Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Advice
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In response to an enquiry from the Golden Jubilee National Hospital

Synovasure® alpha defensin tests, as part of a bundle of tests, for the diagnosis of hip and knee periprosthetic joint infection (PJI)

Advice for NHSScotland

Laboratory-based Synovasure® test, used as part of a bundle of diagnostic tests

It is not possible to establish reliable estimates for the relative accuracy of the laboratory-based Synovasure® bundle of tests compared with standard diagnostic strategies used in NHSScotland. The evidence is insufficient in quality and quantity to draw conclusions on the routine use of Synovsaure® tests as part of a bundle of diagnostic tests for periprosthetic joint infection (PJI).

Currently in Scotland, there is no clearly defined diagnostic strategy for PJI, with variation across hospitals and health boards.

To establish the value in the routine use of the Synovasure® bundle of tests, further research is required to ascertain its relative accuracy compared with current standard diagnostic strategies used in NHSScotland. Research should also capture the impact of the bundle of tests on clinical outcomes and costs.

Point-of-care Synovasure® diagnostic test

The Synovasure® diagnostic test is also available as a point of care test. For people with periprosthetic knee joint infection, the point of care test may represent a valuable additional diagnostic tool for people with equivocal results following standard tests.

NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) advice.

What were we asked to look at?

We were asked to evaluate the clinical and cost effectiveness of a bundle of tests for the diagnosis of hip and knee periprosthetic joint infection (PJI) compared with current practice in NHSScotland. The bundle reflects updated diagnostic criteria, which were proposed at the International Consensus Meeting on orthopaedic infections (ICM 2018), and includes the laboratory-based Synovasure® alpha defensin test.

We were also asked to include any clinical and cost-effectiveness evidence relating to the Synovasure® alpha defensin tests alone for the diagnosis of PJI.

Why is this important?

The Synovasure® test is available in two formats: a point-of-care lateral flow test kit (POCT) and a laboratory-based ELISA (enzyme-linked immunosorbent assay) test. The POCT is available for use in NHSScotland but, at the time of writing (November 2019), laboratory-based testing of alpha-defensin is not available in the UK. There have recently been negotiations around siting a laboratory in Scotland that would offer the laboratory-based alpha defensin assay as part of a bundle of tests (mapped to the proposed ICM 2018 criteria). This SHTG technology assessment will help to inform the use of the bundle of tests within NHSScotland.

What was our approach?

With a focus on the proposed bundle of tests for the diagnosis of PJI, we reviewed relevant clinical and cost-effectiveness evidence. We also conducted a cost analysis comparing the bundle of tests to the current standard diagnostic strategies used in NHSScotland.

Much of the evidence has already been reviewed by Health Technology Wales in their Evidence Appraisal Report' on the use of Synovasure® alpha defensin tests for PJI diagnosis[1].

What next?

SHTG Advice will be used to inform the use of the bundle of tests in diagnostic pathways for infected prosthetic joints in patients presenting with the potential need for revision arthroplasty in NHSScotland. The Advice may also be used to inform the negotiations regarding the siting of a laboratory in NHSScotland, in relation to both the availability of the tests and future research.

Key points

- NHSScotland does not have a clearly defined standard diagnostic pathway for periprosthetic joint infection (PJI), and there appears to be variation across different hospitals and health boards. This means that it is not possible to define a reference point for the diagnostic accuracy of current strategies used in NHSScotland, and the relative accuracy of the proposed new bundle of diagnostic tests will vary across Scotland.

Evidence relating to the proposed bundle of tests mapped to ICM 2018 criteria

- Owing to a lack of accuracy data for the proposed bundle of tests, and uncertainty around the current diagnostic strategies used in NHSScotland, surrogate accuracy estimates were used in this assessment.
- The bundle of tests were mapped to the proposed International Consensus Meeting (ICM) 2018 criteria. The proposed ICM 2018 criteria for diagnosing PJI were based on a paper published by Parvizi *et al* (2018) who reported a sensitivity of 97.7% (95% confidence interval (CI) 94.7% to 99.3%); and a specificity of 99.5% (95% CI, 97.2% to 99.99%). The diagnostic accuracy figures reported by Parvizi *et al* have been used as a surrogate for the proposed bundle of tests.
- The previous version of the ICM criteria (2013) have been used as a surrogate for the current standard diagnostic strategies used in NHSScotland. The ICM 2013 criteria do not include alpha defensin testing and have a lower sensitivity than the more recent Parvizi *et al* criteria (86.8%; 95% CI 81.9% to 91.1%), and similar specificity (99.5%; 95% CI 97.3% to 99.99%).
- Using the same surrogates, an economic evaluation was undertaken which suggests the ICM 2018 criteria is unlikely to be cost-effective compared with the ICM 2013 criteria in patients with suspected PJI having total hip arthroplasty (THA) or total knee arthroplasty (TKA) revision surgery. These findings were robust under an extensive range of sensitivity analyses.
- Key factors most likely to improve the cost effectiveness of the proposed bundle of tests include: a) the availability of robust data to show that bundle of tests provided improvements in diagnostic accuracy beyond those assumed in the analyses, and b) reductions in the cost of the bundle of tests.
- The overall budget impact of introducing the proposed bundle of tests (mapped to ICM 2018 criteria) in Scottish practice to replace the current standard suite of diagnostic tests (assumed to be mapped onto ICM 2013) was estimated to be £662,527 per year in the combined population.

Evidence relating specifically to Synovasure® alpha defensin tests

- One systematic review (10 studies, seven of which were on the laboratory alpha-defensin test) reported that the Synovasure® laboratory-based test's sensitivity for diagnosing PJI is 95%, and specificity is 96%.

- One systematic review (11 studies, six of which were on the lateral flow point of care test) reported that the point of care Synovasure® lateral flow test's sensitivity for diagnosing PJIs is 85% and specificity is 90%.
- For people undergoing TKA, an economic analysis conducted by SHTG suggested that using the Synovasure® point of care test as a further investigation tool in the population with equivocal results - based on preliminary standard diagnostic tests (ICM 2013) - is potentially cost-effective. Probabilistic Sensitivity Analyses (PSA) indicated that the Synovasure® point of care test was associated with a 62% probability of being cost-effective as a further investigation tool in the equivocal TKA population.
- For people undergoing THA, the same economic analysis found that Synovasure® point of care test is unlikely to be cost-effective if used for further investigations in patients with equivocal results.
- The potential overall budget impact of introducing Synovasure® point of care test as an additional testing strategy in the population undergoing THA and TKA revisions with equivocal results on preliminary standard tests was estimated to be £229,341 per year in the combined population (£59,386 in the equivocal knee revision population).

Committee Considerations

- The Committee agreed that there is insufficient evidence to reach firm conclusions towards advising on the use of the proposed bundle of tests. Furthermore, this bundle of tests appears to have evolved since the question was referred to SHTG, and at the time of writing offered additional tests beyond the ICM 2018 criteria (including a sample integrity test and crystal analysis). There is insufficient evidence to support the assertion that a more comprehensive suite of tests may increase the accuracy of diagnosis.
- The Committee noted that topic experts contributing to the assessment have advised that the diagnostic accuracy of 'true' diagnostic strategies used in NHSScotland is likely to be less than would be achieved using the ICM 2013 criteria.
- The Committee recognised that there is a lack of standardisation in PJI diagnosis across Scotland. The Committee indicated a need for a standardised approach.
- The Committee noted that there was limited peer review of the SHTG advice (including only two clinical experts from NHSScotland) despite numerous attempts to recruit additional peer reviewers. The Committee were advised that by liaising with Health Technology Wales on their work on Synovasure® (who shared in confidence their peer review comments), some additional quality assurance for the assessment had been obtained.
- If the use of the proposed bundle of tests is to be pursued, further research is required. Diagnostic accuracy studies are needed to assess the performance of the proposed bundle of tests, and how this compares with current diagnostic strategies used in NHSScotland. In addition, studies that assess subsequent impact on clinical outcomes are desired.

Contents

Research question:

What is the clinical and cost effectiveness of a bundle of tests (mapped to criteria proposed at the International Consensus Meeting on orthopaedic infections in 2018 - the ICM 2018 criteria) in the diagnosis of periprosthetic joint infection (PJI) compared with current practice in NHSScotland?

The bundle of tests (ICM 2018 criteria) includes the Synovasure® alpha defensin test, and the topic referrer also asked for a summary of the evidence on the Synovasure® alpha defensin tests used alone.

Literature search

A systematic search of the secondary literature was carried out between 4 March 2019 and 7 March 2019 to identify systematic reviews, health technology assessments and other evidence based reports. Medline, Medline in process, Embase and Web of Science databases were also searched for systematic reviews and meta-analyses.

The primary literature was also systematically searched between 4-7 March 2019 using the following databases: Medline, Medline in process, Embase and Web of Science.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: periprosthetic joint infection, prosthetic joint infection, PJI, alpha defensin, hip/knee/joint replacement, Synovasure®. A full list of resources searched and terms used are available on request.

Introduction

Periprosthetic joint infection is an uncommon but serious complication of hip and knee replacement surgery, affecting approximately 1% of hip arthroplasties and 1% to 2% of knee arthroplasties[1]. It can lead to additional surgeries, revision, fusion, amputation and in rare cases death[2]. Treatment commonly involves antibiotics plus either a single- or two-stage revision procedure. According to some reports, PJI is the cause of 20-25% of total knee arthroplasty (TKA) failures; and 12-15% of total hip arthroplasty (THA) failures[3].

The most common symptom of PJI is pain. In patients presenting with nonspecific pain, tests are used to differentiate between septic and aseptic causes. This guides subsequent management. PJI is categorised based on the time since initial surgery. An early infection develops within three months of surgery; a delayed infection develops from three months to two years after surgery; and a late infection is defined as developing more than two years after surgery[4].

In an acute infection, signs of inflammation are generally present. These include pain, swelling, erythema and warmth. Compared with early infection, delayed and late infections are often more subtle in their presentation, making diagnosis difficult[3]. Pain is commonly reported, as is loosening of the prosthesis. There is no single accepted set of diagnostic criteria for PJI[5].

In 2011, the Musculoskeletal Infection Society (MSIS) convened a working group to propose a standard definition of PJI which could be universally adopted[5]. This was adapted in 2013 by a large group of experts in Philadelphia as part of an International Consensus Meeting on PJI (ICM 2013)[6]:

1. A sinus tract communicating with the prosthesis.
   Or
2. Isolation of a pathogen from two or more periprosthetic cultures from the affected joint.
   Or
3. Three of the following:
   a. Elevated serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
   b. Elevated synovial fluid white blood cell (WBC) count
   c. Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)
   d. A single positive culture
   e. Positive histological analysis of periprosthetic tissue

The consensus group acknowledged that: an infection could still be present if these criteria were not met; and that some of these criteria may be met in the absence of an infection. It was also noted that few hospitals have the resources to run all of the ICM 2013 criteria tests.

A second international consensus conference was held in 2018. With the recognition of potential new biomarkers for diagnosing infection, and developments of knowledge in this area, a further set of criteria with a scoring system were proposed (Figure 1), which also includes measurement of alpha defensin[7].

Figure 1: Proposed ICM 2018 criteria[7]

Major criteria (at least one of the following)	Decision
Two positive growth of the same organism using standard culture methods	Infected
Sinus tract with evidence of communication to the joint of visualization of the prosthesis	

Minor Criteria	Threshold		Score	Decision
	Acute	Chronic		
Serum CRP (mg/L) or D-Dimer (ug/L)	100 Unknown	10 860	2	Combined preoperative and postoperative score: ≥6 Infected 4-5 Inconclusive* ≤3 Not Infected
Elevated Serum ESR (mm/hr)	No role	30	1	
Elevated Synovial WBC (cells/µL) or Leukocyte Esterase or Positive Alpha-defensin (signal/cutoff)	10,000 ++ 1.0	3,000 ++ 1.0	3	
Elevated Synovial PMN (%)	90	70	2	
Single Positive Culture			2	
Positive Histology			3	
Positive Intraoperative Purulence			3	

An accurate diagnosis of PJI underlies appropriate treatment. The incorrect diagnosis of a PJI in a healthy patient (a false positive result) can lead to more complex surgical management than is actually required. Conversely, a false negative result can lead to less optimal treatment allocations, delayed intervention, and more complex re-operation at a later date. An early diagnosis can lead to less radical treatment[8]. The mean cost of a revision for infection has been estimated to be more than three times than that of an aseptic revision[9].

There is currently no standardised protocol within NHSScotland for the diagnosis of PJI, and clinical expert input advises that there is a high degree of variation amongst different hospitals/health boards. The variation across Scotland was captured in a 2017 survey of 13 Scottish hospitals. This suggested that the diagnostic tests most commonly used in NHSScotland for diagnosing PJI were serum CRP, serum ESR, and microbiology cultures, occasionally combined with other tests such as bone scan or PCR test. One hospital used automated synovial WBC count and automated PMN%, as well as the leukocyte esterase test (LET) in addition to serum CRP and ESR, and microbiology culture. Three of the hospitals reported that they used synovial cell counts (WBC and PMN%), but based on manual counting. Variation regarding the length of the microbiology cultures (between 7-14 days) was found amongst different hospitals. Some health boards reported that they already used the point of care Synovasure® lateral flow test kit (Personal communication. Martin Sarungi, Consultant Orthopaedic Surgeon, Golden Jubilee National Hospital. August 2019).

Health technology description

The Synovasure® test is available in two formats: (1) a point-of-care lateral flow test kit (POCT), and (2) a laboratory-based ELISA (enzyme-linked immunosorbent assay) test. Both formats can be used as standalone tests, but the focus of this assessment is on the laboratory-based Synovasure® alpha defensin test as part of a bundle of diagnostic tests.

The Synovasure® alpha defensin tests and the proposed bundle are described as follows:

Synovasure® alpha defensin tests

Alpha defensins are antimicrobial peptides released by activated neutrophils in response to infection[10]. In response to PJI, levels of alpha defensin increase in the synovial fluid; therefore alpha defensin has been proposed as a synovial fluid biomarker for predicting PJI[1].

The Synovasure® tests (manufactured by Zimmer Biomet, USA) measures human alpha defensins 1-3 in the synovial fluid of people who have had a total joint replacement. The Synovasure® tests are intended to aid in the diagnosis of PJI, along with other clinical and diagnostic assessments. The test is available in two formats, both with Class 1 CE marks:

1. The Synovasure® alpha defensin lateral flow test kit comprises a single use device, similar in size and function to a home pregnancy test. It is a point of care device, which can be used during pre-operative joint aspiration or intra-operatively during revision procedures. Small amounts of synovial fluid are collected with the Microsafe® tube and added to a premeasured dilution buffer. Three drops of this sample are then added to the test device. A control line appears if the test has been performed correctly, and a second line appears if the level of alpha defensin in the sample is greater than a cut-off concentration (approximately 8 micro-ml). Results are available in 10 minutes.

2. The Synovasure® laboratory-based ELISA (enzyme-linked immunosorbent assay) test main components include specimen tubes, a specimen transport biohazard bag, a specimen box, and an

instruction sheet. To perform the test, 0.5mL of synovial fluid must be collected in specimen tubes. The vials are submitted to a laboratory for analysis, and results are typically available in 24 hours.

The Synovasure® tests may be useful to aid the diagnosis of PJI at various stages in the patient pathway:

1. Pre-operatively: Both Synovasure® tests may be used as an adjunct to existing diagnostic tests, or when standard laboratory test results are equivocal or confounded by pre-existing conditions.
2. Intra-operatively: Owing to the quick turnaround time for the results, where there are doubts upon commencement of the surgical procedure, the point of care Synovasure® alpha defensin lateral flow test kit may be used during the operation to help determine whether the joint is infected or not. This may help to guide the required complexity of surgical revision.

Currently, there is no laboratory-based testing of alpha-defensin available in the UK, and the nearest approved laboratory is in Germany (see 'Organisational Issues' section for more details).

Test bundle

The manufacturer of Synovasure®, Zimmer Biomet, has proposed that a laboratory at the Golden Jubilee National Hospital will offer a bundle of tests for the diagnosis of PJI. The manufacturers claim that the bundle has been mapped to the proposed ICM 2018 criteria (Figure 1) and covers criteria from other internationally used PJI algorithms for example, the European Bone and Joint Infection Society criteria. The diagnostic bundle would include the following:

- Standard culture from synovial fluid
- Serum CRP (mg/L)
- Elevated Synovial WBC (cells/micro-L)
- Human Neutrophil Elastase (HNE) – similar to Leukocyte Esterase
- Positive Alpha-defensin (signal/cutoff)
- Elevated Synovial PMN (%)
- Microbial ID – organism identification

Epidemiology

In 2017, there were 7,786 hip replacements in Scotland, and 777 revisions. Of the revisions, 11.1% were due to infection and inflammatory reaction (approximately 86 people). In 2017, there were 7,282 knee replacements, and 463 revisions. Of the revisions, 10.6% were due to infection and inflammatory reaction (approximately 50 people)[11]. These figures have been taken from the Scottish Arthroplasty Project annual report 2018, but the report recognises that these figures may be prone to errors due to limitations with the coding system[11]. This may explain why the figures for Scotland (notably for TKA revisions due to infection), are lower than figures reported elsewhere in the

literature, which state that PJI is the cause of 20-25% of TKA failures; and 12-15% of THA failures[3]. In concordance with these commonly cited figures, the UK National Joint Registry (England, Wales, Northern Ireland and the Isle of Man) reported that in 2018 PJI was the cause of 22.5% of TKA failures and 13.1% of THA failures[12].

The use of the test bundle may be more appropriate in patients where standard testing is equivocal. It is not clear what proportion of patients presenting with suspected PJI would be suitable for the test bundle.

Clinical effectiveness

Synovasure® tests

Health Technology Wales commissioned the ECRI Health Technology Information service to produce a product brief on both Synovasure® alpha defensin tests. The ECRI brief concluded: 'Although two systematic reviews report that Synovasure® alpha-defensin laboratory and lateral flow tests have high specificity that enables PJI detection and high sensitivity that enables ruling out PJI, studies do not report clinical utility data to assess whether alpha-defensin tests alone or in conjunction with current diagnostic procedures reduce revision surgery or reoperation rates in patients with suspected PJI after hip or knee arthroplasty. One study is ongoing but will not address the clinical utility evidence gaps'[1].

The ECRI Product Brief summarises the evidence as follows:

One systematic review (10 studies, seven of which were on the laboratory alpha-defensin test) reported that the Synovasure® laboratory-based test's sensitivity for diagnosing PJI is 95%, specificity is 96%, and accuracy for PJI diagnosis (receiver operating characteristic [ROC] area under the curve [AUC]) is 99%.

One systematic review (11 studies, six of which were on the lateral flow test) reports that the Synovasure® lateral flow test's sensitivity for diagnosing PJIs is 85% and specificity is 90%.

Two diagnostic cohort studies (not included in the systematic reviews) reported that the Synovasure® lateral flow test's sensitivity for diagnosing PJIs is 90%/92%, specificity is 92% /100%, positive predictive value is 100%, and negative predictive value is 95.2%/ 97.6%.

Health Technology Wales identified an additional study on the use of the Synovasure® lateral flow test in patients with equivocal results after standard tests (de Saint Vincent, B *et al*, 2018). This prospective non-randomised study of 42 cases in 39 patients used the ICM 2013 criteria as the reference standard. This authors reported that the Synovasure® lateral flow test had a sensitivity of 88.9% and specificity of 90.6% (confidence intervals not reported). The positive predictive value (PPV) was reported to be 77.8% and the negative predictive value (NPV) was reported to be 94.4%. The authors conclude that the lateral flow test may be useful for ruling out infection in patients with PJI when the diagnosis is in doubt.

Based upon this evidence, the guidance issued by Health Technology Wales states: 'The use of Synovasure® alpha defensin testing shows promise in the diagnosis of peri-prosthetic hip and knee infection but the evidence does not currently support routine adoption. Synovasure® has the potential to further the diagnosis in patients with equivocal results from conventional testing but more convincing evidence is needed. Health Technology Wales therefore recommends further research in this group of patients to define diagnostic accuracy, clinical outcomes and cost consequences of the use of synovasure® in addition to standard investigations.'

For a fuller description of the evidence base on the Synovasure® alpha defensin tests, please refer to the assessment by Health Technology Wales[1].

Test bundle

The proposed ICM 2018 diagnostic criteria were presented at the Second International Consensus Meeting (ICM) on orthopaedic infections[7]. However, other than the conference slides, no publications relating to a final version of the ICM 2018 criteria were identified. It is not clear whether a final version of ICM 2018 is going to be published.

The proposed ICM 2018 criteria were based on a study by Parvizi *et al* (2018)[13]. In this study, Parvizi *et al* describe the development of new criteria for PJI diagnosis; validate the new criteria on an external cohort; and compares its accuracy to previous versions of the criteria (MSIS 2011 and ICM 2013).

To develop the new criteria, Parvizi *et al* conducted a retrospective review of the medical records of all patients undergoing THA and TKA from three academic centres between January 2001 and July 2016. PJI cases (n=684) were defined using the major criteria from MSIS 2011/ICM 2013. Aseptic cases had undergone a one-stage revision for a non-infective indication and this had not failed within 2 years (n=820). A stepwise approach using random forest analysis and multivariate regression were used to generate relative weights for each diagnostic marker, and a scoring system was based on beta coefficients. The proposed criteria are outlined in Figure 2:

Figure 2: Criteria proposed by Parvizi *et al* 2018[14]

Major criteria (at least one of the following)	Decision
Two positive cultures of the same organism	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

		Minor Criteria	Score	Decision
Preoperative Diagnosis	Serum	Elevated CRP *or* D-Dimer	2	≥6 Infected
		Elevated ESR	1	
	Synovial	Elevated synovial *WBC count or LE*	3	2-5 Possibly Infected [a]
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	0-1 Not Infected
		Elevated synovial CRP	1	

	Inconclusive pre-op score *or* dry tap [a]	Score	Decision
Intraoperative Diagnosis	Preoperative score	-	≥6 Infected
	Positive histology	3	4-5 Inconclusive [b]
	Positive purulence	3	
	Single positive culture	2	≤3 Not Infected

Figure 2: Reprinted from The Journal of Arthroplasty, 33/5, Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, et al. 1309-14., Copyright (2018), with permission from Elsevier.

The new criteria were validated on patients from the same three institutions. The validation cohort included 222 infected and 200 aseptic revisions. The authors state that the aseptic cases were a randomly selected sample. For the infected cases, they state that they: 'chose a representative sample of infected cases that was independent from any intrinsic bias from the commonly used definitions for infection'[14]. It is possible that this selection of patients introduced bias into the analysis. The authors reported that the sensitivity of the Parvizi *et al* criteria was 97.7% (95% confidence interval (CI) 94.7% to 99.3%); and the specificity was 99.5% (95% CI, 97.3% to 99.99%). The updated criteria demonstrated a higher sensitivity compared to the ICM 2013 criteria (86.9%; 95% CI 81.8% to 91.1%), and similar specificity (99.5%; 95% CI 97.3% to 99.99%).

The sensitivity and specificity values reported by Parvizi *et al* exclude patients with inconclusive results (2%). This may mean that the sensitivity or specificity were overestimated. Further studies are needed to confirm the diagnostic accuracy figures reported by Parvizi *et al.*

An adapted version of the criteria proposed by Parvizi *et al* was presented at the ICM 2018 conference (Figure 1). There are some small changes to the criteria, notably the way in which the Synovasure® test is incorporated into the algorithm. It is not clear how these adaptations might influence the accuracy figures presented by Parvizi *et al.* Furthermore, it is uncertain whether the

diagnostic accuracy criteria of the new test bundle being offered by Zimmer Biomet (which does not include measurement of ESR) can be assumed to match the accuracy data presented by Parvizi *et al.*

No other studies were identified which evaluated the diagnostic accuracy or clinical utility of the proposed ICM 2018 criteria compared to a standard diagnostic strategy.

Safety

The Synovasure® alpha defensin tests use fluid obtained during routine analysis, and do not require further invasive investigations. The evidence appraisal report by Health Technology Wales stated that searches of the MHRA adverse events database and FDA MAUDE database did not identify any safety concerns[1].

Patient and social aspects

Health Technology Wales states that: 'PJI and the requirement for hip revision surgery is undoubtedly a devastating outcome for a patient. A qualitative study by Moore *et al.* (2015) in which semi-structured interviews were undertaken with 19 patients in England and Wales who had undergone surgical revision following a PJI, illustrates the pervasive impact of PJI on patients' lives. Two-stage revision had a greater impact than 1-stage revision on participants' well-being because the time in between revision procedures meant long periods of immobility and related psychological distress. A further study (Mallon *et al*. 2018), focused on knee PJI, reports similar findings. Early and accurate diagnosis is thus extremely important to patients.[1]

Organisational issues

As stated in the Introduction, there is currently no laboratory-based testing of alpha-defensin available in the UK, and the nearest approved laboratory is in Germany.

At the time of writing this review, negotiations were taking place between Zimmer Biomet and the Golden Jubilee Foundation NHSScotland Special Health Board regarding the siting of a laboratory within the Golden Jubilee National Hospital (Glasgow). The laboratory would offer the alpha defensin assay as part of a bundle together with other diagnostic tests which map to the proposed ICM 2018 criteria. Although integrated operationally with the NHS laboratory at the Golden Jubilee, the service would be owned and run as a commercial enterprise by Zimmer Biomet. The laboratory would serve the whole of the UK and the Republic of Ireland.

Economic considerations

No published economic analyses were identified which considered the cost effectiveness of the Synovasure® alpha defensin tests, or the bundle of tests, compared with existing diagnostic strategies used in NHSScotland.

A de-novo economic evaluation was undertaken by Health Technology Wales and was adapted to the Scottish setting for the purpose of this review. Two separate scenarios were considered in the analysis:

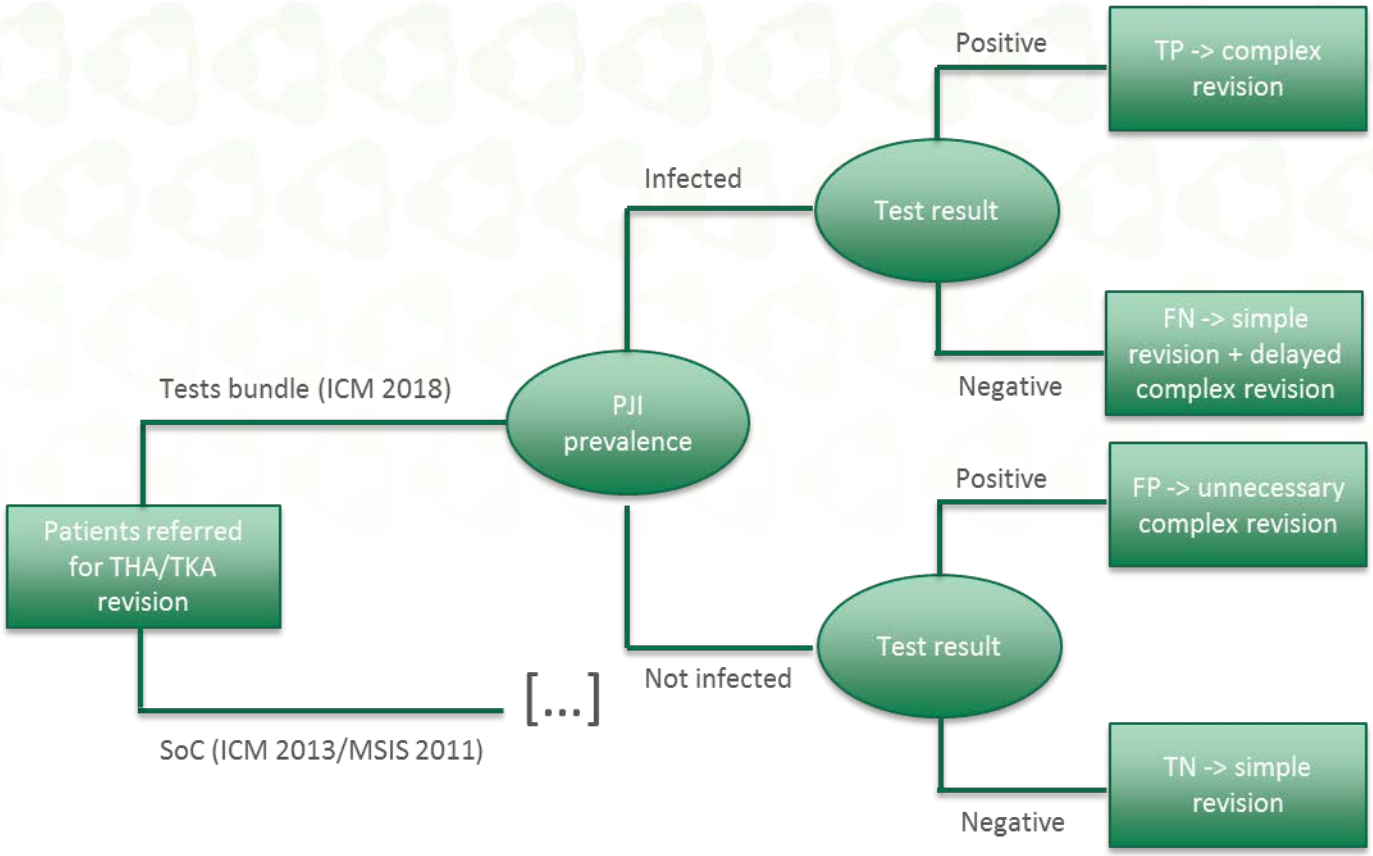
1. Using the Synovasure® laboratory test as part of a bundle of laboratory tests (mapped to the ICM 2018 criteria) in all patients with suspected PJI, compared against tests reflecting 'standard of care' (mapped to the ICM 2013 criteria).

2. Using the Synovasure® POCT in patients that had equivocal results following routine diagnostic strategies (i.e. negative but with continued suspicion of infection). This scenario assumed all equivocal cases would be treated as not being infected. .

A decision-tree model, as depicted in Figure 3, was developed to compare the relative costs and health benefits associated with a change in the criteria of diagnosing PJI. Patients undergoing hip or knee revisions with PJI suspicion enter the model and are tested with either the bundle of tests (which includes Synovasure®) or the standard diagnostic strategies. For the subpopulation with equivocal results following the standard of care (SoC i.e. patients with negative result on standard diagnosing tests but in which infection continues to be suspected on clinical grounds), patients enter the model and receive either a further test with the Synovasure® POCT, or are assumed to be treated based on the results of the initial suite of standard diagnostic tests.

Patients receive a standard revision if infection is ruled out, or a more complex intervention if infection is indicated by the test strategies. In false negative cases, patients may undergo the suboptimal standard revision followed by a delayed complex revision before their symptoms improve. In false positive cases, patients may undergo an unnecessary complex and costly intervention. Hence, the accuracy of the diagnosing criteria utilized is expected to be an important driver of costs and health outcomes.

Figure 3: Decision-tree model structure



The analysis was conducted from the perspective of NHSScotland, over a one year time horizon. Cost-effectiveness is measured in terms of the incremental cost per quality-adjusted life-year (QALY).

The numbers of THA and TKA revisions undertaken per year in Scotland were taken from the Scottish Arthroplasty Report for 2018. Based on this, there were 777 hip revisions and 463 knee revisions in 2017 in Scotland. Given the concerns relating to the accuracy of the Scottish figures (see Epidemiology section), PJI prevalence in the population undergoing revision surgery was estimated using data from the UK National Joint Registry[12] which gives a rates of 13.1% and 22.5% for hip and knee revisions respectively. An important caveat is that the prevalence rates utilised in the model are based on the overall population undergoing revision and may not accurately reflect the prevalence in the target population referred for further testing with the Synovasure® test bundle. This is due to the way the overall population is screened using the major and minor components of the ICM 2018 criteria (Figure 1). For example, it is expected that some infected cases would be identified immediately through the major criteria component (and with absolute or very high accuracy) and hence, in the remaining population that undergoes further investigations based on the minor criteria on which the Synovasure® bundle of tests is mapped, the prevalence is actually lower. For this reason, lower prevalence rates were explored in the sensitivity analysis.

Clinical experts in Wales estimated that around 20% of the population tested for PJI would have equivocal results with standard tests making them difficult to diagnose. This estimate was validated by clinical experts in Scotland (15%-20%, personal communication. Martin Sarungi, Consultant Orthopaedic Surgeon, Golden Jubilee Hospital. August 2019). Applying the 20% estimate to the

population undertaking hip and knee revisions in Scotland resulted in an assumption that 155 hip revisions and 93 knee revisions are viewed as equivocal.

Key clinical data for the economic analysis are the diagnostic accuracy estimates for the Synovasure® bundle of tests versus SoC tests (Table 1). The diagnostic accuracy of the Synovasure® bundle of tests was based on values reported in Parvizi *et al* 2018 that lead to the ICM 2018 criteria. It should be noted the diagnostic algorithm originally proposed in Parvizi *et al* 2018 has since been amended and this will have implications for diagnostic accuracy. It is not possible to specify the impact of the amendment, but it is likely the changes to the way the Synovasure® component is implemented would improve specificity at the expense of some sensitivity, and this can be tested within the economic model. The base case analysis uses a sensitivity of 97.7% and specificity of 97.5%.

Table 1: Diagnostic accuracy estimates applied in the analysis

Test	Sensitivity	Specificity	Source
Package of tests reflecting standard care (mapped onto ICM 2013)	0.869	0.995	Parvizi 2018
Package of tests including Synovasure® (mapped onto ICM 2018)	0.977	0.975	Parvizi 2018 – modified to include patients with inconclusive results
Synovasure® Lateral Flow Point of Care Test (in patients with equivocal results with other tests)	0.889	0.906	De Saint Vincent 2018

There is no standardized protocol within NHSScotland for diagnosing PJI and there appears to be a high degree of variation amongst different hospitals. The most common tests used are serum CRP, serum ESR, and microbiology cultures (Personal communication. Martin Sarungi, Consultant Orthopaedic Surgeon, Golden Jubilee Hospital. August 2019). The lack of robust Scottish data meant that the comparator in the economic analysis was mapped to the ICM 2013 criteria, with the diagnostic accuracy assumed to reflect the comparative data in Parvizi *et al* 2018. Various assumptions in the accuracy were tested in the sensitivity analyses.

Table 2 lists the costs included in the economic model. The cost of Synovasure® POCT and the cost of the new proposed bundle of tests (including the Synovasure® laboratory test) mapped onto the ICM 2018 criteria were provided by the manufacturer. The cost of the POCT used in the analysis was £300, but this only applies if purchased in packs of five tests (£495 when purchased individually). The cost for the standard of care was estimated by Health Technology Wales based on the following suite of tests that were identified by clinical experts to be representative of local practice: serum ESR, serum CRP, full blood count (FBC), synovial fluid white blood cell count, microscopy and culture. The total cost for standard care was estimated to be £38.61 and includes staff time. This cost also includes synovial PMN (part of the ICM 2013 criteria) which, according to expert opinion, is not standard practice in Wales or Scotland. For this reason, the true cost of standard care in Scotland

may be lower. Cost variations were tested within sensitivity analyses but, based on the relatively low costs of tests within ICM 2013 criteria, the impact on results is likely to be low.

The micro-costing approach used to estimate costs - which focuses on the ongoing variable cost of the tests - may underestimate the actual cost of setting up those tests in practice (i.e. fixed costs). it is also recognized that patients with equivocal results may undergo additional sets of expensive tests such as bone scans. One study estimates the mean cost of pre-operative testing in deep infection cases to be £988[15]. Since this is likely to be an important driver of cost-effectiveness, our adaptation of the economic model was extended in sensitivity analyses to incorporate the higher cost of testing in equivocal patients.

The costs for subsequent interventions were derived from NHS Reference Costs. The cost of a single stage revision varies depending on whether the procedure is carried out in a patient with or without an infection. The cost of a two-stage revision was assumed to involve two procedure codes reflecting the two stage process. The first stage was costed as a septic single stage revision while the second was costed as an aseptic single stage revision. Clinical experts suggested that some patients may be eligible for a light touch intervention including debridement, antibiotics and implant retention (DAIR).

Table 2: Costs associated with diagnosis and subsequent management

Test	Cost	Source
Suite of tests offered by manufacturer (Synovasure® laboratory test, microscopy and culture, serum CRP, synovial WBC, leukocyte esterase and synovial PMN)	£450	Zimmer Biomet
Synovasure® lateral flow POCT	£300	Zimmer Biomet
Standard of Care (serum ESR, serum CRP, FBC, synovial fluid WBC, microscopy and culture)	£38.61	Health Technology Wales
Intervention	**Cost***	**Source**
Single-stage revision in patient without infection	£9,683	NHS Reference Costs 2017/18 – HN81
Single-stage revision in patient with infection	£14,571	NHS Reference Costs 2017/18 – HN80
Two-stage revision	£24,254	NHS Reference Costs 2017/18 – Sum of HN81 and HN80

Debridement, antibiotics and implant retention (DAIR) for hip	£5,081	NHS Reference Costs 2017/18 – HN14
Debridement, antibiotics and implant retention (DAIR) for knee	£3,188	NHS Reference Costs 2017/18 – HN24

*Weighted average of respective currencies

The economic model assumed that the results of the diagnostic tests would inform subsequent management as detailed in Table 3. The higher proportion of no treatment in the equivocal population reflects the lower likelihood of the surgeon wanting to operate in this group due to a lower suspicion of PJI. A subset of 76% of the patients with false negative results are assumed to be initially treated erroneously as negative patients, derived based on the treatment distribution for negative results and accounting for the overlapping with the treatment distribution for positive results. These patients subsequently receive the appropriate treatment associated with positive results.

Clinical expert opinion in Scotland suggests the proportion of patients treated with one-stage revision when PJI is confirmed by diagnostic tests is lower, particularly in small centres. The estimate is likely close to 10%, with a greater proportion of patients receiving two-stage revision instead. In patients undergoing knee revision with negative result for PJI, it was suggested the proportion receiving no treatment is higher, closer to 30%. The impact of these stated differences in practice were investigated in the sensitivity analyses.

Table 3: Subsequent management proportions based on test results

Management approach	Proportion	
	Overall population	Patients with equivocal results after initial test
Positive result for PJI		
Two stage	60%	60%
One stage	30%	30%
Debridement, antibiotics and implant retention (DAIR)	10%	10%
Negative result for PJI		
One stage	80%	50%
No treatment	20%	50%

Quality of life (QoL) values were derived from EQ-5D values collected in Eibich *et al* (2018)[16] for patients with good or poor outcomes following primary and revision procedures (summarised in Table 4). Patients with good outcomes were described as being mostly free from pain and satisfied with surgery results, while for patients with poor outcomes, pain and functional limitations persist and they are generally dissatisfied with surgery results. Baseline QoL was assumed to be equal to the value associated with poor outcomes after the initial surgery, which was thought to provide the best approximation as it is likely that patients with suspected PJI would have pain or functional limitations. Patients with PJI that are correctly diagnosed (i.e. true positives) were assumed to have the QoL value associated with good outcomes after a revision. Patients with PJI that are not correctly diagnosed (i.e. false negatives) were assumed to have the QoL value associated with poor outcomes after a revision, but these patients would subsequently receive the appropriate treatment when it is realised that the patient does have PJI. It is difficult to estimate the interval between the initial inappropriate management and the appropriate management that is subsequently received. In the base case, it is assumed that the lower QoL associated with the inappropriate management would apply for 12 months but lower estimates are explored in sensitivity analysis. Patients without PJI were assumed to have the same QoL value as the baseline value regardless of whether they are true negative or false positive. There may be some procedure related decrements associated with receiving inappropriate management as a result of a false positive finding (overtreatment) but no data could be identified which estimated this.

Table 4: Health related QoL values applied in the analysis

Health state	Quality of life value	Source
Baseline QoL	0.517	Arden 2017 – Average QoL value for patients with a poor outcome after primary surgery
QoL after revision surgery with good outcome	0.717	Arden 2017 - Average QoL value for patients with a good outcome after revision surgery
QoL after revision surgery with poor outcome	0.415	Arden 2017 - Average QoL value for patients with a poor outcome after revision surgery

Base case results are presented in Tables 5 and 6, for the overall population and the equivocal population respectively. Although the package of laboratory tests including Synovasure® provides an incremental health benefit compared to the current standard of care, its incremental cost is high, resulting in high incremental cost effectiveness ratios (ICERs) which do not reflect good value for money. The ICER is lower in the knee revisions population due to the increased prevalence of PJI infection in this population, but still too high to be considered good value for money. In the knee revision population that had equivocal results using standard tests, further testing with the Synovasure® point of care to inform treatment decision as opposed to no treating all such cases is associated with an ICER of approximately £16,300/QALY, indicating towards a potential cost-effective intervention in this sub-population.

Table 5: Base case results for the analysis considering the package of laboratory tests including Synovasure® (ICM 2018) in comparison to standard care (ICM 2013)

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Per patient	Incremental	Total	Incremental	
Hip revisions					
Standard care	£9,431	-	0.538	-	-
Synovasure®	£9,990	£559	0.542	0.004	£130,805
Knee revisions					
Standard care	£10,528	-	0.553	-	-
Synovasure®	£11,022	£494	0.561	0.007	£67,254
Hip and knee revisions combined					
Standard care	£9,841	-	0.544	-	-
Synovasure®	£10,375	£534	0.549	0.005	£98,653

Table 6: Base case results for the analysis considering the Synovasure® POCT in patients with equivocal results with standard tests

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Per patient (budget impact)	Incremental	Total	Incremental	
Hip revisions					
Standard care	£6,602	-	0.508	-	-
Synovasure®	£7,696	£1,094	0.531	0.023	£47,688
Knee revisions					
Standard care	£7,867	-	0.502	-	-
Synovasure®	£8,508	£641	0.542	0.039	£16,273
Hip and knee revisions combined					
Standard care	£7,074	-	0.544	-	-
Synovasure®	£7,999	£925	0.549	0.029	£31,795

Extensive deterministic ('one way') sensitivity analyses were conducted in the Health Technology Wales assessment. The analyses were replicated and extended for Scotland, and the scenarios that had a substantial impact on the ICER are reported in Table 7. Additional analyses capturing

variations in Scottish practice were also tested, although it appears these variations in relation to the subsequent management of patients did not have a substantial impact on results.

A lower prevalence of PJI in the target population undergoing testing seems to have an important impact on results, reducing the cost effectiveness of the Synovasure® bundle of tests. Extended analysis that takes into account the likely higher cost of testing in equivocal cases improves the value for money of the bundle, but not enough to change the overall conclusion of the analysis.

The diagnostic accuracy of comparator tests was expected to be an important consideration owing to the uncertainty around this in Scottish clinical practice. The impact on the ICER based on different levels of the sensitivity and specificity for the standard of care is presented in Table 8, where cost-effectiveness improves in all populations for modest decreases in the accuracy of the standard diagnostic tests. It is worth noting that specificity does not have an impact in the equivocal population which consists of patients with negative results on standard tests only. The associated independent accuracy thresholds of the standard tests for which the ICER drops below £20,000 were:

- Full THA population: 53.9% sensitivity; 94.9% specificity
- Full TKA population: 73.2% sensitivity; 95.8% specificity
- Equivocal THA population: 78.9% sensitivity; specificity not a driver of results

The interpretation of this is that the intervention is likely to be cost-effective if for example the accuracy of the comparator is below the ROC curve defined by the points: 53.9% sensitivity and 99.5% specificity in the TKA population; and 86.9% sensitivity and 94.9% specificity in the THA population.

Table 7: Deterministic sensitivity analysis results

Modelled scenario	ICER (cost per QALY)		
	Hip revisions	Knee revisions	Hip and knee revisions
Analysis considering the package of laboratory tests including Synovasure® (ICM 2018) in comparison to standard care (ICM 2013)			
Base case	£130,805	£67,254	£98,653
MSIS 2011 used as comparator	£68,885	£31,696	£50,070
PJI prevalence = 30%	£43,233	£43,016	£43,152

PJI prevalence = 20%	£76,148	£75,738	£75,995
PJI prevalence = 10%	£174,896	£173,906	£174,526
Comparator cost = £20	£132,823	£67,499	£99,774
Comparator cost = £100	£114,089	£56,598	£85,003
Comparator cost = £200	£90,672	£42,970	£66,539
Increased cost of standard testing in equivocal population = £988	£106,946	£51,715	£79,003
Decreased cost of Synovassure® bundle of tests = £300	£93,330	£44,517	£68,634
Subsequent management assumption - Lower proportion of one-stage revisions patients with positive result: 10% instead of 30%	£129,502	£62,173	£95,439
Subsequent management assumption - Higher proportion of no treatment in TKA patients with negative result: 30% vs 20%	-	£68,099	-
Poor outcome value after revision surgery applied for 6 months instead of 12 months	£256,911	£129,916	£192,661
Poor outcome value after revision surgery applied for 3 months instead of 12 months	£513,822	£259,831	£385,322
Analysis considering the Synovasure® lateral flow test in patients with equivocal results with standard tests			
Base case	£47,688	£16,273	£31,795
MSIS 2011 used as initial testing strategy	£20,858	£826	£10,723
PJI prevalence = 30%	£6,658	£5,760	£6,323
PJI prevalence = 20%	£22,505	£21,438	£22,107

PJI prevalence = 10%	£70,047	£68,474	£69,460
Synovasure® POCT cost = £495	£56,191	£21,221	£38,499
Subsequent management assumption - Lower proportion of one-stage revisions patients with positive result: 10% instead of 30%	£53,311	£18,586	£35,743
Subsequent management assumption - Higher proportion of no treatment in TKA patients with negative result: 30% vs 20%	-	£16,273	-
Poor outcome value after revision surgery applied for 6 months instead of 12 months	£95,377	£32,546	£63,589
Poor outcome value after revision surgery applied for 3 months instead of 12 months	£190,754	£65,092	£127,179

Table 8: ICER sensitivity to changes in the comparator accuracy

Full THA revision population						
Sens\Spec	0.9	0.92	0.94	0.96	0.98	1
0.7	Dominant	Dominant	Dominant	£8,185.13	£26,719.95	£45,254.76
0.75	Dominant	Dominant	Dominant	£13,378.76	£35,987.56	£58,596.36
0.8	Dominant	Dominant	Dominant	£21,498.74	£50,477.02	£79,455.31
0.85	Dominant	Dominant	Dominant	£35,988.45	£76,332.78	£116,677.10
0.9	Dominant	Dominant	£2,799.53	£69,180.01	£135,560.50	£201,940.99
0.95	Dominant	Dominant	£35,995.88	£223,167.09	£410,338.29	£597,509.50
1	£378,498.18	£150,149.31	Dominated	Dominated	Dominated	Dominated
Full TKA revision population						
Sens\Spec	0.9	0.92	0.94	0.96	0.98	1
0.7	Dominant	Dominant	Dominant	Dominant	£8,816.05	£18,280.62
0.75	Dominant	Dominant	Dominant	£2,591.65	£14,136.55	£25,681.45
0.8	Dominant	Dominant	Dominant	£7,657.48	£22,454.88	£37,252.27
0.85	Dominant	Dominant	Dominant	£16,697.22	£37,298.55	£57,899.87
0.9	Dominant	Dominant	£3,508.18	£37,404.54	£71,300.90	£105,197.26
0.95	Dominant	Dominant	£37,896.28	£133,472.91	£229,049.53	£324,626.15
1	£152,808.17	£36,204.69	Dominated	Dominated	Dominated	Dominated
Equivocal THA population						
Sens\Spec	0.9	0.92	0.94	0.96	0.98	1
0.7	£6,630.41	£6,630.41	£6,630.41	£6,630.41	£6,630.41	£6,630.41
0.75	£12,963.83	£12,963.83	£12,963.83	£12,963.83	£12,963.83	£12,963.83
0.8	£22,463.96	£22,463.96	£22,463.96	£22,463.96	£22,463.96	£22,463.96
0.85	£38,297.50	£38,297.50	£38,297.50	£38,297.50	£38,297.50	£38,297.50

0.9	£69,964.60	£69,964.60	£69,964.60	£69,964.60	£69,964.60	£69,964.60
0.95	£164,965.88	£164,965.88	£164,965.88	£164,965.88	£164,965.88	£164,965.88
1	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Equivocal TKA population						
Sens\Spec	0.9	0.92	0.94	0.96	0.98	1
0.7	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
0.75	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
0.8	£1,750.46	£1,750.46	£1,750.46	£1,750.46	£1,750.46	£1,750.46
0.85	£10,866.40	£10,866.40	£10,866.40	£10,866.40	£10,866.40	£10,866.40
0.9	£29,098.29	£29,098.29	£29,098.29	£29,098.29	£29,098.29	£29,098.29
0.95	£83,793.94	£83,793.94	£83,793.94	£83,793.94	£83,793.94	£83,793.94
1	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated

To assess the combined parameter uncertainty in the model, a probabilistic sensitivity analysis repeatedly tested model inputs values from distributions fitted around their mean value. The results of 10,000 simulations of model results are presented in Figures 4 and 5 for the full revision population and the equivocal population respectively, and the corresponding cost-effectiveness acceptability curves are plotted in Figures 6 and 7. At a willingness-to-pay threshold of £20,000/QALY, the probability of the proposed bundle of tests mapped on ICM 2018 criteria to be cost-effective compared to the ICM 2013 criteria was 0.03% in the combined population, 0.01% in the THA subpopulation, and 0.26% in the TKA subpopulation. At the same threshold, the probability of Synovasure® POCT to be cost-effective as an additional test in a population of patients with equivocal results following standard tests was estimated to be 34% in the combined equivocal population, 19% in the equivocal THA subpopulation, and 62% in the equivocal TKA population.

Figure 4: Plot of probabilistic sensitivity analysis simulations for the full revision population

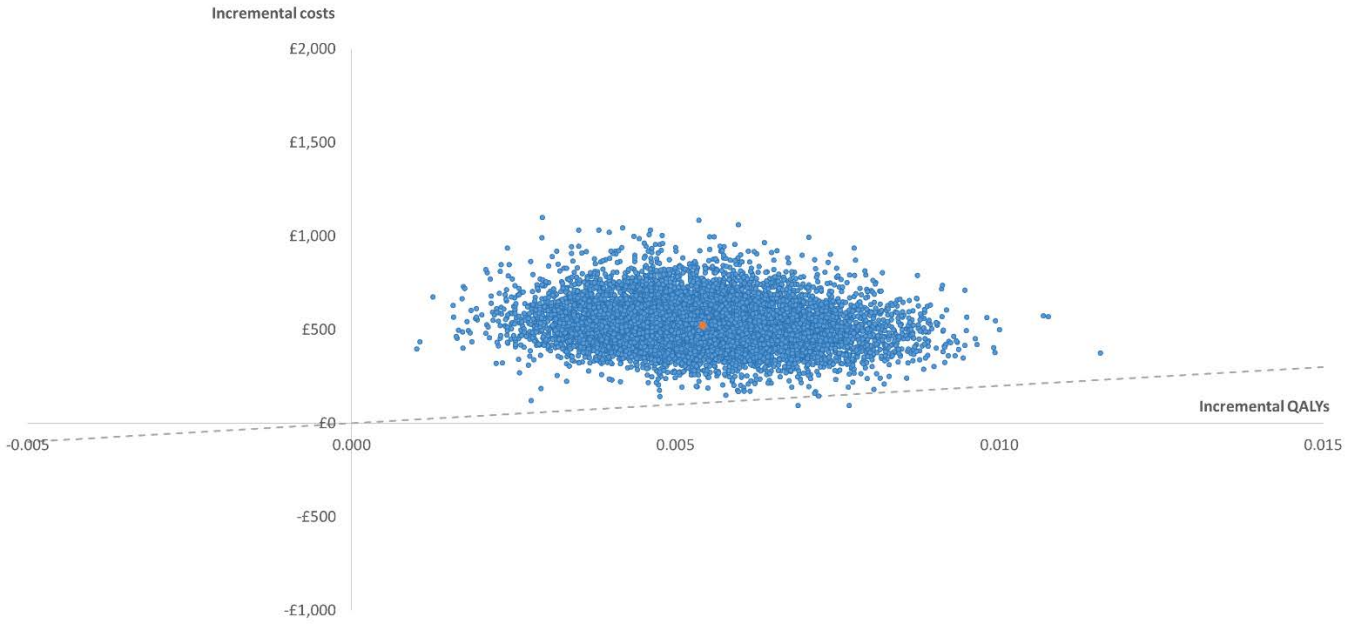


Figure 5: Plot of probabilistic sensitivity analysis simulations for the equivocal population

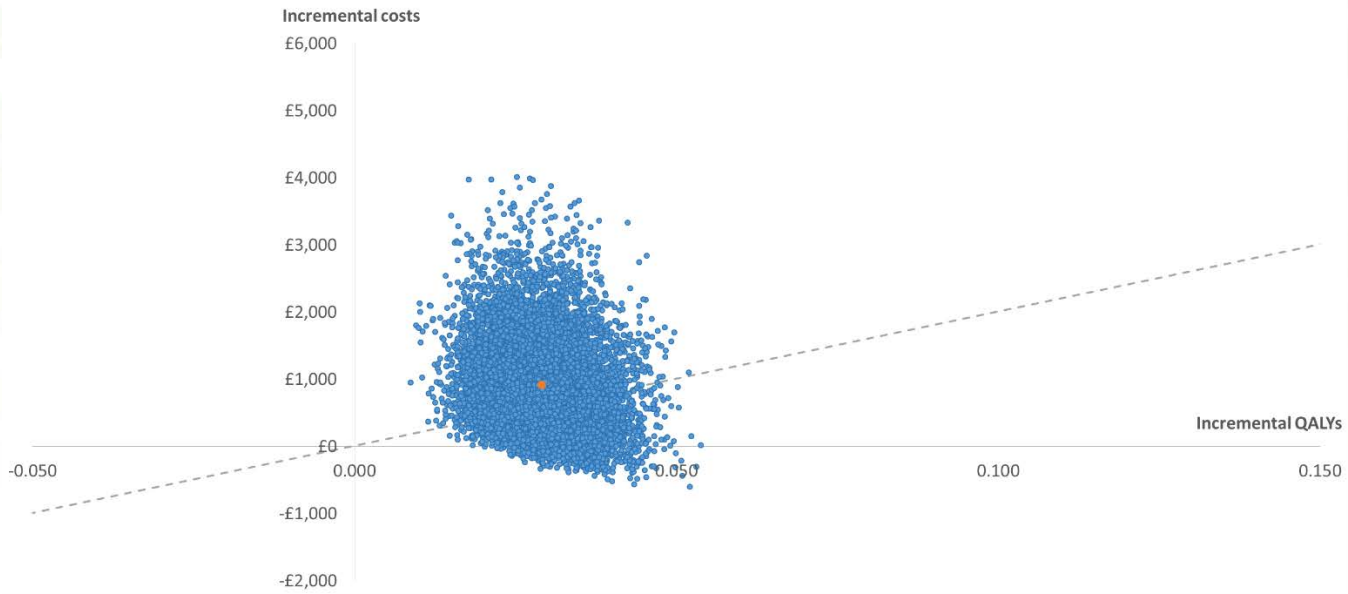


Figure 6: Cost-effectiveness acceptability curve full revision population

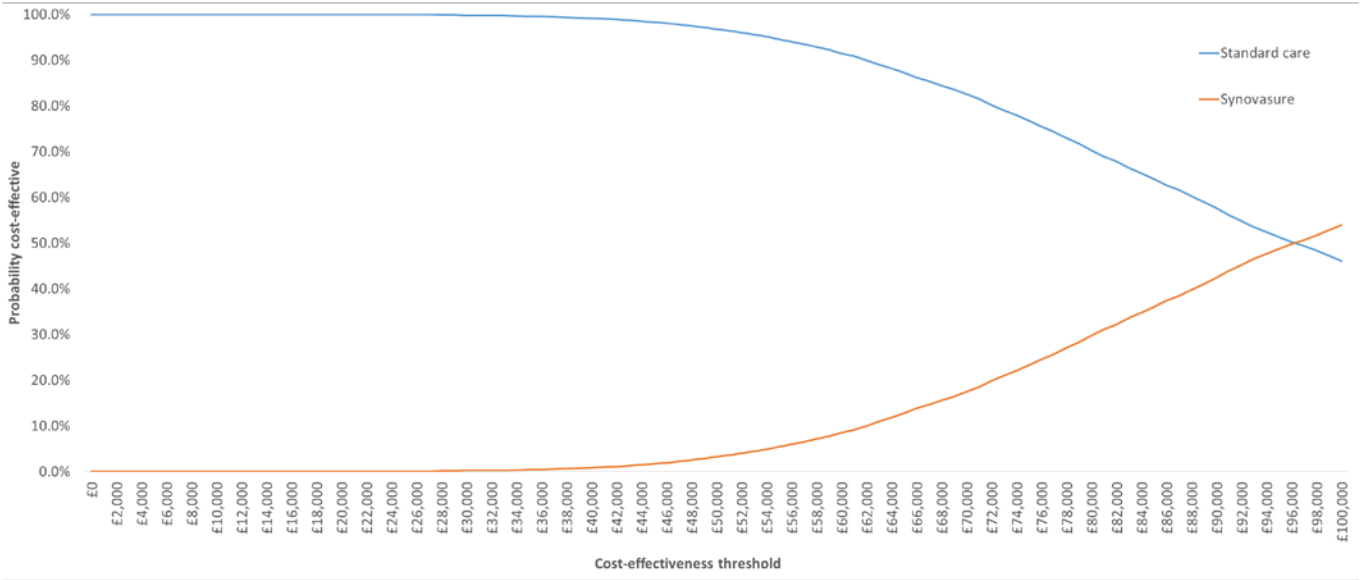
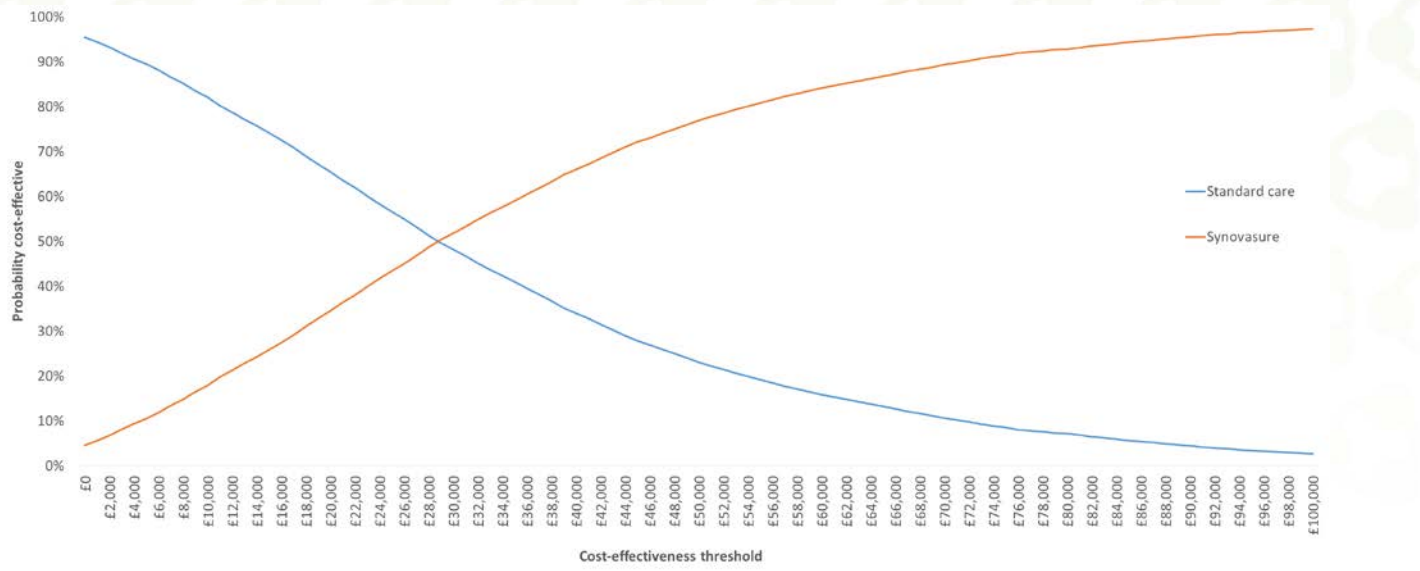


Figure 7: Cost-effectiveness acceptability curve equivocal population



Budget impact

The potential annual budget impact associated with the introduction of the two interventions in Scottish practice is presented in Tables 9 and 10.

Table 9: Potential budget impact of introducing the Synovasure® bundle of tests in the full population of patients undergoing THA and TKA revisions

Cost type	Standard of care (ICM 2013)			Synovasure® bundle (ICM 2018)			Difference		
	Hip revisions	Knee revisions	Combined	Hip revisions	Knee revisions	Combined	Hip revisions	Knee revisions	Combined
Test cost	£177,560.04	£105,805	£283,365	£425,809.62	£251,264	£677,074	£248,250	£145,459	£393,709
Revision costs for patients with PJI	£2,035,949	£2,064,840	£4,100,789	£1,984,706	£2,012,551	£3,997,257	-£51,243	-£52,289	-£103,532
Revision costs for patients without PJI	£5,271,379	£2,801,359	£8,072,738	£5,429,229	£2,883,896	£8,313,125	£157,850	£82,537	£240,387
Total	***£7,484,888***	***£4,972,004***	***£12,456,891***	***£7,839,744***	***£5,147,711***	***£12,987,455***	***£354,857***	***£175,707***	***£530,564***

Table 10: Potential budget impact of introducing the Synovasure® POCT in the population of patients undergoing THA and TKA revisions with equivocal results following standard tests

Cost type	Current practice (not treating equivocal cases)			Further testing with Synovasure® POCT			Difference		
	Hip revisions	Knee revisions	Combined	Hip revisions	Knee revisions	Combined	Hip revisions	Knee revisions	Combined
Test cost	£0	£0	£0	£46,620	£27,780	£74,400	£46,620	£27,780	£74,400
Revision costs for patients with PJI	£338,784	£346,906	£685,690	£267,508	£271,627	£539,135	-£71,276	-£75,279	-£146,555
Revision costs for patients without PJI	£687,926	£382,340	£1,070,266	£882,285	£488,961	£1,371,246	£194,359	£106,620	£300,980
Total	***£1,026,710***	***£729,247***	***£1,755,956***	***£1,196,413***	***£788,368***	***£1,984,781***	***£169,703***	***£59,121***	***£228,824***

Conclusion

The purpose of this review was to assess the clinical and cost effectiveness of a bundle of tests (mapped to proposed ICM 2018 criteria) in the diagnosis of PJI compared with current practice in NHSScotland. This is a reasonable question given the proposed laboratory at the Golden Jubilee National Hospital, but there is insufficient evidence to offer robust conclusions. The final ICM 2018 criteria have not been published, and there are no direct estimates for the diagnostic accuracy of the ICM 2018 criteria. Furthermore, there is no standardised protocol for the diagnosis of PJI in Scotland, which means that the diagnostic accuracy of current standard diagnostic strategies used in NHSScotland could not be established.

In an attempt to support decision-making around the diagnosis of PJI, approximations of diagnostic accuracy were used for both the proposed bundle and current diagnostic strategies used in NHSScotland.

Using the surrogate diagnostic accuracy data, an economic evaluation was undertaken which suggests the new bundle of tests is unlikely to be cost-effective compared to the ICM 2013 criteria in patients with suspected PJI having THA or TKA revision surgery. A sub-group analysis suggested that the use of Synovasure® POCT as a further investigation tool in the population having TKA revision surgery who had equivocal results based on preliminary standard tests is potentially cost-effective.

The 'real-life' diagnostic accuracy figures for current diagnostic strategies used in NHSScotland may be lower than the reported figures for ICM 2013, but this has been impossible to establish. It is also not clear the extent to which the diagnostic accuracy of the Parvizi *et al* criteria matches the diagnostic accuracy of the bundle of tests being offered by Zimmer Biomet. Clarity is also needed in relation to the patient group that the test bundle is intended for (all patients with PJI, or just those in whom diagnosis of PJI is less straight-forward). The results presented in this assessment relate to diagnostic accuracy only, and it has not been possible to assess the impact of the diagnostic bundle, compared with current standard diagnostic strategies used in NHSScotland, on clinical outcomes.

Identified research gaps

Further diagnostic accuracy studies are needed on the bundle of tests being offered by Zimmer Biomet, and how this compares with current standard practice. In addition, evaluations that assess the impact of the bundle of tests compared with standard practice on clinical outcomes are needed.

The ECRI review highlighted one ongoing trial:

Clinical Validation of CD Diagnostics Synovasure® PJI ELISA Test and Synovasure® PJI Lateral Flow Test for Detection of Periprosthetic Joint Infection in Synovial Fluid (NCT02868736). Planned enrolment: 3000.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

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SHTG Advice is produced to inform a decision at a particular point in time and therefore is not routinely updated. The Advice will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the SHTG Advice process see [weblink].

To propose a topic for SHTG consideration, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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Healthcare Improvement Scotland development team

- Lucian Gaianu, Senior Health Economist
- Joanna Kelly, Lead Health Services Researcher
- Paul Herbert, Information Scientist
- Members of the SHTG evidence review committee

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Appendix 1: abbreviations

Abbreviation	
ICM	International Consensus Meeting on Orthopaedic Infections
MSIS	Musculoskeletal Infection Society
POCT	Point of care
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty

Appendix 2: definitions of diagnostic accuracy terms

Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test, that is the number of true positive results divided by the total number with the disease[17].

Specificity: the probability that a person not having a disease will be correctly identified by a clinical test, that is the number of true negative results divided by the total number of those without the disease[17].

Positive likelihood ratio: the probability that a positive test result will occur in a person with the target condition divided by the probability of a positive test result occurring in a person without the disease, that is the sensitivity divided by one minus specificity[17].

Negative likelihood ratio: the probability that a negative test result will occur in a person with the target condition divided by the probability of a negative test result occurring in a person without the disease, that is the 1-sensitivity divided by specificity[17].

Receiver operating characteristic (ROC) curve: a graph used to assess the ability of a diagnostic test to discriminate between people with or without the target condition. For most diagnostic test data the ROC curve plots sensitivity against 1-specificity for different cut-off values[17]. Area under the ROC curve (AUROC) can be used to compare the diagnostic accuracy of tests when multiple ROC curves are plotted on the same graph.