PIM2 & PIM3 for the ANZPIC Registry

Information Booklet

ANZICS

Version 1Sep2011

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PIM2

PIM2 is calculated from the information collected at the time a child is admitted to your ICU. Because PIM2 describes how ill the child was at the time you started intensive care, the observations to be recorded are those made at or about the time of first face-to-face (not telephone) contact between the patient and a doctor from your intensive care unit (or a doctor from a specialist paediatric transport team). Use the first value of each variable measured within the period from the time of first contact to 1 hour after arrival in your ICU. The first contact may be in your ICU, your emergency department, a ward in your own hospital, or in another hospital (e.g. on a retrieval). If information is missing, see the documentation for each field for the correct coding practice.

Calculation of PIM2 (and PIM2 risk of death%)–

PIM2val= (0.01395 * (absolute(SBP-120))) + (3.0791 * Pupils) + (0.2888 * (100*FiO2/PaO2)) + (0.1040 * (absolute Base Excess)) + (1.3352 * MechVent) – (0.9282 * Elective) – (1.0244 * Recovery) + (0.7507 * Bypass) + (1.6829 * HRdiag) – (1.5770 * LRdiag) -4.8841

PIM2 risk of death $= e^{PIM2val} / (1 + e^{PIM2val})$

Example of PIM2 calculation

A patient with hypoplastic left heart syndrome is admitted to intensive care for recovery following an elective Norwood procedure. At the time of admission he is ventilated. The first recorded systolic blood pressure is 55 mmHg, PaO2 is 110 mmHg, FiO2 0.5, base excess -6.0. The pupils are reactive to light. (The low risk diagnoses do not apply to this case).

PIM2val = (0.01395* [absolute(55–120)) + (3.0791*0) + (0.2888* (100*0.5/110)) + (0.104* |–6.0|) + (1.3352* 1) – (0.9282* 1) – (1.0244* 1) +(0.7507 * 1) + (1.6829* 1) – (1.5770 * 0) – 4.8841

$\qquad = -1.4059$

Probability of Death = exp (–1.4059) / [1+exp (–1.4059)]

$\qquad\qquad = 0.1969 \qquad$ or 19.7%

Coding rules and explanation of PIM2 fields –

(These rules must be followed carefully for PIM2 to perform reliably)

1. **SBP**: Systolic Blood Pressure (mmHg). Record SBP as 0 if the patient is in cardiac arrest, record 30 if the patient is shocked and the blood pressure is so low that it cannot be measured. ~~If the measurement is~~ **unknown**, ~~code~~ **999**; this will default to 120 in the PIM2val calculation.

2. **Pupils** (**Pupillary responses to bright light)**: Pupillary reactions to bright light are used as an index of brain function. Do not record an abnormal finding if this is due to drugs, toxins or local eye injury. ~~Codes:~~ >3 mm and both fixed~~=~~**1**, ~~other or unknown~~=**0**.

3. **PaO2**. The **arterial** oxygen tension, mmHg, as measured in an **arterial** blood gas sample only. ~~If measurement not done, code~~ **999** ~~(this will default to zero in PIM2val calculation).~~

4. **FiO2**. The fraction of inspired oxygen being delivered via endotracheal tube (ETT), non-invasive ventilation (NIV), or headbox. Record the FiO2 being given at the same time that the first PaO2 is measured (that is, both the FiO2 and PaO2 that you record must relate to the same time). ~~Code unknown as~~ **999** ~~(this will default to zero in PIM2val calculation). If PaO2 is 999, then FiO2 will also be 999.~~

5. **Base Excess**. The base excess measured in **arterial or capillary** blood, in mmol/l. ~~Code unknown as~~ **999** ~~(this will default to zero in PIM2val calculation).~~

If a variable is not measured within one hour of admission to ICU it should be coded as missing (for example, if the first blood gas is not done until two hours after admission, the base excess and PaO2 should both be coded as unknown).

6. **MechVent**. Mechanical Ventilation. Record whether the patient was mechanically ventilated within the first hour of admission to ICU. Mechanical ventilation refers to both invasive (ETT or tracheostomy), and non-invasive (nasopharyngeal airway, mask or nasal prongs) methods of augmenting work of breathing, using conventional mechanical ventilation (CVM), continuous positive airway pressure (CPAP), biphasic positive airway pressure (BiPAP), or negative pressure ventilation (NPV). High Flow does not constitute mechanical ventilation. Codes: Yes=**1**, No=**0**.

7. **Elective**. Elective ICU admission. The admission is classed as elective if (1) the patient was admitted after an elective procedure (where the ICU admission must have been planned, or, if inadvertently not planned, then could have been foreseen), or (2) for an elective procedure in PICU (e.g. insertion of a central line), or (3) elective monitoring, or (4) review of home ventilation. An admission or an operation is considered elective if it could have been postponed for more than six hours without adverse effect. Note that unexpected admissions (i.e. not planned and could not have been foreseen) after elective surgery are not considered Elective. This field is intended to be a classification of patient characteristics and not administrative booking procedures for ICU beds. Codes: Yes=**1**, No=**0**.

8. **Recovery**. Record whether recovery from surgery or a procedure is the main reason for admission. Do not include patients admitted from the operating theatre where recovery from surgery is not the main reason for ICU admission (for example, a patient with a head injury who is admitted from theatre after insertion of an ICP monitor; in this patient, the main reason for admission is the head injury). Helpful hint: Ask – would patient have been going to ICU anyway if they hadn't been to OT? If answer is NO, then Recovery would be YES. Codes: Yes=**1**, No=**0**.

9. **Bypass**. Record if patient was admitted following cardiac bypass. Codes for data collection are 0=No, 1=admitted following cardiac bypass, 2=bypass procedure during ICU admission, 3= both 1&2 apply. These are recoded for the PIM2val calculation to 0&2=No(**0**), 1&3=Yes(**1**). Note: if this field is coded Yes, then also code Recovery as Yes.

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10. **HRdiag**. PIM2 High Risk Diagnosis (ANZPICR field PIM_UC). Specific conditions associated with increased mortality risk. Codes for data collection are -

   0   None

   1   Cardiac arrest out of hospital - requires either documented absent pulse or the requirement for external cardiac massage (do not include past history of cardiac arrest).

   2   Severe combined immune deficiency - requires the documented diagnosis of SCID.

   3   Leukaemia or lymphoma after 1st induction. Include only cases where the admission is related to leukaemia or lymphoma, or the therapy for these conditions.

   4   Spontaneous cerebral haemorrhage - haemorrhage must be spontaneous (for example, from an aneurysm or AVM). Do not include traumatic cerebral haemorrhage or intracranial haemorrhage that is not intracerebral (eg subdural haemorrhage).

   5   Cardiomyopathy or myocarditis - requires the documented diagnosis of myocarditis or cardiomyopathy.

   6   Hypoplastic left heart syndrome – at any age on admission, but include only cases where a Norwood procedure, or equivalent, is required in the neonatal period to sustain life. If a subsequent heart transplant, then this diagnosis and high risk indicator no longer apply.

   7   HIV infection - requires the document diagnosis of HIV.

   8   Code no longer in use (2009 onwards)

   9   Neurodegenerative disorder - requires a history of progressive loss of milestones (even if no specific condition has been diagnosed) or a diagnosis where this will inevitably occur.

   10   Liver failure - acute or chronic, is the main reason for ICU admission. Include patients admitted for recovery following liver transplantation for acute or chronic liver failure.

   11   Cardiac arrest in hospital - preceding ICU admission requires either documented absent pulse or the requirement for external cardiac massage (do not include past history of cardiac arrest)

These are recoded for the PIM2val calculation to 0=No(**0**), 1-11=Yes(**1**).

11. **LRdiag**. PIM2 Low Risk Diagnosis (ANZPICR field PIM_LR). Specific conditions associated with decreased mortality risk - which must be the main reason for admission.
Codes for data collection are –

   0   None

   1   Asthma is the main reason for ICU admission.

   2   Bronchiolitis is the main reason for admission. Include children who present either with respiratory distress or central apnoea where the clinical diagnosis is bronchiolitis.

   3   Croup is the main reason for ICU admission.

   4   Obstructive sleep apnoea (OSA) is the main reason for ICU admission. Include admissions following adenoidectomy &/or tonsillectomy where OSA is the main or underlying reason for ICU admission (and also code as recovery from surgery).

   5   Diabetic keto-acidosis (DKA) is the main reason for ICU admission.

These are recoded for the PIM2val calculation to 0=No(**0**), 1-5=Yes(**1**).

General guidelines for collecting PIM data

1. Do not over-diagnose the specified conditions - if there is any doubt, do not record a specified condition. For example: do not code cerebral haemorrhage for intracerebral bleeding associated with trauma ; impaired cardiac function associated with sepsis or surgery should not be coded as cardiomyopathy ; and a static disability should not be coded as neurodegenerative (even if it is severe) unless there is progressive ongoing loss of milestones.

2. You should record the first value of each variable from the time of first contact ~~up to one hour after arrival in your ICU~~ (not the worst value). If a variable is not measured within one hour of admission to ICU it should be coded as unknown (for example, if the first blood gas is not done until two hours after admission, the base excess and PaO2 should both be coded as unknown). Missing data is treated as being normal when PIM is calculated.

3. ~~The PIM equation is used to calculate the PIMval. If you are using your own software to calculate the PIMval, and if any information is missing, that variable should add nothing to PIMval. For example, if the PaO2 or the FiO2 is missing, the value of "(0.2888 * (100*FiO2/PaO2))" should be set to zero.~~

4. Record the FiO2 being given at the same time that the first PaO2 is measured (that is, both the FiO2 and PaO2 that you record must relate to the same time). PaO2 must be arterial.

5. Read very carefully the definition for the ELECTIVE field - noting in particular that unexpected ICU admissions (i.e. not planned and that could not have been foreseen) after elective surgery are not classed as Elective.

6. The pupils are only recorded as fixed if both are >3 mm, and both are fixed, and the finding is not caused by drugs or toxins or direct injury to the eye.

7. If systolic blood pressure is not measured in the first hour, ~~record 999~~ - do not record zero.

8. ~~If the field RS_HR124 (mechanical ventilation within the first hour of ICU admission) is "yes" then there must be a corresponding episode of respiratory support (either invasive or non-invasive) recorded.~~ Episodes of HFNC do not qualify as mechanical respiratory support.

9. When carrying out a self-audit at your site, randomly sample about every 20th admission to your ICU and get another person to collect the PIM2 data independently a second time, so that you can check the accuracy of your data.

10. As the accurate recording of physiological measurements has a major impact on the calculated PIM value, it is important that each site develop a recording mechanism to minimize the risk of data interpretation or data entry errors. For example, if the values are to be extracted directly from hand-written observation charts, good local practice would be for the attending clinical staff to write the numerical values as well as plot them. As the values are taken from the first observation only, this should not add to workload.

11. You should include all admissions to your ICU, not just selected cases. For specialist PICUs this should be every admission regardless of age; ~~for other ICUs, this should be all children whose age at admission is less than 16 years.~~

Interpretation/application of PIM2

PIM2 should only be applied to groups of patients. It should not be used to make decisions about the management of individual patients, or even to describe individual patients. By adjusting mortality for severity of illness and diagnosis, individual intensive care units compare the performance of their unit to that of other units using site Standardised Mortality Ratios (SMRs) –see below.

Data for PIM are collected within the first hour of admission, which avoids potential bias from the effects of treatment after admission.

PIM Goals
- simple – easy enough to collect as part of routine activity
- collect information to assess risk before you start treating – so the assessment is not influenced by your treatment
- standardise where possible the point of data capture (1st contact)
- available in public domain

PIM Principles
- estimate probability of death for each patient
- combined effect of risk factors (10 in PIM2)
- increased risk (7 factors), or decreased risk (3 factors)
- not accurate enough to use in individual patients
- aim is to estimate the expected mortality for the population (or unit) overall

SMRs

The first step in calculating an SMR is to assign a risk of death value to each admission using a mortality prediction model (i.e. PIM2). This enables adjustment for the casemix of each site so that its performance is more accurately compared with other sites with a different patient mix.

A site SMR = number of deaths observed / number of deaths expected
> *(where the number of deaths expected = sum of PIM2 probability of death values for site)*

If the site SMR = 1, then the outcome for the site is as expected;
> if > 1 then outcome worse than expected, and if < 1 then outcome better than expected

To accurately report an SMR, it should be presented in conjunction with its 95% confidence interval. If the lower bound of the confidence interval is also greater than 1, then the site SMR is indicative of significantly more actual deaths than predicted. This would flag a site's data for further examination.

PIM2 Q&A

Q: Clarification about what is "first contact" in collecting physiologic values for PIM when patient is a retrieval or first seen elsewhere in hosp.
A: PIM values can be taken in period of first contact up to end of first hour in ICU. First contact to be defined as ICU staff (or retrieval team) taking over management of patient – e.g. if ICU medical staff review a patient on the ward or in ED and admission is not considered necessary at that time, then this review does not constitute "first contact" for PIM measurements if the patient is admitted to ICU at a later time.

Q: Please clarify PIM2 timing requirements for physiological variables in retrievals
A: For retrieved patients, use the 1st measurement recorded after time of first face to face contact with the retrieval team doctor up until 1 hour post admission to ICU. (e.g. if retrieval takes 3 hours from 1ˢᵗ face to face contact until admission then use the first measurement during the 4 hour period.)

1. SBP
Q: For SBP should we use arterial measurements in preference to cuff measurements?
A: If there is an arterial line in situ with an appropriate wave form, use the SBP recorded from the arterial line in preference to SBP measured non-invasively.

Q: Should we delete SBPs during agitation or crying?
A: Use the first SBP recorded in the observation chart.

2. Pupils
Q: What about a child that has received atropine during intubation?
A: If 1 or both pupils were reactive to light before atropine then do NOT code as fixed to light.

3. PaO2
Q: What if the patient has a mixing lesion? Should PaO2 and FiO2 be recorded as 0?
A: Record values measured (not 0).

4. FiO2
Q: FiO2 measurement – can it only be via ETT or headbox?
A: If FiO2 can be measured accurately then it can be recorded, e.g. BiPAP and CPAP with mask sealed tightly. Record FiO2=0.21 for spontaneous breathing of room air, e.g. patient has pneumonia and you are drawing PaO2s but they are breathing on their own with no supplemental O2.

5. Base Excess
Q: Can the values from a venous blood gas be used if no arterial/cap value is available?
A: No, not for the calculation of PIM2 or PIM3. These models have been validated with arterial and capillary values only (taken up to the first hour of admission). This restriction may change for future PIM models if research supports its inclusion.

6. Mechanical Ventilation
Q: Re ventilation in 1ˢᵗ hour - assume tracheostomy is included in this as long as mechanically ventilated?
A: Yes, but tracheostomy & breathing spontaneously does not constitute ventilation.

Q: Should HFNC be considered as respiratory support for PIM field of "Mechanical Ventilation at any time during the first hour in ICU"?
A: No it shouldn't. As per the current PIM definition, "Mechanical Ventilation" is said to include CPAP and BiPAP. Episodes of HFNC are collected as a separate item of respiratory support on the "Episodes" form for the ANZPIC Registry from 2010 onwards, but are not classed as mechanical ventilation.

Q: Does T-bar constitute mechanical ventilation?
A: A T-bar or T-piece that is not connected to a ventilator or CPAP device does not constitute mechanical ventilation.

7. Elective
Q: If a patient is booked for elective surgery (but PICU bed was not booked in advance), how would you code the following two scenarios:
   a) prior to operation, call made to PICU tentatively requesting a bed because of potential complications
   b) during elective procedure, call made to PICU requesting a bed (due to unforeseen complications during operation)
A: Code a) elective admission = yes,   b) elective admission = no.

8. Recovery
Q: Please give further clarification of RECOVERY field used in PIM calculation.
A: Ask – would patient have been admitted to ICU anyway if they hadn't been to OT? If answer is NO, then Recovery would be YES.
Examples: Includes a radiology procedure or cardiac catheter. Do not include patients admitted from the operating theatre where recovery from surgery is not the main reason for ICU admission (e.g. a patient with a head injury who is admitted from theatre after insertion of an ICP monitor; in this patient the main reason for ICU admission is the head injury).

10. High Risk Diagnosis
Q: Re. High Risk code 1 (out of hospital cardiac arrest), should we qualify the time period for the inclusion of this code post cardiac arrest prior to ICU admission (i.e. pick some interval within 6, 24, or 96 hours)? Example – patient has cardiac arrest at another hospital and transfers the next day or patient has cardiac arrest out of the hospital and takes 8 hours to be transported.
A: Cardiac arrest is relevant if the admission to ICU was related to arrest. In the example of the transfer, this would constitute a continuation of an ICU episode and the high risk code should be used in the data from both sites.

Q: Re. High Risk Diagnosis 3 (leukemia or lymphoma after 1st induction): should malignancy after first induction be included or just leukaemia or lymphoma?
A: Code only or leukemia or lymphoma after 1st induction.

Q: PIM high risk code 9 Neurodegenerative disorders – examples?
A: See appendix 3 for list of neurodegenerative disorders and motor neuron diseases (note that not all neurodegenerative disorders will have a specific diagnosis at the time of ICU admission).

11. Low Risk Diagnosis
Q: Can a patient have both a PIM2 high risk and low risk score?
A. Yes, both can be present in an admission record and are used in the calculation of PIM2. Note, however, that for PIM3, while a patient can have a low risk, high risk and very high risk score, only the highest risk score is used in the PIM3 calculation.

Q: How to code admission after T&A because of OSA. (i.e. should OSA be the PDX or T&A?)
A: Code T&A as PDX, with OSA as UDX and PIM Low Risk as "4".

Q: How to code patient with bronchiolitis and subsequent pneumonia – which is the PDX?
A: If the medical diagnosis at the time of ICU admission is pneumonia and this is the primary reason for admission, then code Pneumonia as PDX, with bronchiolitis as an associated diagnosis if a recent history of bronchiolitis is contributing to the current illness. In this situation do not code PIM low risk diagnosis as bronchiolitis because bronchiolitis is not the main reason for admission.

Variable differences between PIM3 and PIM2

○ new/different items

1. The Bypass field is no longer used.

2. **NonCard_PostOp**. (Non-cardiac post operative admission) This is a new field and is centrally created after data submission. Codes are : Yes=**1**, No=**0**, where "yes" is generated if Recovery=1 and PDx is 1100-1899.

3. There are now 3 "risk" indicator fields – Very High Risk (VHRdiag), High Risk (HRdiag) and Low Risk (LRdiag). VHRdiag is a new field, while HRdiag and LRdiag have different inclusions in PIM3 compared to their use in PIM2.

4. Only one of VHRdiag, HRdiag and LRdiag can be included in the calculation of PIM3val, with the most severe risk over-riding the lesser risks. This is different to the use of HRdiag & LRdiag in PIM2 where both could be used in the calculation if applicable.

5. **VHRdiag**. PIM3 Very High Risk Diagnosis (ANZPICR field PIM3_VHR). Specific conditions associated with increased mortality risk. Codes for data collection are -
- 0   None
- 1   Cardiac arrest preceding ICU admission. Includes both in-hospital and out-of-hospital arrest. Requires either documented absent pulse or the requirement for external cardiac massage (do not include past history of cardiac arrest).
- 2   Severe combined immune deficiency - requires the documented diagnosis of SCID.
- 3   Leukaemia or lymphoma after 1st induction. Include only cases where the admission is related to leukaemia or lymphoma, or the therapy for these conditions.
- ④   Bone marrow transplant recipient.
- ⑤   Liver failure - acute or chronic, is the main reason for ICU admission. **DO NOT** Include patients admitted for recovery following liver transplantation for acute or chronic liver failure. (coding of liver transplant patients is different from PIM2)
- ⑥   Necrotising enterocolitis is the main reason for ICU admission.

These are recoded for the PIM3val calculation to 0=No(**0**), 1-5=Yes(**1**).

6. **HRdiag**. PIM3 High Risk Diagnosis (ANZPICR field PIM3_HR). Specific conditions associated with increased mortality risk. Codes for data collection are -
- 0   None
- 1   Spontaneous cerebral haemorrhage - haemorrhage must be spontaneous (for example, from an aneurysm or AVM). Do not include traumatic cerebral haemorrhage or intracranial haemorrhage that is not intracerebral (eg subdural haemorrhage).
- 2   Cardiomyopathy or myocarditis - requires the documented diagnosis of myocarditis or cardiomyopathy.
- 3   Hypoplastic left heart syndrome – any age, but include only cases where a Norwood procedure, or equivalent, is required in the neonatal period to sustain life. If a subsequent heart transplant, then this diagnosis and high risk indicator no longer apply.
- 4   Neurodegenerative disorder - requires a history of progressive loss of milestones (even if no specific condition has been diagnosed) or a diagnosis where this will inevitably occur.
- ⑤   Septic shock. As defined by the International Pediatric Sepsis Consensus Conference, 2002. Requires the presence of the systemic inflammatory response syndrome (SIRS) and suspected or proven infection and cardiovascular organ dysfunction.

These are recoded for the PIM3val calculation to 0=No(**0**), 1-5=Yes(**1**).

7. **LRdiag**. PIM3 Low Risk Diagnosis (ANZPICR field PIM3_LR). Specific conditions associated with decreased mortality risk. Codes for data collection are -

0   None
1   Asthma is the main reason for ICU admission.
2   Bronchiolitis is the main reason for ICU admission. Include children who present either with respiratory distress or central apnoea where the clinical diagnosis is bronchiolitis.
3   Croup is the main reason for ICU admission.
4   Obstructive sleep apnoea. Include patients admitted following adenoidectomy and/or tonsillectomy in whom obstructive sleep apnoea (OSA) is the main reason for ICU admission (and also code as recovery from surgery).
5   Diabetic ketoacidosis (DKA) is the main reason for ICU admission.
⑥   Seizures. Include patients who require admission primarily due to status epilepticus, epilepsy, febrile convulsion, or other epileptic syndrome where admission is required either to control seizures or to recover from the effects of seizures or treatment.

~~These are recoded for the PIM3val calculation to 0=No(**0**), 1-6=Yes(**1**).~~

Appendix 1

Definition of sepsis/SIRS/septic shock:

SIRS: widespread inflammatory response that may or may not be associated with infection. The presence of 2 or more of the following criteria (one of which <u>must</u> be abnormal temperature or leukocyte count):

- ► Core temp > 38.5°C or < 36°C

- ► WBC increased or decreased for age, or > 10% immature neutrophils

- ► Tachycardia (HR > 2 SD above normal for age
            OR   for children < 1 yr, HR < 10th percentile for age)

- ► Bradycardia

- ► Mean respiratory rate > 2 SD above normal for age

Sepsis: SIRS in the presence of, or as a result of, suspected or proven infection.

Septic shock: is sepsis with cardiovascular dysfunction despite the administration of > 40ml/kg of isotonic fluid in one hour.

Appendix 2

Chromosomal abnormalities

Chromosomal abnormalities: Code for conditions that can be detected on routine chromosomal analyses (including FISH studies), e.g. Trisomies, translocations, deletions.

Examples of most common chromosomal abnormalities:

Trisomies. Down syndrome is among the most common of these disorders, affecting about 1 in 800 to 1000 live-born babies. Babies also can be born with extra copies of chromosomes 13 or 18. These trisomies are usually much more severe than Down syndrome, but fortunately less common, each affecting about 1 in 5000 babies. Babies with trisomies 13 or 18 generally have severe mental retardation and many physical birth defects.

Turner syndrome is a sex chromosome abnormality that affects about 1 in 2500 girls. Girls with Turner syndrome have only one X chromosome, instead of the normal two.
About 1 in 1000 to 2000 females has an extra X chromosome, referred to as triple X.

Klinefelter syndrome is a sex chromosome abnormality that affects about 1 in 600 to 800 boys. Boys with Klinefelter syndrome have two, or occasionally more, X chromosomes along with their Y chromosome.

Appendix 3

Neurodegenerative disorders

For the purposes or recording a neurodegenerative disorder in the PIM high risk field, a patient requires a history of progressive loss of milestones (even if no specific condition has yet been diagnosed), or a diagnosis where this will inevitably occur.

Alpers' Disease (Synonym: Progressive Sclerosing Poliodystrophy). Alpers' disease is a rare, genetically determined disease of the brain that causes progressive degeneration of grey matter in the cerebrum. The first sign of the disease usually begins early in life with convulsions. Other symptoms are developmental delay, progressive mental retardation, hypotonia (low muscle tone), spasticity (stiffness of the limbs), dementia, and liver conditions such as jaundice and cirrhosis that can lead to liver failure. Optic atrophy may also occur, often causing blindness. Researchers believe that Alpers' disease is caused by an underlying metabolic defect. Some patients have mutations in mitochondrial DNA.

Cerebro-Oculo-Facio-Skeletal Syndrome (Synonyms: Pena Shokeir II Syndrome, Cockayne Syndrome Type II). Cerebro-oculo-facio-skeletal (COFS) syndrome is a paediatric, genetic, degenerative disorder that involves the brain and the spinal cord. It is characterized by craniofacial and skeletal abnormalities, severely reduced muscle tone, and impairment of reflexes. Symptoms may include large, low-set ears, small eyes, microcephaly (abnormal smallness of the head), micrognathia (abnormal smallness of the jaws), clenched fists, wide-set nipples, vision impairments, involuntary eye movements, and mental retardation, which can be moderate or severe. Respiratory infections are frequent. COFS is diagnosed at birth.

Leigh's Disease (Synonym: Subacute Necrotizing Encephalomyelopathy (SNEM)). Leigh's disease is a rare inherited neurometabolic disorder characterized by degeneration of the central nervous system. Leigh's disease can be caused by mutations in mitochondrial DNA or by deficiencies of the enzyme pyruvate dehydrogenase. Symptoms of Leigh's disease usually begin between the ages of 3 months to 2 years and progress rapidly. In most children, the first signs may be poor sucking ability and loss of head control and motor skills.

Monomelic Amyotrophy (Synonyms: Benign Focal Amyotrophy, Hirayama Syndrome, O'Sullivan-McLeod Syndrome). Monomelic amyotrophy (MMA) is characterized by progressive degeneration and loss of motor neurons, the nerve cells in the brain and spinal cord that are responsible for controlling voluntary muscles. It is characterized by weakness and wasting in a single limb, usually an arm and hand rather than a foot and leg. There is no pain associated with MMA. While some physicians contend that mild sensory loss may be associated with this disease, many experts suggest that such symptoms actually indicate a cause other then MMA. MMA occurs in males between the ages of 15 and 25. Onset and progression are slow. MMA is seen most frequently in Asia, particularly in Japan and India; it is much less common in North America. In most cases, the cause is unknown, although there have been a few published reports linking MMA to traumatic or radiation injury. There are also familial forms of MMA. Diagnosis is made by physical exam and medical history. Electromyography (EMG), a special recording technique that detects electrical activity in muscles, shows a loss of the nerve supply, or denervation, in the affected limb; MRI and CT scans may show muscle atrophy. People believed to have MMA should be followed by a neuromuscular disease specialist for a number of months to make certain that no signs of other motor neuron diseases develop.

Progressive Multifocal Leukoencephalopathy (PML) is an infrequent disorder of the nervous system that primarily affects individuals with suppressed immune systems (including, allograft recipients such as kidney transplant patients; patients with cancers such as leukaemia or lymphoma; and nearly 10% of patients with acquired immune deficiency syndrome (AIDS). The disorder, which is caused by a common human polyomavirus, JC virus, is characterized by demyelination or destruction of the myelin sheath that covers nerve cells. The myelin sheath is the fatty covering – which acts as an insulator – on nerve fibres in the brain. Symptoms of PML include mental deterioration, vision loss, speech disturbances, ataxia (inability to coordinate movements), paralysis, and, ultimately, coma reflecting the multifocal distribution of brain lesions. In rare cases, seizures may occur.

Motor Neuron Diseases
(include as PIM high risk diagnosis of neurodegenerative disorder)

Motor neuron diseases (MNDs) are progressive, degenerative disorders that affect nerves in the upper or lower parts of the body. Some of the diseases are inherited, while others may be acquired. Common MNDs include amyotrophic lateral sclerosis (ALS), progressive muscular atrophy, and postpolio syndrome.

Amyotrophic Lateral Sclerosis (Synonym: Lou Gehrig's Disease).
Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, invariably fatal neurological disease that attacks the neurons responsible for controlling voluntary muscles. In ALS, both the upper motor neurons and the lower motor neurons degenerate or die, ceasing to send messages to muscles. Unable to function, the muscles gradually weaken, waste away, and twitch. Eventually the ability of the brain to start and control voluntary movement is lost. Individuals with ALS lose their strength and the ability to move their arms, legs, and body. When muscles in the diaphragm and chest wall fail, individuals lose the ability to breathe without ventilatory support.

Spinal Muscular Atrophy
Spinal muscular atrophy (SMA) is a genetic, motor neuron disease caused by progressive degeneration of motor neurons in the spinal cord. The disorder causes weakness and wasting of the voluntary muscles. Weakness is often more severe in the legs than in the arms. The childhood SMAs are all autosomal recessive diseases. The gene for SMA has been identified and accurate diagnostic tests exist. There are many types of SMA; some of the more common types are described below.

SMA type 1, also called Werdnig-Hoffmann disease, is evident before birth or within the first few months of life. There may be a reduction in fetal movement in the final months of pregnancy. Symptoms include floppiness of the limbs and trunk, feeble movements of the arms and legs, swallowing and feeding difficulties, and impaired breathing. Affected children never sit or stand and usually die before the age of 2. Symptoms of **SMA type II** usually begin between 3 and 15 months of age. Children may have respiratory problems, floppy limbs, decreased or absent deep tendon reflexes, and twitching of arm, leg, or tongue muscles. These children may learn to sit but will never be able to stand or walk. Life expectancy varies. Symptoms of **SMA type III** (Kugelberg-Welander disease) appear between 2 and 17 years of age, and include abnormal manner of walking; difficulty running, climbing stairs, or rising from a chair; and slight tremor of the fingers. **Progressive spinobulbar muscular atrophy** or Kennedy syndrome may occur between 15 and 60 years of age. Features of this type may include weakness of muscles in the tongue and face, difficulty swallowing, speech impairment, and excessive development of the mammary glands in males. The course of the disorder is usually slowly progressive. Kennedy syndrome is an X-linked recessive disorder. **Congenital SMA with**

arthrogryposis (persistent contracture of joints with fixed abnormal posture of the limb) is a rare disorder. Manifestations include severe contractures, curvature of the spine, chest deformity, respiratory problems, an unusually small jaw, and drooping upper eyelids.

Rett syndrome
Rett syndrome is a childhood neurodevelopmental disorder characterized by normal early development followed by loss of purposeful use of the hands, distinctive hand movements, slowed brain and head growth, gait abnormalities, seizures, and mental retardation. Rett syndrome is caused by mutations in the MECP2 gene, which is found on the X chromosome. The MECP2 gene contains instructions for the synthesis of a protein called methyl cytosine binding protein 2 (MeCP2), which acts as one of the many biochemical switches that tell other genes when to turn off and stop producing their own unique proteins. Because the MECP2 gene does not function properly in those with Rett syndrome, insufficient amounts or structurally abnormal forms of the protein are formed.