# **Medical Services Advisory Committee (MSAC)Public Summary Document**

***Application No. 1689.1 – Quantification of NT-proBNP for risk assessment in patients with previously diagnosed pulmonary arterial hypertension (PAH)***

**Applicant: Janssen-Cilag Pty Ltd**

**Date of MSAC consideration: 27 July 2023**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](http://www.msac.gov.au/)

1. Purpose of application

A resubmission requesting Medicare Benefits Schedule (MBS) listing of N-terminal pro B-type natriuretic peptide (NT-proBNP) biomarker assay for risk assessment of patients diagnosed with pulmonary arterial hypertension (PAH) was received from Janssen-Cilag Australia Pty Ltd by the Department of Health and Aged Care.

The population that is proposed to be eligible for the proposed NT-proBNP test is unchanged from the initial submission (ADAR 1689). All patients who have received a diagnosis of PAH are proposed to be eligible for NT-proBNP testing at the time of routine, recurring follow-up assessments, i.e. every 3–6 months.

The main change from the initial submission appraised by MSAC in July 2022 (ADAR 1689) and the current report, is the release of the 2022 European Society of Cardiology and the European Respiratory Society (ESC/ESR) guidelines[[1]](#footnote-2) in August 2022, detailing updated recommendations for the management of PAH.

The guidelines recommend that initially patients would have a clinical assessment using a multi-parameter 3-stratum risk classification tool. Follow-up assessments would use a 4-stratum model for risk-stratification (Table 1). This tool includes only three non-invasive tests (WHO functional class [FC], 6-minute walking distance [6MWD], and NT-proBNP levels) with additional parameters (such as transthoracic echocardiogram [TTE]) to be considered as needed. The guidelines consider that the main advantage of the four-stratum model over the three-stratum model is better discrimination within the large intermediate-risk group, which helps guide therapeutic decision-making.

Table 1 Variables used to calculate the four-stratum risk-assessment tool



6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide; WHO-FC = World Health Organization functional class.

Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.

Source: Table 18, in the 2022 ESC/ERS Guidelines (Humbert et al 2022)

## 2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the incorporation of a new MBS item for the quantification of NT-proBNP for ongoing risk assessment in patients with previously diagnosed pulmonary arterial hypertension (PAH). This expands on MSAC’s support in July 2022 for a new MBS item for quantification of NT-proBNP in patients with systemic sclerosis for diagnosis of PAH. MSAC also supported extending such funding to cover BNP testing for patients with previously diagnosed PAH to ensure consistency with other MBS items.

MSAC noted that the clinical evidence demonstrates non-inferior safety and effectiveness of NT-proBNP testing as a component of a 4-stratum risk classification tool relative to 3-stratum risk classification tools that include TTE, which are currently used in Australian clinical practice. MSAC considered that NT-proBNP testing, as a component of a 4-stratum risk classification tool, provides better discrimination between risk groups to guide patient management. MSAC noted that it was appropriate to support public funding of this test given that it is recommended by the most recent international clinical guidelines and that NT-proBNP testing is more accessible than TTE. MSAC noted that these considerations also extended to BNP testing in general as a substitute for TTE for ongoing risk assessment in patients with previously diagnosed PAH.

MSAC noted that although there is currently a lack of evidence that NT-proBNP testing leads to a change in patient management, this may be attributable to reduced compliance with guidelines rather than the utility of the test. MSAC considered that improving clinician compliance with existing clinical guidelines for patients with PAH is required to ensure patients are managed optimally.

MSAC considered that while the cost‑effectiveness and total financial impact of the service may be uncertain, listing was still likely to result in cost savings to the MBS or at worst a small net cost. MSAC recommended that to manage the risk of leakage and potential for greater than expected use of NT-proBNP testing, it is reasonable to monitor utilisation of the MBS item after listing and assess whether TTE utilisation is reduced as a result of listing. MSAC proposed a review period of no earlier than two years after listing to allow sufficient time for initial change in clinical practice.

MSAC proposed a MBS item descriptor for NT-proBNP testing of patients diagnosed with PAH. The proposed fee and benefit are the same as for the current MBS Item 66830 (BNP/NT-proBNP testing for the detection of heart failure).

| Category 6 - PATHOLOGY SERVICES – (proposed category description) Group P2 – Chemical (proposed group description)  |
| --- |
| Proposed item descriptor:  Quantification of laboratory-based BNP or NT proBNP testing in a patient with diagnosed pulmonary arterial hypertension for risk assessment. Maximum of ~~4 tests per patient in any one year~~ four tests in a 12-month period. Fee: $58.50 Benefit: 75% = $43.90 85% = $49.75  |

**Explanatory note ​**

NT-proBNP (and BNP) testing in patients with pulmonary arterial hypertension - MBS item XXXX​

A medical practitioner (other than a specialist or consultant physician) requesting the service should only do so in consultation with a specialist or consultant physician who manages the treatment of the patient.​

| Consumer summary |
| --- |
| This is an application from Janssen-Cilag Australia Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of a blood test to measure N-terminal pro B-type natriuretic peptide (NT-proBNP) levels to assess the risk to patients who have been diagnosed with pulmonary arterial hypertension (PAH).PAH is a condition where there is high pressure in the blood vessels that carry blood from the heart to the lungs. Patients with PAH can have shortness of breath, chest pain and fainting. It gets worse over time if not treated and can lead to heart failure. There is no cure for PAH, but it can be managed with a range of medications. Early diagnosis and treatment are important to slow down disease progression.NT-proBNP is a hormone that is released by the heart as pressure in the heart increases. Higher levels of NT-proBNP in the bloodstream may indicate problems with the heart, such as PAH. NT-proBNP can be measured with a blood test. The NT-proBNP results can be combined with the results of other tests (eg. 6-minute walk test and the severity of a patient's symptoms and how these impact on their day-to-day functioning, as rated using the World Health Organisation Functional classification) to work out whether a patient with PAH has a low, intermediate or high risk of death within the next year. If a patient’s doctor has this information, it can help them to decide which treatment(s) a patient should have to manage their PAH. People with PAH are usually monitored regularly using transthoracic echocardiograms (TTEs), along with tests like the 6 minute walk test. A TTE is an ultrasound test of the heart, and is done by a trained sonographer or cardiologist with specialised ultrasound equipment, and it takes about one hour. If a patient’s NT-proBNP level is low, the results of their other tests are within the normal range, they are otherwise stable and they are found to be at low risk of death within the next year, they may not need to have a TTE. Patients found to be at high risk of death within the next year or who have worsening of their medical condition could be referred for a TTE and other tests to further assess the patient’s PAH severity or other problems. MSAC noted that the NT-proBNP blood test would be more accessible, particularly for people in rural and remote communities, compared to a TTE, which is only offered in certain healthcare facilities.MSAC noted that NT-proBNP testing is safe and at least as effective as TTE. MSAC noted that the introduction of NT-proBNP testing may lead to cost savings to the MBS, although they are not likely to be significant.MSAC noted that new guidelines in Europe recently recommended NT-proBNP testing as part of clinical practice. MSAC’s advice to the Commonwealth Minister for Health and Aged CareMSAC supported the decision to list NT-proBNP testing on the MBS to assess PAH. MSAC considered the test to be safe, effective and good value for money, and possibly represented a cost saving. MSAC recognised that this test will be easier to access for people living in rural and regional areas compared to TTE. |

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

MSAC noted that this application from Janssen-Cilag Australia Pty Ltd was for MBS-funding of N-terminal pro B-type natriuretic peptide (NT-proBNP) bioassay testing for the risk assessment and monitoring of patients with diagnosed pulmonary arterial hypertension (PAH). MSAC noted that this application is an expedited resubmission (bypassing PASC). In July 2022, MSAC did not support public funding of NT-proBNP for population 2 (patients who have been diagnosed with PAH) of MSAC Application 1689 (the defined sole target population in this application) because of uncertainty in the estimated cost-effectiveness and the total financial implications.

MSAC noted that in the proposed clinical management algorithm, NT-proBNP would be used alongside the 6 minute walk test and WHO Functional class as part of a risk assessment tool for follow-up assessments of patients with PAH to assess risk of death or clinical worsening.

MSAC noted the release of the 2022 European Society of Cardiology and the European Respiratory Society (ESC/ESR) guidelines in August 2022, which recommend that follow-up assessments would use a four-stratum model for risk-stratification rather than the three-stratum model proposed in the previous submission (1689). This tool includes three non-invasive tests (WHO functional class [FC], 6-minute walking distance [6MWD] and BNP or NT-proBNP levels) with additional parameters (such as TTE and right heart catheterisation) to be considered as needed. Using the results of the tool patients are stratified into one of the following four stratum according to their risk of mortality within the next year: low, intermediate-low, intermediate-high or high risk.

MSAC noted that both the intervention and the comparator were considered to be relatively safe tests whether used as part of a risk classification tool or not. Therefore safety was not discussed further in the resubmitted ADAR and MSAC considered that this was appropriate. ​

In terms of clinical effectiveness in test accuracy, MSAC agreed with the commentary that it was not necessary to re-evaluate the effectiveness of NT-proBNP testing compared to TTE as the non-inferiority of a 3-stratum model including NT-proBNP, to other 3-stratum models that use TTE instead of NT-proBNP had already been established in the previous application (1689). Hence it was only necessary to evaluate the effectiveness of a 4-stratum NT-proBNP based risk classification model against a 3-stratum NT-proBNP based risk classification model. MSAC noted the evidence provided by the commentary for the non-inferiority of the 4-stratum NT-proBNP based risk classification model in predicting mortality outcomes in PAH patients irrespective of the presence of comorbidities, compared to the 3-stratum NT-proBNP based risk classification model.

In terms of other measures of clinical effectiveness, MSAC noted that neither the ADAR nor the commentary identified any evidence to suggest any differences to changes in management that result from a 4-stratum rather than a 3-stratum NT-proBNP-based risk classification model.

MSAC considered the question of whether using NT-proBNP was expected to reduce the number of patients requiring TTE, noting that the ESC/ESR guidelines recommend TTE 3-6 months after a change in therapy, every 3-6 months in cases of clinical worsening, and may be considered every 3-6 months in patients with stable disease (with these intervals to be adjusted according to patient needs, PAH aetiology, risk category, demographics, and comorbidities). MSAC noted that the commentary identified patient groups who may be considered for an additional TTE and based on this estimated that 73.4% of patients would require an additional TTE under the 4-stratum model compared to 69% under the 3-stratum model.

MSAC noted that while the guidelines consider the main advantage of the four-stratum over the three-stratum model is better discrimination within the large intermediate-risk group which helps guide therapeutic decision-making, evidence from the COMPERA and FRENCH PAH registries indicated that the extent to which a change in risk profile leads to a change in medication is uncertain and prescribed drugs did not necessarily follow the treatments recommended for each risk category, i.e. there was no evidence so far that the stratification tool is actually being used for selecting therapy.

MSAC noted that undertaking a cost-minimisation analysis for the economic evaluation was appropriate given the clinical claim of non-inferiority. MSAC noted that the proposed 4-stratum-model with NT-proBNP testing resulted in 4.0 NT-proBNPs and 2.5 TTEs per patient per year compared to 4 TTEs per patient per year under the current 3-stratum model with TTE which is a reduction of 0.38 TTEs per NT-proBNP test performed. However, MSAC noted the following areas of uncertainty in the cost comparison which generated a cost saving estimated to be $126.08 per patient:

* the current frequency of assessment of NT-proBNP and TTE (both assumed to be every 3 months whereas it is unclear whether this is currently reflective of standard clinical practice)
* the proportion of patients who can replace some of their TTEs with NT-proBNP testing (assumed to be 75%) and
* extent of TTE reduction in these patients (assumed to be 2 per patient per year).

MSAC noted the scenario and sensitivity analyses undertaken in the commentary around varying the follow up intervals to 5-6 months and the rates of clinical worsening above the base case rate of 25% suggested that the cost saving estimates for the scenario and sensitivity analyses presented in the ADAR appear to be uncertain, and likely to be overestimated.

MSAC noted that the resubmission estimated a cost saving to the MBS of $232,674 in Year 1 increasing to $351,359 in Year 6, although again these financial estimates are subject to the same uncertainties noted previously for the cost comparison analysis. MSAC noted the sensitivity analyses conducted around the financial estimates by varying follow-up intervals, rates of clinical worsening, number of PAH patients and uptake rates. However, MSAC noted that even if the savings are overestimated, the financial impact is not likely to be significant.

MSAC acknowledged consultation feedback was again supportive of MBS funded NT-proBNP testing, noting that patients face frequent barriers in accessing TTEs and right heart catheterisation in hospitals, including long-distance travel and inability to drive, especially for those living in rural, remote and regional areas.

MSAC considered that overall, despite the uncertainty of the economic and financial analysis, listing of NT-proBNP on the MBS will still likely result in cost savings to the MBS (or at worst a small incremental cost). Additionally, there was a case for listing the proposed test because it has been recommended as part of international clinical guidelines and because NT-proBNP would be a more accessible test (particularly for patients in rural and remote areas) than TTE.

MSAC noted that, to manage the risk of leakage and potential for greater than expected use of NT-proBNP testing, it is reasonable to monitor utilisation of the MBS item after listing and assess whether TTE utilisation is reduced. MSAC recommended that this should be at no sooner than 2 years, to cover the period of initial change in practice habits. MSAC also supported extending such funding to cover BNP testing for patients with previously diagnosed PAH to ensure consistency with other MBS items.

## Other discussion

MSAC requested that the Department write to the Cardiac Society of Australia and New Zealand to inform them of the background to the MBS listing NT-proBNP, to encourage them to set up a registry to monitor the appropriate use of the item and to implement a quality assurance program to monitor compliance with guidelines regarding optimal use of therapeutic agents in PAH. A review after 2 years might also look at uptake by postcode to ensure that there is penetration in relevant parts of Australia.

4. Background

This is a resubmission of MSAC Application 1689 for population 2 (patients who have been diagnosed with PAH), which was considered by MSAC in July 2022.

A summary of the key matters of concern in relation to Population 2 that were identified by MSAC and how the current ADAR addresses these concerns is outlined in Table 2.

Table 2 Summary of key matters of concern to MSAC

| **Component** | **Matter of concern** | **How the current ADAR addressed the concern** |
| --- | --- | --- |
| Clinical evaluation | **MSAC considered the extent to which NT-proBNP would reduce TTE is unclear.** * MSAC noted that the proportion of patients with stable PAH who would not require TTE was not reported.
* MSAC noted that patients with worsening symptoms would also undergo TTE; therefore, the value of NT-proBNP testing for this group of patients was uncertain.
* MSAC also considered the proportion of patients who will have TTE despite “normal” NT-proBNP (such as patients with ongoing symptoms, or to guide therapy) is uncertain.
 | The current ADAR presents an updated clinical management algorithm incorporating a 4-stratum risk calculator based on the 2022 ESC/ERS guidelines[[2]](#footnote-3).The ADAR reports that TTE would only be used in:* Patients with clinical worsening
* Patients who have had a change in therapy

However, the guidelines clearly state that patients with stable disease may be considered for TTE or cMRI every 3-6 months (Table 17 in the guidelines).The reasons for considering right heart imaging in patients with stable disease were not explained. Logically, it would be expected that imaging would mostly occur in patients in the higher risk categories (intermediate-high or high), those with co-morbidities (such as hypertension, diabetes, obesity and coronary heart disease), or in those with connective tissue disease-associated PAH and interstitial lung disease (who have a greater risk of mortality compared to patients with idiopathic PAH)Janssen commissioned an analysis of the PHSANZ registry data to estimate the proportion of patients with: * stable or improved PAH who would not require subsequent TTE and/or RHC, and
* deterioration of symptoms who would undergo NT-proBNP in addition to TTE and/or RHC.

The results of this analysis were included in the ADAR to estimate the extent that NT-proBNP testing will reduce TTE in clinical practice.  |
| Clinical evaluation | MSAC considered that the REVEAL Lite 2 risk stratification calculator (which includes NT-proBNP results) was non-inferior to other calculators in identifying patients who were likely to die in the next year. MSAC also noted that there was limited evidence which suggested that risk stratification calculators that included NT-proBNP were at least as effective as those that did not. | Although MSAC had no concerns about the clinical effectiveness of the intervention in the original ADAR., the intervention in the resubmission proposes a new 4-stratum risk stratification tool that requires reassessment of clinical effectiveness compared to a 3-stratum tool.The ADAR did not include an analysis of the 4-stratum versus the 3-stratum risk classification tools. This was provided by the commentary.However, reassessment of the clinical effectiveness of the NT-proBNP test should not be required. |
| Economic evaluation | MSAC advised that the extent of substitution of TTE is uncertain resulting in uncertainty in the cost-effectiveness and financial impact (MSAC PSD for Application 1689, p.1 & 4)For patients who have been diagnosed with PAH (referred as Population 2 in initial submission), **MSAC considered NT-proBNP may decrease the use of TTE, although MSAC considered the estimated substitution of TTE in the ADAR to be uncertain.** For population 2, NT-proBNP is not expected to effect downstream management or improve outcomes, leading to uncertain clinical utility and cost-effectiveness. MSAC considered that, for population 2 to be reconsidered, the applicant may need to identify a PAH population where NT-proBNP could substitute TTE. MSAC advised a future application for this population would also need to demonstrate that monitoring using NT-proBNP would decrease TTE frequency (using a cost-minimisation analysis) or improve clinical outcomes (using a cost-effectiveness analysis) (MSAC PSD for Application 1689, p.6).There is a risk that the cost savings estimated may be smaller or not be realised if the rate of substitution of TTE is substantially lower than expected and/or the number of NT-proBNP tests per year is higher than expected. However, ESC considered that it was highly likely that substantial substitution of TTE would occur. Sensitivity analysis suggests the economic and financial results are robust to plausible variations in key assumptions with the worst case tested resulting in a small net cost for Government (MSAC PSD for Application 1689, p. 33). | Janssen commissioned an analysis of the PHSANZ registry data to estimate the proportion of patients with: * stable or improved PAH who would not require subsequent TTE and/or RHC, and
* deterioration of symptoms who would undergo NT-proBNP in addition to TTE and/or RHC.

The results of this analysis are included in the current assessment report and provide clarity to the extent that NT-proBNP testing might reduce TTE in clinical practice. Clinical stability, improvement or deterioration was defined by changes in WHO FC and/or 6MWD from baseline to first comprehensive follow-up. These are key risk assessment parameters used in current algorithms and which are consistent with those used in Australian practice, given that NT-proBNP is currently not publicly funded. These estimates have been incorporated into economic evaluation and budget impact analyses to provide greater certainty to the extent of TTE (and RHC) substitution and therefore greater certainty to the cost-effectiveness and total financial implications of MBS funding for this test.Based on the assumption that two TTE tests in the current algorithm would be substituted in the 75% of patients with stable disease, it is assumed that 4.0 NT-proBNP tests would replace 1.5 TTE tests compared to the assumption that 2.15 NT-proBNP tests would replace 2.15 TTE tests in the initial ADAR 1689, (meaning a reduction of 0.38 TTEs per NT-proBNP test performed). |
| Economic issues  | Applying the correct TTE fee to the model would further increase net cost savings. NT-proBNP was cost saving in most clinically plausible sensitivity analyses because it is likely that NT-proBNP will replace at least some TTEs. | Correct TTE test fees for MBS items 55126/55129, 100% Fee: $240.05) applied in the updated cost-minimisation analysis. |
| Financial evaluation | MSAC considered that the high estimates for the number of PAH patients (based on 10% PBS script data that were used in submission’s sensitivity analysis) appear more reasonable as Year 1 estimates are lower than the number of patients treated with PBS subsidised PAH medicines in 2016). | This issue was not addressed in the ADAR. The size of the population may be larger than the estimates.  |
|  | ESC noted that there is a risk that the cost-savings in Population 2 may not be realised, as NT-proBNP has the potential to become an add-on test rather than a replacement prognostic/monitoring test, as some clinicians might still request both TTE and NT-proBNP testing. However, ESC also noted that for Population 2 NT-proBNP would remain cost saving or result in a negligible cost across plausible sensitivity analyses. The model appropriately tested the relevant assumptions, so ESC did not consider that a reanalysis would be required (MSAC PSD for Application 1689, p. 35-36). | Janssen commissioned an analysis of the PHSANZ registry data to estimate the proportion of patients with: * + stable or improved PAH who would not require subsequent TTE and/or RHC, and
	+ deterioration of symptoms who would undergo NT-proBNP in addition to TTE and/or RHC.

These estimates have been incorporated into economic evaluation and budget impact analyses to provide greater certainty to the extent of TTE (and RHC) substitution and therefore greater certainty to the cost-effectiveness and total financial implications of MBS funding for this test.Similar to the economic evaluation, the key assumptions included the same frequency of assessment for NT-proBNP as for TTE (every 3 months), and the reduction in use of TTE occurs in stable patients (75%) (with NT-proBNP assumed to require 2 TTEs per year). |
| MBS Item Descriptor | MSAC thought that it was possible that doctors may use NT-proBNP testing for patients with other types of heart conditions that have not been assessed by MSAC for clinical or cost-effectiveness.MSAC considered whether the requestors should be restricted to specialist physicians such as cardiologists, rheumatologists, respiratory physicians and general physicians. The applicant did not object to limiting who can request the item to minimise leakage. MSAC also considered that a patient’s GP should play a role in testing and coordination. MSAC therefore advised that the item descriptor should state that the test can be requested by a treating medical practitioner “in consultation with a specialist”. GPs are able to refer patients for lung function testing (MSAC PSD for Application 1689, p. 5). | Janssen acknowledged MSAC’s consideration to not restrict the MBS Item to specified specialists and amend the item descriptor to state that the test can be requested by a treating medical practitioner in consultation with a specialist. However, following advice received by expert clinicians, Janssen understands that non-specialist medical professionals are unlikely to be conducting risk assessment or treating patients with PAH. Therefore, this change has not been incorporated in the proposed MBS Item Descriptor. |

ESC = Evaluation Sub-Committee, ESC/ERS = European Society of Cardiology and the European Respiratory Society; GP = general practitioner; MBS = Medical Benefits Schedule; MSAC = Medical Services Advisory Committee; NT-proBNP = N-terminal pro B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PHSANZ = Pulmonary Hypertension Society of Australia and New Zealand; PSD = Public Summary Document; RHC = right heart catheterisation; TTE = transthoracic echocardiogram

Source: Table 1-2, pg 20 of MSAC 1689.1 ADAR

5. Prerequisites to implementation of any funding advice

NT-proBNP tests are TGA approved. There are five companies offering seven assays, and all are subject to RCPA Quality Assurance Programs.

6. Proposal for public funding

The applicant has proposed a new MBS item descriptor for NT-proBNP testing of patients diagnosed with PAH. The proposed fee and benefit are the same as for the current MBS Item 66830 (BNP/NT-proBNP testing for the detection of heart failure).

Table 3 Presentation of the newly proposed MBS item descriptors

| Category 6 - PATHOLOGY SERVICES – (proposed category description)Group P2 – Chemical (proposed group description) |
| --- |
| Proposed item descriptor: Quantification of laboratory-based NT proBNP testing in patients with diagnosed pulmonary arterial hypertension for risk assessment.Maximum of 4 tests per patient in any one year.Fee: $58.50 Benefit: 75% = $43.90 85% = $49.75 |

Source: Table 1-7, pg 34 of MSAC 1689.1 ADAR

The proposed item descriptor is unchanged compared to the proposed item descriptor presented in the ratified PICO and the original submission except for the deletion of the word “ongoing” as this was considered superfluous.

Janssen acknowledges MSAC’s consideration to not restrict the MBS Item to specified specialists and amend the item descriptor to state that the test can be requested by a treating medical practitioner in consultation with a specialist. However, following advice received by expert clinician, Janssen understands that non-specialist medical professionals are unlikely to be conducting risk assessment or treating patients with PAH. Therefore, this change has not been incorporated in the proposed MBS Item Descriptor.

NT-proBNP is a non-invasive blood test already available from many diagnostic laboratories for the detection of heart failure. This application does not include point of care testing for NT-proBNP.

Public funding would make NT-proBNP testing more equitable and accessible. This was acknowledged by MSAC in their initial consideration of funding for this test where they noted “equity of access to TTE was a significant consideration” given that “NT-proBNP would be a more accessible test than TTE, particularly for people who live in rural and remote areas.”

As elevated NT-proBNP levels are not specific to PAH, this test is proposed as part of a risk classification algorithm for patients with PAH.

7. Population

The population that is eligible for the proposed health technology is unchanged from the initial submission (ADAR 1689).

Pulmonary hypertension (PH) is a condition of increased blood pressure in the arteries of the lungs and has been classified into five categories sharing similar pathological findings, hemodynamic characteristics, and management. PAH, which is caused by right heart disease, is classified as World Health Organisation (WHO) Group 1 PH disease. Other causes of PH include left heart disease (WHO Group 2), lung disease (WHO Group 3), chronic arterial obstruction (WHO Group 4). WHO Group 5 is defined as PH caused by unclear or multifactorial mechanisms.

PAH is a rare, severe, intractable, and debilitating progressive clinical condition characterised by a sustained elevation of pulmonary vascular resistance (due to narrowing of the pulmonary arteries), which if left untreated ultimately leads to right heart failure and death.

The symptoms of PAH are initially non-specific and mainly related to progressive right ventricular (RV) dysfunction, with ongoing symptoms typically induced by exertion, including shortness of breath, fatigue, weakness, angina, and syncope. Symptoms at rest occur only in advanced cases.

8. Comparator

As noted previously, what has changed since the previous submission is the update to the ESC/ESR guidelines which now recommend use of the 4-stratum model for risk-stratification, thus requiring a new assessment of the effectiveness of the 4-stratum risk classification models (using NT-proBNP levels) compared to 3-stratum models.

The comparator in the original ADAR was “a risk-assessment tool (without NT-proBNP) every 3-6 months to guide the need for repeat TTE and/or right heart catheterization (RHC) if symptoms worsen or there is a change in therapy.” It should be noted that TTE is a frequently used tool in the risk assessment of PAH patients, and is routinely used in risk management algorithms that do not use NT-proBNP. Thus, in the absence of NT-proBNP, TTE would be used regularly in clinical practice as part of a risk classification tool to guide the need for repeat RHC.

While in the ADAR the 4-stratum model has been correctly placed in the proposed clinical management algorithm, the commentary noted that it has also incorrectly included a 4-stratum model in the current clinical management algorithm. This is incorrect, as the new 4-stratum risk classification tool has not been validated for the use of TTE as one of the parameters and therefore should not be included in the current clinical management algorithm.

As 3-stratum risk calculators using NT-proBNP levels were considered by MSAC in the previous application 1689 to be non-inferior to those using TTE, a finding of non-inferiority between 4-stratum risk classification models using NT-proBNP levels and 3-stratum risk classification models using NT-proBNP levels would also imply non-inferiority between 4-stratum risk classification models using NT-proBNP levels and 3-stratum risk classification models using only TTE levels. Thus the specific 3-stratum tool used for the revised comparison in this ADAR (whether including NT-proBNP or only TTE levels) is not likely to significantly affect the outcome of the comparative assessment. This is of relevance because the commentary was unable to identify any studies which compared the use of the 4-stratum model including NT-proBNP, against a validated 3-stratum model without NT-proBNP - the implications of this are discussed further in section 12.

9. Summary of public consultation input

The previous ADAR 1689 received input from seven (7) organisations and six (6) individuals, five of whom were specialists and one being a nurse. The organisations that submitted input were:

1. Australian Scleroderma Interest Group (ASIG)
2. Scleroderma Australia
3. Thoracic Society of Australia and New Zealand (TSANZ)
4. Australian Rheumatology Association (ARA)
5. Public Pathology Australia (PPA)
6. The Royal College of Pathologists of Australasia (RCPA)
7. Lung Foundation Australia (LFA)

The consultation feedback received for the previous ADAR was generally supportive of public funding of NT-proBNP testing however it should be noted the ADAR for 1689 assessed NT-proBNP use for two populations: patients with systemic sclerosis and patients with previously diagnosed PAH. The current ADAR (for application 1689.1) is only concerned with the second population - patients previously diagnosed with PAH.

Additional feedback was received for the current ADAR 1689.1 from one non-profit organisation (Lung Foundation Australia), one specialty society (Australian Rheumatology Association) and three (3) consumer organisations, these were:

1. Scleroderma Australia
2. Lung Foundation Australia (LFA)
3. Australian Scleroderma Interest Group (ASIG)
4. Australian Rheumatology Association (ARA)
5. Pulmonary Hypertension Association of Australia (PHAA)

The consultation feedback received was again supportive of MBS funded NT-proBNP tests to provide valuable diagnostic and prognostic information for clinicians managing patients with PAH, as well as greatly improve the quality of life of patients with access to timely and less invasive care. Respondents noted that patients face frequent barriers in accessing TTEs and right heart catheterisation in hospitals including long distance travel and inability to drive, especially for those living in rural, remote and regional areas.  The benefits of the proposed medical service for patients were considered to be:

* reduced testing burden on patients with less need for more complex, invasive tests such as TTEs and right heart catherterisation
* reduced costs to patients, health systems and services by reducing the burden of disease on individuals, communities, and governments
* accurate monitoring of PAH disease progression and subsequent treatment management
* potential for improved compliance with regular evaluation which may improve longer term disease management
* equity of access for Australian patients to funded NT-proBNP testing in line with current international availability and Guidelines

Scleroderma Australia was again supportive of the proposition that ability to access MBS funded NT-proBNP tests would greatly improve the quality of life of their members as well as make it easier for them to access timely care. The submission noted that patients with scleroderma and diagnosed PAH face frequent barriers in accessing TTEs in hospitals including long distance travel and inability to drive, especially for those living in rural, remote and regional areas.

No disadvantages or concerns were raised in the consultation feedback in regard to the proposed intervention.

10. Characteristics of the evidence base

An updated search of the medical literature of the Embase (plus Medline) and Cochrane Library was undertaken on 1st December 2022), using the search terms listed in Table 4 to identify relevant studies and systematic reviews/meta-analysis.

Table 4 Search terms used for searching the EMBASE platform

| **Category** | **Description** | **Search terms** |
| --- | --- | --- |
| Population | pulmonary arterial hypertension (PAH), of any aetiology | 'pulmonary arterial hypertension' OR 'pulmonary arterial hypertension'/exp OR 'pah' |
| Intervention | NT-proBNP | 'n terminal pro b type natriuretic peptide' OR 'n terminal pro brain natriuretic peptide' OR 'n terminal probrain natriuretic peptide' OR 'n-terminal pro-brain natriuretic peptide' OR 'nt-probnp' |
| Outcomes | Diagnostic performance | 'accuracy':ti,ab,kw OR 'accurate':ti,ab,kw OR 'sensitivity':ti,ab,kw OR 'specificity':ti,ab,kw OR 'positive predictive value':ti,ab,kw OR 'ppv':ti,ab,kw OR 'negative predictive value':ti,ab,kw OR 'npv':ti,ab,kw OR 'predictive value':ti,ab,kw |

NT-proBNP = N terminal pro b type natriuretic peptide

Source: Table A-2, pg 100 of MSAC 1689.1 ADAR

The ADAR did not provide a description of the number of articles identified for each search string. The use of the diagnostic performance string would not be appropriate to search for articles reporting on health outcomes or on change in management outcomes.

The ADAR identified a total of 4 new primary studies, 2 new systematic reviews/meta-analyses and the 2022 ESC/ESR guidelines for assessing the test accuracy of NT-proBNP assay when used as a part of a 4-stratum risk stratification tool in patients with PAH.

The two systematic reviews and one primary study did not evaluate NT-proBNP levels within the context of being part of an assessment tool. These studies were not further evaluated by the commentary except to note that the results reported in these studies were consistent with the findings in the previous submission.

The literature search should have included another database such as PubMed. A quick literature search of the PubMed database using the same search terms used in the ADAR (listed in Appendix A) for population and intervention (but not outcomes) identified an additional study evaluating the 4-stratum model that was published on-line on 13 October 2022.

A summary of the evidence evaluated in the commentary is provided in Table 5 and Table 6.

Table 5 Key features of the key included evidence

| **References** | **N** | **Study Design** | **Risk of bias** | **Patient population** | **Outcomes** | **Use in modelled evaluation** |
| --- | --- | --- | --- | --- | --- | --- |
| **Ability of NT-proBNP-based risk assessment calculators to predict mortality** |
| Hoeper et al. (2022a) | 1,655 patients from the COMPERA PH registry | Retrospective registry | Low | Treatment-naïve patients aged ≥18 years newly diagnosed with any form of PAH between 1 January 2009 and 31 December 2020 | Mortality | Not used |
| Boucly et al. (2022) | 2,879 patients from the French PAH Registry | Retrospective registry | Low | Patients aged ≥18 years diagnosed with group I precapillary PAH enrolled between 1 January 2009 and 31 December 2020 | Mortality | Not used |
| Hoeper et al. (2022b) | 596 patients from the COMPERA PH registryLikely patient overlap with Hoeper et al. (2022a) | Retrospective registry | Low | Treatment-naïve patients aged 18–80 years newly diagnosed with PAH between 1 January 2009 and 31 December 2020 | Mortality | Not used |
| Rosenkranz et al. (2023)(Identified by the commentary) | 1,120 patients from the COMPERA PH registryLikely patient overlap with Hoeper et al. (2022a) | Retrospective registry | Low | Treatment-naïve patients aged ≥18 years newly diagnosed with IPAH between 1 January 2009 and 31 December 2021 with information about comorbidities | Mortality | Not used |

IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension

Source: Compiled for the commentary based on Table 2-1 on pg 42 of MSAC 1689.1 ADAR

Table 6 type of evidence supplied by the included evidence

| **Criterion** | **Type of evidence** | **Extent of evidence supplied** | **Overall risk of bias in evidence base** |
| --- | --- | --- | --- |
| Accuracy and performance of the test (cross-sectional accuracy) | None | [ ]  k=0 n=0 |  |
| Accuracy and performance of the test (longitudinal accuracy) | Comparison of outcomes in patients receiving *usual care*, conditioned on their mortality risk category | [x]  k=4 n=4,534 | Low risk of bias |
| Change in patient management  | Registry studies reporting on patient disease characteristics and usage of medication | [x]  k=2 n=4,293 | Low risk of bias |
| Health outcomes  | None | [ ]  k=0 n=0 |  |
| Predictive effect |  | [ ]  k=0 n=0 |  |
| Other | None | [ ]  k=0 n=0 |  |

k=number of studies, n=number of patients

Source: Compiled for the commentary based on the evidence base identified in Section 2 of MSAC 1689.1 ADAR

11. Comparative safety

The NT-proBNP test has not changed from the previous ADAR, requiring only a blood sample. TTE was also considered to be a very safe procedure. As both the intervention and the comparator were considered to be *relatively* safe procedures in the previous ADAR, whether used as part of a risk classification tool or not, safety was not discussed further in the resubmitted ADAR.

12. Comparative effectiveness

In the previous submission, MSAC noted that there was limited evidence which suggested that risk stratification calculators that included NT-proBNP were at least as effective as those that did not and considered that the clinical claim of non-inferior comparative clinical effectiveness was reasonable. Thus, only the studies evaluating the new 4-stratum risk assessment tool were evaluated in the commentary.

The ADAR presented summaries of test performance as reported in two systematic reviews and four primary studies, but did not provide a reasonable analysis of the evidence base. The two systematic reviews and one of the primary studies were excluded from further analysis by the commentary because NT-proBNP was evaluated as an independent indicator, rather than as part of an assessment tool.

In the PSD for the previous application, MSAC noted that increasing NT-proBNP levels are associated with worsening morbidity and mortality outcomes in PAH and that NT proBNP is an important variable in the REVEAL Lite 2 risk stratification calculator. It was noted by the commentary that the outcomes reported in the three studies excluded by the commentary aligned with the findings in the previous ADAR.

MSAC concluded that the REVEAL Lite 2 risk stratification calculator (using NT-proBNP levels as a parameter) was non-inferior to other calculators (using TTE) in identifying patients with PAH who were likely to die in the next year. Thus, it is not necessary to re-evaluate the effectiveness of NT-proBNP testing compared to TTE for this population in this commentary.

Therefore, the assessment conducted by the commentary compared the effectiveness of a
4-stratum risk assessment model (proposed in the new 2022 ESC/ESR guidelines) with a
3-stratum assessment model (such as the REVEAL Lite 2 risk stratification calculator) in predicting mortality.

The ADAR had provided only a superficial report, showing the Kaplan-Meier 5-year survival curves reported using the 4-stratum model in the two registry studies that provided the bulk of the evidence base (Hoeper et al., 2022[[3]](#footnote-4); Boucly et al., 2022[[4]](#footnote-5)). The analysis presented below was conducted by the commentary.

### Comparison of 4-stratum and 3-stratum risk stratification calculators that include NT-proBNP in the prediction of mortality and/or morbidity

No studies were identified which were able to compare the use of the 4-stratum model including NT-proBNP, against a validated 3-stratum model without NT-proBNP. The comparison with a
3-stratum model which includes both NT-proBNP and TTE is therefore included. The previous ADAR established that 3-stratum models including NT-proBNP were non-inferior to 3-stratum models using only TTE.

Four studies reported on the risk of death in patients with PAH, as determined using the
4-stratum model proposed in the 2022 ESC/ERS guidelines. Three studies were identified in the literature search conducted in the ADAR and one was identified in a quick literature search conducted by the commentary. There were insufficient data for meta-analysis of any outcome.

The proportion of patients in various risk categories using the 3-stratum versus 4-stratum models, both described in the 2022 ESC/ESR guidelines, at first follow-up was reported for patients from the COMPERA and FRENCH registries, in two studies (Table 7).

Table 7 The proportion of patients in various risk categories using the 3-stratum versus 4-stratum models

|  |  |  |
| --- | --- | --- |
| At first follow-up | 3-stratum model | 4-stratum model |
| Low | Int | High | Low | Int-L | Int-H | High |
| COMPERA registryHoeper et al (2022a)N=1,414 | 282 (19.9%) | 903 (63.9%) | 229 (16.2%) | 240 (17.0%) | 395 (27.9%) | 534 (37.8%) | 245 (17.3%) |
| FRENCH registryBoucly et al (2022)N=2,082 | 812(39%) | 1,103 (53%) | 167(8%) | 687(33%) | 791(38%) | 479(23%) | 125(6%) |

Int = intermediate; Int-L = intermediate-low; Int-H = intermediate-high

Source: Commentary Table 1, pg 52 of Commentary on MSAC 1689.1 ADAR

The majority of patients from both registries fall into the intermediate risk categories in both models. However, when the proportion of patients that changed risk category from baseline is examined, more patients changed risk category using the 4-stratum model (12–16%) compared to the 3-stratum model (10–11%). This increase is largely driven by a change in risk classification within the large intermediate group.

The patients who were separated into intermediate-low and intermediate-high risk groups had distinct mortality risks (Table 8) and these two groups also had distinct predictions of long-term survival using the 4-stratum method (Table 9). Boucly et al (2022) also showed that the Kaplan-Meier curves for the low-risk and high-risk groups from both the 3-stratum and 4-stratum models were similar and that the curve for the intermediate-low and intermediate-high risk groups had distinct survival curves. (Figure 1).

Table 8 1 and 5-year Kaplan-Meier survival estimates after first reassessment.

|  | *4-stratum model* |
| --- | --- |
| *Low* | *Intermediate-low* | *Intermediate-high* | *High* |
| *COMPERA registry**Hoeper et al (2022a)**N=1,414* | *1-year: 98.5%**5-year: 82.8%* | *97.2%**66.8%* | *91.3%**46.5%* | *78.0%**33.3%* |
| *FRENCH registry**Boucly et al (2022)**N=2,082* | *1-year: 97%**5-year: 81%* | *94%**57%* | *81%**31%* | *65%**13%* |

Source: Commentary Table 3, pg 53 of Commentary on MSAC 1689.1 ADAR

Table 9 Cox proportional hazards regression ratios after first reassessment.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | *Low* | *Intermediate-low* | *Intermediate-high* | *High* |
| *FRENCH registry**Boucly et al (2022)**N=2,082* |  *(vs Low)* |  |  |  |
| *3-stratum* | *HR=3.39 (2.80, 4.10)* | *HR=8.95 (6.83, 11.73)* |
| *4-stratum* | *HR=2.65 (2.11, 3.17)* | *HR=5.65 (4.50, 7.11)* | *HR=11.08 (8.23, 14.92)* |

Source: Commentary Table 3, pg 53 of Commentary on MSAC 1689.1 ADAR

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Figure 1 Survival according to the 3-stratum and 4-stratum models after first reassessment

Source: Commentary Figure 1, pg 53 of Commentary on MSAC 1689.1 ADAR (from Boucly et al 2022).

Log rank test p<0.001 for all models.

Hoeper et al (2022) found that the 4-stratum model was more sensitive to prognostically relevant changes in risk of mortality or lung transplantation than the original 3-stratum model. The risk of mortality changed in those whose risk category changed from baseline compared to those whose risk category remained unchanged in both models (Figure 2 and Figure 3).

Note that as the study by Boucly et al (2022) compared the risk of death in patients within different risk groups at the follow-up assessment and Hoeper et al (2022) compared the risk of death in patients who changed risk categories between assessments, the HR values cannot be directly compared between studies.

**

Figure 2 Mortality risk of patients who changed from the intermediate risk categories at baseline compared to patients who remained in their original risk category with the 3-stratum and 4-stratum models

Source: Commentary Figure 2, pg 54 of Commentary on MSAC 1689.1 ADAR (from Hoeper et al 2022a).

HR values are provided where reported.

**

Figure 3 Mortality risk of patients who changed from the risk category at baseline compared to patients who remained in the high risk category with the 4-stratum and 3-stratum models

Source: Commentary Figure 3, pg 54 of Commentary on MSAC 1689.1 ADAR (from Hoeper et al 2022a).

HR values are provided where reported.

The results presented above show that patients with PAH can be separated into intermediate-low and intermediate-high risk groups with distinct mortality risks. Additionally, the Kaplan-Meier curves indicate that the proposed 4-stratum risk classification model appears to be at least non-inferior to the 3-stratum risk classification tool recommended in the ESC/ESR guidelines in determining the risk of mortality. The 2022 ESC/ERS guidelines also concluded that the studies by Boucly et al (2022) and Hoeper et al (2022) showed that the 4-stratum model performed at least as well as the 3-stratum model in predicting mortality.

Therefore, the commentary considered that the 4-stratum model including NT-proBNP is at least non-inferior to other 3-stratum models which use TTE instead of NT-proBNP.

### Change in Management

There was no evidence identified either in the ADAR or by the commentary, assessing the extent of any change in management following the use of a risk classification tool that includes NT-proBNP testing compared to a risk classification tool that does not. There was also no evidence to suggest any differences in the changes in management that results from a 4-stratum rather than a 3-stratum NT-proBNP-based risk classification model.

In the PSD for the previous ADAR, MSAC noted that risk assessment using NT-proBNP would not result in any downstream changes in patient management. Rather, it is expected to reduce the number of patients requiring TTE compared with the current risk calculation algorithm (using TTE). The following section attempts to address these issues.

**Change in TTE usage**

The 2022 ESC/ERS guidelines recommend TTE at baseline for patients newly diagnosed with PAH, as well as 3-6 months after a change in therapy and in case of clinical worsening. However, the guidelines do not rule out the use of TTE in stable patients, as they indicate that TTE may be considered every 3-6 months in stable patients but gave no criteria for this consideration.

The proposed clinical management algorithm suggests TTE may be considered in patients with stable disease who have not had a TTE in the last 12 months, suggesting that all patients would have at least one TTE per year. Reasons for stable patients having more than one TTE per year were also not discussed in the ADAR.

The commentary considered that logically, more frequent imaging of patients with stable disease would mostly occur in those patients at greatest risk of mortality. This would most likely include patients in the higher risk categories, especially those who also have co-morbidities (such as hypertension, diabetes, obesity and/or coronary heart disease), or in those with connective tissue disease (CTD)-associated PAH, especially those with interstitial lung disease.

Thus, some or all patients from the following groups may be considered for an additional TTE (note, all of these groups are mutually exclusive):

* Patients who have a high risk of mortality (6–18% of all patients)
* Patients who have an intermediate-high risk of mortality (23–38%)
* Patients with PAH who have a low risk of mortality but have 3–4 comorbidities (24%)
* Patients with PAH who have a low risk of mortality but have coronary artery disease (25%)
* Patients who have CTD-PAH (20–27%)
	+ Approximately 32% of these patients have interstitial lung disease

The number of patients likely to need a TTE at each assessment for the current 3-stratum tool based on TTE and for 3-stratum and 4-stratum tools based on NT-proBNP levels, was estimated using the data from the COMPERA registry cohort for changes from baseline to first follow-up. These calculations were based on several assumptions described in the footnote to Table 10. However, the true proportions of patients who have further changes at the second and subsequent follow-ups cannot be determined due to a lack of evidence about the clinical status of patients over time.

Table 10 The proportion of patients likely to be referred for TTE using the 3-stratum versus 4-stratum models

|  |  |  |
| --- | --- | --- |
| **At first follow-up** | **3-stratum model** | **4-stratum model** |
| **Low** | **Int** | **High** | **Low** | **Int-L** | **Int-H** | **High** |
| COMPERA registryN=1,414 | 282 (19.9%) | 903 (63.9%) | 229 (16.2%) | 240 (17.0%) | 395 (27.9%) | 534(37.8%) | 245 (17.3%) |
| Risk category worsened from baseline1  |  | 17(1.9%) | 134 (58.5%) |  | 8(2.0%) | 67(12.5%) | 147(60.0%) |
| **No. requiring TTE** | **151 (10.7%)** | **222 (15.7%)** |
| Risk category improved from baseline2 | 185(65.6%) | 104(11.5%) |  | 177(73.8%) | 216(54.7%) | 80(15.0%) |  |
| **No. requiring TTE** | **289 (20.4%)** | **473 (33.5%)** |
| No, with stable disease | 97(34.4%) | 782 (86.6%) | 95(41.5%) | 63(26.3%) | 171 (43.3%) | 387(72.5%) | 98(40.0%) |
| CHD comorbidity3 | 7.5% | 42.5% |  | 7.5% | 18.5% |  |  |
| CTD-PAH + ILD3 | 5.9% | 12.3% |  | 5.9% | 5.9% |  |  |
| **No. additional TTEs (N)** | **13 4** | **428 4** | **95 5** | **9 4** | **42 4** | **194 (50%) 5** | **98 5** |
| No. with stable disease | 536 (37.9%) | 343 (24.3%) |
| **Total no. requiring TTE** | **976 (69.0%)** | **1,038 (73.4%)** |

Assumptions:

The proportion of patients who will have a worsening of risk category, develop comorbidities requiring further evaluation and/or had a recent change in medication at the first follow-up remains constant for all subsequent follow-ups

1 All patients with a worsened risk category would be referred for TTE as per the guidelines

2 Improvement in risk category is due to a recent change in medication and requires TTE to assess effectiveness

3 Proportions for the 3-stratum model assumed from proportions in the low risk, combined intermediate risk groups reported for the 4-stratum tool (only 32% of CTD-PAH patients have ILD)

4 Patients with low, intermediate or intermediate-low stable disease who also had either coronary heart disease as a comorbidity, or CTD-PAH with interstitial lung disease were assumed to require a TTE subsequent to the NT-proBNP test

5 All patients with high-risk stable disease (and half of those with a intermediate-high risk) would be referred for TTE.

ILD = interstitial lung disease; Int = intermediate; Int-L = intermediate-low; Int-H = intermediate-high

Source: Compiled for the commentary from Hoeper et al (2022a)

Overall, the number of patients likely to need a TTE at each assessment (3–6 monthly), when based on the data from the COMPERA registry cohort for changes from baseline to first follow-up, was estimated to be:

* 100% of patients would have a TTE using a 3-stratum risk classification tool using TTE as a parameter (current clinical management)
* 69% of patient would have a TTE using a 3-stratum risk classification tool using NT-proBNP levels as a parameter
* 73% of patient would have a TTE using a 4-stratum risk classification tool using NT-proBNP levels as a parameter (proposed clinical management)

When based on the analysis above, the proposed 4-stratum risk classification tool would result in a slight (4%) increase in the number of TTEs performed on reassessment compared to the
3-stratum risk classification tool proposed in the previous ADAR.

In summary, this analysis suggests that all patients diagnosed with PAH would have a TTE at least once every 12 months, but an estimated 73% of patients would have a TTE every
3 to 6 months. Thus, the use of the NT-proBNP test in all patients at every assessment is expected to reduce the use of TTE between annual assessments by 27%. Consequently, the NNT for NT-proBNP testing in order for one TTE to be avoided, is 4.

**Change in management**

Although MSAC noted that risk assessment using NT-proBNP would not result in any downstream changes in patient management in the PSD for the previous ADAR, the 2022 ESC/ERS guidelines noted that the main advantage of the 4-stratum model compared with the 3-stratum model was “better discrimination within the intermediate-risk group, which helps guide therapeutic decision-making.”

The therapeutic objective for patients with PAH is to achieve or maintain a low-risk profile. However, when the drugs prescribed to patients in the different risk categories included in the COMPERA and FRENCH PAH registries are compared, the extent to which a change in risk profile leads to a change in medication is uncertain. The prescribed drugs did not necessarily follow the treatments recommended for each risk category. Only a small proportion (1.3–7%) of the
15–17% of patients in the high-risk category at baseline had initially been prescribed combination therapy that included an intravenous or subcutaneous prostacyclin analogue, as recommended in the 2022 ESC/ERS guidelines (Hoeper et al 2022).

Boucly et al (2022) suggested that the distinction between intermediate-low and intermediate-high may be clinically useful in determining who would be eligible for lung transplantation and for determining which third medication to add for a patient on dual oral therapy. However, no evidence is available to confirm that these scenarios would occur in a clinical setting.

### Clinical claim

The ADAR concluded that the 7 new studies that were retrieved by the updated literature search further support the conclusions reached by MSAC in July 2022 regarding acceptable accuracy of NT-proBNP in the diagnosis of PAH, and its prognostic and clinical value as part of a multiparameter risk assessment for patients with PAH.

The commentary concluded that although the evidence base was limited to outcomes from patients enrolled in two large PAH registries, the proposed 4-stratum risk classification model appears to be at least non-inferior to 3-stratum risk classification tools also using NT-proBNP as a parameter in predicting mortality.

In the PSD for the previous ADAR, MSAC concluded that the 3-stratum REVEAL Lite 2 risk classification tool was non-inferior to 3-stratum risk classification tools using TTE.

By extrapolation, the commentary concluded that the proposed 4-stratum risk classification tool using NT-proBNP as a parameter would also be non-inferior to 3-stratum risk classification tools that include TTE and are currently used in Australian clinical practice.

13. Economic evaluation

The ADAR 1689.1 presented a cost-minimisation analysis (CMA) for the requested MBS listing of NT-proBNP testing (as a part of 4-stratum risk assessment tool) to assess and monitor patients diagnosed with PAH. As the ADAR 1689.1 did not present claims on the effectiveness and safety of NT-proBNP testing when used as part of a 4-stratum tool, the CMA is appropriate if MSAC accepts the effectiveness and safety of the proposed intervention as non-inferior compared to the 3-stratum risk classification tool (with or without NT-proBNP testing), which was accepted to be non-inferior in its previous consideration of the ADAR 1689.

The MBS fee requested was the same as in the initial ADAR (based on that for NT-proBNP testing Fee: $58.50; MBS item code 66830), and the service fee most likely to be replaced i.e., TTE fee was revised in compliance with MSAC’s advice (Fee: $240.05; MBS item code 55126/55129).

Based on the updated 2022 ESC/ESR guidelines, the ADAR 1689.1 assumed more frequent follow-up visits, i.e. 4 assessments/patient/year (assuming all patients undergoes risk assessment every 3 months), compared to the initial ADAR 1689 where 2.15 tests/patient/year were estimated in each arm (assuming twice per year in 90% of the patients, and three and four times in 5%, respectively). The proposed 4-stratum-model with NT-proBNP testing included
‘4.0 NT-proBNP + 2.5 TTE/patient/year’ compared to ‘4 TTE/patient/year’ in the current
3-stratum model with TTE, therefore a substitution of 1.5 TTE tests was assumed with 4.0 NT-proBNP tests (i.e. reduction of 0.38 TTEs per NT-proBNP test performed). Although this reduction estimate is lower than the assumption in the initial ADAR 1689 (where a reduction of 1.0 TTEs per NT-proBNP test performed was assumed), the number of NT-proBNP tests may be overestimated due to the assumption of 100% adherence every 3 months to either NT-proBNP or TTE (i.e. same frequency of testing in both arms). Given the accessibility and acceptability issues for TTE in the rural and remote areas, patients diagnosed with PAH are likely to receive less than the recommended number of TTE tests (4 TTE/patient in a year), and therefore, the assumption of a 1.5 reduction in TTE testing per year may be an overestimate.

The estimated reduction in TTE tests was based on the assumption that two TTE tests in the current algorithm could be substituted in a proportion of patients (suggested by the ADAR 1689.1 as those with stable disease). This proportion was estimated to be 75% based on PHSANZ data on the proportion of patients with stable or improved disease status according to two parameters (WHO FC and 6MWD), with unknown approaches for the assessment (i.e. 3- or 4-stratum classification). Therefore, this data may include stable patients who require additional TTE tests due to their high-risk categories or comorbidities. A threshold analysis conducted by the commentary suggested that if the proportion of PAH patients who are able to substitute two (of four) TTEs per year remains above 48.8% (average reduction of 0.24 TTE per NT-proBNP test performed), then the conclusion of cost savings would not change.



Figure 4 Threshold analysis for the proportion of patients able to substitute some TTE

Abbreviations: NT-proBNP = N-terminal proB-type natriuretic peptide; TTE = transthoracic echocardiogram

Source: Compiled by the commentary.

\* The average reduction in TTE per NT-proBNP test performed is 0.24.

^ The average reduction in TTE per NT-proBNP test performed is 0.38.

The cost-minimisation analysis, and the resubmission’s base case is presented in the table below. Relative to the previous ADAR, the estimated cost savings are reduced, however due to the issues described above regarding the extent of TTE substitution, the cost savings estimated may remain an overestimate.

Table 11 Total cost per patient in Year 1 associated with current (without NT-proBNP) and proposed (with NT-proBNP) clinical management algorithms in patients diagnosed with PAH

| Parameter | Current clinical management algorithm (without NT-proBNP) | Proposed clinical management algorithm (with NT-proBNP) | Source/Notes |
| --- | --- | --- | --- |
| Unit cost of NT-proBNP test | $58.50 | $58.50 | MBS 66830 |
| Proportion of patients undergoing NT-proBNP test at each visit (baseline, and 3 follow-up visits) | 0% | 100% | 2022 ESC/ERS Guidelines |
| No. NT-proBNP tests/patient/year  | − | 4.0 | ADAR 1689.1 |
|  | - | 2.15 | ADAR 1689 PSD, July 2022, p28 |
| Total NT-proBNP test cost/patient/year | $0.00 | $234.00 | A |
| Unit cost of TTE test | $240.05 | $240.05 | MBS 55126/55129 |
| Proportion of patients undergoing TTE test at baseline | 100% | 100% | 2022 ESC/ERS Guidelines (Humbert et al., 2022);PHSANZ registry analysis (Attachment 1 of the ADAR 1689.1) |
| Proportion of patients undergoing TTE test at follow-up visit 1 | 100% | 100% |
| Proportion of patients undergoing TTE test at follow-up visit 2 | 100% | 25% |
| Proportion of patients undergoing TTE test at follow-up visit 3 | 100% | 25% |
| No. TTE tests/patient/year  | 4.0 | 2.5 | ADAR 1689.1 |
|  | 2.15 | - | ADAR 1689 PSD, July 2022, p28 |
| **Total TTE test cost/patient/year** | **$960.20 a** | **$600.13 b** | B |
| **Total cost per patient per year** | **$960.20** | **$834.13** | = A + B |
| **Net cost difference per patient (with NT-proBNP – without NT-proBNP)** | **-$126.08** | = $834.13 - $960.20 |
|  | -$382.16 | PSD, July 2022, p28 |

Source: Table 3-5, pg 54 of MSAC 1689.1 ADAR

Abbreviations: ESC = European Society of Cardiology; ERS = European Respiratory Society; MBS = Medicare Benefits Schedule; NT-proBNP = N-terminal proB-type natriuretic peptide; PAH = pulmonary arterial hypertension; PHSANZ = Pulmonary Hypertension Society of Australia and New Zealand; TTE = transthoracic echocardiogram

a This is calculated by weighting of proportion of patients undergoing TTE tests at baseline and each of the 3 follow-up visits in a year = $240.05 x [(100% x 1) + (100% x 1) + (100% x 1) + (100% x 1)].

b This is calculated by weighting of proportion of patients undergoing NT-proBNP tests at baseline and each of the 3 follow-up visits in a year = $240.05 x [(100% x 1) + (100% x 1) + (25% x 1) + (25% x 1)].

Note: Grey shading indicates data previously seen by the MSAC.

While the sensitivity analyses (versus the comparator of TTE) presented in the 1689.1 ADAR generally resulted in net cost savings, scenario analyses conducted by the commentary, which explored the impact of different follow-up intervals in the proposed (i.e. every 3 months NT-proBNP testing) and current algorithms (every 5-6 months TTE testing) resulted in net costs, assuming that NT-proBNP would be more accessible than TTE, particularly for people who live in rural and remote areas. Therefore, the cost saving estimates for the scenario and sensitivity analyses presented in the ADAR (given in the table below) appears to be uncertain, and likely to be overestimated.

Table 12 Results of scenario and sensitivity analysis

| Scenario | Net cost difference per patient (with NT-proBNP - without NT-proBNP) |
| --- | --- |
| Rate of clinical worsening: 25% (base case) | Rate of clinical worsening: 35%(Sensitivity 1) | Rate of clinical worsening: 50%(Sensitivity 2) |
| Base case* Time horizon: 1 year
* Follow-up interval: 3 months
* Comparator: TTE
 | -$126.08(cost saving)4 TTE current vs 4 NT-proBNP + 2.5 TTE proposed (reduction of 0.38 TTEs per NT-proBNP test performed) | -$78.064 TTE current vs 4 NT-proBNP + 2.7 TTE proposed (reduction of 0.33 TTEs per NT-proBNP test performed) | -$6.054 TTE current vs 4 NT-proBNP + 3 TTE proposed (reduction of 0.25 TTEs per NT-proBNP test performed) |
| Scenario 1* Time horizon: 2 years a
* Follow-up interval: 3 months

Comparator: TTE | -$612.238 TTE current vs 8 NT-proBNP + 3.5 TTE proposed (reduction of 0.56 TTEs per NT-proBNP performed | -$468.208 TTE current vs 8 NT-proBNP + 4.1 TTE proposed (reduction of 0.49 TTEs per NT-proBNP performed | -$252.158 TTE current vs 8 NT-proBNP + 5 TTE proposed (reduction of 0.38 TTEs per NT-proBNP performed |
| Scenario 2* Time horizon: 1 year
* Follow-up interval: 5-6 months

Comparator: TTE | -$4.543 TTE current vs 3 NT-proBNP + 2.25 TTE proposed (reduction of 0.25 TTEs per NT-proBNP test performed) | $19.473 TTE current vs 3 NT-proBNP + 2.35 TTE proposed (reduction of 0.22 TTEs per NT-proBNP test performed) | $55.473 TTE current vs 3 NT-proBNP + 2.5 TTE proposed (reduction of 0.17 TTEs per NT-proBNP test performed) |
| Scenario 3* Time horizon: 2 years a
* Follow-up interval: 5-6 months

Comparator: TTE | -$490.697 TTE current vs 7 NT-proBNP + 3.25 TTE proposed (reduction of 0.54 TTEs per NT-proBNP performed | -$370.667 TTE current vs 7 NT-proBNP + 3.75 TTE proposed (reduction of 0.46 TTEs per NT-proBNP performed | -$190.637 TTE current vs 7 NT-proBNP + 4.5 TTE proposed (reduction of 0.36 TTEs per NT-proBNP performed |
| Commentary Scenario 1* Time horizon: 1 years
* Follow-up interval:
	+ 3 months for NT-proBNP
	+ 4 months for TTE a, b
* Comparator: TTE
 | -$36.063 TTE current vs 4 NT-proBNP + 1.9 TTE proposed (reduction of 0.28 TTEs per NT-proBNP test performed) | -$0.053 TTE current vs 4 NT-proBNP + 2 TTE proposed (reduction of 0.24 TTEs per NT-proBNP test performed) | $53.963 TTE current vs 4 NT-proBNP + 2.3 TTE proposed (reduction of 0.19 TTEs per NT-proBNP test performed) |
| Commentary Scenario 2* Time horizon: 1 years
* Follow-up interval:
	+ 3 months for NT-proBNP
	+ 6 months for TTE a, c
* Comparator: TTE
 | $53.962 TTE current vs 4 NT-proBNP + 1.3 TTE proposed (reduction of 0.19 TTEs per NT-proBNP test performed) | $77.972 TTE current vs 4 NT-proBNP + 1.4 TTE proposed (reduction of 0.16 TTEs per NT-proBNP test performed) | $113.982 TTE current vs 4 NT-proBNP + 1.5 TTE proposed (reduction of 0.13 TTEs per NT-proBNP test performed) |

Abbreviations: NT-proBNP = N-terminal proB-type natriuretic peptide; TTE = transthoracic echocardiogram; RHC = right heart catheterisation

Source: Adapted from Table 3-7 of MSAC 1689.1 ADAR, and commentary scenario 1 and 2 were conducted during evaluation.

a Commentary Scenario 1 and 2 analyses assume with NT-proBNP a 50% reduction in TTE use in the proportion of patients that do not have worsening symptoms.

b Where TTE is assumed currently every 4 months (i.e. 3 per year), with NTpro-BNP TTE use, stable patients would use 1.5 TTEs, compared to worsening patients who would still use 3 TTEs.

c Where TTE is assumed currently every 6 months (i.e. 2 per year), with NTpro-BNP TTE use, stable patients would use 1 TTEs, compared to worsening patients who would still use 2 TTEs.

14. Financial/budgetary impacts

The epidemiological approach presented in the initial ADAR 1689 was maintained in the resubmission to estimate the financial implications of proposed risk assessment and monitoring of PAH patients using NT-proBNP testing. This approach is not reasonable given that MSAC had previously advised that higher estimates, based on 10% PBS script data used in a sensitivity analysis, were more reasonable. The resulting estimates for the number of PAH patients appear to be underestimated as Year 1 estimates are similar to the number of patients treated with PBS subsidised PAH medicines in 2016. This does not seem reasonable as noted by PBAC in its March 2022 meeting[[5]](#footnote-6), that the PAH incident patient population is stable, and the prevalent patient population is growing.

The resubmission ADAR estimated a cost saving to the MBS of $232,674 in Year 1 increasing to $351,359 in Year 6. Cost savings to the MBS were based on the assumption that, on average, each NT-proBNP test performed would lead to a reduction of 0.38 TTEs. As noted in Section 11, cost savings are uncertain due to assumptions regarding the frequency of assessment of NT-proBNP and TTE (both assumed to be every 3 months), and the proportion of patients who can substitute TTE (75%) and extent of TTE reduction in these patients (2 per year).

As noted in the public consultation feedback for the initial ADAR 1689, due to accessibility and acceptability issues for TTE, patients may not receive the recommended number of TTEs in rural and remote areas. Therefore, the uptake of NT-proBNP (an assumption of 90% in the ADAR 1689.1 base case) may be underestimated as public funding for NT-proBNP testing would provide patients with a more convenient and easily accessible option, which might increase uptake of NT-proBNP.

The financial implications to the MBS resulting from the proposed listing of NT-proBNP are summarised in table below.

Table 13 Net financial implications of NT-proBNP testing to the MBS in patients with PAH (Base Case)

| **Parameter**  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated use and cost of the proposed health technology** |
| Number of PAH patients eligible for NT-proBNP test | 2,414 | 2,935 | 3,498 | 3,548 | 3,597 | 3,646 |
| High estimate based on 10% PBS data a | 3,200 | 3,720 | 4,248 | 4,263 | 4,277 | 4,292 |
| High estimate in ADAR 1689 | 3,200 | 3,705 | 4,218 | 4,738 | 5,266 | 5,801 |
| Number of PAH patients who receive NT-proBNP test (90% uptake rate) | 2,173 | 2,641 | 3,148 | 3,193 | 3,238 | 3,281 |
| Number of PAH patients who receive NT-proBNP test in ADAR 1689 | 2,107  | 2,561  | 3,056  | 3,102  | 3,148  | 3,193  |
| Number of services of NT-proBNP in PAH patients (4/patient/year) | 8,692 | 10,565 | 12,593 | 12,773 | 12,950 | 13,126 |
| Number of services of NT-proBNP in PAH patients (2/patient/year) | 4,214  | 5,123  | 6,113  | 6,205  | 6,296  | 6,386  |
| Cost to the MBS *($49.75, 85% fee)* | $432,428 | $525,604 | $626,525 | $635,479 | $644,266 | $653,005 |
| Cost to the MBS in ADAR 1689 ($49.75, 85% fee) | $209,637 | $254,859 | $304,112 | $308,679 | $313,246 | $317,723 |
| **Change in use and cost of other health technologies** |
| Change in use of TTE(1.5/patient/year) | -3,260 | -3,962 | -4,723 | -4,790 | -4,856 | -4,922 |
| Change in use of TTE in ADAR 1689 (1/pt/yr) | 2,107 | 2,562 | 3,056 | 3,103 | 3,148 | 3,193 |
| Net change in costs of TTE to the MBS ($204.05, 85% fee) | -$665,102 | -$808,414 | -$963,636 | -$977,409 | -$990,923 | -$1,004,364 |
| ADAR 1689 ($200.85, 85% fee) | -$423,191 | -$514,578 | -$613,798 | -$623,238 | -$632,276 | -$641,314 |
| **Net financial impact to MBS** | **-$232,674** | **-$282,810** | **-$337,111** | **-$341,929** | **-$346,657** | **-$351,359** |
| *ADAR 1689 b*  | *-$213,554* | *-$259,718* | *-$309,686* | *-$314,559* | *-$319,030* | *-$323,591* |

Source: Compiled by the commentary from Tables 4-3 through 4-7 in the ‘ADAR 1689.1 NTproBNP MSAC­\_FINAL’ and MSAC and Table 12, pg 31 of MSAC 1689 PSD

MBS = Medicare Benefits Schedule; NT-proBNP N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PSD = Public Summary Document; TTE = Transthoracic Echocardiogram

a The approach used to project patient numbers in subsequent years in ADAR 1689.1 was different compared to the initial ADAR 1689, resulting in substantially lower patient numbers in Years 4−6.

b In the initial ADAR 1689, net financial impact was reported as a total sum for the Population 1 and Population 2. This is calculated by adding the cost of NT-proBNP to the MBS (Row J in Table 4-5) and the total cost changed to MBS due to reduced TTE testing (Row H in Table 4-6).

*Note: Figures in italics are calculated during evaluation.*

*In its pre-MSAC submission the applicant noted that a revised base case based on 10% PBS script data would still result in cost savings to the MBS in each year of the forward estimates period, specifically in total cost savings of $2.3 million over the 6 year forward estimates*.

The sensitivity analyses presented in the resubmission showed that majority of the scenarios resulted in net financial savings. However, this may not be realised if NT-proBNP assessment is conducted more frequently than TTE (i.e. as in all of the analyses the ADAR has assumed the same frequency of assessment for TTE as for NT-proBNP), or the reduction in use of TTE (of two TTEs per year) occurs in at least 48.8% of PAH patients.

Table 14 Sensitivity analyses around ADAR Base Case vs TTE

| Data | Year 12024 | Year 22025 | Year 32026 | Year 42027 | Year 52028 | Year 62029 |
| --- | --- | --- | --- | --- | --- | --- |
| **Base case*** **Follow-up interval: 3 months**
* Rate of clinical worsening: 25%
* Uptake rate: 90%
 | **-$232,674** | **-$282,810** | **-$337,111** | **-$341,929** | **-$346,657** | **-$351,359** |
| **Change in rate of clinical worsening (sensitivity analyses)** |
| Rate of clinical worsening: 35% | -$143,994 | -$175,021 | -$208,627 | -$211,608 | -$214,534 | -$217,444 |
| Rate of clinical worsening: 50% | -$10,974 | -$13,338 | -$15,899 | -$16,126 | -$16,349 | -$16,571 |
| **Follow-up interval (sensitivity analyses)** |
| 5-6 months (25% worsening) | -$8,230 | -$10,004 | -$11,924 | -$12,095 | -$12,262 | -$12,428 |
| 5-6 months (35% worsening) | $36,110 | $43,891 | $52,318 | $53,066 | $53,799 | $54,529 |
| 5-6 months (50% worsening) | $102,620 | $124,732 | $148,682 | $150,807 | $152,892 | $154,966 |
| **Change in number of PAH patients (sensitivity analyses)** |
| Low PBS estimate | -$214,803 | -$264,938 | -$315,794 | -$317,219 | -$318,626 | -$320,024 |
| High PBS estimate | -$308,376 | -$358,511 | -$409,367 | -$410,792 | -$412,199 | -$413,597 |
| **Change in uptake rates (sensitivity analyses)** |
| Decrease in uptake rates: 80% | -$206,822 | -$251,386 | -$299,655 | -$303,937 | -$308,140 | -$312,319 |
| Increase in uptake rates: 100% | -$258,527 | -$314,233 | -$374,568 | -$379,922 | -$385,175 | -$390,399 |

Abbreviations: NT-proBNP N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PBS = pharmaceutical benefits scheme; TTE = transthoracic echocardiogram

Source: Table 4-8, pg 64 and Table 4-10, pg 65 of MSAC 1689.1 ADAR

Table 15 Sensitivity Analyses around the Commentary Scenario with differential follow-up intervals for NT-proBNP and the comparator TTE

| Data | Year 12024 | Year 22025 | Year 32026 | Year 42027 | Year 52028 | Year 62029 |
| --- | --- | --- | --- | --- | --- | --- |
| **Commentary Scenario*** **Follow-up interval for NT-proBNP: 3 months a**
* **Follow-up interval for TTE: 4 months a**
* Rate of clinical worsening: 25%
* Uptake rate: 90%
 | -$55,314 | -$67,232 | -$80,142 | -$81,287 | -$82,411 | -$83,529 |
| **Change in rate of clinical worsening (sensitivity analyses)** |
| Rate of clinical worsening: 35% b | -$10,974 | -$13,338 | -$15,899 | -$16,126 | -$16,349 | -$16,571 |
| Rate of clinical worsening: 50% c | $122,047 | $148,345 | $176,828 | $179,355 | $181,835 | $184,302 |
| **Change in number of PAH patients (sensitivity analyses)** |
| Low PBS estimate | -$51,065 | -$62,984 | -$75,074 | -$75,413 | -$75,747 | -$76,080 |
| High PBS estimate | -$73,310 | -$85,229 | -$97,319 | -$97,658 | -$97,992 | -$98,325 |
| **Change in uptake rates (sensitivity analyses)** |
| Decrease in uptake rates: 80% | -$49,168 | -$59,762 | -$71,237 | -$72,255 | -$73,254 | -$74,248 |
| Increase in uptake rates: 100% | -$61,460 | -$74,703 | -$89,046  | -$90,319 | -$91,568  | -$92,810 |

Abbreviations: NT-proBNP N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PBS = pharmaceutical benefits scheme; TTE = transthoracic echocardiogram

a This analysis assumes 3 TTE tests per patient per year in the current algorithm compared to 4 NT-proBNP + 1.9 TTE tests in the proposed algorithm (reduction of 0.28 TTEs per NT-proBNP test performed).

b This analysis assumes 3 TTE tests per patient per year in the current algorithm compared to 4 NT-proBNP + 2 TTE tests in the proposed algorithm (reduction of 0.24 TTEs per NT-proBNP test performed.

c This analysis assumes 3 TTE tests per patient per year in the current algorithm compared to 4 NT-proBNP + 2.3 TTE tests in the proposed algorithm (reduction of 0.19 TTEs per NT-proBNP test performed.

Source: compiled by the commentary

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

**Main issues for MSAC consideration**

**Clinical issues:**

- The 2023 Australasian position paper on pulmonary arterial hypertension (PAH) (Thoracic Society of Australia and New Zealand and Pulmonary Hypertension Society of Australia and New Zealand) will support the updated four-stratum PAH risk-assessment ESC/ESR guidelines including NT-proBNP as a key parameter for routine follow-up assessments.

* The evidence indicates that the proposed 4-stratum risk classification tool using NT-proBNP as a parameter would be non-inferior to 3-stratum risk classification tools that include TTE and are currently used in Australian clinical practice.
* The ESC/ESR guidelines state that patients with stable PAH “may” also be considered for transthoracic echocardiogram (TTE); however the ADAR assumed that all patients with stable disease would have a TTE at least once a year, but did not discuss the reasons why the minimum TTE would not be more frequent than this. Additional reasons why TTE testing may be more frequent than once per year among stable patients may include medication changes at last follow-up, increased testing frequency for stable patients with higher mortality risk, and individual clinician interpretation of risk factors.

**Economic issues:**

* Cost-minimisation analysis is appropriate if MSAC accepts effectiveness and safety of NT-proBNP as non-inferior when used as a part of the 4-stratum tool rather than the 3-stratum tool.
* The cost-savings of the intervention may be overestimated if the number of patients who have NT-proBNP in addition to TTE, rather than to replace TTE, is higher than modelled. The number of patients that may require additional TTEs due to “clinical worsening” and other factors was also a source of uncertainty and could further contribute to this overestimation.

**Financial issues:**

* The projected patient population for financial estimates is likely to be an underestimate.

**Item descriptor issues:**

- Both general practitioners and specialists should be able to request NT-proBNP testing for patients diagnosed with PAH.

- The proposed MBS item descriptor is for NT-proBNP testing of up to four times per year, the rationale being that more frequent testing may be needed in cases of clinical deterioration or concerns. but this may come with a risk of leakage.

**Other issues**:

- The potential reduced access to TTE in rural and remote areas may imply that there is a case based on equity for funding NT-proBNP as it would be a more accessible test for this population.

**ESC discussion**

ESC noted that the applicant seeks MBS-funding of N-terminal pro B-type natriuretic peptide (NT-proBNP) bioassay testing for the risk assessment and monitoring of patients with diagnosed pulmonary arterial hypertension (PAH).

ESC noted that this application is a resubmission. In July 2022, MSAC did not support public funding of NT-proBNP for Population 2 of [MSAC Application 1689](http://msac.gov.au/internet/msac/publishing.nsf/Content/904A22A8CF9AEC3ACA25874300802B69/%24File/1689%20Final%20PSD_Jul2022-CLEAN.pdf) because of uncertainty in the estimated cost-effectiveness and the total financial implications. ESC noted that, in its resubmission, the applicant has provided additional evidence on the extent to which the proposed service will lead to a substitution away from transthoracic echocardiogram (TTE) services, thereby enabling more reliable estimates of cost-effectiveness and total financial impact for MSAC’s consideration.

ESC noted that the main change since the initial submission is the release of the 2022 European Society of Cardiology and the European Respiratory Society (ESC/ESR) guidelines in August 2022, detailing updated recommendations for the management of PAH. ESC noted that the ESC/ESR guidelines recommend that, initially, patients would have a clinical assessment using a multi-parameter three-stratum risk classification tool to predict mortality within one year. Follow-up assessments would use a four-stratum model for risk-stratification. This tool includes only three non-invasive tests (WHO functional class [FC], 6-minute walking distance [6MWD] and NT-proBNP levels) with additional parameters (such as TTE) to be considered as needed. The ESC/ESR guidelines state that patients with stable disease may be considered for TTE or cardiac MRI (cMRI) every 3–6 months. ESC noted that the ESC/ESR guidelines consider that the main advantage of the four-stratum model over the three-stratum model is better discrimination within the large intermediate-risk group, by stratifying patients into intermediate-low and intermediate-high risk groups, along with the low and high risk groups which help guide clinical decision-making about further testing.

ESC noted that there was one response to public consultation, from Scleroderma Australia. Their members agreed that the ability to access MBS funded NT-proBNP tests would greatly improve their quality of life as well as make it easier to access timely care. Other points noted from this submission were the frequent barriers faced by patients with scleroderma and diagnosed PAH in accessing TTEs in hospitals including long distance travel and inability to drive, especially for those living in rural, remote and regional areas. These travel difficulties are heightened as the disease progresses which places pressure and financial costs on family and friends to assist them in getting to appointments for regular PAH risk assessment and monitoring in the absence of a publicly funded alternative to TTEs. ESC also noted from the submission that patients saw a blood test like NT-proBNP test as being more convenient and less likely to cause test-related discomfort than TTEs which would also be a factor in encouraging patients to keep up with their regular assessments.

ESC noted that the 2023 Australasian position paper on PAH (Thoracic Society of Australia and New Zealand and Pulmonary Hypertension Society of Australia and New Zealand) will support the updated four-stratum PAH risk-assessment including NT-proBNP as a key parameter for routine follow-up assessments. It will also recommend that NT-proBNP testing should be used together with WHO FC and 6MWD parameters as part of a non-invasive approach to routine follow-up risk-assessment, with TTE and/or right heart catheterisation (RHC) being reserved only for risk-assessment following changes in therapy, cases of clinical worsening or when deemed necessary based on individual clinical judgement. ESC noted that these guidelines state that patients with stable pulmonary arterial hypertension (PAH) “may” also be considered for TTE; the ADAR assumed that all patients with stable disease would have a TTE at least once a year, but did not discuss the reasons why the minimum TTE would not be more frequent than this. This has implications for the results of the updated economic evaluation as discussed below. In particular ESC noted that additional reasons why TTE testing may be more frequent than once a year among stable patients may include medication changes at last follow-up, increased testing frequency for stable patients with higher mortality risk and individual clinician interpretation of risk factors.

ESC noted that the applicant has proposed a new MBS item descriptor for NT-proBNP testing of patients diagnosed with PAH. The proposed fee and benefit are the same as for the current MBS item 66830 (BNP/NT-proBNP testing for the diagnosis of heart failure in patients presenting with dyspnoea to a hospital emergency department). ESC queried whether there is likely to be leakage because NT-proBNP testing could be used in patients with suspected heart failure in the out of hospital setting. If MSAC supports the application, ESC considered that monitoring will need to be implemented. However it was noted that an MSAC application covering this population is scheduled for consideration by ESC in the near future. The proposed fee for NT-proBNP of $58.50 (100% fee) remains unchanged from the first submission. This fee is consistent with the existing MBS item 66830 fee that uses this test. ESC noted that the proposed item descriptor is unchanged compared to the proposed item descriptor presented in the ratified PICO and the original submission except for the deletion of the word “ongoing” as this was considered superfluous by the applicant. ESC considered that inclusion or omission of the word did not make a material difference.

ESC noted that in its advice under MSAC Application 1689, MSAC advised that the supported item for NT-proBNP testing in patients with systemic sclerosis should be requested by a specialist, or by a medical practitioner in consultation with a specialist. ESC considered that both general practitioners and specialists should be able to request the test for patients diagnosed with PAH and there was little risk of leakage due to this.

ESC noted that the proposed MBS item descriptor supports testing up to four times per year. ESC also noted that an existing similar MBS item 66830 may only be requested up to six times per year for a given patient. ESC noted the proposal to enable testing up to four times a year will enable clinicians to request NT-proBNP more frequently in instances of clinical deterioration or concerns. ESC considered that despite risk of leakage, a frequency of four times a times may be appropriate if both GPs and specialist are able to request.

ESC agreed with the commentary that the 4-stratum risk assessment tool is not designed to use TTE instead of NT-proBNP, as appropriate cut-offs have not been established. Therefore, the current treatment algorithm presented in the ADAR which incorporates the 4-stratum risk classification tool should be amended to be based on a 3-stratum model that includes TTE. ESC noted the pre-ESC response from the applicant accepting the commentary’s proposal that it would be more appropriate to maintain the 3-stratum risk classification tool with TTE testing in the current clinical management algorithm, as was proposed in the previous MSAC application 1689.

ESC noted that the NT-proBNP test and TTE were previously considered by MSAC to be safe procedures, whether used as part of a risk classification tool or not. ESC noted that safety was not further discussed in the resubmitted ADAR.

ESC noted that an evaluation of the clinical effectiveness of the 4-stratum tool compared with other 3-stratum tools was undertaken by the commentary to ensure that the 4-stratum model is non-inferior to the proposed risk classification tool, the 3-stratum REVEAL Lite 2, which was evaluated in the previous ADAR. The ADAR identified 4 new primary studies and 2 new systematic reviews/meta-analyses. ESC noted the commentary’s assessment that neither of the systematic reviews evaluated NT-proBNP levels within the context of being part of an assessment tool, although one meta-analysis showed that NT-proBNP levels in patients with PAH were significantly higher compared to the levels in controls (i.e. high cross-sectional accuracy). The other meta-analysis showed that higher NT-proBNP levels in patients with PAH were associated with a statistically significant increased risk of mortality compared to those with lower levels (i.e. high longitudinal accuracy). The findings of the meta-analyses were consistent with the findings in the previous submission.

ESC noted that of the four studies further evaluated by the commentary, three studies used the same COMPERA pulmonary hypertension registry with similar inclusion criteria to enrol patients and thus the patient populations almost certainly overlap. Two studies compared the effectiveness of the 4-stratum NT-proBNP-based model with the 3-stratum model in the 2022 ESC/ERS guidelines, which uses both NT-proBNP levels and TTE parameters, in predicting death. ESC noted that one of these studies (Rosenkrantz 2023)[[6]](#footnote-7) reported that the 4-stratum risk tool predicted mortality outcomes in patients with IPAH irrespective of the presence of comorbidities.

ESC noted that there was no evidence identified either in the ADAR or by the commentary, assessing the extent of any change in management following the use of a risk classification tool that includes NT-proBNP testing compared to a risk classification tool that does not; and no evidence to suggest any differences in change in management resulting from use of a 4-stratum rather than a 3-stratum NT-proBNP-based risk classification model. This is consistent with the MSAC conclusion on the previous submission. Therefore, assessment of clinical effectiveness was focused on test accuracy (i.e. prediction of risk of mortality).

ESC noted that the limited evidence indicates that the proposed 4-stratum risk classification model appears to be at least non-inferior to 3-stratum risk classification tools also using NT-proBNP as a parameter in predicting mortality. ESC noted that in the previous submission, MSAC had already concluded that the 3-stratum REVEAL Lite 2 risk classification tool (using NT-proBNP) was non-inferior to 3-stratum risk classification tools using TTE in predicting mortality. Therefore, by extrapolation ESC considered that the evidence indicates that the proposed 4-stratum risk classification tool using NT-proBNP as a parameter would be non-inferior to 3-stratum risk classification tools that include TTE and are currently used in Australian clinical practice.

ESC noted that in terms of impacts on TTE usage, the commentary estimated that the proposed 4-stratum risk classification tool would result in a slight (4%) increase in the number of TTEs performed on each reassessment compared to the 3-stratum risk classification tool proposed in the previous ADAR. ESC noted that according to the commentary’s estimates, the use of the NT-proBNP test in all patients at every assessment is expected to reduce the use of TTE between annual assessments by 27%.

ESC noted that the ADAR’s economic evaluation was a cost-minimisation analysis. While the ADAR did not originally present claims on the effectiveness and safety of NT-proBNP testing when used as part of a 4-stratum tool, this evaluation is still appropriate if MSAC accepts the effectiveness and safety of the proposed intervention as non-inferior compared to the 3-stratum risk classification tool (with or without NT-proBNP testing) as per the extrapolation discussed previously.

ESC noted that the ADAR’s economic evaluation presented 1 and 2 year results. ESC considered that the presentation of 1 year results were appropriate but the justification for also providing the results of a two year time horizon was not provided and does not align with guidelines.

ESC noted that the results and relevance of the economic evaluation for decision making depend heavily on the rate of substitution between NT-proBNP and TTE. ESC noted that in updating the economic evaluation from the previous submission, the ADAR used corrected TTE test fees based on MBS items (55126/55129, 100% Fee: $240.05) as suggested by MSAC in 1689. The ADAR also reported on the results of an analysis of the PHSANZ registry data to estimate the proportion of patients with:

* stable or improved PAH who would not require subsequent TTE and/or RHC, and
* deterioration of symptoms who would undergo NT-proBNP in addition to TTE and/or RHC.

According to this analysis, 75% of patients were symptomatically stable or had improved disease according to both WHO FC and 6MWD parameters while 25% had experienced clinical worsening or deterioration with respect to at least one of the WHO FC or 6MWD parameters. ESC noted that the finding of this analysis of only 25% of patients reporting clinical worsening and therefore requiring additional TTEs (on top of the baseline TTE) underlies the economic evaluation which reported that the intervention resulted in 4 NT-proBNP tests and 2.5 TTEs per year for each patient (as opposed to 4 TTEs under the comparator). However, ESC noted that this rate of substitution (of 2.5 TTEs for every 4 NT-proBNP tests or a reduction of 0.38 TTEs per NT-proBNP test performed) does not account for changes in therapy, nor for patients classified at medium or high risk who all might receive TTE. ESC considered that the assumption of the substitution of TTE tests with NT-proBNP tests in stable patients is uncertain given the 2022 ESC/ERS guidelines which state that patients with stable disease may be considered for TTE or cMRI every 3-6 months. ESC also noted that this rate of substitution does not account for the possible differential use of intervention and TTE, e.g. more regular monitoring of patients with the intervention relative to TTE. In that respect, ESC noted that both the commentary and ADAR assessments may underestimate the amount of NT-proBNP testing while overestimating the amount of TTEs. ESC noted the applicant’s pre-ESC response arguing that these assumptions are conservative particularly over a 1 year period.

ESC noted that based on the above substitution rates, the total cost per patient associated with current algorithm (without NT-proBNP) is $960.20 compared to $834.13 associated with proposed algorithm (with NT-proBNP) in year 1, with four assessments assumed. Thus, the ADAR base case reported that the addition of NT-proBNP testing for the regular assessment of PAH patients would be a cost-saving option with a total year 1 savings of $126.08 per patient. ESC considered the additional sensitivity analyses performed by the commentary showed the results to be sensitive to testing frequency and the proportion of patients with stable disease where substitution from TTE to the intervention occurs. ESC accepted the commentary’s estimate that if the proportion of PAH patients who are able to substitute two (of four) TTEs per year remains above 48.8% (average reduction of 0.24 TTE per NT-proBNP test performed), then the conclusion of cost savings would not change.

ESC noted that the financial analysis reported a projected cost savings to MBS across all years, from a saving of $232,674 in 2023 to $351,359 in 2027. However, ESC considered that several uncertainties in these estimates remain because of:

* likely underestimate of population size (i.e. the number of PAH patients) in the base case compared to what MSAC had considered reasonable previously which was based on higher estimates from Pharmaceutical Benefits Scheme (PBS) script data
* uncertainties in substitution and differential use between intervention/TTE as raised in the economic evaluation
* uncertainty regarding the rate of patients experiencing ‘clinical worsening’

ESC noted that a series of univariate analyses, varying the time horizon (2 years), the comparator, the follow-up period (5–6 months) and rate of clinical worsening of patients (35% or 50%) showed that the proposed MBS funding of NT-proBNP would result in an overall best-case cost saving of $2,731.28 per patient or at worst (a highly conservative) case an incremental cost of $55.47 per patient. However, ESC noted that this assumed that NT-proBNP would be more accessible than TTE, particularly for people who live in rural and remote areas. Therefore, ESC considered that the cost-saving estimates for the scenario and sensitivity analyses presented in the ADAR appears to be uncertain, and likely to be overestimated. ESC considered the maximum exposure for the MBS under the scenario where the listing of NT-proBNP was no longer cost saving i.e., 50% clinical worsening and a reduction of 0.19 TTEs per NT-proBNP test performed, to be between $122,047 in year 1 up to $184,302 in year 6.

ESC noted that the potential reduced access to TTE in rural and remote areas may imply that there is a case based on equity for funding NT-proBNP as it would be a more accessible test for this population. ESC considered that overall there may be a clinical and patient need for this test (not just in terms of accessibility to testing alternatives but also in terms of overall patient discomfort with using TTEs), and that one approach may be to monitor utilisation after listing to evaluate the risk of leakage under the proposed item descriptor.

## 17. Applicant comments on MSAC’s Public Summary Document

The applicant had no comment.

## 18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](http://msac.gov.au/internet/msac/publishing.nsf/Content/Home-1)

1. Humbert, M., et al. (2022). ‘2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.’ *European Heart Journal*, 43(38): 3618-3731 [↑](#footnote-ref-2)
2. Humbert, M., et al. (2022). ‘2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.’ *European Heart Journal*, 43(38): 3618-3731. [↑](#footnote-ref-3)
3. Hoeper, M.M. et al. (2022). ‘COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension.’ *European Respiratory Journal*, 60(1): 2102311. [↑](#footnote-ref-4)
4. Boucly, A., et al.. (2022). ‘External validation of a refined four-stratum risk assessment score from the French pulmonary hypertension registry.’ *European Respiratory Journal*, 59(6): 2102419. [↑](#footnote-ref-5)
5. PBAC Consideration of PBS PAH medicine restriction changes arising from the Post-market Review, p.5, <https://www.pbs.gov.au/reviews/pah-files/March-2022-PBAC-minutes.pdf> [↑](#footnote-ref-6)
6. Rosenkranz S, et al. (2023). ‘Risk stratification and response to therapy in patients with pulmonary arterial hypertension and comorbidities: A COMPERA analysis.’ *Journal of Heart and Lung Transplantation*, 42(1):102-114. [↑](#footnote-ref-7)