NHS Blood and Transplant

HLA Matched Red Cells for Renal Transplant Patients

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NHS Blood and Transplant &

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Background:

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- Average kidney transplant lasts 10-15 yrs;
  - rejection is commonest cause of its failure
- Patients who develop donor-specific HLA Ab's (DSA) are at ↑ risk of rejection/failure
- "treatment" of DSA graft rejection is poor, so mechanisms to prevent DSA are focus
- Pregnancy, previous renal transplant & transfusion are associated with ↑ HLA Ab's
  - Only transfusion is modifiable (review factors - Scarnick. Am J Transpl 2011)

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Background: ctd

- Association of Tx with ↑DSA
  - Willicombe, abstract Renal Ass'n/BRS, Glasgow 2014;
  - Redfield, Nephrol Dial Transpl 2016.

- Even LD blood still a problem as:
  - Lymphocytes 2x10^5 class I HLA per cell
  - Rbc 2x10^3 class I HLA per cell – but 1000x rbc:wbc in unit of red cells (LD);

- (kidney donor transfusion in 1970-80s improved transplant outcome, as 1yr graft survival 60-70%; but now 90% & better IS, so effect not evident)

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Factors in HLA Sensitisation

1. Effect of Tx: down-regulatory in naïve patients but stimulatory in previously exposed patients, so HLA Ab's in transplant candidates is:

– 10-12% if Tx up to 20 units, if no previous pregnancy/transplant. When produced, were low level & disappeared in months, even if further Tx

2. Age: 35% HLA sensitisation in age 5-20 versus 7.5% in age >20

3. Pregnancy alone: 5-33% HLA sensitisation (∞ technique)

– Tx & pregnancy: 40% vs 5% with no Tx; & higher titre & broad sensitisation

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Debate:

- A) Does Tx cause HLA Ab's to ag's from the Tx, which are also on kidney (DSA), so that HLA matched blood would prevent this, **OR**

- B) Does Tx cause general "immune stimulation" so that HLA Ab's formed (resurged from previous cause) even though Tx did not contain corresponding HLA ag's – therefore HLA matching of blood, would NOT prevent this

- Need to determine if patients who form HLA Ab's after Tx, received Tx with the corresponding ag on

Study:

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Renal Transplant Team, IC and NHSBT collaboration

- All renal transplant patients who were transfused: selected
  - 164 who developed kidney donor-specific antibodies (DSA) post-transplant
  - 164 controls, who didn't develop DSA

- To identify if donors of components had corresponding ag to HLA (DSA) Ab developed, needed to HLA type all donors

- IC: list of unit nos: of all components transfused - Maggie Przybysiak: looked up identity of all donors on PULSE
  - list of donors to Colin Brown, H&I – previously HLA typed?
  - rest to contact for HLA typing – need consent therefore for extra samples
  - needed ethics, R&D and BSCARE approvals

Flow Diagram for HLA Ab Study

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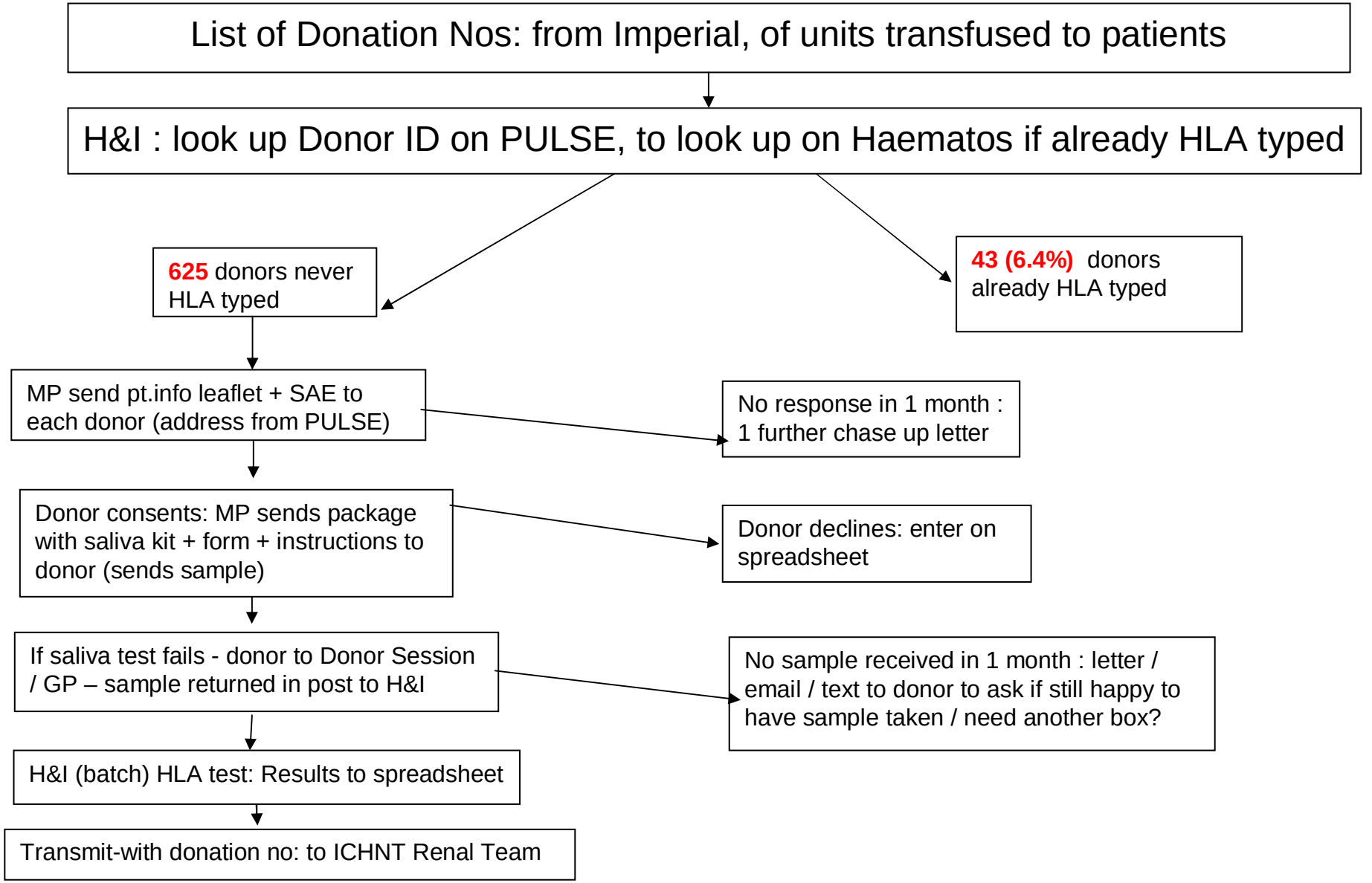

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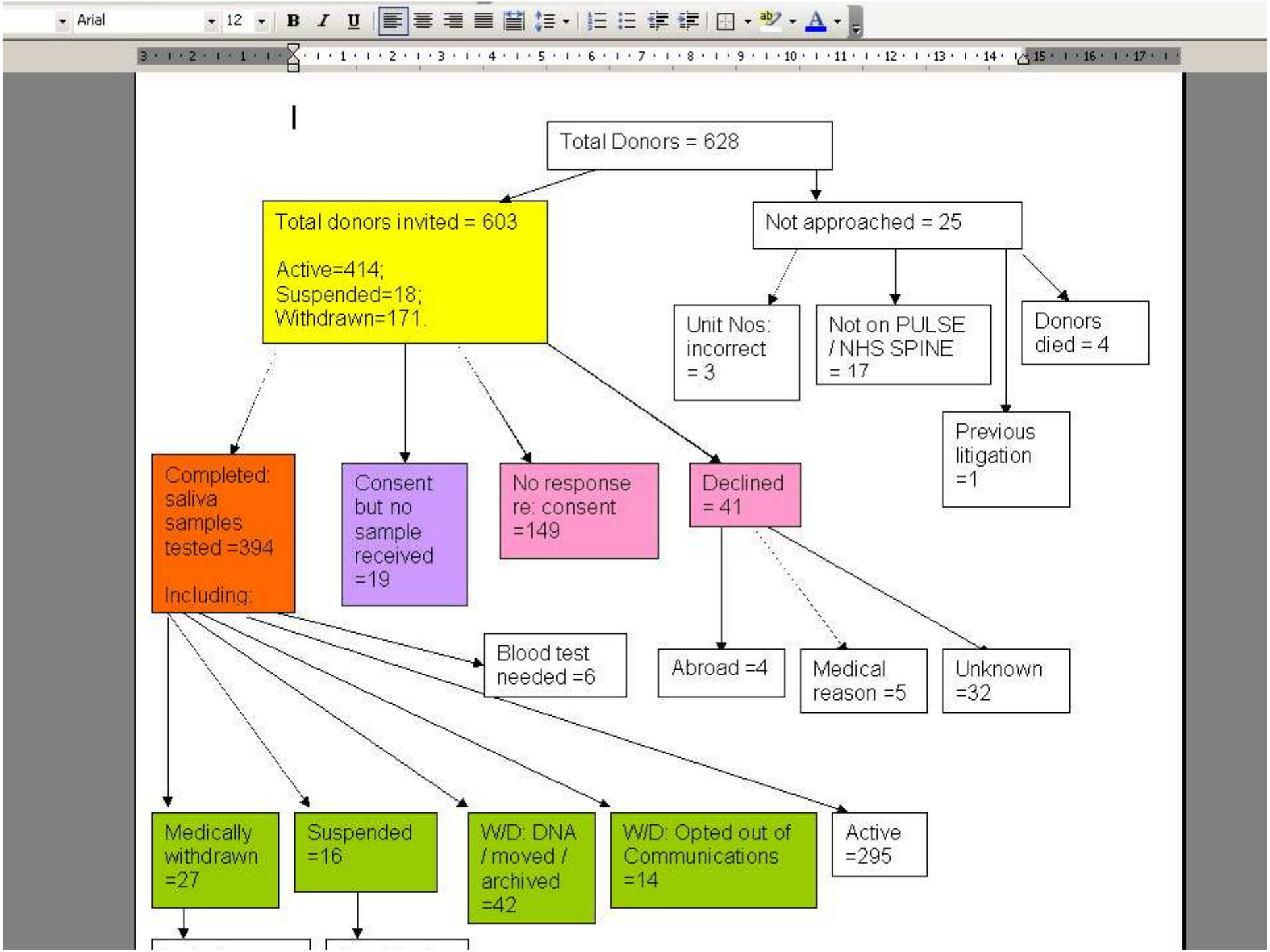
Methodology:

- Designed with H&I (Andrea Harmer, Colin Brown), Donor Services (Nicky Anderson, Jane Griffith – Area Nurse Manager, Eileen Bailey – NCC)
  - Estimated up to 10% might fail saliva kit test – so need blood sample
- Before contacting donors – checked all alive (on NHS Spine)
  - If donors suspended/withdrawn - F. Regan & in some cases, CST Drs Colindale – judged on PULSE reasons, if ok to contact
- Letters to donors (batches per week)
  - Info leaflet with consent form and SAE
  - Offer to answer queries
  - Send saliva kit once consent received: prepaid box to post back to F. Regan & PA
  - Chase up letter 1 month, if no reply

Testing

- H&I test in batches of 90
  - Paid for – on basis would get lot of HLA typed red cell donors out of it, in case need to HLA Match in future!
- Donors warned testing up to 6 weeks later, so may get letter to say “need blood sample” after that
  - Very few needed blood sample: 6 of 150 tested (4%)
- Agreed with Donor Teams nationally that if donor wanted sample taken at session, check with Area Manager first (to avoid overload); fully supportive of Study
  - Had letters with instructions and donors post sample
- Comms: Article in Connect and Donor Magazine – for staff and donor awareness


Total Donors = 628
Total donors invited = 603
Active=414;
Suspended=18;
Withdrawn=171.
Not approached = 25
Unit Nos: incorrect = 3
Not on PULSE / NHS SPINE = 17
Donors died = 4
Previous litigation =1
Completed: saliva samples tested =394
Including:
Consent but no sample received =19
No response re: consent =149
Declined = 41
Blood test needed =6
Abroad =4
Medical reason =5
Unknown =32
Medically withdrawn =27
Suspended =16
W/D: DNA / moved / archived =42
W/D: Opted out of Communications =14
Active =295

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HLA TYPING RENAL STUDY 2015-2017 (RESPONSE RATE = 394/625 = 63%)

Completed 6 needed BLOOD SAMPLE incl. 27 with 'Medical Condition', 16 Suspended/Active (incl. 1 Opt Out of Comms), 12 'Opt Out of Comms', 2 Withdrawn (CLI/ Veins), 1 Withdrawn-Xfer to Wales, 8 Withdrawn for own request (incl. 1 Retired from donating), 32 DNA (incl.1 Opt Out of Comms), 8 DNA/Archived, 4 Moved.	394
Chasing sample boxes (ie: signed Consent Forms) incl. 1 with 'Medical Condition' (16 chasing since 2016, 3 sent boxes recently), 1 Withdrawn (CLI/Underweight), 1 Opt Out of Comms, 1 Archived.	19
Chasing Consent Foms incl. 6 with 'Medical Condition', 2 Suspended, 60 Withdrawn (38 DNA-incl.1 Opt Out of Comms, 9 DNA/Archived, 3 Moved, 6 Moved/Archived, 4 Withdrawn for own request).	150
Did not want to take part incl. 5 with 'Medical Condition', 1 Withdrawn (CLI/VV3), 4 Non UK address (incl. 1 Retired, 1 DNA, 1 Withdrawn for own request, 1 Moved/Archived), 2 DNA, 1 DNA/Archived, 2 Withdrawn for own request, 1 Retired due to age, 2 Moved, *2 agreed (sample box sent)/Disagreed*.	41
Wrong address/No e-mail address (incl. 4 that unable to find in NHS Spine)	17
Deceased (identified in NHS Spine: not contacted)	4
Total	625

BREAKDOWN of donors contacted with Medical Condition (n= 39)

- Completed: 27
- Awaiting sample box: 1
- Declined: 5
- No response: 6 (Chasing Consent Forms)

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LIST OF DONORS WITH MEDICAL CONDITIONS – Total 39

COMPLETED:
Pernicious anaemia (gastro)
Celiac Disease
Splenomegaly
Malignancy x3
Cardiovascular x4
Vasovagal
Anaemia x2
3rd Consecutive Low Hb
Investigations
Renal condition
Drug Induced Hepatitis
High BP
TDW Post 1980
Lymphedema (leg cellulitis)
Dizzy episode
Low grade ductal carcinoma in situ
Colon Polyp – recovered
Stent fitted – narrow artery
Lump
Fractured Finger
Shoulder Injury

CHASING CONSENT FORMS:
Drug (Propiramite preventative)
Faints x2
Neurological (blackout despite)
Heart Attack
Cardiovascular
COPD
CHASING SAMPLE BOXES:
SVT (awaiting cardiac referral)
DID NOT AGREE:
Hypertension
Diabetes (on Metformin)
3 Consecutive Low Hb x2

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Non-”active” donors on PULSE, who completed study (n=68):

Suspended/returning to Active – 16 (4% of all who completed)

(incl. 1 ‘opt out comms’) due to malaria, endoscopy, pregnancy, Low Hb, investigations, own request

Didn`t attend blood session/Moved/Archived – 42 (10.6%)

(incl. 3 ‘opt out comms’)

Withdrawn – 2 (0.5%)

Clinical conditions (2 no suitable veins)

Withdrawn for own request – 8 (2.3%)

(incl. 1 retired from blood donation)

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Results (So far 108 donors tested)

- HLA typed 108 blood donors of 36 patients
  - All 36 patients developed de novo DSA post-transfusion
- 54/108 transfusions resulted in a Transfusion Specific Antibody (TSA): this was in 29 patients
- 33/108 transfusions resulted in a TSA which was the same specificity as the DSA: this was in 17 patients
- (completing further HLA typing by end of May: total 394 donors), plus 43 already HLA typed

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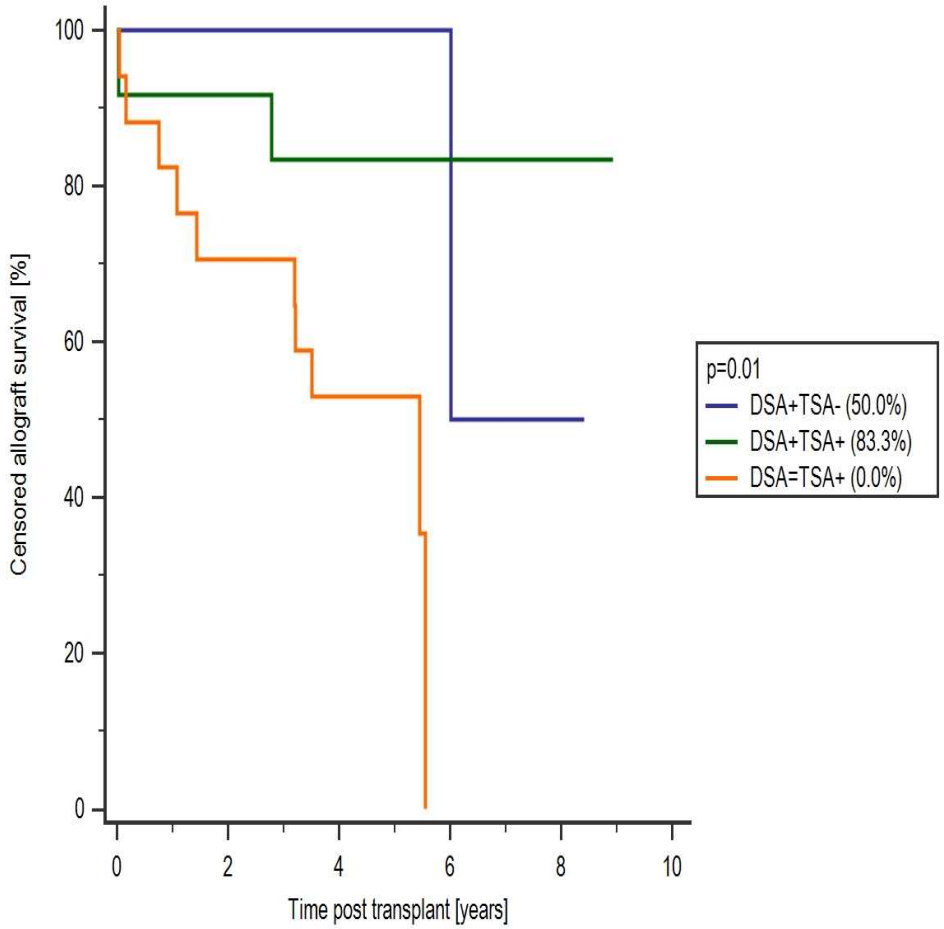
Censored allograft survival (in TSA+=DSA+ patients v TSA-DSA+ and TSA+ ≠ DSA+ patients)



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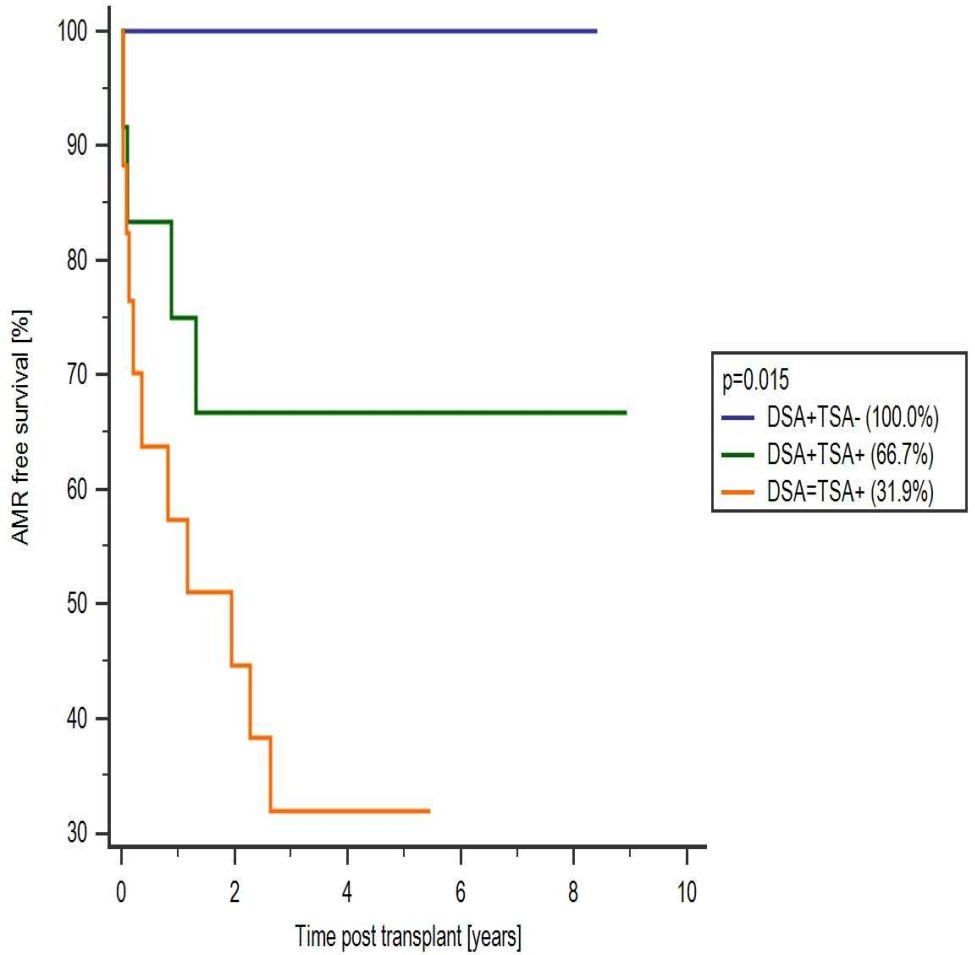
AMR free survival (in TSA+=DSA+ patients v TSA-DSA+ and TSA+ ≠ DSA+ patients)



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Where next?

- Early results: need further numbers to analyse
  - 316 HLA typed now;
  - total samples received = 394;
- Funding application to extend to larger study, to ascertain whether this is true finding.
- Abstract to BRS Meeting in March 2017

Questions