"**C**anadian-**A**ustralasian **R**andomised Trial for **S**creening **K**idney Transplant Recipients for Coronary Artery Disease."

NHMRC

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

Investigators Meeting American Society of Nephrology Kidney Week

"The District" November 4, 2019

Where to find CARSK

- **www.carsk.org**

- **Trial registration**
  The trial is registered at ANZCTR and Clinicaltrials.gov.
  ACTRN12616000736448 (WWW.ANZCTR.ORG.AU)
  NCT03674307 (CLINICALTRIALS.GOV)

- **Trial funding**
  NHMRC Funded Clinical Trial Project Grant #1084454
  CIHR Grant #389992

CARSK Publications

- *CJASN* – How I treat series Jan/2019
  - https://cjasn.asnjournals.org/content/14/1/112
- Trial Protocol - The *American Heart Journal Volume 214* August 2019, Pages 175-183
- Trial Economic model – AJKD in press

CARSK TEAM

- Project Lead: Gillian Hughes
- Steering Committee: Jag Gill, Scott Klarenbach, Joe Kim, John Gill, Greg Knoll, Steve Chadban, Tracey Ying, Charles Herzog, Angela Webster
- Advisory Committee: Tim Ramsay, PJ Devereaux, Rachel Morton, Krish Ramanathan, Cello Tonelli, Patrick Kelly, Ben Chow
- Data Co-ordination – North America, Germany, UK – Vancouver
- Data Co-ordination – Australasia/ Spain - Sydney

SC Meets Every Two Weeks

- Open to any investigator
- Contact Gillian Hughes to join

Clinical Events Committee

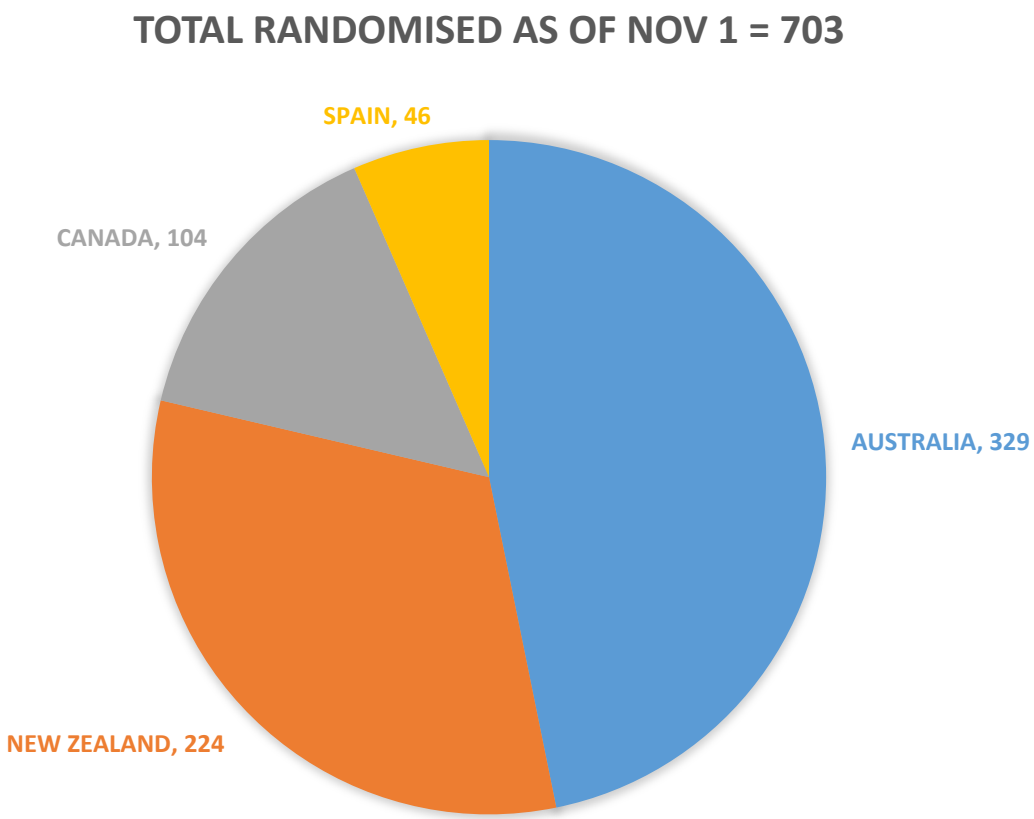
- Chair – Charles Herzog

DSMB

- Andreas Laupacis - Chair
- Andrew Day-Statistician/Queens University
- Brenda Hemmelgarn – Nephrologist/ Dean of Medicine U of A
- Matthew Jose - Nephrologist Tasmania
- Anushka Patel - Cardiologist Sydney/ Royal Alfred

- Independent Statistician – Stephanie Clark

CARSK Total Enrollment = 3306

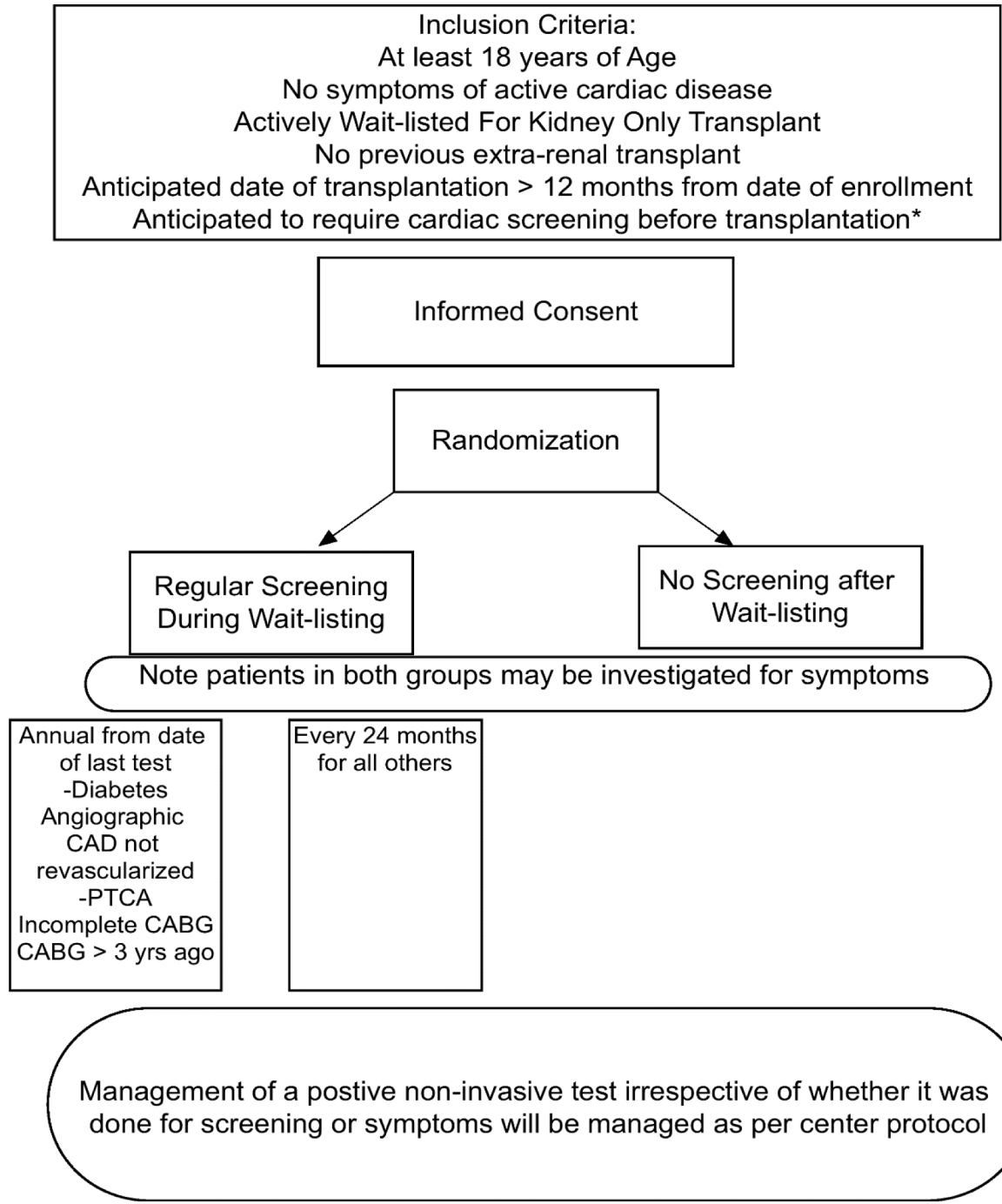


count	Country	City	SITE - 50 patients is minimum commitment	PI	TARGET BY	TARGET BY	TARGET	PROGRESS
1	Australia	Sydney WM	Westmead Hospital	Webster			1000	115
2	Australia	Sydney RPAH	Royal Prince Alfred Hospital	Chadban				111
3	Australia	Clayton	Monash Medical Centre					18
4	Australia	Kogorah	St George Hospital					17
5	Australia	Heidelberg AUS	Austin Hospital					14
6	Australia	Melbourne	Box Hill Hospital					14
7	Australia	Adelaide	Royal Adelaide Hospital	Clayton				10
8	Australia	Sydney RNS	Royal North Shore Hospital					23
9	Australia	Randwick	Prince of Wales Hospital					7
10	Canada	Toronto UHN	University Health Network	Kim	83	7	250	
11	Canada	Toronto UHG	St Michael's Hospital	Prasad	83	7	250	
12	Canada	Ottawa	The Ottawa Hospital	Knoll	66	6	200	
13	Canada	Hamilton	St Joseph's Healthcare	Ribic	50	4	150	
14	Canada	London CAN	London Health Science Centre	Jevnikar / Gunaratna	16	1.5	50	2
15	Canada	Montreal MCG	McGill University Health Centre	Cantarovich	33	3	100	
16	Canada	Halifax	Queen Elizabeth II Health Sciences Centre	Vinson	33	3	100	
17	Canada	Montreal CHUM	University of Montreal CHUM	Cardinal	50	4	150	
18	Canada	Montreal Maison	University of Montreal Maisonneuve-Rosemont	Tran	16	1.5	50	
19	Canada	Laval	University of Laval	DeSerres	16	1.5	50	
20	Canada	Saskatoon	Royal University Hospital	Mainra	16	1.5	50	
21	Canada	Kingston	Kingston General Hospital	Shamseddin	16	1.5	50	
22	Canada	Vancouver SPH	St Paul's Hospital	Gill	116	10	350	65
23	Canada	Vancouver VGH	Vancouver General Hospital	Johnston	100	8	300	37
24	Germany	Heidelberg GER	Universitatsklinikum Heidelberg	Morath				
25	Germany	Berlin	Charite	Budde				
26	New Zealand	Auckland	Auckland City Hospital	Pilmore			206	173
27	New Zealand	Wellington	Wellington Hospital					26
28	New Zealand	Dunedin	Dunedin Hospital					15
29	New Zealand	Christchurch	Christchurch Hospital					10
30	Spain	Barcelona	Bellvitge Hospital	Mellili				46
31	UK	London UK	St George's Hospital	Bannerjee				
32	USA	Austin TX	Baylor Scott White Hospital Systems	Kaplan / Khan				
33	USA	Washinton, DC	George Wash University Hospital	Raj				

Hypothesis

- After screening for wait list entry, non use of cardiac screening tests is non-inferior versus the current standard care, which is screening all asymptomatic wait-listed patients for coronary artery disease (CAD) at regular intervals

- Centres were not willing to forgo screening prior to wait-listing


Inclusion Criteria:
At least 18 years of Age
No symptoms of active cardiac disease
Actively Wait-listed For Kidney Only Transplant
No previous extra-renal transplant
Anticipated date of transplantation > 12 months from date of enrollment
Anticipated to require cardiac screening before transplantation*
Informed Consent
Randomization
Regular Screening During Wait-listing
No Screening after Wait-listing
Note patients in both groups may be investigated for symptoms
Annual from date of last test
-Diabetes
Angiographic CAD not revascularized
-PTCA
Incomplete CABG
CABG > 3 yrs ago
Every 24 months for all others
Management of a postive non-invasive test irrespective of whether it was done for screening or symptoms will be managed as per center protocol

Patient eligibility

- Newly wait-listed and prevalent wait-list patients

Enrollment of Newly Wait-listed Patients

- Patients may be consented at time of their in person transplant center evaluation even if they are not yet activated to the wait-list
  - Patients complete any outstanding tests
  - Patients randomized when they are activated to WL
  - Important to ensure communication between WL clinical team and CARSK clinical trial co-ordinator

Enrollment of prevalent WL patients

- Must be active on WL
- Enrollment can take place at either a WL monitoring visit or during a dialysis treatment
  - We have not operationalized telephone consent for WL patients receiving dialysis at a distance

Patient eligibility

- Patient must require a screening test before anticipated date of transplantation by your site's standard of care
- Suggested screening frequency
  - Diabetes, known coronary disease – yearly
  - All others 2 years

- In general patients expected to undergo transplantation in < 12 months should not be enrolled

NOTE

- CARSK is testing the intention to screen
- Use the date of the last completed screening test to guide your determination of patient eligibility
- If the date of the next screening test by SOC (based on the last available screening test) is < than anticipated date of transplantation the patient is eligible to participate

Example -The following patient is eligible

- Actively wait-listed
- 55 year old Diabetic (mature onset)
- Blood group A, 0% cPRA
- On list for 1.3 years – expected to receive an offer in next 10 months
- Asymptomatic
- Last MIBI 2017 Sept (i.e. 24 months ago)
- Even though the patient will undergo transplant within next 10-12 months, he is past due for a MIBI test by SOC
- If you are happy for him to remain on your from a clinical perspective he can be enrolled and randomized (i.e. you have to be happy with him potentially being randomized to no-screening)
- Caveat if he is randomized to regular screening the MIBI must be ordered right away and completed before the anticipated date of transplantation

Example -The following patient is eligible

- Actively wait-listed
- 50 year old male
- Blood group 0, 40% cPRA
- CABG 33 months ago
- On list for 2.5 years – expected to receive an offer in next 12-15 months
- Asymptomatic, swimming 30 min 3x/ week
- Last MIBI – none since CABG, had echo 1 year post CABG which showed preserved LV function
- Even though the patient will undergo transplant within next 12 months, he will be due for a MIBI test by SOC in 3 months (i.e. 36 months post CABG)
- If you are happy for him to remain on your from a clinical perspective he can be enrolled and randomized
- Caveat if he is randomized to regular screening the MIBI must be ordered to take place in 3 months so that it is done well before the anticipated date of transplantation

Example – This patient is not eligible

- 48 year male PKD – blood group A, cPRA 0, started dialysis 18 months ago, not yet wait-listed, will likely be transplanted in next 4-6 mo
- Last MIBI – 28 months ago, normal
- Asymptomatic, active
- If you are happy for him to be randomized without further testing, he could be enrolled…
- If randomized to regular screening, he would need a MIBI right away
- But - He lives in a remote community and it may be difficult to get MIBI in next 4 mo

Eligibility of patients listed in multiple centers

- We had not considered this issue as not allowed in Canada
- Such patients are not eligible

Patient Follow Up

- We rely on two main strategies for outcome ascertainment

- Clinical standard of care
  - Events in WL patients that could impact transplant eligibility must be reported to Transplant Center
    - Excellent communication between Study Co-Ordinator and Transplant Center WL Staff is essential

- Six-monthly telephone per protocol, or in-patient interviews
  - Documentation of events identified by this mechanism should be ordered by the site PI as clinical SOC rather than for “research purposes”

Adjudicated Events

- Cardiovascular death
- Non-fatal MI
- Urgent revascularization for symptoms
- Hospitalization for unstable angina
- Death from any cause
- Stroke
- Major bleed / procedural bleed

CARSK Timelines

- Complete Enrolment – March 2022
    - CARSK Canada Goal
        - To have every site active by end 2019
            - To have at least 10 patients enrolled in every site
- Last patient follow- up:
    - Patients who remain wait-listed 5-year follow-up – March 1 2027
    - Patients who undergo transplantation – must be followed for 12 months
        - March 1, 2028 is therefore technically the last follow-up date

DSMB will assess trial safety at two *a priori* time points

- We anticipate n = 630 total MACE events
- After accumulation of ¼ of the anticipated MACE Events (n =158)
- After accumulation of ½ of the anticipated MACE Events (n=315)
- DSMB will receive information regarding trial enrolment every 6 months

Contamination

- Off-protocol tests
- Missed screening test

- Communication tools
  - Alerts on transplant center and dialysis chart
  - Letter to primary nephrologist and cardiologist
  - Local “CME”
  - Patient wallet card and diary
  - Patient engagement strategies (TBD)

Data Capture / Integrity

- REDCap
- Regular audits
- Frequent communication with sites

Team Ethos/ Culture

- Horizontal not vertical
- In it for the patients/science

The moral peril of meritocracy

Communications

- Website
- Newsletter
- SC calls Q 2 weekly
- Site PI calls – q 6 months and as needed
- Email anytime

Thank You / Merci !!!!