectiveness of DAC hydrogel due to the limited follow-up in the relevant studies, especially the RCTs (Romanò et al. 2016 and Malizos et al. 2017).
- There were potential biases in the studies. For example, case-control studies involved small sample sizes ( $n < 100$ , range 34 to 54) and adopted a retrospective study design prone to selection bias (Grade assessment for all outcomes: very low quality). Further, the RCTs (Romanò et al. 2016 and Malizos et al. 2017) did not specify whether investigators and patients were blinded to treatment.
- Both randomised studies had issues with the sample size calculation as the incidence of SSI assumed (i.e., 6%) for the control group was much higher than the estimated incidence of SSI, based on the rates of revision for infection in the Australian context (GRADE assessment for periprosthetic SSI: low quality).
- Neither randomised study fulfilled the criteria of ASA score  $\geq 3$  and BMI  $\geq 30$ , which is a requirement for Populations 1 and 4.
- Randomisation had to be broken to estimate separate treatment effects for Population 1 and 3 in the Romanò et al. (2016).
- There was no safety or effectiveness evidence for Population 4b (open fractures).
- Given the small sizes of the studies, it is not possible to rule out the possibility of important rare adverse events.

- The evidence does not allow for a comparison of DAC versus DAC+antibiotics, therefore the role of DAC, as opposed to the antibiotics loaded with DAC, in the reported treatment effect in clinical practice is unclear.

### 13. Economic evaluation

In light of the clinical conclusions, based on low to very low-quality evidence with a number of serious limitations, and the paucity of data to inform the economic evaluation, in consultation with the Department of Health and Aged Care, the DCAR presented:

- exploratory adapted stepped cost-utility analyses for Populations 1 and 3
- cost-consequence analyses for Populations 2 and 4b (closed fracture subpopulation)
- cost-consequence analyses for Population 1 and 3 (presented in the main body of the DCAR only).

Costs directly associated with DAC included the following components: the acquisition cost of DAC; the cost of the antibiotics required to preload the DAC hydrogel; the cost of sterile water to reconstitute the DAC dry powder and to mix the antibiotics to the appropriate concentration if needed.

A key assumption in costing was the average number of DAC 5mL kits required per surgical procedure, estimated separately for each population by modelling the distribution function of the DAC volume across patients. **Redacted.**

#### COST-UTILITY ANALYSES (POPULATIONS 1 AND 3)

Key characteristics of the decision-analytic model are presented in Table 3.

**Table 3 Summary of the cost-utility analysis for Populations 1 and 3**

Perspective	Australian health system
Comparator	Standard surgery without DAC+antibiotics
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Systematic review, AOANJRR registry, AOANJRR data request and clinical expert advice
Time horizon	20 years
Outcomes	QALYs
Methods used to generate results	Markov model
Health states	No periprosthetic deep SSI (only for Population 1), DAIR (only for Population 1), first revision for infection, post-treatment (DAIR or first revision), second revision for infection, post-treatment (second revision), permanent implant removal, death (all cause), death (periprosthetic deep SSI)
Cycle length	One year
Discount rate	An annual rate of 5% for costs and benefits
Software packages used	TreeAge Pro Healthcare 2021 R1.1

Source: Table 3, p36 of MSAC 1629 DCAR

Abbreviations: AOANJRR=Australian Orthopaedic Association National Joint Replacement Registry; DAC=Defensive Antibacterial Coating; DAIR=debridement, antibiotics, and implant retention; QALY=quality-adjusted life-year; SSI=surgical site infection.

The Markov model aimed to represent the clinical algorithms in MSAC 1629 PICO Confirmation, using the available evidence sourced from a systematic literature review. For Population 1, if a patient suffers periprosthetic deep SSI after primary surgery, it can be treated with DAIR, revision

surgery, or permanent implant removal. If there is a recurrent infection, patients can have a second revision or permanent implant removal. For Population 3, the cohort starts in the post-treatment (DAIR or first revision) and then follows the same pathway as the model for Population 1.

Key structural assumptions of the model are:

- A patient can have two revisions at most, reflecting data provided by the AOANJRR.
- Both hip and knee followed the same pathways, but modelled separately using different model inputs.
- DAC+antibiotic treatment effect was only considered over one year model cycle in accordance with Romanò et al. (2016) follow-up.
- A time horizon of 20 years was chosen to reflect life expectancy of the Australian population.
- The preventive effect of DAC+antibiotics for Population 1 was only considered after elective primary TJA (hip or knee), not in further revisions for infection as defined in MSAC 1629 PICO Confirmation (p2, Table 1 of MSAC 1629 PICO Confirmation).
- The model structures of surgery with DAC+antibiotics and surgery without DAC+antibiotics were identical. The difference in parameterisation was given by using DAC+antibiotics in terms of resource use (price and number of kits) and its effect in preventing periprosthetic deep SSI.
- 1-stage and 2-stage revisions were grouped in a health state “revision” according to the definition of the AOANJRR.
- Revisions different than infection were not modelled.
- Patients with periprosthetic deep SSI were assumed always treated either by DAIR (only for Population 1), revision surgery or implant removal.
- SSI rates after primary procedures for Population 1 were sourced from the AOANJRR 2020 report as this data was not available from the AOANJRR data request. The AOANJRR 2020 report does not present the results disaggregated by cementless or hybrid primary fixation, ASA score  $\geq 3$  or BMI  $> 30$  kg/m<sup>2</sup>.
- The probability of receiving DAIR treatment after infection of a primary procedure was not reported by the AOANJRR. Merollini et al. (2013)<sup>16</sup> values were used instead. It was assumed that this was the same between hip and knee.
- Health related quality of life was sourced from the literature as studies included in the DCAR did not present such data specific to each health state or Population.
- A cycle length of one year was chosen in accordance with the data presented from the AOANJRR. A half-cycle correction was used.

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<sup>16</sup> Merollini KM, Crawford RW, Whitehouse SL, Graves N (2013), *Am J Infect Control*, 41(9):803-9

An adapted stepped economic analysis is presented for Population 1 and 3. As there are no direct trial costs or utilities sourced from the included studies, the model was used to estimate costs and benefits. This was carried out in 3 steps:

- Step 1: Modelled results using Romanò et al. (2016) inputs (follow-up, SSI rates, DAC volume, and starting age). A time horizon of one year was according to follow-up from Romanò 2016.
- Step 2: Same model as Step 1 but using Australian SSI rates with DAC+antibiotics effect as relative risk (Table 4).
- Step 3: Modelled evaluation over 20 years.

Costs, QALYs and incremental cost-effectiveness ratios (ICERs) for Steps 1 and 2 are shown in Table 5.

**Table 4 Step 1 and Step 2 SSI inputs**

SSI rate source	Population 1		Population 3	
	DAC+abs	No DAC+abs	DAC+abs	No DAC+abs
Step 1 – Romanò 2016	0.7%	3.0%	0%	13.4%
Step 2 – AOANJRR (SSI rate) and Romanò 2016 (relative risk)	0.26% (hip) 0.37% (knee)	1.08% (hip) 1.58% (knee)	2.09% (hip) 2.27% (knee)	32.66% (hip) 35.33% (knee)

Source: Table 4, p38 of MSAC 1629 DCAR; Romanò et al. 2016 and AOANJRR data

Abbreviations: AOANJRR=Australian Orthopaedic Association National Joint Replacement Registry; DAC+abs=Defensive Antibacterial Coating loaded with antibiotics; SSI=surgical site infection

Note: in step 2 the SSI rate for the DAC+antibiotics arm was derived by applying the relative risk (0.24 for Population 1 and 0.064 for Population 3) from Romanò 2016 to the AOANJRR SSI rate.



**Table 5 Implications for the base case economic evaluation of applying the results of the clinical evaluation (Step 1 then Step 2)**

Population and circumstances of use	Population 1 (hip)		Population 1 (knee)		Population 3 (hip)		Population 3 (knee)	
	Step 1 Romanò 2016	Step 2 AOANJRR SSI	Step 1 Romanò 2016	Step 2 AOANJRR SSI	Step 1 Romanò 2016	Step 2 AOANJRR SSI	Step 1 Romanò 2016	Step 2 AOANJRR SSI
Costs								
Costs of therapy involving DAC+abs	\$25,364	\$25,323	\$24,511	\$24,528	\$33,178	\$33,507	\$25,073	\$25,343
Costs of therapy involving no DAC+abs	\$21,880	\$21,703	\$21,027	\$20,921	\$31,349	\$34,044	\$22,732	\$24,963
Incremental costs	\$3,483	\$3,620	\$3,525	\$3,606	\$1,829	-\$537	\$2,341	\$379
QALYs based on inputs before any extrapolation and/or transformation								
QALYs with DAC+abs	0.85	0.854	0.814	0.815	0.694	0.69	0.68	0.68
QALYs without DAC+abs	0.84	0.852	0.809	0.812	0.685	0.67	0.67	0.65
Incremental effectiveness	0.0043	0.0022	0.0047	0.0029	0.010	0.021	0.014	0.034
<b>ICER (cost/QALY)</b>	\$812,454	\$1,662,778	\$754,451	1,243,016	\$188,380	DAC+abs is dominant	\$164,710	\$11,194

Source: Table 5, pg 39 of MSAC 1629 DCAR

Abbreviations: AOANJRR= Australian Orthopaedic Association National Joint Replacement Registry; DAC+abs=Defensive Antibacterial Coating loaded with antibiotics; ICER=incremental cost-effectiveness ratio; SSI=surgical site infection; QALYs=quality adjusted life years

In Step 1 and 2 for Population 1, DAC is more costly but more effective for hip and knee. When the AOANJRR SSI rates (estimated based on rates for revision for infection) are applied, the ICER increases from Step 1 to Step 2. In Population 3 (hip), the application of AOANJRR SSI rates results in a shift from an ICER of \$188,380 per QALY in Step 1, to DAC+antibiotics being dominant compared to no DAC+antibiotics in Step 2. For Population 3 (knee), in Step 1 the ICER is \$164,710 per QALY, which lowers to an ICER of \$11,194 in Step 2. Both changes are driven by incremental costs.

Costs, QALYs and ICERs for Steps 2 and 3 are shown in Table 6.

**Table 6 Base case economic evaluation results given extrapolation and transformation of the results of the clinical studies (Step 3)**

	Population (joint)	Incremental costs	Incremental effectiveness (QALY)	Incremental cost-effectiveness
Step 2: Same model as Step 1 but using Australian SSI rates with DAC+antibiotics effect as relative risk.	Population 1 (hip)	\$3,620	0.0022	\$1,662,778
	Population 1 (knee)	\$3,606	0.0029	\$1,243,016
	Population 3 (hip)	-\$537	0.021	DAC+abs is dominant
	Population 3 (knee)	\$379	0.034	\$11,194
Base case results (Step 3): Modelled evaluation over 20 years	Population 1 (hip)	\$3,484	0.018	\$189,025
	Population 1 (knee)	\$3,455	0.025	\$140,683
	Population 3 (hip)	-\$3,380	0.21	DAC+abs is dominant
	Population 3 (knee)	-\$1,707	0.25	DAC+abs is dominant

Source: Table 6, pg 41 of MSAC 1629 DCAR

Abbreviations: DAC+abs=Defensive Antibacterial Coating loaded with antibiotics; ICER = Incremental Cost Effectiveness Ratio; QALY=quality-adjusted life-year.

In Population 1, the ICER decreases from Step 2 to Step 3. In Population 3, DAC+antibiotics remains dominant over no DAC+antibiotics for hip, and for knee, the ICER for DAC+antibiotics changes from \$11,194 per QALY (Step 2) to being dominant as well (Step 3). Both changes are mainly driven by the increased time horizon (1 year for Step 2 and 20 years for Step 3), which allows more QALYs to be accrued due to the prevention of infection, resulting in less procedures and increased quality of life. However, the evidence that DAC+antibiotics reduces the rate of periprosthetic SSIs is weak for both Populations 1 and 3. If DAC+antibiotics does not reduce the rate of SSIs, as observed within the upper 95% confidence interval estimated for each relevant study of Populations 1 and 3 (i.e., crossing 1), then DAC+antibiotics will be dominated by no DAC+antibiotics.

The modelled results were sensitive to the DAC+antibiotics treatment effect on incidence of periprosthetic SSI. In each population, hip or knee, using the upper limit of the 95% confidence interval of the relative risk of periprosthetic SSI, DAC+antibiotics was dominated by no DAC+antibiotics, i.e., DAC+antibiotics was more expensive and less effective. It is important to emphasise that the base-case cost-effectiveness results are therefore very uncertain, given the substantial uncertainty in the estimated DAC+antibiotics treatment effects in all populations.

Additionally, DAC+antibiotics becomes less cost-effective when the time horizon is decreased, whereas decreasing the DAC+antibiotics price (using published estimates by Franceschini 2020), lowers the ICER favouring DAC+antibiotics. Particularly for Population 1, the number of kits and using DAC+antibiotics in every surgery (primary total joint arthroplasty and revisions) has a moderate effect in the ICER.

Key drivers of cost-effectiveness are presented in the Table 7 and the sensitivity analyses are presented in Table 8, 9, 10 and 11.

**Table 7 Key drivers of the economic model**

Description	Method/Value	Impact
DAC+antibiotics treatment effect	Estimated upper 95% CI limit for all relative risks of deep SSI	High, favours comparator
Time horizon	1 and 2 years	High, favours comparator
DAC price	Franceschini 2020 (\$382.03)	High, favours DAC+antibiotics
DAC number of kits (Population 1)	redacted kits	Moderate, less kits than base case favours DAC+antibiotics, whereas more favours the comparator
DAC+antibiotics use (Population 1)	DAC+antibiotics used in epTJA and revisions	Moderate, favours DAC+antibiotics

Source: Table 7, pg 42 of MSAC 1629 DCAR

Abbreviations: CI=confidence interval; DAC=Defensive Antibacterial Coating; epTJA=elective primary total joint arthroplasty.

**Table 8 Sensitivity analyses of the economic model (Population 1, hip)**

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
Base Case		\$3,484	0.018	\$189,025	100%
<b>Univariate analyses</b>					
Discount rate (base case 5% costs and outcomes)					
0% costs and outcomes		\$3,476	0.027	\$126,743	-32.95%
3.5% costs and outcomes		\$3,481	0.021	\$169,158	-10.51%
Time horizon (base case 20 years)					
1 year		\$3,620	0.0012	\$3,090,611	1535.03%*
2 years		\$3,546	0.0030	\$1,175,616	521.94%*
5 years		\$3,469	0.0074	\$471,588	149.48%*
10 years		\$3,475	0.012	\$270,642	43.18%*
Relative risk DAC+abs vs. no DAC+abs					
Romanò 2016	lower 95% CI (0.0277)	\$3,425	0.024	\$145,244	-23.16%
	higher 95% CI (2.16)	\$4,018	-0.028	DAC+abs is dominated	NA*
Probabilities					
SSI	+20% (1.30%)	\$3,446	0.022	\$157,692	-16.58%
	-20% (0.86%)	\$3,523	0.015	\$236,454	25.09%
Recurrent SSI	+20% 1 <sup>st</sup> cycle 42.23%	\$3,469	0.019	\$183,678	-2.83%
	+20% 2 <sup>nd</sup> cycle 4.49%	\$3,483	0.018	\$188,695	-0.17%
	+20% 3 <sup>rd</sup> cycle 2.00%	\$3,483	0.018	\$188,896	-0.07%
	+20% 4 <sup>th</sup> cycle 0.48%	\$3,484	0.018	\$188,997	-0.01%
	-20% 1 <sup>st</sup> cycle 28.15%	\$3,498	0.018	\$194,187	2.73%

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
	-20% 2 <sup>nd</sup> cycle 2.99%	\$3485	0.018	\$189,354	0.17%
	-20% 3 <sup>rd</sup> cycle 1.34%	\$3,484	0.018	\$189,154	0.07%
	-20% 4 <sup>th</sup> cycle 0.32%	\$3,484	0.018	\$189,053	0.01%
DAIR	Higher 95% CI (61.51%)	\$3,495	0.018	\$189,683	0.35%
	Lower 95% CI (43.59%)	\$3,472	0.018	\$188,366	-0.35%
Death revision first year	+20% (4.25%)	\$3,484	0.019	\$184,472	-2.41%
	-20% (2.83%)	\$3,483	0.018	\$193,827	2.54%
Death revision second year	+20% (2.35%)	\$3,484	0.019	\$186,670	-1.25%
	-20% (1.57%)	\$3,484	0.018	\$191,440	1.28%
Removal SSI after epTJA	+20% (1.70%)	\$3,484	0.018	\$189,029	0.00%
	-20% (1.14%)	\$3,483	0.018	\$189,020	0.00%
Removal recurrent SSI	+20% (3.06%)	\$3,484	0.018	\$189,022	0.00%
	-20% (2.04%)	\$3,483	0.018	\$189,028	0.00%
Health state costs					
epTJA	+20% (\$25,924.43)	\$3,484	0.018	\$189,025	0.00%
	-20% (\$17,282.95)	\$3,484	0.018	\$189,025	0.00%
DAIR	+20% (\$12,330.53)	\$3,466	0.018	\$188,081	-0.50%
	-20% (\$8,220.35)	\$3,491	0.018	\$189,436	0.22%
Revision	+20% (\$35,368.37)	\$3,505	0.018	\$190,186	0.61%
	-20% (\$23,578.91)	\$3,516	0.018	\$190,801	0.94%
Removal surgery	+20% (\$13,432.72)	\$3,482	0.018	\$188,914	-0.06%
	-20% (\$8,955.14)	\$3,486	0.018	\$189,135	0.06%
Other Costs					
Cost for redacted DAC kit		\$redacted	0.018	\$redacted	redacted%
Cost for redacted DAC kits		\$redacted	0.018	\$redacted	redacted%
Cost for redacted DAC kits		\$redacted	0.018	\$redacted	redacted%*
DAC price Franceschini 2020 lower range (\$382.03)		\$redacted	0.018	\$redacted	redacted%*
Utilities					
No periprosthetic deep SSI	Higher 95% CI (0.884)	\$3,484	0.018	\$189,025	0.00%
	Lower 95% CI (0.877)	\$3,484	0.018	\$191,517	1.32%
DAIR	Higher 95% CI (.976)	\$3,484	0.017	\$205,270	8.59%
	Lower 95% CI (0.184)	\$3,484	0.020	\$175,162	-7.33%
Post treatment	Higher 95% CI (0.906)	\$3,484	0.008	\$447,388	136.68%*
	Lower 95% CI (0.534)	\$3,484	0.029	\$119,826	-36.61%
Revision for infection	Higher 95% CI (0.976)	\$3,484	0.017	\$202,443	7.10%
	Lower 95% CI (0.184)	\$3,484	0.021	\$168,877	-10.66%
Permanent implant removal	Higher 95% CI (0.677)	\$3,484	0.018	\$193,020	2.11%
	Lower 95% CI (0.587)	\$3,484	0.018	\$185,191	-2.03%
Other scenarios					
DAC+abs in every surgery		\$3,000	0.031	\$97,555	-48.39%*
	\$1,061.04	\$3,481	0.018	\$188,873	-0.08%

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
DAIR post-operative antibiotics (Table 159)	\$123.97	\$3,484	0.018	\$189,061	0.02%
Post-operative follow-up costs (Table 67)	\$835.11	\$3,482	0.015	\$188,913	-0.06%
NWAU and NEP surgical procedures costs (Table 64)		\$3,483	0.015	\$188,979	-0.02%

Source: Table 97, pg 223 of MSAC 1629 DCAR

Abbreviations: CI=confidence interval; DAC=Defensive Antibacterial Coating; DAC+abs=Defensive Antibacterial Coating loaded with antibiotics; DAIR=Debridement, antibiotics and implant retention; epTJA=elective primary total joint arthroplasty; ICER = Incremental Cost Effectiveness Ratio; SSI=surgical site infection

Notes: DAC+antibiotics is dominated by no DAC+antibiotics: surgery with DAC+antibiotics is more costly and less effective than surgery without DAC+antibiotics;

\* Considerable change in the ICER

**Table 9 Sensitivity analyses of the economic model (Population 1, knee)**

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
Base Case		\$3,455	0.025	\$140,683	100%
<b>Univariate analyses</b>					
Discount rate (base case 5% costs and outcomes)					
0% costs and outcomes		\$3,452	0.036	\$96,242	-31.59%
3.5% costs and outcomes		\$3,453	0.027	\$126,616	-10.00%
Time horizon (base case 20 years)					
1 year		\$3,606	0.002	\$1,857,731	1220.51%*
2 years		\$3,519	0.005	\$756,992	438.08%*
5 years		\$3,427	0.011	\$325,256	131.20%
10 years		\$3,440	0.018	\$194,459	38.22%*
Relative risk DAC+abs vs. no DAC+abs					
Romanò 2016	lower 95% CI (0.0277)	\$3,388	0.031	\$107,828	-23.35%
	higher 95% CI (2.16)	\$4,062	-0.037	DAC+abs is dominated	NA*
Probabilities					
SSI	+20% 1.90%	\$3,415	0.029	\$118,150	-16.02%
	-20% 1.26%	\$3,498	0.020	\$174,746	24.21%
Recurrent SSI	+20% 1 <sup>st</sup> cycle 46.64%	\$3,435	0.025	\$135,402	-3.75%
	+20% 2 <sup>nd</sup> cycle 3.28%	\$3,454	0.025	\$140,488	-0.14%
	-20% 1 <sup>st</sup> cycle 30.96%	\$3,474	0.024	\$135,402	-3.75%
	-20% 2 <sup>nd</sup> cycle 2.18%	\$3,456	0.025	\$140,878	0.14%
DAIR	Higher 95% CI (61.51%)	\$3,465	0.025	\$141,066	0.27%
	Lower 95% CI (43.59%)	\$3,445	0.025	\$140,299	-0.27%
Death revision first year	+20% (2.94%)	\$3,455	0.025	\$138,271	-1.71%
	-20% (1.96%)	\$3,454	0.024	\$143,187	1.78%
Death revision second year	+20% (5.52%)	\$3,455	0.025	\$136,325	-3.10%
	-20% (3.68%)	\$3,455	0.024	\$136,325	-3.10%
	+20% (0.98%)	\$3,455	0.025	\$140,694	0.01%

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
Removal SSI after epTJA	-20% (0.66%%)	\$3,455	0.025	\$140,671	-0.01%
Health state costs					
epTJA	+20% (\$24,964.99)	\$3,455	0.025	\$140,683	0.00%
	-20% (\$16,643.33)	\$3,455	0.025	\$140,683	0.00%
DAIR	+20% (\$12,371.22)	\$3,444	0.025	\$140,251	-0.31%
	-20% (\$8,247.48)	\$3,466	0.025	\$141,114	0.31%
Revision	+20% (\$25,641.96)	\$3,420	0.025	\$139,279	-1.00%
	-20% (\$17,094.64)	\$3,489	0.025	\$142,087	1.00%
Removal surgery	+20% (\$13,451.98)	\$3,452	0.025	\$140,804	1.00%
	-20% (\$8,967.98)	\$3,458	0.025	\$140,561	-0.09%
Other Costs					
Cost for redacted DAC kit		\$redacted	0.025	\$redacted	redacted%*
Cost for redacted DAC kits		\$ redacted	0.025	\$ redacted	redacted %
Cost for redacted DAC kits		\$ redacted	0.025	\$ redacted	redacted %*
DAC price Franceschini 2020 lower range (\$382.03)		\$ redacted	0.025	\$ redacted	redacted %*
Utilities					
No periprosthetic deep SSI	Higher 95% CI (0.845)	\$3,455	0.029	\$119,037	-15.39%
	Lower 95% CI (0.836)	\$3,455	0.024	\$143,288	1.85%
DAIR	Higher 95% CI (0.741)	\$3,455	0.023	\$148,156	5.31%
	Lower 95% CI (0.259)	\$3,455	0.026	\$133,927	-4.80%
Post treatment	Higher 95% CI (0.923)	\$3,455	0.039	\$366,539	160.54%*
	Lower 95% CI (0.517)	\$3,455	0.039	\$87,557	-37.76%
Revision for infection	Higher 95% CI (0.741)	\$3,455	0.022	\$156,066	10.93%
	Lower 95% CI (0.259)	\$3,455	0.027	\$130,360	-7.34%
Permanent implant removal	Higher 95% CI (0.677)	\$3,455	0.024	\$143,938	2.31%
	Lower 95% CI (0.587)	\$3,455	0.025	\$137,571	-2.21%
Other scenarios					
DAC+abs in every surgery		-\$382	0.048	DAC+abs is dominant	NA*
DAIR post-operative antibiotics (Table 159)	\$1,061.04	\$3,451	0.025	\$140,524	-0.11%
	\$123.97	\$3,456	0.025	\$140,720	0.03%
Post-operative follow-up costs (Table 67)	\$851.16	\$3452	0.025	\$140,563	-0.09%
NWAU and NEP surgical procedures costs (Table 64)		\$3,440	0.025	\$140,074	-0.43%

Source: Table 98, pg 226 of MSAC 1629 DCAR

Abbreviations: CI=confidence interval; DAC=Defensive Antibacterial Coating; DAC+abs=Defensive Antibacterial Coating loaded with antibiotics; DAIR=Debridement, antibiotics and implant retention; epTJA=elective primary total joint arthroplasty; ICER = Incremental Cost Effectiveness Ratio; SSI=surgical site infection

Notes: DAC+antibiotics is dominated by no DAC+antibiotics: surgery with DAC+antibiotics is more costly and less effective than surgery without DAC+antibiotics; DAC+antibiotics dominates no DAC+antibiotics: surgery with DAC+antibiotics is less costly and more effective than surgery without DAC+antibiotics

\* Considerable change in the ICER

**Table 10 Sensitivity analyses of the economic model (Population 3, hip).**

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
<b>Base Case</b>		-\$3,380	0.21	DAC+abs is dominant	NA
<b>Univariate analyses</b>					
Discount rate (base case 5% costs and outcomes)					
0% costs and outcomes		-\$3,860	0.21	DAC+abs is dominant	NA
3.5% costs and outcomes		-\$3,519	0.233	DAC+abs is dominant	NA
Time horizon (base case 20 years)					
1 year		\$1,465	0.020	\$72,245*	NA
2 years		-\$2,555	0.043	DAC+abs is dominant	NA
5 years		-\$3,347	0.082	DAC+abs is dominant	NA
10 years		-\$3,380	0.142	DAC+abs is dominant	NA
Relative risk DAC+abs vs. no DAC+abs					
Romanò 2016	lower 95% CI (0.004)	-\$4,024	0.22	DAC+abs is dominant	NA
	higher 95% CI (1.10)	\$8,820	-0.030	DAC+abs is dominated*	NA
Zagra 2019	RR estimate (0.11)	-\$2,882	0.20	DAC+abs is dominant	NA
	lower 95% CI (0.0063)	-\$3,999	0.22	DAC+abs is dominant	NA
	higher 95% CI (1.97)	\$20,022	-0.35	DAC+abs is dominated*	NA
Capuano 2018	RR estimate (0.67)	\$3,507	0.088	\$39,818*	NA
	lower 95% CI (0.12)	-\$2,773	0.20	DAC+abs is dominant	NA
	higher 95% CI (3.60)	Model error	Model error	DAC+abs is dominated*	NA
<b>Probabilities</b>					
Recurrent SSI	+20% 1 <sup>st</sup> cycle 39.19%	-\$5,458	0.27	DAC+abs is dominant	NA
	+20% 2 <sup>nd</sup> cycle 2.84%	-\$3,335	0.21	DAC+abs is dominant	NA
	+20% 3 <sup>rd</sup> cycle 0.35%	-\$3,375	0.21	DAC+abs is dominant	NA
	+20% 4 <sup>th</sup> cycle 1.44%	-\$3,360	0.21	DAC+abs is dominant	NA
	-20% 1 <sup>st</sup> cycle 26.13%	-\$1,378	0.16	DAC+abs is dominant	NA
	-20% 2 <sup>nd</sup> cycle 1.90%	-\$3,425	0.21	DAC+abs is dominant	NA

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
	-20% 3 <sup>rd</sup> cycle 0.23%	-\$3,385	0.21	DAC+abs is dominant	NA
	-20% 4 <sup>th</sup> cycle 0.96%	\$3,400	0.21	DAC+abs is dominant	NA
Death revision first year	+20% (3.23%)	-\$3,374	0.20	DAC+abs is dominant	NA
	-20% (2.15%)	-\$3,386	0.20	DAC+abs is dominant	NA
Death revision second year	+20% (1.61%)	-\$3,380	0.21	DAC+abs is dominant	NA
	-20% (1.07%)	-\$3,380	0.20	DAC+abs is dominant	NA
Removal SSI	+20% (1.69%)	-\$3,364	0.21	DAC+abs is dominant	NA
	-20% (1.13%)	-\$3,396	0.21	DAC+abs is dominant	NA
Health state costs					
Revision	+20% (\$35,368.37)	-\$5,013	0.21	DAC+abs is dominant	NA
	-20% (\$23,578.91)	-\$1,747	0.21	DAC+abs is dominant	NA
Removal surgery	+20% (\$13,432.72)	-\$3,619	0.21	DAC+abs is dominant	NA
	-20% (\$8,955.14)	-\$3,141	0.21	DAC+abs is dominant	NA
Other Costs					
Cost for redacted DAC kit		-\$redacted	0.21	DAC+abs is dominant	NA
Cost for redacted DAC kits		-\$ redacted	0.21	DAC+abs is dominant	NA
Cost for redacted DAC kits		-\$ redacted	0.21	DAC+abs is dominant	NA
DAC price Franceschini 2020 lower range (\$382.03)		-\$ redacted	0.21	DAC+abs is dominant	NA
Utilities					
Post treatment	Higher 95% CI (0.906)	-\$3,380	0.47	DAC+abs is dominant	NA
	Lower 95% CI (0.534)	-\$3,380	-0.056	\$60,330*	NA
Revision for infection	Higher 95% CI (0.976)	-\$3,380	0.098	DAC+abs is dominant	NA
	Lower 95% CI (0.184)	-\$3,380	0.32	DAC+abs is dominant	NA
Permanent implant removal	Higher 95% CI (0.677)	-\$3,380	0.16	DAC+abs is dominant	NA
	Lower 95% CI (0.587)	-\$3,380	0.26	DAC+abs is dominant	NA
Other scenarios					



Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
Post-operative follow-up costs (Table 67)	\$835.11	-\$3,458	0.21	DAC+abs is dominant	NA
NWAU and NEP surgical procedures costs (Table 64)		-\$3,664	0.21	DAC+abs is dominant	NA

Source: Table 99, pg 230 of MSAC 1629 DCAR

Abbreviations: CI=confidence interval; DAC=Defensive Antibacterial Coating; DAC+abs=Defensive Antibacterial Coating loaded with antibiotics; DAIR=Debridement, antibiotics and implant retention; epTJA=elective primary total joint arthroplasty; ICER=incremental cost-effectiveness ratio; SSI=surgical site infection

Notes: DAC+antibiotics is dominated by no DAC+antibiotics: surgery with DAC+antibiotics is more costly and less effective than surgery without DAC+antibiotics; DAC+antibiotics dominates no DAC+antibiotics: surgery with DAC+antibiotics is less costly and more effective than surgery without DAC+antibiotics

\* Considerable change in the ICER

**Table 11 Sensitivity analyses of the economic model (Population 3, knee)**

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
<b>Base Case</b>		-\$1,707	0.25	DAC is dominant	NA
<b>Univariate analyses</b>					
Discount rate (base case 5% costs and outcomes)					
0% costs and outcomes		-\$2,117	0.37	DAC is dominant	NA
3.5% costs and outcomes		-\$1,826	0.28	DAC is dominant	NA
Time horizon (base case 20 years)					
1 year		\$2,383	0.033	\$72,070*	NA
2 years		-\$709	0.067	DAC+abs is dominant	NA
5 years		-\$1,705	0.11	DAC+abs is dominant	NA
10 years		-\$1,707	0.18	DAC+abs is dominant	NA
Relative risk DAC+abs vs. no DAC+abs					
Romanò 2016	lower 95% CI (0.004)	-\$1,925	0.26	DAC+abs is dominant	NA
	higher 95% CI (1.10)	\$8,903	-0.035	DAC+abs is dominated*	NA
Zagra 2019	RR estimate (0.11)	-\$1286	0.24	DAC+abs is dominant	NA
	lower 95% CI (0.0063)	-\$2,225	0.26	DAC+abs is dominant	NA
	higher 95% CI (1.97)	\$19639	-0.40	DAC+abs is dominated*	NA
Capuano 2018	RR estimate (0.67)	\$4,212	0.104	\$40,605*	NA
	lower 95% CI (0.12)	-\$1,194	0.24	DAC+abs is dominant	NA
	higher 95% CI (3.60)	Model error	Model error	DAC+abs is dominated*	NA
<b>Probabilities</b>					
Recurrent SSI	+20% 1 <sup>st</sup> cycle 42.40%	-\$3,505	0.32	DAC+abs is dominant	NA

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
	+20% 2 <sup>nd</sup> cycle 4.50%	-\$1,647	0.25	DAC+abs is dominant	NA
	+20% 3 <sup>rd</sup> cycle 1.99%	-\$1,683	0.25	DAC+abs is dominant	NA
	+20% 4 <sup>th</sup> cycle 0.38%	-\$1,703	0.25	DAC+abs is dominant	NA
	-20% 1 <sup>st</sup> cycle 28.26%	\$3	0.189	\$18*	NA
	-20% 2 <sup>nd</sup> cycle 3.00%	-\$1,767	0.25	DAC+abs is dominant	NA
	-20% 3 <sup>rd</sup> cycle 1.33%	-\$1,731	0.25	DAC+abs is dominant	NA
	-20% 4 <sup>th</sup> cycle 0.26%	-\$1,711	0.25	DAC+abs is dominant	NA
Death revision first year	+20% (2.71%)	-\$1,700	0.26	DAC+abs is dominant	NA
	-20% (1.81%)	-\$1,713	0.24	DAC+abs is dominant	NA
Death revision second year	+20% (2.77%)	-\$1,707	0.26	DAC+abs is dominant	NA
	-20% (1.85%)	-\$1,707	0.24	DAC+abs is dominant	NA
Health state costs					
Revision	+20% (\$25,641.96)	-\$2,982	0.25	DAC+abs is dominant	NA
	-20% (\$17,094.64)	-\$432	0.25	DAC+abs is dominant	NA
Removal surgery	+20% (\$13,451.98)	-\$1,989	0.25	DAC+abs is dominant	NA
	-20% (\$8,967.98)	-\$1,425	0.25	DAC+abs is dominant	NA
Other Costs					
Cost for redacted DAC kit		-\$redacted	0.25	DAC+abs is dominant	NA
Cost for redacted DAC kits		-\$ redacted	0.25	DAC+abs is dominant	NA
Cost for redacted DAC kits		-\$ redacted	0.25	DAC+abs is dominant	NA
DAC price Franceschini 2020 lower range (\$382.03)		-\$ redacted	0.25	DAC+abs is dominant	NA
Utilities					
Post treatment	Higher 95% CI (0.923)	-\$1,707	0.60	DAC+abs is dominant	NA
	Lower 95% CI (0.517)	-\$1,707	-0.068	\$25,145*	NA
Revision for infection	Higher 95% CI (0.741)	-\$1,707	0.18	DAC+abs is dominant	NA
	Lower 95% CI (0.259)	-\$1,707	0.32	DAC+abs is dominant	NA

Description		Incremental cost	Incremental QALYs	ICER	% change to ICER
Permanent implant removal	Higher 95% CI (0.677)	-\$1,707	0.20	DAC+abs is dominant	NA
	Lower 95% CI (0.587)	-\$1,707	0.31	DAC+abs is dominant	NA
Other scenarios					
Post-operative follow-up costs (Table 67)	\$851.16	-\$1,793	0.25	DAC+abs is dominant	NA
NWAU and NEP surgical procedures costs (Table 64)		-\$2,379	0.25	DAC+abs is dominant	NA

Source: Table 100, pg 232 of MSAC 1629 DCAR

Abbreviations: CI=confidence interval; DAC=Defensive Antibacterial Coating; DAC+abs=Defensive Antibacterial Coating loaded with antibiotics; DAIR=Debridement, antibiotics and implant retention; epTJA=elective primary total joint arthroplasty; ICER = Incremental Cost Effectiveness Ratio; SSI=surgical site infection

Notes: DAC+antibiotics is dominated by no DAC+antibiotics: surgery with DAC+antibiotics is more costly and less effective than surgery without DAC+antibiotics; DAC+antibiotics dominates no DAC+antibiotics: surgery with DAC+antibiotics is less costly and more effective than surgery without DAC+antibiotics

\* Considerable change in the ICER

## 14. Financial/budgetary impacts

The PICO Confirmation for MSAC 1629 indicated that the infection rate for Population 1 would be approximately 1% for all patients with total joint replacement, especially total hip and knee joint replacements. It also considered that the primary population size could be further defined by the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR).

A mixed approach (market share approach: Populations 1, 2 and 4, epidemiological approach: Population 3) was adopted for the budget impact analysis.

The number of patients eligible to receive DAC+antibiotics in Australia, including those not using DAC+antibiotics, is uncertain. Similarly, data relating to the uptake rates of DAC+antibiotics are also not available. It was assumed that there would be a 50% uptake rate at the base case. However, since this rate was highly uncertain, sensitivity analyses were conducted assuming varying uptake proportions.

The current assessment is only relevant to private patients as, if PLAC approves a device for listing, private health insurers must pay for it when used in association with an MBS procedure in a hospital on a privately insured patient. The private patients without appropriate hospital cover will be required to pay the cost of the treatment themselves. The proportion of private patients for each subpopulation was estimated based on the AOANJRR annual report 2020. The average number of DAC 5mL kits required per surgical procedure was estimated separately for each population by modelling the distribution function of the DAC volume across patients. On average, each surgical procedure was estimated to require **redacted, redacted, redacted and redacted** DAC 5mL kits for Populations 1, 2, 3 and 4, respectively.

Since the DAC+antibiotics is to be used in conjunction with the existing MBS items, the DAC+antibiotic hydrogel has no separate financial implications for the MBS. The total financial implication to the MBS was due to the extra time required to prepare and apply the DAC (anaesthesia). The cost to the PBS was primarily due to the use of antibiotics when loading the DAC hydrogel.

## POPULATION 1

Population 1 included patients undergoing an elective primary joint implant at increased risk of infection due to the presence of comorbidities (ASA score  $\geq 3$ ; and BMI > 30; and cementless components). Due to a lack of data for other joints, this assessment report focused on only hip and knee joints.

### POPULATION 1 (HIP)

The estimated cost to private health insurance was **\$redacted** in Year 1 and is expected to remain approximately steady until Year 5, with a total cost of **\$redacted** over five years.

The financial implication to the MBS was \$75,000 in Year 1, which remained approximately steady until Year 5. The total financial implication to the MBS was estimated to be \$390,000 (Table 12).

**Table 12 Estimated number of Population 1 (hip) that are likely to receive the DAC+antibiotics and the total financial implication to the private health insurance, MBS, PBS, and the Government**

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible population size	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients eligible in private setting (60.21%) <sup>a</sup>	redacted	redacted	redacted	redacted	redacted	redacted
Assumed uptake of DAC+abs (assumed 50% in base case)	redacted	redacted	redacted	redacted	redacted	redacted
Cost to private health insurance <sup>b</sup>	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total financial implication to the MBS <sup>c</sup>	\$75,608	\$76,788	\$77,986	\$79,203	\$80,439	\$390,023
Total financial implication to the PBS <sup>d</sup>	\$16,072	\$16,323	\$16,578	\$16,837	\$17,099	\$82,909
Total financial implication to the Government <sup>e</sup>	\$91,680	\$93,111	\$94,564	\$96,039	\$97,538	\$472,932

Source: Table 11, pg 46 of MSAC 1629 DCAR

Abbreviations: DAC+abs= Defensive Antibacterial Coating loaded with antibiotics, MBS= Medicare benefits Schedule; PBS=Pharmaceutical Benefits Schedule

<sup>a</sup> Estimated based on AOANJRR Annual report 2020

<sup>b</sup> Cost to private health insurance is due to the acquisition of DAC kits. These costs were obtained as the product of the assumed number of private patients \* the number of kits required per surgical procedure \* unit cost of DAC 5ml. The estimated number of kits per surgical procedure for Population 1 was **redacted**. Further, the unit cost of DAC 5ml was **\$redacted**.

<sup>c</sup> Financial implication to MBS was due to costs associated with extra time required to prepare and apply the DAC+antibiotics. The estimated cost of extra time per procedure for Population 1 (Hip) was **\$redacted**.

<sup>d</sup> Financial implication to PBS was due to costs associated with the cost of antibiotics for preloading DAC. The estimated cost per procedure for Population 1 (Hip) was **\$redacted**.

<sup>e</sup> Cost to the Government = Cost to MBS + Cost to PBS

### POPULATION 1 (KNEE)

The estimated cost to private health insurance was **\$redacted** in Year 1 and is expected to remain approximately steady to Year 5, with a total cost of **\$redacted** million over five years.

The financial implication to the MBS was \$49,000 in Year 1, which remained approximately steady until Year 5. The total financial implication to the MBS was estimated to be \$245,000 (Table 13).

**Table 13 Estimated number of Population 1 (knee) that are likely to receive the DAC+antibiotics and the total financial implication to the private health insurance, MBS, PBS, and the Government**

Description	Year 1	Year 2	Year3	Year 4	Year 5	Total
Eligible population size	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients eligible in private setting (71.81%) <sup>a</sup>	redacted	redacted	redacted	redacted	redacted	redacted
Assumed uptake of DAC+abs (assumed 50% at base case)	redacted	redacted	redacted	redacted	redacted	redacted
Cost to private health insurance <sup>b</sup>	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total financial implication to the MBS <sup>c</sup>	\$48,886	\$48,934	\$48,983	\$49,031	\$49,079	\$244,913
Total financial implication to the PBS <sup>d</sup>	\$10,415	\$10,425	\$10,435	\$10,446	\$10,456	\$52,176
Total financial implication to the Government <sup>e</sup>	\$59,300	\$59,359	\$59,418	\$59,477	\$59,535	\$297,089

Source: Table 12, pg 47 of MSAC 1629 DCAR

Abbreviations: DAC+abs= Defensive Antibacterial Coating loaded with antibiotics, MBS= Medicare benefits Schedule;

PBS=Pharmaceutical benefits Schedule

<sup>a</sup> Estimated based on AOANJRR Annual report 2020

<sup>b</sup> Cost to private health insurance is due to the acquisition of DAC kits. These costs were obtained as the product of the assumed number of private patients \* the number of kits required per surgical procedure \* unit cost of DAC 5ml. The number of kits per surgical procedure was estimated to be **redacted** for Population 1 (knee). Further, the unit cost of DAC 5ml was **\$redacted**.

<sup>c</sup> Financial implication to MBS was due to costs associated with extra time required to prepare and apply the DAC+antibiotics. The estimated cost of extra time per procedure was **\$redacted** for Population 1 (knee).

<sup>d</sup> Financial implication to PBS was due to costs associated with the cost of antibiotics for preloading DAC. The estimated cost per procedure for Population 1(knee) was **\$redacted**.

<sup>e</sup> Cost to the Government = Cost to MBS + Cost to PBS

## POPULATION 2

The estimated cost to private health insurance was \$ **redacted** in Year 1 and is expected to remain approximately steady until Year 5, with a total cost of \$ **redacted** over five years.

The financial implication to the MBS was \$25,600 in Year 1, which remained approximately steady until Year 5. The total financial implication to the MBS was estimated to be \$129,500 (Table 14).

**Table 14 Estimated number of Population 2 that are likely to receive the DAC+antibiotics and the total financial implication to private health insurance, MBS, PBS, and the Government**

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible population size	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients eligible in private setting (63.96%) <sup>a</sup>	redacted	redacted	redacted	redacted	redacted	redacted
Assumed uptake of DAC+abs (assumed 50% at base case)	redacted	redacted	redacted	redacted	redacted	redacted
Cost to private health insurance <sup>b</sup>	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total financial implication to the MBS <sup>c</sup>	\$25,587	\$25,743	\$25,899	\$26,057	\$26,215	\$129,501
Total financial implication to the PBS <sup>d</sup>	\$15,747	\$15,843	\$15,939	\$16,036	\$16,134	\$79,698
Total financial implication to the Government <sup>e</sup>	\$41,333	\$41,585	\$41,839	\$42,093	\$42,349	\$209,199

Source: Table 13, pg 47 of MSAC 1629 DCAR

Abbreviations: DAC+abs= Defensive Antibacterial Coating loaded with antibiotics, MBS= Medicare benefits Schedule; PBS=Pharmaceutical benefits Schedule

<sup>a</sup> Estimated based on AOANJRR Annual report 2020

<sup>b</sup> Cost to private health insurance is due to the acquisition of DAC kits. These costs were obtained as the product of assumed number of private patients \* number of kits required per surgical procedure \* unit cost of DAC 5ml. The number of kits per surgical procedure for Population 2 was redacted. Further, the unit cost of DAC 5ml was \$redacted.

<sup>c</sup> Financial implication to MBS was due to costs associated with extra time required to prepare and apply the DAC+antibiotics. The estimated cost of extra time per procedure for Population 2 was \$redacted.

<sup>d</sup> Financial implication to PBS was due to costs associated with the cost of antibiotics for preloading DAC. The estimated cost per procedure for Population 2 was \$redacted.

<sup>e</sup> Cost to the Government = Cost to MBS + Cost to PBS

### POPULATION 3

#### POPULATION 3 (HIP)

The estimated cost to private health insurance was \$redacted in Year 1 and is expected to remain approximately steady until Year 5, with a total cost of \$redacted over five years.

The financial implication to the MBS was \$2,100 in Year 1, which remained approximately steady until Year 5. The total financial implication to the MBS was estimated to be \$10,800 (Table 15).

**Table 15 Estimated number of Population 3 (hip) that are likely to receive the DAC+antibiotics and the total financial implication to private health insurance, MBS, PBS, and the Government**

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible population size	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients eligible in private setting (56.23%) <sup>a</sup>	redacted	redacted	redacted	redacted	redacted	redacted
Assumed uptake of DAC+abs (assumed 50% at base case)	redacted	redacted	redacted	redacted	redacted	redacted
Cost to private health insurance <sup>b</sup>	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total financial implication to the MBS <sup>c</sup>	\$2,075	\$2,114	\$2,154	\$2,195	\$2,237	\$10,776
Total financial implication to the PBS <sup>d</sup>	\$861	\$878	\$894	\$911	\$929	\$4,473
Total financial implication to the Government <sup>e</sup>	\$2,936	\$2,992	\$3,049	\$3,107	\$3,166	\$15,248

Source: Table 14, pg 48 of MSAC 1629 DCAR

Abbreviations: DAC+abs= Defensive Antibacterial Coating loaded with antibiotics, MBS= Medicare benefits Schedule; PBS=Pharmaceutical benefits Schedule

<sup>a</sup> Estimated based on AOANJRR Annual report 2020

<sup>b</sup> Cost to private health insurance is due to the acquisition of DAC kits. These costs were obtained as the product of the assumed number of private patients \* the number of kits required per surgical procedure \* unit cost of DAC 5ml. The number of kits per surgical procedure Population 3 (hip) was **redacted**. Further, the unit cost of DAC 5ml was **\$redacted**.

<sup>c</sup> Financial implication to MBS was due to costs associated with extra time required to prepare and apply the DAC+antibiotics. The estimated cost of extra time per procedure for Population 3 (Hip) was **\$redacted**.

<sup>d</sup> Financial implication to PBS was due to cost associated with the cost of antibiotics for preloading DAC. The estimated cost per procedure for Population 3 (hip) was **\$redacted**.

<sup>e</sup> Cost to the Government = Cost to MBS + Cost to PBS

### POPULATION 3 (KNEE)

The estimated cost to private health insurance was **\$redacted** in Year 1 and is expected to remain approximately steady until Year 5, with a total cost of **\$redacted** over five years.

The financial implication to the MBS was \$1,370 in Year 1, which remained approximately steady until Year 5. The total financial implication to the MBS was estimated to be \$7,000 (Table 16).

**Table 16 Estimated number of Population 3 (knee) that are likely to receive the DAC+antibiotics and the total financial implication to the MBS, PBS, and the Government**

Description	Year 1	Year 2	Year 2	Year 4	Year 5	Total
Eligible population size	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients eligible in private setting (69.06%) <sup>a</sup>	redacted	redacted	redacted	redacted	redacted	redacted
Assumed uptake of DAC+abs (assumed 50% at base case)	redacted	redacted	redacted	redacted	redacted	redacted
Cost to private health insurance <sup>b</sup>	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total financial implication to the MBS <sup>c</sup>	\$1,370	\$1,388	\$1,406	\$1,424	\$1,442	\$7,029
Total financial implication to the PBS <sup>d</sup>	\$570	\$578	\$585	\$593	\$601	\$2,927
Total financial implication to the Government <sup>e</sup>	\$1,940	\$1,965	\$1,991	\$2,017	\$2,043	\$9,956

Source: Table 15, pg 49 of MSAC 1629 DCAR

Abbreviations: DAC+abs= Defensive Antibacterial Coating loaded with antibiotics, MBS= Medicare benefits Schedule; PBS=Pharmaceutical benefits Schedule

<sup>a</sup> Estimated based on AOANJRR Annual report 2020

<sup>b</sup> Cost to private health insurance is due to the acquisition of DAC kits. These costs were obtained as the product of the assumed number of private patients \* the number of kits required per surgical procedure \* unit cost of DAC 5ml. The number of kits per surgical procedure was estimated to be **redacted** for Population 3 (knee). Further, the unit cost of DAC 5ml was **\$redacted**.

<sup>c</sup> Financial implication to MBS was due to costs associated with extra time required to prepare and apply the DAC+antibiotics. The estimated cost of extra time per procedure for Population 3 (knee) was **\$redacted**.

<sup>d</sup> Financial implication to PBS was due to costs associated with the cost of antibiotics for preloading DAC. The estimated cost per procedure Population 3 (knee) was **\$redacted**.

<sup>e</sup> Cost to the Government = Cost to MBS + Cost to PBS

## POPULATION 4

### POPULATION 4A (CLOSED)

It was estimated that the average annual number of patients with closed fractures eligible to receive DAC+antibiotics in Year 0 would be **redacted**. In Year 1, it was estimated to reach **redacted**. Assuming the increase rate of 1.75% to remain constant over five years, the number of patients eligible to receive DAC+antibiotics would be **redacted** in Year 5. Overall, **redacted** patients would be eligible to receive DAC+antibiotics over five years.

The number of patients eligible in the private setting was estimated to be 66.80% out of **redacted** patients (i.e., **redacted**), half of which was estimated to uptake DAC+antibiotics (n= **redacted**). Sensitivity analyses were conducted, increasing the uptake rate from 50% to 100% (10% interval) in all years.

The estimated cost to private health insurance was **\$redacted** in Year 1 and is expected to remain approximately steady until Year 5, with a total cost of **\$redacted** over five years.

The financial implication to the MBS was \$12,500 in Year 1, which remained approximately steady until Year 5. The total financial implication to the MBS was estimated to be \$65,000 (Table 17).



**Table 17 Estimated number of Population 4a (closed) that are likely to receive the DAC+antibiotics and the total financial implication to private health insurance, MBS, PBS, and the Government**

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible population size	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients eligible in private setting (66.80%) <sup>a</sup>	redacted	redacted	redacted	redacted	redacted	redacted
Assumed uptake of DAC+abs (assumed 50% at base case)	redacted	redacted	redacted	redacted	redacted	redacted
Cost to private health insurance <sup>b</sup>	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total financial implication to the MBS <sup>c</sup>	\$12,500	\$12,719	\$12,941	\$13,168	\$13,398	\$64,726
Total financial implication to the PBS <sup>d</sup>	\$5,770	\$5,871	\$5,973	\$6,078	\$6,184	\$29,875
Total financial implication to the Government <sup>e</sup>	\$18,270	\$18,589	\$18,915	\$19,245	\$19,582	\$94,601

Source: Table 16, pg 50 of MSAC 1629 DCAR

Abbreviations: DAC+abs= Defensive Antibacterial Coating loaded with antibiotics, MBS= Medicare benefits Schedule;

PBS=Pharmaceutical benefits Schedule

<sup>a</sup> Estimated based on AOANJRR Annual report 2020

<sup>b</sup> Cost to private health insurance is due to acquisition of DAC kits. These costs were obtained as the product of assumed number of private patients \* number of kits required per surgical procedure \* unit cost of DAC 5ml. The number of kits per surgical procedure for Population 4 (closed) was redacted. Further, the unit cost of DAC 5ml was \$redacted.

<sup>c</sup> Financial implication to MBS was due to costs associated with extra time required to prepare and apply the DAC+antibiotics. The estimated cost of extra time per procedure for Population 4 (closed) was \$redacted.

<sup>d</sup> Financial implication to PBS was due to costs associated with the cost of antibiotics for preloading DAC. The estimated cost per procedure for Population 4 (closed) was \$redacted.

<sup>e</sup> Cost to the Government = Cost to MBS + Cost to PBS

#### POPULATION 4B (OPEN)

The estimated cost to private health insurance was \$redacted in Year 1 and is expected to remain approximately steady until Year 5, with a total cost of \$redacted over five years.

The financial implication to the MBS was \$8,000 in Year 1, which remained approximately steady until Year 5. The total financial implication to the MBS was estimated to be \$42,000 (Table 18).

**Table 18 Estimated number of Population 4b (open) that are likely to receive the DAC+antibiotics and the total financial implication to private health insurance, MBS, PBS, and the Government**

Description	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Eligible population size	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients eligible in private setting (66.80%) <sup>a</sup>	redacted	redacted	redacted	redacted	redacted	redacted
Assumed uptake of DAC+abs (assumed 50% at base case)	redacted	redacted	redacted	redacted	redacted	redacted
Cost to private health insurance <sup>b</sup>	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total financial implication to the MBS <sup>c</sup>	\$8,186	\$8,329	\$8,475	\$8,623	\$8,774	\$42,388
Total financial implication to the PBS <sup>d</sup>	\$3,778	\$3,845	\$3,912	\$3,980	\$4,050	\$19,565
Total financial implication to the Government <sup>e</sup>	\$11,965	\$12,174	\$12,387	\$12,603	\$12,824	\$61,953

Source: Table 17, pg 51 of MSAC 1629 DCAR

Abbreviations: DAC+abs= Defensive Antibacterial Coating loaded with antibiotics, MBS= Medicare benefits Schedule; PBS=Pharmaceutical benefits Schedule<sup>a</sup> Estimated based on AOANJRR Annual report 2020

<sup>b</sup> Cost to private health insurance is due to the acquisition of DAC kits. These costs were obtained as the product of the assumed number of private patients \* the number of kits required per surgical procedure \* unit cost of DAC 5ml. The number of kits per surgical procedure for Population 4 (open) was redacted. Further, the unit cost of DAC 5ml was \$redacted.

<sup>c</sup> Financial implication to MBS was due to costs associated with extra time required to prepare and apply the DAC. The estimated cost of extra time per procedure for Population 4 (open) was \$redacted.

<sup>d</sup> Financial implication to PBS was due to costs associated with the cost of antibiotics for preloading DAC. The estimated cost per procedure for Population 4 (open) was \$redacted.

<sup>e</sup> Cost to the Government = Cost to MBS + Cost to PBS

## 15. Other relevant information

### ANTIMICROBIAL RESISTANCE AND STEWARDSHIP

Antimicrobial resistance and stewardship are important public health interest. The application indicated that the application of DAC+antibiotic hydrogel to orthopaedic implants facilitates prophylactic application of antibiotics at the implant with the intention that the DAC+antibiotics prevent bacterial colonisation of the implant thereby reducing SSI/PJI incidence. The DAC+antibiotics hydrogel is bio-resorbed within 72 hours. According to a brochure published by the manufacturer, approximately 60%, 80% and 100% of the antibiotic is released after 4, 24 and 48 hours respectively<sup>17</sup>. The use of antibiotics with DAC would occur in a hospital setting. The prophylactic application of antibiotic loaded DAC to the implant is in addition to systemic prophylactic antibiotics. In Australia, Manning et al. (2020)<sup>18</sup> recently reported that while a range of Gram positive and negative bacteria can cause PJA, methicillin-susceptible *Staphylococcus aureus* (MSSA) was the most common causative organism (41.2%), with methicillin-resistant *S. aureus* (MRSA) isolated from 26 (3.3%) patients with PJI.

<sup>17</sup> Novagenit DAC Bio-resorbable hydrogel barrier against infection  
[https://www.scp.no/media/documents/DAC-Gel\\_brochure.pdf](https://www.scp.no/media/documents/DAC-Gel_brochure.pdf)

<sup>18</sup> Manning L, Metcalf S, Clark B, Robinson JO, Huggan P, et al. (2020) *Open Forum Infect Dis.* 14;7(5):ofaa068. doi: 10.1093/ofid/ofaa068.

The [Therapeutic Guidelines: Antibiotic](#) provide a range of principles for antimicrobial use that cover peri-operative antibiotic prophylaxis for orthopaedic surgery and specific considerations for joint arthroplasty. In the case of orthopaedic surgery, surgical antibiotic prophylaxis is indicated for prosthetic large joint replacement and internal fixation of fractures of large bones. The Therapeutic Guidelines advise that cefazolin is more effective than vancomycin in preventing postoperative infections caused by MSSA. Glycopeptide antibiotics, vancomycin and teicoplanin, are not recommended for surgical prophylaxis, except for patients with severe hypersensitivity (immediate or delayed) to penicillins and/or at increased risk of post-operative infection caused by MRSA. Consistent with this, where antibiotic prophylaxis is indicated for orthopaedic surgery, the Therapeutic Guidelines: Antibiotic recommend cefazolin. For patients colonised or infected with MRSA, or at increased risk of being colonised or infected with MRSA (e.g., patients undergoing a joint arthroplasty procedure that is a reoperation), the Therapeutic Guidelines recommend cefazolin plus vancomycin. This is consistent with the [Australian Orthopaedic Association Guidelines](#) for antibiotic prophylaxis at the time of hip and knee arthroplasty.

The Therapeutic Guidelines do not specifically address or identify whether prophylactic antibacterial coatings similar to DAC+antibiotics in addition to systemic antibiotic prophylaxis is indicated. Therapeutic Guidelines note that it is common practice to use antimicrobial-impregnated cement for fixation of prosthetic devices. However, this is caveated by highlighting that high-quality data to support the efficacy and cost-effectiveness of this practice are limited.

It is noted that the antibiotics nominated in the TGA application and instructions for use (IFU, vancomycin or gentamicin) to be used with DAC differs to the prophylactic antibiotics recommended in the Therapeutic Guidelines for joint arthroplasty (cefazolin or cefazolin+vancomycin if high risk for MRSA). Regarding the use of gentamicin instead of cefazolin, the Therapeutic Guidelines provide that “the Gram-negative spectrum of cefazolin is adequate for most surgical procedures for which Gram-negative activity is required. However, gentamicin continues to be recommended as prophylaxis for the few procedures requiring a broader spectrum of Gram-negative activity. Gentamicin is also used as an alternative when cefazolin is contraindicated”.

Regarding the use of DAC with vancomycin, the guidelines emphasise that vancomycin requires judicious use to limit the emergence of vancomycin resistance and is inferior to beta-lactam antibiotics (e.g., cefazolin) for the treatment of MSSA. With exception of Population 3, the other three proposed populations for DAC+antibiotics do not appear to specifically describe patients with risk factors for MRSA and vancomycin use is therefore inconsistent with the Therapeutic Guidelines. In keeping with antimicrobial stewardship principles, surgeons must reserve selecting vancomycin for patients who meet the proposed patient eligibility criteria for DAC and who are at high risk for MRSA.

In Australia, national safety and quality standards require all health service organisations to have an effective antimicrobial stewardship (AMS) program in place, which is assessed for accreditation. This is also monitored through the Antimicrobial Use and Resistance in Australia (AURA) Surveillance System conducted by the Australian Commission on Safety and Quality Health Care. In regard to antimicrobial use in hospitals, the [AURA 2021 report](#)<sup>19</sup> indicates the use of antimicrobials has increased and that overall the appropriateness of antimicrobial prescribing has not improved. It appears that while some hospital peer groups have shown improvements,

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<sup>19</sup> Australian Commission on Safety and Quality in Health Care. AURA 2021: fourth Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2021.

others have deteriorated. In particular, the rate of appropriate prescribing appears to have deteriorated in the private sector. Further, the report highlights that approximately 42% of antimicrobial use for surgical prophylaxis was inappropriately prescribed.

If DAC is listed on the Prostheses List, the use of DAC+antibiotics would be in addition to systemic antibiotic prophylaxis. Across the 4 populations, it is estimated that approximately **redacted** patients would be eligible for DAC with uptake in roughly **redacted** patients per year. The available evidence appears to indicate a trend for DAC+antibiotics to reduce SSI incidence however this is based on low to very low-quality data. Further, no information is available to understand, should an SSI occur following the use of DAC+antibiotics, whether or not there is increased drug resistance in the causative bacteria.

## 16. KEY ISSUES FROM ESC TO MSAC

### Main issues for MSAC consideration

#### Clinical issues:

- Incremental effectiveness – The claim of superior clinical effectiveness for DAC+antibiotics to reduce periprosthetic deep surgical site infection (SSI) is uncertain due to the limitations and low/very low quality of the clinical evidence. The clinical evidence showed no significant difference in the relative risk of SSI between surgery with DAC+antibiotics and without DAC+antibiotics for all four populations.
- Comparative safety – Studies indicate similar incidence of safety outcomes or complications of surgery with and without DAC+antibiotics across all populations. However, the long-term safety of DAC+antibiotics is uncertain due to the limited follow-up in the studies, especially in the RCTs.
- DAC vs. DAC+antibiotics – The available clinical evidence compares the safety and effectiveness of surgery with or without DAC preloaded with antibiotics (DAC+antibiotics). There is no clinical evidence on the comparative safety and effectiveness of DAC alone (i.e., without antibiotics).
- Applicability of trial SSI rates to Australian population is uncertain – the rate of SSI in the clinical evidence is different to the rate of SSI based on data from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR). ESC acknowledged the known limitations of using the AOANJRR data (used in the economic evaluation) to estimate infection rates. However, ESC did not consider the 6% SSI incidence (used for the RCT power calculations) to be representative of SSI rates in primary joint arthroplasty in Australia. ESC also noted that the AOANJRR uses a more contemporary and consistent definition of revision than the studies which increases the confidence in registry data.
- Applicability in hip/knee vs. other joint arthroplasty – The applicability of the results from studies on the effectiveness of DAC+antibiotics in hip/knee arthroplasty to other joint arthroplasty sites is uncertain. ESC considered that there are many confounders that contribute to periprosthetic deep SSI outcomes, including the type of antibiotics and organisms, and host factors. ESC noted an *in vitro* study reported that DAC+antibiotics (loaded with vancomycin or rifampicin) did not inhibit *Cutibacterium acnes* biofilm formation (most common causative organism in shoulder SSI), suggesting the results on the effectiveness of DAC+antibiotics for preventing hip/knee SSI may not be applicable to shoulder joint arthroplasty.

#### **Economic issues:**

- The ability to model the cost-effectiveness of DAC+antibiotics was limited by the paucity of data and the limitations/uncertainties in the clinical evidence and clinical claim.
- Cost-utility analyses (CUA) were only feasible for Populations 1 and 3. There are several factors that further impact on the uncertainty in the incremental cost effectiveness ratios (ICER) and costs:
  - Clinical inputs to model treatment effect of DAC – there is substantial uncertainty in the treatment effect reported for DAC+antibiotics. The ICERs are sensitive to the treatment effect and when the upper 95% confidence interval (CI) of the treatment effect (i.e., relative risk for periprosthetic deep SSI) was used the intervention was dominated for both Population 1 and Population 3.
  - Rate of SSI –Using SSI rates based on the AOANJRR data had a substantial impact on the ICER (ICER for Population 1 increases and ICER for Population 3 decreases/becomes dominant).
  - Price – the price for DAC has not been justified and a lower price for DAC was reported in a European paper (€500–600 for 10mL); when this estimate (\$382.03 AUD for 5mL) is used the ICER for Population 1 reduces to \$redacted(hip) and \$redacted(knee) and Population 3 remains dominant, but the feasibility of this price is unclear.
  - Assumed number of kits – based on the clinical evidence, the CUA assumed redacted kits and redacted kits used for Population 1 and 3, respectively. When the number of kits was varied (redacted kits), the ICER for Population 1 remains high (\$redacted-\$redacted [hip] and \$redacted -\$redacted [knee]), while Population 3 remains dominant.

#### **Financial issues:**

- The patient cost burdens and inequalities are substantial. The expectation is that much of the cost is borne by the private sector (and/or patients). There is a high risk for DAC+antibiotics to be used beyond the proposed patient populations due to the ambiguity of what is considered high-risk for SSI.

#### **Other issues:**

- DAC is not included on the Australian Register of Therapeutic Goods (ARTG). DAC is currently under evaluation by the Therapeutic Goods Administration (TGA). As per the proposed indication submitted to the TGA for evaluation, DAC must be used with antibiotics (supplied separately).

## **ESC DISCUSSION**

ESC noted that this application from Novagenit Australia seeks MSAC's advice to inform the Prostheses List Advisory Committee (PLAC) on the comparative safety, effectiveness and cost-effectiveness of Defensive Antibacterial Coating 5 ml kit (DAC) for patients at risk of periprosthetic deep surgical site infection (SSI) when undergoing surgery with orthopaedic implant procedures.

ESC noted that DAC is a dry powder that is rehydrated using an antibiotic solution (vancomycin or gentamicin, supplied separately) to form an antibiotic-loaded hydrogel (DAC+antibiotics). DAC is not included on the Australian Register of Therapeutic Goods (ARTG) but is currently under evaluation by the Therapeutic Goods Administration (TGA). As per the proposed indication submitted to the TGA for evaluation, DAC must be used with antibiotics.

ESC noted that there are existing Medicare Benefit Schedule (MBS) items that can accommodate the delivery of DAC+antibiotics and therefore this application is not seeking to create or amend an MBS item.

ESC noted that public consultation feedback highlighted the distress that infection can cause patients, as it results in pain and requires further surgery. Infections are a serious issue in orthopaedic surgeries, as they are often immunosuppressed patients having surgery after radiotherapy or chemotherapy. Infections can lead to amputations shortly after surgical implant surgery. ESC noted feedback from Musculoskeletal Australia (MSK) suggested that, despite modern improvement, infection rates have remained stable. Benefits of DAC that were highlighted in the feedback include reduced risk of infection, reduced hospital stays, less time off work and financial distress for patients, and improved survival. However, feedback noted a potential disadvantage was the high cost.

ESC noted there are four proposed populations:

- Population 1: Patients undergoing an elective primary joint implant at increased risk of infection due to the presence of comorbidities (American Society of Anaesthesiologists [ASA] score  $\geq 3$ , body mass index (BMI)  $>30$  kg/m<sup>2</sup>, and receiving cementless components).
- Population 2: Patients undergoing elective megaprosthesis implantation or elective major revision of joint implants for indications other than periprosthetic infection, including total joint revision, tumour removal and reconstruction.
- Population 3: Patients undergoing surgery for periprosthetic deep SSI with implant replacement.
- Population 4: Patients undergoing open reduction and internal fixation.
  - Subgroup 1 (population 4A): Closed fracture with comorbidities (ASA score  $\geq 3$  and BMI  $>30$ ).
  - Subgroup 2 (population 4B): Open fracture.

ESC noted the intent of the proposed populations is to identify individuals at high risk of SSI following orthopaedic implant surgery. ESC considered that there are other groups that an orthopaedic surgeon would consider at high risk of infection before considering the ASA and BMI. comorbidities, including age, being male, other comorbidities (such as inflammatory joint or liver disease), previous trauma, the location of the joint being replaced and tissue quality. ESC considered that this may lead to DAC+antibiotics being used beyond the patient populations proposed.

ESC noted that the comparator for each population is standard (orthopaedic implant) surgery without DAC+antibiotics.

ESC noted the clinical management algorithms have some limitations. The algorithms are based on the McPherson Classification of Periprosthetic Infection, which is 20 years old and outdated. ESC highlighted that treatment guidelines have evolved, such that treatment of SSI is now more sophisticated. ESC also considered the definition of “acute infection” (and treatment choice) is multivariable taking into consideration time (4 weeks or less), whether there has been haematological spread and the type of organism including antibiotic susceptibility and biofilm formation. As such, some acute infections are treated with debridement, antibiotics, and implant retention (DAIR; per the algorithm) and some acute infections are treated with a 2-stage revision (similar to a chronic infection). While ESC considered the algorithms were a suitable starting point for the assessment, ESC suggested that MSAC take into consideration what is current in

Australia for periprosthetic infection (such as Izakovicova et al. 2019<sup>20</sup> and Wasterlain et al. 2020<sup>21</sup>).

ESC noted the clinical evidence for each population compared standard surgery with or without DAC+antibiotics, that is there was no clinical evidence on DAC alone (without antibiotics). Therefore, the Department Contracted Assessment Report could not compare DAC versus DAC+antibiotics, or standard surgery with and without DAC alone. The effect (if any) of DAC is unknown. ESC also noted that not all antibiotics are compatible with DAC and that there was no evidence for population 4, subgroup 2 (open fractures).

ESC agreed with the DCAR assessment that the evidence for DAC+antibiotics is limited and of low/very-low quality which made any conclusion on the safety and effectiveness uncertain. ESC noted several issues with the evidence, including small patient numbers, short follow-up times and clinical trial data for DAC in population 1 was only available in hip and knee surgery. ESC agreed with the concerns raised in the DCAR regarding the risk of bias in the two RCTs due issues with blinding, outcome assessment and control group measurement. There was also a high risk of bias with the four case-controlled studies due to the study designs (non-randomised, retrospective). ESC also noted that it is difficult to draw conclusions from Capuano 2018<sup>22</sup> which employed different types of revision surgery in the intervention and comparator arm (i.e. compared 1-stage revision with DAC+antibiotics vs. 2-stage revision without DAC+antibiotics).

ESC noted the potential control group measurement bias issue was due to the assumed incidence of SSI (6% for the control group) for power calculations in the RCTs which is not consistent with the incidence of SSI (using the rate of revision procedures for infection) in Australia (~1-2%) based on data from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR). Therefore, the study may be underpowered. ESC also considered the applicability of the evidence to the Australian population was uncertain. ESC noted the pre-ESC response stated that the AOANJRR underestimates the infection rates and cited two publications to support this<sup>23,24</sup>. ESC acknowledged the known limitations of using the AOANJRR data to estimate infection rates. However, ESC did not consider the 6% SSI incidence (used for the RCT power calculations) to be representative of SSI rates in primary joint arthroplasty in Australia. ESC also noted that the AOANJRR uses a more contemporary and consistent definition of revision than the studies which increases the confidence in registry data.

ESC noted the DCAR had queried whether Population 2 should be restricted to cementless megaprotheses due to the limited evidence on DAC+antibiotics with cemented megaprotheses. ESC noted the pre-ESC response did not agree with this proposal. ESC agreed with the pre-ESC response that since most megaprotheses are anchored by cement and the rest of the prostheses is cementless (to which DAC+antibiotics can be applied), ESC did not consider it to be significant factor that warrants restricting to cementless megaprotheses.

Regarding comparative safety, ESC noted that all six studies included in the DCAR reported that there were no detectable adverse events or side effects directly attributable to the DAC+antibiotic hydrogel coating across all populations. Further, no allergies associated with DAC+antibiotics were noted in the studies. The studies indicated similar incidence of safety outcomes or complications of standard surgery with and without DAC+antibiotics across all populations. However, the comparative safety evaluation was limited by short follow-up times.

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<sup>20</sup> Izakovicova P, Borens O & Trampuz A (2019). *EFFORT Open Rev* 4(7):482–494.

<sup>21</sup> Wasterlain AS, Goswami K, Ghasemi SA & Parvizi J (2020). *J Bone Joint Surg Am* 102(15):1366–1375.

<sup>22</sup> Capuano N, Logoluso N, Gallazzi E, et al. (2018) *Knee Surg Sports Traumatol Arthrosc.* 26(11):3362-7

<sup>23</sup> Jin X, Luxan BG, Hanly M, et al. (2022) *Bone Joint J.* 104-B(9):1060-1066

<sup>24</sup> Sinagra ZP, Davis JS, Lorimer M, et al. (2022) *Bone Jt Open.* 3(5):367-373

Regarding comparative effectiveness, ESC agreed with the DCAR that the claim of superior clinical effectiveness is uncertain. ESC noted that while the studies reported the relative risk of SSI was less than 1 (favoured surgery with DAC+antibiotics), due to the wide confidence intervals (all crossing 1), no significant difference in the relative risk for SSI between surgery with and without DAC+antibiotics was reported for all four populations.

ESC considered that there are many confounders that contribute to periprosthetic deep SSI outcomes, including the type of antibiotics and organisms, and host factors. ESC highlighted that the common causative organisms could vary by location and due to this difference, the effectiveness of DAC+antibiotics for hip and knee joint arthroplasty may not be applicable to other locations. ESC noted that an *in vitro* study by Tsikopoulos et al. (2019)<sup>25</sup> reported that DAC+antibiotics (loaded with vancomycin or rifampicin) did not inhibit *Cutibacterium acnes* biofilm formation (the most common bacteria involved in shoulder surgery infection). ESC also highlighted evidence that topical antibiotics (not using DAC) as part of routine treatment for hip and knee arthroplasty does not result in a reduction in infection risk (Wong et al. 2021<sup>26</sup>).

ESC noted that the low/very-low quality evidence limited the ability of the DCAR to present useful economic evaluations for each population and created high uncertainty in the modelled results. As such, a stepped cost-utility analysis (CUA) was only feasible for Population 1 and Population 3, and separated hip and knee. Step 1 used a 1-year time horizon and SSI rates based on trial data, Step 2 used Australian SSI rates, and Step 3 modelled the evaluation over 20 years. ESC noted the pre-ESC response raised a number of points regarding the structure and inputs to the economic model. However, ESC was satisfied that detail in the main body of the DCAR addressed the applicant's points. ESC noted that cost-consequence analyses were also presented for each population except for Population 4B (cost-analysis only due to no available comparative evidence).

ESC noted several assumptions were used for the stepped CUA for Population 1 and 3, including:

- a maximum of 2 revisions
- hip and knee follow the same pathway (but modelled separately using different model inputs)
- treatment effect of 1 year (risk ratio of transition to SSI state)
- time horizon of 20 years in Step 3 (based on the life expectancy of Australian populations)
- SSI rates based on data from the AOANJRR in Step 2 (but not specific to cementless or comorbidity groups)
- health-related quality of life (HRQoL) specific to infection (but not comorbidities) from literature (ESC noted the impact of using HRQoL that are not specific to comorbidities as well was unclear)
- direct intervention costs, including the number of kits, along with relatively small costs for antibiotics, sterile water, syringe and theatre time (8–15 minutes)
- two-stage revisions represented as one revision

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<sup>25</sup> Tsikopoulos K, Bidossi A, Drago L, Petrenyov DR, Givissis P, Mavridis D et al. (2019). *Clin Orthop Relat Res* 477(7):1736–1746.

<sup>26</sup> Wong MT, Sridharan SS, Davison EM, Ng R & Desy NM (2021). *Clin Orthop Relat Res* 479(8):1655–1664.



- other reasons for revisions (other than infection) were not captured but likely not relevant.

ESC noted a key driver of the model was the uncertainty around treatment effect. When the upper 95% confidence interval (CI) was used, the intervention is dominated for both Population 1 and 3. Given the studies have a high risk of bias, that the risk ratio estimates are not statistically significant and the evidence is of low quality, ESC considered it important to consider the impact using the upper 95% CI (for the treatment effect) has on the incremental cost-effectiveness ratios (ICERs).

ESC also noted the rate of SSI was a key driver in the model. ESC noted that Step 1 of the stepped CUA applied the SSI rates from the trial data and when the Australian SSI rates based on AOANJRR data were applied in Step 2 of the stepped CUA<sup>27</sup>, this had a substantial impact on the ICER. For Population 1, the ICER increased from \$812,454/\$754,451 in Step 1 to \$1,662,788/\$1,243,016 in Step 2 (hip/knee respectively). For Population 3, the ICER decreased from \$188,380/\$164,710 in Step 1 to dominant/\$11,194 in Step 2 (hip/knee respectively). ESC noted that the pre-ESC response refuted the use of SSI rates based on the AOANJRR. ESC also noted that the SSI rate based on the AOANJRR is not specific to cementless or patients with comorbidities. However, ESC considered the SSI rates based on the AOANJRR data to be the most appropriate available data.

ESC also considered that another key driver of the model was the time horizon. If a time horizon of 1 year is used (same as duration of treatment effect of DAC is applied in model), the ICERs for Populations 1 and 3 were more than \$1 million and \$72,000, respectively. Other key drivers for population 1 only (population 3 remained dominant) are the number of kits (ICERs of about \$redacted [hip]/\$redacted [knee] for redacted kit, increasing to \$redacted [hip] /\$redacted [knee] for redacted kits), the use of DAC in primary arthroplasty and any subsequent modelled revisions (decreasing the ICER to around \$97,000 for hip, while the ICER for knee is dominant), and the price of DAC. ESC noted that the price of DAC was not justified and is uncertain, ranging from \$redacted (DCAR) to \$redacted (pre-ESC response Special Access Scheme funding). ESC also noted a European study<sup>28</sup> reported the price of the kit to be €500–600 for 10mL. When the lower price from Franceschini et al (2020) was used (\$382.03 AUD for 5mL), the ICER for Population 1 reduced to \$redacted (hip) /\$redacted (knee) and Population 3 remained dominant, but the feasibility of this price is unclear.

ESC noted that the annual cost to the MBS was estimated to be less than \$100,000 in each population as the majority of the cost would be borne by the private sector (private health insurance and/or patients). The estimated annual cost to private health insurance (and/or patients) per population was:

- Population 1: \$redacted (hip), \$redacted (knee)
- Population 2: \$redacted
- Population 3: \$redacted (hip), \$redacted (knee)
- Population 4A: \$redacted
- Population 4B: \$redacted.

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<sup>27</sup> The SSI rates from the AOANJRR were applied to the comparator and the SSI rate for the intervention (DAC+antibiotics) was derived by applying the relative risk (0.24 for Population 1 and 0.064 for Population 3) from Romanò 2016 to the AOANJRR SSI rate.

<sup>28</sup> Franceschini M, Sandiford NA, Cerbone V, de Araujo LCT & Kendoff D (2020). *HIP International* 30(1\_suppl):7–11.

ESC noted that the financial estimates were based on MBS utilisation data (i.e., MBS claims data for relevant MBS items was accessed for each population), then an assumption on the proportion of public and private patients was applied. That is, to estimate the eligible private patient population, the proportion thought to be public patients were removed. ESC noted that the pre-ESC response disputed the ratio of private and public patients treated for closed fractures that was used in the DCAR. ESC agreed with the pre-ESC response that registry data are not an accurate way to determine the ratio of private/public patients treated for closed fractures. However, ESC noted the assumption on the proportion of private/public patients should not have been applied to the estimates. This is because the estimates were based on MBS claims data which do not include services provided by hospital doctors to public patients in public hospitals or services that qualify for a benefit under the Department of Veterans' Affairs National Treatment Account. Therefore, this assumption should be removed, meaning the potential eligible population would increase.

ESC noted the DCAR then assumed that 50% of the eligible population would take up DAC+antibiotics. ESC noted that this assumption (50% uptake rate) was not supported by evidence and is highly uncertain. Although this does impact the financial consequence of the intervention, ESC acknowledged that it may be difficult to obtain more substantial data to inform the assumptions. ESC also noted that the estimated utilisation is higher than the applicant's estimate that less than **redacted** patients would utilise DAC+antibiotics in the first year (**redacted**). However, ESC considered that there is a high risk for DAC+antibiotics to be used beyond the proposed population (i.e. higher utilisation than estimated in the DCAR) due to the ambiguity of what is considered high-risk for SSI. ESC also noted that the financial impact analysis did not include any offsets due to uncertainty after the first year. Overall, ESC considered the estimated utilisation and estimated financial impact were highly uncertain.

## **17. APPLICANT COMMENTS ON MSAC'S PUBLIC SUMMARY DOCUMENT**

Novagenit Australia Pty Ltd respectfully expresses its disappointment with MSAC's appraisal of the cost-effectiveness of the Defensive Antibacterial Coating (DAC) device. Novagenit Australia is concerned that MSAC's analysis relied on factually incorrect AOANJR infection rates and unsubstantiated uptake of DAC, while disregarding published peer-reviewed papers.

Throughout the evaluation process, Novagenit made MSAC aware that the AOANJR does not report on infections, only revisions. Novagenit Australia highlighted that AOANJR's own publications admit that it substantially underestimates the rates of Surgical Site Infections (SSI) in Australia. We were disappointed that MSAC reports compared AOANJR primary infection data to our submitted published papers, which included up to 30% revision patients..

Novagenit Australia strongly disagrees with MSAC's Public Summary Findings, which the applicant considers to be misled by factually incorrect data and incorrect comparisons of patient cohorts.

## **18. FURTHER INFORMATION ON MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)