

# The INTERVAL studies

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## Optimising blood supply and donor health

***David J Roberts***  
***On behalf of INTERVAL study team***

di Angelantonio et al.

Efficiency and safety of varying the frequency of whole blood donation: randomised trial of 45,000 donors

Lancet, in press

# INTERVAL past, present & future



- Background
- INTERVAL Outline
- INTERVAL Study
  - How participants were recruited
  - Who they were and similarity to other donors
  - What data and samples were provided by study participants
- Answers but not results
- The next steps
- Future prospects

# What is the question?

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How can we collect blood safely and effectively ?

# Why?



## ➤ Demographic change

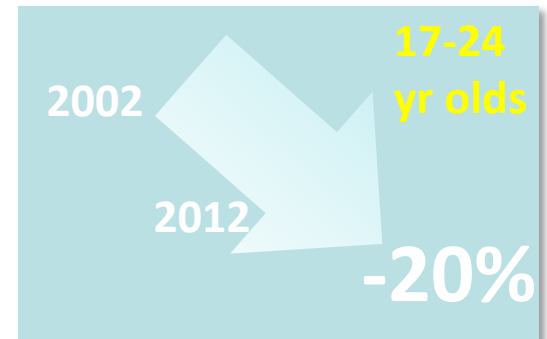
- Elderly get >50% blood transfused (Tinegate *et al*, 2013)
- Decreasing, small pool of eligible donors (currently only 4% of eligible pop<sup>n</sup>)

## ➤ Concerns about the effect of low iron on donors

- duty of care to donors

## ➤ Expectation for targeted, stratified or even personalised approach to health

- donor expectation
- optimise supply of specific types

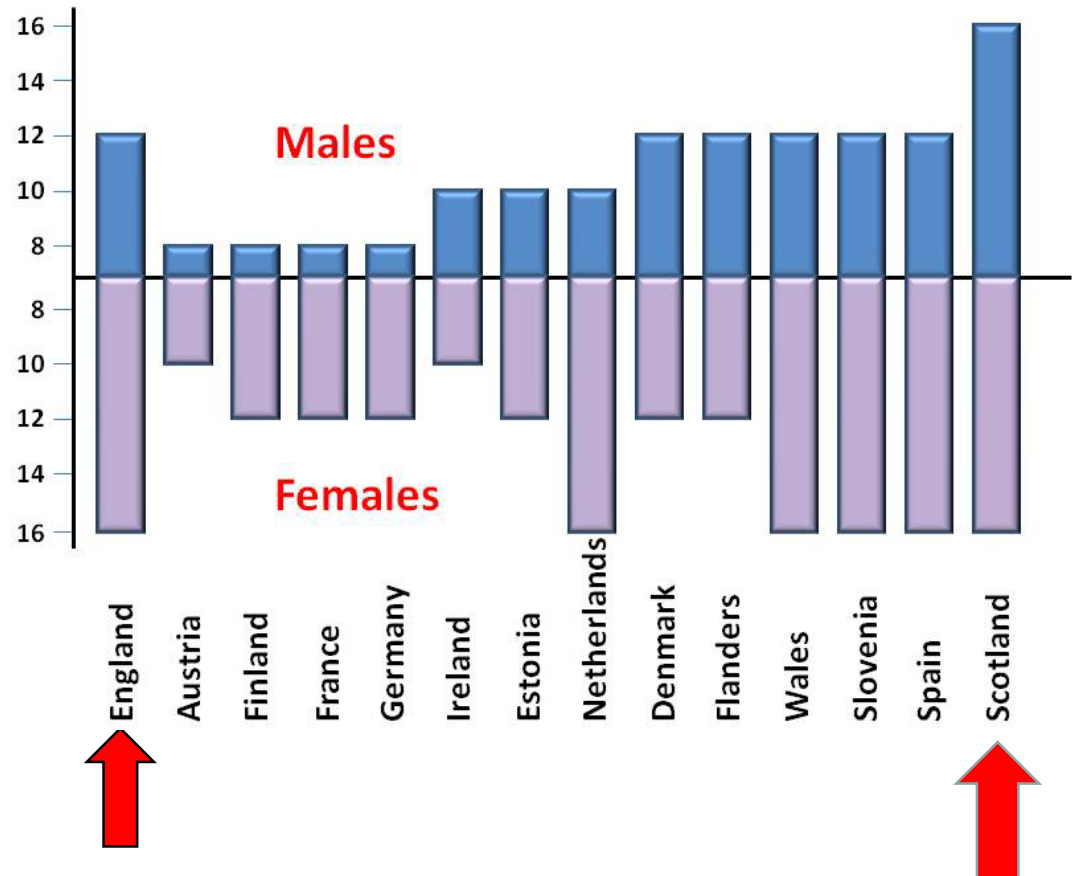


# Optimising donations...



- E.U. Blood Directive 2002/98/EC sets:
  - minimum donation intervals
  - maximum number of donations/yr
  - to minimise risk of iron deficiency in repeat blood donors
- BUT, no RCTs / definitive data to inform policies on donation frequency

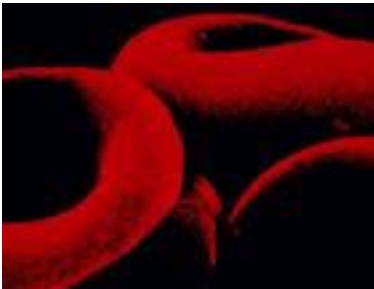
Interval between donations (weeks)



# Goals: to provide evidence



What are the optimum intervals between donations to:



Minimise risk  
of iron  
deficiency



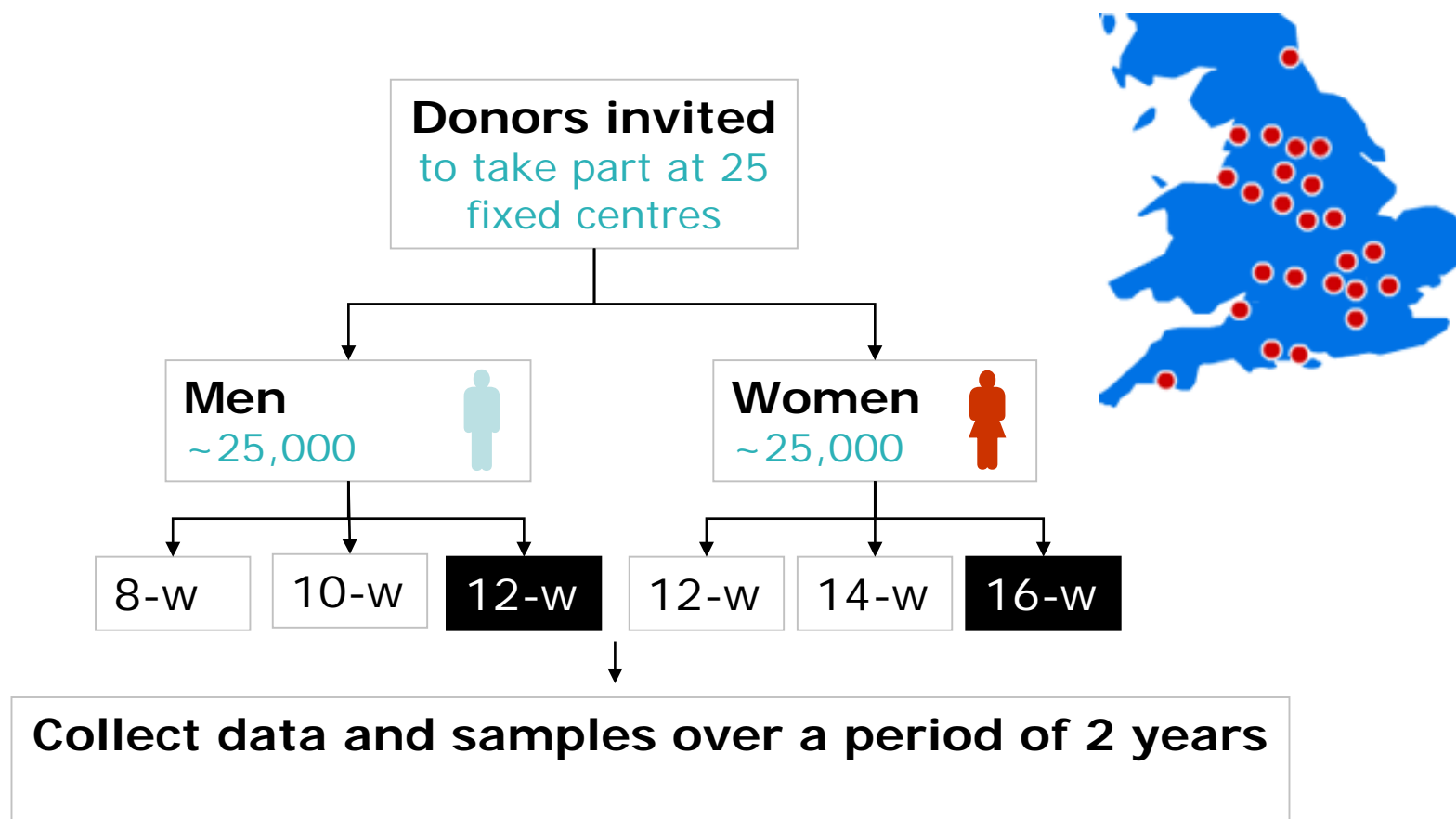
Maintain  
future blood  
supply?



Maintain well-  
being?

Is it appropriate to tailor blood donation intervals  
according to donors' susceptibility to iron deficiency?

# Study design



Pragmatic trial in routine setting

Moore C et al. (2014) *Trials* 15:363



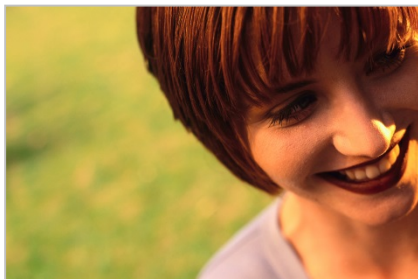
# Study Outcomes



Measuring broad range of outcomes to enable policy-makers to make an informed decision on optimum donation intervals i.e. impact on:



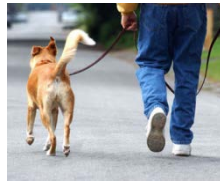
**Blood donations  
(primary)**



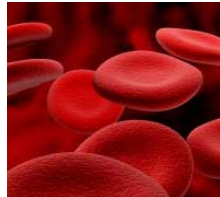
**Well-being  
(key secondary)**



**Cognitive function** 10-minute online tests of fluid intelligence, memory, attention



**Physical activity** objective measures through accelerometers



**Blood markers** iron status e.g. serum ferritin



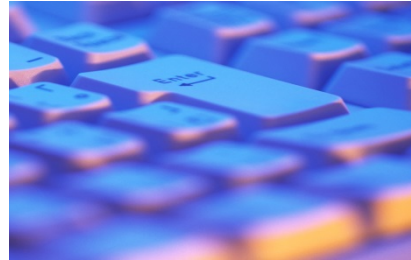
**Cost effectiveness** service / donor / societal and quality of life impact

# Embedding research

## in routine practice



Fieldwork at existing centres by existing donation staff



NHSBT databases used to register donors / make follow-up visits



Similar sample collection protocols as samples for routine testing



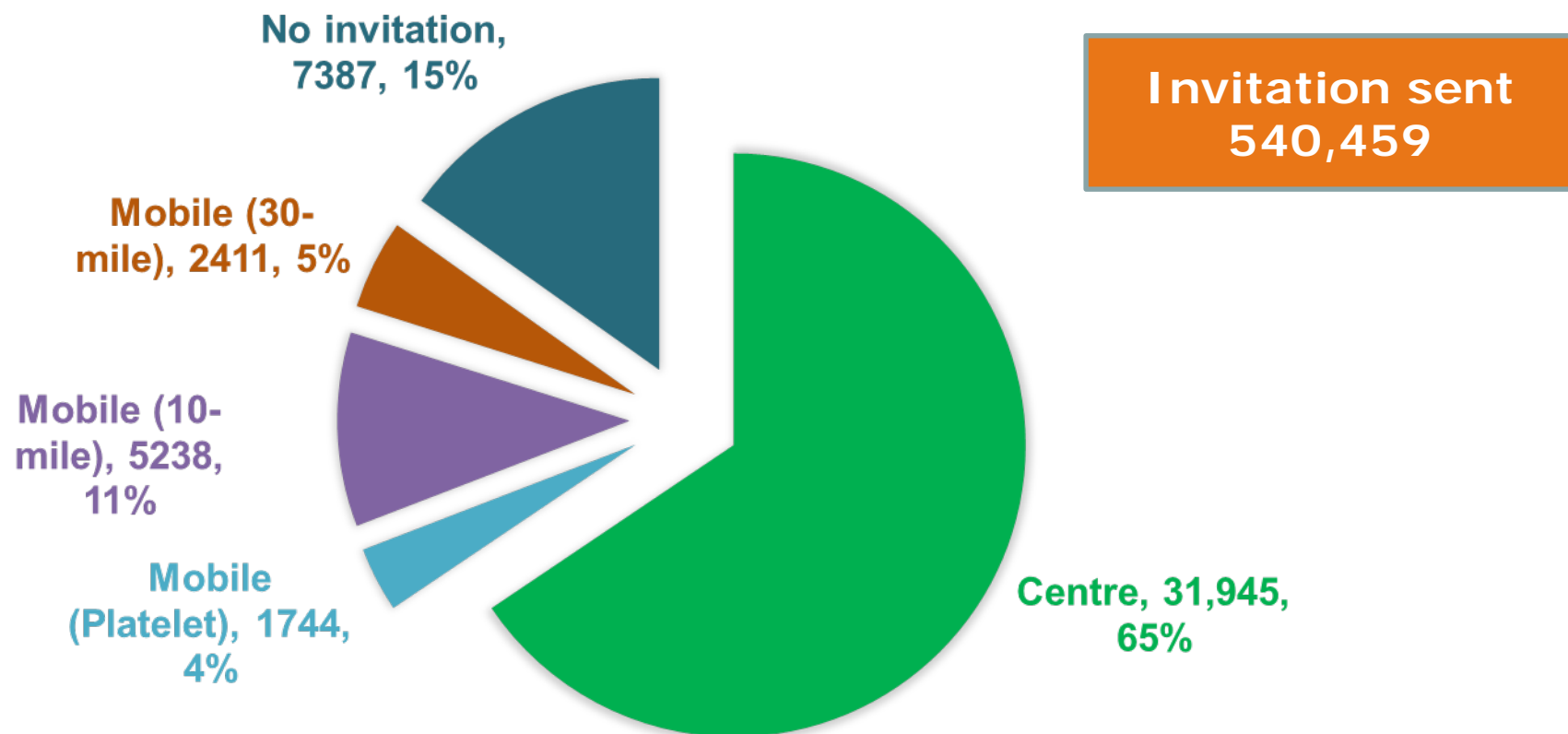
Routine transport systems for sample transfer

## Additional resources

- ☐ NHSBT study administration team (appointments / reminders)
- ☐ Study helpline
- ☐ UK BioCentre - services and facilities for collection of samples and processing, analysis and storage using automated processes/ protocols similar to those previously used in UK Biobank,

# INTERVAL Cohort

by recruitment source

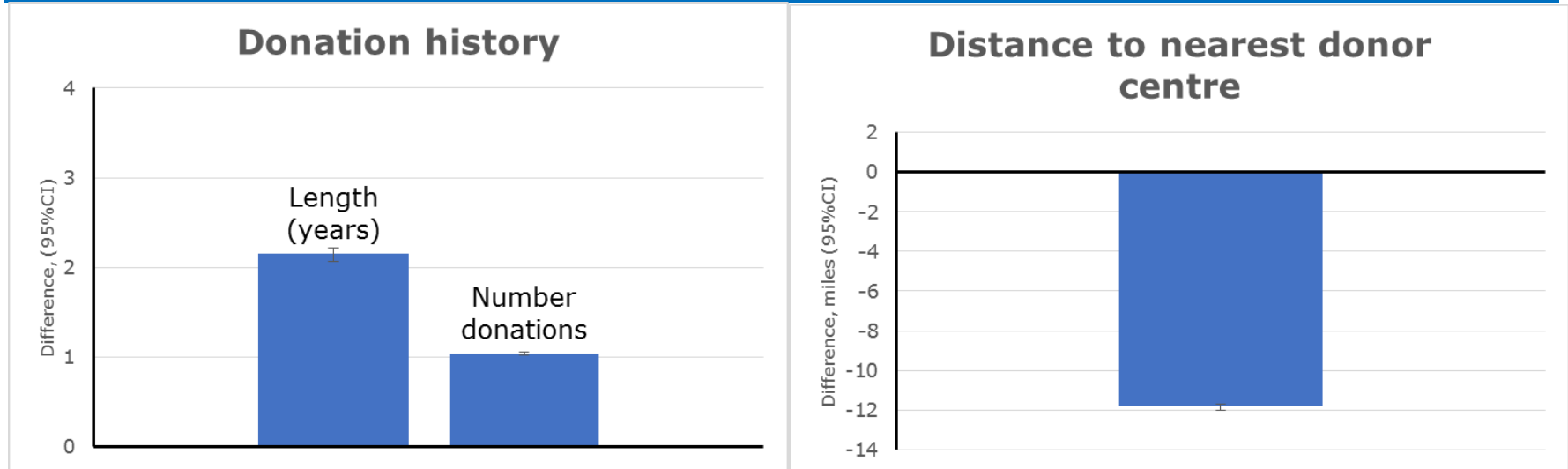


Moore C et al. (2016) *Trials* 17:458

# INTERVAL vs. general donors



## Differences (95% CIs): INTERVAL cohort vs. general donor population

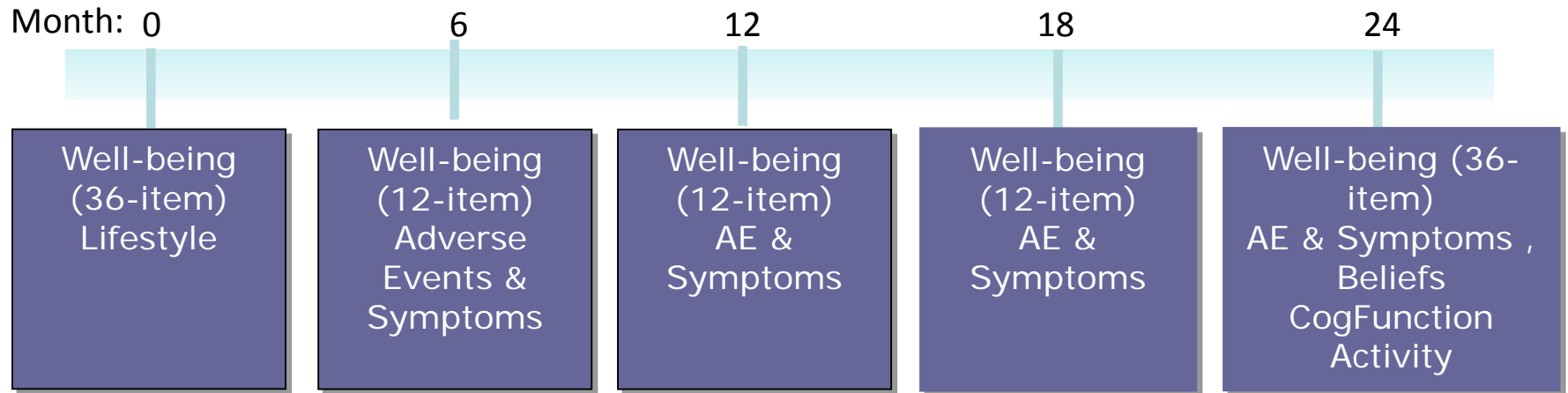


- Subtle differences between recruited sample vs general donor population

# Data collection



- **Daily transfer of NHSBT PULSE data on INTERVAL donors** for e.g. age, ethnicity and donation history and for tracking participation in study
- **Online questionnaires**



- **Physical activity monitoring devices**

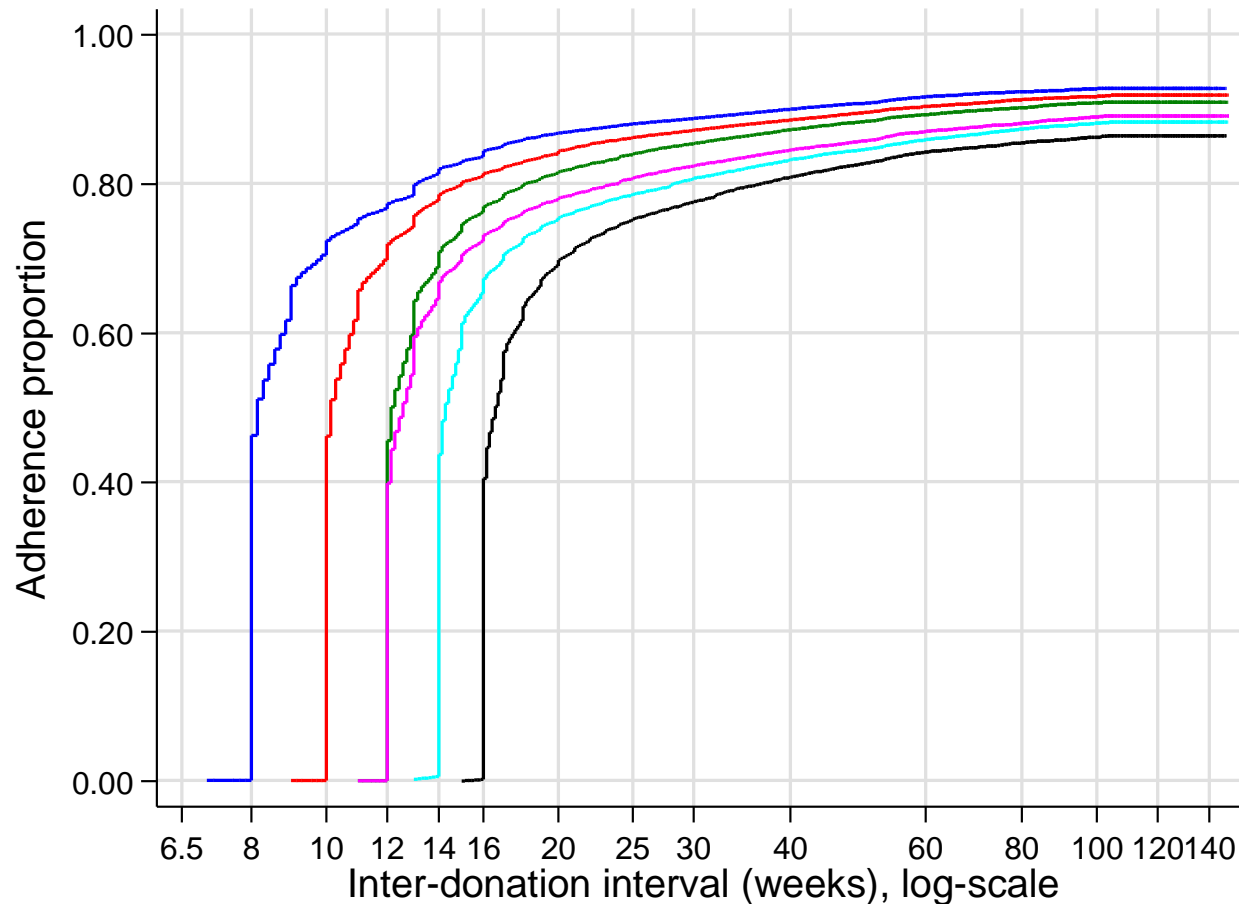
# Protocol: QoL



- Does giving blood frequently and/or iron deficiency impair physical or mental function?
  - symptoms of anaemia
  - chest pain, headache, dizziness, palpitations
  - breathlessness (MRC questionnaire)
  - restless legs syndrome (Cambridge questionnaire)
- Physical activity
- Tests of neurocognitive function – attention, concentration, reasoning, executive function

# Protocol success: adherence

(All donations)



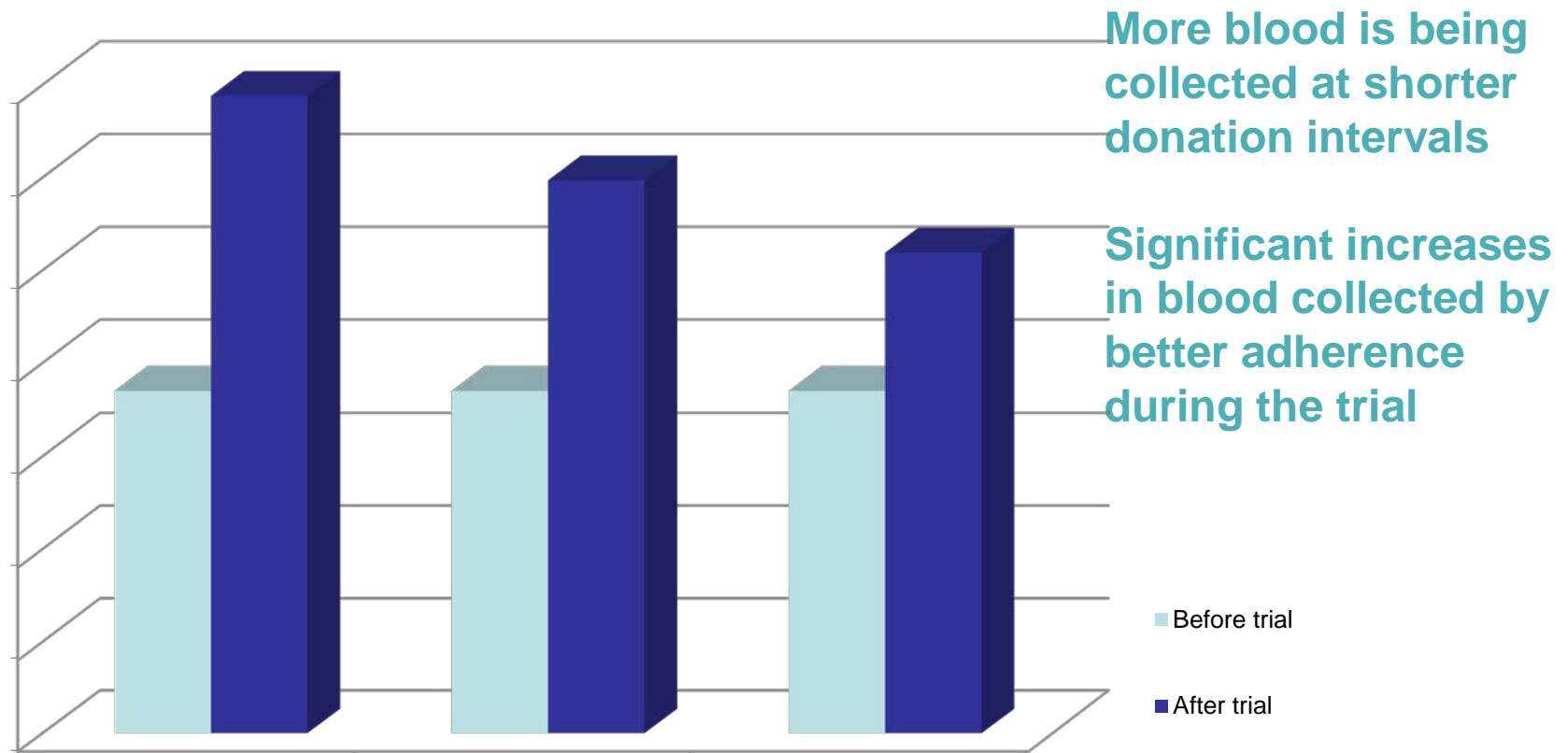
Good adherence  
with shorter intervals

Median time to  
donation

|         |      |
|---------|------|
| 12-week | 12.3 |
| 10-week | 10.1 |
| 8-week  | 8.3  |

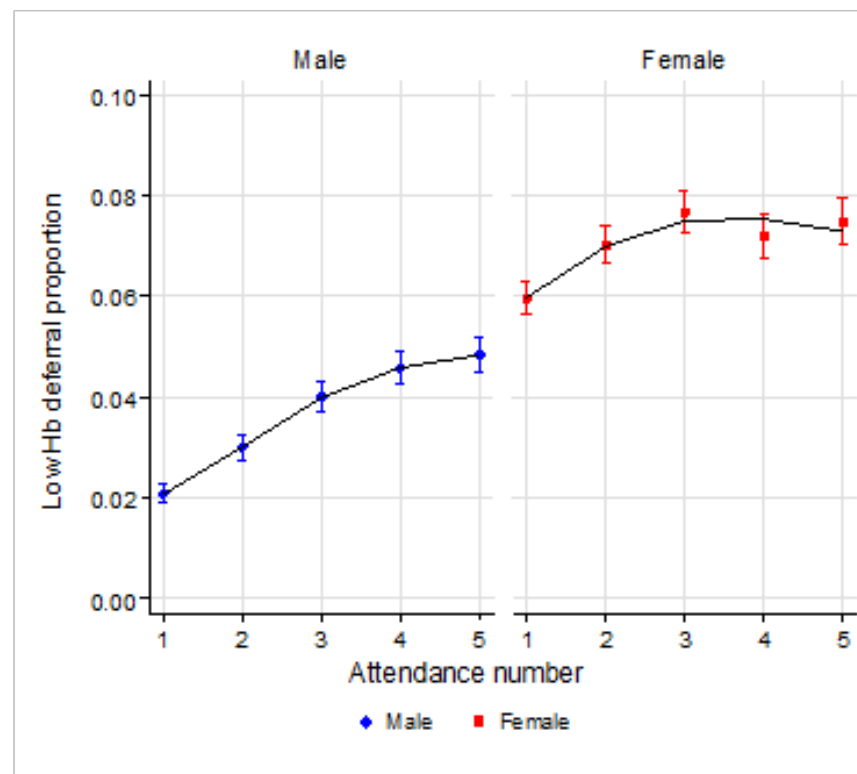
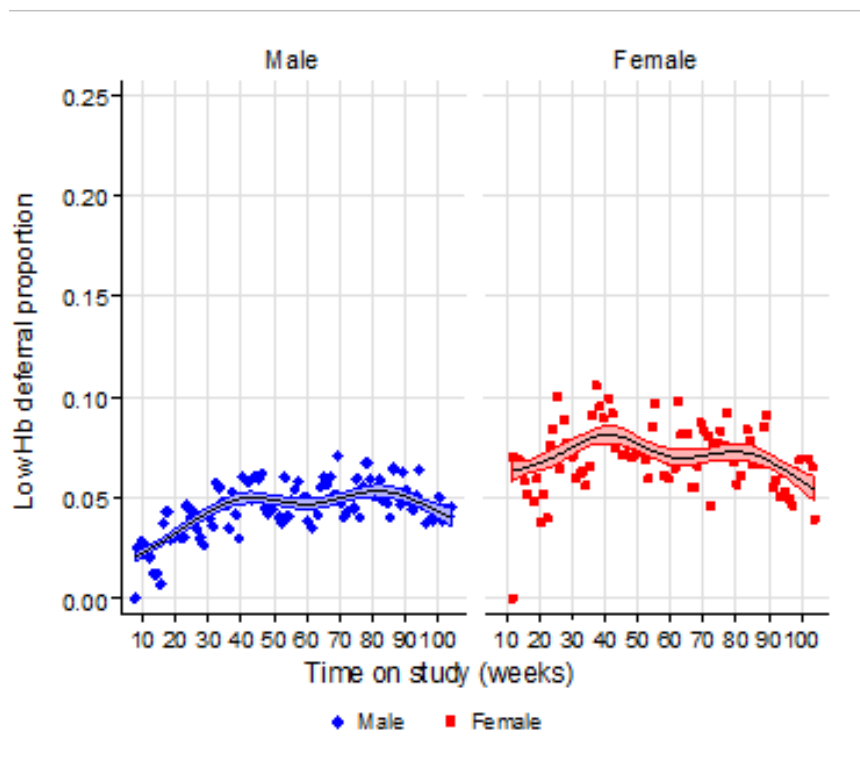
Male 8wk    Male 10wk    Male 12wk  
Female 12wk    Female 14wk    Female 16wk

# Outcomes: blood donation





# During the trial - deferrals

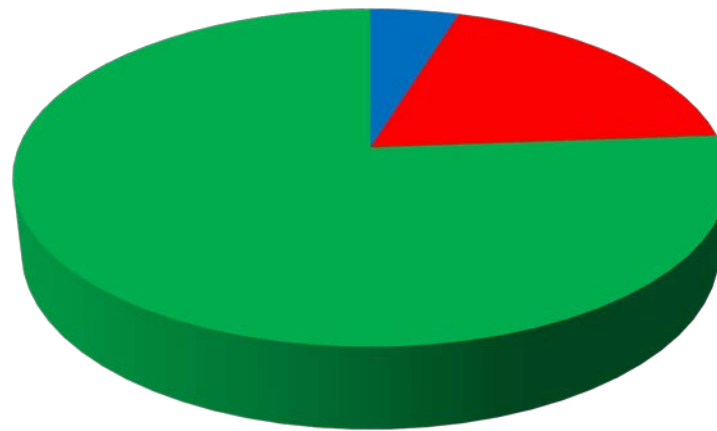


**Increased deferrals and reduced mean haemoglobin and ferritin levels with shorter intervals**

# During the trial - deferrals



## Deferral

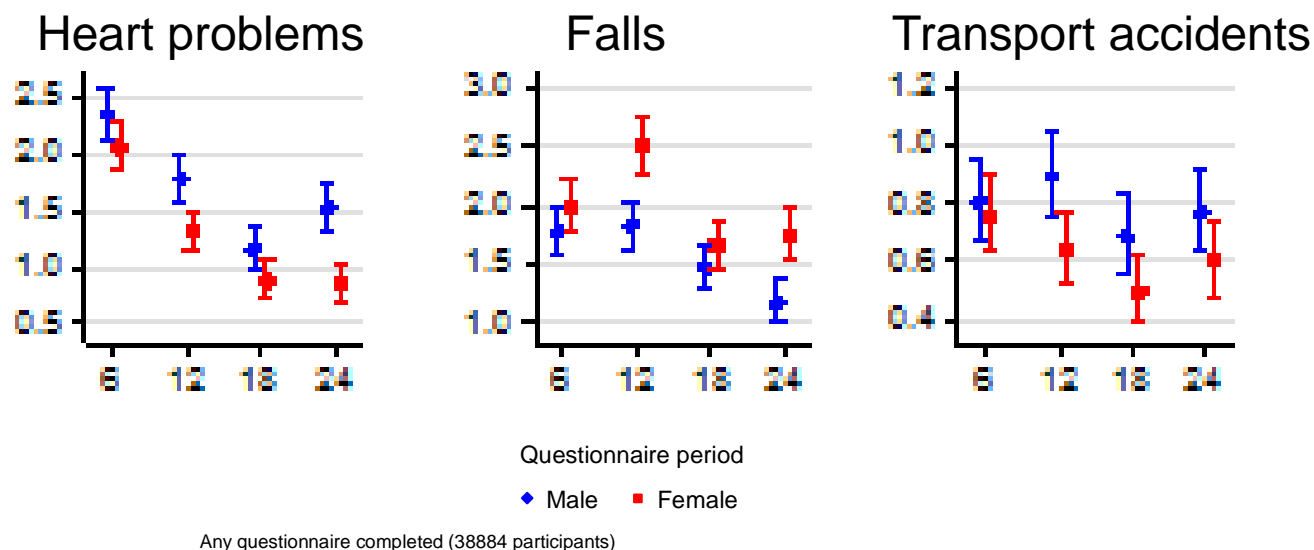


- non Hb  
deferral
- Low Hb  
deferral
- Donate

Not to scale

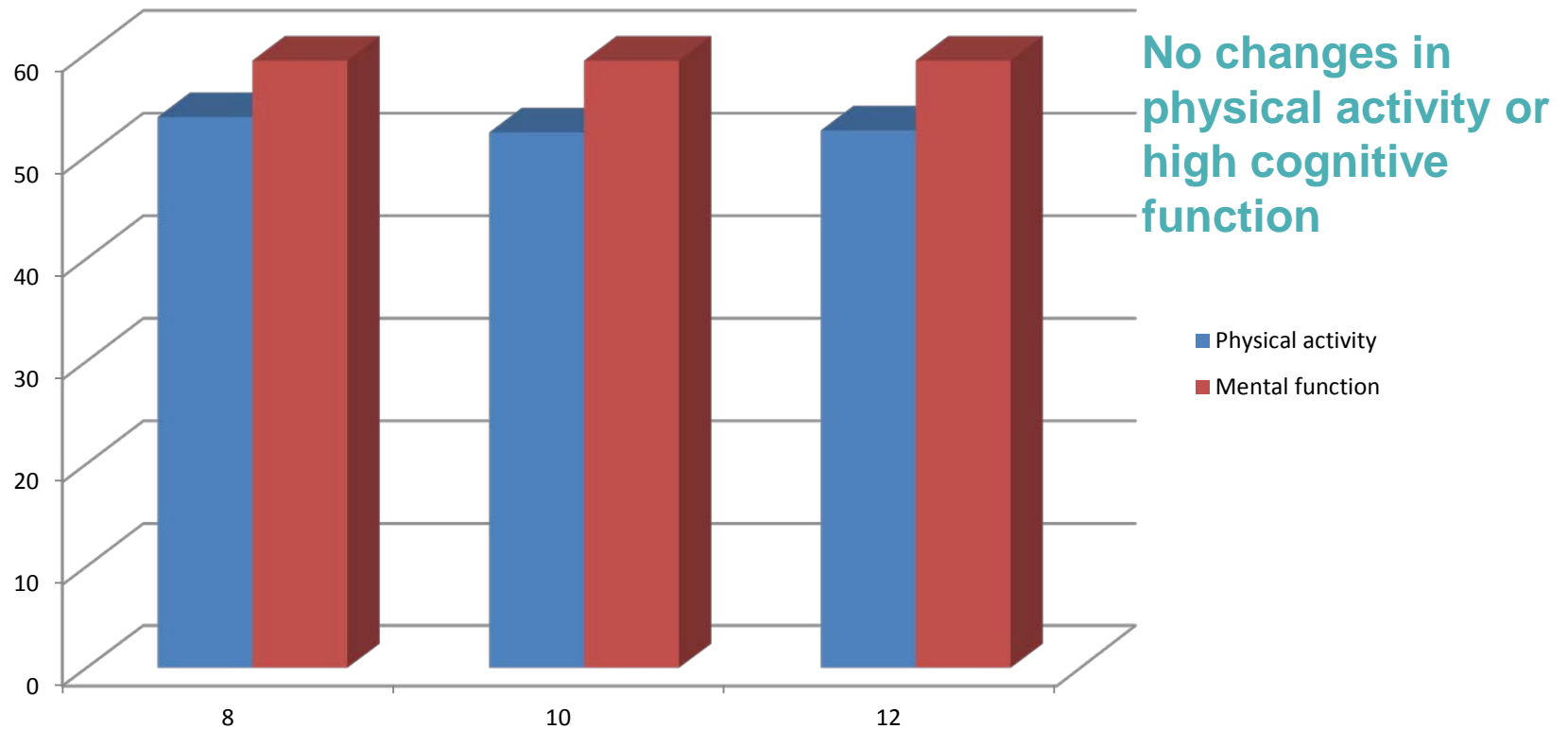
- A very large proportion of people can donate at shortest intervals
- Some donors fail screen on longest intervals
- How do we identify donors likely to fail Hb screen in each group?

# During the trial – major effects

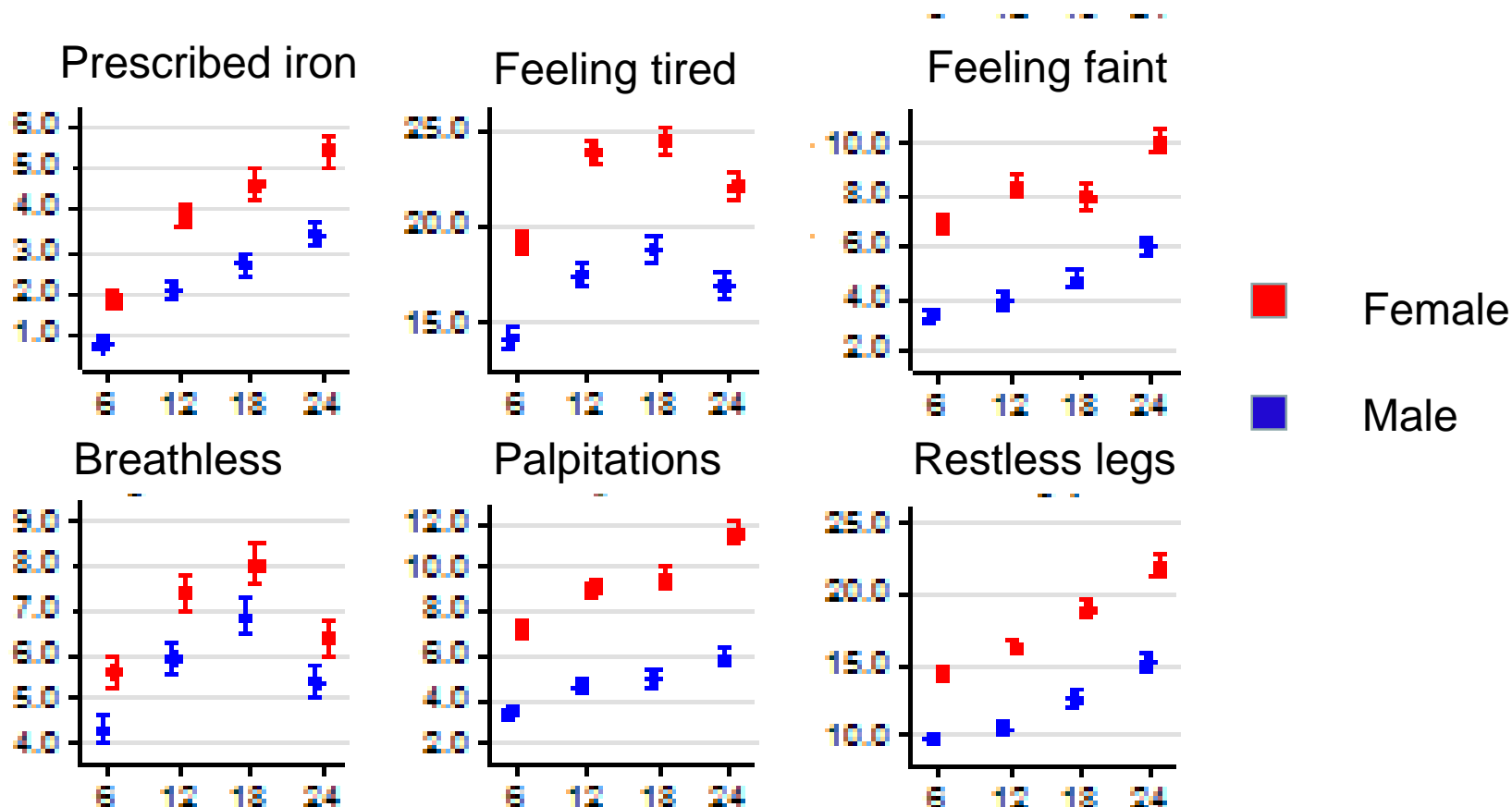


- Trial completed without intervention of Data and Safety Monitoring

# Outcomes: physical and mental function



# During the trial – minor effects



# Outcomes: well-being

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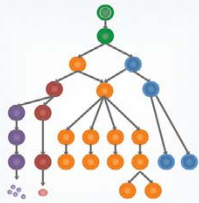
- What is cause of these symptoms?
  - Are symptoms related to donation?
  - Were they related to haemoglobin or ferritin?
- Are they transient?
- Who is susceptible to minor symptoms?
- Do we discuss enough about side effects?

- If donation intervals are shorter we could collect more blood for some donors
  - Significant effects of baseline Hb, baseline ferritin, weight and previous donations
- What is significance of reported side-effects in randomised groups of donors?
- Costs of increased donation
  - Increase deferral due to failure to meet Hb threshold
  - Economic costs if deferral rates are higher

# Blood Traits and Genomics

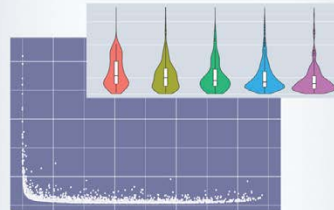


## GWAS discoveries



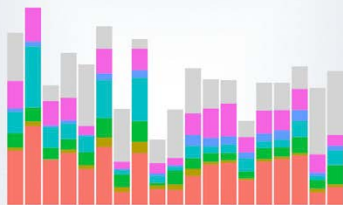
173,480 participants  
36 blood cell indices  
2,706 variants discovered

## Allelic spectrum and heritability



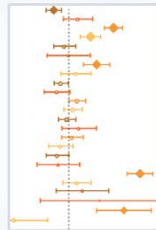
130 rare variants  
210 low-frequency

## Epigenome integration



Integration with chromatin  
states and molecular traits

## Causal contribution to complex disease



Cardiovascular, autoimmune,  
neuropsychiatric disease

Nicole Soranzo

Will Astle et al The allelic  
landscape of blood cell traits  
*Cell* 2016

## Further GWAS for

- iron metabolism
- fainting
- restless legs  
syndrome
- deferral

## Studies may reveal

- mechanisms
- genetic risk scores



# Blood Traits and Genomics

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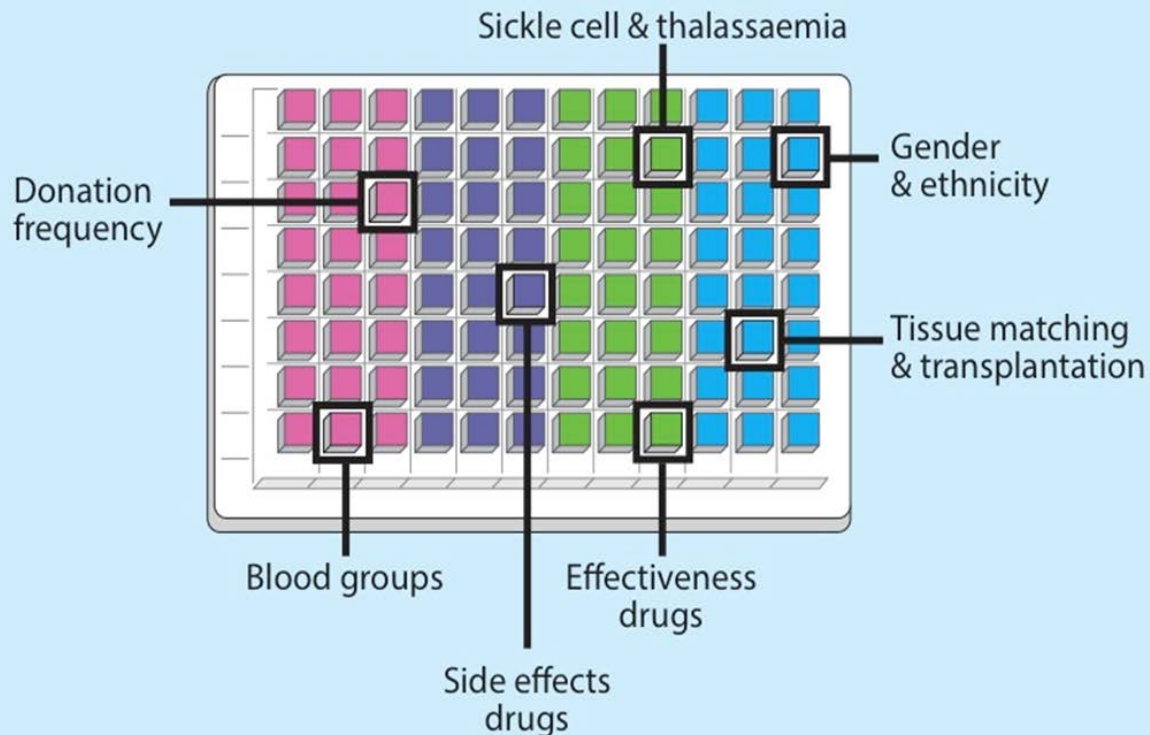


- **GWAS for restless legs syndrome (Schormair et al. Lancet Neurology, in press)**
  - Confirmed six risk loci
  - Identified and replicated 13 new risk loci for restless legs syndrome
  - pathways were related to neurodevelopment and highlighted genes linked to axon guidance, synapse formation and neuronal specification
- **GWAS for high donation of blood and iron metabolism**
  - New loci, pathway(s) unknown

# Blood Types and Genomics



## 1,000,000 DNA variants



NHSBT, Sanguin, Lund, NYBC, Boston and Affy

RBC grouping and HLA, HPA and HNA typing by 2018

Based on INTERVAL thousands of blood donors will be typed with updated content

Clinical validation protocol is being designed

Nick Gleadall unpublished

# Summary I

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- INTERVAL study has been completed and will be published next week
- More blood collected at shorter intervals
- Data and safety monitoring shown no major side effects
- Data show more deferrals and increased reported side effects

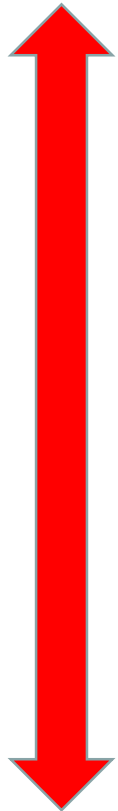
# Summary II

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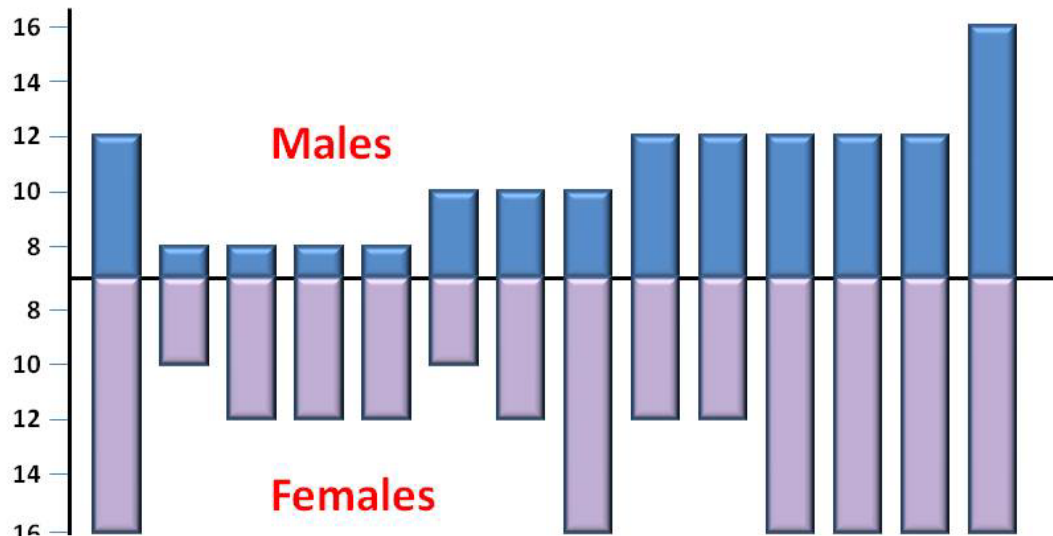


- Follow on studies in progress will look at
  - Non invasive assessment of Hb and/or iron status – post donation testing: the COMPARE study
  - Ability to give blood at different intervals over 2-4 years
  - Trajectory of Hb and ferritin in donors
  - Genetic associations for iron metabolism, fainting(VVR) and restless legs syndrome

# Future prospects



Interval between donations (weeks)



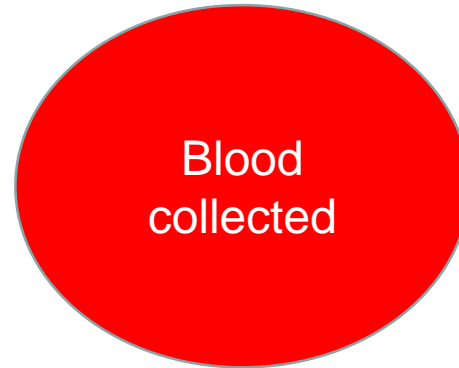
Individual donors

# Future prospects

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- **Moving towards individual or stratified approach to donor care**
- Interventions to avoid deferral using: assessment of Hb and/or iron status and change intervals vs iron supplements
- Large scale genotyping at low cost
- Recall of donors for specific product requirement
- **Further trials and collaboration**

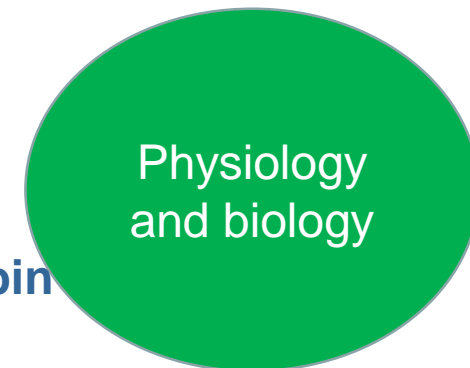
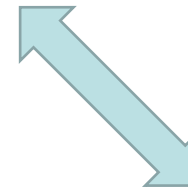
# Future prospects



**Genotyping**

**Quality**

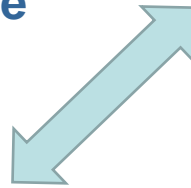
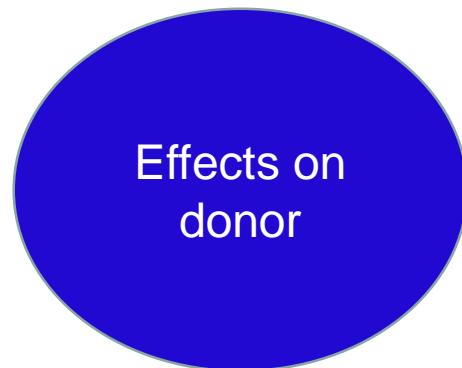
**High specification of components**



**Measuring haemoglobin**

**Predicting Hb and ferritin**

**Stratified donation**



**Risk factors for donors**

**Trials to reduce side effects**

# Who's involved and Acknowledgements



## Trial Management Group

John Danesh (Co-CI)  
David Roberts (Co-CI)  
Willem Ouwehand (PI, Laboratory)  
Emanuele Di Angelantonio (Donor Health Consultant)  
Carmel Moore (Scientific Coordinator)  
Jennifer Sambrook (Laboratory Coordinator)  
Dave Allen (Post-Doc Research Scientist)  
Matthew Walker (Senior Data Manager)  
Claire Thomson (Project Officer)  
Susan Mehenny (Project Lead)  
Tracey Hammerton (Project Manager)

## Steering Group Chair

Prof. Jane Armitage

## Co-applicants / named collaborator

Simon Thompson, Cambridge (Biostatistics)  
Jonathon Mant, Cambridge (Clinical Trials)  
John Gallacher, Cardiff (Cognitive Function)  
Dorine Swinkels, Eindhoven (Sample Assays)  
Simon Cohn, Cambridge (Social Anthropology)

Henrik Ullum and colleagues, Copenhagen

## Managers and staff of Donor Centres

### Blood Donors

### NHSBT management team

Lorna Williamson (Medical and Research Director)  
Clive Ronaldson (Director Blood Supply Chain)  
Jane Pearson (Asst. Director Blood Supply Chain)  
Nick Watkins (Asst. Director R&D)

### BioCentre, Stockport

Kristian Spreckley

### Sysmex

Fraser McGee  
Dean Hunter

---

## Funders

NHSBT and NIHR



# Acknowledgments



Tao Jiang  
John Danesh  
Adam Butterworth  
Dace Ruklisa  
William Astle  
Willem Ouwehand



Dave Allen  
David Roberts



Heather Elding  
Heleen Bouman  
Daniel Mead  
Nicole Soranzo



# Who's involved - Genomics



William J. Astle\* , Heather Elding\* , Tao Jiang\* , Dave Allen, Dace Ruklisa , Heleen Bouman, Fernando Riveros-Mckay, Alice L. Mann, Daniel Mead, Myrto A. Kostadima, John J. Lambourne , Suthesh Sivapalaratnam , Kate Downes, Kousik Kundu, Lorenzo Bomba, Kim Berentsen, John R. Bradley, Louise C. Daugherty, Olivier Delaneau, Stephen F. Garner, Luigi Grassi, Matthias Haimel, Eva M. Janssen-Megens, Anita Kaan, Mihir Kamat, Bowon Kim, Amit Mandoli, Jonathan Marchini, Joost H.A. Martens, Stuart Meacham, Karyn Megy, Jared O'Connell, Romina Petersen, Nilofar Sharifi, Simon M. Sheard, James R. Staley, Salih Tuna, Martijn van der Ent, Shuang-Yin Wang, Eleanor Wheeler, Steven P. Wilder, Valentina Iotchkova , Carmel Moore, Jennifer Sambrook, Hendrik G. Stunnenberg, Emanuele Di Angelantonio, Stephen Kaptoge, Taco W. Kuijpers, Mattia Frontini, John Danesh §, David J. Roberts §, Willem H. Ouwehand §, Adam S. Butterworth§, Nicole Soranzo§

# The next generation....



## Male donors

### Risk score quintile for deferral

|          | 1  | 2  | 3   | 4   | 5 (highest risk) |
|----------|----|----|-----|-----|------------------|
| 8-weeks  | 4% | 8% | 12% | 16% | 20%              |
| 10-weeks | 3% | 6% | 8%  | 12% | 15%              |
| 12-weeks | 2% | 4% | 6%  | 8%  | 10%              |

# The next steps...



## Donor Health2.0

## Male donors

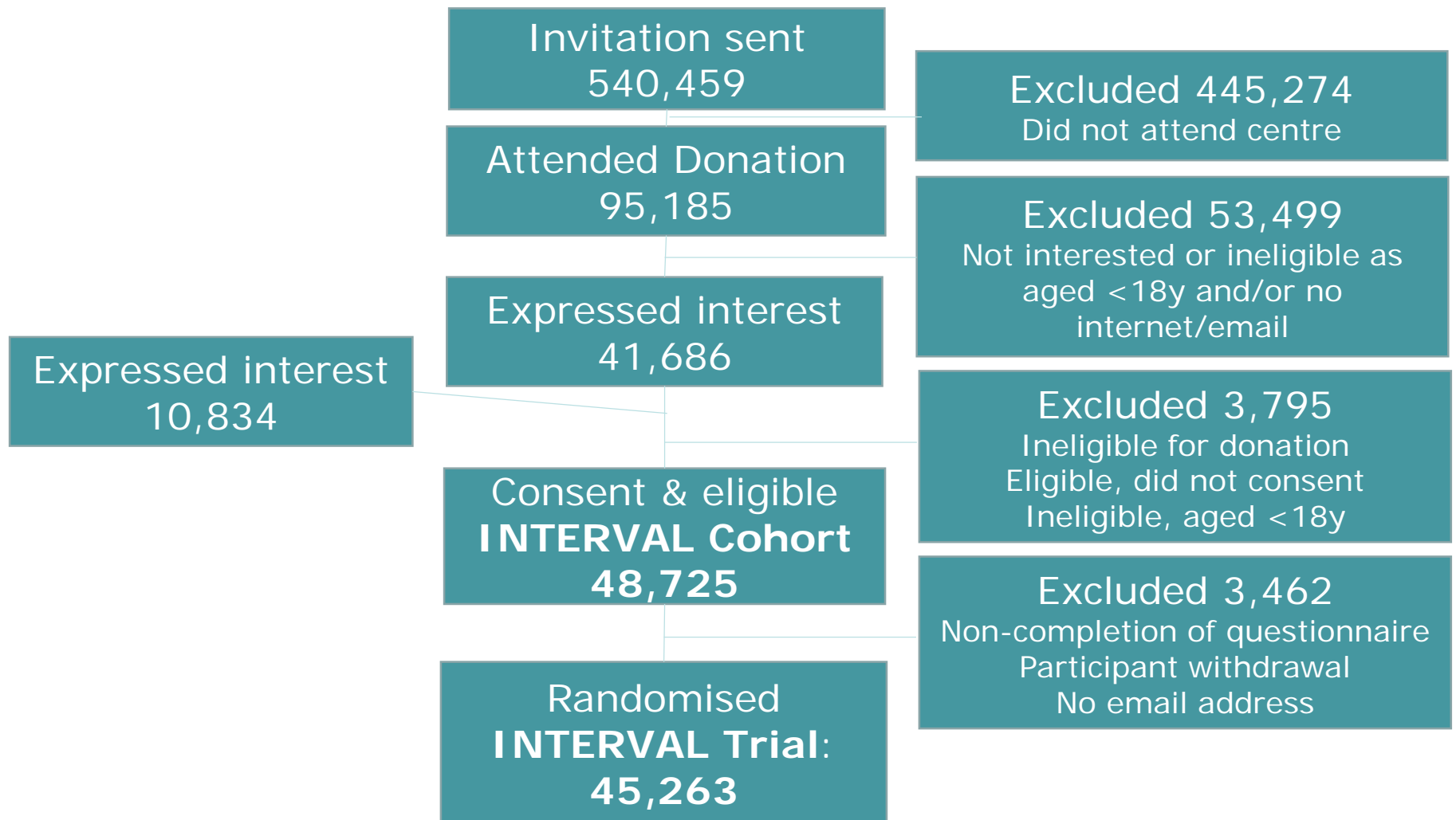
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| 12-weeks | 2% | 4% | 6%  | 8%  | 10%              |

**Aim** If we modulate donation interval by risk of deferral will we be able to collect similar amount of blood with better QoL

# Participation

## Across all sources of recruitment



# Blood Traits and Genomics



**2,706** loci ( $p \leq 8.31 \times 10^{-9}$ ). **210** are low frequency (1-5% MAF) and **130** are rare ( $<1\%$  MAF)

-  Previously reported
-  Novel independent loci
-  Non independent loci
-  Non independent loci

