

Title

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Month Year

MSAC application no. XXXX

Assessment report

VERSION CONTROL

DOCUMENT HISTORY

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1.1	18-Feb-2016	Sean McCandless	Version control introduced
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DOCUMENT APPROVAL

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This report was prepared by XXXX from XXXX. Clinical advice was provided by XXXX – who are members of the Health Expert Standing Panel. The report was commissioned by the Australian Government Department of Health. It was edited by XXXX.

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Please keep the Section Break (Odd Page) below to ensure the page numbering remains consistent.>

CONTENTS

Version Control	ii
Document History.....	ii
Document Approval.....	ii
Contents vii	
Tables.....	xi
Boxes.....	xiii
Figures.....	xiii
Executive Summary	15
Title of Submission	15
Alignment with agreed PICO Confirmation.....	15
Proposed Medical Service	16
Proposal for Public Funding.....	16
Population	16
Comparator Details.....	16
Clinical management algorithm(s).....	16
Key Differences in the Delivery of the Proposed Medical Service and the Main Comparator	16
Clinical Claim	17
Approach Taken to the Evidence Assessment.....	17
Characteristics of the Evidence Base	17
Results.....	18
Translation Issues	21
Economic Evaluation.....	21
Estimated Extent of Use and Financial Implications.....	22
Consumer impact summary	23
<Other Relevant Considerations>.....	23
Acronyms and Abbreviations	24
Section A Context	25
A1 Items in the agreed PICO Confirmation	26
A2 Proposed Medical Service	26
A3 Proposal for Public Funding.....	26
A4 Proposed Population	27
A5 Comparator Details.....	27

A6	Clinical Management Algorithm(s)	27
A7	Key Differences in the Proposed Medical Service and the Main Comparator	28
A8	Clinical Claim	28
A9	Summary of the PICO.....	28
A10	Consumer impact statement.....	30
Section B	Clinical Evaluation	31
B1	Direct Evidence	32
B1.1	Literature Sources and Search Strategies	32
B1.2	Results of Literature Search	32
	Appraisal of the evidence	34
B1.3	Risk of Bias Assessment	34
B1.4	Characteristics of the Evidence Base	35
B1.5	Outcome Measures and Analysis	35
B1.6	Results of the Systematic Literature review	37
	Is it safe?	37
	Harm 1 etc.....	37
	Harm 2 etc.....	38
	Is it effective?	39
	Effectiveness Outcome 1 etc.....	39
	Effectiveness Outcome 2 etc.....	40
B2	Linked evidence approach	41
B2.1	Basis for linked evidence.....	41
B2.2	Steps for linked analysis.....	41
B3	Diagnostic performance.....	42
B3.1	Reference standard	42
B3.2	Literature sources and search strategies	42
B3.2.1	Results of Literature Search	42
B3.3	Risk of Bias Assessment	44
B3.4	Characteristics of the Evidence Base	44
	<.....	45
B3.5	Outcome Measures and Analysis	45
B3.6	Results of the Systematic Literature review	47
	Is it accurate?	47
B3.7	Extended assessment of reliability evidence	48

B3.8	Concordance analysis	48
B3.9	Interpretation of evidence on diagnostic performance	49
B4	Clinical Validity	50
B4.1	Measures of clinical validity	50
B4.1.1	Reference standard.....	50
B4.1.2	Risk of Bias Assessment	50
B4.1.3	Characteristics of the Evidence Base	51
B4.1.4	Outcome Measures and Analysis	51
B4.1.5	Results of the Systematic Literature review.....	53
	Is it accurate?	53
<B4.2	Prognosis or predisposition.....	54
B5	Clinical utility	55
B5.1	Impact on clinical management (Therapeutic efficacy).....	55
B5.1.1	Risk of Bias Assessment	55
B5.1.2	Characteristics of the Evidence Base	55
B5.1.3	Outcome Measures and Analysis	56
B5.1.4	Results of the Systematic Literature review.....	56
	< Does it impact on clinical management?	56
<B5.2	Therapeutic effectiveness (including impact of effect modification).....	57
B5.2.1	Risk of Bias Assessment	57
B5.2.2	Characteristics of the Evidence Base	58
B5.2.3	Outcome Measures and Analysis	58
B5.2.4	Results of the Systematic Literature review.....	61
	<Does the change in management improve health outcomes?	61
B6	Impact of repeat testing/monitoring.....	63
B7	Extended assessment of comparative harms.....	64
B8	Interpretation of the clinical evidence.....	65
Section C	Translation Issues	68
C.1.	Overview	69
C.2.	Applicability translation issues	69
C.3.	Extrapolation translation issues	69
C.4.	Transformation issues.....	70
C.5.	Any other translation issues.....	70

C.6.	Relationship of each Pre-Modelling Study to the Economic Evaluation.....	70
Section D	Economic Evaluation	72
D.1.	Overview	72
D.2.	Populations and settings.....	73
D.3.	Structure and rationale of the economic evaluation.....	73
	Literature review	74
	Structure of the economic evaluation	74
D.4.	Inputs to the economic evaluation.....	77
D.5.	Results of the Economic Evaluation	77
	<Incremental costs and effectiveness.....	78
	<Stepped economic evaluation	78
D.6.	Sensitivity analyses.....	80
Section E	Financial Implications	81
E.1.	Justification of the Selection of Sources of Data	81
E.2.	Use and Costs of XXX	81
E.3.	Changes in Use and Cost of Other Medical Services	82
E.4.	Financial Implications for the MBS	82
E.5.	Financial Implications for Government Health Budgets	83
E.6.	Identification, Estimation and Reduction of Uncertainty	83
Section F	Other relevant considerations	85
<Appendix A	Clinical Experts and Assessment Group	86
	<Health Expert Standing Panel (HESP).....	86
	Assessment group	86
Appendix B	Search strategies	87
	Bibliographic databases	87
	Additional sources of literature (including websites).....	87
Appendix C	Studies included in the Systematic Review.....	88
Appendix D	Evidence Profile Tables.....	89
Appendix E	Excluded Studies.....	91
References	92	

TABLES

Table 1	Proposed MBS item descriptor	16
Table 2	Key features of the included linked evidence.....	17
Table 3	Balance of clinical benefits and harms of intervention , relative to comparator , and as measured by the critical patient-relevant outcomes in the key studies	19
Table 4	Summary statistics for test compared to comparator , against reference standard	19
Table 5	Summary of findings for the linked evidence comparison of intervention , relative to comparator , in patients with condition with assumed pre-test probability (prevalence) of XX%	20
Table 6	Summary of the economic evaluation	21
Table 7	Title	22
Table 8	Key drivers of the economic model	22
Table 9	Total costs to the MBS associated with XXX and subsequent interventions	22
Table 11	Proposed MBS item descriptor	26
Table 12	Relevant MBS item for the comparator	27
Table 13	Search terms used (literature search platform)	32
Table 14	Key features of the included evidence comparing intervention with comparator	35
Table 15	Results of key patient-relevant outcome across the studies/randomised controlled trials	37
Table 16	Results of key patient-relevant outcome across the studies/randomised controlled trials	40
Table 18	Key features of the included evidence comparing intervention with comparator against reference standard	44
<Table 17	Suggested tabular presentation for QUADAS-2 results	44
Table 19	Diagnostic accuracy data extraction	45
Table 20	Results of key accuracy trials comparing intervention and comparator against reference standard	47

Table 21	Summary of findings for the accuracy of intervention , relative to comparator , in patients with condition with assumed pre-test probability (prevalence) of XX%	48
Table 20	Results of reliability trials	48
<Table 17	Suggested tabular presentation for QUADAS-2 results	51
Table 18	Key features of the included evidence comparing intervention with comparator against reference standard	51
Table 19	Diagnostic accuracy data extraction	52
Table 20	Results of key accuracy trials comparing intervention and comparator against reference standard	53
Table 21	Summary of findings for the accuracy of intervention , relative to comparator , in patients with condition with assumed pre-test probability (prevalence) of XX%	54
Table 22	Key features of the included evidence comparing intervention with comparator for patient management outcomes.....	56
Table 24	Key features of the included evidence assessing impact of change in patient management	58
Table 25	Summary of findings assessing whether intervention changes management, relative to comparator , in patients with condition	62
Table 26	Balance of clinical benefits and harms of intervention , relative to comparator , and as measured by the critical patient-relevant outcomes in the key studies	66
Table 27	Summary of findings for the linked evidence comparison of intervention , relative to comparator , in patients with condition with assumed pre-test probability (prevalence) of XX%	66
Table 28	Example of summary of results of pre-modelling studies and their uses in the economic evaluation	71
Table 29	Classification of the comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator and guide to the suitable type of economic evaluation.....	72
Table 30	Summary of the economic evaluation	73
Table 31	Title	78
<Table 32	Implications for the base case economic evaluation of applying the results of the clinical evaluation (Step 1 then Step 2).....	79

<Table 33	Implications for the base case economic evaluation of extrapolating and transforming the results of the clinical evaluation (Step 3)	79
Table 34	Key drivers of the economic model	80
Table 35	Total costs to the MBS associated with XXX	82
Table 36	Evidence profile table for the accuracy of proposed test compared to comparator for population (baseline risk, e.g. prevalence XX%)	89
Table 37	Evidence profile table for the change in management due to proposed test compared to comparator for population	90
Table 38	Evidence profile table for the impact of change in management due to proposed test compared to comparator for population	90

BOXES

Box 1	Criteria for identifying and selecting studies to determine the safety of XXX in patients with XXX	29
Box 2	Criteria for identifying and selecting studies to determine the direct effectiveness of XXX in patients with XXX	29
Box 3	Criteria for identifying and selecting studies to determine the accuracy of XXX in patients with XXX	30
Box 4	Criteria for identifying and selecting studies to determine the impact of the test on patient management of XXX in patients with XXX	30
Box 5	Criteria for identifying and selecting studies to determine the health impact of the change in patient management subsequent to XXX in patients with XXX	30

FIGURES

Figure 1	Clinical management algorithm/s for the proposed new test relative to current clinical practice	28
Figure 2	Summary of the process used to identify and select studies for the assessment	33
Figure 3	Decision analytic structure of the economic evaluation	75

EXECUTIVE SUMMARY

KEEP EXECUTIVE SUMMARY SHORT – 6 - 8 PAGES FOR A TYPICAL TECHNOLOGY WITH ONE CLINICAL INDICATION.

Main issues for MSAC consideration

- *List the key issues that will impact on MSAC decision-making here.*
- *Keep to less than one page.*
- *This should not be a summary of the evidence, but rather, pointing out where critical uncertainties exist.*

Clearly set out the key aspects and issues that were presented in the main body of the assessment report.

Title of Submission

This **submission-based/contracted** assessment examines the evidence to the support listing of **XXXX** on the Medicare Benefits Schedule (MBS). The service would be <exclusively> used in the **XXX** setting for the **treatment/management** of **XXXX**. The target population are people with **XXXX**. **We propose/The applicant has claimed** that the successful listing of the technology in the target population and setting will lead to **XXXX**. >

ALIGNMENT WITH AGREED PICO CONFIRMATION

This <**contracted/submission-based**> assessment of **XXXX** addresses <**all/most/some/none**> of the PICO¹ elements that were pre-specified in the PICO Confirmation that was <**submitted to/ratified by**> the PICO Advisory SubCommittee (PASC) or the Medical Services Advisory Committee (MSAC) Executive. **If deviations from a ratified PICO Confirmation have occurred, please state briefly what has changed and give reasons for the change (including by referring to the relevant section in the main body of the report).** If the PICO Confirmation was not submitted to or ratified by PASC or the MSAC Executive, please state this.

¹ Population, Intervention, Comparator, Outcomes

PROPOSED MEDICAL SERVICE

Describe the key features of the test and associated interventions.

Indicate whether the test is currently funded or reimbursed in private or public setting in Australia for the same or another clinical indication.

PROPOSAL FOR PUBLIC FUNDING

Provide MBS or other public funding descriptors in the table below. Use the proposed item descriptor as set out in the PICO Confirmation. If the PASC process has not been used by the applicant, then please make this clear in the text prior to presenting the proposed MBS item descriptor in the format below.

Table 1 Proposed MBS item descriptor

Category X – XXXXXX
(a)

POPULATION

Briefly describe the population in whom it is proposed the test should be used, and a summary of the frequency (prevalence and/or incidence) of the population or disease in question.

COMPARATOR DETAILS

Briefly describe the main comparator(s) that was agreed in the PICO Confirmation. If there are any additional comparator(s) to those in the agreed PICO Confirmation, please justify their selection.

Briefly describe the reference standard(s) or evidentiary standard used to determine the accuracy of the test if a linked evidence approach has been used.

CLINICAL MANAGEMENT ALGORITHM(S)

Briefly describe how the test fits in the overall management of the condition and why it is needed. You might like to refer to the location of the clinical management algorithms in the main body of the report.

KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

Briefly describe any differences in the delivery/organisation of care associated with the test, associated interventions, and the main comparator.

CLINICAL CLAIM

Provide information about the clinical claim with respect to the proposed investigative test, as set out in the PICO Confirmation. If the applicant has not utilised the PASC process to state the clinical claim, please mention this here and refer to the assessment of the clinical claim in B.8 below.

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

A systematic review of published <and unpublished> literature was undertaken.

Summarise databases searched and/or time period, key study selection criteria (PICO), methods for selecting studies and critical appraisal methods.

Identify whether direct evidence has been used; whether this has been supplemented by linked evidence; or whether a linked evidence approach alone is used.

CHARACTERISTICS OF THE EVIDENCE BASE

Describe the number of studies identified, and the quality of them. Identify any serious issues with the studies (design/population/risk of bias/ relevance of outcome measures, gaps in linked evidence etc) and provide a link to where the information on characteristics can be found in the main document.

<Provide key characteristics of linked evidence studies if applicable, such as number of comparative studies, suitability of the reference standard etc. Tabulate if appropriate.>

Table 2 Key features of the included linked evidence

Type of evidence	Description	Number
<Prognostic evidence>	<Comparison of outcomes in patients receiving usual care conditioned on the presence of absence of test positive status>	k= n=
Comparative diagnostic performance	<Describe study designs used to assess accuracy ^a or analytical concordance ^b >	k= n=
Comparative clinical validity	<Describe study designs used to clinical validity>	k= n=
Therapeutic efficacy	<Evidence to show that test results guides decisions about subsequent clinical management of patients>	k= n=
Therapeutic effectiveness	<Single randomised controlled trial of treatment vs usual care in patients that are test positive in both arms>	k= n=

^a reference standard available; ^b reference standard not available

Is evidence presented to address all parts of the analytical framework proposed to represent a double randomised controlled trial? Mention whether there are gaps in the evidence presented, as this will indicate areas of uncertainty.

Are the bodies of evidence linked meaningfully i.e. are results transferrable across the chain of argument? Is the evidence applicable to the use of the test in Australia? i.e. according to the clinical management algorithm in the approved PICO Confirmation. >

RESULTS

Safety

Test adverse events

Key points from the main body of the report, on harms directly caused by the test or by obtaining a sample for the test. Comment on whether additional test samples are required and whether this will cause further harms to the patient. If the comparator includes an alternate testing strategy, discuss any comparative adverse event data.

Adverse events from change in management

Key points from main body of the report – summarise the results of the most relevant comparative adverse event data presented in Section B.6 of the main body, as measured by the patient-relevant outcomes specified in the PICO Confirmation, if these data are available. Also include any key points from relevant evidence beyond the comparative trials presented in Section B.7. The emphasis should be on whether there are clinically relevant differences in the reported harms, irrespective of whether the results are statistically significant.

Effectiveness

Key points from main body of the report – concentrate on direct comparative effectiveness, as measured by the patient-relevant outcomes specified in the PICO Confirmation, if the data are available.

Direct effectiveness

Does the investigative intervention, and basing treatment on test result, yield better health outcomes for the patients than random allocation to treatment? Is there anything other than the test result that could be responsible for the effect?

An example of the way the information could be presented is given in the table below, based on a GRADE summary of findings table. Present no more than 7 critical or important health outcomes, including both benefits and harms.

Table 3 Balance of clinical benefits and harms of **intervention**, relative to **comparator**, and as measured by the **critical patient-relevant outcomes** in the key studies

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)	Relative effect (95%CI)	Risk with control	Risk or risk difference with intervention	<Comments>
e.g. Quality of life						
e.g. Serious adverse events						

^a GRADE Working Group grades of evidence (Guyatt et al., 2013)

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

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

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

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

On the basis of the benefits and harms reported in the evidence base (summarised above), **it is suggested that, relative to the comparator, the investigative intervention has superior/non-inferior/uncertain/inferior safety and superior/non-inferior/uncertain/inferior effectiveness.**

Effectiveness from linked evidence

1. Accuracy

Indicate whether a reference standard was available, against which the index test/s were compared. An example of how the information for comparative analytical validity and or clinical validity (accuracy) is presented below. If reference standard not available but a constructed reference standard is used (such as the “evidentiary standard”: the test option(s) used in the generation of evidence for subsequent interventions), then modify outcomes (and table) to “estimated sensitivity” etc; or modify table for ‘predictive accuracy’ and present outcomes such as agreement or concordance statistics (kappa). Amend as necessary. The positive predictive value and negative predictive value should be calculated with reference to the relevant prevalence/incidence in the target population.

Table 4 Summary statistics for **test** compared to **comparator**, against **reference standard**

Accuracy (k=)	Index test (n=)	Comparator (n=)
Sensitivity, % [95% CI]	X% [X, X]	X% [X, X]

Specificity, % [95% CI]	X% [X, X]	X% [X, X]
Positive predictive value, % [95% CI]	X% [X, X]	X% [X, X]
Negative predictive value, % [95% CI]	X% [X, X]	X% [X, X]

Mention key points of interest that will affect interpretation above, with respect to effective analytical validity or clinical validity, such as problems with sampling, impact of fixation method on results, reliability of interpretation between laboratories, potential causes of false positives and false negatives, implications of false positives and false negatives given that the test is intended to guide treatment. If possible, perform meta-analyses so summary statistics can be provided.

2. Therapeutic efficacy (change in management)

This is important to show that test results do guide changes in treatment decisions. Also assess when there is evidence available showing that treatment decisions deviate from what is indicated by test results, eg when test negative patients receive the intervention. Does this show potential for leakage and/or the fact that clinicians do not trust the test results?

3. Therapeutic effectiveness (health benefit from change in management)

State whether the change in management, resulting from the test, impacts patient health outcomes in either a statistically significant and/or clinically important way.

A summary of the impact of testing and subsequent treatment can be made in a table similar to below.

Table 5 Summary of findings for the linked evidence comparison of **intervention**, relative to **comparator**, in patients with **condition** with assumed pre-test probability (prevalence) of **XX%**

Outcomes	Participants	Quality of evidence	No. per 100 patients with comparator	No. per 100 patients with intervention	Importance	<Comments>
True positives	k= ; n=					e.g. benefit from earlier diagnosis and treatment
True negatives						e.g. almost certain benefit from reassurance
False positives						e.g. likely anxiety and possible morbidity from additional testing and treatment
False negatives						e.g. possible detriment from delayed diagnosis
Inconclusive results						
Harms						

^a GRADE Working Group grades of evidence (Guyatt et al., 2013)

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

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

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

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

TRANSLATION ISSUES

Briefly indicate the key translation issues and pre-modelling studies that were used to adapt the evidence presented in Section B for the purposes of the economic evaluation (eg the economic model that predicts the cost-effectiveness of the new test, relative to the agreed comparator, if the test is used according to the proposed MBS item descriptor).

If translation of the clinical evidence was not needed or not undertaken, please state this.

ECONOMIC EVALUATION

Based on the evidence supporting the clinical claim, and with reference to Table D.1.2 in the *MSAC Investigative Guidelines*, state what type of economic evaluation has been used in the table below eg cost-effectiveness, cost-utility, cost-minimisation, cost-consequences.

If an economic evaluation is not undertaken, please justify this with reference to Table D.1.2 of the *MSAC Investigative Guidelines* and do not insert the tables below into this section.

Table 6 Summary of the economic evaluation

Perspective	
Comparator	
Type of economic evaluation	Eg. cost-effectiveness, cost-utility, cost-minimisation, cost-consequences.
Sources of evidence	Eg. Systematic review
Time horizon	Eg X years in the model base case
Outcomes	Eg. Name or list the outcome/s used in the model eg. LYG and QALYs
Methods used to generate results	E.g. trial-based, cohort expected value analysis, Markov model
<Health states>	Only put in this row, if it is relevant to your model
<Cycle length>	Only put in this row, if it is relevant to your model
Discount rate	
Software packages used	

See [Table D.3.1](#) in the *MSAC Investigative Guidelines*.

Key structural assumptions of the model are:

< The overall costs and outcomes, and incremental costs and outcomes as calculated for the testing strategy and comparative testing strategy in the model, and using the base case assumptions, are shown in the table below.

Table 7 Title

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Index test and associated interventions					
Comparator					

ICER = Incremental Cost Effectiveness Ratio>

<The modelled results were most sensitive to >

Table 8 Key drivers of the economic model

Description	Method/Value	Impact
Eg Time horizon	25 years; assumed from 6 month trial duration	High, favours intervention
Eg Upper 95% CL of the difference in outcomes	\$100,000/QALY	High; favours comparator
etc		

<Other key areas of uncertainty were >

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

<An epidemiological approach has been used to estimate the financial implications of the introduction of XXX.>

The financial implications to the MBS resulting from the proposed listing of XXX are summarised in Table 9.

Table 9 Total costs to the MBS associated with XXX and subsequent interventions

	2015-16	2016-17	2017-18	2018-19	2019-20
Test					
Number of services					
Sub-total cost					
Subsequent intervention					
Number of services					
Sub-total cost					

	2015-16	2016-17	2017-18	2018-19	2019-20
<Any co-administered services currently MBS listed>					
Number of services					
Sub-total cost					
Total services					
Total cost					

The summary should primarily focus on the financial implications in terms of MBS rebates. If a service is primarily out-of-hospital, then there will need to be a separate analysis of the financial implications to the safety net.

The ratio of in-hospital vs out-of-hospital service needs to be determined and the 75% vs 85% rebate (or if a GP service, 100% rebate), respectively, proportionately assigned in the costing. The Department is interested in the rebate as the input cost, not the schedule fee.

If there is additional relevant information that should be taken account in the financial implications eg cost impacts on other government health budgets, patient costs etc, please mention these here and be guided by the Department as to what data would be expected.

CONSUMER IMPACT SUMMARY

Summarise any feedback received during the public consultation period.

<OTHER RELEVANT CONSIDERATIONS>

This section is reserved for content relating to changes in the organisation of care, social/ethical/legal considerations, specific policy considerations, impact on consumers/patients, access/equity considerations, training/workforce considerations, risk share arrangements etc.. The content of this section is topic-specific; it is, therefore, optional.

ACRONYMS AND ABBREVIATIONS

Add/delete as applicable

AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
CI	confidence interval
HESP	Health Expert Standing Panel
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
MBS	Medicare Benefits Schedule
MD	mean difference
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
PASC	PICO Confirmation Advisory Sub-Committee of the MSAC
QALY	Quality adjusted life year
TGA	Therapeutic Goods Administration

SECTION A

CONTEXT

In this Section: Establish the context for the assessment report. Describe the proposed medical service, its intended use on the MBS or elsewhere, and the medical services that would be co-delivered or substituted (the medical service likely to be most replaced by health care providers in practice is the 'main comparator').

This <contracted/submission-based> assessment of XXX for the <diagnosis/screening/triaging/staging/investigation of XXX> is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

If you are writing a Submission Based Assessment, include the following text:

<Name of applicant has provided a systematic review and economic evaluation of XXXXXX in order to inform MSAC's decision-making regarding whether the proposed medical service should be publicly funded. >

Then, if you are writing a Contracted Assessment, include the following text:

<Name of contracting agency has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of XXXXXX. This assessment has been undertaken in order to inform MSAC's decision-making regarding whether the proposed medical service should be publicly funded. >

<Appendix A provides a list of the people involved in the development of this assessment report, <including clinical expertise sourced from XXX/the Health Expert Standing Panel (HESP).>

Contracted assessors can provide more detail on HESP input here by including the following text. There is no equivalent section for submission-based assessments.

<HESP are a pool of experts collated from various medical fields who have been nominated by their associated professional body or by applicants. HESP members are a panel of the MSAC and are engaged to provide practical, professional advice that directly relates to each application and the service being proposed for the MBS. HESP members are not members of either MSAC or its subcommittees. Their role is limited to providing input and guidance to the assessment groups to ensure that the pathway is clinically relevant and takes into account consumer interests. HESP

member’s advice is used to inform the deliberations that MSAC presents to the Federal Minister for Health.>

<The proposed use of XXXX in Australian clinical practice was outlined in a PICO Confirmation that was presented to, and accepted by, the PICO Confirmation Advisory SubCommittee (PASC). The PICO Confirmation was released for public comment on Day Month Year.> <This application is following a fit-for-purpose pathway, therefore a PICO Confirmation outlining the proposed use of XXXX in Australian clinical practice was not presented to/ratified by the PICO Confirmation Advisory SubCommittee (PASC).>

A1 ITEMS IN THE AGREED PICO CONFIRMATION

<This <contracted/submission-based> assessment of XXXX addresses <all/most/some/none> of the PICO elements that were pre-specified in the PICO Confirmation <that was ratified by/submitted to> PASC.> If deviations from the PICO Confirmation have occurred, please state briefly what has changed. Has the approach suggested in the PICO Confirmation still been addressed but an alternative approach has been presented? Or has the approach suggested in the PICO Confirmation not been addressed and only the alternative approach has been presented? Give reasons for any departure from the PICO Confirmation (including by referring to the relevant section in the main body of the report). If a PICO Confirmation was not presented to PASC or MSAC Executive, please state this.

A2 PROPOSED MEDICAL SERVICE

Describe the proposed medical service as set out in the agreed PICO Confirmation, including the purpose of the investigative medical service, methods used (eg point of care vs laboratory), mode of delivery and other details.

A3 PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 10.

Provide MBS or other public funding descriptors, as set out in the agreed PICO confirmation. If there are differences between the proposed descriptor and the PASC or MSAC Executive ratified item descriptor, those differences should be highlighted and justification provided.

Table 10 Proposed MBS item descriptor

Category X – XXXXXX

A4 PROPOSED POPULATION

Identify the main population(s) described in the PICO Confirmation including key inclusion and exclusion criteria.

Include a high level summary of the frequency (prevalence and/or incidence) of the population or disease in question and where relevant the natural history/pathophysiology of the condition of interest.

A5 COMPARATOR DETAILS

Brief description of the main comparator(s) described in the agreed PICO Confirmation. The comparator is the current practice most likely to be replaced or added to by the proposed medical service (refer to clinical management algorithm). Note that the comparator may be an alternative investigative test, or it may be treatment provided without the use of an investigative test.

If there are any additional comparator(s) to those in the agreed PICO Confirmation, justify their selection.

Note any limitations on provider or the setting in which the comparator can be provided.

The MBS item descriptor/s for the relevant comparator/s is summarised below.

Table 11 Relevant MBS item for the comparator

Category X – XXXXX
MBS

A6 CLINICAL MANAGEMENT ALGORITHM(S)

Present the clinical management algorithm that depicts the context of the intended use of the proposed medical service following a listing on the MBS or other public funding (as listed in the PICO Confirmation).

Present the corresponding algorithm depicting the current context (as listed in the PICO Confirmation).

If possible present the two algorithms next to each other so the differences can be seen easily. Highlight the differences between the two algorithms in the text e.g. change in positioning of a therapy in terms of lines of therapy; expansion/augmentation of the current management options; identification of patients who would now be treated who would previously not been treated.

Indicate whether multiple-listing scenarios are presented.

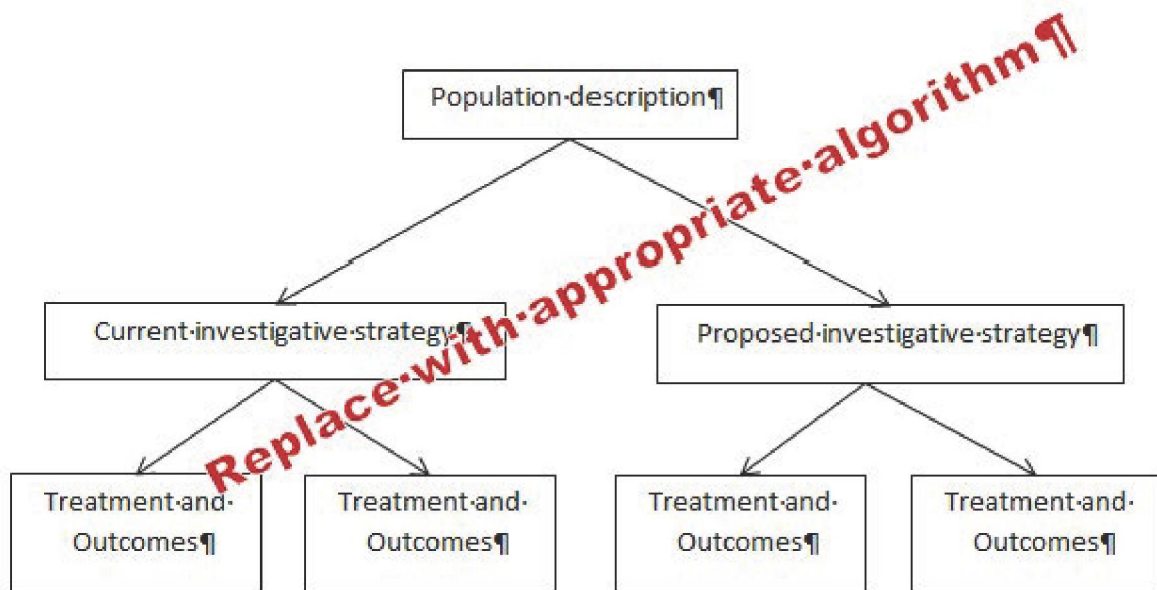


Figure 1 Clinical management algorithm/s for the proposed new test relative to current clinical practice

A7 KEY DIFFERENCES IN THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

Describe the main differences between the proposed medical service and the main comparator, in regards to the indications, contraindications, likelihood and severity of adverse events.

A8 CLINICAL CLAIM

Provide information about the clinical claim with respect to the proposed medical service, as set out in the PICO Confirmation. If the applicant has not utilised the PASC process to state the clinical claim, please mention this here.

A9 SUMMARY OF THE PICO

The guiding framework of a PICO Confirmation is recommended by MSAC for each assessment. The PICO Confirmation describes current clinical practice and reflects the likely future practice with the proposed medical service.

The Population, <Prior tests,> Investigation/Index test, Comparator and Outcomes (PPICO or PICO) that were pre-specified to guide the systematic literature review for direct evidence, are presented in Box 1 and Box 2.

In order to determine the safety of the index test, consideration should also be given to the safety of any sampling required for the test, and any changes in management subsequent to the test should be considered (for true positives and negatives, as well as false positives and negatives).

Box 1 Criteria for identifying and selecting studies to determine the safety of XXX in patients with XXX

Selection criteria	Description
Population	
<Prior tests>	
Intervention	
Comparator/s	
Outcomes	Critical for decision making: Important, but not critical for decision making: Low importance for decision making:
Systematic review question	

The direct effectiveness of the test should consider the health impact that the investigation and associated interventions has on the patient. This is also called the ‘clinical utility’ of the test.

Box 2 Criteria for identifying and selecting studies to determine the direct effectiveness of XXX in patients with XXX

Selection criteria	Description
Population	
<Prior tests>	
Intervention	
Comparator/s	
Outcomes	Critical for decision making: Important, but not critical for decision making: Low importance for decision making:
Systematic review question	

<The Population, <Prior tests,> Investigation/Index test, Comparator and Outcomes (PPICO or PICO) that were pre-specified to guide the systematic literature review for a linked evidence approach, are presented in Box 3 to Box 5.

Please note that there may be multiple reference standards (or evidentiary standards), e.g. for a genetic test, a reference standard of full gene sequencing may be the appropriate reference standard for analytical validity, whereas a clinical diagnosis would be a reference standard for clinical validity. If clinical validity is not available, the penetrance of the disease in those with the specified mutation will need to be discussed.

Box 3 Criteria for identifying and selecting studies to determine the accuracy of XXX in patients with XXX

Selection criteria	Description
Population <Prior tests> Index test Comparator/s <Reference Standard> <Evidentiary standard> Outcomes	
Systematic review question	

Box 4 Criteria for identifying and selecting studies to determine the therapeutic efficacy (change in management) of XXX in patients with XXX

Selection criteria	Description
Population <Prior tests> Index test Comparator/s Outcomes	
Systematic review question	

Box 5 Criteria for identifying and selecting studies to determine the therapeutic effectiveness of the change in patient management subsequent to XXX in patients with XXX

Selection criteria	Description
Population Intervention Comparator/s Outcomes	
Systematic review question	

>

A10 CONSUMER IMPACT STATEMENT

Summarise the key points received during the public consultation period of the PICO Confirmation.

SECTION B

CLINICAL EVALUATION

Determination of the clinical effectiveness of an investigative medical service requires either:

- evidence of the effectiveness of **XXX** from high-quality comparative studies evaluating the use of **XXX** and subsequent treatment compared to **XXX** and treatment (direct evidence). Randomised controlled trials provide the highest quality evidence for this comparison. Or, if this is not available:
- evidence of the treatment effectiveness from high-quality comparative studies evaluating the treatment for **XXX**, linked with applicable and high-quality evidence of the accuracy of **XXX** to **<diagnose/stage/determine prognosis/screen/investigate> XXX** compared to **XXX**. This is called 'linked evidence'.

State whether there was sufficient direct evidence to assess the proposed investigative test, or whether this evidence was supplemented by a linked evidence approach.

Where direct evidence is available, additional information should still be considered:

- The diagnostic performance and clinical validity of the investigative medical service where relevant (Section B3 and B4).
- The clinical impact of false negatives and false positives (if this cannot be extracted from the direct evidence presented (Section B5).
- Impact of repeat testing (if relevant) (Section B6).
- The relative safety of performing the test (Section B7).

B1 DIRECT EVIDENCE

B1.1 LITERATURE SOURCES AND SEARCH STRATEGIES

The medical literature was searched on **Date** to identify relevant studies <and systematic reviews> published during the period **XXX** to **XXX**. Searches were conducted of the databases and sources described in **Appendix B**. <Attempts were also made to source unpublished or grey literature from **XXX**> <Search terms are described in **Table 12**.> **If the search terms are comprehensive, they can be included in an Appendix. It is restrictive to search the literature by including search terms concerning the comparator and/or outcomes – however, in circumstances where the literature is very extensive this might be reasonable. There should be sufficient detail in the search strategy that it allows it to be replicated.** Limits should include the date span of the search and the language. Adapt as required for multiple populations etc.

A single set of searches may be appropriate for all studies which include the new test (i.e. direct evidence of effectiveness, harms, analytical validity and clinical validity (accuracy) and whether there is a change in patient management from the new test). If the final step of a linked evidence approach is to be used (assessing therapeutic effectiveness of patient management changes), an additional set of searches may be required.

Table 12 Search terms used (**literature search platform**)

Element of clinical question	Search terms
Population	
Intervention	
Comparator (if applicable)	
Outcomes (if applicable)	
Limits	

B1.2 RESULTS OF LITERATURE SEARCH

<A PRISMA flowchart (Figure **2**) provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1 and Box 2) (Liberati et al., 2009). >

<Studies were selected **independently by two reviewers/by a single reviewer with a random sample receiving independent assessment by a second reviewer/by a single reviewer.**> **Choose one.**

<Disagreements regarding study selection were resolved by a third independent reviewer.>

<Additional pre-specified criteria for excluding studies included: XXXX>

Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as Excluded Studies in Appendix D. All other studies that met the inclusion criteria are listed in Appendix C.

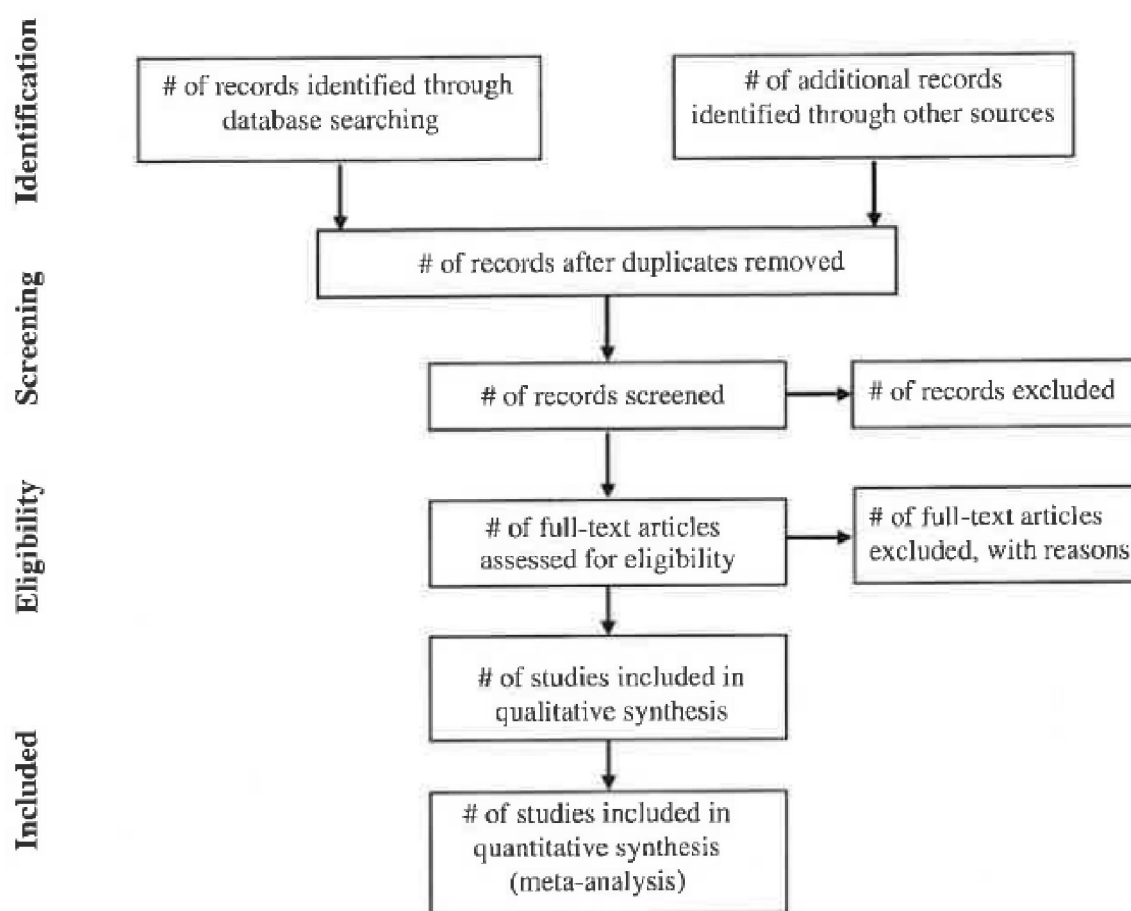


Figure 2 Summary of the process used to identify and select studies for the assessment

This is a picture of a PRISMA flowchart. You will need to construct and adapt these elements for your own search results. Create separate flowcharts for separate searches, if more than one set were required for the purposes of assessing linked evidence, or for multiple indications etc. If you are writing a **contracted assessment** you will then need to save the flowchart as a picture file (TIFF) and copy and paste in, so that web accessibility requirements are met.

A profile of each included study is given in Appendix C. This study profile describes the authors, study ID, publication year, study design <and quality (level of evidence and risk of bias)>, study location, setting, length of follow-up of patients, study population characteristics, description of the

test (and associated interventions), description of the comparator (and associated intervention), description of the reference standard or evidentiary standard and the relevant outcomes assessed.

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in 4 stages:

Stage 1: Appraisal of the risk of bias within individual studies (or systematic reviews) included in the review. <Some risk of bias items were assessed for the study as a whole, while others were assessed at the outcome level>. (Subsections B1.3, B3.3, B4.1.2, B5.1.1)

Stage 2: Appraisal of the precision, size of effect and clinical importance of the results reported in the evidence base as they relate to the pre-specified primary outcomes for this assessment <and determining the assumed baseline risk>. (Subsections B1.6, B3.6, B4.1.5, B5.1.4, B5.2.4)

Stage 3: Rating the overall quality of the evidence per outcome, across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias (Evidence profile tables, Appendix D).

Stage 4: Integration of this evidence (across outcomes) for conclusions about the net clinical benefit of the test and associated interventions in the context of Australian clinical practice. (Section B.8)

B1.3 RISK OF BIAS ASSESSMENT

For direct evidence of effectiveness, and safety, reviewers may choose to use the risk of bias table format in the *MSAC Therapeutic Guidelines*, although it should be noted that not all elements of risk of bias are covered by this format. Alternatives could be the Cochrane risk of bias tool or other tools suitable for RCTs, AMSTAR or PRISMA for systematic reviews, and other validated checklists for non-randomised or observational studies.

Whatever the choice, the method of assessing risk of bias should be transparent and justifiable. Please note – if an indirect comparison is presented then the risk of bias assessment of the individual trials/studies would need to be supplemented with an assessment of the exchangeability of the study populations being compared – that is, the results for the common comparator arms should suggest that the populations are similar.

If following GRADE methodology, risk of bias should be assessed per outcome measure, or per cluster of outcomes (i.e. subjective outcomes and objective outcomes assessed separately, as the impact of blinding etc will differ).

B1.4 CHARACTERISTICS OF THE EVIDENCE BASE

See [Appendix C](#) for details on the individual studies included in the evidence base.

Develop an appropriate way of presenting information on the interventions or associations, and outcomes being tested for these study designs. Depending on the number of trials identified, include the key studies only. Keep this section brief, and provide more detail in the study profiles, in [Appendix C](#). Provide any information about the study/participant characteristics that are not reported elsewhere in B.3-B.5, but which is key to interpreting the implications of the evidence.

A summary of direct evidence is provided in [Table 13](#).

Table 13 Key features of the included evidence comparing [intervention](#) with [comparator](#)

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Jones 2010	225	R, DB 6 mths	Low		Mortality	Not used
Smith 2012	310	R, OL 3 mths	High		Response rate	Not used
Brown 2005	75	CS, OL 8 mths	Low		QoL	Not used
etc						
etc						
Meta-analysis	410 k=			<Fixed effect/random effect> model; <overall pooled> <and> <subgroup analyses> presented; heterogeneity analysis <key outcomes> analysed		Survival gain

<CC=case control; Coh=cohort; CS=case series; DB=double blind; MC=multi-centre; NR=non-randomised; OL=open label (unblinded); QoL=quality of life; R=randomised; SB=single blind; X=cross-sectional..>

Select or add abbreviations as required.

Note – k=no. of studies included in meta-analysis. If the meta-analysis results are provided or relied upon in preference to the individual study results, then the individual studies do not need to be listed here – although they will need to be discussed in Section B.6.

Note – if you are relying on an indirect comparison, you will need to construct the table differently to indicate the common comparator and the two different trials or sets of trials that are being compared. Risk of bias in that situation must consider the exchangeability of the trial populations.

B1.5 OUTCOME MEASURES AND ANALYSIS

See [Appendix C](#) for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

Comment on whether the measurement of outcomes in the included studies was likely to be accurate; discuss the validity of the measurement tools used; and make it clear how you are interpreting a clinically important effect for these outcomes. Discuss whether the statistical analyses

presented in the studies were pre-specified or *post hoc*, and the limitations associated with the latter.

Discuss the methods you have used (and perhaps justification, if the method is unusual) to conduct your own statistical analyses for the assessment eg calculation of confidence intervals, statistical tests and meta-analyses, should be mentioned here.

B1.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT SAFE?

Summary – Research question

Concentrate on comparative safety, as measured by the patient-relevant outcomes specified in the PICO Confirmation, if these data are available. There may be safety implications of retrieving a sample for testing, or the testing procedure itself, or from subsequent interventions. The emphasis should be on whether there are clinically relevant differences in the reported harms, irrespective of whether the results are statistically significant.

The type of information needed per pre-specified outcome (from the PPICO) is given in the table below. The table can be copied for additional pre-specified outcomes. Additional graphical representations might be helpful. The meta-analysis is optional – it will depend on the available evidence base as to whether a meta-analysis can be conducted. If a meta-analysis is conducted, forest plots should be presented.

Describe the evidence base reporting on safety outcomes. Is the evidence base applicable to the populations/settings/circumstances of use in the Australian situation? (this will then be addressed in Section C)

HARM 1 ETC

Brief discussion of the evidence base reporting on this outcome, and the results found, with reference to table below.

Table 14 Results of key patient-relevant outcome across the studies/randomised controlled trials

Study ID	Risk of bias	Index test strategy <n with event/N (%)> <mean ± SD>	Comparator <n with event/N (%)> <mean ± SD>	Absolute difference <RD± NNT/NNH and 95% CI> <mean difference and SD or 95%CI>	Relative difference <OR/RR/HR and 95% CI> <results of statistical testing and p-value and/or 95% CI>
Trial 1					
Trial 2					
etc.					
<Pooled result>				<XX>	<XX>
<Chi-square for heterogeneity: Q= , df= , P=	I ² statistic with 95% uncertainty interval =>				

Define abbreviations used in the table.

If outcome is continuous, please provide the scale.

Note – in table above SD=standard deviation; RD=risk difference; NNT=number needed to treat; OR=odds ratio; RR=relative risk; HR=hazard ratio; NNH=number needed to harm.

HARM 2 ETC

IS IT EFFECTIVE?

Concentrate on comparative direct effectiveness, as measured by the patient-relevant outcomes specified in the PICO Confirmation, if the data are available. The emphasis should be on whether there are clinically relevant differences in the reported results between treatment arms ie statistical significance is important but not sufficient.

Summary – Research question

The type of information needed per pre-specified outcome (from the PICO) is given in the table below. The table can be copied for additional pre-specified outcomes. Additional graphical representations might be helpful. The meta-analysis is optional – it will depend on the available evidence base as to whether a meta-analysis can be conducted. If a meta-analysis is conducted, forest plots should be presented.

Describe the evidence base reporting on the effectiveness outcomes. Is the evidence base applicable to the populations/settings/circumstances of use in the Australian situation? (this will then be addressed in Section C)

EFFECTIVENESS OUTCOME 1 ETC

Brief discussion of the evidence base reporting on this outcome, and the results found, with reference to Table 15 below. This may be adapted to suit, including separate rows where the health outcomes of patients are broken down based on whether they receive a positive or negative result, or different treatment strategies.

Table 15 Results of **key patient-relevant outcome** across the **studies/randomised controlled trials**

Study ID	Risk of bias	Intervention <n with event/N (%)> <mean ± SD>	Comparator <n with event/N (%)> <mean ± SD>	Absolute difference <RD± NNT/NNH and 95% CI> <mean difference and SD or 95%CI>	Relative difference <OR/RR/HR and 95% CI> <results of statistical testing and p-value and/or 95% CI>
Trial 1					
Trial 2					
etc.					
<Pooled result>				<XX>	<XX>
<Chi-square for heterogeneity: Q= , df= , P=		I ² statistic with 95% uncertainty interval =>			

<SD=standard deviation; RD=risk difference; NNT=number needed to treat; OR=odds ratio; RR=relative risk; HR=hazard ratio; NNH=number needed to harm.>

Select or add abbreviations as required.

If outcome is continuous, please provide the scale.

EFFECTIVENESS OUTCOME 2 ETC

B2 LINKED EVIDENCE APPROACH

B2.1 BASIS FOR LINKED EVIDENCE

Provide information as to whether there is a basis to present a linked analysis.

Consider using a linked evidence approach where direct trial evidence of clinical effectiveness of a test is not available, or is inadequate for decision making purposes.

In some cases, evidence of test accuracy would be sufficient, if it is reasonable to assume that the population receiving the new test is the same population who would receive treatment for the condition, and there is good evidence that treatment impacts positively on the health outcomes of the population (this is the *transferability* assumption).

B2.2 STEPS FOR LINKED ANALYSIS

To construct a linked evidence analysis, different evidence requirements are required.

- Consideration of the diagnostic performance and clinical validity (where relevant) of the investigative medical service (Sections B3 and B4)
- Consideration of the clinical utility of the investigative medical service in terms of impact of positive versus negative test results on patient management, the contribution and clinical importance of false negatives versus false positives and direct impact of each therapeutic model service option on health outcomes (Section B5);
- Considerations of the impact of repeat testing (if appropriate) (Section B6); and
- Consideration of the relative safety of performing the investigative service, both immediate safety issues of directly performing the test and 'flow on' safety issues that arise as a result of conducting the investigative service (Section B7).

Provide a narrative linking the above sections. Conclusions linking these should be made in Section B8.

B3 DIAGNOSTIC PERFORMANCE

Use this section to provide information on the accuracy of the proposed investigative medical service, to detect what it is supposed to detect. In most cases, this will be the clinical outcome of interest. However, if a genetic test is being proposed for consideration, the distinction is made between the analytical sensitivity and specificity (i.e. how accurate is the test at detecting the mutations of interest, which should be presented in Section B3), and clinical sensitivity and specificity (i.e. how accurate is the test at predicting the health outcome of interest, which should be presented in Section B4).

For investigative medical services for which there is no reference standard, evidence of concordance needs to be presented (Subsection B3.8) alongside evidence of reproducibility (Subsection B3.7).

B3.1 REFERENCE STANDARD

When linked evidence is used to support the application, a reference standard is needed for the assessment of test accuracy. In the absence of an accepted reference standard, the evidentiary reference standard should be used. An evidentiary standard is the test that was used in the key evidence to support the use of the test.

If a reference standard does not exist, and individual patient data are available, consider constructing a reference standard (Subsection B3.8). If a reference standard is not available and cannot be constructed, evidence of concordance should be presented (Subsection B3.8).

B3.2 LITERATURE SOURCES AND SEARCH STRATEGIES

If separate searches were performed for diagnostic accuracy studies, describe the sources and search strategies here, as per sub-Section B.1

B3.2.1 RESULTS OF LITERATURE SEARCH

<A PRISMA flowchart (Figure 2) provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1 and Box 2) (Liberati et al., 2009). >

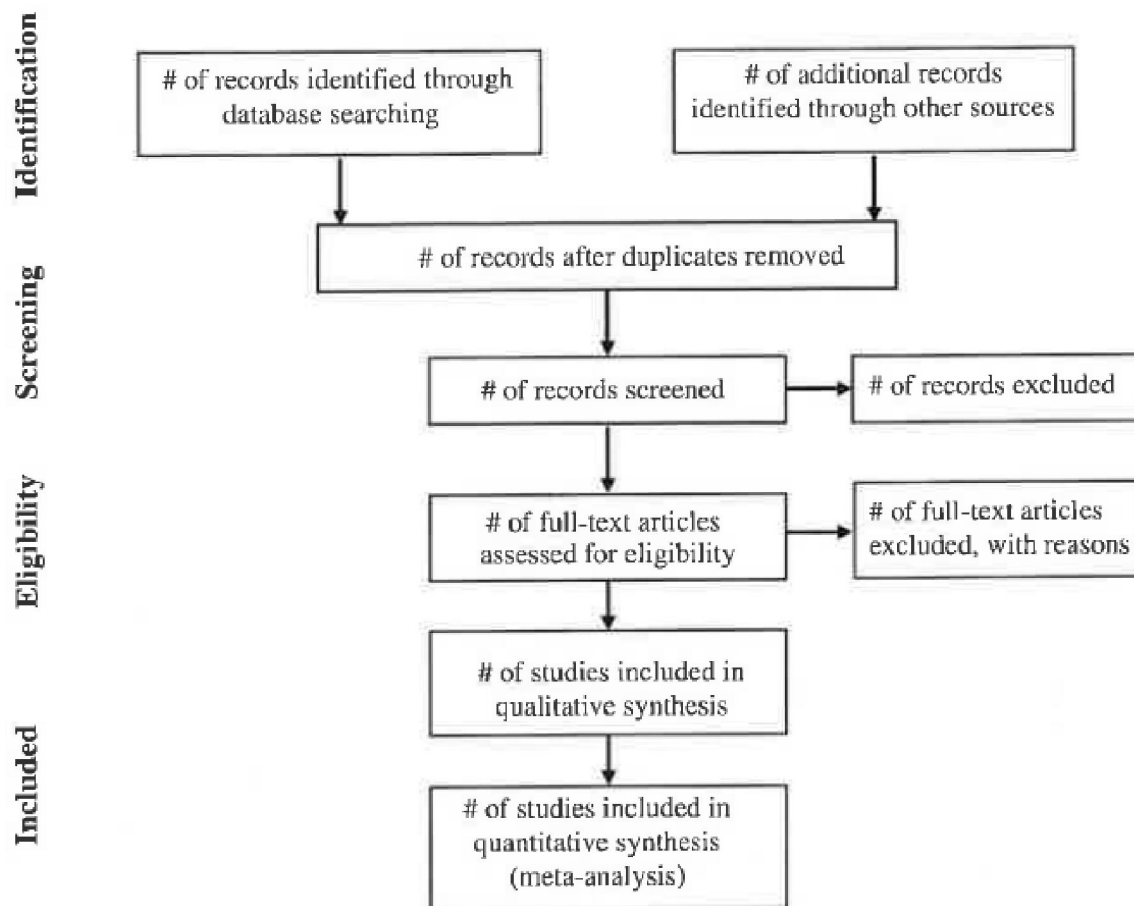


Figure 3 Summary of the process used to identify and select studies for the assessment

If separate searches were performed for diagnostic accuracy studies, include this additional PRISMA flowchart. If you are writing a **contracted assessment** you will then need to save the flowchart as a picture file (TIFF) and copy and paste in, so that web accessibility requirements are met. If no separate searches were performed, simply refer to Subsection B1.1.

A summary of the characteristics of accuracy studies is shown in [Table 16](#). A full profile of each included study is given in [Appendix C](#). Those studies which technically met the inclusion criteria, but which were not included in the results section or meta-analyses, are listed in Appendix E.

Table 16 Key features of the included evidence comparing **intervention** with **comparator** against **reference standard**

Trial/Study	N	Level of evidence	Risk of bias	Patient population	Key outcome(s)	Result used in meta-analysis
Jones 2010	225	III-1	Low		Sensitivity/Specificity	Not used
Meta-analysis	410 k=			<key outcomes> analysed		More accurate More specific/less sensitive

I=systematic review of level II studies;

II=a study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation

III-1=at study of test accuracy with an independent blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation

III-2=a comparison with reference standard that does not meet the criteria for level II and III-1 evidence

III-3=diagnostic case-control study

IV=study of diagnostic yield (no reference standard)>

B3.3 RISK OF BIAS ASSESSMENT

For studies of accuracy, the *MSAC Investigative Guidelines* provide examples of some risk of bias instruments, including the Quality Assessment of Diagnostic Accuracy Studies (QUADAS 2) tool, the Standards for Reporting of Diagnostic Accuracy (STARD) initiative and the ACCE Model Project (for genetic tests).

Whatever the choice, the method of assessing risk of bias should be transparent and justifiable. Please note – if an indirect comparison is presented then the risk of bias assessment of the individual trials/studies would need to be supplemented with an assessment of the exchangeability of the study populations being compared – that is, the results for the common reference standard arms should suggest that the populations are similar.

If there is a large volume of studies, consider presenting the risk of bias assessment in an Appendix.

<Table 17 Suggested tabular presentation for QUADAS-2 results

Risk of bias					Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Study 1	☺	☺	☺	☺	☹	☺	☺
Study 2	☹	?	☺	☺	☹	☺	☺

☺ Low Risk; ☹ High Risk; ? Unclear Risk>

B3.4 CHARACTERISTICS OF THE EVIDENCE BASE

See **Appendix C** for details on the individual studies included in the evidence base.

Develop an appropriate way of presenting information on the interventions or associations, and outcomes being tested for these study designs.

In this section specify whether or not the evidence base in the linked studies matches the proposed MBS populations. Depending on the number of trials identified, include the key studies only. Identify if there are key studies which have a study population applicable to the target population, in regards to the prevalence of disease or outcome of interest, and spectrum of disease.

<

B3.5 OUTCOME MEASURES AND ANALYSIS

See [Appendix C](#) for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

<To assess the diagnostic accuracy of the proposed test, studies were only included if they provided data that could be extracted into a classic 2 x 2 table, in which the results of the index test or the comparator were cross-classified against the results of the reference standard², and Bayes' Theorem was applied:

Table 18 Diagnostic accuracy data extraction

		Reference standard		
		<i>Disease +</i>	<i>Disease –</i>	
Index test	<i>Test +</i>	true positive	false positive	Total test positive
Or comparator	<i>Test –</i>	false negative	true negative	Total test negative
		Total with disease	Total without disease	

>

The key measures of accuracy of interest to MSAC are sensitivity and specificity, but other outcomes which may be reported are likelihood ratios, receiver operator characteristic (ROC) curves and the diagnostic odds ratio (DOR).

² Armitage, P, Berry, G & Matthews, JNS 2002, *Statistical methods in medical research*, fourth edn, Blackwell Science, Oxford.

Deeks, JJ 2001, 'Systematic reviews of evaluations of diagnostic and screening tests', in M Egger, G Davey Smith & DG Altman (eds), *Systematic Reviews in Healthcare: Meta-Analysis in Context*, second edn, BMJ Publishing Group, London, pp. 248–282.

Please note that if a genetic test is being presented to MSAC, a distinction is made between analytical sensitivity and specificity (which should be presented in Section B3) and clinical sensitivity and specificity (which should be presented in Section B4).

Comment on whether the measurement of outcomes in the included studies was likely to be accurate; discuss the validity of the measurement tools used; and make it clear how you are interpreting a clinically important effect for these outcomes. Discuss whether the statistical analyses presented in the studies were pre-specified or *post hoc*, and the limitations associated with the latter.

Discuss the methods you have used (and perhaps justification, if the method is unusual) to conduct your own statistical analyses for the assessment eg calculation of confidence intervals, statistical tests and meta-analyses, should be mentioned here.

If no reference standard is available, then diagnostic yield may relevant to include.

B3.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE?

Summary – Research question

Indicate whether a reference standard was available, against which the index test/s were compared. Use the table below to demonstrate comparative performance. If reference standard not available but a constructed reference standard is used (such as the “evidentiary standard”: the test option(s) used in the generation of evidence for the drug), then modify outcomes (and table) to “estimated sensitivity” etc; or modify table for ‘predictive accuracy’ and present outcomes such as agreement or concordance statistics (kappa). Studies in the table should be ranked according to study quality, or alternatively only summarise results from the highest quality studies. Perform a meta-analysis if evidence is homogenous enough, and sufficient data for summary statistics to be meaningful. If it is possible, assess the likelihood of publication bias.

Comparisons of tests are preferably answered using within-study comparisons, where all tests have been evaluated in the same population and verified using the same reference standard. Within-study comparisons are much less susceptible to confounding than between-study comparisons, where authors should be mindful of differences in the populations, reference standards and study designs. Present direct comparisons of the proposed investigative medical service against the main comparator first, followed by indirect comparisons where there is a common reference standard.

Table 19 Results of key accuracy trials comparing **intervention** and **comparator** against **reference standard**

Study ID	Result	Intervention [95%CI]	Comparator [95%CI]	Difference
Trial 1	Sensitivity	XX% [XX,XX]	XX% [XX,XX]	
	Specificity	XX% [XX,XX]	XX% [XX,XX]	
Trial 2				

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Table 20 Summary of findings for the accuracy of **intervention**, relative to **comparator**, in patients with **condition** with assumed pre-test probability (prevalence) of **XX%**

Outcomes	Participants	Intervention [95%CI]	Comparator [95%CI]	Quality of evidence	<Comments>
Sensitivity					
Specificity					

^a GRADE Working Group grades of evidence (Guyatt et al., 2013)

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

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

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

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

B3.7 EXTENDED ASSESSMENT OF RELIABILITY EVIDENCE <IF REQUIRED>

The term *reliability* (which is analogous to the concept of *precision*) refers to the amount of agreement of different operators or instruments applying the same investigative medical service. That is, a reliable investigative medical service is measuring something consistently. Reliability is sometimes referred to as *reproducibility* or *repeatability*.

Identify studies that clearly included reproducibility analysis of either the proposed investigative medical service or its main comparator; for example, if they reported assessing the same investigative medical service on the same specimens but under different conditions (such as different time intervals, operators or laboratories). Present any differences across laboratories in how they characterise results, such as the kappa or other relevant statistic. Identify whether there is an external quality assurance program by which the studies have specified how laboratories have benchmarked their assays.

Table 21 Results of reliability trials

Study ID	Study characteristics	Summary of reliability results
Trial 1		

B3.8 CONCORDANCE ANALYSIS <IF REQUIRED>

In the absence of a reference standard, and individual patient data are available, consider constructing a reference standard. If a reference standard cannot be constructed, calculate and report measures of agreement between the investigative medical service and a non-reference standard.

Provide the 2 x 2 table of results comparing the candidate test with the comparative method. Calculate and report measures of agreement (in terms of positive percent agreement and negative percent agreement, rather than sensitivity and specificity), comparing the proposed investigative medical service and the comparative method, and specify the method of performing the statistics (please note, there are two different ways of calculating the positive and negative percent agreement, so it is important to be explicit which method is used).

B3.9 INTERPRETATION OF EVIDENCE ON DIAGNOSTIC PERFORMANCE

Provide a summary of the overall evidence presented for diagnostic performance, to conclude whether the proposed investigative medical service is non-inferior (no worse than) or superior compared to its alternatives in terms of diagnostic performance.

B4 CLINICAL VALIDITY

B4.1 MEASURES OF CLINICAL VALIDITY

For applications to MSAC where this section is relevant, provide information on whether clinical validity was measured in the literature. The clinical validity of a test depends on the prevalence (or pre-test probability) of the target condition or outcome of interest. The key measures used are the positive and negative predictive values, which are the probabilities of disease or absence of disease in a tested individual. These measures are heavily dependent on the prevalence of disease in the study population, and cannot be readily transferred to different populations or pooled to produce a summary estimate. This section should therefore estimate of the prevalence of the target population or clinical information of interest based on data available for the target population or a systematic review of prevalence studies (or refer to Subsection A4). The accuracy data from Subsection B3.6 (sensitivity and specificity) can then be used with the relevant prevalence data to derive the positive and negative predictive values.

In the field of genetics, clinical validity refers to a test's ability to detect or predict the clinical disorder or phenotype associated with the genotype, and depends on the penetrance of the gene. For a genetic test, the four most relevant measures are the clinical sensitivity/clinical specificity and clinical positive/negative predictive values.

Amend this section as required. State what measures are used.

B4.1.1 REFERENCE STANDARD

State the appropriate reference standard for measurement of clinical validity (which will differ from the reference standard for accuracy/analytical validity in Section B3). As clinical validity refers to the predictive validity of a test for a given clinical outcome, the reference standard for clinical validity should be a clinically relevant outcome.

<

B4.1.2 RISK OF BIAS ASSESSMENT

If the studies included in this section are different from Section B3, then summarise the risk of bias for the clinical validity studies here (in the same manner as Subsection B3.3). If there is a large volume of studies, consider presenting the risk of bias assessment in an Appendix.

<Table 22 Suggested tabular presentation for QUADAS-2 results

Risk of bias					Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Study 1	☺	☺	☺	☺	☹	☺	☺
Study 2	☹	?	☺	☺	☹	☺	☺

☺ Low Risk; ☹ High Risk; ? Unclear Risk

B4.1.3 CHARACTERISTICS OF THE EVIDENCE BASE

See Appendix C for details on the individual studies included in the evidence base.

If studies included in this section are different from Section B3, describe the characteristics of the evidence base here. Depending on the number of trials identified, include the key studies only.

A summary of the characteristics of accuracy studies is shown in Table 16. Those studies which technically met the inclusion criteria, but which were not included in the results section or meta-analyses, are listed in Appendix E.

Table 23 Key features of the included evidence comparing intervention with comparator against reference standard

Trial/Study	N	Level of evidence	Risk of bias	Patient population	Key outcome(s)	Result used in meta-analysis
Jones 2010	225	III-1	Low		Sensitivity/Specificity	Not used
Meta-analysis	410 k=			<key outcomes> analysed		More accurate More specific/less sensitive

I=systematic review of level II studies;

II=a study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation

III-1=at study of test accuracy with an independent blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation

III-2=a comparison with reference standard that does not meet the criteria for level II and III-1 evidence

III-3=diagnostic case-control study

IV=study of diagnostic yield (no reference standard)

B4.1.4 OUTCOME MEASURES AND ANALYSIS

See Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

<To assess the diagnostic accuracy of the proposed test, studies were only included if they provided data that could be extracted into a classic 2 x 2 table, in which the results of the index test or the

comparator were cross-classified against the results of the reference standard³, and Bayes' Theorem was applied:

Table 24 Diagnostic accuracy data extraction

		Reference standard		
		<i>Disease +</i>	<i>Disease –</i>	
Index test	<i>Test +</i>	true positive	false positive	Total test positive
Or comparator	<i>Test –</i>	false negative	true negative	Total test negative
		Total with disease	Total without disease	

>

Comment on whether the measurement of outcomes in the included studies was likely to be accurate; discuss the validity of the measurement tools used; and make it clear how you are interpreting a clinically important effect for these outcomes. Discuss whether the statistical analyses presented in the studies were pre-specified or *post hoc*, and the limitations associated with the latter.

Discuss the methods you have used (and perhaps justification, if the method is unusual) to conduct your own statistical analyses for the assessment eg calculation of confidence intervals, statistical tests and meta-analyses, should be mentioned here.

Diagnostic accuracy outcomes are intermediate outcomes. Sensitivity, specificity, false positive rate, false negative rate, negative predictive value and positive predictive value are preferred – easy to understand and use in the economic model.

³ Armitage, P, Berry, G & Matthews, JNS 2002, *Statistical methods in medical research*, fourth edn, Blackwell Science, Oxford.

Deeks, JJ 2001, 'Systematic reviews of evaluations of diagnostic and screening tests', in M Egger, G Davey Smith & DG Altman (eds), *Systematic Reviews in Healthcare: Meta-Analysis in Context*, second edn, BMJ Publishing Group, London, pp. 248–282.

B4.1.5 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE?

Summary – **Research question**

Indicate whether a reference standard was available, against which the index test/s were compared. Use table below to demonstrate comparative performance. If reference standard not available but a constructed reference standard is used (such as the “evidentiary standard”: the test option(s) used in the generation of evidence for the drug), then modify outcomes (and table) to “estimated sensitivity” etc; or modify table for ‘predictive accuracy’ and present outcomes such as agreement or concordance statistics (kappa). Studies in the table should be ranked according to study quality, or alternatively only summarise results from the highest quality studies. Perform a meta-analysis if evidence is homogenous enough, and sufficient data for summary statistics to be meaningful. Separate tables may be required if there are comparisons against multiple reference standards, i.e. analytical validity against a genetic testing gold standard, and clinical validity against a clinical diagnosis.

Table 25 Results of key accuracy trials comparing **intervention** and **comparator** against **reference standard**

Study ID	Result	Intervention [95%CI]	Comparator [95%CI]	Difference
Trial 1	Sensitivity	XX% [XX,XX]	XX% [XX,XX]	
	Specificity	XX% [XX,XX]	XX% [XX,XX]	
	PPV	XX% [XX,XX]	XX% [XX,XX]	
	NPV	XX% [XX,XX]	XX% [XX,XX]	
Trial 2				

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Table 26 Summary of findings for the accuracy of **intervention**, relative to **comparator**, in patients with **condition** with assumed pre-test probability (prevalence) of **XX%**

Outcomes	Participants	Quality of evidence	Intervention [95%CI]	Comparator [95%CI]	Importance	<Comments>
Sensitivity						
Specificity						
True positives	k= ; n=		XX per 100 patients tested (95% CI)	XX per 100 patients tested (95% CI)		
True negatives			XX per 100 patients tested (95% CI)	XX per 100 patients tested (95% CI)		
False positives			XX per 100 patients tested (95% CI)	XX per 100 patients tested (95% CI)		
False negatives			XX per 100 patients tested (95% CI)	XX per 100 patients tested (95% CI)		
Inconclusive results						

^a GRADE Working Group grades of evidence (Guyatt et al., 2013)

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

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

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

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

<B4.2 PROGNOSIS OR PREDISPOSITION

State whether the information generated as a result of providing the investigative medical service under consideration is of prognostic value or generates information about predisposition.

Provide a summary of the key literature supporting the prognostic value of the information generated by the proposed investigative medical service or literature supporting its use as a predisposition test.

Summarise the key measures of association generated out of the cited literature (relative risk, etiologic fraction, odds ratio, hazard ratios etc). These findings will provide a baseline for the analysis conducted in Section B5 on clinical utility for those investigative medical services for which these measures would be referenced against as a 'baseline' if subsequent treatment were to be offered. >

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B5 CLINICAL UTILITY

Clinical utility refers to how likely the test is to significantly impact on patient management and health outcomes.

If the new test is as accurate, or less accurate, than the current test, and less safe, an assessment of the clinical utility of the investigative medical service would not be required, as there is a net harm.

If the new test is as, or more accurate, and as safe as, or safer than, the current test, then the clinical utility of the test should be evaluated. If the new test is more accurate but less safe, or less accurate but safer, the impact of change in patient management should be evaluated, as there is a trade-off.

B5.1 IMPACT ON CLINICAL MANAGEMENT (THERAPEUTIC EFFICACY)

B5.1.1 RISK OF BIAS ASSESSMENT

State the method for assessing the risk of bias in the studies included for clinical utility, and tabulate the risk of bias for the studies for this section. If there is a large volume of studies, consider presenting the risk of bias assessment in an Appendix.

For evidence of change in management, reviewers may choose to use the risk of bias table format in the *MSAC Therapeutic Guidelines*, although it should be noted that not all elements of risk of bias are covered by this format. Alternatives could be the Cochrane risk of bias tool or other tools suitable for RCTs, AMSTAR or PRISMA for systematic reviews, and other validated checklists for non-randomised or observational studies.

Whatever the choice, the method of assessing risk of bias should be transparent and justifiable. Please note – if an indirect comparison is presented then the risk of bias assessment of the individual trials/studies would need to be supplemented with an assessment of the exchangeability of the study populations being compared – that is, the results for the common comparator arms should suggest that the populations are similar.

If using the GRADE methodology, assessment of risk of bias should be performed per outcome.

B5.1.2 CHARACTERISTICS OF THE EVIDENCE BASE

See [Appendix C](#) for details on the individual studies included in the evidence base.

Develop an appropriate way of presenting information on the interventions or associations, and outcomes being tested for these study designs.

In this section specify whether or not the evidence base in the linked studies matches the proposed MBS populations. Depending on the number of trials identified, include the key studies only.

Studies which provided evidence on the impact of the test on patient management are characterised in **Error! Reference source not found..**

Table 27 Key features of the included evidence comparing **intervention** with **comparator** for patient management outcomes

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)	Result used in meta-analysis
Jones 2010	225	6 mths	Low			

<CC=case control; Coh=cohort; CS=case series; DB=double blind; MC=multi-centre; NR=non-randomised; OL=open label (unblinded); R=randomised; SB=single blind; X=cross-sectional..>

B5.1.3 OUTCOME MEASURES AND ANALYSIS

See **Appendix C** for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

Comment on whether the measurement of outcomes in the included studies was likely to be accurate; discuss the validity of the measurement tools used; and make it clear how you are interpreting a clinically important effect for these outcomes. Discuss whether the statistical analyses presented in the studies were pre-specified or *post hoc*, and the limitations associated with the latter.

Discuss the methods you have used (and perhaps justification, if the method is unusual) to conduct your own statistical analyses for the assessment eg calculation of confidence intervals, statistical tests and meta-analyses, should be mentioned here.

B5.1.4 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

< DOES IT IMPACT ON CLINICAL MANAGEMENT?

Summary – **Research question**

If a patient was identified as having the target condition or clinical information of interest (regardless of whether they were correctly identified), determine whether this translates to a net change in clinical management and present key evidence supporting this.

This is important to show that test results do guide changes in treatment decisions. Also assess whether there is evidence available showing that treatment decisions deviate from what is indicated by test results, e.g. when test negative patients receive the intervention or test positive patients do not receive the intervention. Does this show potential for leakage and/or the fact that clinicians do not trust the test results?>

Consider the relative clinical impact of false negatives and false positives arising from the test.

The format of results for therapeutic efficacy outcomes may differ to a large degree.

If following the GRADE methodology, produce a summary of findings table to summarise the important outcomes.

<B5.2 THERAPEUTIC EFFECTIVENESS (INCLUDING IMPACT OF EFFECT MODIFICATION)

For each therapeutic medical service option for which there is evidence of health outcomes, it is important to present the key findings of this evidence. Rather than go down an exhaustive approach as described in the Therapeutic Guidelines (Part II, Section B) for each therapeutic medical service option, it is recommended that applicants present a summary of the body of evidence supporting each option. To some extent, this will be left to the discretion of the applicant.

This section may not be required, if the test is found to be as accurate, but not as safe (net harm), or if the test is as accurate, and as safe (no added benefit; a cost minimisation analysis would be required). If there is no change in patient management, and the spectrum of patients treated is the same with the proposed test as with the existing test strategy, then a review of treatment effectiveness would not be required. For more details see Merlin et al (2013).

B5.2.1 RISK OF BIAS ASSESSMENT

State the method for assessing risk of bias, and tabulate the risk of bias for the studies in this section. If there are a large amount of studies, consider putting the risk of bias table in an Appendix.

For evidence of effectiveness, reviewers may choose to use the risk of bias table format in the *MSAC Therapeutic Guidelines*, although it should be noted that not all elements of risk of bias are covered by this format. Alternatives could be the Cochrane risk of bias tool or other tools suitable for RCTs, AMSTAR or PRISMA for systematic reviews, and other validated checklists for non-randomised or observational studies.

Whatever the choice, the method of assessing risk of bias should be transparent and justifiable. Please note – if an indirect comparison is presented then the risk of bias assessment of the individual trials/studies would need to be supplemented with an assessment of the exchangeability of the

study populations being compared – that is, the results for the common comparator arms should suggest that the populations are similar.

B5.2.2 CHARACTERISTICS OF THE EVIDENCE BASE

See [Appendix C](#) for details on the individual studies included in the evidence base.

Develop an appropriate way of presenting information on the interventions or associations, and outcomes being tested for these study designs.

In this section specify whether or not the evidence base in the linked studies matches the proposed MBS populations. Depending on the number of trials identified, include the key studies only.

If a new test leads to earlier, new or alternative treatments, the impact of these should be assessed. If the new test results in additional cases being detected, the spectrum of disease in the diagnosed population changes, and evidence of treatment effectiveness in the broader population (by means of a systematic review of treatment effectiveness) is needed. If there is no change in patient management from the new test, the last step of linked evidence is not required.

A summary of the trial characteristics of studies providing evidence relating to the health impact from the change in management is provided in **Error! Reference source not found.**

Table 28 Key features of the included evidence assessing [impact of change in patient management](#)

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Jones 2010	225	R, DB 6 mths	Low		Mortality	Not used
Smith 2012	310	R, OL 3 mths	High		Response rate	Not used

<CC=case control; Coh=cohort; CS=case series; DB=double blind; MC=multi-centre; NR=non-randomised; OL=open label (unblinded); R=randomised; SB=single blind; X=cross-sectional..>

>>

B5.2.3 OUTCOME MEASURES AND ANALYSIS

See [Appendix C](#) for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

Comment on whether the measurement of outcomes in the included studies was likely to be accurate; discuss the validity of the measurement tools used; and make it clear how you are interpreting a clinically important effect for these outcomes. Discuss whether the statistical analyses

presented in the studies were pre-specified or *post hoc*, and the limitations associated with the latter.

Discuss the methods you have used (and perhaps justification, if the method is unusual) to conduct your own statistical analyses for the assessment eg calculation of confidence intervals, statistical tests and meta-analyses, should be mentioned here.

B5.2.4 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

<DOES THE CHANGE IN MANAGEMENT IMPROVE HEALTH OUTCOMES?

Summary – Research question

Determine the implications of treatment of test positives (true positives and false positives), the implications of non-treatment (or alternative treatment) for test negatives (true negatives and false negatives), and prognostic or further clinical evidence if required.

The method of presenting this section will vary greatly depending on the impact that the test has on the management of patients.

For those following the GRADE methodology, specify the importance (in regards to patient relevant implications) of the true positive results, the true negative results, false positive results and false negative results, as: 'not important' (score 1-3), 'important, but not critical' (score 4-6), or 'critical' (score 7-9).

If following the GRADE methodology, produce a summary of findings table to summarise the important outcomes.

Table 29 Summary of findings assessing whether **intervention** changes management, relative to **comparator**, in patients with **condition**

Outcomes	Participants	Quality of evidence	Intervention [95%CI]	Comparator [95%CI]	Importance	<Comments>

B6 IMPACT OF REPEAT TESTING/MONITORING

Assessing the performance of an investigative medical service as part of a monitoring strategy generally requires longitudinal data prospectively generated from trial and/or cohort studies. Present in Section B6 of the assessment report, the relevant data that addresses the clinical validity, responsiveness, signal to noise ratio, detectability of long-term change, and practicality (as described in the Investigative Guidelines), to inform whether the proposed investigative medical service is justified to be used as part of a monitoring strategy.

B7 EXTENDED ASSESSMENT OF COMPARATIVE HARMS

This section allows for post-market surveillance/unpublished data on harms to be included if it is relevant to the assessment being undertaken. This might include data captured in administrative data sets, registry data, and recalls by regulatory agencies and from industry. This section is supposed to complement on the earlier safety section rather than replicate it, and is important for detecting rare adverse outcomes that might occur in the long term. Where these complementary data are from non-comparative sources, an overall comparative conclusion should be drawn.

B8 INTERPRETATION OF THE CLINICAL EVIDENCE

It is important to classify the therapeutic profile of the proposed investigative test and associated interventions in relation to its main comparator (i.e. whether it is therapeutically superior, inferior or equivalent to the comparator).

On the basis of the evidence profile (summarised in Error! Reference source not found.Error! Reference source not found.), it is suggested that, relative to the comparator, the test and associated interventions has superior/non-inferior/uncertain/inferior safety and superior/non-inferior/uncertain/inferior effectiveness.

You might like to discuss here how you came to the conclusions above.

The table below is based on the GRADE summary of findings, with a couple of minor modifications. Error! Reference source not found. provides a summary of findings suitable for inclusion if direct evidence of health benefit is available. Error! Reference source not found. gives an example of a summary of findings if a linked evidence approach has been used.

Please consult the GRADE Guideline development handbook⁴ for information on how to complete the table. If including linked evidence, the table should consider what the consequences of being falsely or truly identified as having or not having the disease. The importance of the accuracy outcomes will therefore depend on the evidence regarding the impact on management, and whether this results in superior or inferior health outcomes. Please explain in the comments column.

⁴ <http://www.guidelinedevelopment.org/handbook/>

Table 30 Balance of clinical benefits and harms of **intervention**, relative to **comparator**, and as measured by the **critical** patient-relevant outcomes in the key studies

Outcomes (units) Follow-up	Participants (studies)	Quality of evidence (GRADE)	Relative effect (95%CI)	Risk with control	Risk or risk difference with intervention	<Comments>

^a GRADE Working Group grades of evidence (Guyatt et al., 2013)

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

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

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

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

Table 31 Summary of findings for the linked evidence comparison of **intervention**, relative to **comparator**, in patients with **condition** with assumed pre-test probability (prevalence) of **XX%**

Outcomes	Participants	Quality of evidence	No. per 100 patients with comparator	No. per 100 patients with intervention	Importance	<Comments>
True positives	k= ; n=					e.g. benefit from earlier diagnosis and treatment
True negatives						e.g. almost certain benefit from reassurance
False positives						e.g. likely anxiety and possible morbidity from additional testing and treatment
False negatives						e.g. possible detriment from delayed diagnosis
Inconclusive results						
Harms						

^a GRADE Working Group grades of evidence (Guyatt et al., 2013)

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

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

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

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

SECTION C

TRANSLATION ISSUES

Where **consistency, indirectness, applicability or other considerations have impacted on the confidence in the estimates (ie very low to moderate quality)** in the summary of findings table above, please indicate in Section C below how the data are translated for use in the economic model (if an economic model is produced).

For example, if **consistency** was poor (eg high heterogeneity in a meta-analysis), a subgroup analysis may be undertaken or referred to in Section C and then modelled in Section D. According to the *MSAC Therapeutics Guidelines*, this would be classified as an Applicability Translation Issue. Example tables and approaches are suggested in the *Guidelines*.

If the **directness** (applicability) of the evidence to the target Australian population is poor, because the people participating in the studies (in the evidence base) were different, then Section C may require a description of the baseline risk in the Australian population which - in the model - can then be multiplied by the relative treatment effects reported in the evidence base. This is also classified as an Applicability Translation Issue in the *MSAC Therapeutic Guidelines*. If, however, the generalisability of the evidence to the Australian population is poor because the trial follow-up was not representative of the use of the test in practice (ie an “**other consideration**”), then this is an Extrapolation Translation Issue according to the *MSAC Therapeutic Guidelines*.

If the **directness** (applicability) of the evidence is poor in terms of the healthcare context, then Section C would need to provide a list and unit costs of the healthcare resource usage likely in the Australian setting. This is an Applicability Translation Issue according to the *MSAC Therapeutic Guidelines*.

If the outcomes used are **indirect** (eg the use of surrogate or intermediate outcomes) then this will require translation for use in the economic model eg transformation of the surrogate or intermediate outcomes in order to estimate clinically relevant outcomes such as QALYs. This would be a Transformation Issue according to the *MSAC Therapeutic Guidelines*.

Briefly indicate the key translation issues and pre-modelling studies that are used to adapt the evidence presented in Section B for the purposes of the economic evaluation (eg the model that predicts the cost-effectiveness if the new test is used according to the proposed MBS item descriptor). Please read Section C of the *MSAC Therapeutic Guidelines* for guidance on how to address each type of translation issue.

If translation of the clinical evidence is not needed or not undertaken, please state this.

C.1. OVERVIEW

Provide an overview of the model to be used in Section D, and explain where the evidence in Section B needs to be translated in order to fit the model.

C.2. APPLICABILITY TRANSLATION ISSUES

Define application issues: Describe any ways in which the participants and circumstances of use in the studies presented in Section B differ from the proposed population for treatment (including the baseline risk of participants and circumstances of use).

Present and justify a focused analytical plan (which specifies details of data, sources, methods and analyses) to address each applicability issue identified. Convert each defined applicability issue into a succinct question that can be addressed in a pre-modelling study.

Present the results of each pre-modelling study undertaken to address each applicability issue specified. Estimate the comparative treatment effect as results for the proposed investigative medical service; its main comparator; and the increment with its 95% confidence interval.

Discuss the results of each pre-modelling study and explain how they will be used in the economic evaluation (Section D).

C.3. EXTRAPOLATION TRANSLATION ISSUES

Define extrapolation issues: State whether there is a need to extrapolate the outcomes reported in the clinical evaluation beyond the study horizon.

Present and justify a focused analytical plan (which specifies details of data, sources, methods and analyses) to address each extrapolation issue identified. Convert each defined extrapolation issue into a succinct question that can be addressed in a pre-modelling study.

Present the results of each pre-modelling study undertaken to address each extrapolation issue specified. Estimate the comparative treatment effect as results for the proposed investigative medical service; its main comparator; and the increment with its 95% confidence interval.

Discuss the results of each pre-modelling study and explain how they will be used in the economic evaluation (Section D).

C.4. TRANSFORMATION ISSUES

Define transformation issues: State whether there is a need to transform the nature of the outcomes measured in the clinical evaluation (i.e. taking a surrogate or intermediate endpoint, and transforming it to a QALY or equivalent).

Present and justify a focused analytical plan (which specifies details of data, sources, methods and analyses) to address each transformation issue identified. Convert each defined transformation issue into a succinct question that can be addressed in a pre-modelling study.

Present the results of each pre-modelling study undertaken to address each transformation issue specified. Estimate the comparative treatment effect as results for the proposed investigative medical service; its main comparator; and the increment with its 95% confidence interval.

Discuss the results of each pre-modelling study and explain how they will be used in the economic evaluation (Section D).

C.5. ANY OTHER TRANSLATION ISSUES

Define any other translation issues: State whether there is any other need to translate from the clinical evaluation.

Present and justify a focused analytical plan (which specifies details of data, sources, methods and analyses) to address each translation issue identified. Convert each defined translation issue into a succinct question that can be addressed in a pre-modelling study.

Present the results of each pre-modelling study undertaken to address each translation issue specified. Estimate the comparative treatment effect as results for the proposed investigative medical service; its main comparator; and the increment with its 95% confidence interval.

Discuss the results of each pre-modelling study and explain how they will be used in the economic evaluation (Section D).

C.6. RELATIONSHIP OF EACH PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION

Provide a summary from Sub-section C2, C3, C4 and C5 and their uses in response to Section D.

Table 32 Example of summary of results of pre-modelling studies and their uses in the economic evaluation

Section	Pre-modelling study	Results used in Section D	Cross-reference	Results used in Subsection D.6	Cross-reference
Applicability					
	Study 1				
	Study 2				
Extrapolation					
	Study 3				
Transformation					
	Study 4				
Other					
	Study 5				

SECTION D

ECONOMIC EVALUATION

D.1. OVERVIEW

The clinical evaluation suggested that, relative to the comparator, the test and associated interventions has superior/non-inferior/uncertain/inferior safety and superior/non-inferior/uncertain/inferior effectiveness based on the evidence profile given in Error! Reference source not found. Error! Reference source not found.. Table 33 sets out the framework that was used to classify the clinical evidence in Section B so that a decision could be made about the type of economic analysis to undertake (if any) in this Section.

Table 33 Classification of the comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Non-inferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Non-inferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

^a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

^b An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

It was therefore decided that a XXXX analysis would be undertaken for the economic evaluation.

An economic evaluation should be presented in all assessment reports to be considered by MSAC except when a service is indisputably demonstrated to be associated with net clinical harms to patients (as it is unlikely that MSAC will recommend government subsidy of the service).

State whether the base case of the economic evaluation is generated by:

- a trial-based economic evaluation (i.e. based on randomised controlled trials presented in section B)

- a stepped economic evaluation (i.e. derived from randomised controlled trials presented in Section B using variables reported in Section C of the assessment report)
- a modelled economic evaluation based on an indirect comparison of randomised trials or non-randomised studies.

D.2. POPULATIONS AND SETTINGS

Describe and justify the demographic and patient characteristics of the population included in the economic evaluation.

Describe and justify the circumstances in which the proposed medical service and main comparator are used in the economic evaluation.

Assess the consistency of the demographic and patient characteristics and of the specified circumstances of use across the study populations, the population in the economic evaluation and the population for whom listing is sought.

Provide information to allow MSAC to assess whether the evidence presented is applicable and generalizable to the population and circumstances of use for which the service is proposed.

D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in [Table 34](#).

Table 34 Summary of the economic evaluation

Perspective	
Comparator	
Type of economic evaluation	Eg. cost-effectiveness, cost-utility, cost-minimisation, cost-consequences.
Sources of evidence	Eg. Systematic review
Time horizon	Eg X years in the model base case
Outcomes	Eg. Name or list the outcome/s used in the model eg. LYG and QALYs
Methods used to generate results	E.g. trial-based, cohort expected value analysis, Markov model
<Health states>	Only put in this row, if it is relevant to your model
<Cycle length>	Only put in this row, if it is relevant to your model
Discount rate	
Software packages used	

See Table D.3.1 in the *MSAC Therapeutic Guidelines*.

LITERATURE REVIEW

A search the literature should be conducted for published cost-effectiveness analyses of the proposed service.

STRUCTURE OF THE ECONOMIC EVALUATION

Specify the name and version of any software package used to conduct the economic evaluation.

The description of the economic evaluation should include:

- a description of the testing options for which costs and outcomes are estimated in the economic evaluation
- a statement defining in detail the therapy options for which costs and outcomes are estimated in the economic evaluation
- a description of each of the types of event and health states possible in the economic evaluation, together with a justification of the selection of each health state for inclusion in the evaluation and a justification for those that were considered potentially suitable but that were excluded to avoid excessive complexity (if relevant)
- a description of the relationships and interactions between the various events and health states possible in the economic evaluation (including, where relevant for a state transition model, a detailed description of all possible transitions between the health states)
- a description of all assumptions made in the construction of the economic evaluation
- a decision tree diagram summarising the structure of the economic evaluation
- the methods used to calculate the results of the economic evaluation (e.g. cohort expected value analysis, Monte Carlo simulation).

The structure of the economic evaluation is shown in [Figure 4](#).

If you are writing a **contracted assessment** you will need to save the decision analytic or state transition diagram as a picture file (TIFF) and copy and paste in, so that web accessibility requirements are met.

Figure 4 Decision analytic structure of the economic evaluation.

Assumptions incorporated into the model structure:

Justify the economic evaluation characteristics summarised in Table 34. Justify the appropriateness of the structure in reflecting the context of use of the compared alternatives and the outcomes of their use.

Define and justify the time horizon and nature of the outcomes used in the economic evaluation.

Describe the methods used to calculate the results of the economic evaluation (e.g. cohort expected value analysis, Monte Carlo simulation).

D.4. INPUTS TO THE ECONOMIC EVALUATION

Present, as a minimum, the following information for each variable used in the economic evaluation:

- name (and definition, as necessary)
- quantity in natural units (as appropriate; for example, this is not applicable for unit costs); and
- source.

Identify and list the direct health care resource items for which there would be a change in use associated with substituting the proposed medical service for the main comparator and define each in terms of natural units.

Estimate the present value of direct health care resource costs and health outcomes.

Discuss the implications for the economic evaluation of any important deficiencies in the available evidence base.

Summarise this information in a table for each type of variable and provide further details of calculations, as necessary.

D.5. RESULTS OF THE ECONOMIC EVALUATION

Present the cost per patient per course if the proposed medical service is for acute or self-limited therapy, or the cost per patient per year if the proposed medical service is for chronic or continuing therapy.

Present the remaining results of the economic evaluation first in a disaggregated form, then in increasingly aggregated forms. Use discounting as appropriate.

Present the appropriately aggregated and discounted results separately for outcomes and costs, and separately for the proposed medical service and its main comparator.

Present separate estimates of the incremental cost and the incremental effectiveness of substituting the proposed medical service for the main comparator.

For cost-effectiveness and cost-utility analyses, present the incremental cost-effectiveness ratio as the incremental cost of achieving each extra unit of outcome with the proposed medical service substituted for the main comparator (the base case of the economic evaluation).

Draw a conclusion from the base-case economic evaluation that reflects the degree of uncertainty around the presented incremental cost-effectiveness ratios.

Two different formats for presenting the findings of the economic evaluation are provided below. Choose which of these is appropriate for the evaluation that has been undertaken. Please delete the inappropriate one and/or incorporate additional summary information, as required.

<INCREMENTAL COSTS AND EFFECTIVENESS

The overall costs and outcomes, and incremental costs and outcomes as calculated for the test and comparator in the model, with the base case assumptions, are shown in the table below.

Table 35 **Title**

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Intervention					
Comparator					

ICER = Incremental Cost Effectiveness Ratio>

<STEPPED ECONOMIC EVALUATION

The results of a stepped analysis of the base case economic evaluation are given in the tables below.

<Table 36 Implications for the base case economic evaluation of applying the results of the clinical evaluation (Step 1 then Step 2)

Population and circumstances of use	As defined in trial(s) using ITT population	As defined by the requested restriction ^a
Costs		
Costs of test and associated therapy	(Trial-based)	(Trial-based) ^b
Costs of comparator	(Trial-based)	(Trial-based) ^b
Incremental costs	(Trial-based)	(Trial-based) ^b
For each trial-based outcome relied on in the economic evaluation before any extrapolation and/or transformation		
Extent of outcomes with the proposed medical service		
Extent of outcomes with the main comparator		
Incremental effectiveness (with 95% CI)	(From Subsection B.6)	(From Subsection C2-C5)
ICER (cost/XXX)	XXX (Step 1)	XXX (Step 2)

CI=confidence interval; ICER=incremental cost-effectiveness ratio; ITT=intention to treat >

^a If there is no need to apply the results of the clinical evaluation, the data in this column should be identical to the data in the adjacent column reporting the incremental impacts using the results for the study/trial's ITT population.

^b Justify any variation in estimate of incremental costs from the trial-based costing.

Subsections refer to the *MSAC Therapeutic Guidelines*.

<Table 37 Implications for the base case economic evaluation of extrapolating and transforming the results of the clinical evaluation (Step 3)

	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness
For each trial-based outcome relied on in the economic evaluation without further modification	(From corresponding row of Step 2 in <Table 36)	(From corresponding row of Step 2 in <Table 36)	(From corresponding row of Step 2 in <Table 36)
For any trial-based outcome relied on in the economic evaluation <i>with any extrapolation from the time horizon of the trial(s) only</i>	(Based on corresponding extrapolation of duration of treatment, if any)	(From Subsection C.3 if extrapolation is required)	(Alternative Step 3a)
For any important outcome generated for or by the economic evaluation from the trial-based outcome(s) (' <i>transformation of nature of outcome</i> ' only)	(Include here any modelled increases in the provision of some resources and any modelled offsetting decreases of others)	(From Subsection C.4 if possible, or if this approach is used, explain why a presentation here is not possible)	(Alternative Step 3a)
For the final outcome relied on in the economic evaluation generated as a valuation of the trial-based outcome(s) (' <i>value transformation</i> ' only)	(Should not change from Step 2 because nature of outcome does not change)	(From Section C if possible, or if this approach is used, explain why a presentation here is not possible)	(Alternative Step 3a)

For the final outcome relied on in the economic evaluation combining any <i>extrapolation</i> from the time horizon of the trial(s) with any <i>transformation</i> of the trial-based outcome(s)			(Completed Step 3 and expected base case) XXX (Step 3)
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--	--	---------------------------------------------------------------------

>

Subsections refer to the *MSAC Therapeutic Guidelines*.

D.6. SENSITIVITY ANALYSES

Present univariate (one-way) sensitivity analyses on all variables using plausible extremes of values, and justify the selection of those extreme values.

Tabulate all univariate sensitivity analyses alongside the base case.

Present multivariate sensitivity analyses combining variables shown to be sensitive in the univariate analyses.

Examine and present the sensitivity of the results of the economic analysis to any changes in assumptions concerning the structure of the modelled economic evaluation that are important but uncertain.

The modelled results were most sensitive to >

Table 38 Key drivers of the economic model

Description	Method/Value	Impact
Eg Time horizon	25 years; assumed from 6 month trial duration	High, favours intervention
Eg Upper 95% CL of the difference in outcomes	\$100,000/QALY	High; favours comparator
etc		

SECTION E

FINANCIAL IMPLICATIONS

E.1. JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

Where data are available (published or unpublished) from one or more types of data sources:

- summarise the methods used to obtain the data
- present the relevant main results
- interpret the findings
- discuss the limitations (including the representativeness of the results) and biases of the method adopted.

Where data are obtained via one or more studies commissioned for the assessment report:

- describe the gap in the information to be addressed by the commissioned analysis
- summarise the methods used to obtain and analyse the data
- present the relevant main results
- interpret the findings
- discuss the limitations (including the representativeness of the results) and biases of the method adopted.

<An epidemiological approach has been used to estimate the financial implications of the introduction of **XXX**.>

E.2. USE AND COSTS OF **XXX**

Estimate the number of patients with the medical condition targeted by the proposed medical service, the number who would be eligible for the requested restriction and the number of patients likely to use the proposed medical service.

Estimate the number of times the proposed medical service is delivered in each year over five years (disaggregated into proportions for MBS-funding, and by beneficiary type).

Estimate the costs for each form of the proposed medical service in each year over five years.

Aggregate these cost calculations for the proposed medical service overall in each year over five years.

E.3. CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

Identify the other MBS-funded medical services that are likely to be affected by listing the proposed medical service.

For each proposed medical service, estimate the extent of change in the number of times the proposed medical service is delivered each year over five years (disaggregated into proportions for the MBS and by beneficiary type).

Aggregate both these cost calculations for the other affected medical services in each year over five years.

E.4. FINANCIAL IMPLICATIONS FOR THE MBS

Estimate the net financial implications for the MBS in each year over five years by subtracting the net cost offsets for both the aggregated estimates calculated in Subsection E.3 from the corresponding estimates calculated in Subsection E.2.

The financial implications to the MBS (inclusive of safety net implications) resulting from the proposed listing of **XXX** are summarised in **Table 39**.

Table 39 Total costs to the MBS associated with **XXX**

	2015-16	2016-17	2017-18	2018-19	2019-20
Test					
Number of services					
Sub-total cost					
Associated interventions					
Number of services					
Sub-total cost					
<Any co-administered services currently MBS listed>					
Number of services					
Sub-total cost					
Total services					
Total cost					

This section should primarily focus on the financial implications in terms of MBS rebates. If a service is primarily out-of-hospital, then there will need to be a separate analysis of the financial implications to the safety net. The ratio of in-hospital vs out-of-hospital needs to be determined and the 75% vs 85% rebate (or if a GP service, 100% rebate), respectively, proportionately assigned in the costing. The Department is interested in the rebate as the input cost, not the schedule fee.

E.5. FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

Estimate the extent of net change in the number of prescriptions processed by Medicare Australia for payment (and, where appropriate, the net change in the number of authorisations by Medicare Australia) in each year over five years.

Estimate the net financial implications for Medicare Australia in each year over five years of:

- processing treatments for payment
- all these costs aggregated together.

Estimate the extent of net change in the number of each type of affected MBS item provided in each year over five years.

Estimate the net financial implications for each affected MBS item in each year over five years, multiplying the extent of change of each MBS item by the following unit costs:

- the schedule fee
- the appropriate benefit (i.e. with the appropriate patient co-payment removed).

Aggregate both these cost calculations across all affected MBS items to estimate the net financial implications for the MBS in each year over five years.

Estimate the net financial implications for government health budgets in each year over five years.

E.6. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

- In each step of the calculations, assess the sources of uncertainty and distinguish the type and degree of uncertainty in utilisation and financial estimates.
- Where possible, explain the nature of each uncertainty and its impact on the overall estimates.
- Estimate the level of the uncertainty and propose ways to reduce it.

E.5 and E.6 may be integrated, as needed, so the sensitivity analyses are presented immediately after the base calculations estimated in E.5.

SECTION F

OTHER RELEVANT CONSIDERATIONS

Over time, a number of issues have arisen that are important for some assessment reports, but are not necessary for all assessment reports. These have included include access/equity principles, 'rule of rescue', organisation of care, impact on consumers/patients and other relevant factors that can affect MSAC's assessment of proposed medical services.

Discussion of key trials that are ongoing and due to be report results could also be discussed here.

If the assessment report raises any equity assumptions that particularly affects consideration of the cost-effectiveness of the proposed medical service, describe the implications, where appropriate, with reference to a sensitivity analysis.

If the assessment report makes any claim that the 'rule of rescue' is applicable, set out the basis for that claim.

If the assessment report identifies any other relevant factor not requested elsewhere, discuss it in response to this Section.

The content of this section is topic-specific; it is, therefore, optional.

<Appendix A Clinical Experts and Assessment Group

This Appendix is only relevant for contracted assessments. Delete for submission-based assessments and re-label the subsequent Appendices.

<HEALTH EXPERT STANDING PANEL (HESP) (IF ALLOCATED)

Member Expertise or affiliation

Name Expertise

ASSESSMENT GROUP

XXXX

Name Position

Noted conflicts of interest

There were no conflicts of interest.>

APPENDIX B

SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES

Electronic database	Time period searched
Embase <i>Note – Embase.com and the previous 12 months of PubMed would be more comprehensive as Embase.com includes both Embase and Medline entries and PubMed includes unindexed (pre-Medline) entries</i>	
Medline	
The Cochrane Library (CDSR, Central, DARE, HTA, HEED)	

Add rows if needed

ADDITIONAL SOURCES OF LITERATURE (INCLUDING WEBSITES)

Source	Location
Australian Clinical Trials Registry	
National Institutes of Health	

Add rows if needed

APPENDIX C

STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Profiles of studies on **XXXX** included in the systematic literature review

Authors Study ID Publication Year	Study design/ duration	Level of evidence ^a and risk of bias assessment ^b	Location Setting Length of follow-up	Study population characteristics Eg N, age, gender, co-morbidities, disease description and severity, baseline function	Description of Intervention <including duration of treatment>	Description of Comparator <including duration of treatment>	Description of Reference standard	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis

<tudy design characteristics such as CC=case control; Coh=cohort; CS=case series; DB=double blind; MC=multi-centre; NR=non-randomised; OL=open label (unblinded); R=randomised; SB=single blind; X=cross-sectional etc>

^a source: see [NHMRC hierarchy of evidence](#) .; ^b risk of bias as it relates to primary outcomes of the systematic review

Create separate tables for different types of linked evidence, as included, and amend as necessary.

APPENDIX D

EVIDENCE PROFILE TABLES

In order follow GRADE methodology, the full evidence profile tables should be included (with footnotes), per comparison, including all the critical and important outcomes. It is suggested that for accuracy, the ‘indirectness’ of Patient, Intervention, and Comparator be assessed, but not the Indirectness of Outcomes, as all accuracy outcomes are indirect.

If no evidence for individual critical outcomes is identified, a row in the table could be included with a comment that no data were found. Examples of how evidence profile tables may be formatted are shown below (amend as required). It is suggested that these data are condensed into a ‘Summary of findings’ table, to be included in the main body of the report (Section B.8).

Table 40 Evidence profile table for the accuracy of **proposed test** compared to **comparator** for **population** (baseline risk, e.g. prevalence **XX%**)

Proposed test (sensitivity **XX**, 95%CI **XX** to **XX**; specificity **XX**, 95%CI **XX** to **XX**), **Comparative test** (sensitivity **XX**, 95%CI **XX** to **XX**; specificity **XX**, 95%CI **XX** to **XX**),

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (e.g. publication bias)	Number of patients per 100 tested for proposed test	Number of patients per 100 tested for comparator test	Test accuracy QoE	Importance
True positives										
False negatives										
True negatives										
False positives										

QoE=quality of evidence

Table 41 Evidence profile table for the change in management due to **proposed test** compared to **comparator** for **population**

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (e.g. publication bias)	Result for proposed test	Result for comparator test	Change in management QoE	Importance

QoE=quality of evidence

Table 42 Evidence profile table for the impact of change in management due to **proposed test** compared to **comparator** for **population**

Outcome	No. of participants, No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (e.g. publication bias)	Result	Result	Impact of change in management QoE	Importance

QoE=quality of evidence

APPENDIX E

EXCLUDED STUDIES

Only list studies which would technically meet the inclusion criteria, but have been excluded from the review for some reason (i.e. could not extract data, duplicated data, of a low level evidence etc).

REFERENCES

Guyatt, G, Oxman, AD, Sultan, S, Brozek, J, Glasziou, P, Alonso-Coello, P, Atkins, D, Kunz, R, Montori, V, Jaeschke, R, Rind, D, Dahm, P, Akl, EA, Meerpohl, J, Vist, G, Berliner, E, Norris, S, Falck-Ytter, Y & Schunemann, HJ 2013, 'GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes', *J Clin Epidemiol*, vol. 66, no. 2, Feb, pp. 151-157.

Merlin, T, Lehman, S, Ryan, P, Hiller, JE 2013, 'The "Linked evidence approach" to assess medical tests: a critical analysis', *International Journal of Technology Assessment in Health Care*, vol. 29, no. 3, pp. 343 – 350.