Title

The date should reflect the date the final report is submitted to the Department.

Month Year

MSAC application no. XXXX

Critique report

Prepared by Assessment Group

VERSION CONTROL

DOCUMENT HISTORY

Version Number	Date Changed	Author	Reason for Change
1.1	18-Feb-2016	Sean McCandless	Version control introduced
2.1	9-Mar-2016	Sean McCandless	Added Alt text to Version Control tables Change name and printed to Portable Document Format in preparation for publishing Online.
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DOCUMENT APPROVAL

Version Number	Date Changed	Author	Reason for Change
2.0	18-Feb-2016	Sean McCandless	Version control introduced
3.0	9-Mar-2016	Sean McCandless	Document Released
4.0	28-Jul-2016	Sean McCandless	Document Released

Note to reader: this document contains hidden text. Please click on the show/hide icon ¶ in the Home menu so that you can see the instructions and suggestions for filling in this template. Delete this text prior to finalisation of the document.

This template is meant for use when critiquing a submission-based assessment (SBA) of an investigative test (i.e. for diagnosis, prognosis, staging, screening, etc).

This text is written in hidden text. The **hidden (red) text** provides instructions or suggestions for completing the different sections of the template. *Hidden text styles can be selected from the Font menu.* All hidden text has a dotted underline under it. When you have finished addressing the hidden text in this template, please remember to delete it and change the style to normal (non-hidden) text. If you don't do this you will have large blank areas in your document.

This template is written in Microsoft Word 2010 – this is because some people may not yet be using Word 2013.

This document is a **template file (ie .dotx**). This means if you double-click on the file it will open as a new Word document but it will contain the same formatting (fonts, heading styles) and structural elements as included in the template. This will help with maintaining consistency in the presentation and data elements across all critiques of SBAs.

Any **text written in black** in the template **must** be included in the report *unless* the text is surrounded by this type of parentheses < >. These parentheses indicate that the text is optional or its inclusion will depend on a specific circumstance. Please remember to *remove* the < > , if you decide to *include* the optional text in the report. Please remember to delete the < > *and* the text it surrounds if you decide to *exclude* the optional text from the report.

The critique template is structured into Sections A, B, C, D, E and F in order to align with the *MSAC Technical Guidelines – Investigative* which are available on the MSAC website.

When writing your critique of the statements made in the SBA, you should **use the "Comment" style** which ensures the text is in italics ie. *all comments should be written in italics.*

Following completion of the report, the hidden text on this page and throughout the document – as well as the next page break - should be deleted.

CONTENTS

TABLES

FIGURES

EXECUTIVE SUMMARY

KEEP EXECUTIVE SUMMARY SHORT – 6 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 or critique, but rather, pointing out where critical uncertainties exist.*

Clearly set out the key aspects and issues that arose during the critique. For each section in the executive summary, keep the text very brief.

A submission based assessment (SBA) requesting MBS listing of <insert name of investigative service> for <insert description of patient population(s)> was received from <insert applicant's name> by the Department of Health in <insert month & year SBA was received>.

<This application is following a fit-for-purpose pathway, therefore a PICO Confirmation outlining the proposed use of <investigative service> in Australian clinical practice was not <presented to/ratified by> the PICO Confirmation Advisory Sub-Committee (PASC).>

If this is the case, then Table 1 below does not need to be inserted.

ALIGNMENT WITH AGREED PICO CONFIRMATION

<A PICO Confirmation for MSAC Application <number> was approved by the PICO Advisory Sub-Committee (PASC) of MSAC on <insert month, year>. A comparison of the consistency of this SBA with the PASC-approved PICO Confirmation is given in Table 1.>

If there was a PASC-approved PICO Confirmation then the checkbox below should be completed, providing a summary of whether the SBA has followed the PICO Confirmation. If the SBA has provided reasons as to why the PICO Confirmation was not followed, provide a very brief summary in the table of the justification for the change. If you wish to comment on whether the justification is reasonable, do so briefly (in italics – use the table text comment style provided) and expand in the relevant section of the executive summary if needed. If no justification is provided, indicate that the rationale was not given.

Table 1 PICO Confirmation checkbox

PASC-approved PICO Confirmation Item	Compliance	Change and justification provided in SBA
Proposed MBS listing	<*Yes/No*>	
Population / clinical indication	<*Yes/No*>	
Comparator	<*Yes/No*>	
Reference/evidentiary standard	<*Yes/No*>	
Clinical management algorithm	<*Yes/No*>	
Clinical outcomes assessed	<*Yes/No*>	
Healthcare resources	<*Yes/No*>	

Source: <Table/Figure, p/pp of SBA> <*Table constructed during the evaluation*>

NA=not applicable; PASC=PICO Confirmation Advisory Sub-Committee

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 SBA.

Table 2 Proposed MBS item descriptor

Category <Insert proposed category no> – <INSERT CATEGORY NAME>
<Insert intervention name> <Specify any restrictions on use e.g., patient characteristics to be satisfied, limits on frequency of use, limits on who can provide the item, or where it can be provided, etc> <Specify any relevant explanatory notes>
Fee: <insert proposed MBS fee>

Source: <Table/Figure>, <p/pp of the SBA>

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

State comparator name or provide a short description.

Comment if not the appropriate comparator and, in a sentence, state why. Recommend an alternative comparator. Is the comparator hospital based or MBS listed?

If this aspect is complex, reference the in-depth discussion in Section A.4. Ensure that any information here is also in Section A.4 (i.e., no new information here).

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.

Comment if not the appropriate reference standard and, in a sentence, state why.

Clinical management algorithm(s)

Comment on the proposed algorithm – is it realistic? Is it based on an evidence based or consensus-based clinical practice guideline? You might like to refer to the location of the clinical management algorithms in the main body of the report.

Are there any limitations on how the investigative test would be provided or the setting in which the test can be provided?

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.

Comment briefly on whether the claim has been supported by the evidence base.

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 3 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. >

Comment on the quality of the evidence base and the risk of bias associated with the key safety and effectiveness outcomes.

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

Summarise the results of comparative safety presented in Section B of the SBA. Include a summary table from B.6, if relevant.

Identify the main adverse events (AEs).

Comment on whether there are clinically relevant differences in the reported harms, irrespective of whether the results are statistically significant. Note if there is a risk with use outside the immediate indication.

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.

Comment on the results. Has the investigative test met the trial requirements for superiority, equivalence, non-inferiority, etc? Note key issues discussed in Section B that may require the results to be interpreted with caution or that may invalidate the results (consider bulleting).

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 4 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.**

Comment on whether the clinical claim is reasonable and justify your view.

Comment on the balance of clinical benefit and harms associated with the proposed medical service.

Effectiveness from linked evidence

1. Accuracy

Indicate whether a reference standard was available, against which the index test/s were compared. The positive predictive value and negative predictive value should be calculated with reference to the relevant prevalence/incidence in the target population. 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.

Comment on the accuracy results, and any key points of interest that will affect interpretation of them.

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?

Comment on the change in management results, and whether the changes are likely applicable to the Australian setting.

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.

Comment on the therapeutic effectiveness results. What are the uncertainties surrounding the clinical benefit?

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.

Comment on the results of the pre-modelling studies, do they appropriately address the issues? Reference further discussion for complex items in Section C.

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 5 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*.

Comment briefly on the model, is it appropriate, are there any assumptions that have not been justified or may not be reasonable? Does it adequately represent reality?

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. **Where you have re-calculated a number due to an error in the SBA then write the modified number in italics immediately below the calculation from the SBA (this would include the ICER).**

Table 6 Title

Test	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Index test and associated interventions	$XXX	$XXX	XX	XX	$XXX/QALY
Comparator	$XXX	$XXX	XX	XX	$XXX/QALY

ICER = Incremental Cost Effectiveness Ratio>

Comment on the ICER and whether it accurately represents the cost-effectiveness, in the evaluator's judgment, of listing the intervention.

<The modelled results were most sensitive to >

Table 7 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 >

Did the sensitivity analysis cover all important aspects of the model? Is there a need for sensitivity analyses undertaken from a re-specified base case? Include important sensitivity analyses undertaken during the course of the evaluation.

Comment on the areas of uncertainty raised by sensitivity analyses.

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 8. Where you have re-calculated a number due to an error in the SBA then write it in italics immediately below the calculation from the SBA.

Table 8 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					
<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.

Provide an overall statement regarding the intervention cost per patient versus the cost of the comparator. *Indicate whether the estimate in the SBA is reasonable or uncertain.*

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.

Provide an overall statement regarding how many patients are estimated to receive treatment and, if relevant, how many services per patient will be administered (pick a consistent time frame if needed). *Indicate whether the estimate in the SBA is reasonable or uncertain.*

Comment on the estimated net financial implications for the MBS in each year over five years – are the uncertain/over-estimated/under-estimated? Provide revised estimates if necessary.

<There is potential for the net cost/year to the MBS to be <greater/less> than estimated in the SBA.>

CONSUMER IMPACT SUMMARY

Summarise any feedback received during the public consultation period.

<OTHER RELEVANT CONSIDERATIONS>

Are there specific matters 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. that have not been mentioned in the SBA and will likely be important considerations for MSAC?

If these matters are mentioned in the SBA, are there any that require comment or amendment? Justify.

SECTION A CONTEXT

The fundamental aim of this first section of the critique is to provide a summary and evaluation of the proposed context in which the investigative test will be used.

A submission based assessment (SBA) requesting MBS listing of <insert name of investigative test> for <insert description of patient population(s)> was received from <insert applicant's name> by the Department of Health in <insert month & year SBA was received>.

A1 ITEMS IN THE AGREED PICO CONFIRMATION

<This application is following a fit-for-purpose pathway, therefore a PICO Confirmation outlining the proposed use of <intervention> in Australian clinical practice was not <presented to/ratified by> the PICO Confirmation Advisory Sub-Committee (PASC).> If this is the case, then Table 9 below does not need to be inserted.

<A PICO Confirmation for MSAC Application <number> was approved by the PICO Confirmation Advisory Sub-Committee (PASC) of MSAC on <insert month, year>. A comparison of the consistency of this SBA with the PASC-approved PICO Confirmation is given in Table 9.>

If there was a PASC-approved PICO Confirmation then the checkbox below should be completed, providing a summary of whether the SBA has followed the PICO Confirmation. Has the approach suggested in the PICO Confirmation still been addressed but an alternative approach has also been presented? Or has the approach suggested in the PICO Confirmation not been addressed and only the alternative approach has been presented?

If the SBA has provided reasons as to why the PICO Confirmation was not followed, provide a very brief summary in the table of the justification for the change. If you wish to comment on whether the justification is reasonable, do so briefly (in italics – use the table text comment style provided) and expand below the table. If no justification is provided, indicate that the rationale was not given.

Table 9 PICO Confirmation checkbox

PASC-approved PICO Confirmation Item	Compliance	Change and justification provided in SBA
Proposed MBS listing	<*Yes/No*>	
Population / clinical indication	<*Yes/No*>	
Comparator	<*Yes/No*>	
Reference/evidentiary standard	<*Yes/No*>	
Clinical management algorithm	<*Yes/No*>	
Clinical outcomes assessed	<*Yes/No*>	
Healthcare resources	<*Yes/No*>	

Source: <Table/Figure, p/pp of SBA> <*Table constructed during the evaluation*>

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.

Has MSAC previously considered an application requesting listing of this item and/or have any reviews relating to this intervention been conducted? If it has previously been considered, in a few sentences indicate the result of that consideration and main reason for the return of the proposal. What is different with the new SBA?

<MARKETING STATUS OF DEVICE / TECHNOLOGY>

If the investigative test does not require a new device but is instead a service, this section does not need to be completed. However, information on training/credentialing of service providers should still be critiqued in Section F.

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). MSAC will not consider a therapeutic product for reimbursement if the device is not listed on the ARTG. *Comment if there are any pre-requisites to implementation of any funding advice (eg. relevant ARTG numbers, etc) that have not been met.*

<OTHER INDICATIONS>

<Mention whether the investigative test is currently used for other clinical indications in Australia.>

<CURRENT FUNDING ARRANGEMENTS>

<*If relevant, comment on whether the intervention is currently delivered and funded by the public health sector (eg public hospitals) and whether an MBS item listing is likely to shift practice from the public health sector to the private health sector.*>

A3 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 SBA.

The MBS item descriptor proposed in the SBA is summarised in Table 10.

Table 10 Proposed MBS item descriptor

Category X – XXXXXX
<Insert intervention name> <Specify any restriction on use eg. patient characteristics to be satisfied, limits on frequency of use, limits on who can provide the item, or where it can be provided, etc> <Specify any relevant explanatory notes>
Fee: <insert proposed MBS fee>

Source: <Table/Figure>, <p/pp of the SBA?

Consider the proposed item descriptor in relation to what was in the PICO Confirmation (if one was provided to PASC) – is it the same, is it different? If the latter, then indicate the differences, discuss the rationale for them (if offered by the SBA) and comment on any implications.

Comment whether the item descriptor includes any restrictions to patients with specific clinical indications or due to prior interventions.

Compare the requested listing with other items that are listed on the MBS for the same patient group. If there is an inconsistency between the proposed listing(s) and listings for interventions already on the MBS, ask the MSAC to consider whether something should be included to maintain consistency between restrictions.

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 SBA.

Is the specified comparator the current practice that is most likely to be replaced or added to by the proposed medical service (refer to clinical management algorithm)? Is the comparator hospital based or MBS listed?

Comment if it is not the appropriate comparator and, in a sentence, state why – with reference to the PASC-ratified PICO Confirmation (if one was undertaken). Recommend an alternative comparator.

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)

Comment on the proposed algorithm – is it realistic? Is it based on an evidence based or consensus-based clinical practice guideline?

Highlight the differences between the current and the proposed algorithms e.g. change in positioning of an investigative test; expansion/augmentation of the current management options; identification of patients who would now be treated who would previously not been treated.

Comment on any uncertainties (e.g., if the SBA assumes an investigative test is used only once annually but the proposed item descriptor does not limit the frequency of use of the test).

Are there any limitations on how the investigative test would be provided or the setting in which the test can be provided? Discuss with reference to Prerequisites below.

PREREQUISITES

- Specify whether delivery/ordering of the investigative test should be limited to a specific type of referrer or provider (e.g., specific qualifications or training or accreditation).
- Specify any requirements in terms of geography, facilities or location of delivery of service (e.g., limited to hospital setting or to approved laboratories; specification of any specific equipment or facilities that need to be available, prerequisites such as quality assurance or licensing requirements).
- If relevant, identify any required changes in capital equipment, and/or issues of location of the technology.
- If relevant, provide details of any quality assurance program that will apply to the proposed intervention.

CO-ADMINISTERED AND SUBSTITUTED INTERVENTIONS

The main co-administered <intervention is/interventions are> <list>.

- If relevant, summarise any interventions (including diagnostic and monitoring tests) that are required to be co-administered with the proposed intervention as part of a course of treatment (which may be before the delivery of the intervention, during the delivery of the intervention (e.g., drugs administered to minimise risk of or to manage adverse reactions),

or following delivery of the intervention (e.g., pathology tests used in the monitoring of patients for outcome from the intervention).

Therapies likely to be prescribed less frequently are <list>.

- Identify interventions or therapies likely to be substituted by the proposed intervention, or used to manage adverse events associated with the proposed intervention.

Confirm that details provided for co-administered or substituted interventions are consistent with the relevant recommendations in relation to the use of the proposed intervention. Where the SBA claims that the intervention will substitute for another intervention, consider the potential for the proposed intervention to be used as an adjunct to the currently available therapies rather than as a substitute.

Confirm that all interventions and therapies are appropriately included in the economic evaluation. If any therapies are excluded from the economic evaluation, consider whether the SBA provides adequate justification for the exclusion. Reference the place in Section D where this is discussed in more detail.

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

Describe any differences in the delivery/organisation of care between the intervention and main comparator. If there are differences, then note the strengths and weaknesses of the different models of care.

A8 CLINICAL CLAIM

State the clinical claim proposed in the SBA. For example, the investigative has superior safety and effectiveness, relative to the main comparator. If a clinical claim is not provided in the SBA, this should also be stated.

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. Provide a summary of the PICO.

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).

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.

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.

If the PICO were not presented to PASC or the MSAC executive, comment on whether the PICO chosen are appropriate.

SECTION B CLINICAL EVALUATION

The fundamental aim of this section of the critique is to provide an assessment of the evidence presented in the SBA that demonstrates the comparative effectiveness and safety of the intervention versus the appropriate comparator. A lot of guidance on presentation of clinical evidence is provided in the MSAC Guidelines. Much information on the intent of each of the sections included in Section B can be found in those Guidelines so keep a set handy while you are doing an evaluation.

Also keep in mind the goal of providing clear, concise, plain English evaluation. Focus on the key issues and append sections where there are no major problems to discuss.

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.

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.

Comment on the thoroughness and currency of the literature search. Was it comprehensive? Was it consistent with the pre-specified PICO?

An independent search located <no other/several potentially> relevant <trials/studies>. Overall, the literature search is <un>satisfactory.

B1.2 RESULTS OF LITERATURE SEARCH

Comment on whether the stated process of study selection (eg number of reviewers) is open to bias. If the study selection process is not mentioned in the SBA, then state this.

Comment on whether a PRISMA flowchart has been provided, and whether it enables a clear understanding of how the evidence base was selected. If there is insufficient information provided to determine whether the study selection is consistent with the pre-specified study eligibility/inclusion criteria (with reference to the PICO), then state this.

Comment whether there are any contentious exclusions of trials/studies. Present in a way that MSAC can easily gauge the impact of the exclusion of these trials/studies.

If trials/studies that should have been included have been excluded, comment on the possible implications of including the omitted trials in the analysis.

B1.3 Risk of Bias Assessment

Has an appropriate method been used to determine the risk of bias associated with the findings presented in the SBA? Comment on whether the method used is likely to identify all of the potential areas where bias might have impacted on study findings eg in the design and execution of the studies/trials. Is the risk of bias assessment transparent and justifiable?

If a risk of bias assessment has not been performed, then provide an overview of the bias associated with the included studies using an appropriate method. The depth of this critical appraisal will depend on the number of trials and studies included in the SBA and the time available. Only concentrate on the key studies – those that are pivotal to the clinical claim. If you cannot provide a proper critical appraisal in the time available, state this.

B1.4 Characteristics of the Evidence Base

A full description of the studies included to support the submission is given in Attachment B.

Comment on the quality of the evidence base and the risk of bias associated with the key safety and effectiveness outcomes. Are the populations and settings applicable?

B1.5 Outcome Measures and Analysis

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

If relevant, comment whether the outcomes extracted from the studies included in the SBA are consistent with those specified in the PICO Confirmation. If a PICO Confirmation was not provided to PASC, then comment on whether the outcomes chosen are clinically important and patient relevant.

Comment on whether the measurement of outcomes in the included studies was likely to be accurate; discuss the validity of the measurement tools used. Are the outcomes objectively or subjectively measured? (with the latter more prone to bias)

Make it clear how you are interpreting a clinically important effect for these outcomes and whether this differs from the interpretation used in the SBA. If a non-inferiority trial is used in the submission be sure to discuss the minimal clinically important difference (MCID) that is specified in the SBA and comment on whether this MCID is appropriate or not (and consistent with the literature).

B1.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT SAFE?

Main Issues

- *List the main safety issues that will impact on MSAC decision-making here. These should be consistent with the main issues summarised in the Executive Summary. If there are no safety issues, state this.*

Comment on the comparative safety, with particular reference to the patient-relevant outcomes specified in the PICO Confirmation (if presented to PASC). The emphasis should be on whether there are clinically relevant differences in the reported harms, irrespective of whether the results are statistically significant.

Is the evidence base applicable to the populations/settings/circumstances of use in the Australian situation? (this should then be addressed in Section C of the SBA)

If the investigative test alters management, have the safety implications of these management changes been considered? (i.e. the safety implications of over- or under-treatment, or early versus late treatment 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.

Main Issues

- *List the main issues regarding comparative effectiveness that will impact on MSAC decision-making here. These should be consistent with the main issues summarised in the Executive Summary. If there are no problems with the assessment of comparative effectiveness, then state this.*

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.

<EFFECTIVENESS OUTCOME 1>

Brief discussion of the evidence base reporting on this outcome, and the results found, with reference to Table 12 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 12 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.

Comment on the comparative effectiveness, with particular reference to the patient-relevant outcomes specified in the PICO Confirmation (if presented to PASC). 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.

<EFFECTIVENESS OUTCOME 2>

Same format as above.

Is the evidence base applicable to the populations/settings/circumstances of use in the Australian situation? (this should then be addressed in Section C of the SBA)

B2 LINKED EVIDENCE APPROACH

B2.1 BASIS FOR LINKED EVIDENCE

Comment on whether a linked evidence approach was used, and whether all components were assessed, or just some.

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).

Comment if the reference standard is appropriate and why – with reference to the PASC-ratified PICO Confirmation (if one was undertaken).

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

Comment on the thoroughness and currency of the literature search. Was it comprehensive? Was it consistent with the pre-specified PICO?

An independent search located <no other/several potentially> relevant <studies>. Overall, the literature search is <un>satisfactory.

B3.2.1 RESULTS OF LITERATURE SEARCH

Comment on whether the stated process of study selection (eg number of reviewers) is open to bias. If the study selection process is not mentioned in the SBA, then state this.

Comment on whether a PRISMA flowchart has been provided, and whether it enables a clear understanding of how the evidence base was selected. If there is insufficient information provided to determine whether the study selection is consistent with the pre-specified study eligibility/inclusion criteria (with reference to the PICO), then state this.

Comment whether there are any contentious exclusions of studies. Present in a way that MSAC can easily gauge the impact of the exclusion of these studies.

If studies that should have been included have been excluded, comment on the possible implications of including the omitted studies in the analysis.

B3.3 Risk of Bias Assessment

Has an appropriate method been used to determine the risk of bias associated with the findings presented in the SBA? Comment on whether the method used is likely to identify all of the potential areas where bias might have impacted on study findings eg in the design and execution of the studies/trials. Is the risk of bias assessment transparent and justifiable?

If a risk of bias assessment has not been performed, then provide an overview of the bias associated with the included studies using an appropriate method. The depth of this critical appraisal will depend on the number of studies included in the SBA and the time available. Only concentrate on the key studies. If you cannot provide a proper critical appraisal in the time available, state this.

Is the accuracy of the investigative test and the comparator assessed within the same studies, or are they compared in an indirect comparison with a common reference standard?

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.

<Table 13 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

Comment on the quality of the evidence base and the risk of bias associated with the accuracy outcomes. Do the studies meet the inclusion criteria as outlined in the PICO Confirmation (if applicable), or did the criteria have to be broadened to answer the research questions? Are the studies applicable to the target population and setting?

B3.5 OUTCOME MEASURES AND ANALYSIS

See Attachment B for details on the diagnostic accuracy outcomes measured in the studies included in the SBA, along with the statistical methods used to analyse the results.

If relevant, comment on whether the outcomes extracted from the studies included in the SBA are consistent with those specified in the PICO Confirmation.

B3.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE?

Main Issues

- *List the main accuracy issues that will impact on MSAC decision-making here. These should be consistent with the main issues summarised in the Executive Summary.*

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 14 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				

>

Table 15 Summary of findings for the accuracy of intervention, relative to comparator

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.

Comment on the accuracy evidence. Was the selection of studies in the meta-analyses performed appropriate? Were the studies providing evidence on the intervention and the comparator in the same studies, or similar enough populations to compare?

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 16 Results of reliability trials

Study ID	Study characteristics	Summary of reliability results
Trial 1		

Comment on the reliability evidence.

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).

Comment on how much the investigative test agrees with the comparative test(s).

B3.9 INTERPRETATION OF EVIDENCE ON DIAGNOSTIC PERFORMANCE

Comment on whether the claim regarding the diagnostic performance is reasonable and justified in your view.

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 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 if a genetic test). 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.

If the reference standard is different than what is outlined in B3.1, comment if the reference standard is appropriate and why – with reference to the PASC-ratified PICO Confirmation (if one was undertaken).

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.

Has an appropriate method been used to determine the risk of bias associated with the findings presented in the SBA? Comment on whether the method used is likely to identify all of the potential areas where bias might have impacted on study findings eg in the design and execution of the studies/trials. Is the risk of bias assessment transparent and justifiable?

<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>

B4.1.3 CHARACTERISTICS OF THE EVIDENCE BASE

See Attachment B 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.

Comment on the characteristics of the evidence base, and whether the studies are applicable to the target population and setting.

A summary of the characteristics of accuracy studies is shown in **Error! Reference source not found.**.Those studies which technically met the inclusion criteria, but which were not included in the results section or meta-analyses, are listed in Attachment B.

Table 18 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 Attachment B 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.

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.

B4.1.5 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT ACCURATE?

Main Issues

- *List the main clinical validity issues that will impact on MSAC decision-making here. These should be consistent with the main issues summarised in the Executive Summary.*

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 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]	
-	PPV	XX% [XX,XX]	XX% [XX,XX]	
-	NPV	XX% [XX,XX]	XX% [XX,XX]	
Trial 2				

>

Comment on the clinical validity data. Were the positive predictive values and negative predictive values calculated using an appropriate prevalence for the target population?

<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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Comment on the information from the investigative test provides prognostic value, and how it compares to the comparative test(s), or what incremental value it provides over the prior tests/clinical information etc.

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

Has an appropriate method been used to determine the risk of bias associated with the findings presented in the SBA? Comment on whether the method used is likely to identify all of the potential areas where bias might have impacted on study findings eg in the design and execution of the studies/trials. Is the risk of bias assessment transparent and justifiable?

If a risk of bias assessment has not been performed, then provide an overview of the bias associated with the included studies using an appropriate method. The depth of this critical appraisal will depend on the number of studies included in the SBA and the time available. Only concentrate on the key studies. If you cannot provide a proper critical appraisal in the time available, state this.

B5.1.2 CHARACTERISTICS OF THE EVIDENCE BASE

See Attachment B for details on the individual studies included in the evidence base.

Comment on the characteristics of the evidence base for change in management, and whether the evidence is applicable to the target population / setting.

Studies which provided evidence on the impact of the test on patient management are characterised in Table 20.

Table 20 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 Attachment B 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?

Main Issues

- *List the main change in management issues that will impact on MSAC decision-making here. These should be consistent with the main issues summarised in the Executive Summary.*

Comment on the evidence regarding how the investigative test impacts on clinical management, compared to what is done in the absence of the test.

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.

<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

Has an appropriate method been used to determine the risk of bias associated with the findings presented in the SBA? Comment on whether the method used is likely to identify all of the potential areas where bias might have impacted on study findings eg in the design and execution of the studies/trials. Is the risk of bias assessment transparent and justifiable?

If a risk of bias assessment has not been performed, then provide an overview of the bias associated with the included studies using an appropriate method. The depth of this critical appraisal will depend on the number of studies included in the SBA and the time available. Only concentrate on the key studies. If you cannot provide a proper critical appraisal in the time available, state this.

B5.2.2 CHARACTERISTICS OF THE EVIDENCE BASE

See Attachment B for details on the individual studies included in the evidence base.

Comment on the characteristics of the evidence base, and whether the evidence base is applicable to the populations/settings/ circumstances of use in the Australian situation (if not, this should then be addressed in Section C of the SBA).

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 Table 21.

Table 21 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 Attachment B for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

If relevant, comment whether the outcomes extracted from the studies included in the SBA are consistent with those specified in the PICO Confirmation. If a PICO Confirmation was not provided to PASC, then comment on whether the outcomes chosen are clinically important and patient relevant.

Comment on whether the measurement of outcomes in the included studies was likely to be accurate; discuss the validity of the measurement tools used. Are the outcomes objectively or subjectively measured? (with the latter more prone to bias)

Make it clear how you are interpreting a clinically important effect for these outcomes and whether this differs from the interpretation used in the SBA. If a non-inferiority trial is used in the submission be sure to discuss the minimal clinically important difference (MCID) that is specified in the SBA and comment on whether this MCID is appropriate or not (and consistent with the literature).

Discuss whether the statistical analyses presented in the studies were pre-specified or post hoc, and the limitations associated with the latter. Only elaborate with a brief description of the statistical methodology if there is a problem, i.e. inappropriate statistical methodology has been used.

B5.2.4 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

<DOES THE CHANGE IN MANAGEMENT IMPROVE HEALTH OUTCOMES?

Main Issues

- *List the main therapeutic effectiveness issues that will impact on MSAC decision-making here. These should be consistent with the main issues summarised in the Executive Summary. If there are no problems with the assessment of comparative effectiveness, then state this.*

Comment on the therapeutic effectiveness results, with particular emphasis on patient-relevant outcomes specified in the PICO Confirmation (if presented to PASC). 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.

Are there any reasons why the therapeutic effectiveness results in the studies may not reflect the benefit that will likely occur if listed on the MBS? What are the uncertainties? Have all the people who receive the investigative test been considered, or only those with a positive/negative result, or those with a correct result?

B6 IMPACT OF REPEAT TESTING/MONITORING

Highlight if there are any concerns raised by findings from post-market surveillance/unpublished data on harms. This might include data captured in administrative data sets, registry data, and recalls by regulatory agencies and from industry.

B7 EXTENDED ASSESSMENT OF COMPARATIVE HARMS

Highlight if there are any concerns raised by findings from post-market surveillance/unpublished data on harms. This might include data captured in administrative data sets, registry data, and recalls by regulatory agencies and from industry.

B8 INTERPRETATION OF THE CLINICAL EVIDENCE

On the basis of the benefits and harms reported in the evidence base, the submission based assessment proposes that, relative to <the comparator>, <the intervention> has <superior/non-inferior/uncertain/inferior> safety and <superior/non-inferior/uncertain/inferior> effectiveness.

Comment on whether the components of linked evidence have been appropriately linked together in the SBA, so that it is clear what the health impact of the investigative test is, or whether there are gaps in the logic.

Comment on whether the clinical claim is reasonable and justify your view. Is the interpretation of the evidence in line with the clinical claim made in Section A?

Comment on the balance of clinical benefit and harms associated with the proposed medical service.

If a GRADE evidence profile has been provided, please reproduce here and critically discuss the findings and/or disagreements you may have with the conclusions that have been drawn.

Note – for a GRADE summary table, where a meta-analysis is not able to be done to arrive at a summary estimate of effect for each critical patient relevant outcome, it is suggested that the results from one or more of the better quality studies is presented and that the range of effects in these studies, with/without calculation of a median effect, is provided.

Please consult the paper by Guyatt et al 2013 (see reference list) for further information on interpreting GRADE summary tables. Please note, though, that the overall confidence in effect estimates ratings across outcomes (ie which would relate to the overall clinical claim in this instance) is usually based on the critical outcome that provides the lowest confidence in the effect estimates.

Table 22 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 23 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

This section should be used to highlight the shortcomings of the clinical data for the purposes of constructing an economic evaluation that appropriately captures all the issues. The premodelling studies then undertaken in Section C should in theory address these shortcomings.

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).

Comment on the results of the pre-modelling studies – are they reasonable? Are they accurate? Do they answer the proposed applicability question? Comment on any variation of treatment claim from Section B. Issues in this section are likely to be related to issues in D.2; avoid excessive repetition.

Provide detail on applicability issues NOT identified in the SBA but likely, in the evaluator's judgement, to be critical for the decision.

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).

Comment on the results of the pre-modelling studies – are they reasonable? Are they accurate? Do they answer the proposed extrapolation question? Comment on any variation of treatment claim from Section B.

Provide detail on extrapolation issues NOT identified in the SBA but likely, in the evaluator's judgement, to be critical for the decision.

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).

Comment on the results of the pre-modelling studies – are they reasonable? Are they accurate? Do they answer the proposed transformation question? Comment on any variation of treatment claim from Section B.

Provide detail on transformation issues NOT identified in the SBA but likely, in the evaluator's judgement, to be critical for the decision.

If data from the trials have been converted (e.g. from continuous to dichotomous or dichotomous to time-to-event outcomes) weigh up the additional uncertainty against the improved ease of interpretation of outcomes.

Markov models require probability over time (t) rather than rates. The SBA should transform from rate (r) to probability (P) and vice versa correctly ($P = 1 - e^{-rt}$).

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 24 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				

Comment on key issues but only if there are important points re validity/value of results presented. The comment can be placed in italics in the table if very short otherwise place in paragraphs below the table but do not spend time repeating the issue. Summarise from the Section C.3 above.

SECTION D ECONOMIC EVALUATION

D.1. OVERVIEW

The clinical evaluation suggests that, relative to <the comparator>, <the investigative test> has <superior/non-inferior/uncertain/inferior> safety and <superior/non-inferior/uncertain/inferior> effectiveness <based on the evidence profile given in Table 22 and Table 23. The appropriate economic analysis for the evaluation should therefore have been <refer to appropriate economic analysis in Table 25> (see Table 25). This <was/was not> provided in the submission based assessment.

Table 25 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

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).

The SBA presents <a trial-based economic evaluation, based on direct randomised trials only/a stepped economic evaluation, based on direct randomised trials and implementing a modelled evaluation using variables reported in Section C/a modelled economic evaluation based on an indirect comparison of <randomised/nonrandomised> studies>.

D.2. POPULATIONS AND SETTINGS

Comment on the demographic and patient characteristics of the population included in the economic evaluation. Are they appropriate to the proposed MBS listing? Justify. Refer to any analyses presented in Section B and C.3 to address the applicability of the population used in the model for the proposed restriction.

The population in the model is <not> representative of the population for whom MBS listing is sought.

D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in Table 26.

Table 26 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

Comment whether a search of the literature was conducted by the applicant for published cost-effectiveness analyses of the proposed service. Is the approach suggested in the SBA consistent with other published economic evaluations on the topic? Are departures from the approaches in the literature justified?

STRUCTURE OF THE ECONOMIC EVALUATION

Comment on whether the structure of the model is appropriate – does it accurately reflect the treatment algorithm for the use of the intervention?

The description of the economic evaluation should include:

- 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

Assumptions incorporated into the model structure:

Have the economic evaluation characteristics summarised in Table 26 been appropriately justified? Comment and suggest/justify appropriate alternatives. For example,

- *Comment on the appropriateness of the time horizon in terms of whether it accurately reflects the natural history of the medical condition, the clinical management algorithm and the time over which outcomes may occur. Is it long enough to capture important clinical events?*

- *Comment on whether the outcomes represent final outcomes and if so, how these have been translated from surrogate outcomes.*

Comment on whether the health states, cycle length and duration of time spent in health states are appropriate.

D.4. INPUTS TO THE ECONOMIC EVALUATION

COSTS

- *Discuss the appropriateness of any assumptions regarding the cost of the intervention such as the length and number of specialist visits required, costs of equipment use, co-interventions.*

- *Verify these costs and their use in the model. Check the model and locate the values if possible.*

- *Verify the sources are up to date and check the latest prices on the MBS and PBS.*

- *If costs have not been incorporated in the economic evaluation that ought to be, the evaluator can copy the health care resource items summary table provided in the SBA and add to it using italics. Comment below the table as to why these costs should not be omitted. Comment whether the SBA provides an appropriate justification for their exclusion. If possible a new base case in the economic evaluation may be developed using the new cost information. Reference this and the updated results.*

- *Consider the potential costs of adverse events if these are likely to differ between the intervention arm and the comparator arm of the model.*

- *Consider ongoing monitoring costs of patients. Do these differ between arms of the model?*

HEALTH OUTCOMES

Comment on the health outcomes used. Consider whether the variables that generate the incremental treatment effect are reasonable.

- Describe the outcomes used in the economic evaluation, and reference (to Section C) any transformation or extrapolation of outcomes based on the clinical trials to outcomes used in the economic evaluation.

- Must include a statement about the treatment effect of the intervention, the source of the treatment effect from Sections B or C, the duration the model assumes the treatment effect will continue beyond the trial period (assuming that costs are not continuing).

- If the SBA provides a table highlighting the variables that generate the incremental treatment effect, then reproduce this table.

Comment on whether the extrapolation of effect is reasonable given the length of trial data.

Comment on whether the assessment report assumes all patients receiving the intervention will experience the improved health outcomes? Is this reasonable?

TRANSITION PROBABILITIES USED IN THE ECONOMIC EVALUATION

Comment on the transition probabilities, focusing on whether they are reasonable. Do they accurately represent movement between health states? Do they reflect what is observed in the clinical evidence?

- If the economic evaluation uses transition probabilities, provide them here in table form. If there are a large number of transition probabilities, include them in an attachment and reference them here.
- Identify temporary or absorbing health states.
- State the source of the transition probabilities and describe whether they are constant or change over model cycles.
- If probabilistic modelling is presented, include the type of probability distribution used and discuss its justification.
- Markov models require probability over time (t) rather than rates. Comment, if necessary, on whether the SBA has transform from rate (r) to probability (P) and vice versa correctly ($P = 1 - e^{-rt}$).

UTILITY/DISUTILITY VALUES

Comment on the utility values, focusing on the source and how the values were obtained (reference Section B or Section C if discussed there), and whether the values are reasonable.

- List the utility values used in the economic evaluation in a table, along with their sources and cross-reference to Section B or Section C if discussed there.
- State whether they are trial-based or result from a translation issue in Section C (make a cross reference).
- Specify for how long the utility values are applied. This will be related to the length of time that patients spend in particular health states.
- If some utility or disutility values occur in one arm of the economic evaluation but not another then highlight this.

DISCOUNT RATE

If a value different from 5% for both costs and outcomes is used, comment on the justification provided by the assessment report.

- State if a discount rate is used in the economic evaluation and what value is used.
- Identify whether both costs and outcomes are discounted at the same annual rate.

D.5. RESULTS OF THE ECONOMIC EVALUATION

Has the SBA presented 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?

Has the SBA presented the remaining results of the economic evaluation first in a disaggregated form, then in increasingly aggregated forms, using discounting as appropriate?

Has the SBA presented the appropriately aggregated and discounted results separately for outcomes and costs, and separately for the proposed medical service and its main comparator?

Has the SBA presented 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, has the incremental cost-effectiveness ratio been presented 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)?

What is the impact of any departures from the suggested approaches above, in terms of confidence in the estimates provided in the economic evaluation in the SBA?

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. **Where you have re-calculated a number due to an error in the SBA then write the modified number in italics immediately below the calculation from the SBA (this would include the ICER).**

Table 27 Title

Test	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Intervention	$XXX	$XXX	XX	XX	$XXX/QALY
Comparator	$XXX	$XXX	XX	XX	$XXX/QALY

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. **Where you have re-calculated a number due to an error in the SBA then write it in italics immediately below the calculation from the SBA.**

<Table 28 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*.

Comment on the ICER and whether it accurately represents the cost-effectiveness, given the methodology used, of listing the intervention.

- Consider which step in the economic evaluation appears to contribute most to the final ICER.
- If the SBA presents Markov traces or other model traces, present those here.
- If the SBA has not presented model traces and they provide some insight into what is driving the model, then present them here and *comment*.

- *Comment on whether the model traces make sense – do they correspond to empirical data, or what would be expected with the disease or condition?*

<Table 29 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 28)	(From corresponding row of Step 2 in <Table 28)	(From corresponding row of Step 2 in <Table 28)
For any trial-based outcome relied on in the economic evaluation *with any* ***extrapolation*** *from the time horizon of the trial(s)* ***only***	(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) (***'transformation of nature of outcome' 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)* ***('value transformation' 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 extrapolation* from the time horizon of the trial(s) ***with*** *any transformation* 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

Has the SBA presented univariate (one-way) sensitivity analyses on all variables using plausible extremes of values, and justified the selection of those extreme values?

Has the SBA tabulated all univariate sensitivity analyses alongside the base case?

Has the SBA presented multivariate sensitivity analyses combining variables shown to be sensitive in the univariate analyses?

What is the impact of any departures from the suggested approaches above, in terms of confidence in the estimates provided in the economic evaluation in the SBA?

The modelled results were most sensitive to >

Table 30 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		

Comment on the appropriateness of the sensitivity analyses presented and the implications of these analyses in terms of the uncertainty in the modelled estimates.

Did the sensitivity analysis cover all important aspects of the model? Is there a need for sensitivity analyses undertaken from a re-specified base case?

Which sets of variable changes have the largest impact on the results? Is it realistic that these simultaneous changes could occur? If so, what is the impact on the ICER?

SECTION E FINANCIAL IMPLICATIONS

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

Comment on the data sources used to estimate the financial impact of an MBS listing of the proposed medical service. Were the methods used appropriate? Discuss the limitations (including the representativeness of the results) and biases of the method adopted.

- In this section the applicant is required to demonstrate that they have obtained published or unpublished data appropriate to support estimates. Applicants may identify and use a variety of sources.
- Critically evaluate the sources presented for representativeness, applicability and reliability. Comment can be within a copy of the SBA's table if short or otherwise presented in paragraphs below.
- Be pragmatic with comments recognising that the relevant data is often limited or not available and uncertainty will be inherent.
- Are there any other appropriate sources that have not been identified?

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

E.2. USE AND COSTS OF <INVESTIGATIVE TEST>

ELIGIBLE POPULATION FOR THE REQUESTED RESTRICTION

List the assumptions or statements made in the SBA that are used to derive the estimates of eligible patients per year over a five year period.

State how these are supported by the source documents (E.1). References are important for the assumptions

Estimated number of eligible patients/year for <proposed intervention> in the SBA: <XXX>

<This estimate is likely to be reasonably accurate> <There is the potential for the number of eligible patients to be <greater/less> than this estimate.>

- Comment on the accuracy of the calculations and include corrections for arithmetic errors in italics in the table copied from the SBA (if relevant).
- Comment on whether the assumptions are reasonable and give reasons.
- State and comment on factors that contribute to any uncertainty around the number of eligible patients. These may include:
    - Uncertainties in the assumptions used.
    - Extent of clinical need in currently eligible population.
    - Possibility that listing this intervention would change clinical management patterns.
    - Consistency between the expected clinical management, model structure and inputs and methods for estimating the extent of use of the intervention.
    - Potential for this intervention to 'grow the market for treatment of this disease.

NUMBER OF PATIENTS LIKELY TO USE THE INTERVENTION

State the how the SBA derived the number of eligible patients likely to use the intervention in each year (uptake rate) over five years.

Comment on how well this is justified or supported. Consider:

- Potential acceptance of the new intervention by clinicians, hospitals, specialists.
- Overseas guidelines -check NICE advice, CADTH, SMC.
- Applicability of clinical trials to the Australian population (Section C).
- Administration issues that affect uptake.
- Health system issues that would limit uptake.
- False positives resulting from a companion diagnostic test.

The estimate provided in the SBA of the number of patients/year likely to use <the intervention> is <reasonable/uncertain>.

A revised estimate of the number of patients/year likely to use <proposed intervention> undertaken during the evaluation is:

- This not obligatory but can be useful in exploring the impact of uncertainty on the estimates.
- The evaluator may be able to calculate another estimate, particularly in circumstances where the SBA chooses a prevalence rate at one extreme of the range in published literature. If there are a series of highly uncertain assumptions in place it may not be worth recalculating each step. Note that this may also be considered in sensitivity analysis later in Section E.
- With revised estimates, a brief justification of the more appropriate assumptions should be provided.

<NUMBER OF SERVICES>

As the estimated number of patients may not correspond to how often an intervention is used (i.e. a service may be repeated) then it is necessary to provide an estimate of the number of services. If this number will not differ from the number of patients, then this does not need to be included.

The number of services associated with <intervention>, as estimated in the SBA, is:

State the how the SBA derived the number of services associated with the intervention in each year (uptake rate) over five years.

Comment on how well this is justified or supported. Consider:

- whether there is a difference between the estimate of the number of patients likely to be treated per year (above) and the number of services provided per patient. Discuss the reasons for the difference.
- presenting a table to set out the methods used to calculate the number of services.

The SBA's estimate of the number of services per year is <reasonable/uncertain>.

- If uncertain summarise the main reasons but without repeating in extensive detail issues raised previously (uncertainties will flow through the calculations).
- Consider likely compliance and persistence, initiations and withdrawals through the year.

<There is the potential for the number of services to be <greater/less> than this estimate.>

A revised estimate of the number of services/year undertaken during the evaluation is:

- As above with the revision of patient numbers, this is not obligatory but can be useful in exploring the impact of uncertainty on the estimates.

- The evaluator may be able to calculate another estimate, particularly where there is a high level of uncertainty in the estimates of eligible patients or services/patient/year.

- Just write a sentence with the average co-payment per patient, no need to present tables for the co-payment.

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, has the SBA estimated 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)?

Comment on the approach taken, the estimates in the SBA, and provide some discussion of the implications. Example statements are provided below – please remember to provide justification for the statements.

- Does the approach correspond well with the economic evaluation presented in Section D? That is, the costs or cost-savings due to changes in services modelled in D should also feature here in a similar way. Raise the issue if this is not consistent.

<There is potential for the use of other MBS services to be <greater/less> than estimated in the SBA.>

<Other services that are likely to be substituted, but are not identified in the SBA, are <list>. >

- Provide revised estimates including the likely extent of substitution and cost implications of substitution for these services.

<Other services that are likely to be co-provided with listing of the proposed intervention, but that are not identified in the SBA, are <list>. >

- If included, provide revised estimates including the likely extent of provision and the cost implications for these services.

- Check with what the SBA has mentioned in Section A and ensure that this is treated consistently here in Section E.

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 31. Where you have re-calculated a number due to an error in the SBA then write it in italics immediately below the calculation from the SBA.

Table 31 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					

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

The ratio of in-hospital vs out-of-hospital service needs to be determined in the SBA's analysis 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.

Comment on the estimated net financial implications for the MBS in each year over five years – are the uncertain/over-estimated/under-estimated? The cost offsets from Subsection E.3 should have

been subtracted from the corresponding estimates calculated in Subsection E.2. Include these in the table above if helpful.

<There is potential for the net cost/year to the MBS to be <greater/less> than estimated in the SBA.>

E.5. Financial Implications for Government Health Budgets

Comment on whether MBS listing of the proposed intervention is likely to have financial implications for other parts of the Australian Government's health budget eg state and territory Government health budgets, including public hospitals.

The Broader Impact on the MBS

The MBS includes a number of elements that applicants are not expected to estimate. This includes the cost of safety nets and incentives. Where possible, applicants should provide any additional information that will allow the Department to assess these factors.

Other Government Impacts

Other Australian Government agencies are typically impacted by the implementation of new and amended medical services.

Comment, if relevant, on the estimated extent of the net change in the number of PBS 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.

State and Territory Government Health Budgets

Comment on any stated financial implications for state and territory Government health budgets, such as for public hospitals (including inpatient admissions, emergency department visits and outpatient clinic visits).

- There is controversy about valuing freed hospital resources in Government health budgets because, in the Australian public hospital system, the freed resources are typically redeployed to improve the health of the next available patient rather than being realised as financial cost reductions.

Is there any justification to support any claim for financial cost offsets from any reduction in the need to provide a public hospital resource? For example, is there a basis for concluding that the expected change is large enough that a resulting change in the provision of the resource would become a viable option for hospital management or other appropriate decision-makers?

Comment on the estimated net financial implications for government health budgets in each year over five years.

E.6. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

E.4 and E.6 may be integrated, as needed, so the sensitivity analyses are presented immediately after the base calculations estimated in E.4.

The SBA should identify the uncertainties, assess the extent and direction of these and make a statement about the impact on financial estimates.

Comment on the sensitivity analyses, focusing on whether they are appropriate and whether they provide reasonable estimates, particularly if the evaluation in E.2 – E.5 has highlighted uncertainties not considered in the SBA.

Provide the results of any sensitivity analyses of the financial implications presented by the SBA using tables as appropriate (include the base case financial implications for comparison). An example is provided below.

If the SBA has not provided any additional analyses, or there are important analyses that should be conducted, briefly describe them.

Table 32 Sensitivity analysis of the estimated net cost to the MBS

EXAMPLE	2012	2013	2014	2015	2016
Overall net cost base case					
Increased patient numbers					
Increased services per patient					
Reduced substitution					

Source: <Table/Figure>, <p/pp of the SBA>

SECTION F OTHER RELEVANT CONSIDERATIONS

Are there specific matters 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. that have not been mentioned in the SBA and will likely be important considerations for MSAC?

If these matters are mentioned in the SBA, are there any that require comment or amendment? Justify.

Discuss any key trials that are ongoing and due to report results shortly.

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.

ATTACHMENT A

Additional information or tables relating to Section A should be included here.

ATTACHMENT B

Additional information or tables relating to Section B should be included here.

ATTACHMENT C

Additional information or tables relating to Section C should be included here.

ATTACHMENT D

Additional information or tables relating to Section D should be included here.

ATTACHMENT E

Additional information or tables relating to Section E should be included here.