Safety and Biovigilance in Organ Donation (SAFEBOD) in NSW, Australia

TECHNICAL REPORT

Centre for Organ Donation Evidence

Acknowledgements and Disclaimers

The analysis presented in this report was undertaken by the SAFEBOD team. The interpretation is theirs alone.

Corresponding author:
Professor Angela Webster

Professor of Clinical Epidemiology

The University of Sydney

Room 129A, Edward Ford Building (A27)

Camperdown NSW 2006 Australia

Phone:

Email: angela.webster@sydney.edu.au

The research was undertaken, and the Report written by (in alphabetical order): Nicole L De La Mata, James A Hedley, Patrick J Kelly, Brenda M Rosales, Imogen Thomson, Karen Waller, Angela C Webster and Kate Wyburn.
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1.0 Introduction

Health burden: End-Stage Kidney Disease (ESKD) treatment is highly costly; 30,000 Australian adults will require treatment by 2020, costing over $1.8 billion annually [1]. Kidney transplantation brings improvements in survival and quality of life and is more cost effective than any alternative dialysis treatment [2].

Acting to maximise transplantation opportunity: The Australian Government formed the Organ and Tissue Authority (OTA) in 2009, to increase capability and capacity to maximise donation rates, and to promote organ and tissue donation. Since then the number of deceased organ donors has more than doubled and the number of transplant recipients has increased by 75%, but Australia still lags internationally with 20.8 donors per million population (dpmp) (Spain 47; USA 32; UK 23 dpmp) [3]. Improvements in donation rates in Australia have not occurred evenly. Although NSW has the greatest number of donors each year, when standardised for population size, it lags other jurisdictions (**Figure 1**) [4].

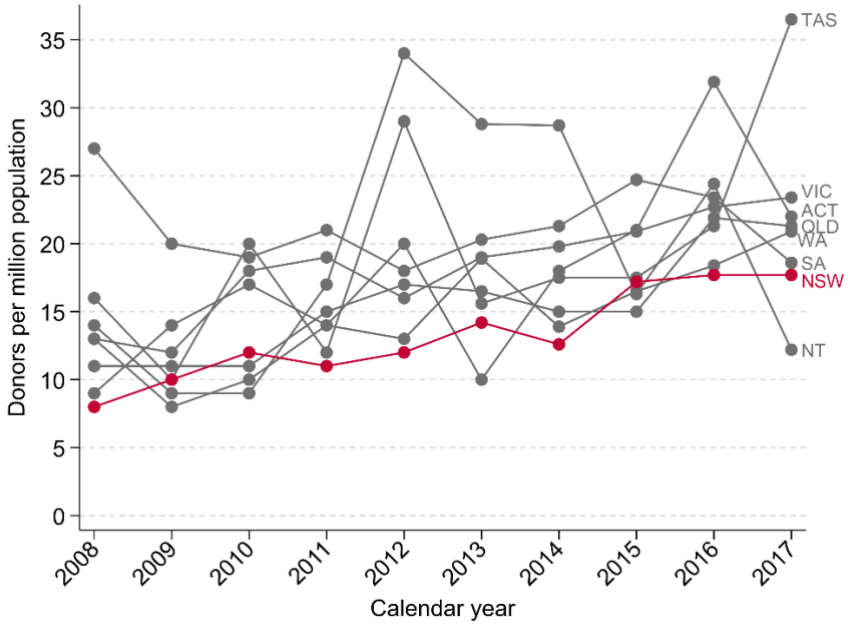


Figure 1. Kidney donor activity by state over time (donors per million population).

The organ donor referral pathway in NSW: As well as greater absolute numbers of donors and of people waiting for a kidney transplant, NSW has more complex service delivery compared to other jurisdictions. Where Queensland, South Australia and Western Australia each have one centre performing kidney transplant operations for the state, and one organ retrieval team, NSW has six centres performing kidney transplants in adults and two organ retrieval teams. Waiting lists are dynamic and change daily, as people are transplanted, become unwell and so are temporarily or permanently removed from the waiting list, die waiting, or are added anew. **Table 1** shows a snapshot of transplant activity in 2018.

Kidney transplant centre (adults)	Under assessment	Active waiting list	2017 transplants
Royal Prince Alfred	167	151	121
Westmead	150	159	106
Prince of Wales	86	61	43
Royal North Shore	120	47	32
John Hunter	48	40	31
St Vincent's	12	8	12
Total	*583*	*466*	*345*

Table 1. Snapshot of adult kidney transplant waiting list patients who hope to undergo transplantation in NSW (November 2018), and 2017 kidney transplant activity, by transplanting centre. Note: waiting list is dynamic, changing daily.

Despite large increases in donor referrals to the organ donation service in NSW, there has not been a proportional increase in actual donation. Any further donor gain will require tackling challenging core issues.

Biovigilance as a barrier to kidney transplantation: Inadvertent transmission of infectious diseases or cancer with donor organs is a central concern in transplant programs (biovigilance). In tension with biovigilance is that people wait-listed have substantially reduced quality of life (QoL) may die waiting [5]. Donation decisions for cadaveric organs are time-sensitive and occur unpredictably, mostly outside regular working hours. Making evidence-based decisions under time pressure needs accurate estimates of biovigilance risk. However, current estimates of infection and cancer transmission from donor organs are based on low quality evidence and have mostly not been verified [6, 7]. Current donor policy is risk averse and informed by very sparse data [7]. Biovigilance transmission estimates are likely to be biased due to different approaches to data collection and monitoring by transplant services around the world, and because of inherent protection of anonymity within organ allocation systems and the complexities of tracing subsequent events in multiple recipients back to donor past events [8-11]. Publication bias is also a big concern [12]. It is likely that more events of disease transmission are published, than events where disease was not transmitted from donor to recipient.

Current risk estimation: Donor medical suitability assessment is based on perception of the biovigilance risk a donor poses. Often medical history is gleaned by proxy (family members or friends), with variable access to past medical records. Currently there are limited possibilities to within the donor assessment time frame, for donor coordinators to confirm perceived risk. Thus the "truth" is often speculated when decision-making happens, and clinicians make recommendations and decisions cognisant of these uncertainties. Biovigilance decision points are shown in **Figure 2**.

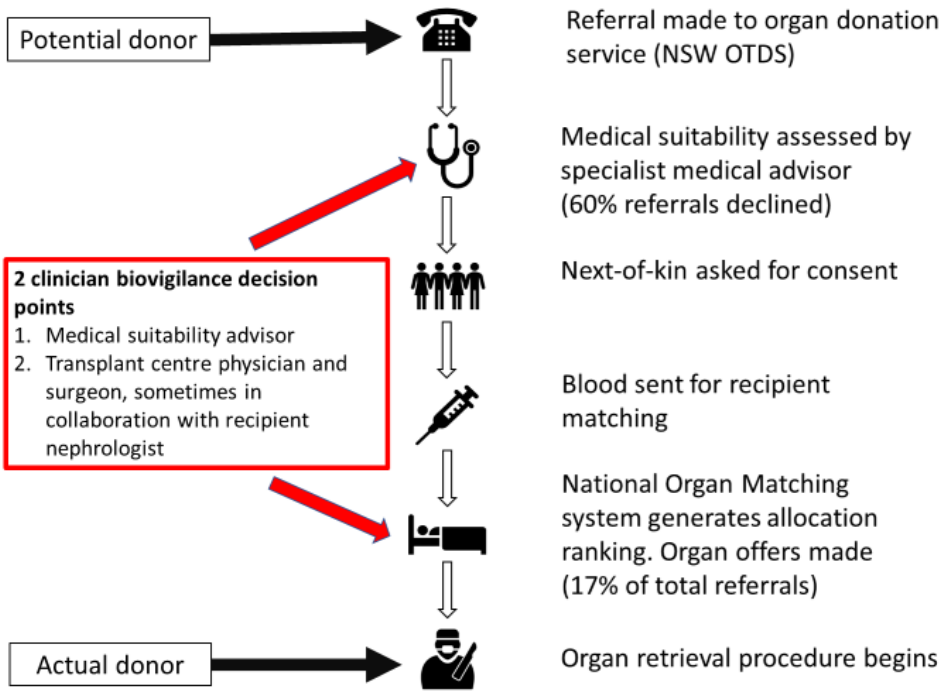


Figure 2. Organ donor referral process in NSW, showing biovigilance decision points.

Making better use of existing data to generate evidence for decision making: Nationally and by state, data is only aggregated for referrals who do go on to donate [4], but not for those referrals that are declined**.** However, understanding more about donors who are declined may give systems insights into ways and means to increase the proportion of referrals that go on to become donors. This may occur from accessing more information about the referrals medical history, verification of details that are uncertain, or decision support about the absolute risks to any recipient, should the referral proceed to donation.

As the first step**,** the CODE team has worked since 2015 to build the Organ Referral Characterisation Database (ORCHARD) characterising all organ donor referrals in NSW since 2010.

As the second step, with the aim of increasing the amount and quality of unbiased evidence on biovigilance risk, the CODE team has worked with the Ministry of Health to use the NSW Public Health Act 2010 to link together key NSW datasets, with the twofold aim of verifying the risk history of donor referrals and estimating transmission and non-transmission event rates of cancers and infections from donors to recipients. The initial linkage has been completed, and repeat linkage is anticipated in 2020.

The purpose of this report is to outline the insights into organ donor procurement that have be gained through the ORCHARD and SAFEBOD studies.

2.0 Organ Donor risk profile in NSW and the ACT over time (the ORCHARD study)

The Organ donor Characterizing risk profile of Donors (ORCHARD) study was established in collaboration with the NSW Organ and Tissue Donation Service (OTDS) in 2010 to describe trends in organ donor referrals. This study is a retrospective clinical audit of all patients referred to the OTDS for deceased organ donation in NSW. Importantly, findings from several projects within ORCHARD highlighted the limitation of referral log information and the potential for linked datasets to address these limitations.

Study methods and findings are described below.

2.1. Process of aggregating data

The organ referral process in NSW includes assessment of medical suitability by hospital intensivists, transplant clinicians and OTDS staff and, attainment of family consent (**Figure 3).** Family consent is often sought by dedicated donation specialists resident in the referring hospital, however this conversation can be led by other clinical staff.

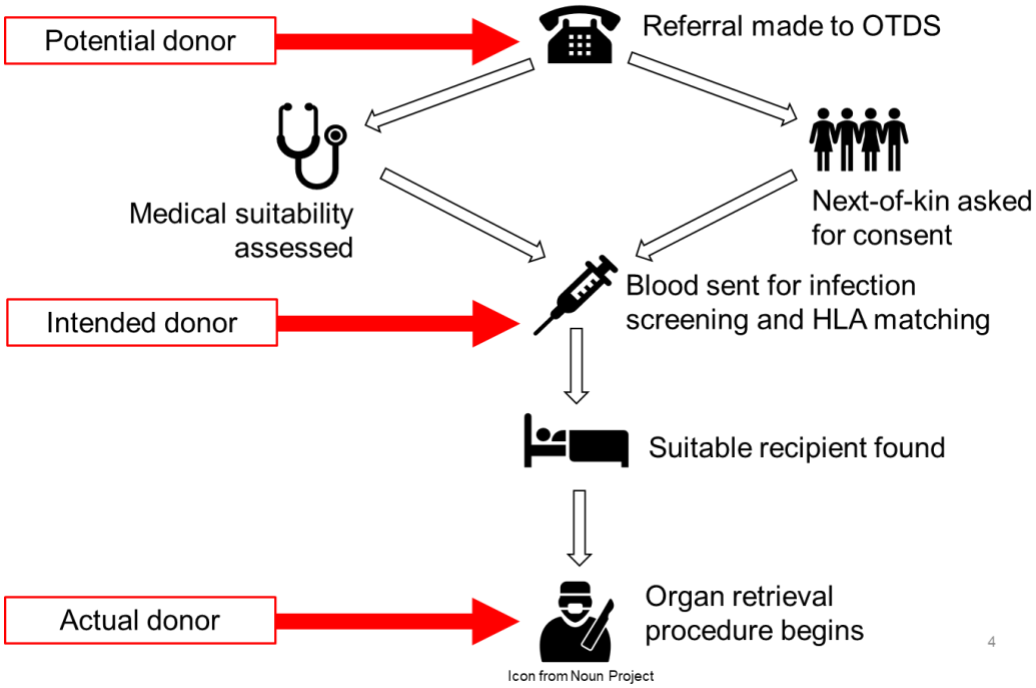


Figure 3. Organ referral process in NSW.

We used routinely collected administrative data in the form of referral logs acquired and stored by the NSW OTDS, 2000-2018. This electronic dataset collects demographic, clinical and social information discovered during the organ donor referral process. This data-collection is unique to NSW for this time-period. Prior to 2014, complete records were only stored for actual donors (referrals that proceeded to donation). Where possible, electronic records were confirmed by the original paper trail recorded by donor coordinating nurses. By using ORCHARD study data, we have a better understanding of the information available for

potential (donors that did not proceed to donation), intended (donors that were medically suitable and consented but did not proceed to donation) and actual donors at the time of referral.

2.2. Findings from ORCHARD

Understanding the referral volume needed to produce organ donors

Recent efforts to increase donation rates have successfully led to a greater number of deceased organ donors in NSW (**Figure 4**). However, these measures have also resulted in an increase in potential donors referred to the NSW OTDS for consideration for donation, with a growing proportion of these never proceeding to donation. While this reflects positively on initiatives to increase donation rates, it also poses challenges in terms of effectively evaluating multiple referrals concurrently. Additionally, referrals are not evenly distributed over time, with between 0 and 8 referrals received per day, up to a peak of 25 in a single week in 2015. As a result, a greater volume of referrals is increasingly being required to lead to organ donation.

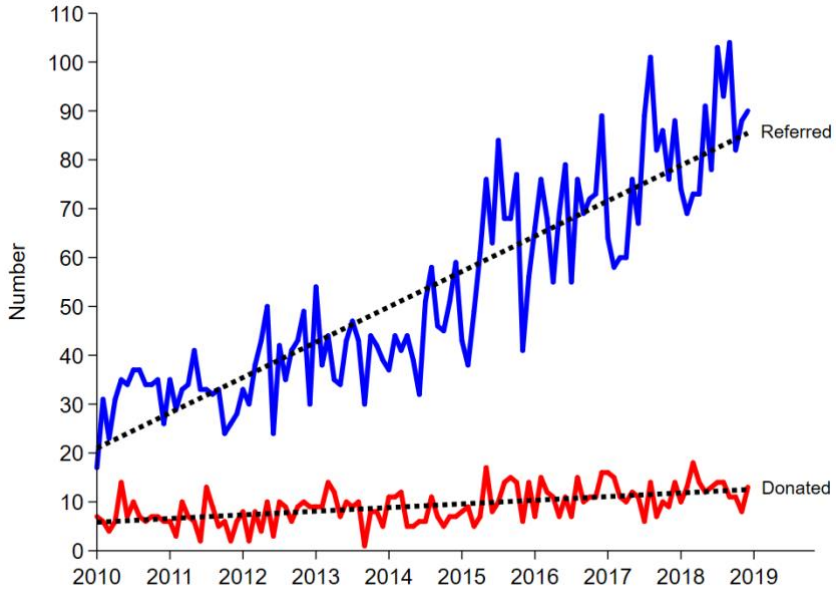


Figure 4. Number of organ donor referrals which proceeded (donors) and did not proceed (non-donors) in NSW, 2010-2018.

Insights into characteristics of organ donor referrals

- Religion and ethnicity

In order to understand the characteristics that differentiate referrals whose families consent to organ donation and those that refuse, we compared the demographic and socioeconomic characteristics of referred donors. Characteristics included donor age, sex, religion, socioeconomic background, ethnicity, reason for family refusal and referring hospital. Religion and ethnicity were not routinely reported for all referrals until 2014, and reporting has continued to improve over time. Therefore, a large proportion of referrals are missing

information about religion (53%) and ethnicity (33%). Nevertheless, the distribution of religion and ethnicity for referrals from 2014-2016 by their referral outcome are presented in **Figure 5**.

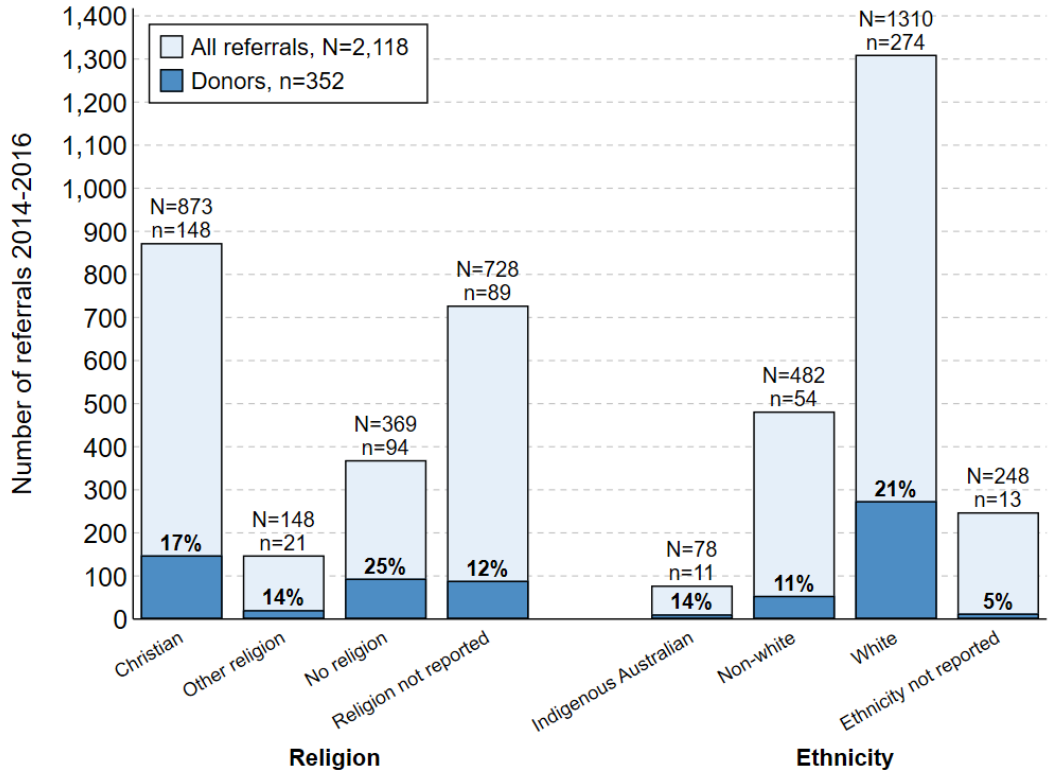


Figure 5. Distribution of religion and ethnicity in NSW organ donor referrals, 2010-2016.

Referrals were most commonly white and Christian. We found there was evidence that religion and ethnicity independently associated with likelihood of referrals proceeding to donation, and strongly associated with family consent. However, a large proportion of information was missing (55% religion and 39% ethnicity) and it is difficult to make claims or recommendations based on this evidence.

- Comorbidity burden

Referrals with a greater comorbidity burden are increasingly being referred for organ donation. The average age of both referrals and donors increased significantly from 2010-2015, from 58.9 to 62.0 years for non-donors and 47.0 to 52.2 years for donors. With the exceptions of cerebrovascular disease and hyperlipidaemia, the prevalence of all comorbidities was greater among non-donors than donors, and this prevalence increased from 2010-2015 for almost all comorbidities.

Our analyses evaluated the impact of the presence of comorbidities on likelihood of organ donation **(Table 2).** Of individual comorbidities, malignancy, and chronic kidney disease (CKD) had the greatest impact on outcome, with the presence these conferring odds ratios of a referral not proceeding to donation of 3.91 and 3.45, respectively. Similarly, age >65 strongly predicted non-donation, with an odds ratio of 3.23. From our multivariate regression analysis, we derived predicted probabilities of donation given the presence of absence of

combinations of referral comorbidities. The likelihood of donation varied widely depending on the comorbidities present, from <1% to 54%.

			Malignancy +				Malignancy -			
			Age ≥65		Age <65		Age ≥65		Age <65	
			CLD +	CLD -	CLD +	CLD -	CLD +	CLD -	CLD +	CLD -
CKD +	Cardiac disease +	CVD -	<1	1	1	3	2	3	3	12
		CVD+	<1	2	2	4	2	7	7	15
	Cardiac disease -	CVD -	<1	2	2	5	3	5	6	18
		CVD+	<1	2	3	8	4	11	10	34
CKD -	Cardiac disease +	CVD -	2	3	3	9	5	12	10	29
		CVD+	2	6	4	15	5	18	18	40
	Cardiac disease -	CVD -	2	6	10	18	10	21	20	43
		CVD+	4	9	9	23	13	28	28	54

Table 2. Predicted probability (%) of a referral proceeding to donation given the presence or absence of comorbidities. CKD, chronic kidney disease. CLD, chronic liver disease. CVD, cerebrovascular disease.

These findings indicate that referral comorbidities impact likelihood of organ donation in a predictable and quantifiable way. This information could be used to prioritise referrals in times of referral pressure, particularly as organ donor referrals continue to increase.

- Bloodborne viruses

Solid organ transplantation carries a risk of disease transmission, including that of blood borne viruses (BBV). Among actual donors, rates of BBV are low – in 2017, 2.4% were hepatitis C exposed, 5.6% were hepatitis B exposed, and 0.2% had active hepatitis B [13]. We identified referrals with recorded BBV history, positive serology, or risk behaviours for BBV acquisition. In total, 11.6% of all referrals were at increased risk of infection transmission. These referrals were younger than other referrals by on average 10 years and tended to have fewer comorbidities.

Infection risk is determined at time of referral by history, examination and blood tests, assessing for active infection, or recent risk behaviours leading to risk of window period infection. Among all referrals with increased infection risk, there was a spectrum of risk (**Figure 6**). Many referrals were not tested for blood borne viruses at the time of transplantation, hence had uncertain risk pertaining to infection.

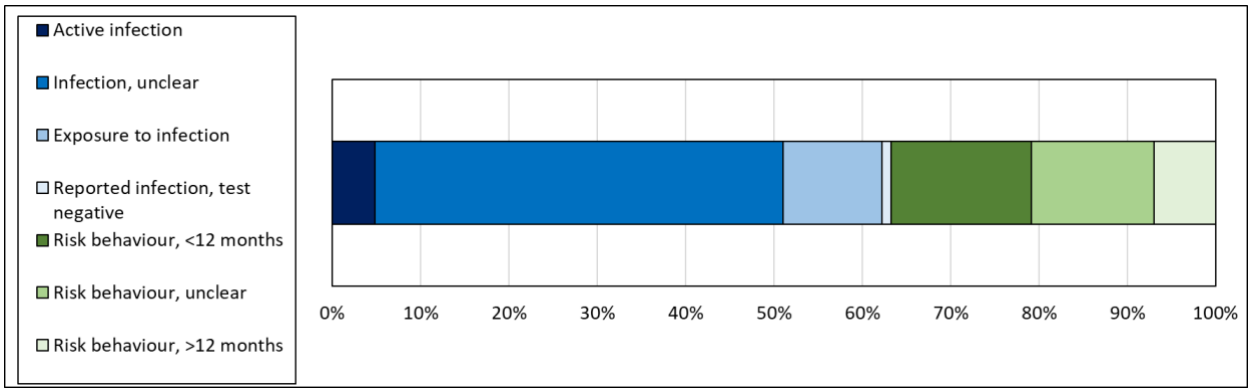


Figure 6. Infection risk profile of referrals deemed to have increased viral infection risk.

On multivariate analysis a history of hepatitis C or injecting drug use within 12 months significantly decreased the likelihood of donating. In total, 85 referrals over 6 years did not donate due to their perceived BBV transmission risk. With new curative treatment for hepatitis C, a large proportion of the 85 excluded referrals may be able to donate, but it is difficult to quantify the missed opportunities without virus test results.

- Cancers

We were able to determine the perceived presence of cancer at referral in 2,957 organ donor referrals from 2010-2015. Brain cancers were the most common, present in 77 referrals (3%). Other common cancer sites included: 44 (1%) colorectal, 42 (1%) breast, 34 (1%) leukaemia, 33 (1%) lung, 33 (1%) prostate, and 30 (1%) skin (melanoma). The prevalence of perceived cancers in referrals are presented in **Figure 7**.

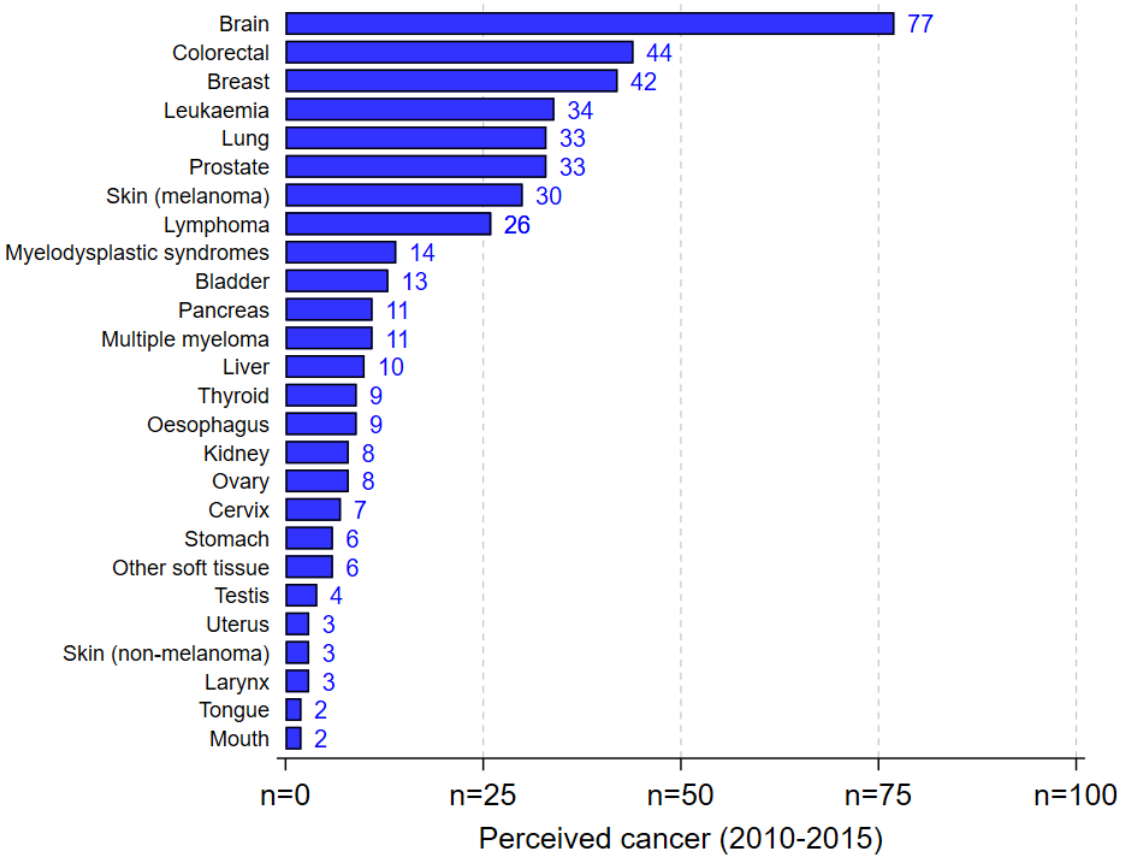


Figure 7. Cancer diagnosis prior to referral in organ donor referrals, 2010-2015.

3.0 Safety and biovigilance in organ donation (the SAFEBOD study)

The SAFEBOD study is an extensive data linkage project that was conceived to address the limitations of the ORCHARD dataset and explore transmission and non-transmission events between organ donors and transplant recipients. SAFEBOD is a Public Health Register. The data linkage process and study cohorts established from SAFEBOD are outlined below.

3.1. Data linkage process

Data included for linkage were NSW health outcome datasets (HIV and AIDS Notifications and Surveillance Data; Notifiable Conditions Information Management System, NCIMS; NSW Admitted Patient Data Collection, APDC; NSW Emergency Department Data Collection, EDDC; NSW Central Cancer Registry; and NSW Registry of Births, Deaths and Marriages), recipient registers (Australian and New Zealand Dialysis and Transplant Register, ANZDATA; Australian and New Zealand Cardiothoracic Register, ANZCOTR; Australian and New Zealand Islet and Pancreas Register, ANZIPTR; Australian and New Zealand Liver Transplant Register, ANZLTR), and organ donor registers and datasets (ORCHARD; National Organ Matching System dataset, NOMS; Australian and New Zealand Organ Donor Register, ANZOD; Australian and New Zealand Living Donor Kidney Register).

Probabilistic data linkage was undertaken by The Centre for Health Record Linkage (CHeReL) to link all organ donors to transplant recipients, and these both to NSW health outcome datasets, using best-practice privacy-preserving protocols (**Figure 8**). Matching was based on personal identifiers including full name, sex, date of birth and date of death. Only de-identified data was made available to researchers after data linkage was complete.

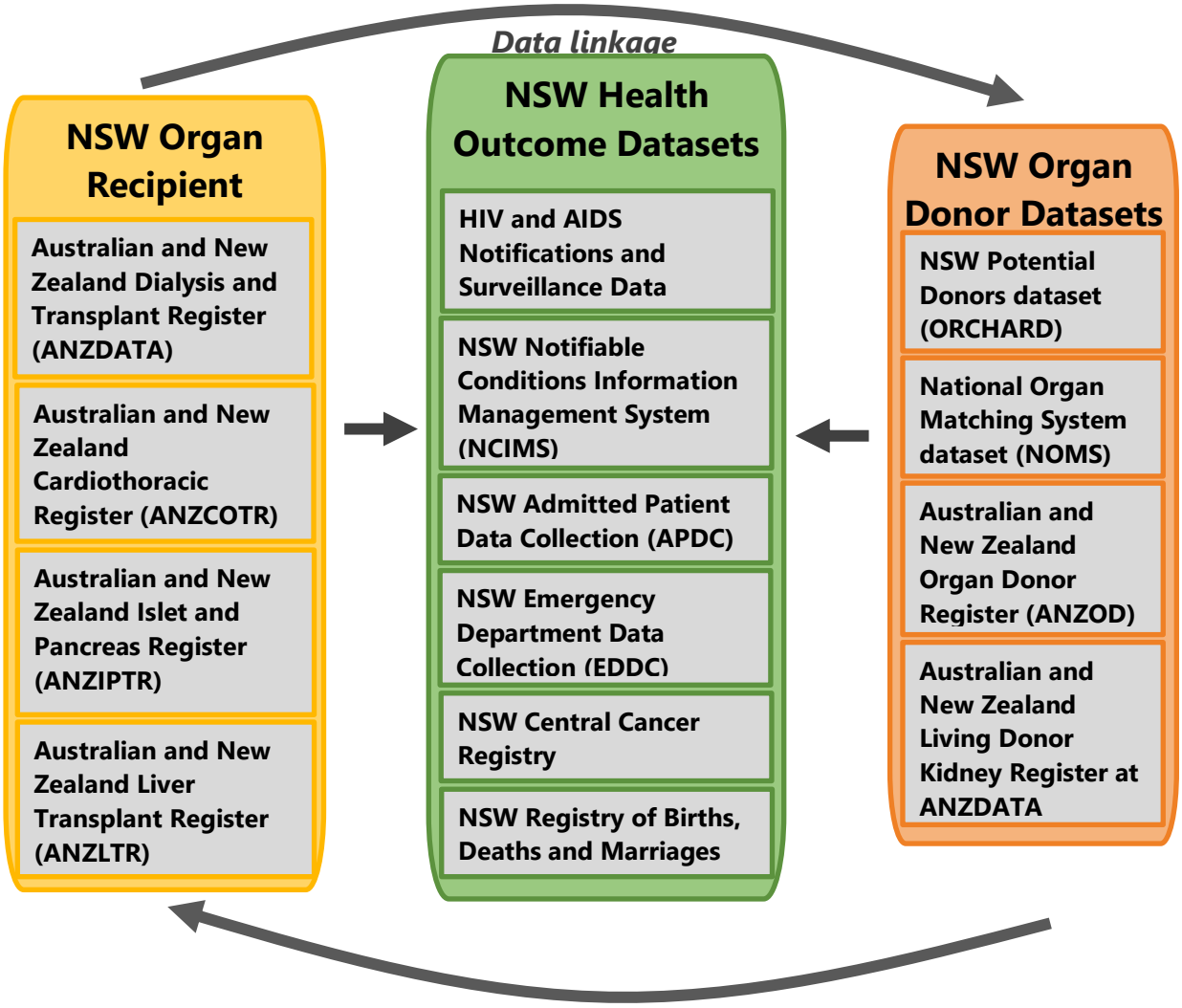


Figure 8. SAFEBOD data sources and data linkage process between NSW organ recipient datasets, organ donor datasets and health outcome datasets.

The calendar year that data collection began varied among the numerous datasets included in SAFEBOD (**Figure 9**). The most recent data we have available is up to 2017. Analyses on organ donor referrals were limited from 2010 onwards, as the ORCHARD study collating the organ donor referral log was established in this year. While analyses on transmission and non-transmission events were limited from 2000 onwards, where most NSW health datasets and transplant recipient registers had available data.

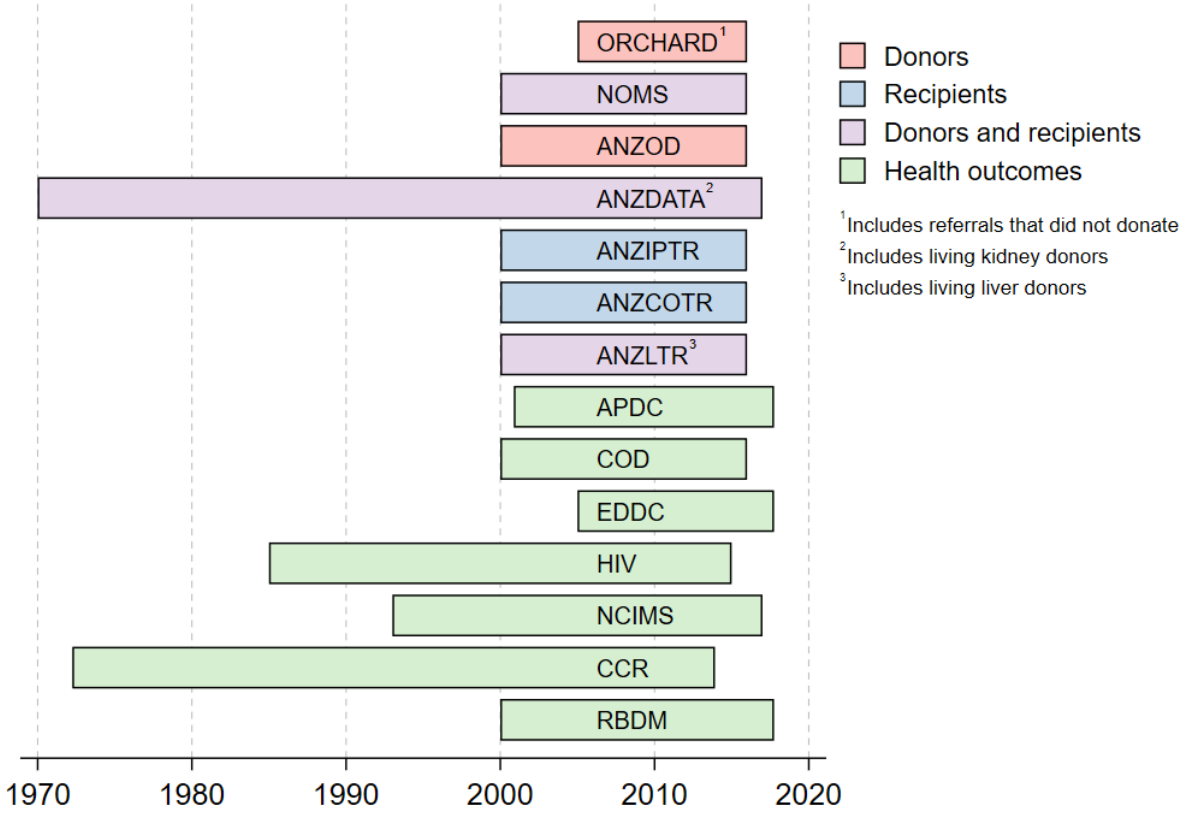


Figure 9. Data sources included in the SAFEBOD study, with date range of data requested.

Determining state of residence

In order to establish the missed opportunities and biovigilance cohorts, we defined people as NSW residents based on their postcode. Where postcode was not available, we used other information including their reported state of residence, and the state of their referring or treating hospitals. We categorised each person's residence as either NSW, NSW border, or interstate.

We included postcodes as NSW border if they 1) covered area on both sides of a NSW border; or 2) were in NSW and adjacent to a NSW border. Two examples of this are presented in **Figure 10**.

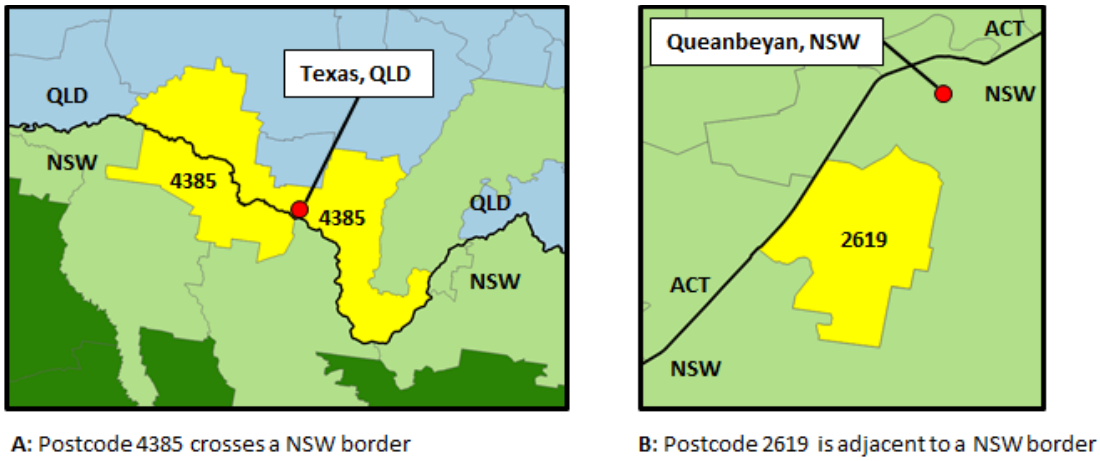


Figure 10. Example of postcodes classified as New South Wales border.

Due to its small size and proximity to NSW, we classified all postcodes within the ACT (including Jervis Bay Territory) as NSW border. Additionally, we identified four hospitals near a NSW border; Albury hospital, Queanbeyan hospital, John Flynn hospital, and The Tweed hospital. Where postcode was not reported and state of residence was based on referring or treating hospital, these hospitals were classified as NSW border. A map of postcode classifications and hospitals near a NSW border is shown in **Figure 11**. To ensure our study cohorts included as many people as possible, we included all people whose state of residence was classified as either NSW or NSW border. We conducted further sensitivity analyses to examine whether people on the NSW border had differing results.

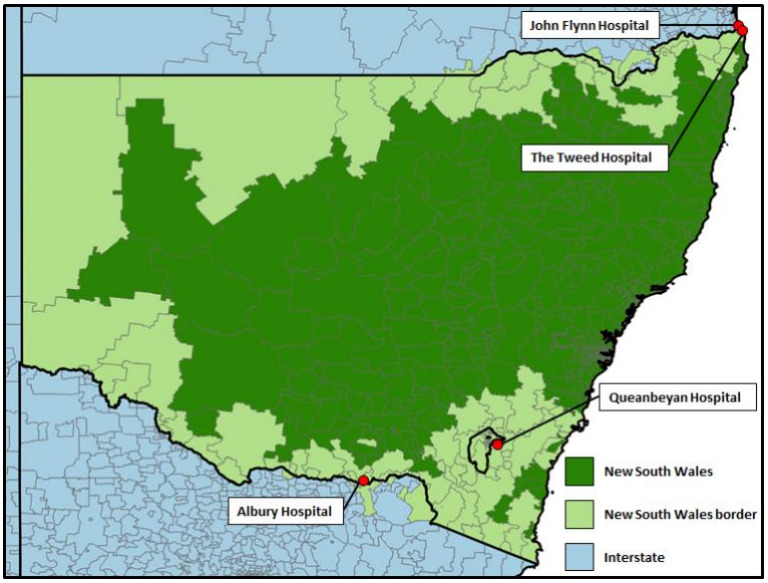
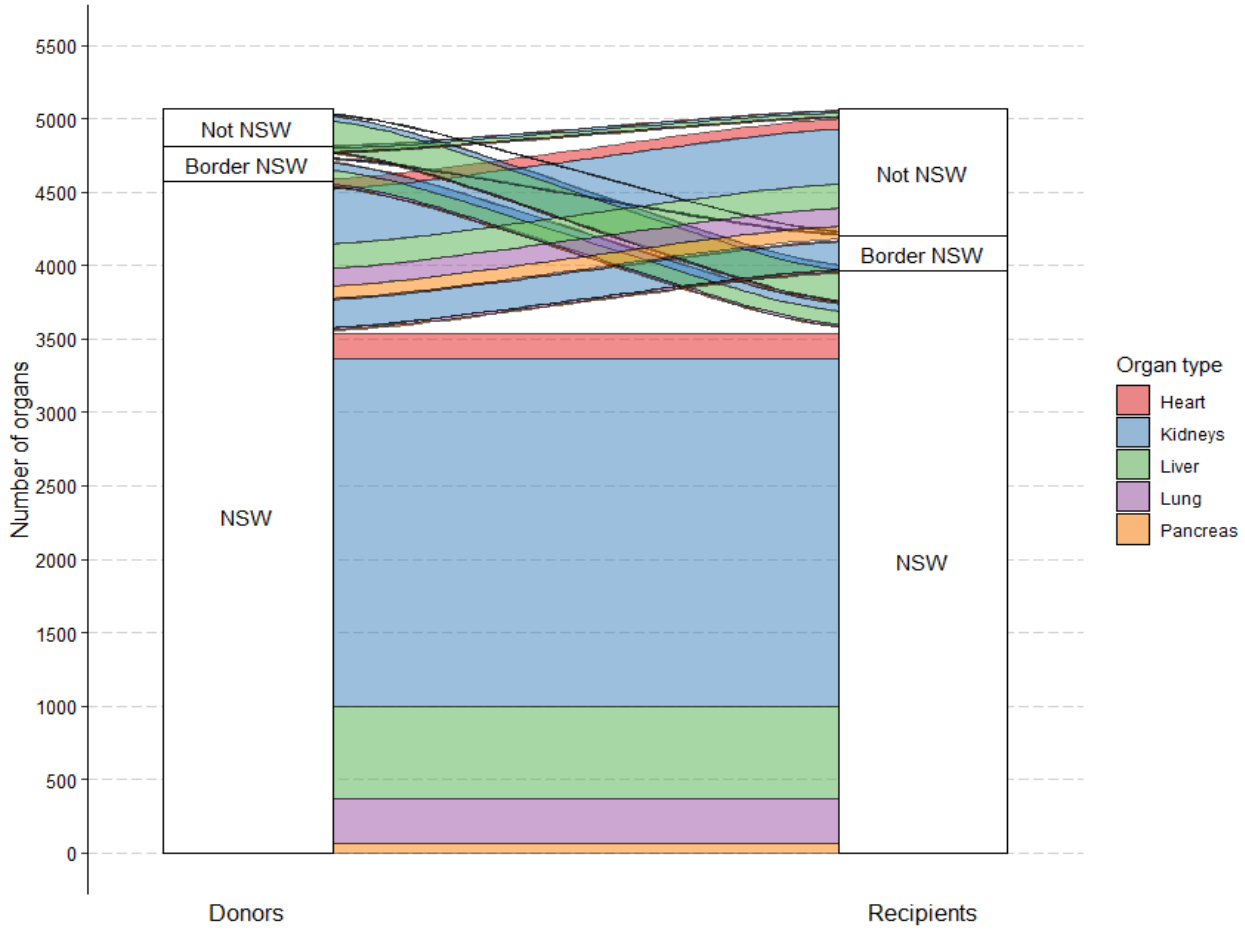


Figure 11. Map of postcode classification and hospitals near a New South Wales border.

3.2. Profile of recipients & donors

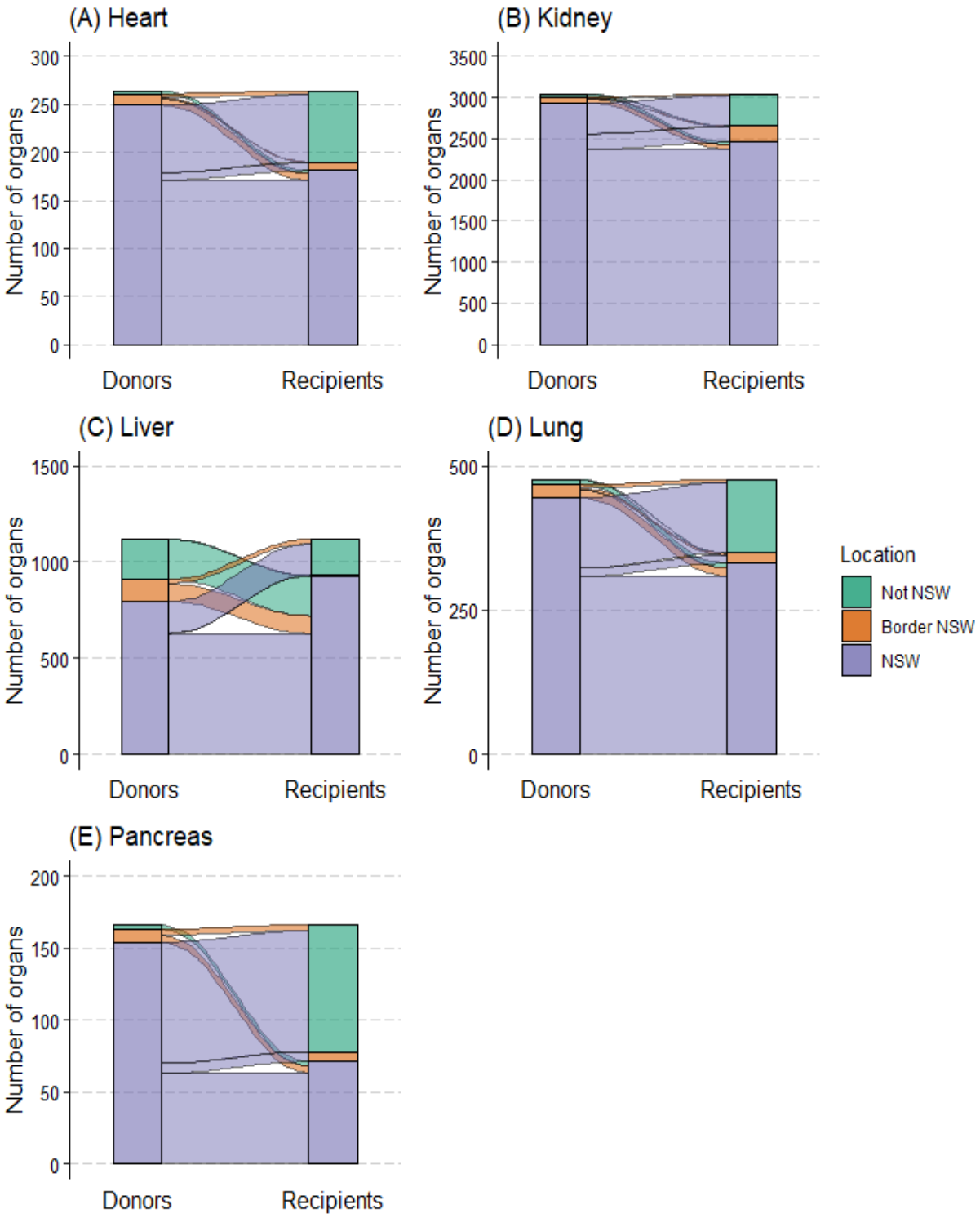
The SAFEBOD cohort included a total of 4,118 recipients with 2,484 donors from 2000-2015, and an additional 2,961 donor referrals from 2010-2015. Overall, 4,576 organs and 232 organs were donated from NSW donors and border NSW donors **(Figure 12**). An additional 260 organs were donated to NSW or border NSW recipients from non-NSW donors. Approximately 18% of organs from NSW and border NSW donors were given to non-NSW recipients. Conversely, 6% of NSW and border NSW recipients received organs from non-NSW donors.



Note: This figure excludes organs from not NSW donors to not NSW recipients, occurring when at least one organ from a not NSW donor has been given to a NSW or border NSW recipient. This is not representative of the movement of interstate organs.

Figure 12. Movement of organs between donor location and recipient location, by organ type.

However, the movement of organs does differ by organ type **(Figure 13)**. A greater proportion pancreas from NSW donors were given to non-NSW recipients and, to a lesser extent, for hearts and lungs. While a greater proportion of livers received by NSW recipients were from non-NSW donors.



Note: This figure excludes organs from not NSW donors to not NSW recipients, occurring when at least one organ from a not NSW donor has been given to a NSW or border NSW recipient. This is not representative of the movement of interstate organs.

Figure 13. Movement of organs between donor location and recipient location for: (A) Heart; (B) Kidney; (C) Liver; (D) Lung, and; (E) Pancreas.

3.3. Establishing the study cohorts

We established two study cohorts to address the SAFEBOD objectives: 1) the potential missed opportunities cohort; and, 2) the biovigilance cohort.

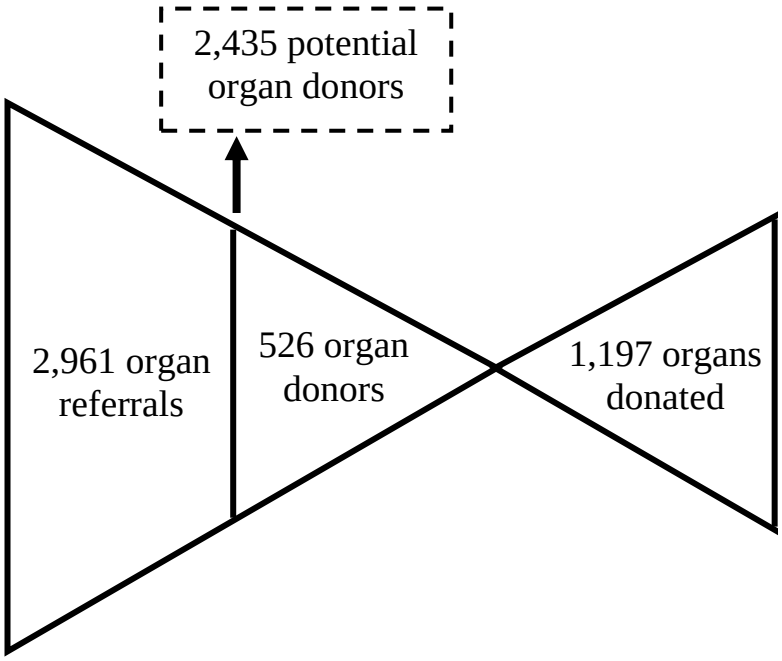
Potential missed opportunities cohort

We wished to critically examine potential donors foregone and re-evaluate their suitability to donate with enhanced information from the SAFEBOD data. The missed opportunities cohort was used to evaluate all NSW organ donor referrals, 2010-2015, by comparing medical information known at the time of referral with previous medical records retrieved through data linkage with NSW health datasets. During this period, there were a total of 2,961 organ donor referrals of which 505 proceeded to actual donation (**Figure 14A**). There were 104 referrals from persons residing on the NSW border, where 21 persons donated 49 organs. SAFEBOD data can show where or how medical information collected at the time of referral was incomplete or misleading.

Biovigilance cohort

The biovigilance cohort is used to identify all transmission and non-transmission events that have occurred between NSW organ donors and NSW transplant recipients in 2000-2015, using medical records pre- and post-transplant captured through data linkage with NSW health datasets. The likeliness of transmission from donor to recipient will be determined using the current published algorithm [11, 14] and considering the time frame between transplant and recipient diagnosis of new condition. During this period, there were 2,194 organ donors who donated organs to 3,765 transplant recipients (**Figure 14B**). Of which, 103 organ donors and 219 transplant recipients resided on the NSW border. Transmission events occur if a recipient contracts a medical condition from the organ donor after transplantation. Non-transmission events occur if the recipient does not contract a medical condition from the organ donor after transplantation, despite being present in the organ donor.

A) Missed opportunities cohort, 2010-2015



B) Biovigilance cohort, 2000-2015

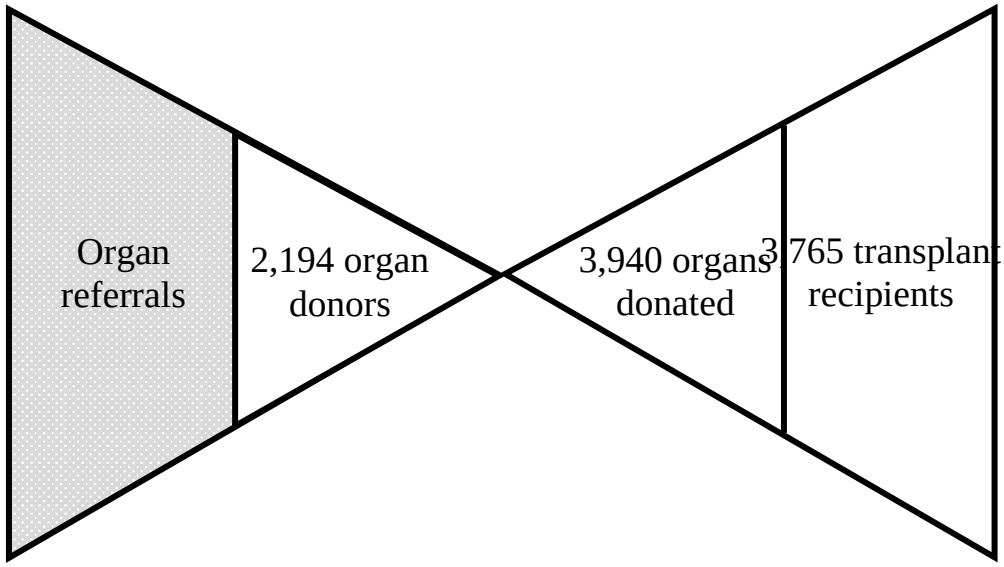


Figure 14. Flowchart of the two SAFEBOD study cohorts: A) Missed opportunities cohort, 2010-2015, including all NSW organ donor referrals; and B) Biovigilance cohort, 2000-2015, including all NSW organ donors and NSW transplant recipients.

4.0 System insights – Where are the missed opportunities?

The SAFEBOD study used NSW health datasets to provide richer data on all NSW organ donor referrals in 2010-2015. Using this data, we were able to evaluate how other factors, such as culture and language, or high-risk behaviour, impacted on the assessment of organ donor referrals, and compare whether the perceived risk determined at referral was consistent with the verified risk from NSW health outcome data captured in SAFEBOD.

4.1. Culturally and linguistically diverse organ donor referrals

The SAFE-BOD study allowed us to understand the impact of diversity on the referral process through the additional linked data. Data on ethnicity (39% missing) and religion (53% missing) were not provided, however preferred language and country of birth were reported in the Admitted Patient Data Collection (APDC) and Emergency Department Data Collection (EDDC). Among 2,650 potential donors from 2010-2015, primary language was only missing for 239 (9%), and country of birth was only missing for 171 (6%). We analysed the impact of primary language other than English and birthplace outside Australia on referral medical suitability for donation, families being asked for consent to donation, and families providing consent to donation.

There was no significant in the proportions of referrals whose dominant language was not English, or whose birthplace was overseas whose families were asked for consent to donation, compared to other referrals (Figure 15). There was a strong reduction in rates of consent to donation being given by families of those born overseas, or whose primary language was not English, compared to other referrals (Figure 15). There was no difference in medical suitability for referrals whose language was not English compared to dominant English language referrals, or referrals who were born overseas compared to Australian-born referrals (**Figure 15**). Similar results were also shown in organ donors who resided on the NSW border.

Australia is a diverse country, and approximately 30% of the population are born overseas, hence differences in consent in these populations have a large impact. To increase donation rates, we must continue a focus on culturally and linguistically diverse communities, and training support for clinicians in approaching these families. Hopefully, repeated analysis over time would show a diminishing difference between these populations if interventions are effective.

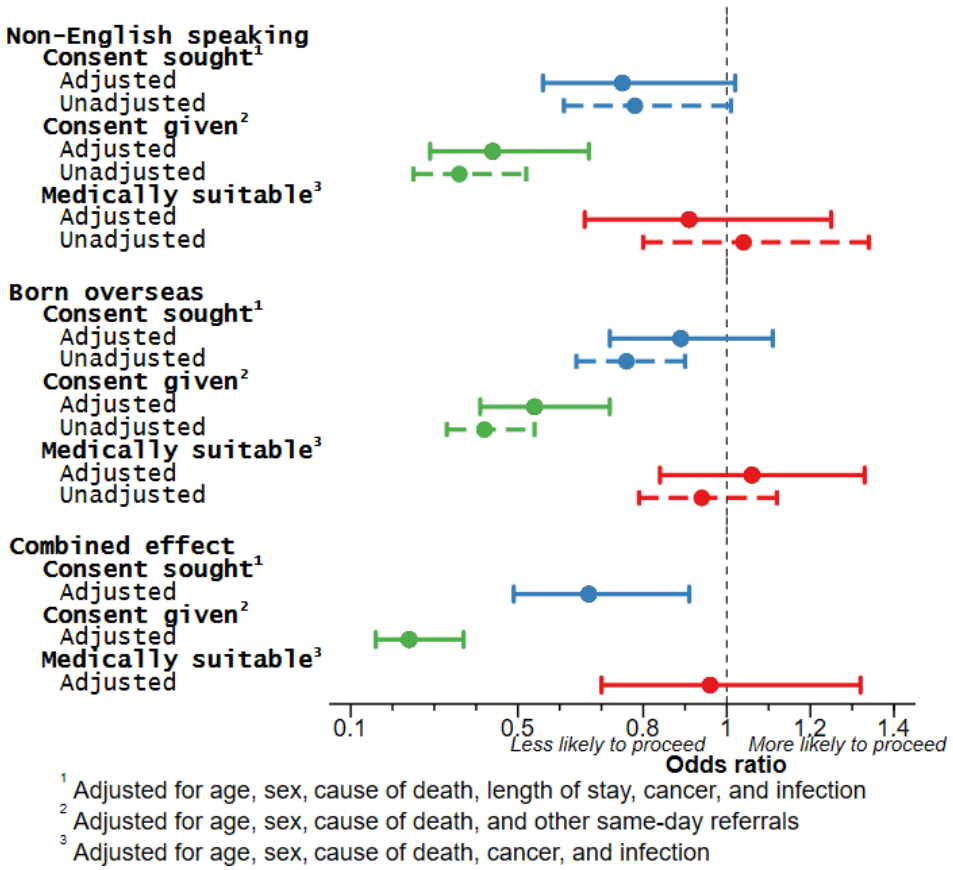


Figure 15. Forest plot of adjusted likelihood of referrals having consent for donation sought, families providing consent to donation or being deemed medically suitable for donation, by primary language and place of birth

4.2. Bloodborne viruses (BBV)

We evaluated potential missed opportunities for organ donation arising from organ donor referrals which did not proceed due to increased risk of viral infection. Increased risk of viral infection at referral was determine as any high-risk behaviour (including injecting drug use, high-risk partner, incarceration and commercial sex work), and past history or current HIV, HCV or HBV infection. A total of 165 organ donor referrals did not proceed to donation as they were considered at an increased risk of BBV infection at the time of referral (**Figure 16**). No evidence of any active infection was found in 35% of referrals. The vast majority of any active BBV infection and history of infection were from HCV infections. Two of the 165 organ donor referrals resided on the NSW border, where one had an active HCV infection indicated by SAFEBOD data only.

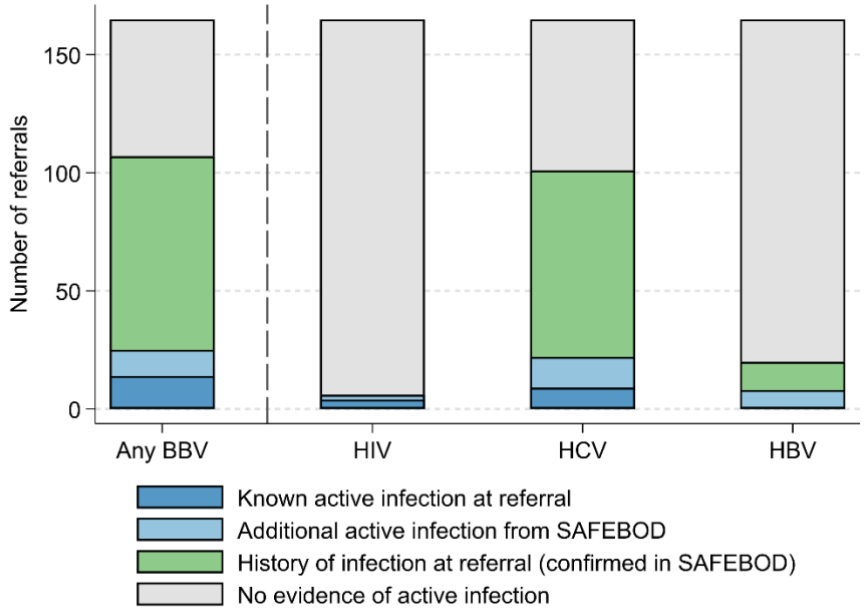


Figure 16. Organ donor referrals that did not proceed to donation due to increased bloodborne virus (BBV) risk (n=165).

4.3. Other notifiable conditions

There were other notifiable conditions reported in the organ donor referrals (**Figure 17**). Of the 2,961 persons referred for organ donation, 0.7% had influenza, 0.1% had gastrointestinal infections, 0.7% had respiratory infections and <0.1% had other conditions diagnosed within 2 weeks prior to donation. No organ donor referrals had any diagnoses of sexually transmissible infections. The one other infection was lead poisoning. 104 of the 2,961 organ donor referrals resided on the NSW border, of which one had a gastrointestinal infection and one had pneumococcal disease within 2 weeks prior to donation.

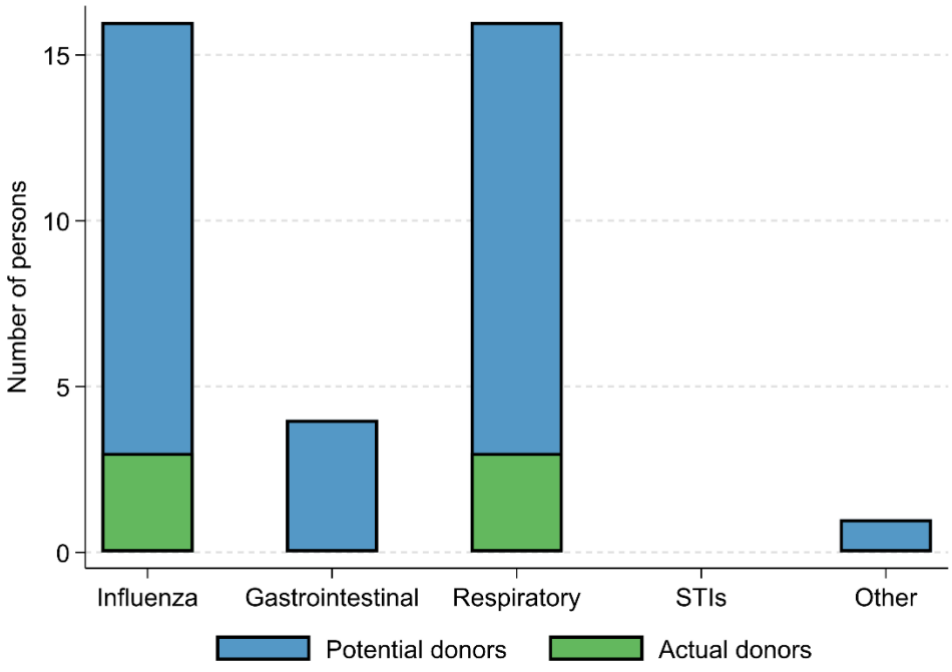


Figure 17. Other notifiable infectious diseases in NSW organ donor referrals, 2010-2015.

4.4. Tumours & malignancies

All tumours

We used SAFEBOD datasets to find additional evidence for cancers perceived to be present in donor referrals based on ORCHARD. Brain cancers were most common but were only verified in 43% of perceived cases. Other common cancers included colorectal, breast, leukaemia, prostate and lung, which were verified in 56%-94% of perceived cases (**Figure 18).**

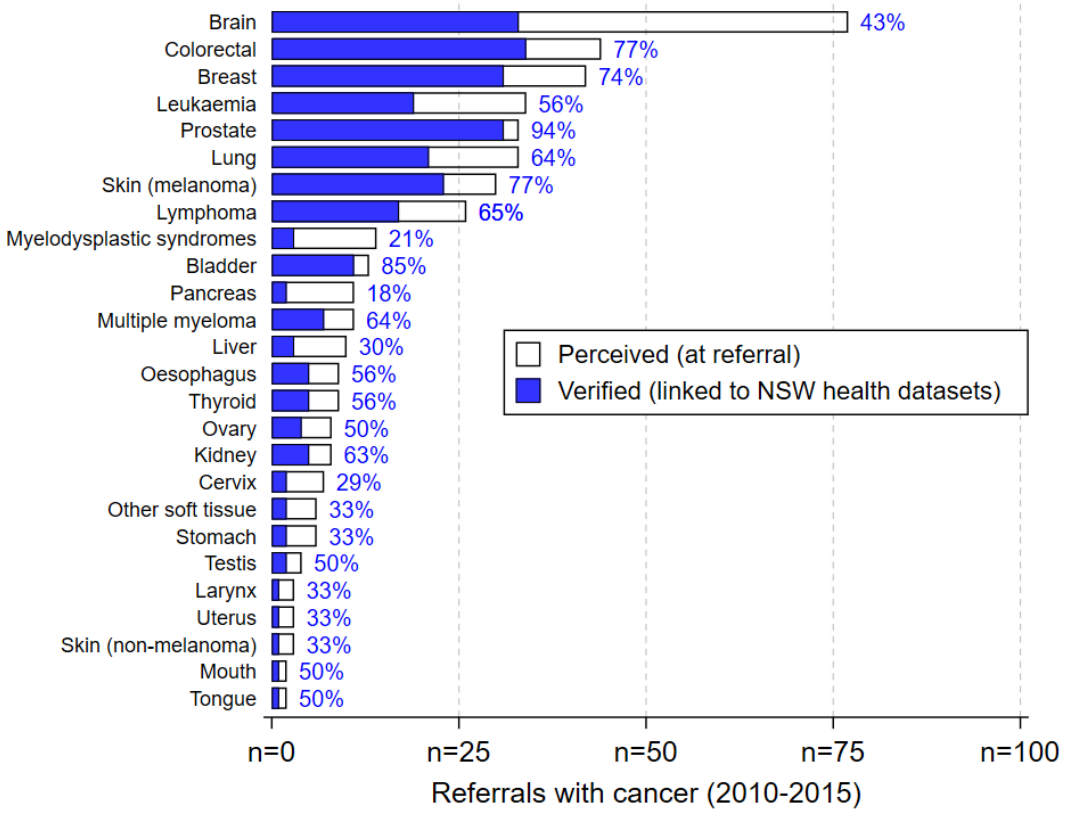


Figure 18. Perceived cancers at referral and verified cancers from SAFEBOD in donor referrals, 2010-2015.

Referrals that did not proceed to donation due to perceived cancer risk that could not be verified in other NSW health datasets represent potential missed opportunities for organ donation.

Primary brain malignancies (PBM)

A total of 77 potential donors with PBMs were referred for donation between 2010-2015. Of these, 10 (13%) became donors, and 19 (25%) were missed opportunities excluded from donation on the basis of the presence of PBM alone. The remainder of PBM referrals did not proceed to donate for other reasons, such as medical unsuitability or family non-consent. Both referrals and donors with PBMs were significantly younger than all referrals and donors, with mean ages of 50.4 vs. 58.8 years for referrals and 44.4 vs. 49.8 for donors with PBMs with and without PBMs respectively. Missed opportunities were also significantly younger, and had a lower comorbidity burden, than other donors.

All donors with PBMs had tumours that were WHO Grade I or II and that were classified as donation not contraindicated by TSANZ. No PBM referrals with a ventriculo-peritoneal shunt became donors. PBM missed opportunities had a different risk profile compared with PBM donors; with 14 (73%) having WHO Grade III or IV tumours, and 13 (68%) having PBMs deemed intermediate risk by TSANZ (**Figure 19**). Further, disagreements in those with low or intermediate perceived risk tended overestimate the verified risk (75% of low perceived risk; 16% of intermediate risk) (**Figure 20**).

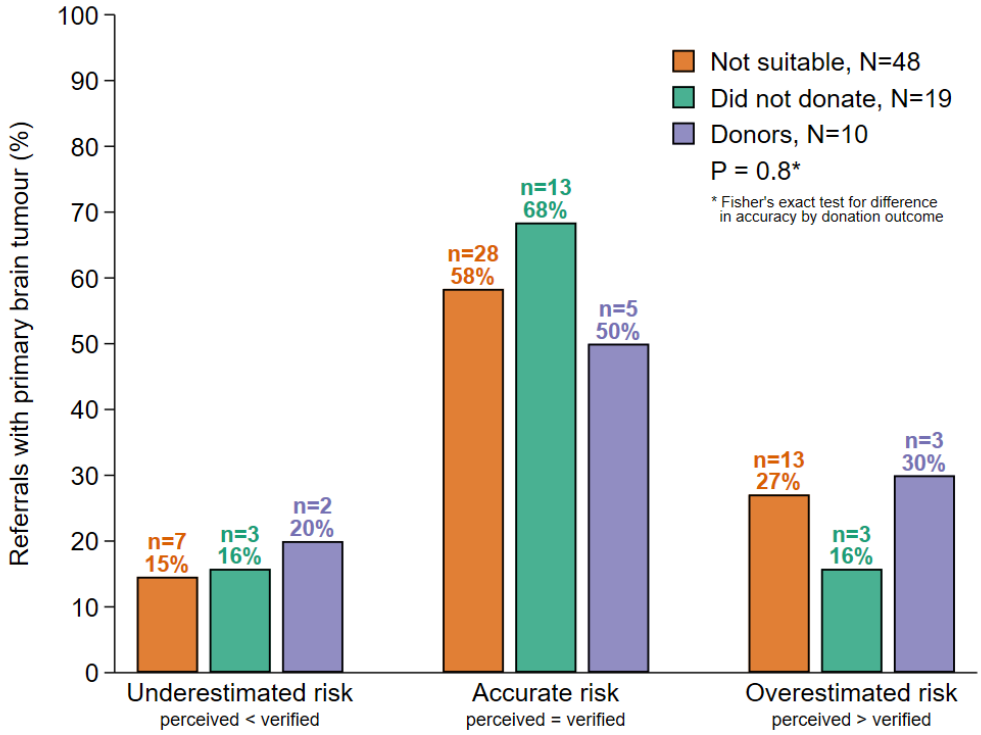


Figure 19. Perceived transmission risk determined at referral and verified transmission risk using SAFEBOD data for organ donor referrals with primary brain tumour, 2010-2015.

Glioblastoma multiforme (GBM) was the most common PBM among missed opportunities (11, 63%). No referrals with PBMs who proceeded to donate had GBM, so transmission risk could not be inferred from our results, but other studies have estimated this at approximately 2.2%. These results highlight that there exist opportunities to increase organ donation rates in NSW through greater consideration of referrals with PBMs. However, these risks must be balanced against the risk of transmission, especially when evaluating referrals with higher-grade tumours such as GBM. Three missed opportunities with unspecified PBMs were excluded from risk and grading analyses as these could not be determined.

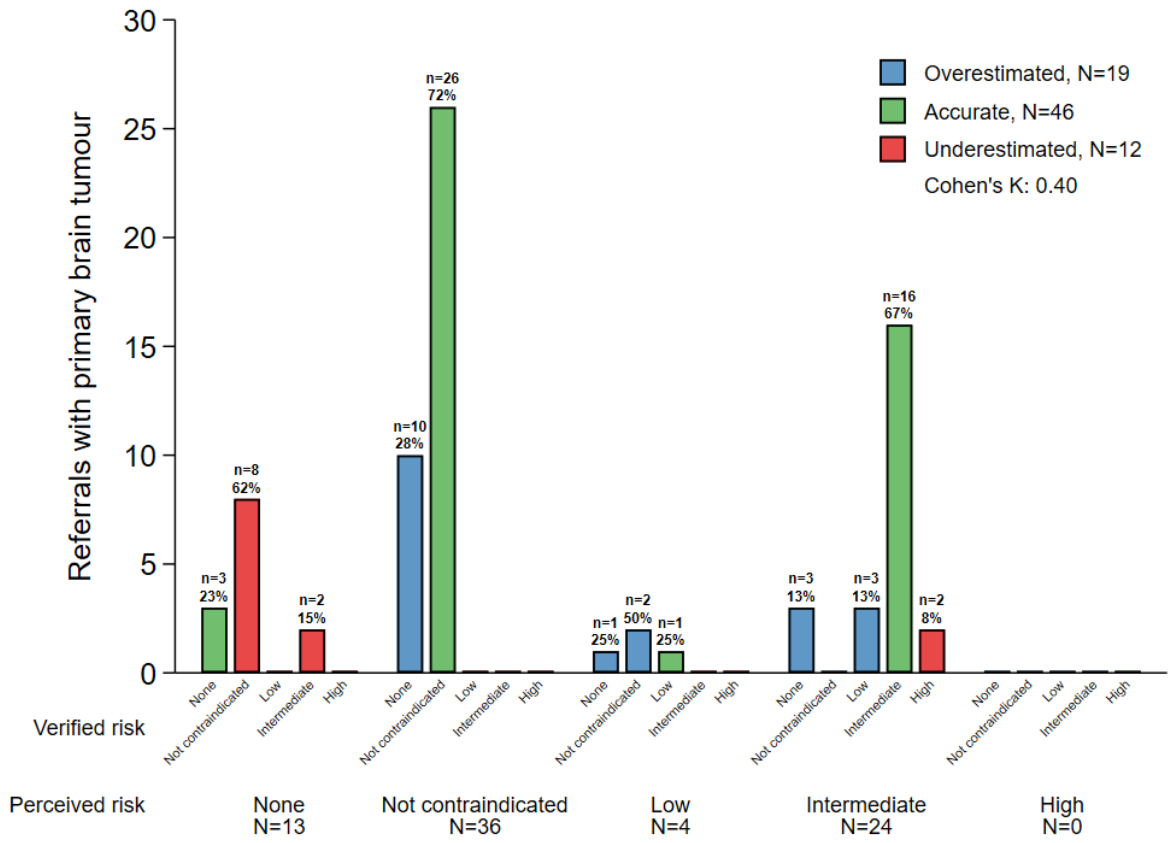


Figure 20. Agreement of perceived vs verified risk of primary brain malignancies (PBM) in all NSW referrals, 2010-2015.

5.0 Biovigilance insights – Were there transmissions?

The SAFEBOD linkage of NSW health datasets to transplant recipients and organ donors allowed for evaluation of transmission and non-transmission events, 2000-2015. However, our findings below are limited to NSW and it remains possible that a transmission event may have occurred to an interstate recipient or after the follow up period.

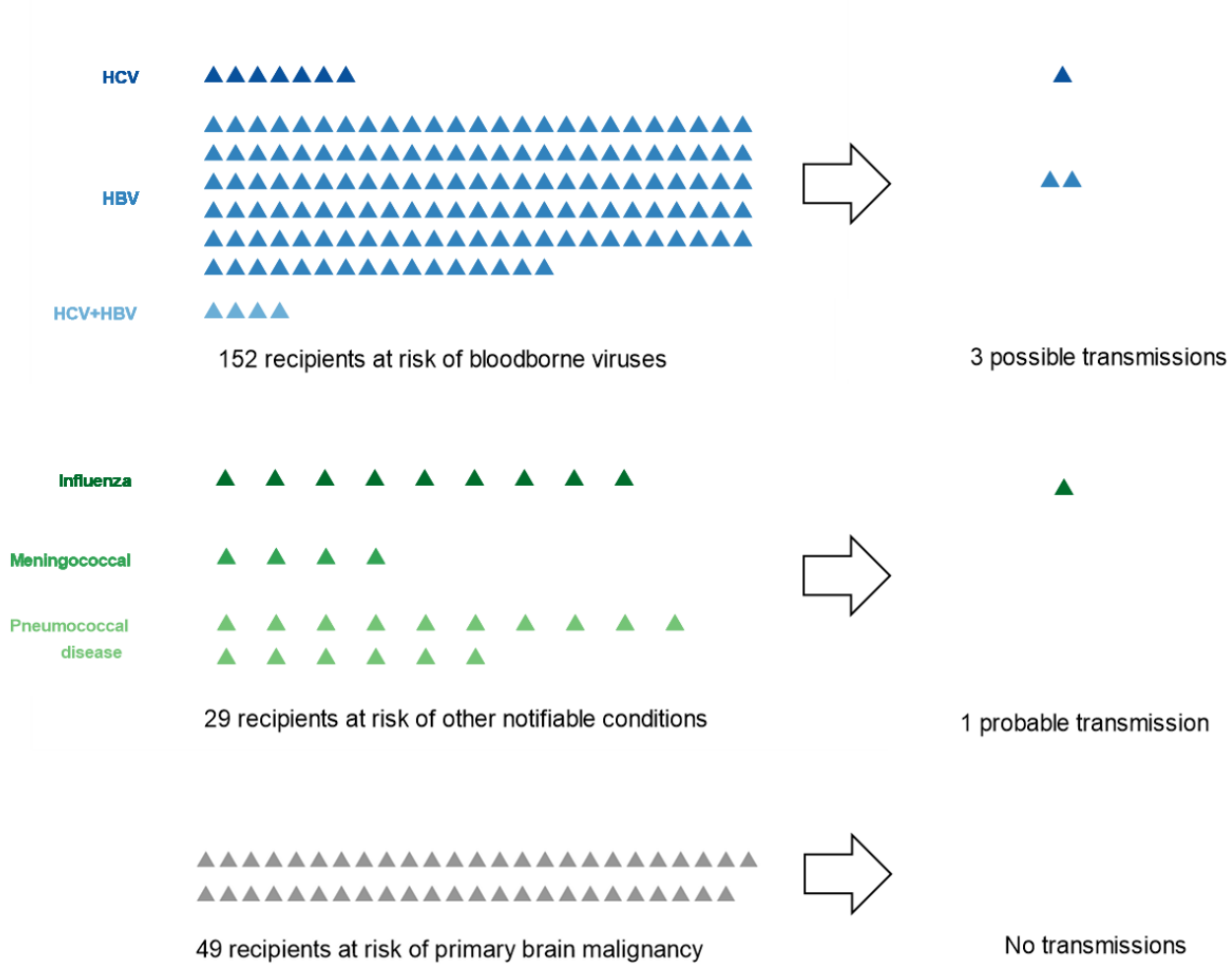
5.1. Bloodborne viruses (BBV)

There were 73 donors with a history of BBV infection (11 HCV, 57 HBV and 5 HCV+HBV), but few of these donors had active infection at the time of donation (n = 14). These 73 donors donated 182 organs (100 kidneys, 46 livers, 26 lungs, 6 hearts and 4 pancreases) to 176 transplant recipients. Of the 176 transplant recipients, 24 recipients had an active or past BBV of the same type as the donor and 152 recipients were at risk of BBV transmission, including 7 HCV, 141 HBV and 4 HCV+HBV (**Figure 21**). Three of the 152 recipients contracted the same BBV infection as the donor within 12 months of transplant (1 HCV, 2 HBV). Only two of the donors with a history of BBV infection resided on the NSW border, where both recipients had pre-existing HCV diagnoses. Conversely, six recipients residing on the NSW border were at risk of contracting HBV from their donor. None of these recipients contracted a BBV after transplant.

A further 17 recipients contracted a BBV infection within a year after transplant (1 HIV, 10 HCV and 6 HBV), where their organ donors were not known to have a past or active BBV infection prior to donation. None of these recipients or organ donors resided on the NSW border. In all cases, no more than one recipient from each donor had a new BBV diagnosis.

5.2. Other notifiable conditions

For the other notifiable conditions, 3 donors had influenza, 6 donors had respiratory infections and 1 donor had meningococcal within two weeks prior to donation. These 10 donors donated 31 organs to 29 recipients (9 at risk of influenza, 4 at risk of meningococcal and 16 at risk of pneumococcal disease) (**Figure 21**). Of which, only one recipient was diagnosed with influenza within 2 weeks after transplant. No infections were present in the 103 organ donors who resided on the NSW border.



Note: Probable transmissions are where donor to recipient transmission is likely given the timeframe between transplant and diagnosis of new condition, with laboratory evidence in both donor and recipient.
Possible transmissions are where donor to recipient transmission is suspected but less likely then probably given the time frame between transplant and diagnosis of new condition, with laboratory evidence in both donor and recipient.

Figure 21. Non-transmission and transmission events for bloodborne viruses, other notifiable conditions and primary brain malignancy where donors were known to have the condition prior to donation.

A further eight recipients had influenza, three recipients had Salmonella and one recipient had Syphilis diagnosed within 2 weeks after transplant. In these recipients, the same condition was not known to be present in the donor within 2 weeks prior to donation. Two of the recipients with influenza diagnoses had the same donor, while in all other cases only one recipient for each donor had a new diagnosis.

5.3. Tumours & malignancies

All tumours

We have identified one transplants that potentially resulted in transmission of cancer from a donor to a recipient. A deceased donor with renal cell carcinoma identified during organ

retrieval donated a double lung to one recipient, who developed lung, liver, and bone marrow metastases 6 months after transplant. We are currently determining the number of transplants from donors with cancer that did not result in transmission to a recipient (non-transmission events), however these results are not yet available.

Primary brain malignancies (PBM)

There were 16 donors (15 deceased and 1 living) who donated organs to 49 recipients in NSW, including 23 kidneys, 12 livers, 10 lungs, 4 hearts, and 1 pancreas (**Figure 21**). After 4,634 months of total follow up (mean 95 months per recipient), no transmission events occurred. Our findings are in keeping with the literature on this topic, which highlights the very low risk of PBM transmission in solid organ donation.

When border areas were excluded from NSW, one deceased donor who donated a kidney was excluded, resulting in no transmissions over a total of 4,506 months of total follow-up (mean 94 months per recipient).

6.0 Final remarks

The ORCHARD and SAFEBOD projects are dynamic and evolving. This report represents an overview of study activity to date.

6.1. Filling the gaps

In the first round of data linkage for SAFEBOD, we were unable to link to tuberculosis (TB) surveillance clinics in NSW. In future linkage we hope to ascertain attendance as a case or contact of a case at a TB clinic, to better differentiate baseline risk of latent or active TB among donor referrals.

A large proportion of referral in ORCHARD are missing data for ethnicity and religion. Future rounds of SAFEBOD data linkage could include ethnicity and religion from NSW health datasets (e.g. APDC) so we can explore the possibility of an association between donor referral outcomes and other cultural factors alongside language and country of birth. Furthermore, these characteristics could also be adjusted for in all future SAFEBOD analyses.

6.2. Future directions

SAFEBOD and ORCHARD represent only two components of the research program of the CODE. Future evolution of the research program of CODE will be steered by the research team and our collaborators, with the overarching aim of integrating evidence and decision support into the organ procurement pathway, to improve organ donation for Australians waiting for a transplant.

7.0 SAFEBOD publications

7.1. Conference abstracts

Published

15th Congress of the International Society for Organ Donation and Procurement, 2019

1. Waller K, De La Mata N, Hedley J, Rosales B, Kelly P, Wyburn K, O'Leary M, Cavazzoni E, Webster A. Assessment of blood borne viruses risk in organ donation: Use of linked health data to identify missed opportunities and transmissions in an Australian cohort. *Transplantation,* 2019. 103(S11)
2. Waller K, Hedley J, Rosales B, De La Mata N, Kelly P, Wyburn K, O'Leary M, Cavazzoni E, Webster A. Effect of language and country of birth of potential donors on organ donor outcomes: a data-linked cohort study from New South Wales, Australia 2010-2015. *Transplantation,* 2019. 103(S11)

Conference Connecting Donation and Transplantation, hosted by the Organ and Tissue Authority, 2019

3. De La Mata N, Waller K, Hedley J, Rosales B, O'Leary M, Cavazzoni E, Kelly P, Wyburn K, Webster AC. Bloodborne virus infections in New South Wales organ donor referrals: The SAFE-BOD cohort 2010-2015. *Transplantation Direct*, 2019. 5(S4).
4. Rosales B, Hedley J, De La Mata N, Wyburn K, Kelly P, O'Leary M, Cavazzoni E, Webster AC. Effect of language and country of birth on medical suitability and consent in solid organ donor referrals in New South Wales 2010-2015: A linked-data cohort study. *Transplantation Direct*, 2019. 5(S4).
5. Hedley J, Thomson I, De La Mata N, Rosales B, O'Leary M, Cavazzoni E, Kelly P, Wyburn K, Webster AC. Donor referrals with primary brain tumour: Perceived vs verified risk. *Transplantation Direct*, 2019. 5(S4).
6. Hedley J, De La Mata N, Rosales B, O'Leary M, Cavazzoni E, Kelly P, Wyburn K, Webster AC. Cancer incidence in donor referrals, a New South Wales cohort study 2010-2015 using data linkage. *Transplantation Direct*, 2019. 5(S4).
7. Waller K, De La Mata N, Kelly P, Ranachandran V, Rawlinson W, Wyburn K, Webster AC. Incidence, prevelence and residual risk of blood borne virus infection when Australian organ donor referrals with increased risk test negative: a systematic review and meta-analysis. *Transplantation Direct*, 2019. 5(S4).
8. Thomson I, Rosales B, Kelly P, Wyburn K, O'Leary M, Webster AC. Comorbidities influencing the outcome of organ donor referrals in New South Wales: cohort study 2010-2015. *Transplantation Direct*, 2019. 5(S4).

37th Annual Scientific Meeting of The Transplantation Society of Australia and New Zealand, 2019

9. De La Mata N, Waller K, Hedley J, Rosales B, Kelly P, Wyburn K, O'Leary M, Cavazzoni E, Webster AC. Missed opportunities for organ donation? Use of linked health data to verify increased bloodborne virus (BBV) risk among NSW organ donor referrals, 2010-2015. *Transplantation Direct,* 2019. 5(S10).

10. De La Mata N, Waller K, Hedley J, Rosales B, Kelly P, Wyburn K, O'Leary M, Cavazzoni E, Webster AC. Bloodborne virus (BBV) infections in NSW organ donor referrals using linked health data: The SAFEBOD cohort, 2010-2015. *Transplantation Direct*, 2019. 5(S10).
11. Thomson I, Hedley J, De La Mata N, Rosales B, O'Leary M, Cavazzoni E, Kelly P, Wyburn K, Webster AC. Donor referrals with primary brain tumour – percieved vs. verified risk. *Transplantation Direct*, 2019. 5(S10).
12. Thomson I, Hedley J, De La Mata N, Rosales B, O'Leary M, Cavazzoni E, Kelly P, Wyburn K, Webster AC. Missed opportunities organ donation among donors with primary brain malignancies (PBMS): New South Wales (NSW) cohort study 2010-2015. *Transplantation Direct*, 2019. 5(S10).
13. Hedley J, Thomson I, De La Mata N, Rosales B, O'Leary M, Cavazzoni E, Kelly P, Wyburn K, Webster AC. Cancer Incidence in Donor Referrals – a NSW cohort study 2010-2015 using data linkage. *Transplantation Direct*, 2019. 5(S10). **(Early Career Investigator Award)**
14. Waller K, Hedley J, De La Mata N, Rosales B, Wyburn K, Kelly P, O'Leary M, Cavazzoni E, Webster AC. Effect of language and country of birth on medical suitability and consent in solid organ donor referrals in New South Wales 2010-2015: A linked-data cohort study. *Transplantation Direct*, 2019. 5(S10). **(Presidents Prize Session, Early Career Investigator Award)**

35th Annual Scientific Meeting of The Transplantation Society of Australia and New Zealand, 2017

15. **Waller K,** Wyburn K, Thomson I, Hancock R, O'Leary M, Rawlinson W, Ramachandran V, Webster AC. Referrals at risk for blood borne virus transmission in New South Wales, 2010-2015. *Transplantation Direct*, 2017

Accepted

1. Hedley J, De La Mata N, Rosales B, Waller K, O'Leary M, Cavazzono E, Kelly P, Wyburn K, Webster AC. Perceived vs. verified risk of cancer transmission from deceased organ donors – a NSW cohort stuyd 2010-2015 using data linkage. *The Transplantation Society of Australia and New Zealand: 38th Annual Scientific Meeting*, 2020. **(President's Prize Symposium)**

2. Waller K, De La Mata N, Hedley J, Rosales B, O'Leary M, Cavazzoni E, Ramachandran V, Rawlinsom W, Kelly P, Wyburn K, Webster AC. New blood borne virus infections among organ transplant recipients: a data-linked cohort study examining transmission and de novo hepatitis B, C and HIV infections. *The Transplantation Society of Australia and New Zealand: 38th Annual Scientific Meeting*, 2020. **(President's Prize Symposium)**

3. De La Mata N, Rosales B, Kelly P, Webster AC. Relative survival in kidney transplant recipients with de-novo cancers vs non-transplant cancer patients: a population study 1980-2016. *The Transplantation Society of Australia and New Zealand: 38th Annual Scientific Meeting*, 2020.

4. Rosales B, Hedley J, De La Mata N, Waller K, O'Leary M, Kelly P, Wyburn K, Webster AC. Suspected vs. verified melanoma in NSW deceased organ donor referrals: a data-linkage cohort study, 2010-2015. *The Transplantation Society of Australia and New Zealand: 38th Annual Scientific Meeting*, 2020.

5. Thomson I, Hedley J, De La Mata N, Rosales B, O'Leary M, Cavazzoni E, Kelly P, Wyburn K, Webster AC. Missed opportunities organ donation among donors with primary brain tumours in Australia; cohort study 2010-2015. *28th International Congress of The Transplantation Society,* 2020.

6. Rosales B, Hedley J, De La Mata N, Waller K, O'Leary M, Kelly P, Wyburn K, Webster AC. Verification of suspected melanomas in deceased organ donor referrals: a population-based cohort study using data-linkage, 2010-2015. *28th International Congress of The Transplantation Society,* 2020.

7. Hedley J, De La Mata N, Rosales B, Waller K, O'Leary M, Cavazzono E, Kelly P, Wyburn K, Webster AC. Perceived vs. verified risk of cancer transmission from deceased organ donors – a NSW cohort stuyd 2010-2015 using data linkage. *28th International Congress of The Transplantation Society*, 2020

8. Waller K, De La Mata N, Hedley J, Rosales B, O'Leary M, Cavazzoni E, Ramachandran V, Rawlinsom W, Kelly P, Wyburn K, Webster AC. New blood borne virus infections among organ transplant recipients: a data-linked cohort study examining transmission and de novo hepatitis B, C and HIV infections. *28th International Congress of The Transplantation Society*, 2020

9. Waller K, De La Mata N, Wyburn K, Kelly P, Ramachandran V, Shah K, Morton R, Rawlinsom W, Webster AC. Vaccine-preventable infections among solid organ transplant recipients: a data-linked cohort study, Australia, 2000-2015. *28th International Congress of The Transplantation Society*, 2020

7.2. Other presentations

1. Webster AC, Wyburn K, Kelly P, O'Leary M, Vajdic C, Chapman J, Rosales B, De La Mata N, Hedley J, Taylor L. Safety and Biovigilance in Organ Donation: a retrospective cohort study using data linkage of existing data sets in NSW, Australia (SAFEBOD study). *Donation and Transplantation Conference*, 2017.

2. Wyburn K & Webster AC. Safety and biovigilance in organ donation in NSW (ORCHARD & SAFEBOD study). *Organ and Transplant Authority Meeting*, 2017.

3. Webster AC, Wyburn K, Rosales B, De La Mata N, Hedley J. Safety and Biovigilance in organ donation in NSW, Australia (SAFEBOD study). *NSW Ministry of Health: Epidemiology Special Interest Group,* 2017.

4. Rosales B, Hedley J, De La Mata N, Waller K, O'Leary M, Kelly P, Wyburn K, Webster AC. Verification of suspected melanomas in deceased organ donor referrals: a population-based cohort study using data-linkage, 2010-2015. *Sydney Health Partners – Renal: NSW Has Scientific Talent Awards,* 2020. **(Finalist)**

7.3. Publications

Published

1. Waller KM, De La Mata NL, Kelly PJ, Ramachandran V, Rawlinson WD, Wyburn KR, Webster AC. Residual risk of infection with blood-borne viruses in potential organ donors at increased risk of infection: systematic review and meta-analysis. *Medical Journal of Australia*. 2019. 211(9)
2. Hedley JA, Chang N, Kelly PJ, Rosales BM, Wyburn K, O'Leary M, Cavazzoni E, Webster AC. Weekend effect: analysing temporal trends in solid organ donation. *Australian and New Zealand Journal of Surgery,* 2019. 89(9).
3. Waller KMJ, Wyburn KR, Shackel NA, O'Leary MJ, Kelly PJ, Webster AC. Hepatitis Transmission Risk in Kidney Transplantation (the HINT study): A Cross-Sectional Survey of Transplant Clinicians in Australia and New Zealand. *Transplantation,* 2018. 102(1).
4. Thomson IK, Rosales BM, Kelly PJ, Wyburn K, Waller KMJ, Hirsch D, O'Leary MJ, Webster AC. Epidemiology and Comorbidity Burden of Organ Donor Referrals in Australia: Cohort Study 2010-2015. *Transplant Direct,* 2019. 5(11).
5. Waller KMJ, Hedley JA, Rosales BM, De La Mata NL, Thomson IK, Walker J, Kelly PJ, O'Leary MJ, Cavazzoni E, Wyburn KR, Webster AC. Effect of language and country of birth on the consent process and medical suitability of potential organ donors; a linked-data cohort study 2010-2015. *Journal of Critical Care,* 2020. 57.

In press

1. Rosales B, Hedley J, De La Mata N, Vajdic C, Kelly P, Wyburn K, Webster AC. Safety and Biovigilance in Organ Donation (SAFEBOD) Study: a protocol for a population based cohort study. *JMIR Research Protocols,* in submission.
2. Waller K, De La Mata N, Hedley J, Rosales B, O'Leary M, Cavazzoni E, Ramachandran V, Rawlinson W, Kelly P, Wyburn K, Webster AC. New blood borne virus infections among organ transplant recipients: an Australian data-linked cohort study examining donor-transmissions and other HIV, hepatitis C and hepatitis B notifications, 2000-2015. *Transplant Infectious Diseases,* in press.

7.4. Clinical Guidelines

In addition to the work above, CODE publications have generated evidence included in the following published clinical practice guidelines;

1. Chadban SJ, Barraclough KA, Campbell SB, Clark CJ, Coates PT, Cohney SJ, Cross NB, Eris JM, Henderson L, Howell MR, Isbel NM, Kanellis J, Kotwal SS, Manley P, Masterson R, Mulley W, Murali K, O'Connell P, Pilmore H, Rogers N, Russ GR, Walker RG, Webster AC, Wiggins KJ, Wong G, Wyburn KR. KHA-CARI guideline: KHA-CARI adaptation of the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Nephrology,* 2012. 17(3)

2. White SL, Rawlinson W, Boan P, Sheppeard V, Wong G, Waller K, Opdam H, Kaldor J, Fink M, Verran D, Webster A, Wyburn K, Grayson L, Glanville A, Cross N, Irish A, Coates T, Griffin A, Snell G, Alexander SI, Campbell S, Chadban S, Macdonald P, Manley P, Mehakovic E, Ramachandran V, Mitchell A, Ison M. Infectious disease transmission in solid organ transplantation: donor evaluation, recipient risk, and outcomes of transmission. *Transplantation Direct,* 2018. 5(1).

8.0 References

1. Cass, A., et al. The economic impact of end-stage kidney disease in Australia: Projections to 2020. Sydney, Australia: The George Institute for Global Health; 2006. [Cited 10 Jul 2019.] Available from URL: https://kidney.org.au/cms_uploads/docs/kha-economic-impact-of-eskd-in-australia-projections-2020.pdf
2. Howard, K., et al., *The cost-effectiveness of increasing kidney transplantation and home-based dialysis.* Nephrology (Carlton), 2009. **14**(1): p. 123-32.
3. Project., S.A.O.A. *Australian organ donation performance - leading practice & global comparison*. 2018; Available from: http://www.sharelife.org.au/australian-organ-donation-comparison.
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9. Kucirka, L.M., et al., *Risk of window period HIV infection in high infectious risk donors: systematic review and meta-analysis.* Am J Transplant, 2011. **11**(6): p. 1176-87.
10. Nalesnik, M.A., et al., *Donor-transmitted malignancies in organ transplantation: assessment of clinical risk.* Am J Transplant, 2011. **11**(6): p. 1140-7.
11. Ison, M.G., et al., *Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee.* Am J Transplant, 2009. **9**(8): p. 1929-35.
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14. Green, M., et al., *Donor-derived transmission events in 2013: a report of the Organ Procurement Transplant Network Ad Hoc Disease Transmission Advisory Committee.* Transplantation, 2015. **99**(2): p. 282-7.