Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1391 – Rapid point-of-care combined Antigen/Antibody HIV test to aid in the diagnosis of HIV infection

Applicant: **ANZPI, Alere Pty Ltd**

Date of MSAC consideration: **MSAC 64th Meeting, 30-31 July 2015**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au.

1. Purpose of application and links to other applications

An application was submitted by Inverness Medical Innovations Australia Pty Ltd for MBS listing of a rapid point-of-care combined Antigen/Antibody test for diagnosis of human immunodeficiency virus (HIV) infection for use in GP and sexual health clinics. The test for HIV infection is intended to be used in individuals where an HIV test is indicated and in those who are at high-risk of HIV infection. The evidence for assessment of this application was submitted in May 2015.

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of the rapid point-of-care combined antigen/antibody HIV test, MSAC did not support public funding because of uncertain clinical effectiveness and cost-effectiveness. MSAC considered it was particularly unclear whether the necessary behaviours would change (in the direction claimed) across the spectrum of prevalence, and thus whether health outcomes would be improved.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that the intended role for the rapid point-of-care testing was to increase HIV testing overall in the high-risk population and lead to earlier diagnoses for individuals who tend to delay testing or have never been tested. However, MSAC noted that wide-spread use of the test in a low prevalence setting would not accrue any of the benefits of point-of-care testing for this population of high-risk individuals who otherwise would not have had the serology test, noting also that the number of these individuals having serology testing would vary across this population.

MSAC advised that an indication for a high risk, high prevalence population such as men who have sex with men (MSM) may be more clinically- and cost-effective.

MSAC considered the safety, efficacy and cost-effectiveness for HIV point-of-care tests in high risk patients where a HIV test is indicated compared to standard laboratory-based serology HIV testing. MSAC noted that standard laboratory-based testing is also required following a positive result on the point-of-care test.

MSAC considered there were no real safety issues in regards to the point-of-care test procedure. A meta-analysis of two Australian studies showed that the point-of-care test had a sensitivity of 87.8% and a specificity of 99.4% compared to laboratory-based testing. MSAC was concerned that the lower specificity and sensitivity of the point-of-care tests compared to laboratory-based testing could result in more false positives with associated anxiety until confirmed (or not) by serology HIV testing, and more false negatives with associated harms of undiagnosed HIV infection and the potential for infecting others. MSAC also noted that the point-of-care test returns a higher rate of false negatives in the early stages of infection. MSAC noted the pre-MSAC response which stated that the risk in early infections could be mitigated by current clinical practice for HIV serology to be routinely performed whenever a rapid HIV test is performed.

MSAC noted that the randomised trial presenting impacts on patient management indicated that for the primary outcome of HIV tests over 18 months, there was no statistically significant difference between the rapid point-of-care test and conventional HIV testing. An initial increase in the rate of testing with point-of-care tests was not sustained and did not result in a higher test volume over 18 months. However, MSAC also noted the results of a patient satisfaction questionnaire which showed that one in five men would not have been tested if the point-of-care test was not available.

MSAC noted that current practice for laboratory-based serology HIV testing also includes testing for other sexually transmitted infections. MSAC considered that the use of the point-of-care test may reduce testing for these other infections, because of the need for blood to be taken for testing for other STIs.

Overall, it was unclear to MSAC whether the availability of point-of-care testing in Australia would change testing behaviour across the spectrum of prevalence.

MSAC noted that the point-of-care test is not a replacement for laboratory-based serology investigation, but rather an additional component of the diagnostic pathway. The base case economic model predicted that 10 fewer cases of HIV will be detected via screening with the point-of-care test compared to laboratory serology testing at an incremental cost of $941,454. This analysis was sensitive to the assumption that availability of the test would mean a greater proportion of MSM will be tested.

MSAC were unclear what the uptake of the point-of-care tests would be, therefore considered that the financial and budgetary impacts were highly uncertain.

MSAC noted the letter from the Kirby Institute discussing the falling numbers of men who have MSM who have been tested, and the fact that only half of individuals from high prevalence countries have been tested. They also noted evidence of a strong preference for point-of-care testing. However, MSAC considered that the evidence presented in the application did not strongly support these points.

4. Background

This application has not been previously considered by MSAC.

Rapid point-of-care testing is currently offered in a number of clinics Australia wide. Funding arrangements for rapid point-of-care HIV testing exist in some States and Territories, for example, the Queensland Government provides rapid point-of-care HIV tests for free under the Community HIV Education and Prevention (CHEP) program. The Victorian PRONTO! Clinics also offer the test for free, in partnership with the Victorian AIDS Council and the Burnet Institute.

The applicant stated that in clinics where no external funding arrangement exists, patients being tested currently pay for the test privately. One clinic reported that the cost associated with the test is $25 (for cost recovery). It is presumed that the funding arrangements in place for rapid point-of-care testing apply to all individuals who undergo the test (ie. that it is not only applicable to high-risk individuals).

5. Prerequisites to implementation of any funding advice

The applicant's rapid test which detects both HIV antigen and antibodies to HIV is currently approved by the TGA for point-of-care use by medical professionals trained in its use and interpretation of results in Australia. The TGA has placed clear restrictions on the use of this test.

6. Proposal for public funding

The proposed item descriptor by the applicant for rapid point-of-care testing for HIV is as follows:

Table 1 Proposed MBS item descriptor for rapid point-of-care testing for HIV

Category 6 - Pathology	**Group P9 – Simple Basic Pathology Tests**
MBS [item number] Point of care HIV antigen/antibody test by one or more immunochemical methods in a blood sample from a high-risk patient. **Fee**:$30 **Benefit**: 75%=22.50 85%=$25.50	

Source: p5 of the 1391 Protocol – specifies a fee of $30.00, the 75% and 85% benefits were calculated during the assessment

The applicant requested listing in Group P9- Simple Basic Pathology Tests. This category is for pathology tests performed and analysed by a medical practitioner in an approved practice rather than a pathology laboratory, As such a management fee is applicable to pathology tests if the service is bulk-billed. This fee is similar to the Patient Episode Incitation fee collected by pathology laboratories and ranges from $7.05 to $10.65 (85% benefit of $6.00 to $9.10) depending on the location of the practice.

MSAC discussed the suitability of Group P9 as an appropriate place for the proposed service and the conditions that would be required outside the laboratory based accreditation framework to ensure safety and quality. MSAC also considered that another funding model outside the MBS may be may be more appropriate. There was concern that a MBS listing would result in worse outcomes due to the issues around the sensitivity and specificity of the test.

7. Summary of Public Consultation Feedback/Consumer Issues

Feedback was provided from five organisations, all supportive of the application. The feedback stated support for MBS listing of any TGA registered rapid HIV test, not just limited to Ag/Ab tests. MBS listing of rapid HIV testing would increase access, particularly for an at risk population, and make rapid HIV testing more affordable and accessible. Support was also stated for rapid HIV testing to be offered with testing for other STIs where appropriate. Increased HIV testing should lead to earlier detection of HIV infections and allows a reduction of transmission to others due to awareness of the HIV status, modifying risk practices and commencement of treatment.

8. Proposed intervention's place in clinical management

The test is a qualitative "reactive" or "non-reactive" immunoassay. This is in contrast to quantitative methods such as enzyme immunoassay (EIA) where a quantitative result is obtained and a diagnostic cut-off is used. Sample collection for the test is a finger prick procedure.

The rapid point-of-care HIV Antigen/Antibody test for HIV infection is intended to be used in individuals where an HIV test is indicated and in those who are at a high-risk of HIV infection. The Protocol stated that there are a number of contexts where HIV testing would be indicated, including:

- clinical suspicion of HIV infection;
- inclusion of HIV within the differential diagnosis;
- diagnosis of a condition with shared transmission route;
- reported high-risk exposure;
- unprotected sexual intercourse with a partner whose HIV status is unknown;
- reported reuse of equipment used for skin penetration; and
- in the setting of contact tracing.

The Protocol defined those at "high-risk of HIV infection" to be those with one or more of the following risk factors:

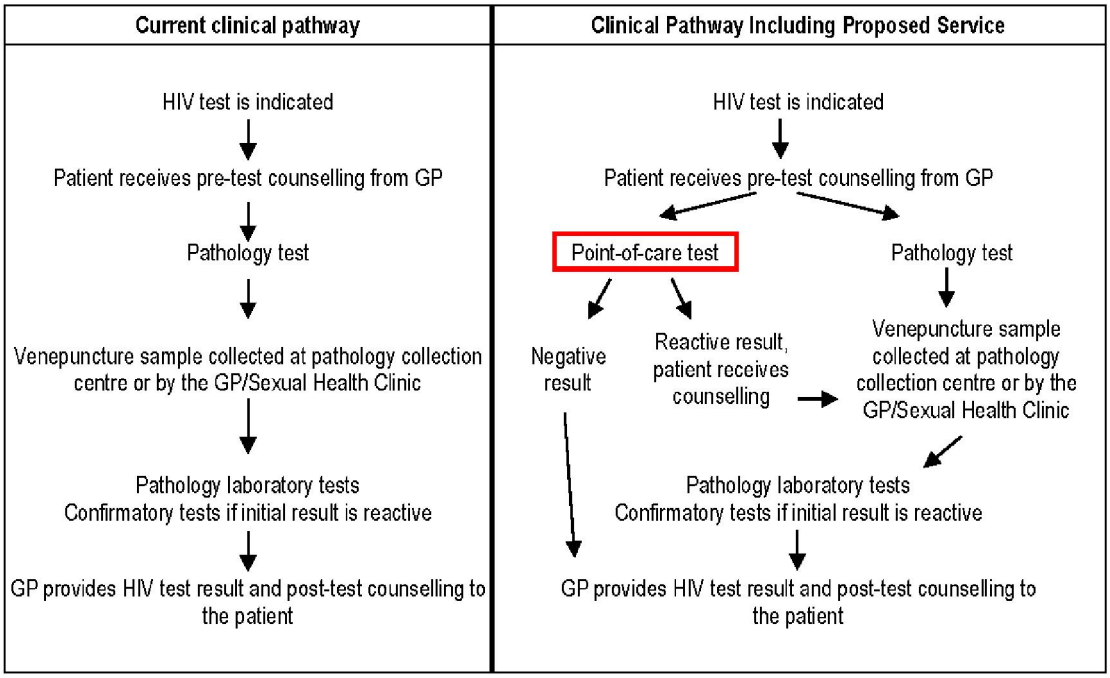
- men who have sex with men (MSM);
- injecting drug use;
- heterosexual contact with a person from a high prevalence country;
- heterosexual contact with a partner with/at risk of HIV infection; and
- needle-stick injury.

Although each of the groups listed above could be considered to be at high-risk, a population that would be a particular target group for this diagnostic test would be MSM, given the prevalence of HIV in this population.

The rapid point-of-care HIV Antigen/Antibody test is NOT intended for HIV testing performed on blood donations, for other organ or tissue donations or for routine microbiological serology during pregnancy. It is also not intended to be used as a HIV screening test.

The proposed clinical pathway for rapid point-of-care testing for HIV is shown below.

Figure 1 Current and proposed clinical decision tree



The proposed clinical management algorithm implies that rapid point-of-care testing will substitute for laboratory testing for HIV, in patients with a negative point-of-care test result. MSAC noted that the intended rationale for the rapid point-of-care testing would be to increase HIV testing overall in the high-risk population and also lead to earlier diagnoses for individuals who tend to delay testing.

MSAC noted that a positive rapid point-of-care HIV Ag/Ab test result would require confirmation by serology testing.

MSAC questioned the benefit of identifying HIV infections in people who would not seek treatment or change their behaviour based on the positive result.

MSAC stated that the proposal needs a clearer delineation between the point-of-care testing pathway and the current clinical pathway, however highlighted that in the correct circumstances the test could be valuable.

9. Comparator

The comparator to assess the safety, effectiveness and cost-effectiveness of the rapid point-of-care HIV Antigen/Antibody (Ag/Ab) test was pathology laboratory-based serology testing for HIV.

The testing performed by the laboratory will depend on the diagnostic algorithm in use, but would typically consist of a full testing protocol, ie. initial and confirmatory testing. Expert opinion sought during the assessment indicated that standard practice would be the use of a fourth generation Ag/Ab screening assay. The advice also indicated that in some instances, a reactive HIV sample might undergo (in total) testing in four different fourth generation HIV Ag/Ab EIAs (where only a single MBS item billing applies), as well as a HIV Western Blot (no MBS item number applies) and any other supplementary tests as indicated.

Expert opinion sought during the assessment indicated that in a Melbourne clinic using the rapid point-of-care HIV Ag/Ab test, venous samples were still being collected on the same day as the rapid test for laboratory testing (regardless of whether the rapid point-of-care HIV Ag/Ab test was reactive or not); indicating that the rapid point-of-care HIV Ag/Ab test may be an additional, rather than an alternative test to serology.

The expert advice also indicated that this was an opt-out system for those who are adamant they do not want a venous sample taken (less than 10 in 100 would decline); and that individuals suspected of early HIV seroconversion were particularly encouraged to undergo additional laboratory testing or should not be tested with a rapid test at all. Given testing for syphilis and other sexually-transmitted infections is recommended at the time of HIV testing and requires venepuncture and serology, it is not unreasonable to use serology to test for HIV at the same time (and could be considered inappropriate not to do so). MSAC noted that a shift to rapid point-of-care HIV Ag/Ab testing from serology testing could either decrease the rate of diagnosing other sexually-transmitted infections in high-risk individuals, or continue to require additional serology testing for these other infections anyway.

10. Comparative safety

No studies assessing the comparative safety of rapid point-of-care testing and serology testing for HIV were identified.

With regard to the procedures undertaken to collect specimens for testing, a finger-prick for rapid point-of-care testing or venepuncture for serology, respectively, no real safety issues are associated with either, provided the person drawing the samples is trained and sterile equipment is used. In addition, as the rapid point-of-care HIV Ag/Ab test requires the same or fewer blood withdrawals than the comparators, it is reasonable to conclude that the test is safe.

However, as noted below, HIV rapid tests can be less specific (ie. can have more false-positive results) and can be less sensitive (ie. can miss more cases of infection) than conventional machine controlled tests used in contemporary laboratories. The consequences of false-positive or false-negative results from the rapid point-of-care test should therefore be considered.

With regard to false-positive results, where the rapid point-of-care test indicates the presence of HIV infection, but confirmatory serology testing does not; it would be anticipated that the anxiety felt in the time period before delivery of the serology test results would be greater than for those who are undergoing routine testing with serology testing (with no rapid point-of-care test result). The positive rapid point-of-care result would also be accompanied by counselling for the results according to the proposed clinical decision pathway.

With regard to false-negative results, where the rapid point-of-care test indicates no HIV infection, but confirmatory serology testing would; there is potential for those individuals to have worse health outcomes in the longer term due to having an undiagnosed HIV infection. There is also the potential for these individuals to unknowingly transmit HIV to other individuals until such time they undergo further testing and are diagnosed. As noted above, the current practice in at least one Melbourne clinic is to collect a venous sample on the same day as rapid testing for serology testing for HIV. If this applies nationally, the risk of false-negative results should be no greater than is currently the case. The risk of false-negative results in practice may also be mitigated through information provided in the product's instructions for use and through training of health professionals performing the test. The

product's instructions for use detail the limitations of the test, including the limitation of the test during the early stages of infection. These limitations are explained to health professionals performing the test when they are trained in the use of the product. Expert advice has suggested that individuals suspected of early HIV seroconversion were particularly encouraged to undergo additional laboratory testing, or should not be tested with a rapid test at all.

11. Comparative effectiveness

Diagnostic accuracy

A meta-analysis of the two identified Australian studies (Conway (2014) and Eu (2014)) indicated that the sensitivity of the rapid point-of-care HIV Antigen/Antibody test was 87.8% (95% CI: 75.2%, 95.4%) and the specificity was 99.4% (95% CI: 99.1%, 99.7%) compared with serology testing for the diagnosis of HIV infection. These data differ from the sensitivity and specificity reported for the rapid point-of-care HIV Antigen/Antibody test provided in the product insert which states that the test is 100.00% across 1,179 specimens positive for various types and subtypes of HIV. The specificity of the test is 99.61% for the antigen test line and the 99.21% for the antibody test line across 1,783 HIV-negative specimens. MSAC noted that the pre-ESC response provided a third study (Debattista (2015)), but concluded that the additional data did not materially change the conclusions of the meta-analysis.

The differences in the reported sensitivity of the rapid point-of-care HIV Antigen/Antibody test from these Australian studies and the product insert are likely to be driven by a relatively high false-negative rate observed in the studies ((5/39; 12.8%) observed among men with early HIV infection (4/5; 80%) in Conway (2014) and among 1 of 10 (10%) cases and 1 of 3 (33%) seroconverters in Eu (2014)).

MSAC noted that the differences may be explained by differences in the sampling of cases and controls. Given HIV test results are affected by the time since infection, the proportion of newly infected patients tested is likely to influence diagnostic results (eg. spectrum bias) because they will generate false-negative test results before becoming sufficiently seropositive to exceed detectable levels. In contrast, oversampling from the two extreme ends of the spectrum (ie. confirmed seronegative and seropositive specimens), as relied upon in the product insert, tends to overestimate diagnostic accuracy (Knottnerus 2002).

Impact on patient management

The results of the single identified randomised trial by Read (2013) indicated that there was no statistically significant difference between rapid point-of-care testing and serology testing groups for the primary outcome of "HIV tests over 18 months" or the secondary outcomes of syphilis, chlamydia and gonorrhoea testing over 18 months. Hence, the possibility of having HIV tests by rapid point-of-care testing did not result in higher testing frequency over the study period of 18 months.

The authors also undertook *post-hoc* analyses considering only the first HIV test after enrolment and considering only subsequent HIV tests (excluding first tests). A statistically significantly greater number of first HIV tests/year after the enrolment test was observed in those randomised to the HIV testing by the rapid point-of-care test compared with conventional testing, however no differences were observed in the number of HIV tests/year when only considering subsequent tests. Based on these results, the authors concluded that *post-hoc* analysis showed an initial increase in the rate of testing that was not sustained.

The exclusion of "never" testers in the trial limits any increase in testing that may or may not have been observed if they had also been enrolled. This is of particular relevance when considered in the context that the results of the patient satisfaction questionnaire reported in Eu (2014) indicated that one in five men would not have been tested if rapid point-of-care testing was not available.

12. Economic evaluation

The data reported in Conway (2014) and Eu (2014) indicated that the rapid point-of-care HIV Ag/Ab test has inferior diagnostic accuracy for detecting HIV compared to serology testing; whereas data reported in Read (2013) indicated that there was no statistically significant difference between the groups randomised to rapid point-of-care testing and serology testing in terms of number of tests/year for HIV. Therefore, to account for the differential diagnostic accuracy, a cost-effectiveness analysis was presented.

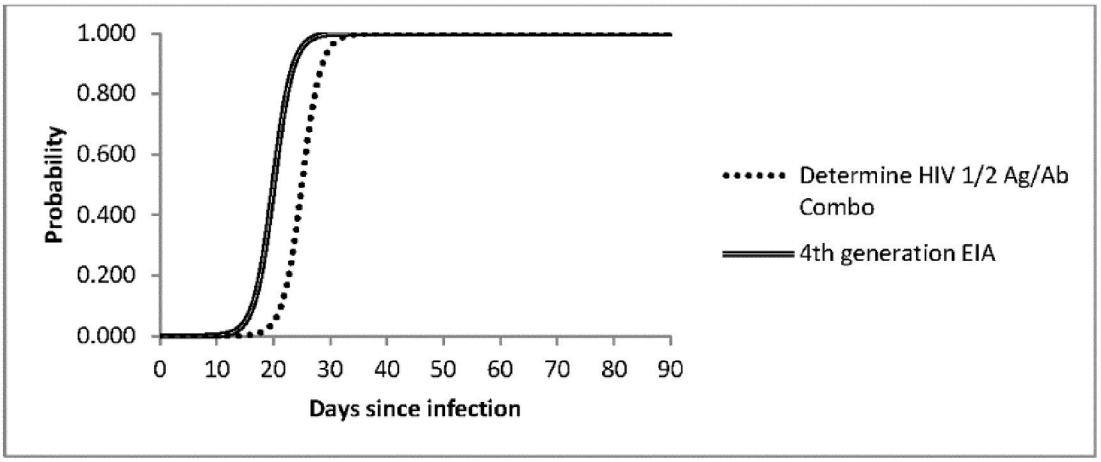
The base case of the model assumed no difference in testing frequency between the two arms of the model. Sensitivity analyses were conducted modifying some assumptions to attempt to capture other reasonable scenarios, including the qualitative patient satisfaction evidence in Eu (2014) and the *post-hoc* analysis in Read (2013).

The type of economic evaluation presented is a novel static cost-consequences analysis which estimates cost per various test outcomes associated with the rapid point-of-care HIV Ag/Ab test and conventional testing (fourth generation EIA) over one year. The population in the model is assumed to be all Australian MSM without diagnosed HIV, and includes individuals who are seropositive, seroconverting and seronegative.

A decision analytic Markov model was used to estimate the cost per various test outcomes over a one year time horizon with three-monthly cycles, of a scenario where the rapid point-of-care HIV Ag/Ab test is available for screening HIV in high-risk individuals. MSM without a diagnosis of HIV are assumed to commence each cycle in one of four health states (i) "Seropositive", (ii) "Seroconverting", (iii) "Seronegative" , (iv) "HIV diagnosed". Monte Carlo simulation is used to accommodate the heterogeneous population, conditional transition state probabilities, and incorporates a tracker variable for number of tests required by the clinical evidence available.

There is no precise "window period" during which a HIV test will detect an infection that it would not have detected prior to this time. Therefore, in the seroconverting state, the probability of a positive diagnosis is assumed to increase over time (Owen 2008). Wilson (2011) modelled the window periods of the third and fourth generation EIA and point-of-care tests using a logistic growth curves. The medians are set equal to the defined window periods for each test after the detection of HIV ribonucleic acid (RNA) with the Nucleic Acid Test, 10 days for the rapid point-of-care HIV Ag/Ab test and five days for fourth generation EIA. However, there is an eclipse period between the day of infection and the day when HIV markers are detectable. The eclipse period is approximately 2 weeks from infection to antigen, suggesting the median window periods for fourth generation EIA and the rapid point-of-care HIV Ag/Ab test are approximately 20 and 25 days respectively (Figure 2, Cohen 2010).

Figure 2 The median window periods for fourth generation EIA and the DHC test



The base case of the modelled economic evaluation predicted 10 fewer cases of HIV will be detected via screening with the rapid point-of-care HIV Ag/Ab test compared to standard laboratory testing, largely due to the window periods assumed for the tests. Of those not diagnosed, all commenced in the seronegative health state and were infected within the year. The incremental cost of the rapid point-of-care HIV Ag/Ab test is $941,454, therefore the strategy is dominated (ie. less effective and more expensive). This result is consistent with the assumption of no differences in testing frequency, and with the increased cost/test for the rapid point-of-care HIV Ag/Ab test compared with serology testing.

The results of the sensitivity analyses demonstrate that the ICER is most sensitive to the assumption that the availability of the rapid point-of-care HIV Ag/Ab test would encourage a greater proportion of MSM to be tested (ICER=$46,689/additional HIV detection; assuming an increase from 55% to 58% of MSM are tested) and assumed increases in testing frequency with the rapid point-of-care HIV Ag/Ab test compared with serology testing (ICER=$32,217/additional HIV detection).

13. Financial/budgetary impacts

The number of tests that are likely to be undertaken amongst high risk individuals is unknown.

Assuming direct substitution and 45,000 rapid tests per year (Protocol, p5), the total cost to the Australian healthcare system would be approximately $249,300, where the additional cost is associated with fewer HIV diagnoses.

Assuming sequential use and 45,000 tests per year, the total cost would be approximately $1,175,850, where the additional cost would be associated with no differences in the number of HIV diagnoses.

Based on the number of tests estimated in the base case of the modelled economic evaluation of 119,889 tests per year, assuming direct substitution, the total cost to the Australian healthcare system would be approximately $664,185 (additional cost with fewer HIV diagnoses); assuming sequential use, the total cost would be approximately $3,132,700 (additional cost is associated with no differences in the number of HIV diagnoses).

14. Key issues from ESC for MSAC

ESC noted that comparator issues were whether the public funding of point-of-care HIV testing would increase the overall volume of HIV testing and, if so, the extent to which this would represent increased testing of individuals who would be less inclined to be tested otherwise, and the extent to which this would represent additional testing of individuals already being tested. ESC noted the emphasis on these matters in the applicant's pre-ESC response.

ESC advised that a key issue for consideration would therefore be the performance of the test in early infections, noting the Conway et al. paper suggested the sensitivity rate in these populations was 66.7%. Differences across the tests in the "window period" between acquiring an HIV infection and having detectable seropositivity are relevant considerations in judging the comparative performance of the test options and in judging the performance of the point-of-care test for high-risk individuals not getting or delaying serology testing.

ESC noted that the economic model had attempted to deal with poor performance of the test during the seroconversion period through the incorporation of the testing window. The base case concluded that funding the point-of-care test would increase costs and decrease HIV diagnoses, which has important negative consequences for subsequent health outcomes. However, ESC considered that, overall, the economic model did not reflect the clinical evidence well, particularly for early infections. Increasing the number of tests conducted overall increased costs further, but did suggest a decrease in HIV diagnoses.

ESC also noted that the model was highly sensitive to assumptions regarding behaviour change, which might be attributed to the faster turnaround time of 20 to 30 minutes rather than two to three days with serology testing, and that there was no sensitivity analysis of diagnostic accuracy.

ESC considered that key uncertainties in the financial analysis were whether, and to what degree, point-of-care testing would substitute for serology testing or be provided sequentially as an additional test, and whether the availability of point-of-care testing would increase the proportion of the overall high-risk population which is tested. ESC noted the total financial implications of funding the point-of-care test was calculated to be up to $6 million with an increase in HIV diagnoses if testing were to increase by three per cent.

The Protocol stated that the proposed MBS item descriptor (or an accompanying explanatory note) would need to explain that the test must be performed at the point-of-care, and that the MBS item cannot be claimed on laboratory testing.

ESC considered that the proposed item descriptor would need an explanatory note which explicitly stated whether the test should be used in GP or sexual health clinics, as intended, and should exclude the use for screening of blood or organ donation specimens or use in routine pre-natal testing (which is also intended).

Consideration would also be required as to how the test would be billed in the event of an invalid test result, or if a clinician decided to repeat the test in the event of an initial reactive result prior to referral for serology testing.

An additional management fee is applicable to Group P9 - Simple basic pathology tests if the service is bulk-billed, ranging from $7.05 to $10.65 (85% benefit of $6.00 to $9.10) depending on location.

There are numerous MBS item numbers applicable to serology-based HIV testing, with a relevant associated direct fee of $15.65 (85% benefit of $13.35) plus additional fees of $2.40 to $9.95 (85% benefit $2.05 to $8.50) depending on the circumstances of the test.

ESC considered that, should this be recommended for funding, the item descriptor could be improved by including clearer exclusion criteria for appropriate clinical settings and definitions of high-risk individuals, clarifying rules around billing for invalid and repeat tests, and restricting claims for confirmatory serology testing (which would impact cost-effectiveness).

ESC agreed that further clarification about the assessment report modelled economic evaluation should be requested.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

Alere is disappointed with the decision not to recommend funding of rapid point of care HIV testing but acknowledges the areas of uncertainty that were identified by MSAC. New Australian evidence has recently been presented showing that the availability of rapid HIV testing significantly increases testing in high-risk groups and is cost-effective. Alere considers that this new evidence may address the areas of uncertainty identified by MSAC and will explore if a resubmission is possible.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.