NHS BLOOD AND TRANSPLANT
National Organ Donation Committee
SIGNET Study Report

Background

1. NIHR Health Technology Assessment Program have funded a 4 year multicentre randomised controlled trial of simvastatin in DBD. The primary outcome is a composite measure of death, renal replacement therapy or mechanical cardiac support in cardiac recipients at 30 days. SIGNET will recruit an estimated 2600 donors. (https://www.nhsbt.nhs.uk/clinical-trials-unit/current-trials-and-studies/signet/)

2. Study is being run by NHSBT's Clinical Trial Unit.

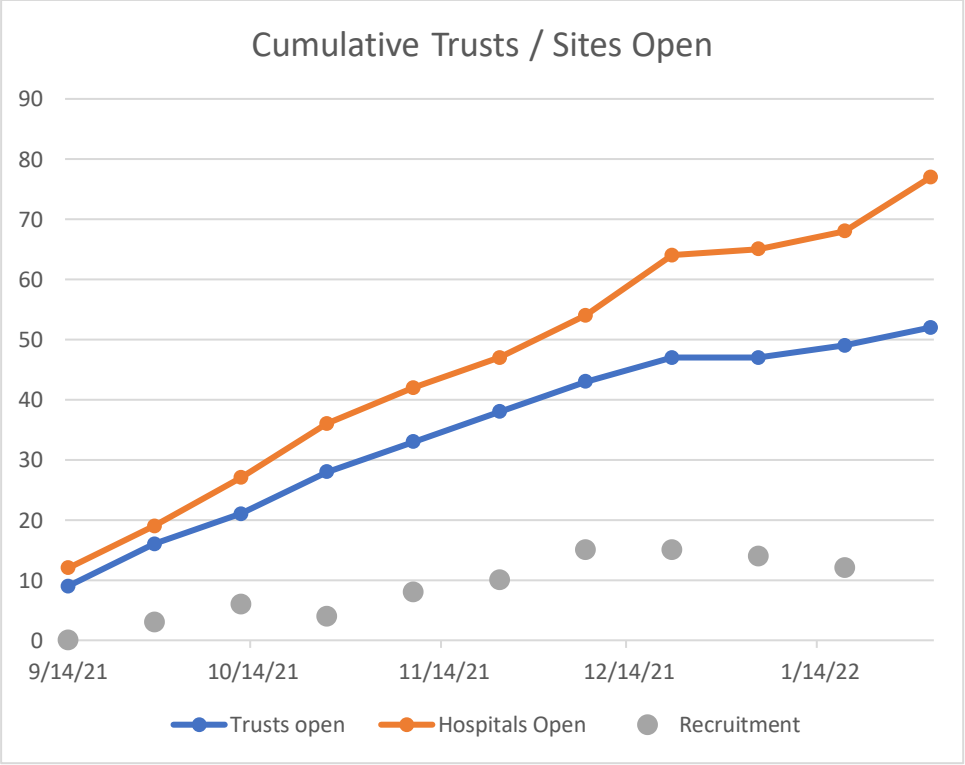
3. Start date planned for July 2021, actual start date Sept 2021 delayed by regulatory and internal approvals, training and COVID.

4. The study includes 1 year targets for site opening, recruitment and intervention adherence that NIHR will use to determine if funding should be continued past the first "pilot" year.

5. **Site opening.**

    a. Planned to open in all Level 1 & 2 donating hospitals (79 Trusts). Our aim was to open all sites in the first 3 months, although this was unlikely to be achieved during a 3rd and 4th wave of COVID. Many Trusts have significantly reduced the number of non-pandemic studies open.

    b. As of Feb 1st (5 months) 76 sites are open in 52 Trusts, with another 21 in set up (73 Trusts in total). 1 Trust has declined to take part, 1 is prevented in doing so by NIHR restrictions, the remaining 4 sites are considering their ability to join the study.

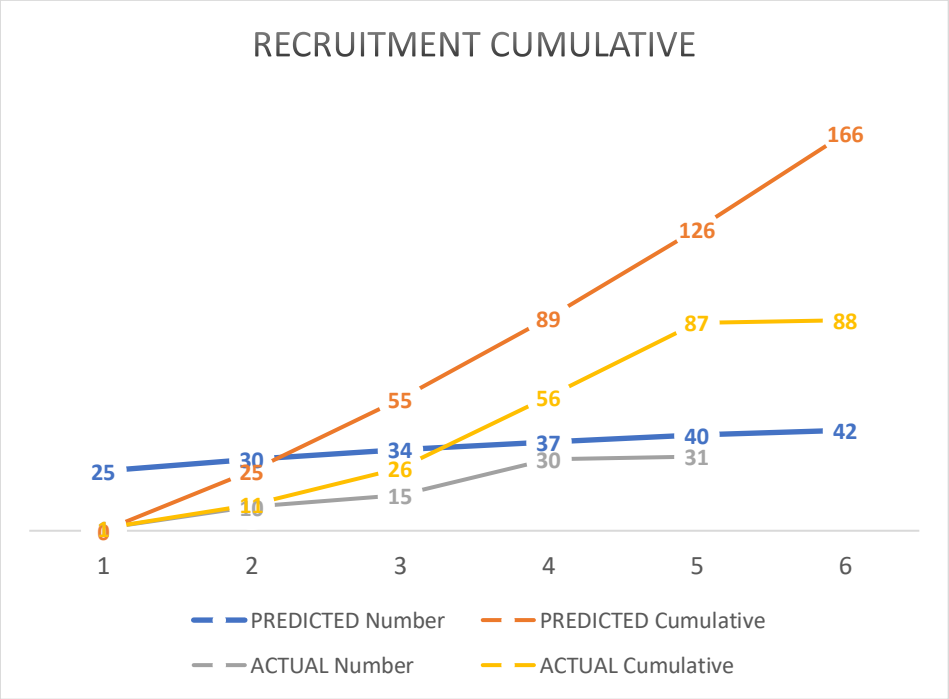


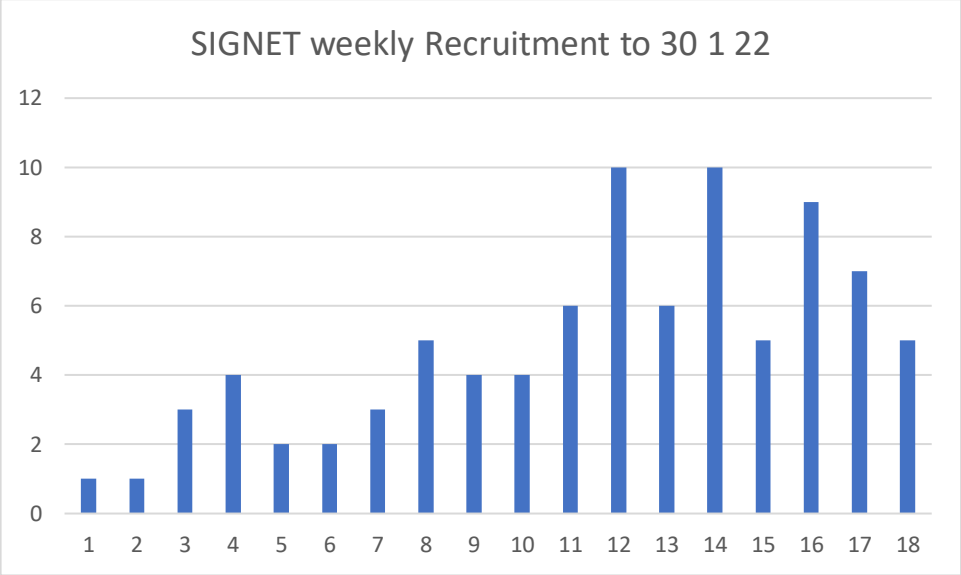
6. Recruitment

a. 88 donors have been randomised to date from total eligible donors within open sites of 102 (84%). The SIGNET study is powered on an assumption of recruitment of 80% of eligible donors, which therefore looks accurate and achievable so far.

b.

		PREDICTED		ACTUAL	
Date	Month	Number	Cumulative	Number	Cumulative
Sep-21	1	25	0	1	1
Oct-21	2	30	25	10	11
Nov-21	3	34	55	15	26
Dec-21	4	37	89	30	56
Jan-22	5	40	126	31	87
Feb-22	6	42	166	1	88





c. SIGNET overall recruitment is behind predicted due to consecutive site opening rather than original plan to open all Level 1s simultaneously (which is not possible with concurrent Urgent Public Health NIHR priorities), however last 2 months have been at approx. 75% predicted with a number of Level 1 sites still to open. Predicted recruitment looks achievable and realistic by the end of the Year 1 pilot phase.

d. Although absolute DBD donor numbers are down by 16% compared to pre pandemic levels, cardiothoracic DBD donor rates are up by 5%. This will have the effect of reducing the overall no of DBD donors required in SIGNET to generate adequate power for primary outcome.

e. Critical Care studies report consent rates poorly, and when they do often as a fraction of approached rather than eligible patients. Randomisation of >80% of eligible donors is a fantastic achievement which is testament to pragmatic and practical methodology, protocol & training, the commitment and support of SNODs & sites, and the willingness of donor families to consider research as a component of donation.

f. There are no formal screening logs within the SIGNET methodology (to reduce site / SNOD workload), and approach & consent for individual research studies is not included within the PDA or DonorPath. Therefore, to determine exact reasons for loss to recruitment requires individual free text review of DonorPath, where this data may be missing. The SIGNET team are considering best options to monitor, share, review and publish this important data (a “performance” paper).

g. Further detailed qualitative understanding of the factors which influence consent for interventional research in organ donation is required. An NHSBT funded service evaluation project in partnership with City University will use qualitative research methods (focused interviews) with staff and families with experience of SIGNET consent to investigate this.

7. Governance & Risk

a. Governance is a shared responsibility of the CTU / study sponsor and NHSBT. Incidents should be reported both to the study sponsor and via the usual clinical pathways.

b. Site monitoring has commenced, and will run annually throughout the study.

c. Study safety and oversight is maintained via an independent Data Monitoring Committee chaired by Prof. Lorraine Ware (Vanderbilt University, USA)

d. No specific governance incidents, data or reports will be provided to NODC on this basis, however concerns or required changes in processes or protocol will be reported.

e. It has become apparent that during the pandemic a significant proportion of organ donation consent conversations occur prior to the declaration of death by neurological criteria, and are not repeated / continued after the diagnosis. A further application to the Research Ethics Committee is planned to request permission to seek consent for SIGNET prior to the declaration of death by neurological criteria to reflect this practice. In the meantime there is a provision for SIGNET consent via telephone.

f. No discernible risk to the donation pathway as a result of the first major multicentre randomised interventional controlled trial has been identified thus far.

g. Co-enrolment agreements are in preparation to ensure that transplant studies continue and can take due account of randomisation in SIGNET and visa versa.

h. Of potential concern to the SIGNET study is the use of perfusion technologies in specific centres outside of usual practise or randomisation in studies. This has the potential to skew the results of the study in ways which cannot be statistically controlled for. The SIGNET team are considering how this risk can best be mitigated.

i. As a single blinded study, accidental unblinding of transplant teams is possible at donor sites. We have impressed upon sites the importance of due care and attention to prevent this.

8. Linked Studies

a. NHSBT service evaluation of consent for interventional research in organ donation with City University. REC approval has been given and the study should commence within the next 3 months.

b. NIHR Efficacy and Mechanism Evaluation funded study into the mechanisms of action of simvastatin in potentially ameliorating the impacts of brain stem compression on organ function. This study will utilise QUOD samples taken concurrently to SIGNET under separate consent mechanisms from the same donors. An example of the power and value that can be gained from integration of research into usual clinical pathways.

9. Presentations & Promotions

a. The SIGNET study has been presented at the UK Critical Care Research Group Conference, The Canadian Critical Care Forum, The British Transplant Society and at all NHSBT Regional Collaboratives and Organ Advisory Groups.

b. Positive media representation at launch in September (https://www.theguardian.com/society/2021/sep/19/use-of-10p-statins-in-organ-donation-could-save-thousands-of-lives)

(https://www.nihr.ac.uk/news/uk-launches-worlds-largest-ever-randomised-controlled-trial-in-organ-donation/28710)

10. Next Steps

a. Clarify a process for the intermittent review of a sample of sites / regions / durations to determine consent rate for SIGNET, and ensure this remains high.

b. Establish a clinical reference group for advisory support.

c. Investigator meeting to accompany NHSBT events, UK Critical Care Research Group Conference, and / or Intensive Care Society State of the Art meeting. Associate PI meeting to support and encourage next generation of donation researchers.

d. Open related studies.

e. Publish Protocol paper (BMJ Open) & team considering “Performance” paper.

f. Take the learning from SIGNET to our next major research project.

Dan Harvey

Co-Chief Investigator & National Lead for Innovation & Research in Organ Donation

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