Improving Indigenous Kidney Transplant Outcomes (IKTO) Meeting

14 – 15 October 2013
Darwin
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<th>Time</th>
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<tr>
<td>1500</td>
<td>Open and Welcome</td>
<td>Alan Cass</td>
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<td>1510</td>
<td>Welcome to Country</td>
<td>Larrakia Nation</td>
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<td>1515</td>
<td>Setting the scene – Chair <strong>William Majoni</strong>&lt;br&gt;• National – who, where and when&lt;br&gt;  o Kidney and Liver transplants&lt;br&gt;• Jurisdictional presentations –&lt;br&gt;  o Transplant numbers, outcomes and patterns of infections</td>
<td>Stephen McDonald - ANZDATA&lt;br&gt;Geoff McCaughan - Liver National&lt;br&gt;WA - Suda Swaminathan&lt;br&gt;SA/NT - Michael Burke,&lt;br&gt;Qld - Scot Campbell,&lt;br&gt;NWS - Paul Snelling</td>
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<td>1630</td>
<td>Afternoon Tea</td>
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<td>1650</td>
<td>Infectious Diseases – Chair <strong>Bart Currie</strong>&lt;br&gt;• Overview of infectious diseases&lt;br&gt;• Patterns and specific issues by region&lt;br&gt;• Management strategies</td>
<td>Qld - David Looke&lt;br&gt;NT - Catherine Marshall/Saliya Hewagama&lt;br&gt;WA - Peter Boan&lt;br&gt;SA - Morgyn Warner</td>
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<td>1830</td>
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<td>1930</td>
<td>Dinner</td>
<td>Guest Speaker - Patient</td>
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Objectives of the Meeting
(Alan Cass)

• To facilitate a focused discussion to address issues on improving kidney transplantation outcomes amongst indigenous Australians.

• Provide jurisdictional representation of general and transplantation nephrologists, surgeons, infectious disease physicians and nursing staff who are invested in patient care and understand the challenges.

• Address the following key questions:
  • What are we currently doing to improve kidney transplantation outcomes amongst indigenous Australians?
  • How are we going to improve kidney transplantation outcomes amongst indigenous Australians?
  • What are the similarities between jurisdictions? Any common aspects that are replicable/transferable?
  • What are the patterns?
  • What data do we have?
  • What protocols do we use?
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<td>Stephen McDonald</td>
<td>National kidney transplant</td>
<td>► Waitlisted Indigenous patients have more co-morbidities such as diabetes, vascular disease and heart disease&lt;br&gt;► High number of HLA mismatches&lt;br&gt;► Graft survival much less than non-indigenous&lt;br&gt;► No clear survival advantage compared to dialysis.&lt;br&gt;► Outcomes have improved for all ethnicities (but no decrease in the relative risk among indigenous)</td>
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<td>Geoff McCaughan</td>
<td>National liver transplant</td>
<td>► Grappling with same issues as kidney transplants&lt;br&gt;► Higher levels of liver disease in ATSI population&lt;br&gt;► Causes of liver disease bilaryatresia, Hep C and alcoholism.&lt;br&gt;► Very little immuno-suppression required in liver transplants.&lt;br&gt;► Small number of chronic rejections.</td>
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**Q) Can you elaborate on acute rejection rates?**

We collect all episodes of rejection accounting for poorer matching and other factors such as age. There is still a higher rate of acute rejection and long term graft loss related to rejection amongst Indigenous vs non Indigenous patients. How much higher is dependent on how much you adjust for various predictors, it can be 1.5 - 1.8 fold higher. Based on data from last 10 years, not going back over 20 years.

**Q) What are the challenges of liver transplantation, can you comment?**

2 out of 3 adults lost their grafts from chronic rejection, usually 3-5% in non-Indigenous populations, there are very small numbers. Anecdotally immunosuppression compliance is more of an issue.

**Q) The results are good, compared to the results showed in kidney transplantation. One similarity with adult cohort, if curves truncated at about 3 years, Indigenous are doing better than non-Indigenous in first year, similar to what we see in kidney transplantation, but then the curves seem to drop?**

The curve has been left out of graft survival, as the numbers are very small over the 20 years, the curve drops off quickly with very small numbers in Indigenous population.

**Q) There is a high prevalence of Hep B in the territory, is that a factor in liver disease or is that treatable?**

Uncommon for patients with liver disease with Hep B to get a transplant. Liver cancer is becoming a major indicator for liver transplantation in non-Indigenous. Indigenous patients do not get picked up from screenings and present with advanced liver cancer, unsuitable for transplantation because it is too late.
### Setting the Scene

(Chair William Majoni)

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| Suda Swaminathan | WA Perspective | - RPH does most indigenous transplants in WA  
- Predominantly cadaveric  
- Increased incidence of infections, complications including higher admissions, length of stay and ICU  
- 50% of failures due to non-compliance, rejection at 10 months, coinciding with return to community  
- eGFR poor at all time points after transplant in ATSI compared to non-ATSI  
- Higher rate of infection in Indigenous but believes remoteness is not a factor  
- Diabetes and obesity combination has a hazard ratio greater than 30  
- Modification of immuno-suppression for Indigenous patients |
| Paul Snelling    | NSW Perspective | - Small numbers over last decade  
- Small numbers waitlisted and very little infection as rejection |

**Q)** *Delayed graft function is interesting, how long does the DGF last in your population?*

A couple of people have had CNI sparing regiments, took longer than expected. Late presentation with AGR, have used thymoglobulin/similar but very cautious as not a normal protocol.

**Q)** *To what degree is sepsis related to immuno-suppression?*

Relation between late graft loss and non-compliance, need to be treated for acute rejection, and have used thymoglobulin or a similar combination with plasma exchange. Can present with infections a few months later and therefore any AGR treatment is combined with anti-infective prophylaxis. Something not included here is when patients lose their graft, after they go on dialysis they die of severe sepsis.

**Q)** *The breakdown of remoteness or rural?*

No breakdown in NSW, however in our unit there is a mix of 50% urban and 50% remote.*
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| Michael Burke | SA/NT       | ► Followed outcome in first two years in indigenous transplant patients between 2001 and 2011  
► Pre transplant 60% diabetics, 40% heart disease  
► More than 90% had 5 and 6 HLA mismatches  
► 45% experience rejection in first two years  
► High level of vascular rejection 20%  
► 45% received thymoglobulin which led to increased level of infection  
► Mean inpatient days varied from 42 – 78 days  
► Increased level of infected admissions for NT patients from lung, urinary tract and skin 50% CMV, 20% died in first 2 years |
| Scot Campbell | QLD         | ► Very low numbers of transplanted ATSI patients  
► Very strict criteria for acceptance – no smokers, no vascular disease for diabetes, no coronary disease in recognition of poorer outcomes in indigenous patients  
► Graft survival 66% at 5 years and 31% at 10 years  
► Increase in fungal and general infection rates. |
| Greg Perry    | NT          | ► Reduced number of people on transplant list  
► Significant non-immunological barriers to accessing transplants  
► Need increased focus on nephrological care in remote areas |

**Q) What is the comparison of non-indigenous hospitalisation data?**

In Alice springs the difference is substantial. In WA most non indigenous have no admissions in first year, the average hospitalisation is 2.3% for patients.

**Q) Is it the same pattern in WA? Impression from WA experience is there was significant amount of infection related to non-compliance?**

Difficult to establish, retrospectively it is difficult to assess adherence. Some patients were model patients who died, some patients might have had early rejection that was treated with good graft function but then 12 months later became suddenly unwell.

**Q) Numbers of patients gone up because of proportion of dialysis gone up?**

Numbers have gone up specifically due to the effort to increase numbers on transplant waiting list. No change in the acceptance criteria over period of time.
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| David Looke          | QLD Perspective | Good outcomes dependent on careful donor selection, pre-screening and eradication of infection before hand and close monitoring, identification and prompt treatment of infection post.  
|                      |              | **Infection = Inoculum X virulence/ host resistance**  
|                      |              | Consider source of organisms – donor/organ, host/recipient, environmental, cross-infection, zoonotic  
|                      |              | Immuno-suppressed state leads to delayed and muted response to infection until viral load very high  
|                      |              | Ensure all childhood and other vaccines up to date pre – Transplant  
|                      |              | Prophylaxis A/B – pre surgery, PCP, CMV, consider TB, antifungal, Hep B  
|                      |              | Seek quantitative data and root cause analysis |
| Catherine Marshall   | NT – TE Perspective | Admissions for all infections are 20x that of non-indigenous person.  
|                      |              | CMV most prevalent in ATSI population  
|                      |              | BK infection is rising  
|                      |              | Bacteraemia in dialysis patients 12%  
|                      |              | More likely to be admitted to ICU but mortality is the same as non-indigenous.  
|                      |              | Diabetic foot admissions 58% were CKD patients  
|                      |              | 15% of dialysis population was admitted for diabetic foot |
| Saliya Hewagama      | NT – CA Perspective | Impact of socio-economic determinants of health – town camps, over crowding, bore water  
|                      |              | High levels of skin and soft tissue infections in Indigenous population  
|                      |              | Strongyloides, Bronchiectasis, STI and Bacteraemia (Staph)  
|                      |              | HTLV1 higher rates, 31% of dialysis patients positive, plus evidence of association with other infections eg bronchiectasis  
|                      |              | Tx patients – CMV and BK viraemia, Cryptosporidial diarrhoea, microsporidiosis, and high fungal rate in Alice Springs patients  
|                      |              | Discussion on screening organ donors, effectiveness of current testing regimes and use of PCR vs plasma-viral loads |
| Peter Boan           | WA Perspective | Low HTLV1, HepC HIV in population but high rates of CMV, EBV and VZV  
|                      |              | Increase in invasive fungal infections (14%)  
|                      |              | Rise in BK positive (30%) Mean prevalence of BK-nephritis ~5%. – usually present 3-4 months post Tx  
|                      |              | Reducing immuno-suppression effective in 85%  
|                      |              | Screening and pre-emptive strategy better than late action – suggest monthly screening |
Infectious Diseases
(Chair Bart Currie)

Morgyn Warner Perspective

CMV usually develops in first three months post transplant
Incidence highest amongst R-/D+ and those receiving lymphocyte depletion therapy (thymoglobulin, ATG etc)
Prophylaxis vs pre-emptive positives and negatives in both, but preferable to do prophylaxis
Prophylaxis – no viral load monitoring, effective but late onset in R-/D+ and increase in leukopaenia
Pre-emptive – more CMV, requires ongoing monitoring, difficult to coordinate,
no difference in graft loss, acute rejection or mortality
Comparison of regimes used around Aust – prophylaxis vs pre-emptive, longer vs shorter duration, higher vs lower dose, oral vs IV
Require better collection of data including risk factors,

Summary of Infectious Diseases (Bart Currie)

- Infections are one of the big differentials for indigenous kidney transplant patients – each story is different for the individual, need to understand the different pathways.
- Diversity by region:
  - Central Australia – high level of HTLV1, Hep C and fungal infections
  - Top End – High rates of bacterial infections
  - WA – BK virus
  - SA – CMV disease
  - QLD – Multi Resistant Gram Negatives (MRGN)
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| 0830  | Issues and Approaches – Chair Stephen McDonald  
   - HLA mismatches and immunological differences  
   - Summary of immunosuppressant regimes  
   - WA innovations  
   - Informal question and answer | Toby Coates  
   Graeme Russ  
   Suda Swaminathan |
| 1000  | Morning Tea                                  |                                               |
| 1030  | Strategies and Outcomes – Chair Graeme Russ   
   - After the first month  
     - Support systems for patients post transplant  
     - Interaction with primary care  
   - Surgical issues  
   - Discussion | Chris Russell  
   Kevin Warr  
   Richard Baer and Bronwyn Hayes  
   William Mahoni |
| 1230  | Lunch                                        |                                               |
| 1330  | Putting the learnings in to practice – Facilitator Paul Snelling  
   - What should we do about immunosuppression  
   - What should we do about anti-infective prophylaxis  
   - Common protocol  
   - Common outcome measurement | All |
| 1530  | Afternoon Tea                                |                                               |
| 1600  | Next Steps - Facilitator Paul Snelling  
   - Determining research priorities | All |
| 1730  | Close – Alan Cass                            |                                               |
### Issues and Approaches

(Chair Stephen McDonald)

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| Toby Coates     | HLA mismatches and immuno-logical differences | - Predominantly indigenous blood types are O and A, not B  
- Innate and Adaptive immunity different in Indigenous with much higher levels of Immunoglobulin  
- Have lower rate of HLA immune related disorders  
- High rates of HTLV1 in CA which is associated with other infectious diseases  
- HLA distribution pattern very different between indigenous, non-Indigenous and donor pool  
- HLA matching is also different for Indigenous across regions  
- Eplet matching used in Europe to treat highly sensitised patients  
- Eplet matching looks at structure of HLA rather than numerical matching. Assesses component of HLA that can be accessed by antibodies to determine risk.  
- TSANZ supports review of major allocation protocols but eplet modelling will effect how people are allocated and receive transplants – there are always winners and losers  
- HLA Matchmaker is US based software and next release will include HLA profile of Indigenous Australians..  
- Joint project between SA/WA to model Indigenous SA/NT/WA patients underway (Wai Lim and Germaine Wong) |

| Suda Swaminathan | WA innovations | Improved compliance and family support  
Criteria more stringent - excluded combination of obesity and diabetes for transplant wait list  
Avoided use of steroids - use symphony protocol  
Standard review process for all Indigenous patients - important to establish strong social support  
Use belatacept and MMF for rejection and undertake biopsies at 3 and 6 months |

**Q) Why not eplet match everyone?**

Eplet matching is cutting edge – but unable to offer this potentially to the whole population. Personal view is to eplet match children and high risk groups. The drugs in the general population are doing extremely well.

**Q) Was there some form of comparison of what would happen if done with old protocol?**

Haven’t done a form of comparison however can look at number of people denied for the waiting list, only done in last 12 months. Lloyd working with Wai Lim to look at WA ATSI group to see if eplet matching can make a difference.

**Q) It is important to step back and reflect on what you have done, have you communicated the change in acceptance to those externally or a more broader audience?**

Have discussed at the general hospital meetings and several presentations at national renal meetings and also at NAIDOC week.
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| Graeme Russ | Summary of immunosuppressant regimes | - Less good HLA matching for indigenous patients
- DGF and rejection common in aboriginal patients

**Issues:**
- Do not provide adequate level of immuno-suppression. (high risk patients)
- High rates of viruses- how do we identify them, and need for prophylaxis
- Low dose TAC – 12% rejection at 12 months
- Graft survival better but no change in patient survival
- Do any agents contribute specifically to:
  - Compliance – baldness, weight increase (steroids)
  - High rates of infection
  - Poor cardiovascular outcomes
  - Rejection is more common in high immuno-suppression use, with ATG, steroids and higher risk of infection
  - Induction agent - is it needed?
- Maybe withdraw CNI at some stage, however associated with increased rejection.
- Steroid withdrawal is associated with more rejection.
- Steroid use is associated with increased risk of infections and development of diabetes

**Options:**
- Simplifying immuno-suppression regimen
- Daily vs BD
- Depot long lasting 6 months.
- Suggest increased immuno-suppression initially + prophylaxis regime
- Then withdraw and reduce immuno-suppression
- ATG rather Basiliximab
- Steroid avoidance/early withdrawal
- Possible CNI withdrawal/avoidance
- Monthly IV dose
- Compare adherence and outcomes

**Graeme’s 3 key focus points:**

**Agreement to progress**
1. Immunosuppressive protocol for indigenous patients
2. Prophylactic regimen
3. New allocation system
## Strategies and Outcomes

(Chair Graeme Russ)

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| Chris Russell    | Wound issues| ► Higher risk of death and infection with higher BMI  
                 |             | ► BMI in indigenous people different  
                 |             | ► Body structure different, skinny arms and legs and big girth, overhanging apron  
                 |             | ► Suggest using waist hip ratio as more relevant than BMI  
                 |             | ► Tight glycaemic control and apronectomy pre-emptively |
| Kevin Warr       | WA          | ► Post transplant follow up, need good communication and sharing of data  
                 |             | ► Notification of results  
                 |             | ► Underutilisation of telehealth  
                 |             | ► Interested in comparing management and outcomes or urban indigenous with non-urban indigenous |
| Richard Baer and Bronwyn Hayes | QLD | ► Post transplant management at 8 weeks  
                                 |             | ► Use other transplant patients to talk to pre-transplant patients  
                                 |             | ► Wait for patients to approach them about transplant work up  
                                 |             | ► Encourage them to do their own test and follow up  
                                 |             | ► Psychological preparedness assessments  
                                 |             | ► Text messaging all appointments  
                                 |             | ► Medication management - cater for cyclones  
                                 |             | ► Patients have been compliant with appointments  
                                 |             | ► Do a dummy run to Brisbane to familiarise with town and facility  
                                 |             | ► Post transplant have had issues with food poisoning due to cultural welcome home parties  
                                 |             | ► Greater utilisation of ACCHOs and improved education with GPs  
                                 |             | ► Current considerations: do they train blood group A patients for home HD as these are more likely to be transplanted?  
                                 |             | ► Need protocols for early treatment of rejection/infection in ACCHOS. |
| William Majoni   | NT          | ► Problems in remote clinics with high staff turnover  
                 |             | ► Social issues  
                 |             | ► Managing immunosuppression  
                 |             | ► Managing acute problems in transplant patients. |

### Risk factors:
- Diabetes
- Immunosuppression
- Obesity
- Post op haematoma

**Issue:** Young indigenous male patients who return to community, go out to initiation for a month (bush) do not receive immunosuppression.

**Q)** Difference in outcomes in TSI and Aboriginals?
Have not split it, but there is a feel that TSI seem to do better mentally and physically compared to Aboriginals, more support for TSI.

**Q)** Is there a push for transplantation of indigenous patients? There appears to be a difference in how it is approached from other areas. Don’t like idea of pushing transplantation, it is about getting them ready. They make the decision to approach staff about transplantation and undertake the work up. Then it is felt they are psychologically ready.

**Q)** Is there a need for interpreters/cultural advisors?
We offer that service when we discuss transplantation with the patient. Majority of them want an interpreter. QLD/Adelaide – interpreters are a big gap in the service, no interpreters for individual patients.
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<td>Basant Pawar Alice Springs</td>
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<td>Patients have a big expectation that transplantation will get them home.</td>
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<td>There is a struggle with providing dialysis patients accommodation. Most have to stay in a hostel with varying levels of support.</td>
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<td>Common for carers, support workers to abandon their dialysis patients.</td>
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<td>The problem we currently face is the high turnover of staff at nursing and doctor level.</td>
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<td>Use interpreters and social workers to feed information back to patients. If an interpreter is from the same family group it will be delivered in different ways. Good information will be delivered accurately, bad information will not be passed on (cultural issue).</td>
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<td>Most patients carry pre-paid mobile phones with no credit on it.</td>
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<td>Patients need to be more independent /self-sufficient if being worked up for transplantation eg being able to monitor their own blood sugars.</td>
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1) Infectious Screening and Prophylaxis

- Discussion on Hep B and treatment protocols – no clear outcomes
- PCP management - Bart Currie recommends that dose is not reduced even for those intolerant, should undertake de-sensitisation and/or treat symptoms. PCP can reactivate with inadequate compliance.
- Low dose can be effective but not for skin and soft tissue infection, melioid, lung and urine. Is a higher dose more effective at keeping these infections at bay?
- Screening of TB and use of isoniazid – TB in transplant population not an issue in NT
- Discussion regarding quantiferon vs two stage mantoux for screening, reactivation is late, often many years
- Microspirodia very rare
- Cryptospirodia – environmental conditions - housing situation, small bowel biopsy for detection not practical as a screening mechanism

Screening

| Transplant wait list should have mandatory screening for EBV and CMV, HTLV1, Hep B and C – chronic sepsis, osteomyelitis |
| Think about CT scans for thorough lung assessment – TB, bronchiectasis |
| Up to date immunisation before transplant |
| Cryptococcus and melioid testing |
| Prophylaxis vs pre-emptive strategy for CMV management |
| Should prophylaxis be matched to immuno-suppression? |
| Discussion on shorter or longer prophylaxis regimes |
| Should it be adjusted related to when they go home? |
| Recommend prophylaxis for minimum 6 months but danger in keeping people longer than 6 months due to severe neutropaenia. |
| Evidence that CMVreactivates relating to reduction in prophylaxis. |
| If CMVreactivates leads to other infections. |
| Surveillance testing - query monthly |
| Viral load monitoring |
| Use of prophylaxis for 1 -3 months post treatment for ATG rejection |

- Fungal infections: need systematic data collection
- Need to understand impact of environmental issues.
- Need better understanding of potential prophylaxis regimes – query fluconazole
- most drugs are IV, only couple are oral, problems with absorption.
- Screening 3 months for Cryptococcus and antigens
- Repeat when immuno-suppression heavy
- Focus on good management of diabetes
- Head CT scan for virulen pools, ear and sinus.
- How to test for other fungal infections? Some test require interstate assessment.
- Need to review patients that got fungal infections, look at causes, environment, infective agents and immuno-suppression regimes.

Risk Factors:
- Neutropaenia
- Iron Overload
- Exposure to dirt
- Poor Management of diabetes

Agreement
- Ongoing Bactrim for 6 months

Outcome:
- Suggested development of protocols based on collection of base line data + prospective qualitative data that relates to testing regimes and treatment strategies/establish national database.
Learnings into Practice
(Facilitator Paul Snelling)

2) Immuno-suppression

- Perhaps increase suppression in first 3 months with prophylaxis antibiotics
- then reduce suppression with steroid withdrawal
- Belatacept instead of steroids and CNI
- Discussion for and against for long active immunosuppressives
- Maybe useful if greater support and supervision is available for patients.

Proposals:

- Steroid avoidance not supported
- Several want more experienced review of patients and more frequently
- Support for standardised protocol for indigenous patients, not sure how it would look.

3) Non immunological factors

- Great need for interpreter services
- Education materials – format/medium needs to be appropriate for each region
- Cultural issues vary across regions – need to connect with their value systems
- More frequent contact with patient in own environment
- Outreach transplant clinics
- Consumer groups
- Education for health clinics – high staff turnover in all communities across country
- Protocols for registrar such as weaning prednisolone and prophylaxis regimes need to be more accessible.

Determining research and service priorities (Facilitator Paul Snelling)

- Discussion regarding what is already sent to ANZDATA and possible linkages with clinical systems such as pathology labs, hospital admissions
- Small number of indigenous people who have had a transplant - may be easier to do a control case review of graft failures to determine issues
- BC recommends prospective data collection, reviewing patient history including qualitative data. Needs patient consent
- Suggest project officer to collect data, review records and determine parameters of prospective data collection
- Eplet modelling can happen and will happen with changes to software with additional HLAs being added for indigenous patients
- Germaine Wong from SA and Lloyd D’ Orsogna and Wai Lim from WA working on modelling indigenous transplant waitlist cohort.
- Pharmakinetics/pharmagenetics possible field of research. is there a reason why indigenous patients do so badly? Possibility of developing a research proposal around this.
- Models of care and support identifying patients requirements. Qualitative study information will come from IMPAKT study, which is to be written up.