

INTERVAL

Progress and future prospects

David Roberts
On behalf of INTERVAL study team

INTERVAL past, present & future

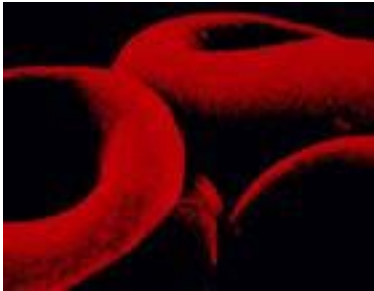


- Background
- INTERVAL Outline
- INTERVAL Progress
 - Recruitment
 - Outcome measures
- Possible answers
- The next steps
- Future prospects

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?

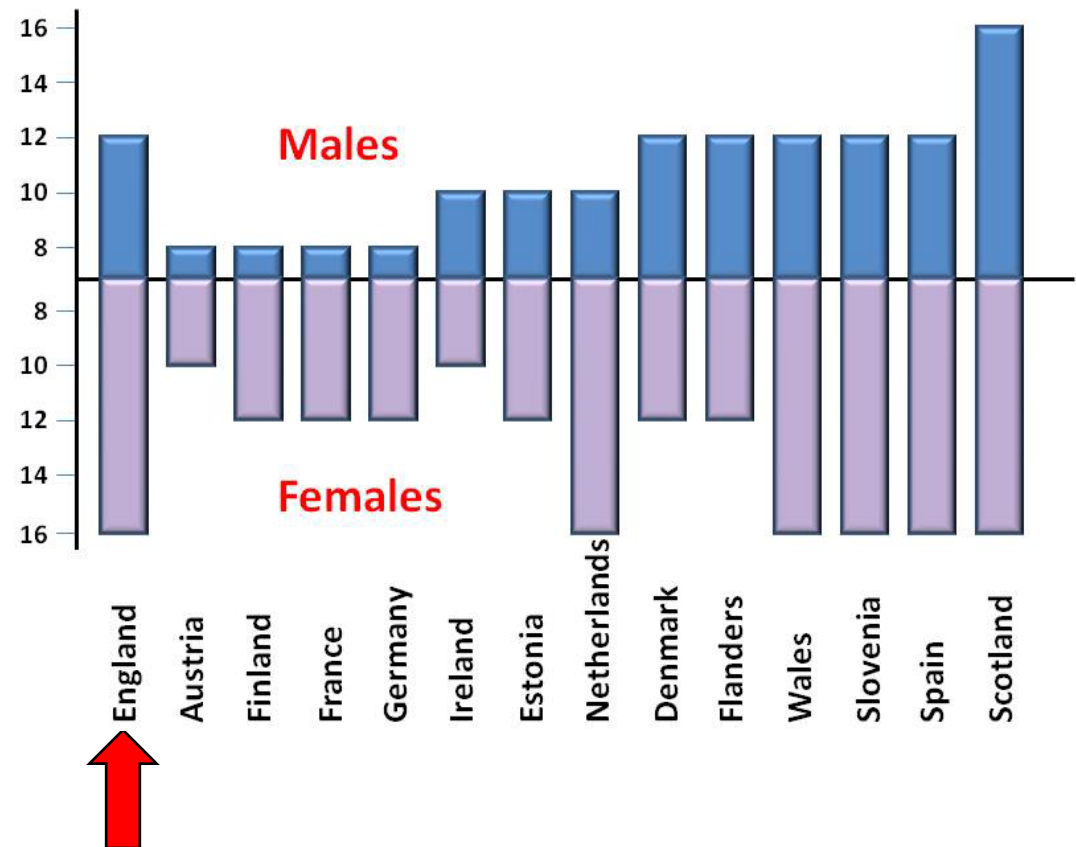
Optimising donations...



Decrease interval between donations

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

Interval between donations (weeks)



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

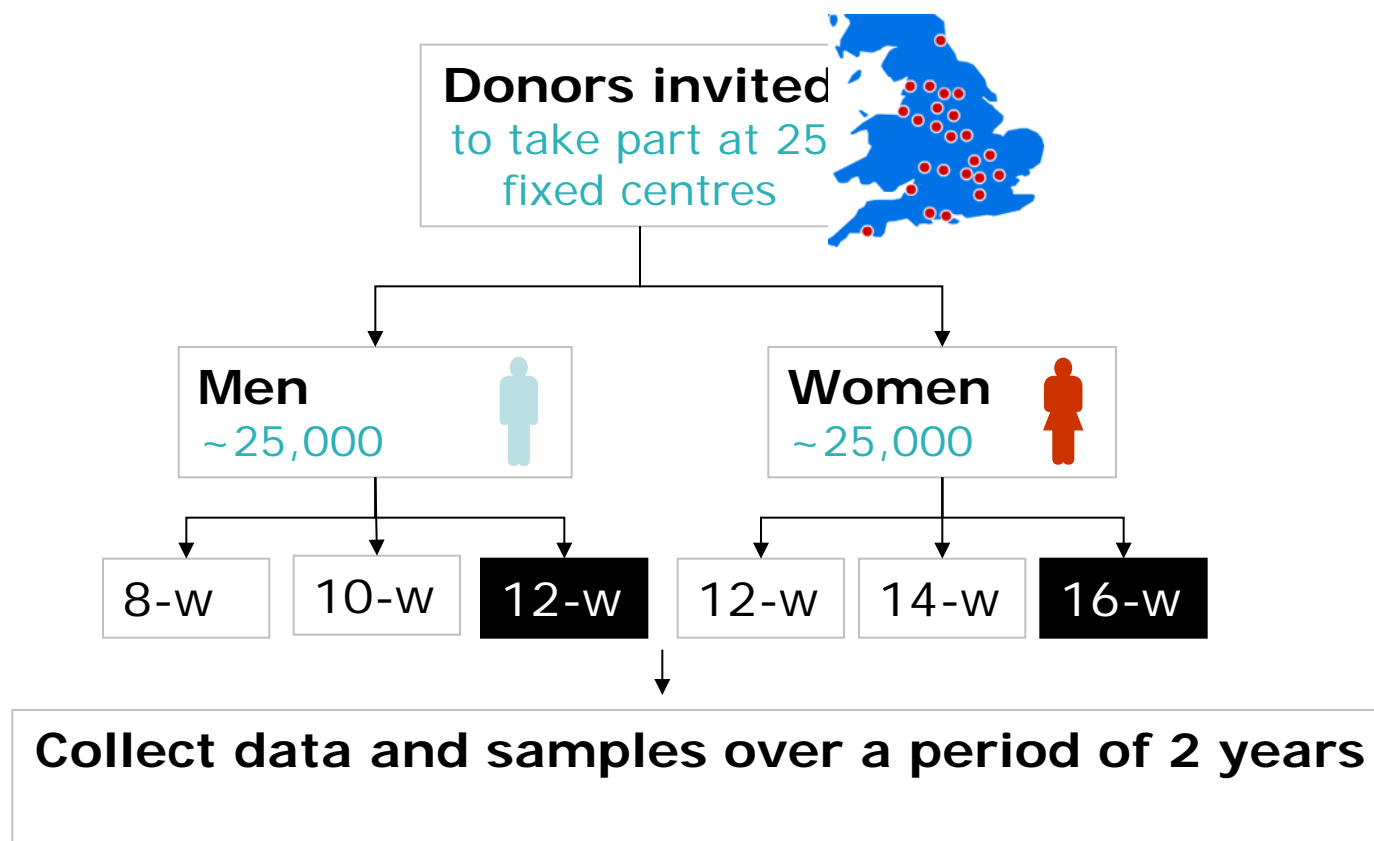


Blood markers iron status e.g. serum ferritin



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

Study design



Pragmatic trial in routine setting

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,

Sample collection & processing



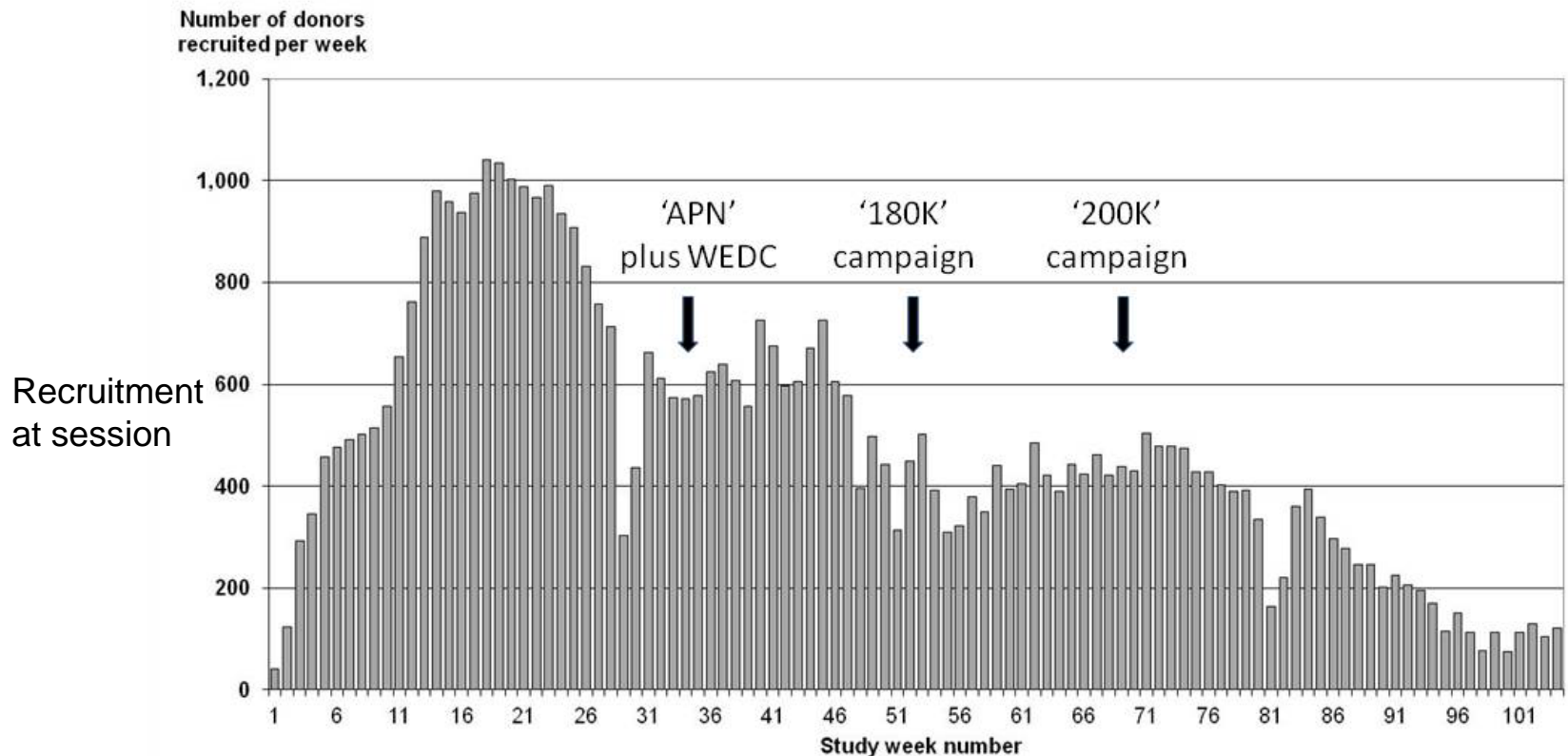
- FBCs
- Plasma
- Serum
 - ferritin, CRP.
 - hepcidin
- Buffy coat (DNA)
- Stored at Biocentre



Achievements: recruitment



- Staggered roll out of recruitment at a rate of one centre / week
- All 25 centres involved in recruitment by end November 2012
- **50,000** donors recruited in 15 June 2014



Achievements: recruitment



➤ Where are the INTERVAL donors from?

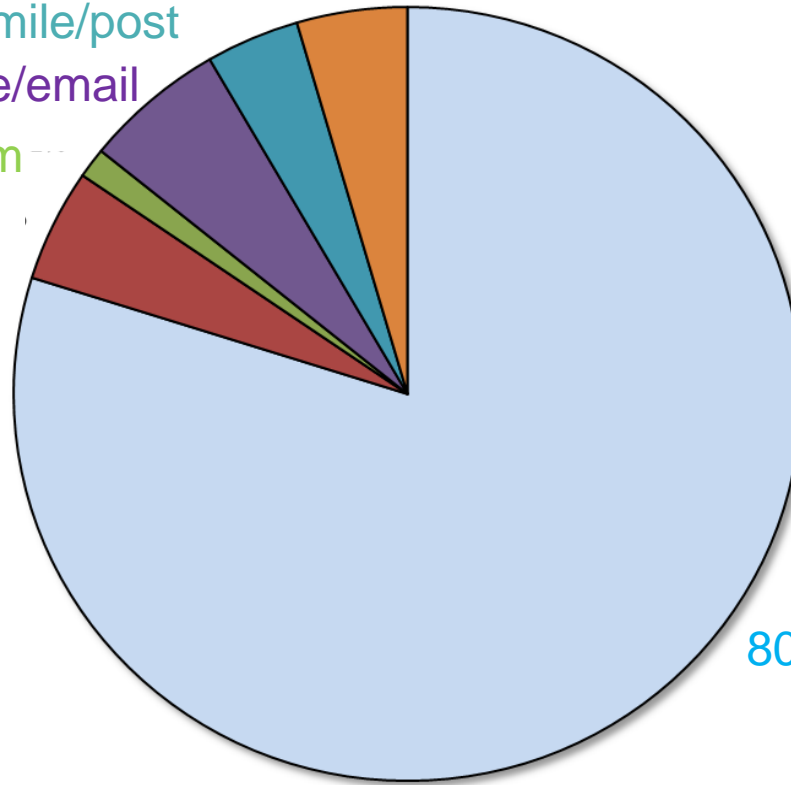
4% from 30 mile zone

4% from 10 mile/post

6 % from 10 mile/email

1 % from WEDC 5m

5 % from APN list

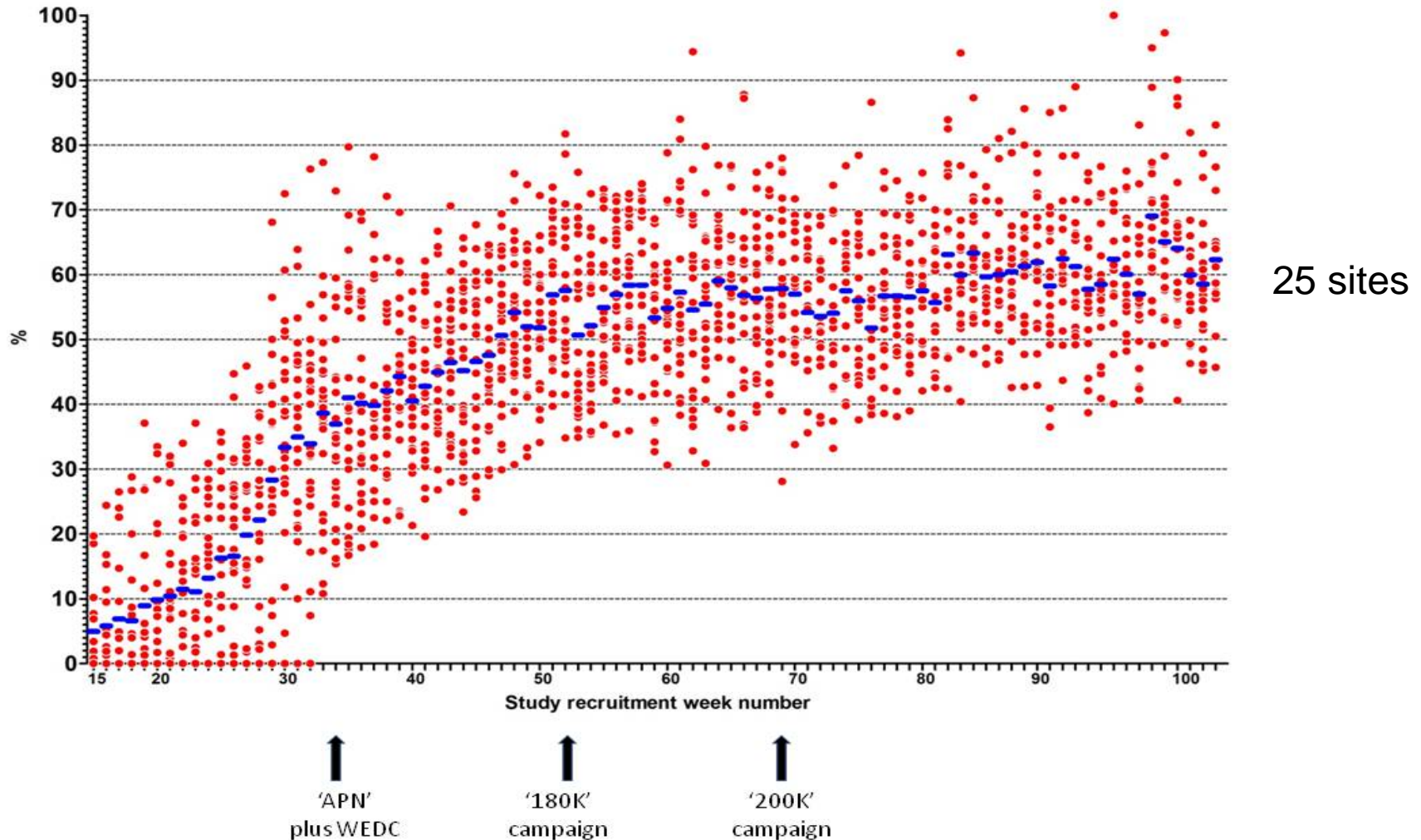


80% from fixed donor sessions

Achievements: recruitment

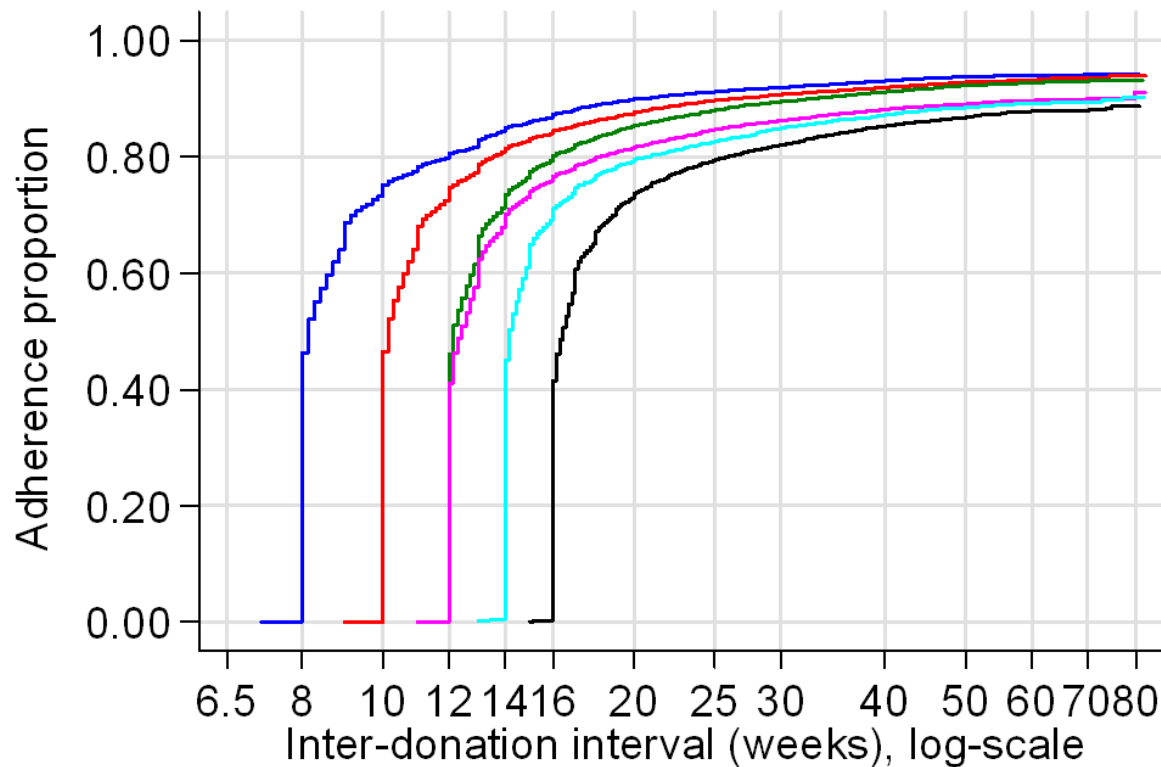


- Percentage of donors attending centre already joined in INTERVAL



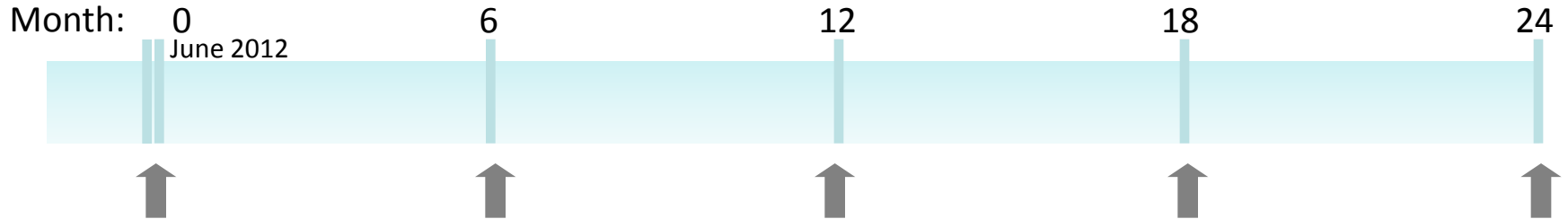
Protocol success: adherence

(All donations)



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

Protocol success - collections



Blood

Samples (x3)
Complete set
97% donors

Samples (x3)
Underway

Questionnaires

SF-36
(+ lifestyle)
**93%
response**

SF-12
(+ AE)
**81%
response**

SF-12
(+AE)
**78%
response**

SF-12
(+AE)
**First issued
Dec 2013**

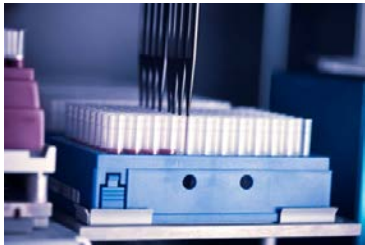
SF-36
(+AE)
In progress

Blood sample management



3ml EDTA, 6ml EDTA and 6ml serum tubes collected at donor centres; **97%** retrieval rate.

Transported at RT to NHSBT holding sites, couriered to central laboratory (UK Biocentre)



98% processed within 1 day of collection

3ml EDTA – Full blood count (sysmex)

6ml EDTA – storage -80°C plasma and buffy coat

6ml serum – storage -80°C of serum

Sample analysis:

- Genotyping using the state-of-the-art Affymetrix “Biobank” array containing ~820,000 variants plus imputation of at least 20M variants
- Customised to include blood group, platelet group, HLA and iron metabolism loci

Biological measurements

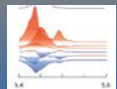


Extended haematology profile | ~200 blood cell traits



Clinical biomarkers

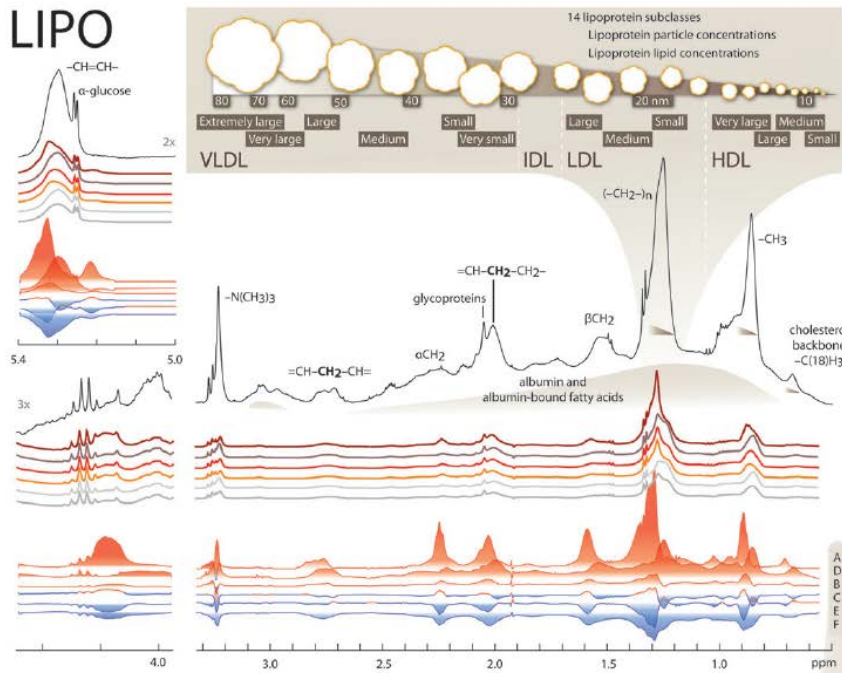
| ~ 40 analytes



NMR metabolomics

| ~250 analytes

NMR metabolite profiling



~ 80 lipoprotein characteristics
(e.g. lipoprotein size, cholesterol content, triglyceride content, phospholipid content etc.)

~ 20 serum lipid concentrations

> 20 low molecular weight metabolite concentrations
(e.g. amino acids and other small metabolites)

>100 derived measures
(e.g. metabolite ratios, reflecting enzyme activities)

Wuertz et al, *Mol Bio Sys* 2010
Kettunen et al, *Nat Genet* 2012

Protocol success: 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),
 - pica
 - tests of neurocognitive function – attention, concentration, reasoning, executive function
 - physical activity

Other phenotypes



Physical activity profiling:

7 day accelerometer recordings



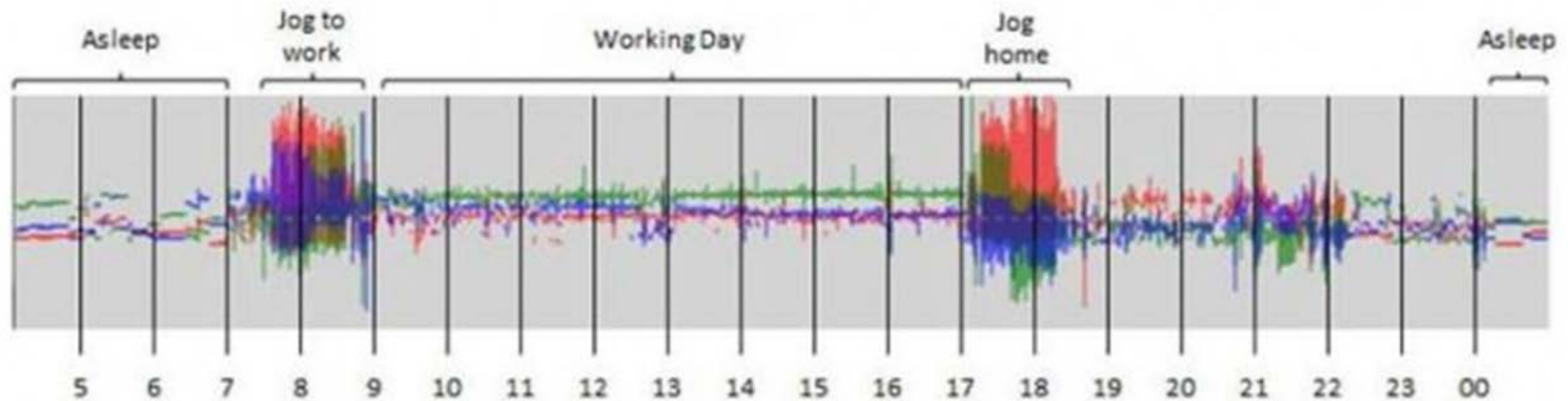
Cognitive function tests:

- Attention (Stroop test)
- Memory (Pairs test)
- Executive function (Trail test)
- Intelligence (Reasoning test)

Remote data collection



- 7000 participants
- Wrist-worn AX3 accelerometers to monitor changes in how fast and in what direction the body is moving
- Measure 3 directions of movement and each can be plotted on a chart to build up a picture of movement throughout the day



Protocol success: QoL



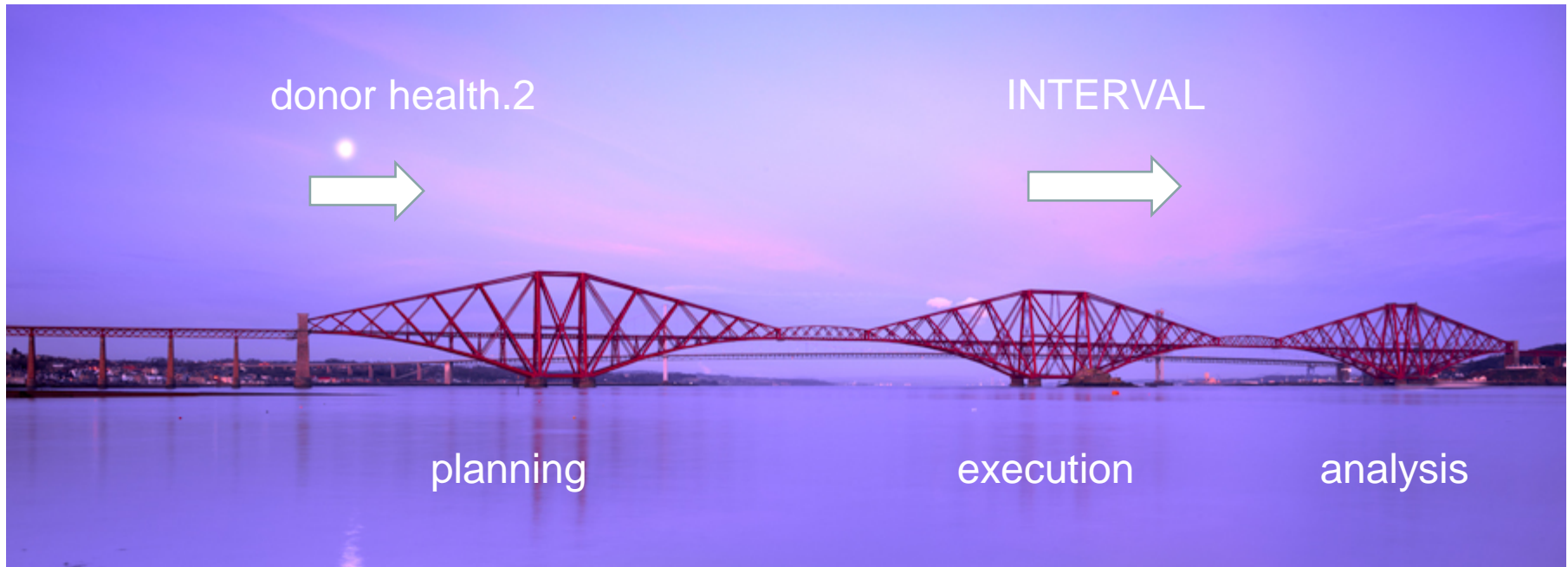
- **If deferral rates are higher**
 - **Should and could we tailor blood donation intervals according to donors' susceptibility to iron deficiency?**
- If iron deficiency affects physical and mental function
 - Should we aim to maintain iron stores
 - Tailor blood donation intervals
 - Dietary advice
 - Iron supplementation

Protocol success: QoL

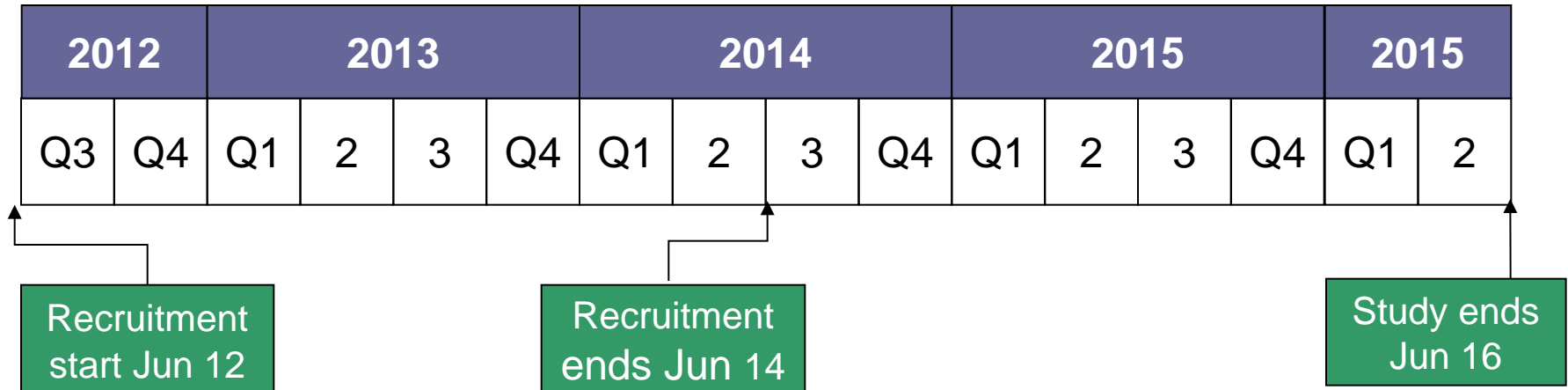


- If deferral rates are high
 - Should we tailor blood donation intervals according to donors' susceptibility to iron deficiency?
- **If iron deficiency affects physical and mental function**
 - **Should we aim to maintain iron stores**
 - **Tailor blood donation intervals**
 - **Dietary advice**
 - **Iron supplementation**

The next steps



Next steps: Act II?



Proposed continuation on study beyond 2 years

- Acceptability: Proportions of donors agreeing to continue?
- Sustainability: Impact on study outcomes (blood collected, well-being, donor deferrals) beyond 2 years?
- Donor management: Difference in the number of donations collected comparing “active” approaches to reminding of donors vs. “routine” reminding of donors?

The next steps



- Factors affecting haemoglobin and iron stores over time
 - Full genome sequence in 20,000
 - Iron metabolism - hepcidin
 - Modelling of trajectory of Hb and ferritin
- Stratification of donor care manage donors using their likely risk of deferral
 - Age, gender, weight, Hb, iron stores, genotype
- Long term outcome

The next steps



Donor Health 2.0

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

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%
16-weeks					8%

Aim to collect similar amount of blood with better QoL

Future prospects

- Moving towards individual approach to donor care
 - Intervals
 - Appointments and reminders
 - Interventions to avoid deferral
 - Recall of donors for specific product requirement
 - Non invasive assessment of Hb and/or iron status

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)
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Jennifer Sambrook (Laboratory Coordinator)
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Matthew Walker (Senior Data Manager)
Claire Thomson (Project Officer)
Susan Mehenny (Project Lead)
Tracey Hammerton (Project Manager)

Steering Group Chair

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Co-applicants / named collaborator

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Jonathon Mant, Cambridge (Clinical Trials)
John Gallacher, Cardiff (Cognitive Function)
Martin Daumer, Munich (Physical Activity)
Dorine Swinkels, Eindhoven (Sample Assays)
Fenella Kirkham, London (Neurology)
Simon Cohn, Cambridge (Social Anthropology)

NHSBT management team

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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

Managers and staff of Donor Centres

Blood Donors

Funders

NHSBT and NIHR

The next steps



- Bioresource has great breadth and depth
- What studies would you suggest and would like to do?
 - *Staph aureus* carriage
 - CMV infection and load
 - Component quality