Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Synovasure® Alpha Defensin Test for diagnosing Periprosthetic Joint Infection

Synovasure® point of care test

1. Purpose of the evidence appraisal report

The Evidence Appraisal Report is a rapid systematic literature search of published evidence and websites to identify the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Periprosthetic Joint Infection (PJI) 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 (Kapadia et al. 2016, Lenguerrand et al. 2017). Treatment commonly involves antibiotics plus either a single or two stage revision procedure. Infections are the most common cause (25%) of revisions after knee arthroplasty and account for some 15% of revision procedures after hip arthroplasty (Kapadia et al. 2016).

The National Joint Registry (www.njrcentre.org.uk/njrcentre/default.aspx) which collects details of hip and knee joint replacements in England, Wales and Northern Ireland reported 992,090 primary hip replacements procedures between 2003 and 2017, and 27,605 revisions during this time. Of this number of revisions, 3,872 (14%) were due to infection. There were 1,087,611 primary knee replacements during the same period and 28,717 revisions. The prosthesis time incidence rate (PTIR) of infections resulting in a revision was 0.93 per 1000 years of prosthesis time at risk.

PJI, especially when chronic, is difficult to diagnose because its symptoms resemble those of other arthroplasty failure causes such as implant malposition, aseptic loosening and instability. Management of PJI differs however from that of other causes of arthroplasty failure and therefore

accurately identifying the presence of a PJI is essential to guide subsequent care and choice of treatment pathway. Missing a diagnosis of PJI can lead to delayed intervention and a more complex re-operation at a later date, as well as increased risk of morbidity and mortality for the patient. On the other hand, incorrectly diagnosing PJI in a patient without infection will lead to more complex surgical management than is required (Wyatt et al. 2016). The cost of a revision procedure for infection has been estimated to be more than three times that of an aseptic revision (Kallala et al. 2015). There is however no agreed gold standard test for identifying PJI (Parvizi et al. 2014).

In the absence of a definitive test, the Musculoskeletal Infection Society (MSIS) convened a consensus group in 2013, to propose a standard set of criteria to assist with identifying PJI. These were subsequently widely adopted in practice and research (Parvizi et al. 2014), however the proposers of the criteria acknowledged that it was still possible for infection to be present without the criteria being met, and vice versa. Also, it was noted that not all hospitals may be able to run all the tests. The 2013 MSIS international consensus meeting (ICM) criteria comprise the following:

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

With the recognition of potential new biomarkers for diagnosing infection, and developments in knowledge in this area over recent years, a further set of criteria with a scoring system and diagnostic algorithms were developed using a more robust methodology than was employed in 2013(Parvizi et al. 2018). These included measurement of the novel synovial biomarker Alpha defensin. The new criteria were validated and were reported to achieve a higher sensitivity than the 2013 ICM criteria with no loss in specificity. The proposed criteria and algorithm were taken to an International Consensus Meeting in 2018, and were accepted with some minor modifications. These proposed new 2018 ICM criteria are presented below (Abdel Karim et al. 2019):

Table 1. ICM 2018 criteria for the diagnosis of PJI

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 or visualisation of the prosthesis				
Minor criteria	**Threshold**		**Score**	**Decision**
	Acute†	**Chronic**		
Serum CRP (mg/L) Or D-Dimer (µg/L)	100 Unknown	10 860	2	Combined preoperative and postoperative score: ≥6 infected 4-5 inconclusive* ≤ not infected
Elevated serum ESR (mm/hr)	No role	30	1	
Elevated synovial WBS (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	

*For patients with inconclusive minor criteria, operative criteria can also be used to fulfill definition for PJI
† Criteria was not validated on acute infections
‡ No role in suspected adverse local tissue reaction

3. Health technology

Alpha defensin is an antimicrobial peptide that disrupts the synthesis of bacterial cell walls. Activated neutrophils release alpha defensin in response to microbial pathogens. PJIs cause the release of alpha defensin directly into synovial fluid, a viscous fluid in synovial joints that reduces friction in joint cartilage. In response to PJI, levels of alpha defensin increase dramatically in synovial fluid; therefore, alpha defensin has been proposed as a synovial fluid biomarker for predicting PJI.

The Synovasure® alpha defensin test (Zimmer Biomet, Warsaw, IN, USA, which acquired CD Diagnostics in August 2015) is intended to identify elevated levels of alpha defensin in synovial fluid for aiding diagnosis of PJI. It is available in two test formats (both with Class 1 CE marks): a

laboratory-based ELISA (enzyme-linked immunosorbent assay) format; and a lateral flow immunochromatographic test format. The ELISA laboratory test's main components include specimen tubes, a specimen transport biohazard bag, a specimen box, and an instruction sheet. To perform the test, 0.5 mL of synovial fluid must be collected in the specimen tubes. The vials are submitted to CD Diagnostics laboratories for analysis, and results are typically available in 24 hours. The lateral flow test kit is composed of the test device, all necessary tubes and sample collection material, and a sample cup. The test is similar in size and function to a home pregnancy test. To perform the test, the physician adds the synovial fluid sample to a premeasured buffer and adds the two to the test. The sample migrates over a gold-conjugated antidefensin antibody and across a control and test line. If the levels of alpha defensin in the sample are greater than those of the threshold cutoff concentration, the control and test line on the test device change color, indicating a positive sample. If only the control line changes color, alpha defensin levels in the synovial fluid are not elevated. This test format is performed at the point of care and requires approximately 15 minutes to complete.

The product indication of both the laboratory test and the point of care state that the tests are indicated for pre-operative use as an adjunct to existing diagnostic tests particularly when these are equivocal, or confounded by pre-existing conditions. The point of care test can also be applied intra-operatively during a revision procedure to rapidly assist decision making.

4. Evidence search methods

The Population-Intervention-Comparator-Outcomes framework for the evidence appraisal (Appendix 1) was developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts. This was then shared with the ECRI Health Technology Assessment Information service (www.ecri.org) who were commissioned by Health Technology Wales to produce an ECRI Custom Product Brief on this technology.

ECRI searched PubMed, EMBASE, and selected web-based resources including clinicaltrials.gov for documents relevant to this topic and published between January 1, 2014, and January 4, 2019. Their search strategies included the following keywords: Synovasure®; synovial fluid α-defensin; synovial fluid alpha defensin. Further details of the search strategy are available on request from Health Technology Wales.

A large amount of literature was retrieved, therefore ECRI focused upon on the best available evidence. This was defined as systematic reviews (SRs), and diagnostic cohort studies not included in the SRs that assessed 100 or more patients, and which assessed the Synovasure® alpha defensin laboratory-based or lateral flow tests' clinical validity for identifying PJIs using MSIS PJI diagnostic criteria as the reference standard.

Following advice from clinical experts, a further search was undertaken by HTW to identify studies which assessed the use of the Synovasure® laboratory test in combination with other tests and the use of the Synovasure® lateral flow test in patients that have equivocal results with other tests.

The search for evidence on the use of Synovasure® in combination with other tests was used to assess the potential effectiveness of the laboratory service being proposed by the manufacturer. This system involves using the Synovasure® laboratory test in combination with all the other tests proposed in the 2018 ICM criteria.

The search for evidence on the use of the Synovasure® lateral flow test in patients that have equivocal results with standard tests reflects the manner in which Synovasure® is most likely to be used in current clinical practice (based on advice from clinical experts). Note that this search was restricted to the Synovasure® alpha defensin lateral flow test because the laboratory-based Synovasure® test is only being offered in conjunction with standard tests.

Another search was undertaken by HTW to identify UK and Wales specific epidemiological and contextual information. Patient safety and organisational issues were identified from the papers retrieved for the clinical utility and diagnostic accuracy sections of this report, the topic proposal

documentation received from Zimmer Biomet and expert advice; no specific searches were undertaken.

5. Clinical utility and diagnostic accuracy

5.1. Clinical utility

No studies were identified which examined the clinical utility of Synovasure® alpha defensin tests in improving patient outcomes. RCTs which compare standard-of-care PJI diagnostic methods alone to standard of care PJI diagnostic methods plus Synovasure® alpha defensin tests and report on patient-oriented outcomes (e.g. revision surgery rates, mortality, reoperation rates, quality of life) are needed to assess alpha defensin tests' clinical utility.

5.2. Diagnostic accuracy

5.2.1. Synovasure® test alone

The identified literature focussed upon diagnostic accuracy of the tests. ECRI included two SRs with meta-analyses with partial overlap (Marson et al. 2018, Suen et al. 2018). Both SRs were included because one was considered by ECRI to report the most complete and most recent set of studies assessing the Synovasure® alpha defensin laboratory-based test, and the other reported the most complete and most recent set of studies assessing the Synovasure® alpha defensin lateral flow test. ECRI also identified but excluded four SRs (Ahmad et al. 2018, Eriksson et al. 2018, Li et al. 2017, Xie et al. 2017) which overlapped with the included SRs but include fewer studies for the Synovasure® alpha defensin tests, or combined the findings for the two test formats. The included systematic reviews provide an update to evidence described within the Innovative Medical Technology Overview (IMTO) produced by the Scottish Health Technologies Group (SHTG 2017) for both the Synovasure® lab test and the lateral flow point-of-care test (POCT). For the former, the selected SRs exclude a study included within the SRs used within the IMTO as it did not use the MSIS criteria as a reference standard and did not report sensitivities and specificities of the test. Also several studies which were described in the IMTO but not included within the SRs are now brought together with the earlier evidence in a meta-analysis. Likewise, the new SRs combine the individual studies relating to the lateral flow point of care test, which were described individually in the IMTO, plus a more recently published study, in the form of a meta-analyses.

The first systematic review (Suen et al. 2018) (10 studies, n=759) assessed Synovasure's® alpha defensin lateral flow and laboratory tests' clinical validity for detecting PJIs, using MSIS PJI diagnostic criteria as the reference standard, in patients with possible PJIs. It reported sensitivity, specificity, and the Area Under the Curve (AUC). Seven studies assessed the Synovasure® alpha defensin laboratory test, and three studies assessed the lateral flow test. The second SR (Marson et al. 2018) (11 studies, n=1,063) assessed Synovasure's® alpha defensin lateral flow and laboratory tests' clinical validity for detecting PJIs using MSIS PJI diagnostic criteria as the reference standard in patients scheduled to undergo revision hip or knee arthroplasty, and reported on sensitivity and specificity. This SR included five studies that assessed the Synovasure® alpha defensin lab test, five studies that assessed the lateral flow test, and one study that assessed both tests.

Both systematic reviews rated the included studies to be at low risk of bias according to the QUADAS-2 tool for appraising diagnostic studies. There is however heterogeneity among the included studies for example in the tests carried out as part of the reference standard, the previous use or otherwise of antibiotics and the presence of concomitant inflammatory diseases. The Suen et al. (2018) review includes a study (Frangiamore 2015) which is excluded by Marson et al. (2018) as it relates to the use of the Synovasure® lab test in diagnosing PJI in shoulder joints only. Details of the two systematic reviews and their findings are summarised in Tables 2 and 3.

Both systematic reviews considered only the accuracy of alpha defensin compared with the MSIS critera as reference standard. They did not identify and report any studies where other tests available for diagnosing PJI were compared with the alpha defensin test, using the same reference standard.

A further diagnostic cohort study (Plate et al. 2018) meeting the inclusion critiera and not included in either systematic review was also included. This study of 109 cases assessed Synovasure® alpha defensin lateral flow test's clinical validity for detecting PJIs, using the MSIS PJI diagnostic criteria as the reference standard, in patients with suspected PJIs. It reported sensitivity, specificity, and positive/negative predictive values. Sensitivity of the test was found to be 90% (95% CI 68.3%-98.8%) and specificity 92.1% (84.5 to 96.8%). The authors concluded that a negative synovial alpha defensin lateral flow test can reliably rule out a PJI. However the test can result in false positives, for example when underlying non-infectious inflammatory disease is present. They propose that the test shows potential for application, but in conjunction with assessment of the MSIS criteria. It should be noted that this study was only available as an abstract. As such the study has not been subject to a peer review process and only limited details were available for review by ECRI.

5.2.2. Synovasure® test in combination with other tests

The further search conducted by HTW identified one relevant study which considered the use of Synovasure® in combination with other tests (Table 4). Parvizi 2018 used a retrospective analysis of patients undergoing hip and knee revisions to develop and externally validate a new diagnostic criteria for PJI. The external validation component was based on 222 infected and 200 aseptic revisions. The diagnostic accuracy of the new criteria was compared against older diagnostic criteria (MSIS 2011 and ICM 2013).

Parvizi 2018 reported that the new diagnostic criteria had a sensitivity of 97.7% (CI 94.7 to 99.3) and a specificity of 99.5% (CI 97.2 to 99.99). The ICM 2013 criteria had a sensitivity of 86.9% (CI 81.8 to 91.1) and a specificity of 99.5% (CI 97.3 to 99.99). The MSIS 2011 criteria had a sensitivity of 79.3% (CI 81.8 to 91.1) and a specificity of 99.5% (CI 97.3 to 99.99). Thus the new criteria is reported to be more sensitive without decreasing specificity.

However, it should be noted that the sensitivity and specificity values reported for the new diagnostic criteria exclude patients with inconclusive results. Patients with inconclusive results are reported separately to positive and negative results. Indeed identifying patients that are inconclusive is reported as a benefit of the new criteria as it is reflective of clinical practice. While this may be true, this approach potentially introduces a bias in favour of the new diagnostic criteria as patients that were particularly difficult to diagnose have only be been included in the accuracy estimates for the comparator criteria (MSIS 2011 and ICM 2013).

The accuracy estimates for the new diagnostic criteria could be modified to include patients with inconclusive results by making an assumption as to whether the patient would be treated as having a positive or negative result. Assuming that clinicians would want to adopt a conservative approach whereby they don't risk under-treatment then these inconclusive results may be called as positive. In which case, the sensitivity would increase to 97.7% while specificity would decrease to 97.5%. Alternatively, if the results were to be called as negative then sensitivity would decrease to 95.5% while specificity would increase to 99.5%.

While the evidence from Parvizi 2018 provides the best available evidence on the use of Synovasure® in combination with other tests, it does not match the latest diagnostic criteria (ICM 2018). The ICM 2018 criteria updates the criteria presented in Parvizi 2018 and changes the way that the Synovasure® test result is incorporated into the algorithm. In the original algorithm reported in Parvizi 2018 a positive result was considered as an additional factor that would contribute to the overall score. In the updated ICM 2018 algorithm, Synovasure®, leukocyte

esterase or synovial WBC are combined into one category with a positive result with any of the tests contributing to the overall score. Therefore the updated algorithm is likely to give less positive results overall and so, in comparison to the algorithm in Parvizi 2018, sensitivity may be lower and specificity may be higher.

5.2.3. Synovasure® test in patients with equivocal results after standard tests

The further search conducted by HTW identified one relevant study which considered the use of the Synovasure® lateral flow test in patients with equivocal results after standard tests (Table 5). De Saint Vincent 2018 considered the diagnostic accuracy of the alpha defensin test in microbiologically complex situations presenting diagnostic challenges. De Saint Vincent 2018 was a prospective non-randomised study of 42 cases in 39 patients in single referral centre in France. The MSIS PJI diagnostic criteria was used as the reference standard.

De Saint Vincent 2018 reported that the Synovasure® lateral flow test had a sensitivity of 88.9% and specificity of 90.6% (CIs not reported). The positive predictive value (PPV) was reported to be 77.8% and the negative predictive value was reported to be 94.4%.

The authors conclude that the use of Synovasure® should be considered in patients with suspected PJI when the diagnosis is in doubt and that the high NPV of the test suggests that it may be particularly useful for ruling out infection. They also suggest that, given the high cost of the test, the decision to use Synovasure® should be made on a case by case basis.

While the results demonstrate the potentially utility of using the Synovasure® lateral flow test in this patient group, further evidence is required to confirm these findings.

Table 2. Systematic review: Suen et al. (2018)

Included studies	PICO	Quality	Observations/notes
Review period: Studies published before 1st April 2017 Author (year) (n=no of patients) **Synovasure® lab test** Bonanzinga (2017) (n=156) Frangiamore (2015) (n=33) Frangiamore (2016) (n=102) Deirmengian (2014) (n=149) Deirmengian (2015) (n=95) Deirmengian (2015) (n=46) Bingham (2014) (n=59) **Synovasure® lateral flow POCT** Sude (2017) (n=30) Sigmund (2017) (n=49) Kasparek (2017) (n=40)	**Research question:** to compare the accuracy of the alpha defensin laboratory-based immunoassay and the lateral flow test kit for the diagnosis of PJI **Population**: clinical studies were included where there was uncertainty about whether or not patients had a PJI **Intervention**: Synovasure® alpha defensin lab test or Synovasure® alpha defensin lateral flow POCT **Comparator**: MSIS PJI diagnostic criteria **Primary outcome measure:** Diagnostic accuracy (sensitivity, specificity, area under the curve)	**Study design:** Systematic review with meta-analysis **Risk of bias: (Not assessed by ECRI)** All studies included within the review were judged by the review author to be at low risk of bias according to the QUADAS-2 appraisal of diagnostic studies tool.	Includes a study which comprises only shoulder joints (Frangiamore 2015)

Results	Authors' observations
Synovasure® lab test Sensitivity: 0.953 (95% confidence interval (CI) 0.87 to 0.984) Specificity: 0.965 (95% CI 0.943 to 0.979) Positive likelihood ratio (PLR) and were 34.86 (95% CI 19.34 to 62.85) Negative likelihood ratio (NLR) 0.02 (95% CI 0.00 to 0.11). **Synovasure® lateral flow POCT** Sensitivity 0.774 (95% CI 0.637 to 0.870) Specificity 0.913 (95% CI 0.828 to 0.958) PLR 8.675 (95% CI 4.229 to 17.794) NLR 0.248 (95% CI 0.147 to 0.418)	Pooled sensitivity and specificity of the lateral flow test was lower than the α-defensin laboratory immunoassay test. The lateral flow test has not been proven to be more accurate than other biomarkers such as the leukocyte esterase test. Although the lateral flow test is widely and readily available, care must be taken with its interpretation. Processing of samples for the α-defensin laboratory based immunoassay involves centrifugation before testing which removes cellular and particulate matter. The quick lateral flow test has a filter that removes cellular material. We suggest that these are not equivalent methods of processing and testing samples, and could be one reason for the reduced accuracy of the lateral flow test.

Table 3. Systematic review: Marson et al. (2018)

Included studies	PICO	Quality	Observations/notes
Review period: studies published before 17th January 2018 **Synovasure® lab test** (*included in meta-analysis) Bonanzinga (2017)* (n=156) Deirmengian (2014a)* (n=149) Frangiamore (2016)* (n=116) Gehrke (2018)* (n=195) Bingham (2014) (n=61) Deirmengian (2014b) (n=95) **Synovasure® POCT** Balato (2017) (n=51) Berger (2017) (n=121) Gehrke (2018) (n=195) Kasparek (2016) (n=40) Sigmund (2016) (n=19) Suda (2017) (n=30)	**Research question:** to evaluate the available literature and to calculate the pooled sensitivity and specificity for the different alpha defensin test systems that may be used to diagnose periprosthetic joint infection **Population**: Patients scheduled to undergo hip or knee revision arthroplasty **Intervention**: Synovasure® alpha defensin lab test Synovasure® alpha defensin lateral flow test POCT **Comparator**: MSIS PJI diagnostic criteria **Primary outcome measure:** Diagnostic accuracy (sensitivity, specificity)	**Study design:** Systematic review with meta-analysis **Risk of bias: (Not assessed by ECRI)** All studies included within the review were judged by the review author to be at low risk of bias according to the QUADAS-2 appraisal of diagnostic studies tool.	Provides a more comprehensive meta-analysis of the POCT test than the Suen 2018 review. Also, the lab test meta-analysis, while including fewer studies than Suen 2018 is restricted to studies adopting the same cut off point, so potentially less heterogeneous sample. Results however are similar to Suen et al.

Results	Authors' observations
Synovasure® lab test (based upon four studies with a threshold level of 5.2 mgl^{-1}) Sensitivity 0.95 (95% CI 0.91 to 0.98) Specificity was 0.97 (95% CI 0.95 to 0.98) PLR was 31 (95%CI 18 to 54) NLR was 0.05 (95%CI 0.03 to 0.1) **Synovasure® POCT** Sensitivity 0.85 (95% CI 0.74 to 0.92) Specificity 0.90 (95% CI 0.91 to 0.98) PLR was 17 (95%CI 6 to 48) NLR 0.2 (95%CI 0.1 to 0.4)	Laboratory-based alpha defensin testing remains a promising tool for diagnosing PJI. The lateral flow cassette has a significantly lower performance and pooled results are comparable to the leucocyte esterase test. Further studies are required before the widespread adoption of the lateral flow cassette alpha defensin test

Table 4. Parvizi 2018

Descriptive details	PICO	Observations/notes
US retrospective analysis used to develop and validate a new diagnostic algorithm for PJI. External validation was carried out in a different population to the development cohort, although drawn from the same 3 institutions. External validation cohort included 222 infected and 200 aseptic revisions.	**Research question:** to develop and evaluate a proposed diagnostic algorithm for PJIs **Population**: Retrospective cohort of patients that have undergone hip or knee revision arthroplasty **Intervention**: new diagnostic algorithm **Comparator**: Previous algorirthms: MSIS PJI diagnostic criteria (2011) ICM PJI diagnostic criteria (2013) **Primary outcome measure:** Diagnostic accuracy (sensitivity, specificity)	Provides the best available evidence on the diagnostic accuracy of the combinations of laboratory tests (including Synovasure®) being proposed by the manufacturer. However, the algorithm has since been updated and the changes will influence diagnostic accuracy. Diagnostic accuracy of the new algorithm excludes patients with inconclusive results. The diagnostic accuracy of the older criteria are likely to be the best approximation for the combinations of tests used in current practice.
Results		**Authors' observations**
MSIS PJI diagnostic criteria (2011) Sensitivity 0.793 (95% CI 0.734 to 0.844) Specificity was 0.995 (95% CI 0.973 to 0.9999) **ICM PJI diagnostic criteria (2013)** Sensitivity 0.869 (95% CI 0.818 to 0.911) Specificity 0.995 (95% CI 0.973 to 0.9999) **New algorithm** Sensitivity 0.977 (95% CI 0.947 to 0.993) Specificity 0.995 (95% CI 0.972 to 0.9999)		New algorithm is the first evidence based criteria for diagnosing PJI after hip and knee arthroplasty. The new definition can be used to guide clinicians and further improve the quality of research in this area.

Table 5. De Saint Vincent 2018

Descriptive details	PICO	Observations/notes
Single centre, France Prospective study, non-randomised. 42 cases in 39 patients between October 2017 to October 2019. 61.5% male and 38.5% female, aged 35 to 87 years.	**Research question:** to evaluate the diagnostic accuracy of alpha defensin test in microbiologically complex situations presenting diagnostic challenges **Population**: Patients in microbiologically complex situations presenting diagnostic challenges **Intervention**: Synovasure® alpha defensin lateral flow test **Comparator**: MSIS diagnostic criteria used as reference standard **Primary outcome measure:** Diagnostic accuracy (sensitivity, specificity)	Provides the only evidence specifically investigating the use of the Synovasure® lateral flow test in patients with equivocal results with other tests. However, one patient was included because of concomitant antibiotic use.
Results		**Authors' observations**
Synovasure® POCT Sensitivity 0.889 Specificity 0.906 PPV 0.778 NPV 0.944 Note confidence intervals were not reported.		Use of Synovasure® deserves consideration in patients with suspected PJI when the diagnosis is in doubt. The high NPV of the alpha defensin test suggests that the test may be particularly useful for ruling out infection in doubtful cases. Given the high cost of the test, decision to use Synovasure® should be made on a case by case basis.

5.3. Ongoing trials

Table 6. Ongoing trials

Study name/identifier/Location	Planned enrollment	Study Design/Stated Objectives/ Primary Endpoints	Estimated date of completion
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)/USA	3,000	Diagnostic cohort study to assess Synovasure's® lateral flow and laboratory test's clinical validity using the MSIS PJI diagnostic criteria as the reference standard. Primary outcome: "evaluation of laboratory results and physical findings required to diagnose PJI	May 2017 (last verified August 2016)
Investigation of a novel new test to aid revision surgery following hip or knee replacement infection (ISRCTN94873042)/UK	50	Prospective diagnostic cohort study of patients undergoing a second stage revision surgery following periprosthetic joint infection of either hip or knees. Aim is to find out if a negative alpha defensin test result is a good indicator of a successfully treated PJI	February 2019

6. Safety

The Synovasure® tests use fluid obtained during routine analysis, and do not require further invasive investigations. Thus it is not expected that they would introduce any additional safety risk to patients or staff. Searches of the MHRA adverse events database and FDA MAUDE database did not identify any safety concerns.

7. Economic evaluation

7.1. Existing economic evidence

No relevant health economic analyses were identified which considered the cost effectiveness of Synovasure® compared with the standard of care.

Health Technology Wales were aware of a resource impact analysis developed by the manufacturer as part of an Innovative Medical Technology Overview: Number 009/2015 by the Scottish Health Technologies Group (SHTG), which evaluated Synovasure® (SHTG 2017). The analysis suggested that using Synovasure® as an adjunct to standard of care may result in net cost savings in Scotland.

7.2. De novo economic evaluation

An economic analysis was undertaken to estimate the cost-effectiveness of Synovasure® to diagnose PJI in people that have undergone a total hip arthroplasty (THA) or total knee arthroplasty (TKA). Two separate scenarios were considered in the analysis:

1. Using the Synovasure® laboratory test as part of a package of laboratory tests in all patients with suspected PJI
2. Using the Synovasure® lateral flow test in patients that had equivocal results with standard tests

In the first scenario the package of laboratory tests including Synovasure® is compared against a package of laboratory tests without Synovasure® (reflecting standard care). The standard of care in Wales for clinical suspicion of PJI was advised by experts to include erythrocyte sedimentation rate (ESR) PJI, serum CRP, FBC, synovial fluid white blood cell count and microscopy and culture.

In the second scenario the Synovasure® lateral flow test is used in patients that had equivocal results with standard tests. The comparator for this analysis is treating patients based on the initial test results.

The analysis was developed in Microsoft Excel® and was conducted from the perspective of the Wales NHS and Personal Social Services (PSS). The model considered a one year horizon. The analysis measures effectiveness in terms of quality adjusted life years (QALYs) such that cost-effectiveness can be assessed against the threshold of £20,000 per QALY that is commonly applied in UK evaluations.

7.2.1. Population

The number of people undergoing THA and TKA revision in Wales were estimated from National Joint Registry data in combination with ONS data. Data from the National Joint Registry showed that there were 8,073 hip revisions and 6,289 knee revisions in 2017 in England, Wales, Northern Ireland and the Isle of Man. ONS population estimates (mid-year 2017) were used to estimate the proportion of this population that reside in Wales (5%). This weighting was applied to the total figure from the National Joint Registry to estimate the number of revisions in Wales. Thus the number of hip revisions in Wales in 2017 was estimated to be 416 and the number of knee revisions was estimated to be 324. PJI prevalence in the population undergoing revision surgery was estimated using data from the National Joint Registry. It was reported that there were 106,200 hip revision procedures between 2003 and 2017. Of these, 13,885 were due to infection giving a prevalence estimate of 13%. It was reported that there were 68,148 knee revision procedures between 2003 and 2017. Of these, 15,311 were due to infection giving a prevalence estimate of 22%.The total numbers of revisions resulting from PJI in Wales were thus estimated as 54 and 74 for THA and TKA, respectively.

The proportion of patients with equivocal results from standard tests was estimated based on assumptions from clinical experts. It was estimated that around 20% of the population tested for

PJI would have equivocal results with standard tests making them difficult to diagnose. This amounts to 83 hip revisions and 65 knee revisions.

The prevalence of PJI was estimated for this group based on the assumption that patients with equivocal findings would be a subset of patients with negative tests after the initial set of standard tests. That is, the equivocal population are those that are technically negative (according to criteria) but with some reason for continuing suspicion of PJI (such as being very close to being positive or discordant results with different tests). It was then further assumed that all false negative results with the initial set of standard tests would fall within this population. The remainder of the population was therefore comprised of true negative results after the initial test. Using this set of assumptions in combination with the diagnostic accuracy data for standard tests (described in subsequent sections), gives PJI prevalence estimates of 9% in the population undergoing hip revisions and 15% in the population undergoing knee revisions.

7.2.2. Clinical input data

The key clinical data for the economic analysis was the diagnostic accuracy of strategies under consideration (presented in table 7). The diagnostic accuracy of the package of tests including the Synovasure® laboratory test was based on values reported in Parvizi 2018 for the new diagnostic algorithm. The diagnostic accuracy of the package of tests reflecting standard practice was based on values reported for the older algorithms reported in Parvizi 2018. In the base case it was assumed that the ICM 2013 provides the best approximation to standard care but data for the MSIS 2011 are applied in a sensitivity analysis. As discussed previously, the values for the new diagnostic algorithm did not include those patients with uncertain results. In order to include patients with uncertain results, it was assumed that they would be treated as having a positive result. Therefore the base case analysis uses a sensitivity of 97.7% and specificity of 97.5%. An alternative scenario where it was assumed that they would be treated as having a negative result was explored in sensitivity analysis.

It should be noted that while the values from Parvizi 2018 represent the closest approximation to the diagnostic accuracy of the intervention and comparator strategies, neither are perfect matches. The diagnostic algorithm originally proposed in Parvizi 2018 was subsequently amended and these amendments will have implications for diagnostic accuracy. It is difficult to know the impact of all the amendments but it is likely that the changes to the way that the Synovasure® component is incorporated would improve specificity at the expense of some sensitivity. Similarly the extent to which the ICM 2013 criteria represents current clinical practice is not known with certainty. There is likely to be variation in current clinical practice and in some instances practice may not be up to the standard of the ICM 2013 criteria. However, the ICM 2013 criteria was considered to the best approximation available as there is very little evidence on the accuracy of test combinations.

In order to explore the uncertainty around diagnostic accuracy estimates, numerous sensitivity analyses were conducted. This includes scenarios where alternative assumptions were made about the tests that may be employed in current practice. The diagnostic accuracy estimates in these scenarios were estimated by using individual test accuracy estimates and making some assumptions about how tests are combined.

Table 7. Diagnostic accuracy estimates applied in the analysis

Test	Sensitivity	Specificity	Source
Package of tests reflecting standard care	0.869	0.995	Parvizi 2018
Package of tests including Synovasure®	0.977	0.975	Parvizi 2018 – modified to include

Test	Sensitivity	Specificity	Source
			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

7.2.3. Costs

Table 8 lists the test costs that were applied in the analysis. The cost of the Synovasure® POCT and the cost of a suite of tests including the Synovasure® laboratory test were provided by the manufacturer. The cost of the lateral flow POCT kit was £495 per test or £300 if purchased in a pack of 5 tests. The base case analysis assumes that the tests would be bought in packs of 5 and therefore the £300 value has been applied. These test costs match those used in the analysis conducted as part of the SHTG IMTO on Synovasure® (SHTG 2017). The cost of the suite of laboratory tests including the Synovasure® laboratory test was quoted by the manufacturer as being £450.

The costs of the laboratory tests for PJI which comprise the standard of care in Wales (ESR PJI, serum CRP, FBC, synovial fluid white blood cell count and microscopy and culture) were provided by experts. However, it should be noted that the cost of a microbiology investigation for PJI includes synovial PMN, which was not considered by experts to be the standard of care in Wales. The cost associated with staff time was estimated from the PSSRU. The total cost estimate for standard care was estimated to be £38.61.

Table 8. Test costs

Test		Cost	Notes	Source
Point of care test				
Synovasure® lateral flow POCT		£300	Discounted price when Synovasure® is purchased in a pack of 5; cost is £495 when purchased individually	Zimmer Biomet
Laboratory tests				
Suite of tests offered by manufacturer	Synovasure® laboratory test, microscopy and culture, serum CRP, synovial WBC, leukocyte esterase and synovial PMN	£450	Estimated price quoted in January 2019	Zimmer Biomet
Standard of care	ESR	£2.40		Obtained through correspondence with experts
	Serum CRP	£3.15		Obtained through correspondence with experts
	FBC	£4.15		Obtained through correspondence with experts

Test		Cost	Notes	Source
	Staff time (ESR, CRP, FBC)	£6.56	Hospital-based scientific and professional staff 2017/2018. The cost per hour for a radiographer was used, as a conservative assumption. A simple average of bands 4-7 was taken, based on expert advice. Estimated resource use 3 minutes for each of ESR, CRP and FBC, based on duration of CRP test when undertaken by a general practitioner used in a published study[a].	PSSRU[b]
	Microbiology investigation for synovial fluid including microscopy, culture, white cell count and synovial PMN %	£22.35	Cost includes staff time	Obtained through correspondence with experts
	TOTAL	£38.61		

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FBC: full blood count; PJI: periprosthetic joint infection; POCT: point-of-care test; PMN: polymorphonnuclear neutrophils; WBC: white blood cell count

[a] Hunter 2015

[b] Curtis 2018

It was assumed that the results of the diagnostic tests would be used to guide subsequent management decisions. The proportions of patients undergoing each type of management were estimated based on advice from clinical experts and are shown in table 9. It was assumed that 60% of patients with positive results for PJI would have a two stage revision while 30% would have a one stage revision and 10% would have a debridement, antibiotics and implant retention (DAIR) procedure. In patients with negative results for PJI, it was assumed that the management proportions would vary depending upon whether it was the overall population or the population that have equivocal results after the initial test. In the overall population, it was assumed that 80% would have a one stage revision while 20% have no treatment. In the population with equivocal results after the initial test it was assumed that 50% would have a one stage approach while 50% have no treatment. 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.

Table 9. Subsequent management proportions

Management approach	Proportion	
	Overall population	Patients with equivocal results after initial test
Positive result for PJI		
Two stage	60%	60%
One stage	30%	30%

DAIR	10%	10%
Negative result for PJI		
One stage	80%	50%
No treatment	20%	50%

The table above fully describes the management approaches received in patients with true positive, false positive and true negative results for PJI. However, a further assumption is required in patients with false negative results. These patients are assumed to be initially treated erroneously as negative patients. It is then assumed that these patients would receive the appropriate treatment associated with positive results. However, some of the patients with negative results that were initially treated with a one stage resection were assumed to be adequately treated by their initial management. This proportion was assumed to be the same as the proportion of patients with positive results that would be adequately treated by a one stage resection (30%).

The cost of revision surgery and DAIR were obtained from NHS Reference Costs 2017/2018 and are listed in table 10 (NHS Improvement 2018). The cost of a single stage revision varies depending on whether the procedure is carried out in a patient with or without an infection (£14,571 and £9,683, respectively). 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. Thus, the total cost of a two stage revision was estimated to be (£24,254). The cost of the DAIR procedure varies depending on whether the procedure is being performed in the hip or the knee (£5,081 and £3,188).

Table 10. UK NHS costs of revision of total hip and knee arthroplasty

Intervention	Cost	Reference
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
DAIR for hip	£5,081	NHS Reference Costs 2017/18 - HN14
DAIR for knee	£3,188	NHS Reference Costs 2017/18 - HN24

PJI: periprosthetic joint infection; THA: total hip arthroplasty; THK: total knee arthroplasty; DAIR: debridement, antibiotics and implant retention

7.2.4. Health related quality of life

The model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining life year estimates with quality of life (QoL) values associated with being in a particular health state. The analysis did not consider differences in survival and therefore QALY differences were driven entirely by differences in QoL.

QoL values were sourced from Arden 2017, a health technology appraisal of a tool to predict outcome and failure after lower limb arthroplasty. QoL values were estimated as part of the economic evaluation conducted for the appraisal. EQ-5D values for patients undergoing primary and revision procedures were sourced from the Hospital Episode Statistics (HES) patient reported outcome measures (PROMS) dataset. The analysis reported different QoL scores for patients with good and poor outcomes following the procedure. Patients with good outcomes were described as being mostly free from pain and satisfied with surgery results while pain and functional limitations persist in patients with poor outcomes who are generally dissatisfied with surgery results.

The analysis used separate QoL estimates for different age groups and genders. For the purpose of this analysis, a crude average across age and genders has been estimated. Baseline quality of life was assumed to be equal to the value associated with poor outcomes after the initial surgery (0.517). This value 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 (0.717). This is based on the assumptions that their health state would improve following appropriate management of PJI. 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 (0.415). This is based on the assumptions that their health state would deteriorate as a result of receiving inappropriate management for PJI (undertreatment). It is assumed that these patients would subsequently receive the appropriate treatment when it is realised that the patient does have PJI. However, 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 (0.517) 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 11. Health related quality of life 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

7.2.5. Results

Base case results

The results of the base case analyses are presented in table 12 and table 13. Table 12 shows the results of the analysis considering the package of laboratory tests including Synovasure® in comparison to standard care. It can be seen that the package of laboratory tests including

Synovasure® was found to be more effective and more costly than standard care when used for hip revisions, knee revisions or the combined population. The incremental cost-effectiveness ratio (ICER) result was found to be above £20,000 per QALY in all populations and therefore the package of laboratory tests including Synovasure® would not be considered cost-effective. However it is notable that the ICER result is much lower in the knee revision population than the hip revision population. This is a result of the higher reported prevalence of PJIs in the knee revision population.

Table 13 shows the results of the analysis considering the use of the Synovasure® lateral flow test in patients with equivocal results with standard tests. It can be seen that the use of the Synovasure® lateral flow test was found to be more effective and more costly than standard care when used for hip revisions, knee revisions or the combined population. The ICER result was found to be above £20,000 per QALY in the hip revision population but below this threshold in the knee revision population. Therefore the use of the Synovasure® lateral flow test would be considered cost-effective when used for knee revisions but not for hip revisions. This is a result of the higher reported prevalence of PJIs in the knee revision population. When looking at the overall population (hip and knee revisions combined), the ICER result was found to be above £20,000 per QALY and therefore not cost-effective.

Table 12. Base case results for the analysis considering the package of laboratory tests including Synovasure® in comparison to standard care

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Hip revisions					
Standard care	£9,446	-	0.538	-	-
Synovasure®	£9,998	£552	0.542	0.004	£129,326
Knee revisions					
Standard care	£10,616	-	0.553	-	-
Synovasure®	£11,037	£421	0.561	0.007	£57,388
Hip and knee revisions					
Standard care	£9,958	-	0.545	-	-
Synovasure®	£10,453	£495	0.550	0.006	£88,148

Table 13. Base case results for the analysis considering the Synovasure® lateral flow test in patients with equivocal results with standard tests

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Hip revisions					
Standard care	£6,602	-	0.508	-	-
Synovasure®	£7,696	£1,094	0.531	0.023	£47,688
Knee revisions					

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Standard care	£7,867	-	0.502	-	-
Synovasure®	£8,508	£641	0.542	0.039	£16,273
Hip and knee revisions					
Standard care	£7,156	-	0.506	-	-
Synovasure®	£8,051	£896	-0.536	0.030	£29,706

Deterministic sensitivity analysis

A series of deterministic sensitivity analyses were conducted, whereby an input parameter was changed, the model was re-run and the new cost-effectiveness result was recorded. This form of analysis is a useful way of exploring alternative assumptions and determining the key drivers of the model results. The results of the deterministic sensitivity analysis are presented in table 14 and table 15.

The conclusion of the analysis was not found to change in most of the modelled scenarios considering the package of laboratory tests including Synovasure® in comparison to standard care. The notable exceptions were the scenarios in which the diagnostic accuracy of standard care was reduced. In a scenario where sensitivity and specificity values used in the economic analysis in the SHTG IMTO on Synovasure® were applied, the use of the laboratory tests including Synovasure® was found to be dominant (i.e. more effective and less costly). Note that it is primarily the change to the specificity value that results in the dramatic change in the result. In another scenario where the diagnostic accuracy of standard care was estimated assuming ESR and CRP followed by culture would be used, the Synovasure® laboratory service was found to be cost-effective when used in the overall and knee population but not in the hip population.

The conclusion of the analysis considering the Synovasure® lateral flow test in patients with equivocal results after standard tests was found to change in several modelled scenarios. The Synovasure® lateral flow test was no longer considered to be cost-effective for knee revisions in scenarios with less favourable assumptions, including lower PJI prevalence, higher Synovasure® cost and reducing the QoL benefit associated with accurate diagnosis. Conversely, the Synovasure® lateral flow test became cost-effective for hip revisions or in the overall population in scenarios with more favourable assumptions, including higher PJI prevalence or worse diagnostic accuracy with the initial test.

Table 14. Deterministic sensitivity analysis results for the analysis considering the package of laboratory tests including Synovasure® in comparison to standard care

Modelled scenario	ICER (cost per QALY)		
	Hip revisions	Knee revisions	Hip and knee revisions
Base case	**£129,326**	**£57,388**	**£88,148**
MSIS 2011 used as comparator	£69,106	£24,073	£43,329
Diagnostic accuracy of comparator based on economic	Dominant	Dominant	Dominant

Modelled scenario	ICER (cost per QALY)		
	Hip revisions	Knee revisions	Hip and knee revisions
analysis in IMTO (sensitivity = 85%, specificity = 81%)			
Diagnostic accuracy of comparator estimated based on ESR and CRP followed by culture (sensitivity = 69%, specificity = 98%)	£25,403	£975	£11,848
Diagnostic accuracy of comparator based on protocol from South Tees – assumes ESR and CRP followed by synovial aspiration culture and WCC (sensitivity = 84%, specificity = 98%)	£72,364	£27,121	£46,467
Parvizi data modified assuming that patients with inconclusive results would be treated as negatives	£109,145	£47,847	£74,057
Sensitivity of laboratory test package including Synovasure® = 99%	£113,583	£49,047	£76,642
Sensitivity of laboratory test package including Synovasure® = 90%	£512,935	£260,620	£368,508
Sensitivity of laboratory test package including Synovasure® = 85%	Dominated	Dominated	Dominated
Specificty of laboratory test package including Synovasure® = 99%	£93,647	£39,168	£62,463
Specificty of laboratory test package including Synovasure® = 90%	£307,724	£148,484	£216,574
Specificty of laboratory test package including Synovasure® = 85%	£426,655	£209,215	£302,191
PJI prevalence = 30%	£41,683	£31,086	£37,043
PJI prevalence = 20%	£72,622	£61,832	£67,897
PJI prevalence = 10%	£165,441	£154,070	£160,462
Standard care test costs = £100	£114,960	£49,027	£77,220
Standard care test costs = £200	£91,543	£35,400	£59,406

Modelled scenario	ICER (cost per QALY)		
	Hip revisions	Knee revisions	Hip and knee revisions
Subsequent management assumption – all positives treated with two stage revision	£137,891	£65,298	£96,338
Subsequent management assumption – all negatives treated with one stage revision	£121,789	£51,702	£81,671
Poor outcome value after revision surgery applied for 3 months	£487,156	£206,810	£326,683
Poor outcome value after revision surgery applied for 6 months	£243,578	£103,405	£163,342

Table 15. Deterministic sensitivity analysis results for the analysis considering the Synovasure® lateral flow test in patients with equivocal results with standard tests

Modelled scenario	ICER (cost per QALY)		
	Hip revisions	Knee revisions	Hip and knee revisions
Base case	**£47,688**	**£16,273**	**£29,706**
MSIS 2011 used as initial test	£20,812	£799	£9,356
Diagnostic accuracy of comparator based on economic analysis in IMTO (sensitivity = 85%, specificity = 81%)	£38,298	£10,866	£22,596
Diagnostic accuracy of comparator estimated based on ESR and CRP followed by culture (sensitivity = 69%, specificity = 98%)	£5,313	Dominant	Dominant
Diagnostic accuracy of comparator based on protocol from South Tees – assumes ESR and CRP followed by synovial aspiration culture and WCC (sensitivity = 84%, specificity = 98%)	£35,241	£9,106	£20,281
Synovasure® POCT cost = £495	£56,191	£21,221	£36,174
Synovasure® POCT sensitivity = 85%, specificity = 90% (Marson)	£54,586	£19,997	£34,787
Synovasure® POCT sensitivity = 74%, specificity = 91% (Suen)	£58,675	£22,282	£37,843
PJI prevalence = 30%	£6,658	£5,760	£6,265
PJI prevalence = 20%	£22,505	£21,438	£22,038

Modelled scenario	ICER (cost per QALY)		
	Hip revisions	Knee revisions	Hip and knee revisions
PJI prevalence = 10%	£70,047	£68,474	£69,358
Subsequent management assumption – all positives treated with two stage revision	£69,636	£30,991	£47,515
Subsequent management assumption – all negatives treated with one stage revision	£25,604	£2,463	£12,358
Poor outcome value after revision surgery applied for 3 months	£190,754	£65,092	£118,824
Poor outcome value after revision surgery applied for 6 months	£95,377	£32,546	£59,412

Threshold analysis

The results of the deterministic sensitivity analysis indicated that the diagnostic accuracy of standard care is a key driver of the results of the analysis. For this reason, a threshold analysis was conducted to determine the sensitivity and specificity required for the package of laboratory tests including Synovasure® to be cost-effective in comparison to standard care. Similarly a threshold analysis was conducted to determine the sensitivity required for the Synovasure® lateral flow test to be cost-effective in patients with equivocal results after standard tests (no threshold analysis was conducted for specificity as it was not influential in this scenario).

The results for the threshold analysis considering the package of laboratory tests including synovasure® in comparison to standard care showed that a sensitivity value of 68.4% was required for the laboratory system with Synovasure® to be cost-effective. When considering the indicated populations separately it was found that a sensitivity value of 54.0% and 77.5% was required for the laboratory system with Synovasure® to be cost-effective for the hip and knee populations, respectively. When considering specificity it was found that a specificity value of 95.5% was required for the laboratory system with Synovasure® to be cost-effective. When considering the indicated populations separately it was found that a specificity value of 94.9% and 96.4% was required for the laboratory system with Synovasure® to be cost-effective for the hip and knee populations, respectively.

The results for the threshold analysis considering the Synovasure® lateral flow test in patients with equivocal results after standard tests showed that a sensitivity value of 84.1% was required for the Synovasure® lateral flow test to be cost-effective. When considering the indicated populations separately it was found that a sensitivity value of 78.9% and 88.0% was required for the Synovasure® lateral flow test to be cost-effective to be cost-effective for the hip and knee populations, respectively.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000

runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

The figures below show the ICER scatterplots and CEAC for the analysis considering the package of laboratory tests including Synovasure® in comparison to standard care. The results are shown for the combined hip and knee population. From the ICER scatterplot, it can be seen that the vast majority of results reside in the north east quadrant indicating that the laboratory system with Synovasure® is more effective and more costly than standard care in most modelled scenarios. The CEAC shows that the probability of the laboratory system with Synovasure® being cost-effective increases as the cost-effectiveness threshold increases. At a threshold of £20,000 per QALY, the laboratory system with Synovasure® was found to have a 0% probability of being cost-effective while standard care had a 100% probability of being cost-effective. When considering the hip and knee populations separately the probability of the laboratory system with Synovasure® being cost-effective was 0% and 2%, respectively.

Figure 1. ICER scatterplot for analysis considering the package of laboratory tests including synovasure® in comparison to standard care

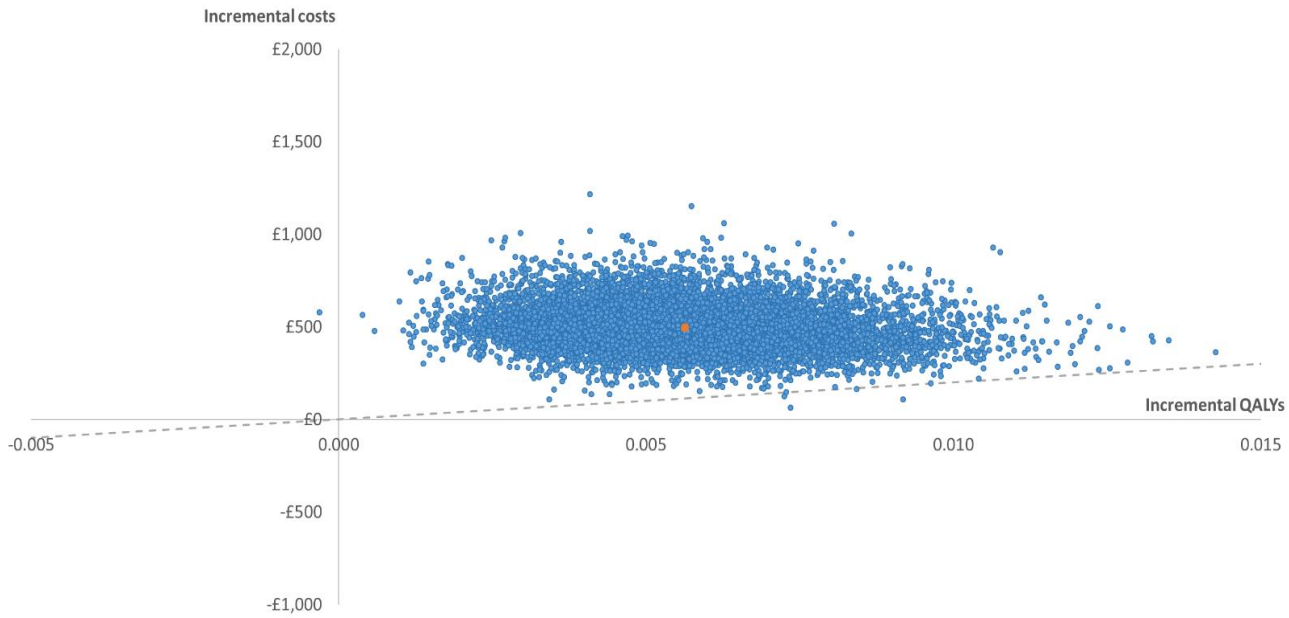
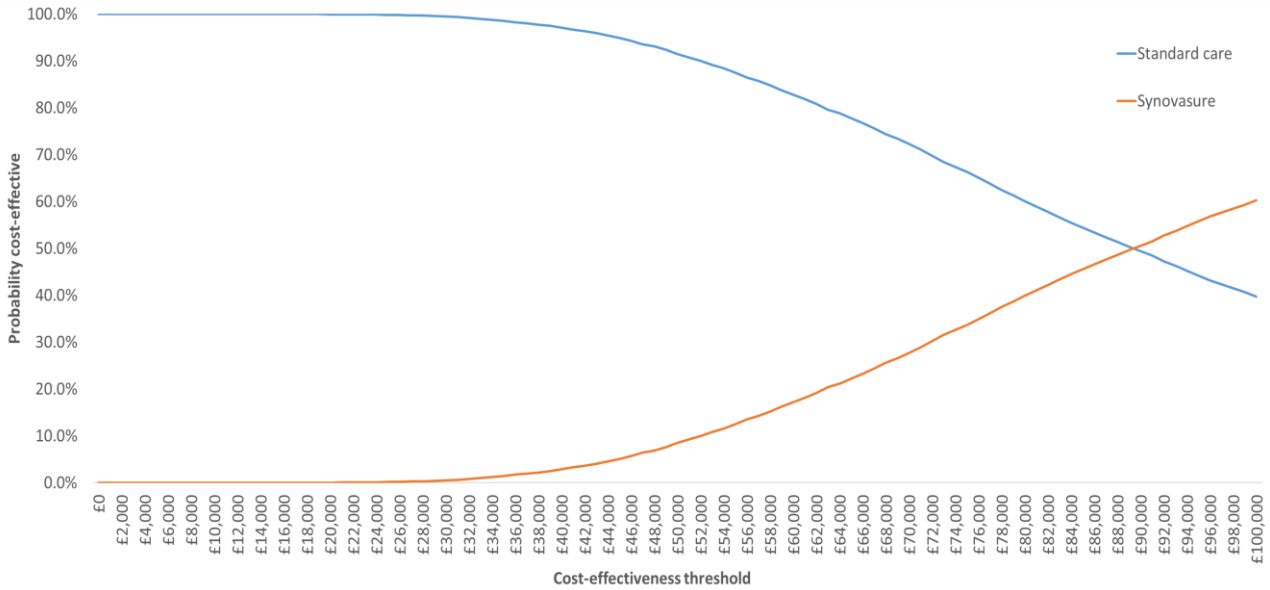


Figure 2. CEAC for analysis considering the package of laboratory tests including synovasure® in comparison to standard care



The figures below show the ICER scatterplots and CEAC for the analysis considering the Synovasure® lateral flow test in patients with equivocal results with standard tests. The results are shown for the combined hip and knee population. From the ICER scatterplot, it can be seen that the vast majority of results reside in the north east quadrant indicating that the Synovasure® lateral flow test is more effective and more costly than standard care in most modelled scenarios. The CEAC shows that the probability of the Synovasure® lateral flow test being cost-effective increases as the cost-effectiveness threshold increases. At a threshold of £20,000 per QALY, the Synovasure® lateral flow test was found to have a 38% probability of being cost-effective while standard care had a 62% probability of being cost-effective. When considering the hip and knee populations separately the probability of the Synovasure® lateral flow test being cost-effective was 18% and 62%, respectively.

Figure 3. ICER scatterplot for analysis considering the Synovasure® lateral flow test in patients with equivocal results with standard tests

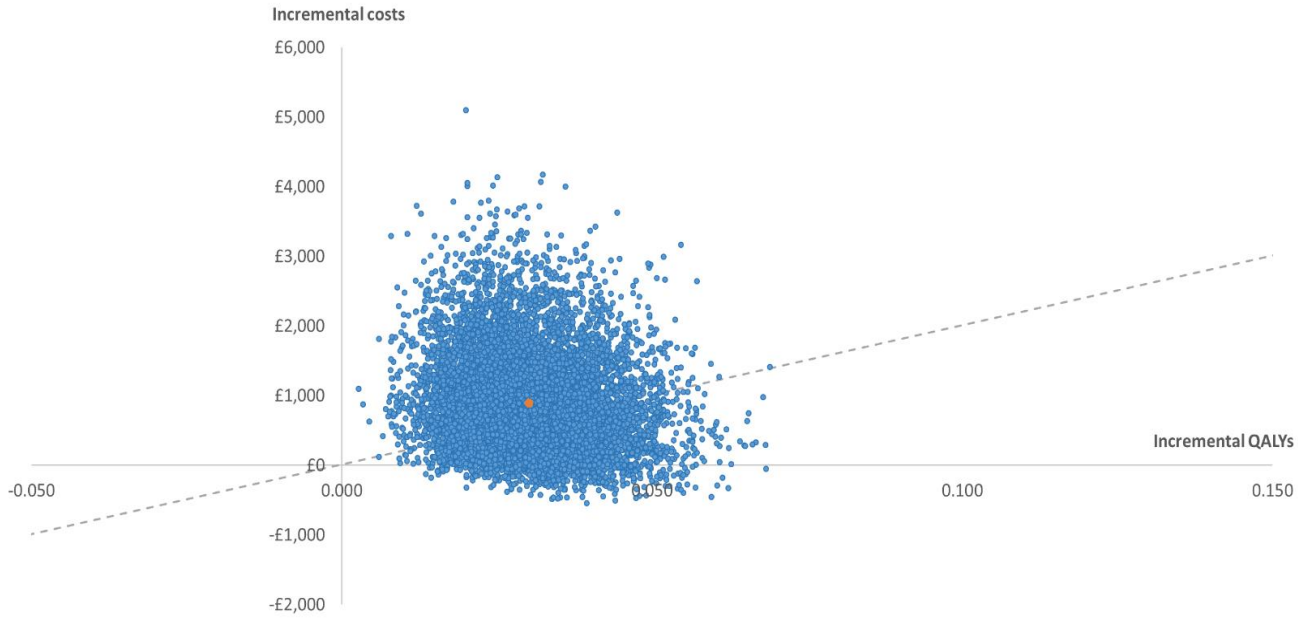
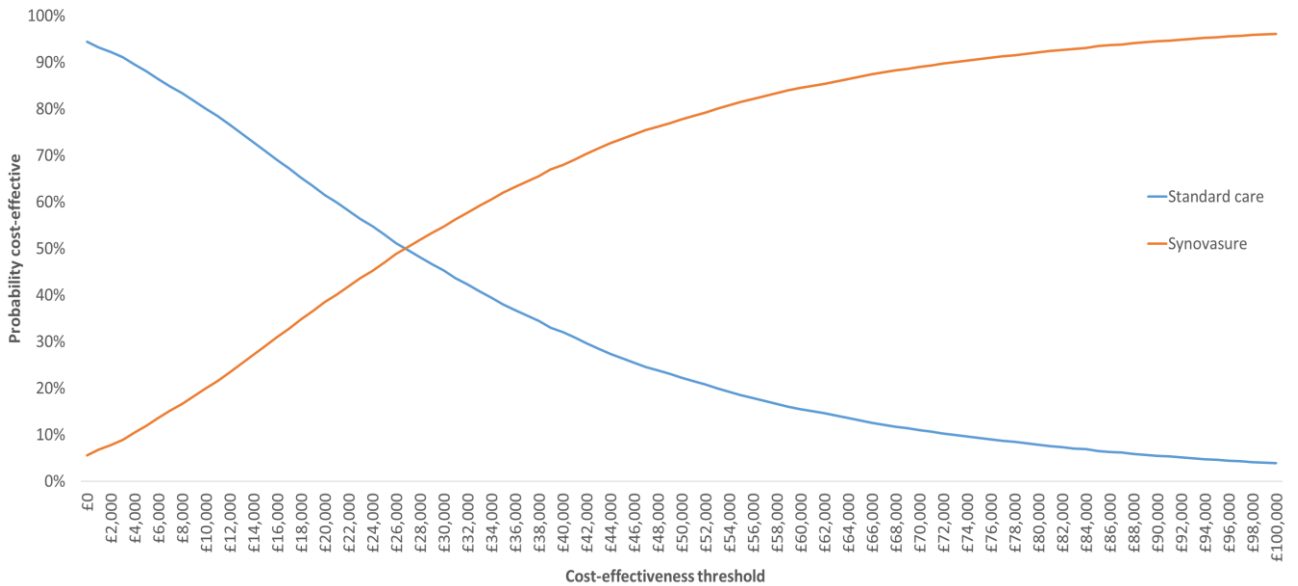


Figure 4. CEAC for analysis considering the Synovasure® lateral flow test in patients with equivocal results with standard tests



Potential budget impact

The potential budget impact associated with introducing the Synovasure® laboratory service was estimated using the population estimates and cost estimates described above and are shown in table 16. The cost impact estimates show that the increased costs associated with testing are partially offset by cost savings associated with the better management of patients with PJI. The overall cost impact was estimated to be £229,555 for hip revisions and £136,363 for knee revisions with a combined cost impact of £365,918.

Table 16: Potential budget impact of introducing Synovasure® laboratory service

Treatment strategy	Test cost	Revision costs for patients with PJI	Revision costs for patients without PJI	Total costs
Hip revisions (n=416)				
Standard care	£16,605	£1,090,135	£2,819,929	£3,926,130
Synovasure®	£187,046	£1,064,268	£2,904,372	£4,155,685
Cost impact	£170,980	-£25,867	£84,442	£229,555
Knee revisions (n=324)				
Standard care	£12,515	£1,465,802	£1,959,158	£3,437,475
Synovasure®	£145,712	£1,411,245	£2,016,881	£3,573,837
Cost impact	£133,197	-£54,557	£57,723	£136,363
Hip and knee revisions (n=739)				
Standard care	£28,580	£2,555,937	£4,779,088	£7,363,605
Synovasure®	£332,757	£2,475,513	£4,921,252	£7,729,523
Cost impact	£304,177	-£80,424	£142,165	£365,918

The potential budget impact associated with introducing the Synovasure® lateral flow test in patients with equivocal results with standard tests was estimated using the population estimates and cost estimates described above and are shown in table 17. The cost impact estimates show that the increased costs associated with testing are partially offset by cost savings associated with the better management of patients with PJI. The overall cost impact was estimated to be £90,918 for hip revisions and £41,532 for knee revisions with a combined cost impact of £132,450.

Table 17: Potential budget impact of introducing Synovasure® lateral flow test

Treatment strategy	Test cost	Revision costs for patients with PJI	Revision costs for patients without PJI	Total costs
Hip revisions (n=83)				
Standard care	£0	£180,722	£368,104	£548,826
Synovasure®	£24,939	£142,700	£472,104	£639,743
Cost impact	£24,939	-£38,022	£104,000	£90,918
Knee revisions (n=65)				
Standard care	£0	£241,928	£267,524	£509,452
Synovasure	£19,428	£189,429	£342,126	£550,984
Cost impact	£19,428	-£52,499	£74,602	£41,532
Hip and knee revisions (n=148)				

Treatment strategy	Test cost	Revision costs for patients with PJI	Revision costs for patients without PJI	Total costs
Standard care	£0	£422,650	£635,627	£1,058,277
Synovasure®	£44,368	£332,129	£814,230	£1,190,727
Cost impact	£44,368	-£90,521	£178,603	£132,450

8. Organisational issues

Currently there is no laboratory-based testing of alpha defensin available in the UK. The nearest approved laboratory is Germany. Zimmer Biomet has plans to license the hospital laboratory and provide a laboratory testing service in the UK. This testing service would provide alpha defensin alongside other tests specified in the MSIS 2018 protocol. Additional microbial ID and neutrophil elastase tests will also be made available.

The alpha defensin point of care test has currently been employed in around fifteen different hospitals within Wales, although experts note limited use due to cost factors. As detailed in the Welsh Government policy on the Management of Point of Care testing (Welsh Scientific Advisory Committee 2017), point of care diagnostic tests should be subject to scrutiny and quality control, including assessment in an appropriate external laboratory.

9. Patient issues

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. No specific issues for patients for this diagnostic test were identified compared with the current standard of diagnostic assessment.

10. Conclusions

The clinical evidence base for alpha defensin testing appears fairly large in terms of there being a number of reasonable quality systematic reviews with meta-analyses published. However, while the primary studies are deemed by the review authors to be at low risk of bias, they are not all prospective, do not all include consecutive patients, a number of the studies are conducted by the same research groups, there are close links with the manufacturer within several of the studies, and for the most part, the studies comprise small numbers of patients. There is also considerable heterogeneity among the studies in terms of threshold values, reference standard used, time since index surgery, presence of acute or chronic infection and patient characteristics. All of the studies are focussed upon diagnostic accuracy and none measure impact on the patient pathway of the use of the test.

In general, the two SRs and the additional cohort study suggest that the diagnostic accuracy of the alpha defensin laboratory test is high. Bonanzinga (Bonanzinga et al. 2019) reports that the alpha defensin laboratory test has demonstrated the best combination of sensitivity and specificity to date for diagnosing PJI quoting a number of individual studies. The diagnostic accuracy of the alpha defensin lateral flow POCT is generally reported to be lower than the laboratory test. There are various possible reasons for the difference in accuracy observed put forward by the study

authors. These include technical aspects of the conduct of the testing, and biases introduced through patient selection and manufacturer involvement, but these are speculative and there remains uncertainty. Despite being of lower accuracy than the lab test, the POCT does have potential for use when a rapid result is required, but the results should be interpreted with caution and in the light of the other MSIS criteria test results.

The Synovasure® test is indicated as an adjunct to current diagnostic approaches. However, there is no literature available on the diagnostic accuracy of alpha defensin testing when used in combination with existing tests, such as proposed in the 2018 MSIS criteria, either for the lab test or the point of care test. The nearest approximation that can be obtained from the literature for the laboratory alpha defensin test used in combination, is the sensitivity (97.7% CI 94.7 to 99.3) and specificity (99.5% CI 97.2 to 99.99) values reported by Parvizi for the 2018 diagnostic algorithm as whole. The Synovasure® lab test that will shortly become available from a laboratory within NHS Scotland and will offer the alpha defensin test as part of package of tests included within the 2018 MSIS ICM criteria and not a single test. Thus decision making around its use by NHS Wales needs to be based upon this position.

Advice from clinical experts was that the use of Synovasure® in current practice in NHS Wales is reserved for patients with equivocal results after standard tests. This restricts use to the Synovasure® lateral flow test because the laboratory-based Synovasure® test is only being offered as part of a laboratory service where the test is offered in conjunction with standard tests. There was little evidence that specifically addressed this population. The most relevant evidence that was identified was a prospective non-randomised study (De Saint Vincent 2018), which considered the diagnostic accuracy of the alpha defensin test in microbiologically complex situations presenting diagnostic challenges. While the results of the study were promising, the study population was relatively small (42 cases in 39 patients) and so further evidence is required to confirm the findings.

No relevant health economic analyses were identified which considered the cost effectiveness of Synovasure® versus the standard of care. A de novo economic evaluation was therefore undertaken. The analysis separately considered the use of the package of laboratory tests including Synovasure® and the use of the Synovasure® lateral flow test in patients with equivocal results after standard tests. The results of the analysis suggested that the package of laboratory tests including Synovasure® was unlikely to be cost-effective in comparison to standard care. The use of the lateral flow test in patients with equivocal results after standard tests was found to have a greater probability of being cost-effective. In particular, it was found to have a reasonably high probability of being cost-effective when used for knee revisions and was found to have an ICER value below £20,000 per QALY in the base case. The greater potential for cost-effectiveness when used for knee revisions reflects the much higher prevalence of PJI in this group.

There should also be consideration given to the availability of other POCT biomarker tests, although the relative accuracy and costs of these and alpha defensin are still largely uncertain. Opening of a laboratory within the UK may enable greater use of the lab based testing and offer access to validation of the POCT.

11. Further research

Further diagnostic studies are needed which compare different biomarker tests, and also which compare the accuracy of the laboratory based Synovasure® package of tests with current standard practice. These studies should include the gathering of patient related outcomes and costs such that the relative costs and benefits of the different tests can be assessed in an economic evaluation.

12. Contributors

The HTW staff and contract researchers involved in writing this report were:

- K MacPherson – systematic literature reviewer, wrote first draft of EAR
- J Washington – carried out literature searches
- S Hughes – economic evidence appraisal, wrote first draft of economic section
- M Prettyjohns - revised economic analysis and literature review post-consultation
- S Myles – project oversight

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

Experts who contributed to this appraisal:

- Jeff Stonadge Topic referrer, Zimmer Biomet
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- Joanna Kelly Researcher, SHTG
- Gillian Coward Patient Representative, National Joint Registry steering committee and panel member; NJR research sub-committee

Review period

Two years after the date of publication, a high-level literature search will be undertaken to determine if there is new evidence that could alter the conclusions of this report. If so, the appraisal will be updated.

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Appendix 1. PICO framework for additional search undertaken by HTW

Table 18: PICO framework for systematic review of Synovasure® alpha defensin laboratory test in combination with standard tests in people with suspected PJI

P (population)	People who have undergone hip or knee arthroplasty and have suspected PJI.
I (intervention)	Synovasure® alpha defensin laboratory test in combination with standard tests
C (comparator(s))	Combination of tests reflecting standard care
O (outcomes)	Diagnostic accuracy; patient morbidity and mortality; perioperative outcomes; length of stay; resource use

Table 19: PICO framework for systematic review of Synovasure® alpha defensin lateral flow test in people with suspected PJI after equivocal results with standard tests

P (population)	People who have undergone hip or knee arthroplasty and have suspected PJI after equivocal results with standard tests
I (intervention)	Synovasure® alpha defensin lateral flow test kit
C (comparator(s))	Management based on results from standard tests
O (outcomes)	Diagnostic accuracy; patient morbidity and mortality; perioperative outcomes; length of stay; resource use

Appendix 2 - PRISMA flow diagram outlining selection of papers for HTW search