1335 and 1351

Protocol to guide the assessment of point of care tests to exclude preterm labour

November 2013

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health and Ageing (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a protocol that will be used to guide the assessment of an intervention for a particular population of patients. The protocol will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the question for public funding the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use

Intervention – specification of the proposed intervention and how it is delivered

Comparator – specification of the therapy most likely to be replaced by the proposed intervention

Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Summary of matters for consultation

Specific areas on which PASC sought public consultation feedback are listed below:

- feedback on the place for transvaginal ultrasound to measure cervical length (TVCL) in the current and proposed clinical management algorithms, given that proposed use of the tests may be in addition to TVCL in hospitals that do provide TVCL or as an alternative to TVCL in health care settings where TVCL is available

- the parameters that may be included with the MBS item descriptor to describe the delivery of the tests and possible wording to describe the following possible parameters:
    - Should the use of the test/tests be only described for situations where TVCL is not available?
    - It has not been proposed that the number of tests be limited per patient but should there be a minimum number of days for symptoms to persist before a patient is eligible for retesting?
    - Should the item descriptor specify that the test is qualitative, quantitative or either?
    - Should testing be limited to maternity clinics/hospitals where staff are speculum trained (and to exclude use of the test/s to where other causes of the symptoms are able to be excluded)?
    - A generalised descriptor about a class of tests that include point of care tests is needed to be included in the MBS item descriptor.

Summary of matters for consideration by the applicant

The PASC requests that the applicants note the following issues and consider addressing the issues in its application:

- PASC advised that the applicants will need to provide justification for the item fee proposed, in particular justification for:
    - Inclusion of labour costs (if they can be justified, then which practitioner's salary costs should be used, e.g. obstetricians midwife or nurse practitioner)
    - Cost of the qualitative fFN test
    - Cost of the quantitative fFN test
    - Why overhead costs are included (17% overhead cost figure has been used).

- The need to present analytical sensitivity and specificity separate of the tests from their clinical sensitivity and specificity

Purpose of application

A proposal for an application requesting MBS listing of Phosphorylated Insulin-like Growth Factor Binding Protein (phIGFBP-1) test for excluding false preterm labour was received from Alere Pty Ltd (Inverness Medical Innovations Australia) by the Department of Health in September 2012. This proposal relates to a new intervention requesting listing on the MBS.

PASC, at its 18 April 2013 meeting, requested that a joint application of the phIGFBP-1 test and other routinely used tests for excluding preterm labour, the fetal fibronectin (fFn) tests, be submitted for evaluation as a point of care test for the exclusion of preterm labour. PASC requested a combined draft protocol be developed due to the similarity of the tests as they are both point of care tests for diagnosing preterm labour. A pre-assessment document, Part C, from Hologic to initiate an application to MSAC, was received on 19 July 2013.

The Deakin Health Technology Assessment Group, under its contract with the Department of Health, drafted this combined decision analytical protocol to guide the preparation of an assessment of the safety, effectiveness and cost-effectiveness of the phIGFBP-1 test and the fFN test for excluding false preterm labour to inform MSAC's decision-making regarding public funding of these interventions.

Background

Current arrangements for public reimbursement

Currently, the phIGFBP test is not publicly reimbursed in Australia and it has not been previously considered by MSAC. The phIGFBP-1 test is registered by the Therapeutic Goods Administration (TGA) for use in Australia. Similarly, fFN, is also not publicly reimbursed in Australian but it has been considered by MSAC. An application for listing of fFN was assessed by MSAC in November 2006. The fFN tests evaluated for this assessment were, both the pathology based and point-of-care test, to assess risk of preterm delivery in pregnant women: who present with symptoms suggestive of preterm labour; whose pregnancies are singleton or twin gestations; who are at stages of pregnancy from 24 to 33 weeks 6 days gestation; who present with intact amniotic membranes; and whose cervical dilation is less than 3 cm. MSAC determined that the test is safe but effectiveness has not been demonstrated and did not support public funding.

The application for the phIGFBP-1 test reports that "In many hospitals in Australia, identification of patients at low risk of pre-term birth is already performed using a variety of diagnostics including phIGFBP-1 or fetal fibronectin" and that the phIFGBP-1 test currently receives some state public funding through the public hospital system. The phIGFBP-1 test is provided in a limited number of facilities including tertiary public hospitals, community/regional public hospitals and private hospitals that provide maternity services. In the case of public patients in public hospitals the service is funded through the state hospital budget. In the case of private patients in public hospitals or private hospitals the service is reimbursed by private health insurance, the cost is absorbed by the hospital, or the service is funded directly by the patient.

There are preterm labour clinical guidelines available to public health practitioners in Australia to guide treatment of women presenting with symptoms of preterm labour. The Royal Australian and New

Zealand College of Obstetricians and Gynaecologists (RANZCOG) issued a statement in November 2011 (an update on the statement endorsed in November 2008) which concluded that "a negative fFN in symptomatic women has been associated with reduced transfers to tertiary centres, reduced admissions from threatened preterm labour, reduce use of tocolytic agents and corticosteroids and reduced mean cost of treatment" and that all units providing obstetric care should have access to beside fFN testing to assist with clinical decision making in women presenting with ALL of the following:

- Symptomatic preterm labour, between 24 and 34 weeks' gestation;
- Intact membranes; and
- At less than 3 cm cervical dilatation.

The specimen should be collected from the posterior fornix during a speculum examination (RANZCOG Statement 2011)[1]

This official statement also states that phIGFBP-1 may be less costly and less subject to interpretation problems if the patient has coexisting antepartum haemorrhage or if transvaginal ultrasound is not available. In addition the statement reports that the interpretation of the phIGFBP-1 test results may be simpler than for fFN if the patient has had coitus or a vaginal examination within the last 24 hours. Its sensitivity and specificity for the prediction of preterm birth is slightly inferior to the same properties of fFN.[1]

The majority of publically available guidelines recommend that for women who present with symptoms of preterm labour but who do not have an effaced and/or dilated cervix, the exclusion of and subsequent management depends on the results of the fetal fibronectin (fFN)[2] though not all guidelines make this recommendation.[3]

It is requested that if phGFBP-1 testing is used, on more than an adhoc basis, in Australian hospitals (public or private) or in private practice, that the applicant provide this information. The applicant reports that in 2012, approximately 3,000 tests were supplied, mainly to regional public hospitals.

Regulatory status

Phosorylated insulin like growth factor binding protein-1 test

An application to the TGA for phIGFBP-1, an in vitro diagnostic test (Actim Partus), was submitted on 10 August 2012 and the certificate is effective from 05/11/2012. The ARTG inclusion number is 202704. The proposed indication, provided on the ARTG inclusion is as follows: intended to be used for the detection of clinical hormones such as IGFBP-1 (insulin-like growth factor binding protein-1) in vaginal or cervical samples to aid in the diagnosis of pregnancy complications. The ARTG certificate covers both Actim Partus and another related but distinct diagnostic test, Actim PROM.

The approved intended use for Actim Partus is: a visually interpreted, qualitative immunochromatographic dipstick test for detecting the presence of phosphorylated IGFBP-1 (insulin like growth factor binding protein-1) in cervical secretions during pregnancy. The test is intended for professional use to help predict the risk of preterm or imminent delivery when fetal membranes are intact. A negative test result is a clear indication that the patient will not deliver within 7-14 days.

PASC noted that phosphorylation has a short half-life, and it is requested that the applicant indicate the half-life of phIGFBP-1 that is present due to tissue disruption and evidence that the test is then able to detect its presence.

The approved intended use of the phIGFBP-1 test, is a narrower definition than the proposed indication, because, as the applicant notes, the ARTG certificate covers multiple products and tests. In particular the test appears capable of testing for clinical hormones in addition to IGFBP-1, and to test for the presence of IGFBP-1 in vaginal as well as cervical samples. The broader definition of the proposed indication indicates the potential of this test to be used on a broader population than that defined in the approved intended use of the test. For example, a recent study, Kallioniemi et al 2013[4], compares the first trimester vaginal fluid phIFGBP-1 testing to cervical fluid phIFGBP-1 testing to predict preterm delivery (PTD) at <32 or <37 weeks.

Fetal fibronectin test

The application is for two fFN tests; the qualitative QuikCheck™ system and the quantitative Rapid 10Q® system which are produced by Hologic Australia Pty Ltd. These tests do not have individual listings and are included on the Therapeutic Goods Administration database as other therapeutic goods under listing 63516. The ARTG summary is: Cytyc Australia Pty Ltd – ADEZA biomedical range of diagnostic goods invitro – human origin.

Regulatory information detailing the analytic specificity of these tests, phIGFBP-1, qualitative fFN or quantitative fFN, is not available at either the FDA or TGA sites. The applicants will need to provide further information that can be used to undertake a quality assurance for these tests. This information should include the change in the levels of these molecules during gestation periods.

Intervention

IGFBP-1 is a major protein of human decidua. During pregnancy, insulin growth factors and their binding proteins are important for the growth and differentiation of both maternal and fetal tissues. From early development, nearly all fetal tissues produce these peptides and express their specific receptors[5,6,7]. The highly phosphorylated isoform of IGFBP-1 (phIGFBP-1), which is produced by decidua but is not present in aminiotic fluid, can be detected by monoclonal antibody (Mab) 6303. The presence of phIGFBP-1 after the 23 week of gestation may indicate tissue disruption at the chorio-decidual interface and an increased risk of preterm delivery[8].

Fetal fibronectin is a glycoprotein normally present in the cervicovaginal secretions of pregnant women up to 22 weeks gestation. fFN is believed to be the major component of the chorio-decidual interface-the union between fetal and maternal tissues. The presence of fFN during the later stages of pregnancy is thought to indicate a disruption of the chorio-decidual interface caused by mechanical or inflammatory mediated injury. Chorio-decidual disruption and the presence of fFN between 24 and 34 weeks gestation may be related to the initiation of labour[9,10]. Elevated levels of fFN (above 50 ng/mL) in cervicovaginal secretions between 22 and 35 weeks gestation are postulated to be associated with

an increased risk of preterm birth. The presence of fetal fibronectin in cervical and vaginal fluid can be detected by a specific monoclonal antibody, FDC-6.

The utility of tests for preterm labour lie in being able to identify women who will not go on to deliver early. A negative test would be used to avoid unnecessary treatments, such as tocolysis, magnesium sulphate (if the foetus is less than 30 weeks) and steroids and could avoid protracted hospital stays. In particular, such a test could be of particular utility in rural and remote areas to prevent unnecessary and distressing transport of women away from their homes[11].

Description

phIGFBP-1 test

The phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) test is a rapid point of care test, intended to identify patients presenting with threatened preterm labour who are at low risk of giving birth. When true labour is imminent a small amount of phIGFBP-1 may begin to leak into cervical secretions and it can be detected using the test. This test is a qualitative test, giving a positive, negative or invalid result.

Fetal fibronectin test

The two fetal fibronectin tests are rapid point of care tests, intended to identify patients presenting with threatened preterm labour who are at low risk of giving birth. Fetal fibronectin can be detected in cervicovaginal secretions of women throughout pregnancy by use of monoclonal antibody-based immunoassay. The association between increasing levels of fFN measured in vaginal fluid and increased preterm birth risk has been documented[12,13]. Both systems provide a qualitative result; positive, negative or invalid. The instrument-based system also provides a quantitative result, indicating the levels of fibronectin present.

The test is a two-step procedure. The first step requires obtaining a cervicovaginal sample from a patient during a standard speculum examination. The second involves using an immunochromatographic assay to detect the presence of fetal fibronectin and to produce either a qualitative or quantitative result.

It is proposed that the phIGFBP-test or the fetal fibronectin test can be used by physicians to quickly distinguish between: false labour where there may be contractions and other signs of labour but the women does not deliver in the next 7 days; and true labour where the women gives birth in the next 7 days.

Medical condition

Threatened preterm labour is defined as the presentation of the symptoms of labour between 24 and 37 weeks of pregnancy and management of threatened preterm labour is one of the most important considerations in maternity care. Infants born premature, especially at 30 weeks gestation and earlier, often have life-threatening medical conditions. Preterm birth rates have risen in Australia in the last two decades, mostly accounted for by the rise in late preterm births (34 and 36 plus 6 weeks after last menstrual cycle). Late preterm births (34-36 weeks) account for approximately 70% of all preterm births approximating to 16,000 births in Australia in 2009[14].

Diagnosis of preterm labour is made with a history of regular (≥ 4 per hour) painful contractions and dilation of the cervix. The most useful findings are initial cervical dilation of 3 cm or more, and/or cervical effacement[15]. False preterm labour is uterine contractions not associated with cervical dilation and effacement. Contractions usually resolve within 24-48 hours.

According to the guidelines for preterm labour, threatened preterm labour is notoriously difficult to diagnose with accuracy.

Preterm births have been associated with a number of maternal and medical factors although in half of all women progressing into actual preterm labour there are no additional risk factors. However, some risk factors may increase clinical suspicion[16, 17] (e.g. previous preterm birth, multiple pregnancy, preterm pre labour rupture of membranes (pPROM), infection, antepartum haemorrhage (APH), uterine abnormalities such as bicornuate uterus, previous cervical conisation). In these cases if preterm labour is ruled out admission for an additional period of observation may need to occur.

In Australia in 2009, 8.2% of babies were born preterm (before 37 completed weeks of gestation). Preterm birth occurred for 7.4% of all mothers in 2009 (21,852 babies in total). The average duration of pregnancy in Australia was 38.8 weeks. A small proportion of mothers gave birth at 20-27 weeks (0.8%) and 28-31 weeks (0.7%), while 5.9% gave birth at 32-36 weeks. There was a higher proportion of preterm birth in the Northern Territory (9.3%) than elsewhere (Table 3.16). This is likely to be associated with the different age structure of the population and higher proportion of births to Indigenous mothers.[18] The more remote from term, the greater is the burden of morbidity and mortality for the neonate[19].

Table 2 provides birth information, by pregnancy weeks, for each state of Australia for 2009.

Table 2: Women who gave birth, by duration of pregnancy and state and territory, 2009

Duration of pregnancy (weeks)	NSW	Vic	Qld	WA	SA	Tas	ACT	NT	Australia
Mean	38.9	38.8	38.8	38.7	38.7	38.8	39.0	38.7	38.8
20-27	642 (0.7)	807 (1.1)	481 (0.8)	264 (0.9)	159 (0.8)	46 (0.7)	49 (0.9)	39 (1.0)	2,487 (0.8)
28-31	565 (0.6)	529 (0.7)	464 (0.8)	224 (0.7)	163 (0.8)	31 (0.5)	41 (0.7)	44 (1.1)	2,061 (0.7)
32-36	5,095 (5.4)	4,118 (5.7)	3,864 (6.3)	1,906 (6.2)	1259 (6.4)	438 (7.0)	347 (6.0)	277 (7.2)	17,304 (5.9))
37-41	87,957 (92.5)	65,447 (90.6)	55,784 (91.4)	28,166 (91.6)	17,941 (91.5)	5,730 (91.2)	5,202 (90.7)	3,466 (89.8)	269,693 (91.6)
42 and over	774 (0.8)	984 (1.4)	422 (0.7)	200 (0.7)	79 (0.4)	35 (0.6)	96 (1.7)	32 (0.8)	2,622 (0.9)
Not stated	5 (0.0)	360 (0.5)	0.0	—	—	—	1 (0.0)	1 (0.0)	373 (0.1)
Total	**95,038**	**72,245**	**61,021**	**30,760**	**19,601**	**6,280**	**5,736**	**3,859**	**294,540**

Source: Table 3.16[3]

The number of public hospital separations in Australia for patients with false labour (AR-DRG number 064A), in 2009-10 was 4,816 for patients <37 weeks gestation (ALOS 1.86) and 6,640 for patients equal to or greater than 37 weeks gestation (1.47). The number of private hospital separations in Australia for patients with false labour was 1,834 for patients <37 weeks gestations (ALOS 1.8 days) and 1,145 for patients equal to or greater than 37 weeks gestation (ALOS 1.12). The number of pre-term births may represent only approximately 30 percent of all suspected pre-term labours[18].

The "true" incidence rate for false pre-term labour and therefore the likely population for this test may be difficult to estimate accurately. Many patients with uterine contractions may have their contractions cease soon after speculum examination, before transfer or during transfer. Others may arrive at an emergency department, but soon after their contractions may cease and they are not admitted. Expert advice is that there are important conditions that are mistaken for preterm labour e.g urinary tract infection, pyelonephritis, placental abruption, appendicitis for which testing will be required to exclude preterm labour.

The standard protocol for the management of patients with threatened preterm labour is a 24 hour admission to the delivery suite for tocolysis and corticosteroids. Tocolytic agents are given to delay delivery to allow transfer to a tertiary centre for administration of corticosteroids to enhance fetal lung maturation. Magnesium sulphate is also administered to some women (who are less than 30 weeks gestation) for neonatal neuroprotection. The use of these treatments only delays true preterm labour, hopefully sufficiently for the corticosteroids to enhance fetal lung maturation; they do not stop true preterm labour from proceeding.

Maternity services are unique in that they provide care for two recipients; mother and baby, whose needs often need to be counterbalanced. In Australia, approximately one-third of women live outside major cities and 3% (approximately 8000 women) live in areas considered remote or very remote. The availability of maternity services in rural and remote areas of Australia is declining. In 2005 it was reported that 130 small rural maternity units had closed since 1995[20] and by 2008 that over 50% of small rural maternity units had been closed in the previous decade[21]. As a result, increasing numbers of pregnant women living in rural and remote areas relocate to give birth in hospitals in major cities or regional centres, often staying in hostels or self-care units for up to a month prior to birthing, often leaving other children behind. The support available for these women is often inadequate[22].

Using the ABS Australian Standard Geographical Classification (ASGC) Remoteness Areas Structure, in 2010, of the 293,112 women who gave birth, 30% lived outside *Major Cities* (by the usual residence of the mother) and 2.7% live in areas designated as remote or very remote (approximately 8,000 mothers). Of these 293,112 women who gave birth, 11,458 had Indigenous status, and of these 26.6% lived in remote or very remote areas. The distribution of remoteness varies by state and territory, in comparison to the Australian average, 59.9% of women in Queensland live in *Major Cities* and in the Northern Territory all women live outside *Major Cities* (in *outer regional, remote or very remote* areas) (Tables 3.5 and 3.6)[23].

Overwhelmingly in Australia, women give birth in hospital, 96.9% (214,727), with the rest in birth centres, 2.2%, at home 0.5% or at other 0.5% (in the NT these usually refers to remote community health centres) (Table 3.19[23]). Of these hospital admissions, 65% (139,486) were in public hospitals and 32.8% (70,332) in private hospitals, with the remaining not stated (Table 3.43[23]). Expert advice is that perhaps half of all births occur in hospitals that do not have the capacity to deal with preterm birth, and will require transfer to a different centre should preterm labour be suspected (A/Prof Stephen J Robson, advice to PASC, 16th April, 2013).

Rural and remote families experience higher rates of maternal death; rural women have significantly higher rates of neonatal deaths and remote women have higher rates of fetal deaths[23].

There is a broad population that may benefit from proposed use of the phIGFBP-1 test or fFN test. These include women who have the symptoms of threatened preterm labour, especially women who live in rural and remote areas who may need to travel long distances to access neonatal intensive care beds or special needs nursery beds. In addition there may be other women who may benefit from these tests if they are able to indicate when labour may have commenced. These are asymptomatic women who are at high risk of preterm labour, either because of a previous history or because they have a multiple pregnancy.

Additional pregnant women who may benefit are those residing in rural and remote areas of Australia, who are not at risk of preterm labour, but may need to travel large distances to access maternity care, which can entail spending up to a month absent from their families and living in special accommodation[22]. For example, under AR-DRG 064A (separation for false labour) in public hospital (2009-10) the largest number 6,640 patients were at least 37 weeks gestation compared to 4,816 patients <37 weeks gestation[18].

Although there may be a number of populations who may benefit from these tests, PASC advice is that the population for the tests are patients with the symptoms of preterm labour (i.e. excluding asymptomatic 'high-risk' pregnancies) who are between 24 weeks and less than 34 weeks. PASC has requested that the use of these tests in a subset of the population, that is women with multiple pregnancies who are symptomatic, be presented separately.

The likely population for this test annually, will include the number of preterm babies (21,852 in 2009) plus the number of hospital separations for patients with false labour <37 weeks (AR-DRGm064A), in public hospital (4,816) and private hospital (1,834). This is a total of 28,502 swabs if each patient had only one swab done. However, patients who present to hospital for elective preterm birth or premature rupture of membranes (PROM) would need to be excluded from this total as the tests have no utility in this population. Expert advice is that the estimate of 28,502 swabs per annum is likely an underestimate of the likely population for these tests. This is because the applications propose the use of these tests in multiple settings outside a hospital setting picking up a broader population than those who have been discharged from hospital for false labour (would include those who are correctly diagnosed with preterm labour), many pregnant women present with pain or symptoms that would result in a test being done and repeated testing is likely. The ABS reported that in 2010, 30% of women who gave birth lived outside Major Cities (as defined as a statistical region).

Delivery of the intervention

Phosphorylated insulin-like growth factor binding protein

The test is a two-step procedure. The first step requires obtaining a cervicovaginal sample from a patient and the second involves using an immunochromatographic assay to detect the presence or absence of phIGFBP-1.

During a speculum examination of the cervix, a polyester swab, that comes with the kit, is inserted into the external cervical orifice and left in place for 10-15 seconds, after which it is placed in a test tube containing 0.5 mL of the specimen extraction solution (buffer solution). The test tube is then swirled around vigorously for approximately 10 seconds and then the swab is discarded. The yellow area of the dipstick (included in the kit) is then dipped into specimen extraction solution and held there until the liquid front reaches the result area (around 15 seconds). After removing the dipstick from the solution and holding it horizontal for 5 minutes the test provides a qualitative result that is interpreted as:

- negative=one blue line; highly unlikely the patient will deliver within the next two weeks,
- positive=two blue lines; the risk of preterm delivery is clearly higher, and if
- no blue lines appear the test is interpreted as invalid[24],[25].

The test is based on immunochromatography and has a detection limit of 10 ug/L.

The test is to be performed in pregnant women who are 24 to 33 weeks 6 days gestation presenting with symptoms of threatened preterm labour.

The proposal for a listing has indicated that the proposed setting for where the phIGFBP-1 test will be done:

- inpatient private hospital
- inpatient public hospital
- outpatient clinic
- emergency department
- consulting rooms; and
- patient's home.

The proposal indicates, in Section B10, that the test could be done at the patient's home, if the pregnant woman is under the care of a midwife.

The proposal states that each patient would require phIGFBP-1 testing only once for a threatened preterm labour episode. The proposal estimates the failure of the test to be in the range of 1-2%.

For the test to be used by midwives in the patient's home, it would require that the test is able to be carried around as a supply for a period of time. The following information is provided on the Medix biochemica website. Storage of the kit is at room temperature of +2–+25ºC (also +2–+30ºC for 2 months). The shelf life of the product is 24 months from the date of the manufacture. The kit sizes are:

- *10 tests, (ref. 31931ETAC)*
- *1 test, (ref. 31930ETAC)-*
- *Sample Collection kit, (ref. 31935ETAC)—includes 20 buffers and 20 swabs.*

The phIFGBP-1 test kit contains all the material needed for performing the test. The collection of cervical specimens requires sterile speculum examination and trained personnel. This is a procedure than can be undertaken by trained medical and midwifery professionals. [26]

In respect of the phIGFBP-1 test PASC notes that the molecular basis for the assay proposed in the application is not clear and that no clinical data were presented to support the clinical meaningfulness of the test. The lack of information has an impact on biological plausibility particularly due to the known rate of breakdown of phosphorylated protein; more information would need to be presented to address this concern, including the test performance at the difference stages of gestation. PASC noted that the performance of the test depends heavily on the quality of the sample.

PASC also noted that no details were given as to whether the test would be repeated if no blue lines appeared and that this detail will need to be clarified by the applicant. The applicant needs to provide advice from the applicant about the reproducibility of the test results. For instance, if a positive test result was given but no labour proceeded, what would be the validity of a result if the patient gave a negative value on a future test? What would the test's positive (or negative) predictive value be at that point when the same patient had given both a positive and negative result? Is the test validity equal on every testing occasion regardless of previous test result?

<u>Fetal fibronectin</u>

The applicant reports two tests are currently available in Australia for the testing of fFN, the quantitative system 10Q system (introduced in May 2013) and the qualitative QuikCheck test (the fFN TL_{iQ} system has been recently discontinued in Australia). The applicant adds that the quantitative

test, 10Q analyser, has greater diagnostic accuracy than the QuikCheck test, due to inherit limitations of a test strip. The 10Q analyser also has the functionality of testing quantitatively. *PASC has advised that both of these tests can be considered bedside tests.*

The bedside tests for fFN are a two step-procedure. The first step is to obtain a cervicovaginal sample from a patient during a standard speculum examination; a sterile applicator tip (swab) is lightly rotated in the posterior fornix for 10 seconds to absorb cervicovaginal secretions. *It is recommended that the sample be collected before the performance of any activities or procedures which might disrupt the cervix e.g. digital cervical examination, vaginal ultrasound.* The second step involves processing the sample to detect the presence of fFN using either of the systems.

For accurate test results it is recommended that:

- Specimens are obtained prior to digital examination or manipulation of the cervix. Manipulations of the cervix within 24 hours of collection may lead to falsely elevated fFN levels (positive results).
- The specimen is taken from the posterior fornix of the vagina only.
- Care is taken not to contaminate cervicovaginal fluid with topical agents such as lubricants, disinfectants, or creams (e.g. K-Y® Jelly lubricant), Betadine® disinfectant, Monistat® cream, hexachlorophene). These substances may interfere with the specimen collection process and/or the antibody-antigen reaction of the fFN Test.
- Precaution taken when the patient has had sexual intercourse within 24 hours as this can cause false positive results. However, even when a patient reports having had intercourse in the previous 24 hours, a negative fetal fibronectin test result <10ng/mL is valid.
- Patients with suspected or known placental abruption, placenta previa, or moderate or gross vaginal bleeding should not be tested[27]. Testing a bloody sample may lead to falsely elevated results. A quantitative fFN result <10 ng/mL is still valid. Minimal bleeding is reported to not interfere with the fFN result.

Qualitative fFN Test

With the qualitative fFN test step two is to remove the applicator and insert the tip into the test tube with buffer and mix vigorously in the buffer solution for 10-15 seconds, then discard the applicator. Insert the test strip (dip area indicated by arrows) into the buffer for exactly 10 minutes. Remove the strip and record results. The test provides qualitative results in the form of lines which may vary in appearance from very faint to very dark.

- negative=one distinct red line: a control line
- positive=two red lines: a distinct red control line and another red line; and
- no red lines appear the test is interpreted as invalid and must be repeated

At the control line, residual unbound anti-human fibronectin polyclonal antibody-gold migrates across the membrane and binds to immobilized plasma fibronectin, providing an inbuilt assay control.

Quantitative fFN Test

The quantitative fFN system is a bedside test/point of care test. It is a portable system that can be used at either the workstation, within a maternity ward, clinic or laboratory (the analyser weighs 0.707kg) and provides a quantitative result in 10 minutes. It provides the clinician with a measure of the amount of fFN present in the cervicovaginal fluid. Step two processes the sample using a Rapid fFN Cassette, a lateral flow, solid-phase immunochromatographic quantitative assay using FDC-6 monoclonal antibodies with optical reader.

Information provided by the applicant reports that the quantitative system can aid clinicians in determining the most optimal time for steroid administration. The amount of fFN in cervicovaginal stratifies preterm birth risk. Symptomatic women with fFN levels less than 10 ng/mL have only a 1.5% risk of preterm birth prior to 34 weeks gestation, those women with fFN levels greater than 500 ng/mL have a 75% chance of delivering an neonate requiring neonatal intensive care. Symptomatic women with fFN levels less than 200 ng/mL are not at elevated risk for delivery preterm within 7 days. However, those with fFN levels between 50 and 199 ng/mL, are at elevated risk for delivering within 14 days. Symptomatic patients with a negative fetal fibronectin test are still at increased risk for prematurity, simply because they present for unscheduled care.

The applicant notes that the qualitative test and the quantitative test are completely different in technical specifications, and thus the diagnostic accuracy of both tests differs. Due to the difference in clinical efficacy of the two tests, the applicant appropriately intends to provide two separate economic analyses.

More information about the shelf life of the tests and whether usage would likely progress from medical professional usage to personal/at home usage, should be provided.

Prerequisites

The proposed applications suggest that it will be physicians, participating nurse practitioners or participating midwives, who are speculum trained, who will perform the phIGFBP-1 and fFN tests. No additional specialised training or qualifications are required by these practitioners to perform this test. In terms of the quantitative fFN system, the application indicates that the test can also be performed by all levels of healthcare providers but that some minimal training is required which is provided free of charge by the manufacturer.

For midwives and nurse practitioners to be eligible for a Medicare provider number they must be:

- *registered under the National Registration Accreditation Scheme; and*
- *endorsed as a nurse practitioner by the Nursing and Midwifery Board of Australia, or*
- *be notated as an eligible midwife by the Nursing and Midwifery Board of Australia, and*
- *be in a private practice to access MBS services, refer to specific specialists and request some pathology and diagnostic items.*

In addition nurses or Aboriginal and Torres Strait Islander health practitioners are able to perform a MBS rebateable service if it is provided on behalf of, and under the supervision of, a medical practitioner.

Co-administered and associated interventions

The application for the phIGFBP-1 test stated that the sample collection for phIGFBP-1 testing would likely take place as part of a consultation or attendance for preterm labour such as MBS 16502 or MBS 16508. These items are listed in Table 3.

Table 3: Medicare Benefits Schedule – items relevant to clinical examination of patient with symptoms of PTD

Category 3 – Therapeutic Procedures
MBS 16502 Polyhydramnios, Unstable Lie, Multiple Pregnancy, Pregnancy complicated by DIABETES OR ANAEMIA, THREATENED PREMATURE LABOUR TREATED by bed rest only or oral medication, requiring admission to hospital each attendance that is not a routine antenatal attendance, to a maximum of 1 visit per day Fee: $47.15 Benefit:75%=$35.40 85%=$40.10
MBS 16508 PREGNANCY COMPLICATED BY acute intercurrent infection, intrauterine growth retardation, threatened premature labour with ruptured membranes or threatened premature labour treated by intravenous therapy, requiring admission to hospital – each attendance that is not a routine antenatal attendance, to a maximum of 1 visit per day Fee: $47.15 Benefit:75%=$35.40 85%=$40.10

Both MBS Items 16502, 16508, assume the patient with threatened premature labour will require admission to hospital and the test performed during admission. *However, if the test is undertaken outside the hospital setting, as proposed, then these MBS items may not be relevant.*

The point of care nature of the test means that it can be easily performed wherever obstetric services are delivered. The applications propose that the test can be conducted in situations where a woman presents with threatened preterm labour:

- *Before the patient is admitted to hospital, e.g. in an outpatient clinic or in the emergency department (both private or public hospitals)*
- *After the patient has been admitted, as an inpatient to a hospital (private or public)*
- *The consulting rooms of the patient's obstetrician*
- *In the patient's home when the patient is under the care of an attending midwife.*

All patients presenting with the symptoms of preterm labour:

- *Lower abdominal cramping*
- *Pelvic pressure*
- *Lower back pain*
- *Vaginal spotting or 'show'*
- *Regular uterine activity*

Irrespective of the clinical setting patients will, in addition to a clinical examination (vital signs, abdominal examination, fetal heart rate) and the taking of a clinical history, undergo a sterile speculum examination to exclude premature rupture of the membranes (PROM). Only if PROM has been excluded will a patient then be eligible to have a phGFBP-1 test or a fetal fibronectin test. The

following table, Table 4, lists additional MBS items covering clinical examination and sterile speculum examination of the pregnant women, in the variety of clinical settings that the patient may present, that may be co-administered with the test

Table 4: Medicare Benefits Schedule – items relevant to clinical examination of patient with symptoms of PTD

Category 8 – Miscellaneous Services
MBS 82105 Short antenatal professional attendance by a participating midwife, lasting at least 40 minutes Fee: $32.00 Benefit:75%=$24.25 85%=$27.50
MBS 82110 Long antenatal professional attendance by a participating midwife, lasting at least 40 minutes Fee: $53.00 Benefit:75%=$40.05 85%=$45.40 Medicare Benefits are only payable for clinically relevant services. Clinically relevant in relation to midwifery care means a service generally accepted by the midwifery profession as necessary to the appropriate treatment of a patient's clinical condition. Medicare benefits are payable for an antenatal service where a midwife provides a clinically relevant service in respect of a miscarriage.
Category 3 –Therapeutic Procedures
MBS 16400 Antenatal service provided by a midwife, nurse or an Aboriginal and Torres Strait Islander health practitioner if; (a) the service is provided on behalf of, and under the supervision of, a medical practitioner; (b) the service is provided at, or from, a practice location in a regional, rural or remote area RRMA 3-7; (c) the service is not performed in conjunction with another antenatal attendance item (same patient, same practitioner on the same day); (d) the service is not provided for an admitted patient of a hospital; and to a maximum of 10 services per pregnancy Fee: $27.25 Benefit: 85%=$23.20
Category 1–Professional Attendances
MBS 501 MEDICAL PRACTITIONER (EMERGENCY PHYSICIAN) ATTENDANCES – EMERGENCY DEPARTMENT LEVEL 1 Professional attendance on a patient at a recognized emergency department of a private hospital by a medical practitioner who is an emergency physician in the practice of emergency medicine. Attendance for the unscheduled evaluation and management of a patient requiring the taking of a problem focused history, limited examination, diagnosis and initiation of appropriate treatment interventions involving straightforward medical decision making. Fee: $34.20 Benefit:75%=$25.65 85%=$29.10
MBS 503 MEDICAL PRACTITIONER (EMERGENCY PHYSICIAN) ATTENDANCES – EMERGENCY DEPARTMENT LEVEL 2 Professional attendance on a patient at a recognized emergency department of a private hospital by a medical practitioner who is an emergency physician in the practice of emergency medicine. Attendance for the unscheduled evaluation and management of a patient requiring the taking of an expanded problem focused history, expanded examination of one or more systems and formulation and documentation of a diagnosis and management plan in relation to one or more problems, and the initiation of appropriate treatment interventions involving medical decision making of low complexity.

Fee: $57.80 Benefit:75%=$43.35 85%=$49.15
MBS 507 MEDICAL PRACTITIONER (EMERGENCY PHYSICIAN) ATTENDANCES – EMERGENCY DEPARTMENT LEVEL 3 Professional attendance on a patient at a recognized emergency department of a private hospital by a medical practitioner who is an emergency physician in the practice of emergency medicine. Attendance for the unscheduled evaluation and management of a patient requiring the taking of an expanded problem focused history, expanded examination of one or more systems, ordering and evaluation of appropriate investigation, the formulation and documentation of a diagnosis and management plan in relation to one or more problems, and the initiation of appropriate treatment interventions involving medical decision making of moderate complexity. Fee: $97.00 Benefit:75%=$72.80 85%=$82.50

Note: MBS Items 511 and 515 involve increasing levels of complexity of treatment of a patient within an emergency department. In listing the associated intervention, these two items are not included as it is assumed that once, the condition of the patient is assessed, investigations undertaken, diagnosis reached and treatment plan agreed that a patient with threatened preterm labour would be admitted to the public hospital or transferred for further treatment rather than be treated for a longer period in the emergency department.

PASC was concerned that the proposal stated that the intervention is likely to be used in conjunction with MBS items 16502 and 16508. Both these items cover admission to a hospital that is not for a routine antenatal attendance.

This conflict of likely associated MBS items versus potential wider usage necessitates an identification and presentation at the evidence state of this wider range of MBS items and/or associated costs and the percentage likelihood of usage at each of these settings.

Patients who are suspected of being in preterm labour may receive associated treatments with tocolytics, magnesium sulphate and steroids.

Tocolytics , such as nifedipine or salbutamol, are used to delay delivery for 24-48 hours, allowing time for transfer to hospital with appropriate neonatal facilities and/or administration of corticosteroids. Tocolysis is generally not indicated when fetal gestation is >34 weeks. Magnesium sulphate is used in Australia for neonatal neuroprotection if birth less than 30 weeks is imminent (in other countries it is sometimes also used as a tocolytic medicine to slow uterine contractions during preterm labour[1]). Steroids may be given to pregnant women suspected of preterm labour to enhance fetal maturation before preterm birth and decrease the rate of respiratory distress syndrome, intraventicular haemorrhage and neonatal death. The use of antenatal corticosteroids is also associated with decreasing the incidence of necrotising enterocolitis and systemic infections in the neonate in the first 48 hours following birth.

[1] FDA issued a drug safety communication on 30 May 2013, advising health care professionals against using magnesium sulphate injection for more than 5-7 days to stop pre-term labour in pregnant women. Administration of magnesium sulphate injection to pregnant women longer than 5-7 days may lead to low calcium levels and bone problems in the developing baby or foetus, including thin bones (osteopenia), and fractures. The shortest duration of treatment that can result in harm to the baby is not known.

These associated treatments are not specific to the use of the phIGFBP-1 test, but a negative test, either phIGFBP-1 or fFN, result may lead to a reduction in the use of tocolysis, magnesium sulphate and steroids.

Listing proposed and options for MSAC consideration

Proposed MBS listing

The proposed MBS item descriptors proposed by the applicant for phIGFBP-1 test are presented in Table 5.

Table 5: Proposed MBS item descriptor for [item]

Category 2 – Diagnostic Procedures and Investigations
MBS [item number] Detection of Phosphorylated Insulin-like Growth Factor Binding Protein (phIGFBP-1) in cervical secretion specimen by an immunochemical method for the assessment of threatened preterm labour where premature rupture of membranes (PROM) has been excluded Fee: $81.97 Benefit 75%= $61.44 85%=$69.83
MBS [item number] Detection of Phosphorylated Insulin-like Growth Factor Binding Protein (phIGFBP-1) in cervical secretion specimen by an immunochemical method for the assessment of threatened preterm labour where premature rupture of membranes (PROM) has been excluded—by a participating nurse practitioner Fee: $81.97 Benefit 75%= $61.44 85%=$69.83
MBS [item number] Detection of Phosphorylated Insulin-like Growth Factor Binding Protein (phIGFBP-1) in cervical secretion specimen by an immunochemical method for the assessment of threatened preterm labour where premature rupture of membranes (PROM) has been excluded—by a participating midwife Fee: $81.97 Benefit 75%= $61.44 85%=$69.83

The applicant amended their application to recommend that the MBS item descriptor would be better placed in Category 2, as opposed to Category 6- Pathology Services, as the phIGFBP-1 test would be performed in a wide range of settings outside of NATA accredited laboratories, and, also they noted the recent inclusion of *in vitro* diagnostic investigations onto Category 2.

The medical condition which is proposed for this test is that of threatened preterm labour.

The proposal is nominating a rapid point of care test for pregnant women who are presenting with the symptoms of preterm labour. One of the proposed benefits of this test, is that is it able to be conducted in multiple clinical facilities and its application is not limited by the need for access to a laboratory or any special training. PASC advised that the MBS item descriptor should include that the proposed phIGFBP-1 test is a rapid point of care test.

Although the MBS descriptors limits the item to pregnant women with threatened preterm labour, the descriptor does not limit this population to women who are > 24 weeks and <34 weeks gestation as indicated throughout the proposal. A minimum number of weeks of gestation separate out the

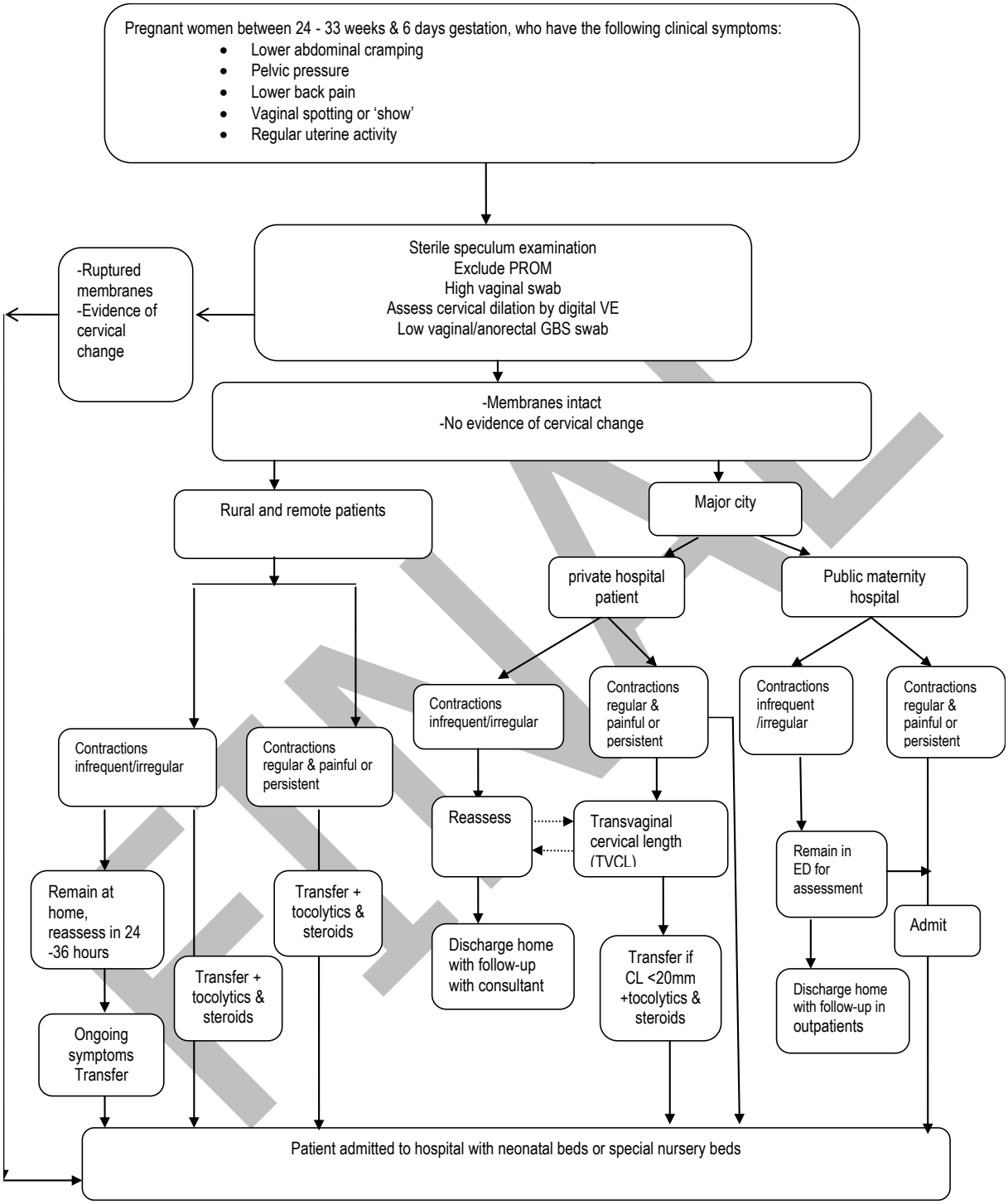
population of pregnant women who are considered to have a viable foetus from those who are considered to not have a viable foetus. As the test is to be used for the diagnoses of threatened preterm labour, the descriptor should include the number of weeks of gestation, at a minimum, a woman will need to be to be eligible for this test.

PASC agreed that the proposed 24 weeks-33 weeks 6 days gestation period was appropriate for this test as this period is consistent with the critical window when steroids are administered to promote fetal lung maturation. Babies born prior to 24 weeks are not offered resuscitation according to guidelines and babies born after 33 weeks 6 days gestation are not likely to require special care. Both applicants are in agreement with this proposal.

Clinical place for proposed intervention

Access to the intervention is suggested for pregnant women, between 24 and 33 weeks and 6 days gestation who present with the symptoms of threatened preterm labour and are found to have intact amniotic membranes on sterile speculum examination of the cervix. The proposal recommends multiple clinical settings in which the test can be performed. The current clinical management algorithm presented in Figure 1, shows the clinical care of these patients in the absence of the listing of either the two fFN tests or the phIGFBP-1 test on the MBS.

Figure 1: Current clinical management algorithm for symptomatic patients no testing available



The current clinical algorithm separates out the populations according to location and access to hospital, other diagnostic tests in addition to standard care. The greatest utility of the test maybe for those patients who reside in non-metropolitan centres, and have limited access to alternative tests and hospitalisation, however this will need to be confirmed by evidence.

Figure 1 shows that patients who present with the symptoms of premature labour have their clinical history taken and a clinical examination, including a sterile speculum examination/or a swab to exclude PROM. Expert advice is the current standard management of patients in rural and remote patients (this nomenclature is used to include patients who may reside on the outskirts of major cities in which small regional hospital care only is available) who present with the symptoms of premature labour is:

1) *First patients will have a vaginal examination to exclude PROM if positive evidence of PROM the clinician will commence antibiotics and transfer the patient to a facility with neonatal beds.*
2) *Patient history and clinical examination taken to exclude other causes for the symptoms the pregnant woman may be experiencing.*
3) *Pregnant women whose symptoms are not explained by other causes will be transferred to a hospital with neonatal intensive care beds. Depending on the location this may involve, road ambulance, helicopter or fixed wing aircraft.*
4) *Patients in rural and remote areas do not have access to transvaginal ultrasound to measure cervical length. This procedure requires highly experienced technicians because of the risk associated with placing an instrument into the vagina when there is likely to be bulging membranes and is a procedure only available in specialist maternity hospitals (and often not available out of hours). A cervical length (CL) <20 mm is considered to indicate an increased risk of delivery within 7 days.*

For patients who reside in a major city, the clinical management plan separates them according to whether their care is in a private hospital or a public hospital. This is because only major public tertiary teaching hospitals provide neonatal intensive care beds. Therefore, pregnant women being cared for in a private hospital who are suspected of being in preterm labour will require transfer to a public hospital with neonatal beds. The clinical management algorithm (Figure 1) shows that some women who present to a private hospital with the symptoms of preterm labour, will have a TVCL and only if this tests measures CL as <20mm will they be transferred, some will have watchful waiting (those whose symptoms are judged to be mild, and contractions infrequent) and some will be directly transferred to a hospital with neonatal beds (this may be based on clinical judgement, prior history or lack of access to TVCL).

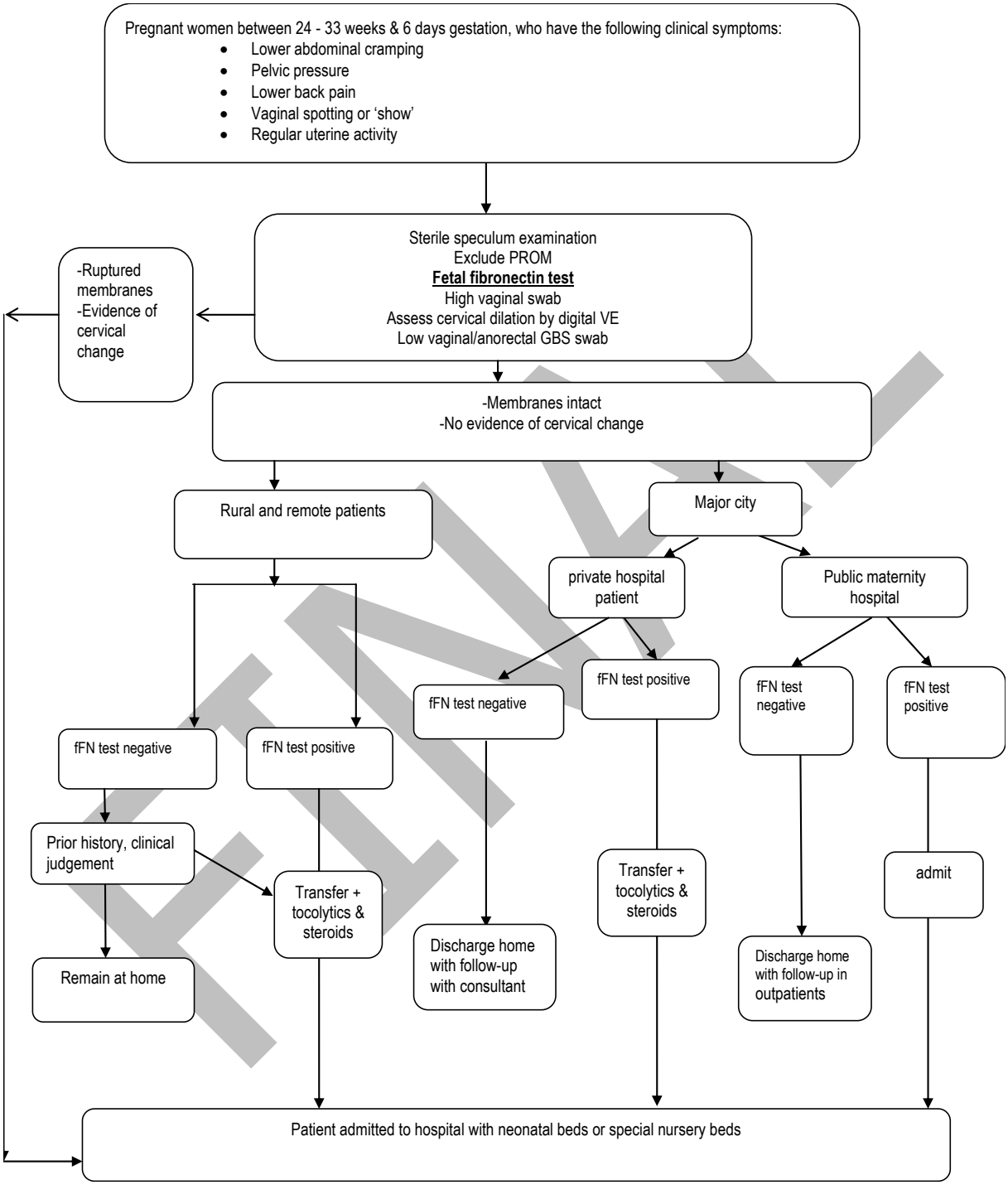
For patients who present to a major public hospital, if their contractions are considered severe and persistent they will be admitted. Other patients may stay in the emergency department for assessment or be discharged home. The algorithm assumes that if a patient's symptoms require a TVCL they will be admitted to a public hospital with neonatal intensive care or special nursery beds..

PASC agreed that the use of TVCL in this population in unresolved. Consultation advice is requested from the public on the current use of TVCL (in the absence of these point of care tests) in pregnant women with the symptoms of preterm labour (but not with PROM), in both the public and private hospital settings. Is it likely that a patient being treated in a private hospital will first require a TVCL

before a decision is made to transfer this patient to a public hospital with neonatal intensive care or special nursery beds?

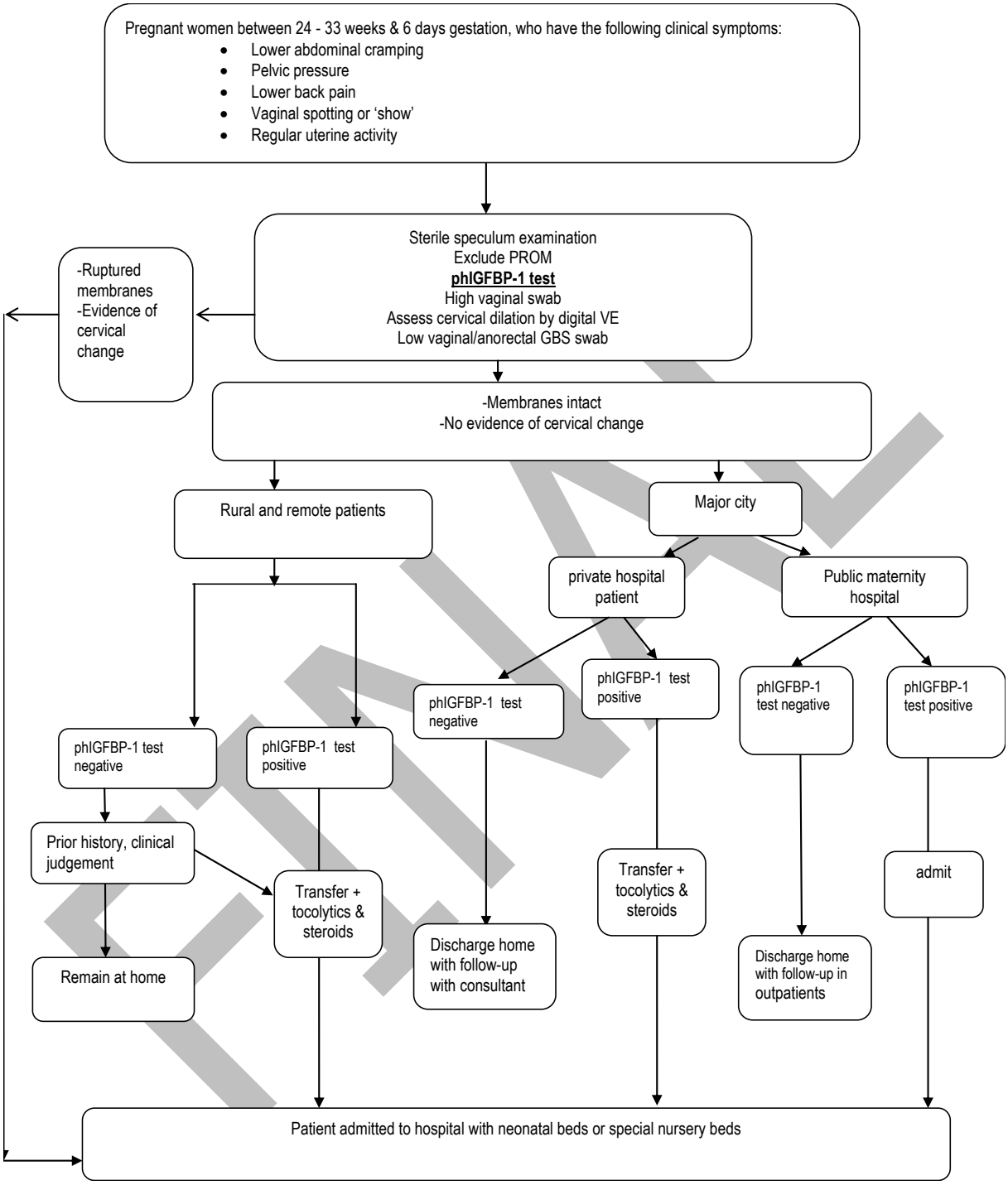
Figure 2 and Figure 3 below present proposed clinical management algorithms if either of the fFN tests or phIGFP-1 test, or both, are reimbursed on the MBS.

Figure 2: Proposed clinical management algorithm with a fFN test reimbursed on MBS



Note: Both the fFN tests have been calibrated to give a qualitative negative result if the level of fibronectin detected is less than 50 ng/mL. The quantitative test can also provide a quantitative reading of the actual fetal fibronectin level detected.

Figure 3: Proposed clinical management algorithm with the phIGFBP-1 test reimbursed on MBS



The clinical management algorithm presented in Figure 2, is for the situation where either of the fFN tests may be listed on the MBS. As both fFN tests are considered point of care tests, and will be used in the same situations and undertaken in similar ways, the clinical algorithm presented is the same, (the difference between the tests will lay in their respective analytical specificity and clinical sensitivity and specificity and to a minor degree the time required to perform the tests).

Figure 2, indicates that for rural and remote patients, the listing of the fFN test on the MBS will determine, in most situations, whether a patient will be transferred or not. Pregnant women with the symptoms of preterm labour will still require vaginal examination to exclude PROM or bleeding or other causes of their symptoms. Patients with PROM or with bleeding present will be transferred. Patients who have intact membranes may then be swabbed and tested for the presence of fFN. If the test is positive patients will be transferred to a hospital with neonatal intensive care beds. If the test is negative patients will remain at home. The exception to this will be where clinical judgement, such as a patient's prior history or the patient has multiple foetuses may result in the clinician still referring the patient to a hospital with specialised neonatal care available.

For patients who are treated privately in a major city, the availability of the fFN test on the MBS, will determine, whether a patient will be transferred or not (Figure 2). Pregnant women, between 24 weeks and less than 34 weeks gestation, with the symptoms of preterm labour will firstly require vaginal examination to exclude PROM or bleeding or other causes of their symptoms. Patients with PROM or with bleeding present will be transferred to a public hospital with specialist neonatal beds. Patients who have intact membranes, where doctors wish to exclude preterm labour as a diagnosis, will then be swabbed and tested for the presence of fFN. If the test is positive, the clinical management algorithm assumes, these patients will be transferred to a hospital with neonatal intensive care beds. It is assumed that TVCL would not need to be done to confirm this diagnosis prior to a patient being transferred. If the test is negative patients can be discharged home and followed up with their consultant, unless there is some other reason for them to remain in hospital. The clinical management algorithm in Figure 2 shows that the availability of the fFN test on the MBS can be used to determine if a patient should be transferred to a public hospital with specialist neonatal beds, to remain where they are or to be discharged home.

Pregnant women, with the symptoms of preterm labour, who present to the emergency department of a major maternity hospital, who have had PROM excluded, where doctors wish to exclude preterm labour as a diagnosis, will have the fFN test done. If the test is positive they will be admitted and if the test is negative they can be discharged home (unless there is some other reason for them to be admitted) and followed up in the outpatients clinic.

It is reported that with the fFN tests, increased false positive results may occur in situations where there has been cervical manipulation within the previous 24 hours, such as coitus, digital vaginal examination and transvaginal ultrasound examination. Fetal fibronectin is found in blood and semen, and these may cause false positive results. However, negative results in any of these settings can still be considered reliable. Increased negative results may result from the use of intravaginal lubricants and disinfectants which interfere with the antibody reaction, leading to an increase in false negative results. Because of the risk of increased false positive results it is assumed that fFN testing is performed prior to any other tests to minimise this likelihood.

Figure 3 presents the same clinical management algorithm as that for Figure 2 but with the phIGFBP-1 test available on the MBS. This is because of the similarity of the tests, that is, they are both bedside tests in which the results are rapidly available. Figure 3 indicates that for rural and remote patients, the listing of the phIGFBP-1 test on the MBS will determine, in most situations, whether a patient will be transferred or not. Pregnant women with the symptoms of preterm labour will still require vaginal examination to exclude PROM or bleeding and other causes for their symptoms. Patients with PROM or with bleeding present will be transferred. Patients who have intact membranes will then be swabbed and tested for the presence of phIGFBP-1. If the test is positive patients will be transferred to a hospital with neonatal intensive care beds. If the test is negative patients will remain at home. The exception to this will be where clinical judgement, such as a patient's prior history or the patient has multiple foetuses may result in the clinician still referring the patient to a hospital with specialised neonatal care available.

For patients who are treated privately in a major city, the availability of the phIGFBP-1 test on the MBS, will determine whether a patient will be transferred or not (Figure 3). Pregnant women, between 24 weeks and less than 34 weeks gestation, with the symptoms of preterm labour will firstly require vaginal examination to exclude PROM or bleeding or other causes of their symptoms. Patients with PROM or with bleeding present will be transferred to a public hospital with specialist neonatal beds. Patients who have intact membranes, where doctors wish to exclude preterm labour as a diagnosis, will then be swabbed and tested for the presence of phIGFBP-1. If the test is positive patients will be transferred to a hospital with neonatal intensive care beds. It is assumed that a TVCL would not need to be done to confirm this diagnosis prior to a patient being transferred. If the test is negative patients can be discharged home and followed up with their consultant, unless there is some other reason for them to remain in hospital. The clinical management algorithm in Figure 3, shows that the availability of the phIGFBP-1 test on the MBS can be used to determine if a patient should be transferred to a public hospital with specialist neonatal beds, to remain where they are or to be discharged home.

Pregnant women who present to the emergency department of a major maternity hospital, who have had PROM excluded, where doctors wish to exclude preterm labour as a diagnosis, will have the phIGFBP-1 test done. If the test is positive they will be admitted and if the test is negative they can be discharged home (unless there is some other reason for them to be admitted) and followed up in the outpatients clinic.

PASC agreed that the use of TVCL to diagnose preterm labour, or confirm a diagnosis of preterm labour where the phIGFBP-1 and/or fFN point of care tests are available, is not known. Consultation advice is requested on the likely future use of TVCL in pregnant women with the symptoms of preterm labour (but not with PROM), in both the public and private hospital settings, where testing for phIGFBP-1 or fFN testing is available. Is it likely that a patient being treated in a private hospital, who has had a positive phIGFBP-1 or fFN would then undergo a TVCL test before a decision is made to transfer the patient to a public hospital with neonatal intensive care or special nursery beds?

Neither Figure 2 nor 3 include the possibility of repeat testing for patients whose initial test is negative but whose symptoms continue for a number of days. Expert advice is that repeat testing is likely to occur for some patients. The clinical management algorithm assumes retesting would occur after the patient has been discharged home and when they re-present to the hospital or maternity unit and it is

therefore not included in the presented clinical management algorithms. The likely numbers of patients who will require retesting and the number of retests that individual patients may receive are important to estimate for the economic evaluation. Consultation advice is requested for the time period that symptoms of preterm labour would need to continue for retesting to occur and how often some patients may require retesting. Initial advice is three days.

Comparator

Fetal Fibronectin Test 1

As shown in the management algorithms, Figures 1 and 2, the most appropriate comparator involves clinical judgement and standard care for excluding preterm labour. However, standard care may include or exclude the use of cervical ultrasound. For patients in rural and remote areas of Australia, the fFN test will be compared to clinical judgement and standard care only. Symptomatic patients in major cities, treated privately, may receive a TVCL, to confirm the likely presence of preterm labour, prior to being transferred. For these patients, the fFN test may need to be compared to clinical judgement and standard care plus TVCL. For patients treated in a public hospital, it is assumed that if a TVCL is performed, it is likely to happen only after a patient has been admitted as an in-patient. For these patients the fFN test will need to be compared to clinical judgement and standard care only.

Phosphorylated Insulin-like Growth Factor Binding Protein-

As shown in the management algorithm, Figures 1 and 3, the most appropriate comparator involves clinical judgement and standard care for excluding preterm labour. However, standard care can include or exclude the use of cervical ultrasound. For patients in rural and remote areas of Australia, the phIGFBP-1 test will be compared to clinical judgement and standard care only. Symptomatic patients in major cities, treated privately, may receive a TVCL, to confirm the likely presence of preterm labour, prior to being transferred. For these patients, the phIGFBP-1 test may be compared to clinical judgement and standard care plus TVCL. For patients treated in a public hospital, if a TVCL is performed, it is likely to happen only after a patient has been admitted as an in-patient. For these patients the phIGFBP-1 test will be compared to clinical judgement and standard care only.

PASC recommends that each applicant, in addition to presenting a comparison of their test versus clinical judgement and standard care, should provide a second comparator which is the alternative test, to provide MSAC with comparative evidence. That is Hologic should present in their application the qualitative fFN test compared to the phIGFBP-1 test, and the quantitative test compared to phIGFBP-1 test. Alere should provide a comparison of the phIGFBP-1 test versus the qualitative fFN test (and if public evidence is available versus the quantitative fFN test).

A specific MBS item for transvaginal ultrasound is not listed on the MBS, but an ultrasound for pregnancy complications is listed on the MBS. An increased risk of preterm delivery has been associated with a decreased cervical length, and the shorter the cervical length the higher the risk of preterm labour[28]. Australian hospital guidelines on preterm labour use a cutoff of <20mm. There are three methods of ultrasound cervical assessment: transvaginal (TVU), transabdominal (TA), and transperineal (TP). Transvaginal ultrasound is recommended in guidelines used in Australian hospitals[2],[3]. An MBS item specific to transvaginal ultrasound is not listed as the MBS, although MBS

item 55718 or 55722 allows for an ultrasound scan on a patient presenting with pregnancy complications, such as preterm labour. Table 6 describes this MBS item.

Table 6: Current MBS item descriptor for 55718

Category 5 – Diagnostic Imaging Services
MBS 55718 Pelvis or abdomen, pregnancy related or pregnancy complication, fetal development and anatomy, ultrasound scan (not excelling 1 service or in any 1 pregnancy) of, by any or all approaches, if: (a) the patient is referred by a medical practitioner or participating midwife; and (b) the dating of the pregnancy (as confirmed by ultrasound) is after 22 weeks gestation; and (c) the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies; and (d) if the patient is referred by a medical practitioner – the referring medical practitioner is not a member of a group of practitioners of which the providing practitioner is a member; and (e) if the patient is referred by a participating midwife—the referring midwife does not have a business or financial arrangement with the providing practitioner; and (f) the service is not performed in the same pregnancy as item 55723; and (g) 1 or more of the following conditions are present: (i) Known or suspected fetal abnormality or fetal cardiac arrhythmia; (ii) Fetal anatomy (late booking or incomplete mid-trimester scan); (iii) Malpresentation; . . . (xviii) premature labour; . . Fee: $100.00 Benefit:75%=$75.00 85%=$85.00
MBS 55722 Pelvis or abdomen, pregnancy related or pregnancy complication, fetal development and anatomy, ultrasound scan (not excelling 1 service or in any 1 pregnancy) of, by any or all approaches, if: (h) the patient is referred by a medical practitioner or participating midwife; and (i) the dating of the pregnancy (as confirmed by ultrasound) is after 22 weeks gestation; and (j) the service is not associated with a service to which an item in Subgroup 2 or 3 of this group applies; and (k) the referring practitioner is not a member of a group of practitioners of which the providing practitioner is a member; and (l) the service is not performed in the same pregnancy as item 55723 or 55726; and (m) one or more of the following conditions are present: (i) Known or suspected fetal abnormality or fetal cardiac arrhythmia; (ii) Fetal anatomy (late booking or incomplete mid-trimester scan); (iii) Malpresentation; . . . (xviii) premature labour; . . Fee: $50.00 Benefit:75%=$37.50 85%=$42.5

The extent to which a transvaginal ultrasound (TVCL) is available as part of standard care depends on its availability in different settings. TVCL may be available at major public and private hospitals, but it may not be available afterhours. A high level of expertise is required to perform this diagnostic test as the placing of a device into the vagina of a patient with potentially bulging membranes carries potential risk of complications. Advice is requested to understand the likely use of TVCL to exclude preterm labour in patients presenting with the symptoms of preterm labour.

Table 7 shows the likely MBS item descriptor.

Table 7: Proposed MBS item descriptor for [item]

Category 2 – Diagnostic Procedures and Investigations
MBS [item number] Preterm testing of a cervical secretion specimen, using a point of care test, in symptomatic women, for the assessment of threatened preterm labour where gestation is greater than 24 weeks and less than 34 weeks gestation and premature rupture of membranes (PROM) has been excluded Fee: $xx.xx Benefit 75%= $xx.xx 85%=$xx.xx

The proposed descriptor specifically describes the population likely to benefit from this test. In addition, the description of the test specifies that it is a point of care test and a diagnosis is rapidly obtained.

Finalising the MBS item descriptor is premature at the protocol development stage but possible parameters that may be included have been discussed. PASC requested consultation advice around whether the following parameters should be included in the item descriptor, and if yes, likely wording for the parameters.

1) *Should the use of the test/tests be only described for situations where TVCL is not available?*
2) *No limit on the number of tests has been proposed in the item descriptor. However, should there be a minimum number of days for symptoms to persist before a patient is eligible for retesting?*
3) *Should the item descriptor include whether the test is a qualitative or quantitative test?*
4) *Should testing be limited to maternity clinics/hospitals where staff are speculum trained (and to exclude use of the test/s to where other causes of the symptoms are able to be excluded)?*
5) *A generalised descriptor about a class of tests that include point of care tests is needed to be included in the MBS item descriptor.*

PASC advised that the applicants would need to provide justification for the item fee proposed, In particular justification for:

- *Inclusion of labour costs (if they can be justified, then which practitioners salary costs should be used, e.g. obstetricians, midwife or nurse practitioner)*
- *Cost of the qualitative fFN test*
- *Cost of the quantitative fFN test*

- *Why overhead costs are included (17% overhead cost figure has been used).*

Clinical claim

Phosphorylated Insulin-like Growth Factor Binding Protein-1

It is anticipated that an assessment report considering the comparative effectiveness and safety of the proposed phIGFBP-1 testing, in pregnant women whose foetus is between 22-34 weeks and 6 days gestation, presenting with the symptoms of preterm labour compared to standard care will claim that:

- phIGFBP-1 testing is superior to the current standard management when fetal fibronectin testing or cervical ultrasound or is not available, and
- phIGFBP-1 is non-inferior ("no worse than") to the fetal fibronectin test
- phIGFBP-1 will be at least as safe as standard of care or standard of care with cervical ultrasound or fetal fibronectin testing

Although the proposal has claimed that phIGFBP-1 testing is no worse than fetal fibronectin testing, it notes that phIGFBP-1 has advantages in that the fFN test cannot be performed after the use of lubricants or disinfectants or within 24 hours of coitus. None of these limitations apply to the phIGFBP-1 test.

The claimed key benefit from the phIGFBP-1 test will be to identify those not at immediate risk of giving birth. Identification of such patients may reduce unnecessary use of therapies such as tocolytics and corticosteroids. The use of both of these drugs has been associated with adverse events in both the mother and foetus. The use of the phIGFBP-1 test may result in a change in patient management. Patients at low risk of preterm delivery may not be admitted, avoiding unnecessary treatment and hospitalisation.

The proposal claims that the use of a phIGFBP-1 test is superior to standard care where fFN or TVCL is not available. However, the proposal does not claim that the test has a clinical superiority over standard of care in terms of clinical outcomes for the foetus or mother. The standard outcome for women at risk of preterm delivery is very conservative with hospitalisation the preferred treatment. The claimed superiority of the use of the phIGFBP-1 test is in terms of hospitalisation for false preterm labour. The proposal claims that where standard care incorporates fFN plus or minus TVCL, then phIGFBP-1 plus or minus TVCL will be as safe as fFN and non-inferior for clinical efficacy. The proposal does not provide any specific information on the type of economic evaluation that it plans to present. Given that the proposal makes no specific claims of clinical superiority for the test, when compared to fFN plus standard of care or fFN testing plus standard of care plus TCVL then the most appropriate economic evaluation would be a cost minimisation analysis.

Fetal Fibronectin

It is anticipated that an assessment report considering the comparative effectiveness and safety of the proposed fFN testing, in pregnant women whose foetus is between 22-34 weeks and 6 days gestation, presenting with the symptoms of preterm labour compared to standard care will claim that:

- fFN testing is superior to the current standard management when phIGFBP-1 testing or cervical ultrasound or is not available, and
- the quantitative fFN test is superior to the phIGFBP-1 test
- the qualitative fFN test is non-inferior to the phIGFBP-1 test
- the qualitative fFN test will be at least as safe as standard of care or standard of care with cervical ultrasound or phIGFBP-1 testing
- the quantitative fFN test will be at least as safe as standard of care or standard of care with phIGFBP-1 testing or cervical ultrasound

The claimed benefit of fFN testing is that a low fFN result (<50 ng/mL), would indicate that preterm delivery within 7-14 days highly unlikely and this would prevent unnecessary hospitalisations and treatment in the relevant population. Additionally, the quantitative system is able to provide a quantitative result giving the treating physician additional information on which to assess risk. The application claims that there is evidence that the relative risk of spontaneous preterm birth increases significantly as fFN concentration increases, providing additional guidance to the treating physician of on the use of tocolytics and steroids.

The application claims that the use of fFN tests will not change clinical outcomes for the mother or foetus, when compared to standard of care or phIGFBP-1 testing, eliminating the need for cost-effectiveness or cost-benefit assessment. The applicant proposes a cost minimisation analysis comparing the current clinical pathway versus the proposed pathway for fFN testing would be needed because evidence supports change in patient management pathways when the fFN test is applied. The claimed superiority of the quantitative test is in its negative predictive value (NPV) compared to the phIGFBP-1 test resulting in an increase in patients who are not hospitalised or exposed to unnecessary treatment with tocolytics or corticosteroids.

Outcomes and health care resources affected by introduction of proposed intervention

Clinical outcomes

It is proposed that the effectiveness of the phIGFBP-1 and the fFN test for diagnosing false preterm labour can be assessed by considering their use in the relevant population (symptomatic women between 24 weeks and less than 34 weeks gestation):

- Clinical outcomes will need to report the diagnostic accuracy of the tests
    - Sensitivity and specificity of the test
    - Negative predictive values (NPV) of the tests.
    - Evidence will need to be presented if the tests are to be used alone. If the tests are used sequentially (it will need to be identified which test is used first, at what interval and why), or both tests are used together as validators of each other. Summary receiver operating characteristic (SROC) curve analysis to examine the trade-off between sensitivity and specificity will need to be presented.
- Indirect evidence in whether the use of the test changes clinical management, for example, this can be measured by
    - Change in the number of patients transferred (and treatment for preterm labour)

- Change in the number of patients hospitalised (and treatment for preterm labour)

The patient-relevant clinical effectiveness outcome for this intervention is the safe delivery of a premature baby. *PASC was particularly concerned about the effect of false negative results, and what is the likely outcome of a false negative. NPV will need to be reported in the population of predicted use.*

PASC requested that where possible the clinical outcomes are reported separately for those patients who have multiple pregnancies.

PASC agreed that the quality assurance process for the tests was to be presented at the evidence stage, so as to ensure consistency of test results, no matter who was performing the test, e.g. obstetrician, midwife or nurse practitioner.

Safety issues

- The use of the test is not considered to have safety issues, the kit is sterile and the personnel who will do the testing are experienced and aware of the consequences of introducing items into the vagina of a woman who may be in labour.

In addition to the patient relevant outcomes of using the phIGFBP-1 test to diagnose low risk of preterm delivery, listed above, the following outcomes are relevant:

- *Hospitalisations*
- *Number of hospital transfers (air transport (fixed or helicopter) or road ambulance)*
- *Rates of use of tocolytics in women admitted with threatened preterm delivery.*
- *Use of steroids*
- *The consequences for women and infants of a false negative test result that results in a change in their clinical management*

Analytical sensitivity and specificity

PASC advised that separate outcomes for analytical sensitivity and specificity of the tests will need to be reported separately from the diagnostic (clinical) sensitivity and specificity. The analytical sensitivity of an assay is that assay's ability to detect a low concentration of a given substance in a biological sample (e.g. phIGFBP-1) and the lower the detectable concentration, the greater the analytical sensitivity. The analytical specificity is the ability of the assay to exclusively identify a target substance or organism rather than similar but different substances in a sample of specimen[29]. This outcome reporting should also include the change in the level of molecules (phIGFBP-1 or fFN) during the gestation periods. PASC advised that phosphorylation is known to have a short half-life, so the application for MBS listing for phIGFBP-1 should include how short that half-life is and the ability of the phIGFBP-1 test to detect the presence of phIGFBP-1 during this period.

Health care resources

The applications have indicated that no other health care resources are required to be delivered at the same time as the nominated comparator. The test may be undertaken during the course of sterile speculum examination of the patient's cervix, or after a swab to exclude PROM, after the practitioner has determined that it is safe to insert a swab into the cervix.

The proposals have indicated that an application would include an assessment of any changes in the likely rates of hospitalisation of women with threatened preterm labour, the likely reduction in unnecessary medication for both the mother and foetus and the unnecessary transfer of mothers to tertiary institutions from other or remote locations. In addition, the proposal has indicated that an application would include an assessment of the likely change in the use of the MBS item related to an ultrasound to determine cervical length.

Proposed structure of economic evaluation (decision-analytic)

Table 9, sets out a summary of the extended PICO for the comparison phIGFBP-1 (fFN) for diagnosing low risk of preterm labour with fFN and standard of care (with or without TVCL) and a comparison of phIGFBP-1 with standard of care (with or without TVCL).

Table 9: Summary of extended PICO to define the question for public funding that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Pregnant women presenting with threatened preterm labour with intact amniotic membranes who are 24-33 weeks 6 days gestation	*1)* phIGFBP-1 test *2) (fFN test)*	1)fFN test (quantitative and qualitative) plus standard care (standard care may include TVCL or not) *2) phIGFBP-1 test plus standard care (standard care may include TVCL or not)*	*-Diagnostic sensitivity and specificity* *-NPV* *-Analytical sensitivity and specificity* *-SROC for each test* *-change in patient management* *-hospitalisations* *-Use of tocolytics* *-Use of corticosteroids* *-Numbers of transfers to hospitals for threatened PTD* *-consequences of a false negative test result that leads to a change in patient management*	*-Cost of the test* *-cost of TVCL if available* *-hospitalisations costs of pre-term labour* *-cost of drugs to suppress labour* *-cost of drugs to increase fetal lung maturation* *-ambulance (road and air*)
Pregnant women presenting with threatened preterm labour with intact amniotic membranes who are 24-33 weeks 6 days gestation	1) phIGFBP-1 test *2)* (fFN) test	*Standard care (standard care may or may not include TCVL)*	*-Diagnostic sensitivity and specificity* *-NPV* *-Analytical sensitivity and specificity* *-SROC for each test* *-change in patient management* *-hospitalisations* *-Use of tocolytics* *-Use of corticosteroids* *-Numbers of transfers to*	*-Cost of the test* *-cost of TVCL if available* *-hospitalisations costs of pre-term labour* *-cost of drugs to suppress labour* *-cost of drugs to increase fetal lung maturation* *-ambulance (road and air)*

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
			hospitals for threatened PTD *-consequences of a false negative test result that leads to a change in patient management*	

1) What is the safety, effectiveness, and cost-effectiveness of phIGFBP-1 (fFN) testing performed by a medical practitioner, nurse practitioner, or participating midwife for excluding false preterm labour in patients presenting with threatened preterm labour compared with fetal fibronectin (phIGFBP-1) testing performed by a medical practitioner, nurse practitioner, or participating midwife and standard medical management, that may or may not include transvaginal ultrasound?
2) What is the safety, effectiveness, and cost-effectiveness of phIGFBP-1 (fFN) testing performed by a medical practitioner, nurse practitioner, or participating midwife for predicting false preterm labour in patients presenting with threatened preterm labour compared with standard medical management, that may or may not include transvaginal ultrasound?

The applications state that the number or preterm and at term deliveries would not be altered by funding of phIGFBP-1 or fFN testing, it is simply proposed that the rate of hospitalisation for false labour would be reduced with resulting cost savings and a reduction in unnecessary treatment of pregnant women and their foetuses.

Figure 5 presents a decision analytic model that compares the cost and outcomes of testing to predict false preterm labour to current clinical management. In the event that testing is funded and available to the patient then pregnant women presenting with threatened preterm labour with intact amniotic membranes who are 24-33 weeks and 6 days gestation would have a phIGFBP-1 or fFN test unless contraindicated. The result of the test determines clinical management, and there are four outcomes:

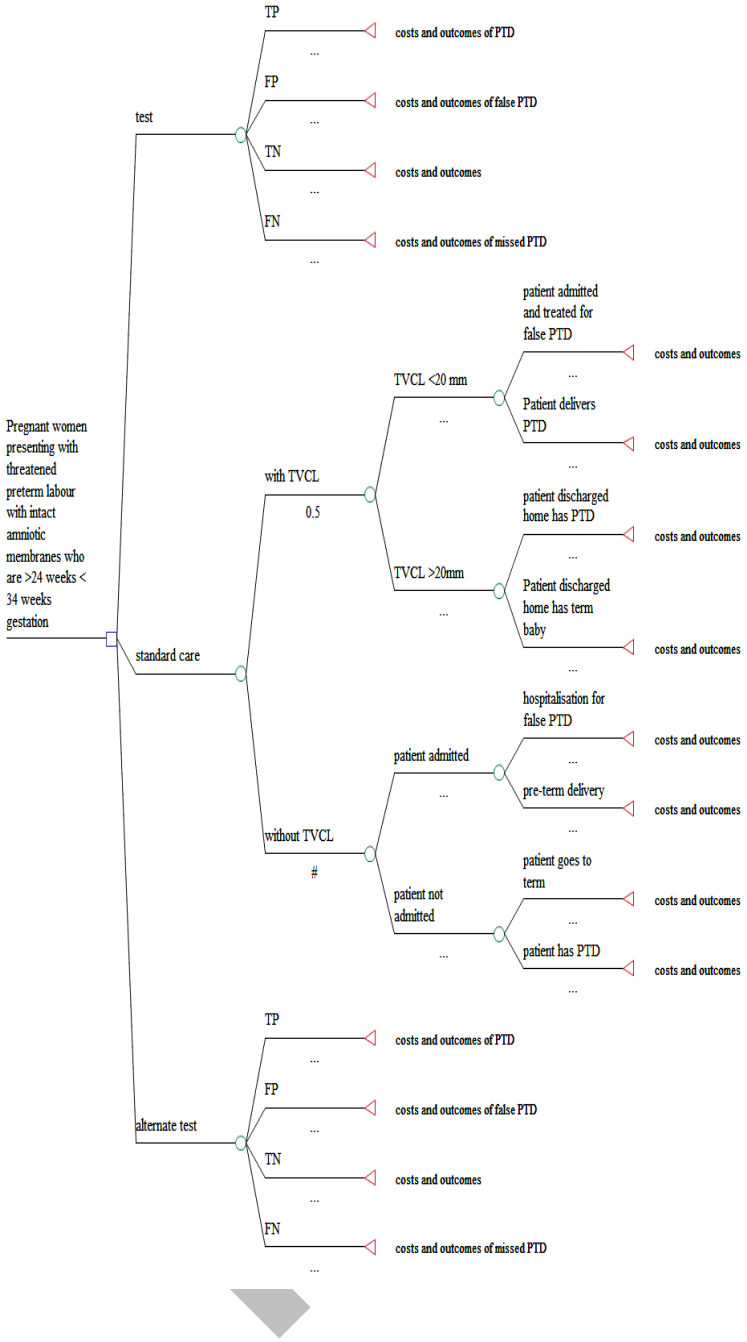
- True positive (TP)–these patients are admitted to hospital, treated for premature delivery and will go on to deliver prematurely
- False positive (FP)–these patients are hospitalised for false labour. The patient is treated for premature delivery but does not deliver in the next 7-14 days
- True negative (TN) result–the patients are discharged for outpatient follow-up and do not deliver in the next 7-14 days
- False negative (FN) result–these patients are discharged for outpatient follow-up but will deliver prematurely. Treatment and hospitalisation for premature delivery may be delayed.

The comparator arms are,

- standard care. Current clinical management may include:
    - Standard care without TVCL; and
    - Standard care with TVCL. If TVCL is included in current clinical management then the diagnostic accuracy of this test will be included in the decision analytic model.
- alternate test (if decision analytic is for phIGFBP then this arm would be for fFN testing and vice versa if the decision analytic is for fFN testing then this arm would be for phIGFBP-1 testing)
    - the four possible outcomes of this arm are: TP, FP, TN,FN

Figure 5 illustrates the decision analytic model

Figure 5: Proposed basic decision analytic for tests to exclude preterm labour



For patients who receive only standard care, (that is no TVCL test), the decision analytic assumes these patients are admitted or not based on clinical judgement only and treated for preterm delivery and that a minority will go on to deliver preterm but for the majority their symptoms will subside and they will not deliver in the next 7-14 days. *Evidence on whether all patients in this arm are admitted to hospital or only a proportion will need to be provided from a literature search*.

The applications report that the proportion of patients presenting with threatened labour who deliver preterm compared to at term is available from a number of sources including epidemiological data and studies, hospital utilisation data and expert opinion.

The availability of the tests is not proposed to affect the number of preterm or term births or their morbidity or mortality. The economic evaluation, based on the decision analytic presented, assumes the outcomes do not differ between the different treatment pathways, however, the proportion of patients who will receive or not receive treatment, and the costs associated with these treatments will differ.

A decision analytic tree for the use of the quantitative fFN test will include further stratification based on the quantification of fFN levels which are proposed to provide further guidance on clinical management of patients and are reported by the applicant to provide enhanced diagnostic accuracy compared to the qualitative fFN test.

Given the claims in the proposal of non-inferiority in respect to clinical effectiveness and safety compared to ffN plus standard care (with or without TVCL), there may be substantial savings then a cost minimisation or cost-effectiveness analysis would be the most appropriate economic evaluation.

Table 10 provides a list of the resources to be included in the economic evaluation.

Table 10: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
- Not applicable										
-										
Resources provided to deliver proposed intervention										
- Cost of test	Alere	community	? (50%)	1 (?)	$69.83				$12.14	81.97
- Cost of test	Alere	hospital	? (50%)	1 (?)	$61.44				$20.53	81.97
Resources provided in association with proposed intervention										
- MBS items (82105, 16400,501,503,507) Medical practitioners, midwives, nurse practitioners	MBS	multiple	?	?						
- MBS item 82110 (midwife)	MBS	Home or hospital	?	?	45.40				$7.60	$53.00
- MBS item 16400 (Midwife, nurse practitioner ATSI health)	MBS	Rural or remote	30%	?	$23.20				$4.05	$27.25
- MBS item 503 (Medical practitioner)	MBS	Private Hospital	?	?	$49.15				$8.65	$57.80
- Transvaginal US 55718	MBS	hospital	?	?	$85.00				$15.00	$100.00
- Transvaginal US - MBS 55722	MBS	hospital	?	?	$42.5				$7.50	$50.00
-										
Resources provided to deliver comparator 1										
- Cost of test	Hologic	community	? (50%)	1 (?)	$88.4				$15.6	$104
- Cost of test	Hologic	hospital	?(50%)	1 (?)	$78.00				$26.00	$104
Resources provided in association with comparator 1 (e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)										
- MBS items (82105, 16400,501,503,507) (Medical practitioners, midwives, nurse practitioners)	MBS	multiple	?	?						
- MBS item 82110 (Midwife)	MBS	Home or hospital	?	?	45.40				$7.60	$53.00
- MBS item 16400 - (Midwife, nurse practitioner ATSI health)	MBS	Rural or remote	30%	?	$23.20				$4.05	$27.25
- MBS item 503 (Medical practitioner)	MBS	Private Hospital	?	?	$49.15				$8.65	$57.80
- Transvaginal US 55718	MBSr	hospital			$85.00				$15.00	$100.00
- Transvaginal US - MBS 55722	MBS	hospital			$42.5				$7.50	$50.00
-										
-										
Resources provided to deliver comparator 2, etc										
- Transvaginal US	MBS	hospital			$85.00				$15.00	$100.00

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
55718										
- Transvaginal US - MBS 55722	MBSr	hospital			$42.5				$7.50	$50.00
-										
Resources provided in association with comparator 2, etc										
- Resource 1										
- Resource 2, etc										
Resources used to manage patients successfully treated with the proposed intervention										
- Hospitalisation for preterm delivery DRG 060A - (vaginal +CCC)	State gov't	hospital	?	1						$7,512
- Neonate (cost depends on weight) - DRG P62Z (750-999Gms)	State gov't	hospital	?	1						$131,650
- Hospitalisation for false preterm labour DRG 064A	State gov't + private	Public +private hospital	?	1 (may be >1)						$2,372
- transport costs - -air ambulance - -road ambulance	State gov't	community								
- drug costs - - tocolytics (nifidepine, -	Gov't	PBS hospital		20mg (then 10 mg x 4)						
- bethamethasone	Gov't	PBS hospital	?	12 mg						
- magnesium sulphate	Gov't	hospital	?	4 g IV (20mins) then 1g/hr for 24 hrs						
Resources used to manage patients successfully treated with comparator 1, etc										
- Hospitalisation for preterm delivery DRG 060A - (vaginal +CCC)	State Gov't	hospital	?	1						$7,512
- Neonate (cost depends on weight) - DRG P62Z (750-999Gms)	State Gov't	hospital	?	1						$131,650
- Hospitalisation for false preterm labour DRG 064A	State gov't + private	Public + private hospital	?	1 (may be >1)						$2,372
- Transport costs - -air ambulance - - road ambulance	State gov't	community								
- drug costs - - tocolytics (nifidepine, -	Gov't	PBS hospital		20mg (then 10 mg x 4)						
- bethamethasone	Gov't	PBS	?	12 mg						
- magnesium sulphate	Gov't	hospital	?	4 g IV (20mins) then 1g/hr for 24 hrs						

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
-										

* Include costs relating to both the standard and extended safety net.

Table 11 lists the health care resources that may be used in the delivery of the phIGFBP-1 test. Given the similarity of delivery of the phIGFBP-1 test to the fFN, it is expected that similar resources will also be used for delivery of the fFN test with the exception that the cost of the test would be for either the qualitative test or the quantitative test and the resources used for delivery of the comparator would be for the phIGFBP-1 test. For this reason a duplicate of this table for fFN has not been provided.

Cost of the test

PASC advised that the applicants will need to provide justification for the item fee proposed, in particular justification for:

- *Inclusion of labour costs (if they can be justified, then which practitioners salary costs should be used, e.g. obstetrician, midwife or nurse practitioner)*
- *Cost of the qualitative fFN test*
- *Cost of the quantitative fFN test*
- *Why overhead costs are included (17% overhead cost figure has been used).*

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