

Registry based trials in dialysis and transplantation - lessons learned

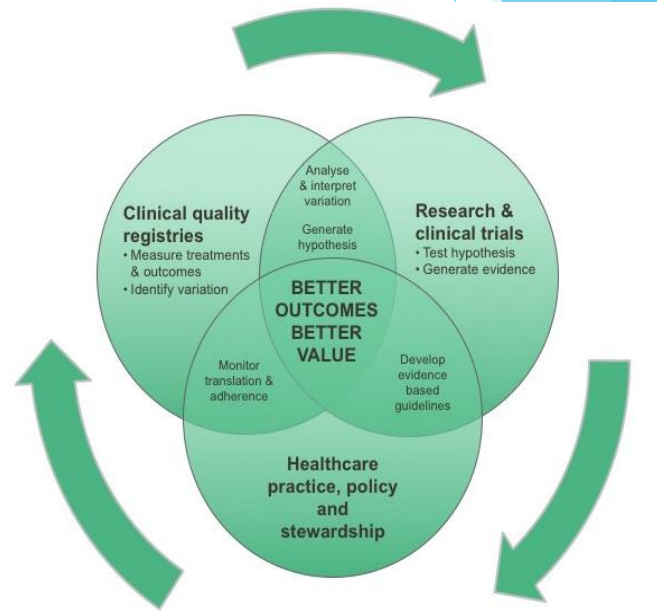
Stephen McDonald



ACTA Registry based trials workshop
19 May 2020

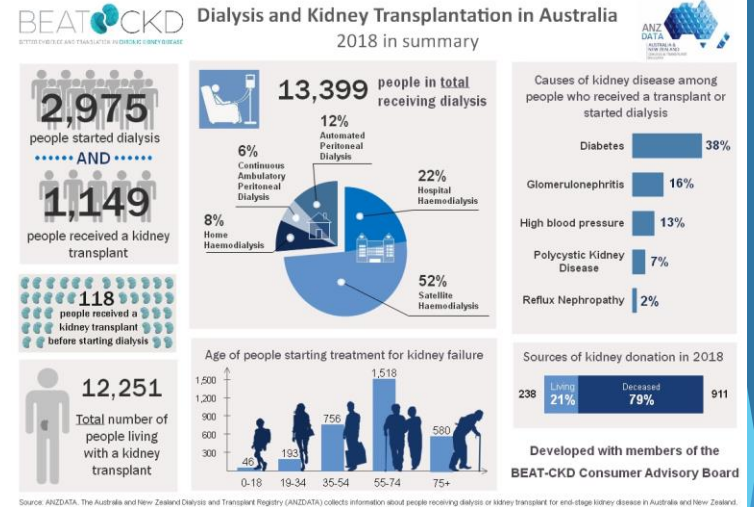
What do we mean by “Registry”?

- ▶ Difficult to categorise
- ▶ Cohort study, ongoing
 - ▶ Typically multiple aims, diverse funding
- ▶ 3 broad groups
 - ▶ Clinical quality Registry
 - ▶ Device / drug Registry
 - ▶ Rare disease Registry
- ▶ Varying consent arrangements



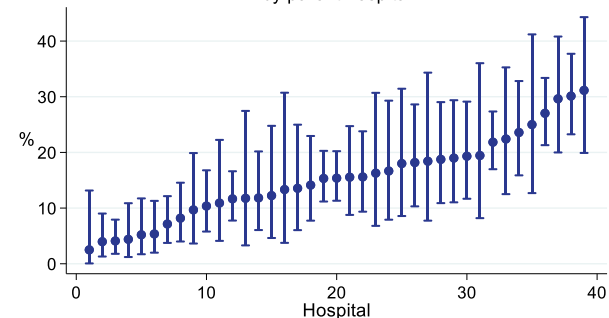
ANZDATA Background

- ▶ Clinical Quality Registry
- ▶ Coverage
 - ▶ Long term dialysis and kidney transplantation
 - ▶ All Renal units in Australia and New Zealand participate
- ▶ Data collected
 - ▶ For key events
 - ▶ At yearly census



Source: ANZDATA. The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) collects information about people receiving dialysis or kidney transplant for end-stage kidney disease in Australia and New Zealand.

Proportion of patients, with predicted 5-year survival $\geq 80\%$, who were wait-listed at 31-Dec-2018 by parent hospital



Only includes patients who had been on dialysis for at least 1 year
Excludes hospitals with <30 dialysis patients with $\geq 80\%$ predicted survival

Background



Background - trials

A Randomized Controlled Trial of Cyclosporine Withdrawal in Renal-Transplant Recipients: 15-Year Results

Martin P. Gallagher,^{1,6} Bruce Hall,² Jonathan Craig,³ Geoffrey Berry,⁴ David J. Tiller,⁵ and Josette Eris,⁵ on behalf of the Australian Multicenter Trial of Cyclosporine Withdrawal Study Group and the ANZ Dialysis and Transplantation Registry

Background. In renal transplantation, the immunosuppressive efficacy of cyclosporine is counterbalanced by its nephrotoxicity. Although cyclosporine improves short-term graft survival, its long-term effects are unclear.

Methods. Recipients of first cadaver renal transplants were randomized into three groups between 1983 and 1986: azathioprine and prednisolone alone (AP, n=158), long term cyclosporine alone (Cy, n=166), and short-term cyclosporine followed by azathioprine and prednisolone (CyAP, n=165). All groups received methylprednisolone induction.

Results. There were no significant differences in patient survival at 15 years (48 vs. 56 vs. 51%, $P=0.14$), and 15-year graft survival (censored for death) in those patients in the CyAP group (47 vs. 44 vs. 59%, $P=0.06$) was not significantly different statistically. When deaths or graft losses before 12 months were censored, the differences in 15-year graft survival between the groups were significant (58%, 51%, 70%, $P=0.01$). The CyAP group also had lower mean serum creatinine at all time points beyond 3 months posttransplant out to 10 years (143 vs. 169 vs. 131 $\mu\text{moles/L}$, $P=0.04$). Per protocol analysis, after censoring patients at change in therapy, increased the observed differences in 15-year graft survival between the groups (54 vs. 38 vs. 65%, $P=0.01$).

Conclusion. Survival and function of first cadaveric kidney transplants is improved by use of short-term cyclosporine followed by azathioprine and prednisolone. Long-term cyclosporine use reduces long-term graft survival.

Keywords: Kidney transplantation, Cyclosporine, Graft survival.

(*Transplantation* 2004;78: 1653–1660)

A Randomized Controlled Trial of Cyclosporine Cyclosporine Withdrawal Improves Long-Term Graft Survival in Renal Transplantation

Martin Gallagher,^{1,5} Meg Jardine,¹ Vlado Perkovic,¹ Alan Cass,¹ Stephen McDonald,² James Petrie,³ and Josette Eris⁴

Background. The reduction in renal transplant rejection rates achieved over the last 20 years have not translated into a commensurate improvement in long-term graft survival. Cyclosporine has been central to immunosuppressive regimens throughout this period but its effect on long-term transplant outcomes remains unclear.

Methods. This randomized controlled trial allocated first cadaveric renal transplant recipients in seven centers around Australia to three immunosuppressive regimens: azathioprine and prednisolone (AP), long-term cyclosporine alone (Cy), or cyclosporine initiation followed by withdrawal at 3 months and azathioprine and prednisolone replacement (WDL).

Results. Between 1983 and 1986, 489 patients were randomized with 98% follow-up to a median of 20.6 years. Mean graft survival (censoring deaths) was superior in the WDL group (14.8 years) when compared with both AP (12.4 years, $P=0.01$ log-rank test) and Cy (12.5 years, $P=0.01$ log-rank test) groups by intention-to-treat. Without death censoring, graft survival with WDL was superior to AP (9.5 years vs. 6.7 years, $P=0.04$) and of borderline superiority to Cy (9.5 years vs. 8.5 years, $P=0.06$). Patient survival was not different between the three groups. Renal function was superior in AP (at 1, 10, and 15 years posttransplant) and WDL (at 1, 5, 10, 15, and 20 years) groups when compared with Cy.

Conclusion. This study illustrates superior long-term renal transplant survival and preservation of renal function with a protocol using cyclosporine withdrawal. If long-term renal transplant outcomes are to improve, we should reconsider guidelines recommending universal maintenance use of cyclosporine.

Keywords: Kidney transplantation, Cyclosporine, Graft survival.

(*Transplantation* 2009;87: 1877–1883)

(*Transplantation* 2004;78: 1653–1660)

A Randomized Controlled Trial of Cyclosporine Cyclosporine Trial in Kidney Transplant Graft Long-Term Cancer Risk of Immunosuppressive Regimens after Kidney Transplantation

Martin
Webster

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translated into
immunosuppressive

ABSTRACT

Cancer is a widely recognized complication of transplantation, and the effects of various immunosuppressive drugs on cancer risk remains controversial. This randomized trial allocated 489 recipients of first cadaveric renal transplants to one of three groups: Azathioprine and prednisolone, cyclosporine monotherapy, or cyclosporine monotherapy followed by a switch to azathioprine and prednisolone after 3 months. Here, we report cancer outcomes by non-skin cancer (including melanoma) and skin cancer (excluding melanoma) for 481 patients during a median follow-up of 20.6 years. A total of 226 patients developed at least one cancer: 95 with non-skin cancer and 171 with skin cancer. In the intention-to-treat analysis, mean times to first non-skin cancer (16.0, 15.3, and 15.7 years for groups 1 through 3, respectively) and first skin cancer (13.6, 14.3, and 15.2 years, respectively) were not different among the three groups or between any subgroup. In multivariate analyses, non-skin cancer associated with increasing age and previous smoking history, whereas skin cancer associated with increasing age, nonbrown eye color, fairer skin, and a functioning transplant. Treatment allocation did not associate with development of either form of cancer in multivariate analyses. In conclusion, these immunosuppressive regimens, widely used in recent decades, carry similar risks for carcinogenicity after kidney transplantation.

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Previous uses of ANZDATA for trial

A Randomized Controlled Trial of Cyclosporine

Cyclosporine Versus Mycophenolate Mofetil in Kidney Transplant Graft

Long-Term Cancer Risk of Immunosuppressive

Re Mycophenolate Versus Azathioprine for Kidney

Transplantation: A 15 Year Follow Up

OPEN ACCESS Freely available online



Long-Term Survival and Dialysis Dependency Following Acute Kidney Injury in Intensive Care: Extended Follow-up of a Randomized Controlled Trial

Martin Gallagher^{1,2*}, Alan Cass^{1,3}, Rinaldo Bellomo⁴, Simon Finfer^{1,2}, David Gattas^{1,5}, Joanne Lee¹, Serigne Lo¹, Shay McGuinness⁶, John Myburgh^{1,7}, Rachael Parke⁶, Dorrilyn Rajbhandari¹, for the POST-RENAL Study Investigators and the ANZICS Clinical Trials Group^{¶1}

1 The George Institute for Global Health, Sydney, Australia, **2** University of Sydney, Sydney, Australia, **3** Menzies School of Health Research, Darwin, Australia, **4** Austin Hospital, Heidelberg, Australia, **5** Royal Prince Alfred Hospital, Camperdown, Australia, **6** Auckland City Hospital, Auckland, New Zealand, **7** St. George Clinical School, University of New South Wales, Sydney, Australia

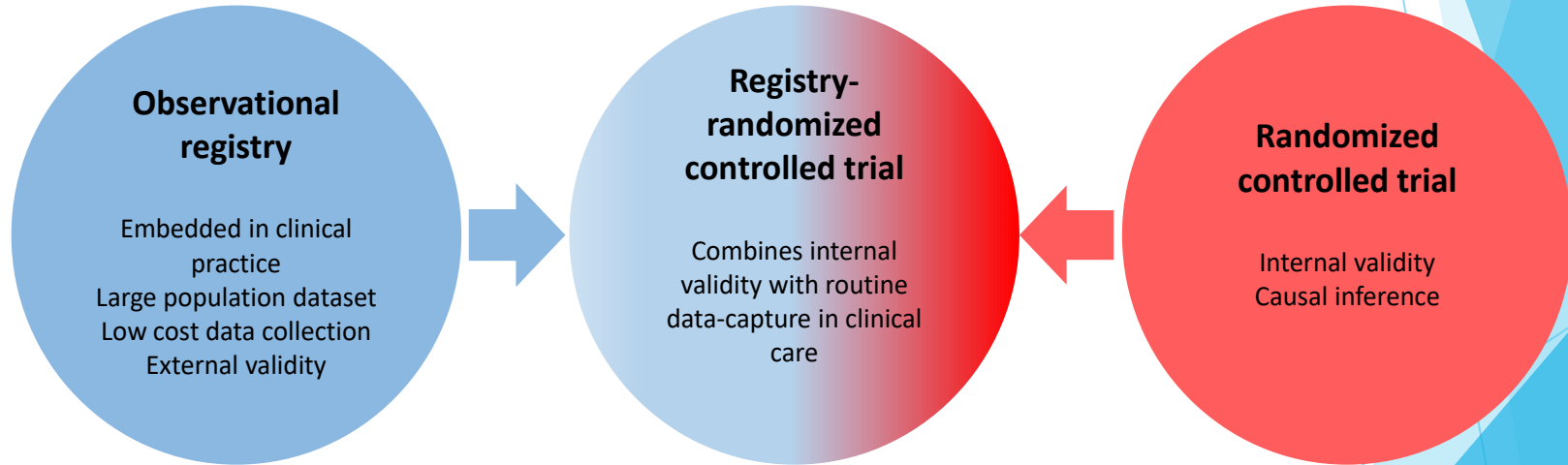
MMF was rare.

Conclusions. This long-term examination, although limited by small numbers, found little evidence for the superiority of MMF over AZA.

Keywords: Mycophenolate, Azathioprine, Immunosuppression, Transplantation, Randomized controlled trial, Registry.

(*Transplantation* 2012;94: 152–158)

Embedding trials in Registries



Why embed trials in a Registry?

Benefits to trials

- ▶ An ability to easily follow up patients long term (without need for data linkage)
- ▶ Users already have familiarity with the system and routinely use it
- ▶ Minimization of duplicate data collection, costs
- ▶ Trials can benefit from functionality of robust registry data collection system
- ▶ Direct link to evaluation of practice change

Benefits to Registries

- ▶ Routine data collection for trials helps to increase quality of registry information
- ▶ Promotion of trials increases user engagement and enthusiasm towards the registry
- ▶ Bridge gap between research and clinical practice

What are we doing?

- ▶ The ANZDATA Registry currently hosts 4 active registry trials:

RESOLVE



BEST Fluids



TEACH PD



SWIFT



Primary outcomes

RESOLVE

The logo for the RESOLVE trial, featuring the word "resolve" in a lowercase, sans-serif font. The letter "o" is stylized with a red heart shape inside it.

Randomised Evaluation of Sodium
dialysate Levels on Vascular Events

Hospitalised
AMI / stroke
/ all cause
mortality

BEST Fluids

The logo for "The BEST-Fluids trial". It features a blue circular icon with a white shape inside, followed by the text "The BEST-Fluids trial" and "AKTN 15.02" below it.

Delayed graft
function

TEACH PD

The logo for "The TEACH-PD trial". It features a green circular icon with a white shape inside, followed by the text "The TEACH-PD trial" and "AKTN 17.03" below it.

Time to first PD
related infection

SWIFT



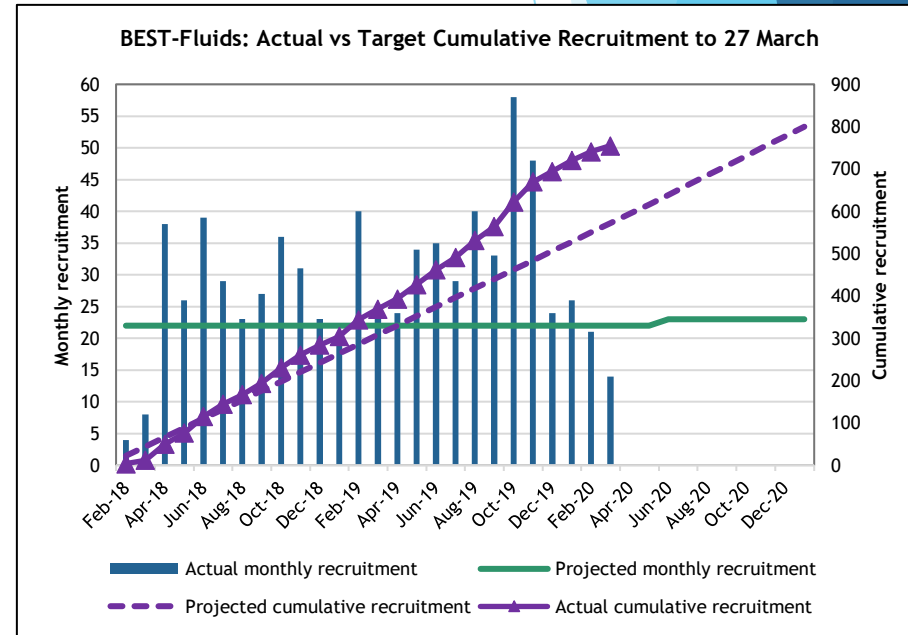
QOL - EQ-5D
(Tablet)

All required some modification of Registry based data collection....

Example 1:



- ▶ Normal Saline vs Plasmalyte for IV fluid replacement post DD kidney transplantation
- ▶ Individual level RCT; opt-in consent
- ▶ Primary outcome early graft function
 - ▶ Other endpoints cover short and long term outcomes



Example 1:



Enrolment

Randomisation

Data Collection

Reporting

At point of transplantation, randomise patients from ANZDATA through an automated connection to external randomisation system (Flexetrial, NHMRC CTC)



Enter variables
for minimisation



Randomisation



Allocation received

Example 1:



Enrolment



Randomisation



Data Collection



Reporting

Short term trial specific data

Long term follow up data

ANZ
DATA

AUSTRALIA &
NEW ZEALAND
DIALYSIS & TRANSPLANT
REGISTRY

ANZDATA database

No need for probabilistic data linkage!

Example 2:



Enrolment



Randomisation




Data Collection



Reporting

Data items seamlessly integrated within regular ANZDATA collection

Peritonitis Episode 

Add Episode


What type of PD-related infection? *

Date of Infection *

Technique at Time of Infection

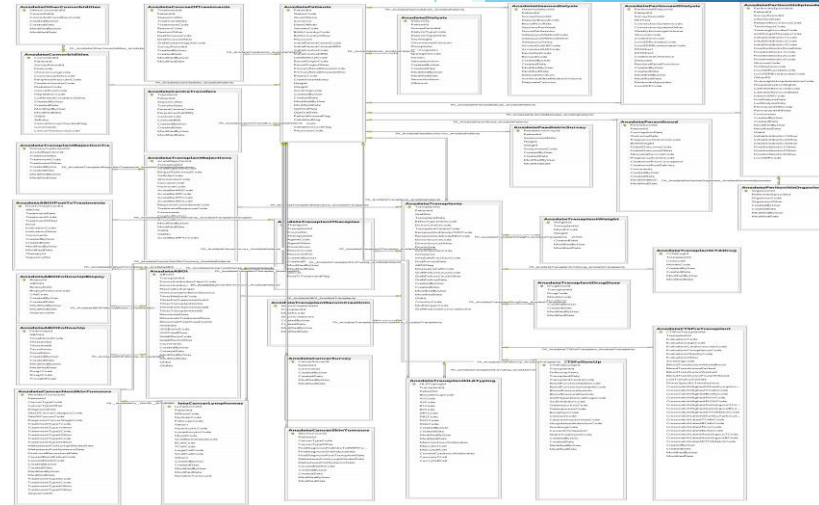
- 1 - Peritonitis
- 2 - Exit site infection
- 3 - Tunnel infection

Patient enrolled in



Not all is roses...

- ▶ Registry data collections less flexible
- ▶ Registry data has breadth not depth
 - ▶ Multiple other stakeholders may limit choices
- ▶ Differences in data standards
- ▶ Differences in time frames
 - ▶ Reflected in infrastructure, processes



Not all is roses.....

- ▶ Registries lack ability for detailed AE/SAE collection
 - ▶ Limited data collection infrastructure
- ▶ Relevance of this limitation depends on intervention
 - ▶ To date, ANZDATA trials have not used novel / investigational products
 - ▶ SAE data collections for trials use separate dataset

Not all is roses....

- ▶ Registry data collected generally to clinical, not research standards
 - ▶ Validation typically “ad-hoc”
- ▶ Outcomes chosen for a variety of reasons
 - ▶ Generally few
 - ▶ Comorbidities?

NEPHROLOGY



Nephrology 15 (2010) 491–501

Original Article

Validity of registry data: Agreement between cancer records in an end-stage kidney disease registry (voluntary reporting) and a cancer register (statutory reporting)

ANGELA C WEBSTER,^{1,2,3} RAJAH SUPRAMANIAM,⁴ DIANNE L O'CONNELL,⁴ JEREMY R CHAPMAN³ and JONATHAN C CRAIG¹

¹School of Public Health, University of Sydney, ²Centre for Transplant and Renal Research, Westmead Hospital, ³Cancer Epidemiology Research Unit, Cancer Council New South Wales, Sydney, New South Wales and ⁴Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, Adelaide, South Australia, Australia

NEPHROLOGY



Original Article | [Full Access](#)

Comparison of cause of death between anzdata and the Australian national death index

Matthew P Sypek , Kathryn B Dansie, Phil Clayton, Angela C Webster, Stephen McDonald

First published: 01 March 2018 | <https://doi.org/10.1111/nep.13250>

 PDF  TOOLS  SHARE

Example 3:



- ▶ Collecting PROMs in Registries (and routine health care) is a critical challenge
- ▶ Novel elements
 - ▶ Multiple data sets (PROMS in Qualtrics)
 - ▶ Patient - reported outcomes -> uploaded from tablet
- ▶ Electronic data entry (via tablet)
 - ▶ Critical model for PREMs PROMs for registries

Symptom monitoring with feedback trial (SWIFT)*

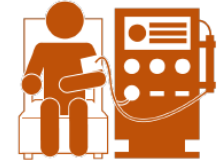
This large simple trial is asking whether monitoring of symptoms for people treated with haemodialysis and feedback of the symptom information to doctors and nurses can improve quality of life in one year?

SWIFT includes adults 18 years or older who are treated with haemodialysis at dialysis centres in Australia and New Zealand.

ABOUT

180

DIALYSIS UNITS
ARE EXPECTED
TO JOIN



In the CONTROL dialysis units

Patients will receive their usual care but without filling out the symptom survey (they will still fill out a survey on their quality of life every 6 months).



At the start, 6 months and 1 year we will ask ALL patients about quality of life and find out if measuring symptoms made any difference.



In the INTERVENTION dialysis units
EVERY 3 MONTHS for 1 year

Patients will be invited to fill out a survey asking about symptoms (called the IPOS-Renal survey)



The survey results will be sent to dialysis doctors and nurses.



Doctors and nurses will be encouraged to talk about symptoms with patients.



Other approaches: Symptom Monitoring with Feedback Trial (SWIFT)



INTERVENTION



3-monthly IPOS-Renal (Symptoms)



Results sent to dialysis nurse unit manager and nephrologist



Nephrologist/nurse encouraged to discuss symptoms at next clinical encounter

Does measuring a problem cause change?

Symptom Monitoring with Feedback Trial (SWIFT) at a global level



INTERVENTION



3-monthly IPOS-Renal (Symptoms)



Results sent to dialysis nurse unit manager and nephrologist



Issues around outcomes

Registry outcomes

- ▶ “Pragmatic”; rarely surrogate
- ▶ Not audited or “validated”
- ▶ Oriented to longer term
- ▶ Not necessarily targeted to intervention

RCT outcomes

- ▶ Carefully defined to fit intervention
- ▶ May be surrogate
- ▶ Audited
- ▶ Defined to fit time frame of trial

Reflections

- ▶ Registry outcomes measures need to be quick, easy, unambiguous, cheap to measure and robust
 - ▶ works for large, multicentre, highly pragmatic trials with clinically easily measurable endpoints
 - ▶ Won't work for many other situations
- ▶ “Validated” endpoints not readily available in Registries
 - ▶ Involvement in trials will likely lead to increase audit / validation of Registry
- ▶ Other models of embedding trials in Registries
 - ▶ Platforms; linkage for followup
 - ▶ Opportunity for validation of surrogate endpoints.....

Ultimate aim: a linked and learning health system



Registry - ANZDATA
Trials Network - AKTN
Guidelines - CARI
Evidence Synthesis - Cochrane

ANZSN
KHA
TSANZ



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Organ and Tissue Authority



Australian Government
National Health and
Medical Research Council

