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UKCRC Registered Clinical Trials Units

NHS Blood and Transplant

The PITHIA Trial:

a stepped wedge, cluster randomised, registry based national trial with economic evaluation

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Current developments in cluster randomised trials and stepped wedge designs, 12th November 2019

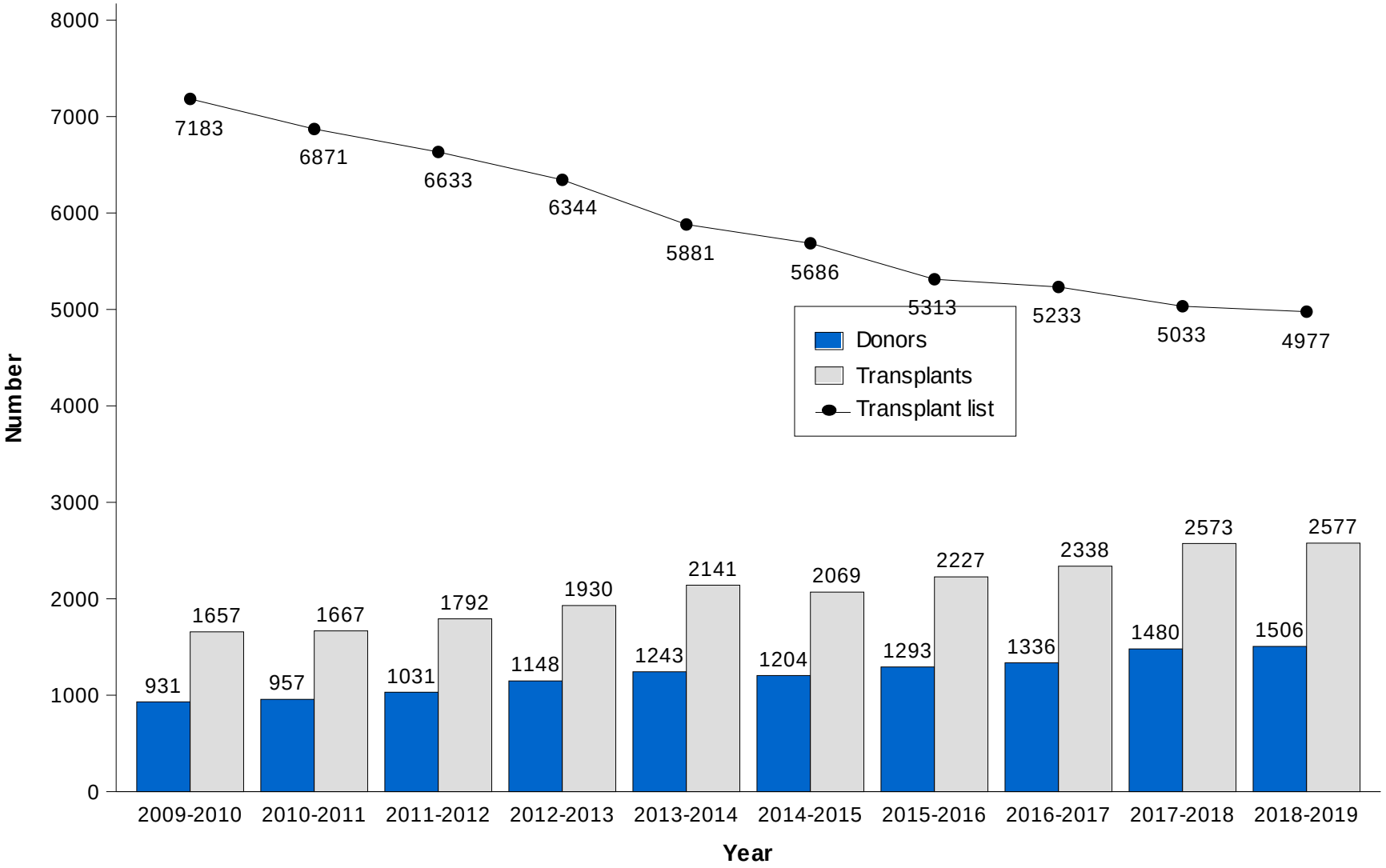
@PITHIA_trial
@NHSBT_CTU

Caring Expert Quality

Background

NHS Blood and Transplant

Deceased donor kidney programme in the UK, 1 April 2009 - 31 March 2019,
Number of donors, transplants and patients on the active transplant list at 31 March



Background

NHS Blood and Transplant

Shortage of kidneys

> 70% people dying in critical care >50 years

Use of kidneys from older donors has increased donation

More than twice as likely to lose kidney if donor > 60 years

Higher complication rates: Primary non-function (PNF) 4.2% vs 1.9% PNF mortality – 25% at 1 year

How to sort the transplantable from the not?

Remuzzi Score

NHS Blood and Transplant

- Take a small (4mm) biopsy from donor kidney, which is scanned and emailed to the histopathologist, who scores the kidney

- Remuzzi score measures background injury and based on 4 clinical variables
- Score provides guidance on how the kidney should be implanted

PITHIA

NHS Blood and Transplant

- **P**re-**I**mplantation **T**rial of **H**istopathology **I**n renal **A**llografts
- Ancient History: The Pythia was consulted for predictions about the future

- **Idea:** Performing an urgent biopsy of the donor kidney will help to identify those kidneys which are suitable for transplantation, improve function and improve utilisation of kidney if it is transplanted

Trial design

NHS Blood and Transplant

- Stepped wedge, cluster randomised
  - To allow all centres the chance to have access to the biopsy service at some point during the trial
  - Logistically easier
- Registry based
  - Majority of the outcome data will be obtain from the UK Transplant Registry, held by NHS Blood and Transplant
  - Only one additional data collection form, to collect the histopathology information and Remuzzi score
- Blinding
  - No blinding to the intervention, once the date of switch from control to intervention has been revealed (3 months prior to switch)
- Economic evaluation
  - decision-model based to determine whether the intervention is cost-effective

Summary of the trial

NHS Blood and Transplant

- **P**opulation: Kidneys from deceased donors aged over 60
- **I**ntervention: Recipient centres have access to national histopathology service
- **C**omparator: Usual care i.e. no access to national histopathology service
- **O**utcome:

Primary

- Proportion of kidneys that are transplanted on first offer
- Estimated glomerular filtration rate (eGFR) measured at one year after transplant

Secondary

- Proportion of kidneys utilised
- Total number of kidney transplants performed
- Number and proportion of ‘single’ vs ‘dual’ kidney transplants performed
- Biopsy utilisation and fidelity: defined as the proportion of kidneys that are biopsied in concordance with the education plan, out of all kidney biopsies
- Survival of the kidney and patient

Trial team

- Principal Investigator: Gavin Pettigrew
- Sponsor: Cambridge University
- Funder: NIHR Research for Patient Benefit
- NHS Blood and Transplant Clinical Trials Unit
- Karla Hemming (member of TMG) and Richard Hooper (member of TSC)
- Embedded into the UK Organ Donation and Transplantation Community
  - All 22 UK Kidney Transplant Centres
  - NHSBT Organ Donation and Transplantation Hub
  - >200 Specialist Nurses for Organ Donation, 10 National Organ Retrieval Teams
  - 6 laboratories with biomedical scientists, 16 Histopathologists
  - Patient representatives and charities

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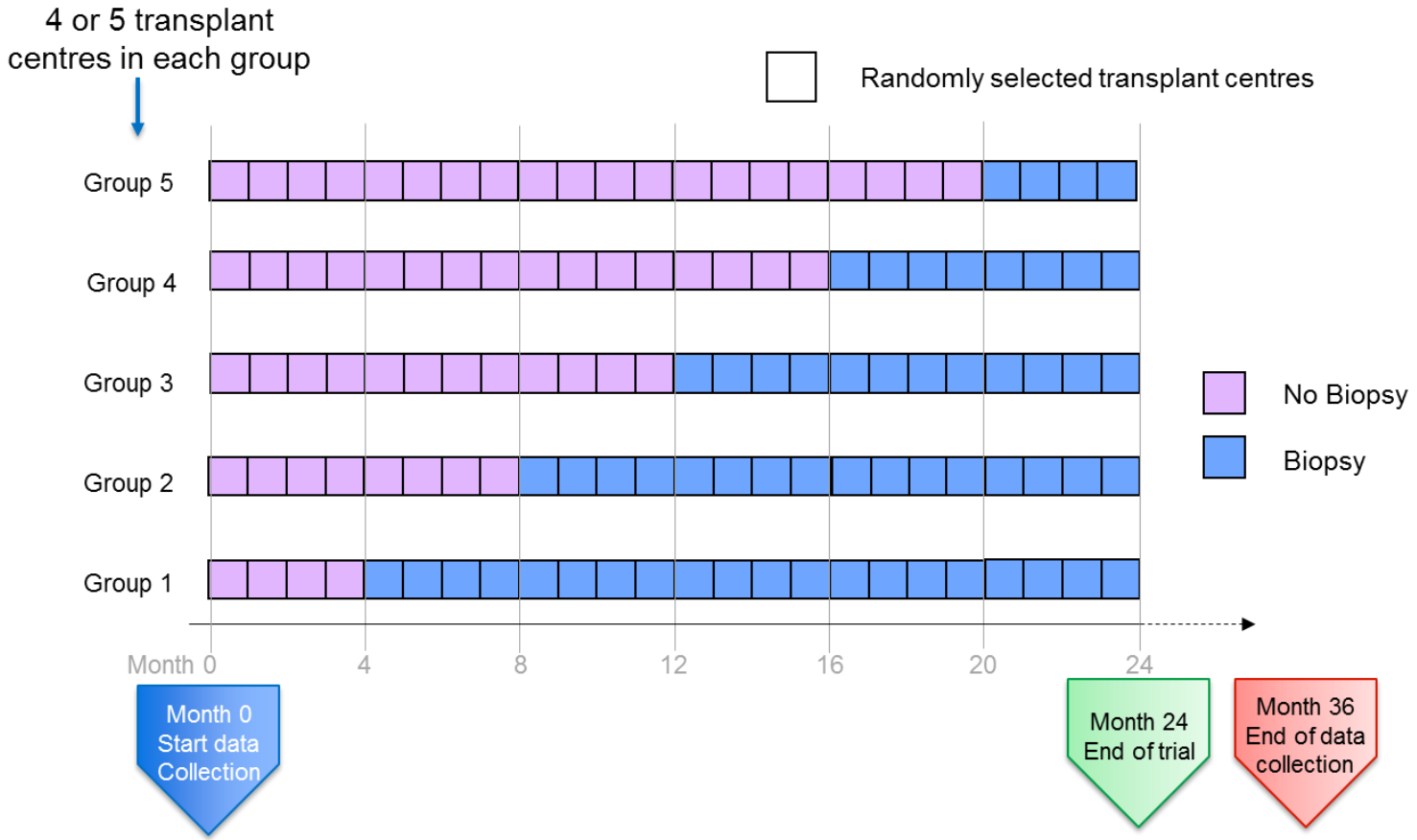
Sample size and randomisation

Sample size

NHS Blood and Transplant

- Based on 20 centres (allow for subsequent nonparticipation - albeit unlikely)
- No planned ‘roll-out’ periods within the study



- Didn’t allow for variation in cluster size as SW designs minimally affected*

*Martin, J. Advancing knowledge in stepped-wedge cluster randomised trials. *Univ. Birmingham, Unpubl. Dr. thesis* (2017).

Sample size

NHS Blood and Transplant

- Estimates for the sample size calculations were obtained from the UK Transplant Registry, held by NHS Blood and Transplant
- Methodology: Hooper et al. (2016)[1] and Hooper and Bourke (2015)[2]
- Implemented using SAS and an RShiny app
  https://clusterrcts.shinyapps.io/rshinyapp/
- As we have two primary outcomes a Bonferroni correction was applied and hence a 2.5% significance level was used
- Checked sensitivity to these power calculations across a range of intra-cluster correlations (ICCs), Cluster Autocorrelations (CAC) and baseline proportions

[1] Hooper, R., Teerenstra, S., de Hoop, E. & Eldridge, S. Sample size calculation for stepped wedge and other longitudinal cluster randomised trials. *Stat. Med.* **35,** 4718–4728 (2016).

[2] Hooper, R. & Bourke, L. Cluster randomised trials with repeated cross-sections: some alternatives to parallel group designs Cluster randomised trials with repeated cross sections: alternatives to parallel group designs. *BMJ* **350,** (2015).

First primary outcome

NHS Blood and Transplant

Proportion of kidneys that are transplanted on first offer

- Data extracted on first kidney offers from deceased donors aged ≥60yrs in the UK, 1 April 2014 - 31 March 2016

Median number first offers per centre per month (pcpm)	Median number first offers pcpm transplanted
4.38	1.21
Current utilisation rate: 28%	

First primary outcome

NHS Blood and Transplant

Proportion of kidneys that are transplanted on first offer

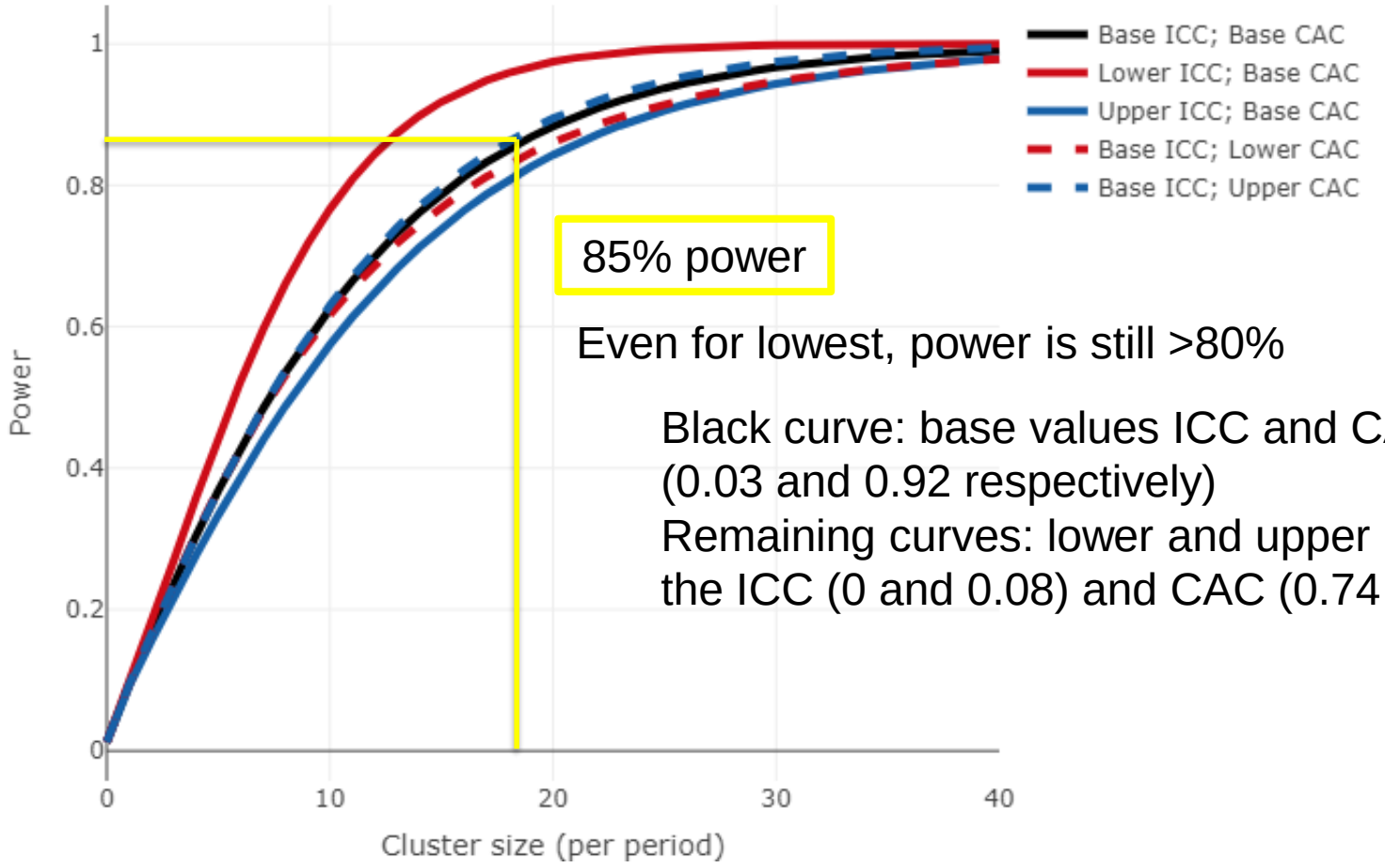
- Fitted a mixed logistic regression model
  - A binary outcome: whether the offer resulted in a transplant
  - Fixed effect for period
  - Random effect for cluster
  - Random interaction between cluster and period
  - Restricted maximum likelihood was used for model estimation
- From this model, obtained
  - within period intra-cluster correlation (ICC) = 0.03
  - cluster autocorrelation (CAC) = 0.92
- Assumed
  - Average cluster-period size = 18
  - Aiming to detect an 11% increase in the number of first offers transplanted i.e. from 28% (current utilisation rate) to 39%

First primary outcome

Proportion of kidneys that are transplanted on first offer

NHS Blood and Transplant

Power curve



85% power

Even for lowest, power is still >80%

Black curve: base values ICC and CAC (0.03 and 0.92 respectively)
Remaining curves: lower and upper levels of the ICC (0 and 0.08) and CAC (0.74 and 1)

Second primary outcome

Estimated eGFR at one year after transplant

NHS Blood and Transplant

- Data extracted: Kidney only transplants from deceased donors, aged ≥60yrs in the UK, 1 April 2014 and 31 March 2016

Mean eGFR	Standard deviation
41.89 ml/min	16.05 ml/min

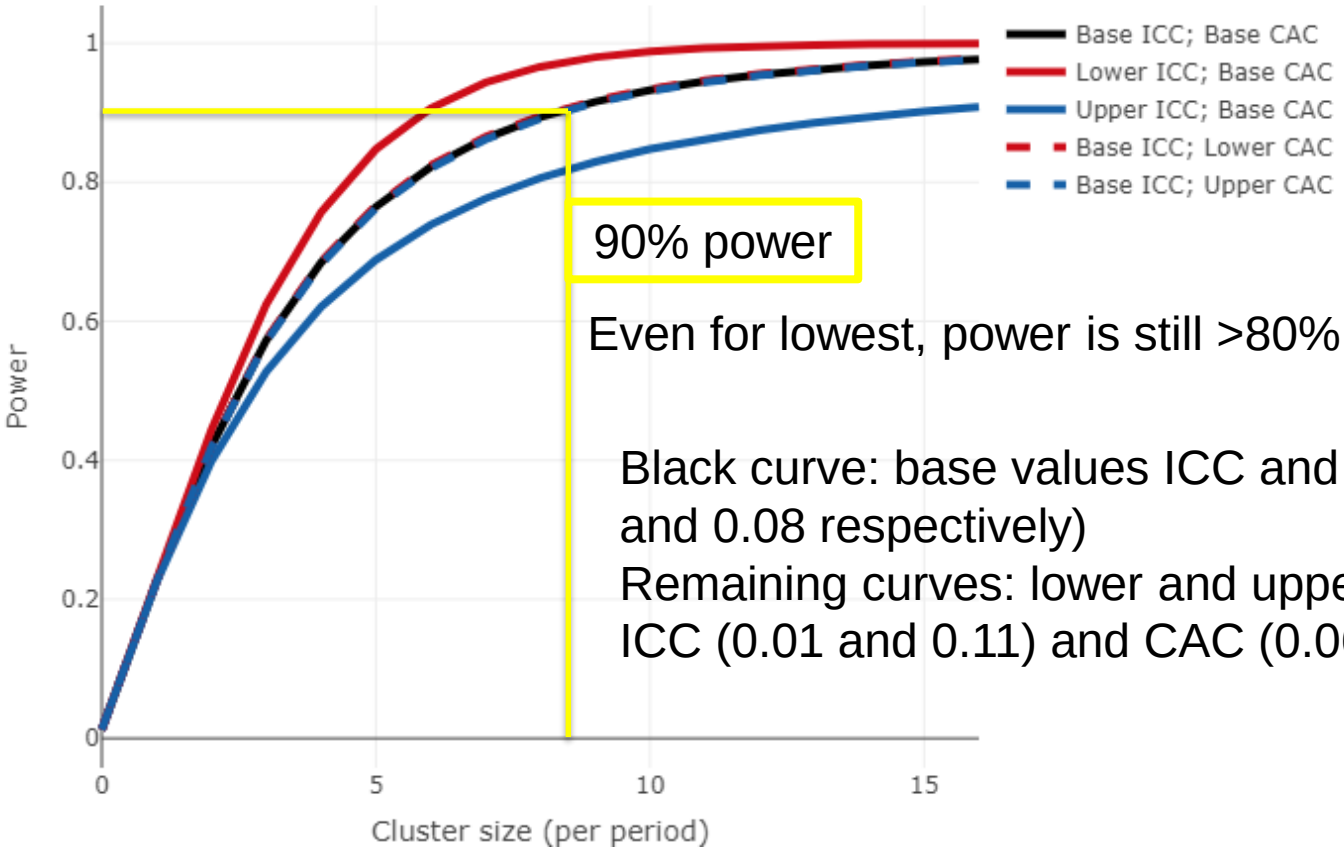
- Fitted mixed linear regression model, from which obtained
  - within period intra-cluster correlation (ICC) = 0.06
  - cluster autocorrelation (CAC) = 0.08
- Assumed average cluster-period size = 8
- Aiming for a standardised effect of 0.25, which is equivalent to a change in eGFR of about 6 ml per minute

Second primary outcome

Estimated eGFR at one year after transplant

NHS Blood and Transplant

Power curve



Even for lowest, power is still >80%

Black curve: base values ICC and CAC (0.06 and 0.08 respectively)
Remaining curves: lower and upper levels of the ICC (0.01 and 0.11) and CAC (0.06 and 0.10)

As the CAC was particularly small, separately explored CAC=0.8 and found this had minimal impact

Limitations

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- Calculations were performed Autumn 2017
- The assumed two parameter correlation structure probably unrealistic
- More realistic assumption may have been
  - discrete time
  - continuous time decay correlation structure
- Checked correlation structure of historical routinely collected data

Model	AIC	BIC	-2ResLL
Cluster auto-correlation set to 1 (Random intercept for cluster/ Hussey and Hughes model)	278165	278168	278161
Cluster auto-correlation without a decay (Random cluster-period interaction)	**278059**	**278064**	**278053**
Exponentially decaying cluster auto-correlation (Exponential decay for correlations between cluster-period random effects)	278161	278165	278026

  - In exponential decay model, the estimate of the decay parameter was negative
  - May be a more complex correlation structure

Randomisation

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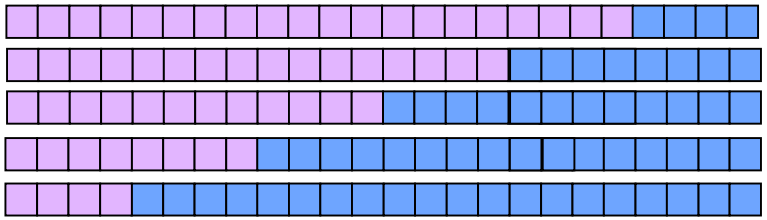
- Restricted randomisation technique to randomly allocate the clusters to their cross-over date
- Created 10,000 allocation sequences: unique combinations of grouping clusters into 5 groups
- Used historic data and for each sequence calculated the number who would have been exposed to intervention and control group

Balance statistic = **Total number of first offers in intervention** minus Total number of first offers in control



- Randomly selected 1 allocation sequence, constrained so that the total sums (kidneys) exposed to intervention and control statuses were no different than expected middle 25th percentile range of differences
- Independent statistician ran the randomisation program and produced randomisation envelopes

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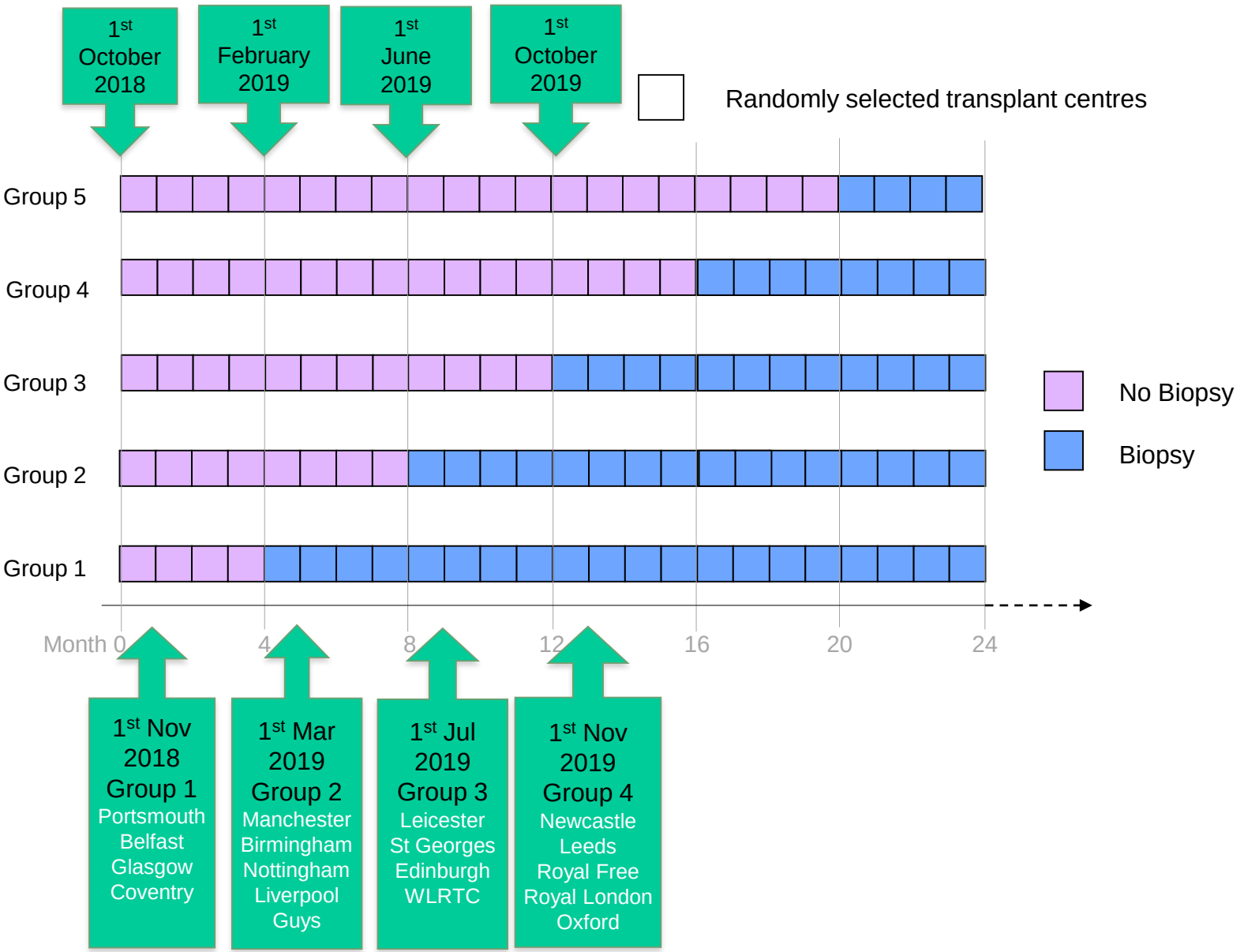
The trial so far

PITHIA trial design

NHS Blood and Transplant



Our experience so far

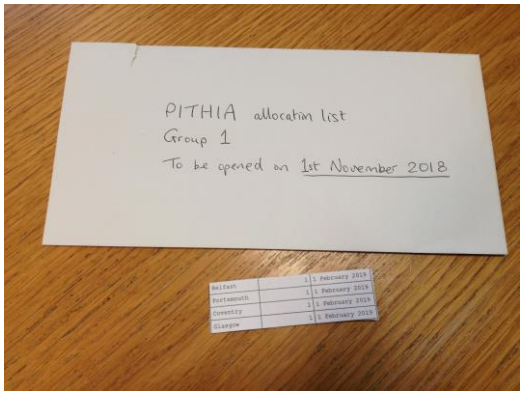
NHS Blood and Transplant

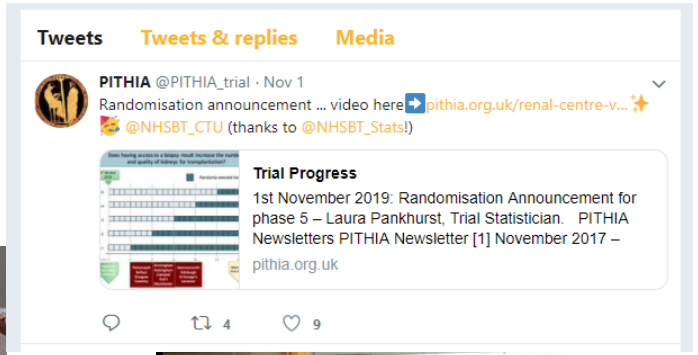
- From ethics being granted (December 2017) it took 10 months for all sites to give approval
- Phased roll out of the intervention
  - Logistically complex, allow colleagues to become familiar with process
  - Lots of people involved, colleagues still finding it a “new” process
- Intervention is access to the biopsy service
  - Slow uptake in using the service
  - Fewer biopsies have been requested than initially thought
- Trial was paused for 1 week due to safety concern
  - Not in PITHIA but in a research study utilising a similar biopsy technique
  - Slight modifications to the biopsy technique were made
- Non-familiarity with the design

Our experience so far

NHS Blood and Transplant

- Randomisation announcements have been a good way to engage sites





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Analysis

Analysis

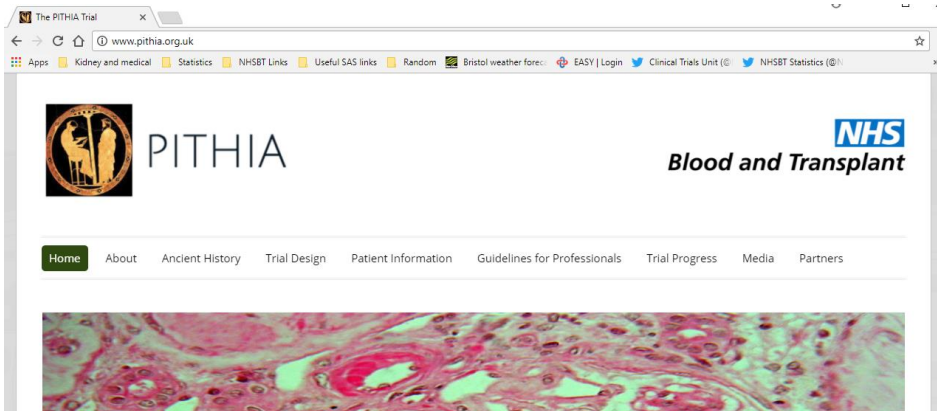
NHS Blood and Transplant

- All primary and secondary outcomes will adjust for cluster and cluster by period (random effects) and for period (fixed effect)
- First primary outcome: Proportion of kidneys transplanted on first offer
  - Logistic regression model for hypothesis t… …nfidence interval
  - Binomial model with identity lin…
- Second primary out… …1 year post transplant
  - Normal linear regr… …model
  - Sensitivity analysis will explore effect of participants who do not make it to 1 year post transplant (due to death or loss of kidney)
- Now considering whether a different correlation structure would be more appropriate for the analyses

November 2017

Summary

- PITHIA is a Stepped Wedge Cluster Randomised, registry trial looking to assess whether access to a National Histopathology Service increases utilisation and improve outcomes
- Exciting to be involved in NHSBT's first SW-CRT
- 24 months in duration and currently 14 months into the trial
- Logistically challenging, involving lots of different people
- More information:
  - Ayorinde JOO, Summers DM, Pankhurst L, et al. PreImplantation Trial of Histopathology In renal Allografts (PITHIA): a stepped-wedge cluster randomised controlled trial protocol. BMJ Open 2019;9:e026166. doi:10.1136/ bmjopen-2018-026166
  - Twitter - @PITHIA_trial
  - www.PITHIA.org.uk



Disclaimer

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Thank you

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