STRIDES trial – Statistical analysis plan for principal paper

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1. Background

Vasovagal reactions (VVRs) are the most common acute complication related to blood donation. VVRs are characterised by a general feeling of discomfort and weakness with anxiety, dizziness and nausea (moderate reactions), which may progress to loss of consciousness (severe reactions) with complications such as fall and fractures. VVRs can therefore be associated with substantial morbidity among donors and medicolegal liability for blood services.

The Strategies to Improve Donor Experiences (STRIDES) trial, is a large cluster-randomised trial conducted across all National Health Service Blood and Transplant (NHSBT) sites in England UK (involving more than 1.4 million whole blood donors) to test the impact of four interventions to prevent VVRs among whole blood donors.

2. Aim

The purpose of this document is:

- to clarify the analyses to be conducted in the STRIDES trial for the principal outcomes paper;
- to minimise misleading inferences that could arise from post hoc analyses.

Thus, this plan has been written in advance of looking at the outcome data from the trial, and is based on what was specified in the protocol.

The final version of this plan will be uploaded onto the STRIDES trial website in advance of undertaking the principal trial analyses.

There will be a number of additional subsidiary papers from the STRIDES trial and its sub-studies, which are not discussed in detail here.

3. Summary of trial design

The STRIDES trial is an open cluster-randomised cross-over/stepped-wedge factorial trial involving randomisation of 73 teams ("clusters") conducting routine blood collection in the whole of NHSBT in England for 36 months to test four interventions to reduce VVRs compared to current usual NHSBT practice, specifically:
(1) isotonic hydration before donation (ISO), comparing 500ml isotonic drink *vs* current 500ml plain water;
(2) time on donation chair after donation (CHA), comparing 3-minutes rest on donation chair before standing *vs* current 2-minutes;
(3) modified applied muscle tension (AMT), comparing new AMT *vs* current practice of AMT;

(4) psychosocial intervention (PSY), comparing provision of preparatory materials *vs* current practice of nothing.

The 73 teams ("clusters") are randomised to receive one or more interventions during each of four nine-month periods using principles of cross-over (for isotonic drink and time spent in donation chair), stepped-wedge (for the modified AMT and psychosocial interventions, since these interventions cannot be "un-learned" by participants once introduced to the trial) and factorial trial design to construct the temporal sequence of interventions.

All clusters began the first set of study interventions on 04 November 2019 with changes to interventions occurring every 9 months over a total of 36 months trial duration (i.e. 4 periods). All donors who attended a blood donation session during this period are eligible to participate in the main trial (unless they choose to opt-out). A subset of donors who consent to join the STRIDES/NIHR BioResource additionally provide blood samples and complete a baseline questionnaire.

Specific objectives

The primary objective of the STRIDES trial is to determine the optimum intervention(s) to prevent vasovagal reactions in whole blood donors (singly or in combination).

A secondary objective is to advance understanding of the determinants of VVRs and to develop prevention strategies for VVRs tailored to specific donor sub-populations (e.g., stratified by demographic, biological, psychosocial, and other characteristics).

Outcomes

The primary outcome is the number of in-session VVRs with loss of consciousness (i.e. episodes involving loss of consciousness of any duration, with or without additional complications).

Secondary outcomes will include:
(i) All in-session VVRs (i.e. with and without loss of consciousness)
(ii) All delayed VVRs (i.e. with and without loss of consciousness after leaving the donation venue)
(iii) Delayed VVRs with loss of consciousness
(iv) Any in-session non-VVR adverse events or reactions

In terms of missing data:

- The data on the primary and secondary outcomes are complete by design.
- Data on questionnaires and haematology markers will be available only in the subset of participants who consent to join the STRIDES/NIHR Bioresource.

Power calculations have been based on the primary endpoint (defined above), assuming a 5% type I error probability. For the two interventions being assessed using a cross-over design (i.e. isotonic hydration and time on donation chair after donation), there is >90% power to detect an odds reduction of >9% (odds ratio of 0.92). For the two interventions being assessed using a stepped-wedge design (i.e. modified AMT and

psychosocial intervention), there is >90% power to detect an odds reduction of >14% (odds ratio of 0.87).

4. Timelines and scope

The STRIDES trial will complete on 03 November 2022. Data cleaning and preliminary analyses (blinded to randomised group) will begin in October 2022, according the plan outlined here, in order to develop cleaning and analysis code to streamline the final analyses. The main trial data will be analysed from November 2022, with the intention of reviewing primary results at the next trial steering group meeting and working towards submitting a paper for publication before the end of Q1 2023. Presentations at relevant conferences, and dissemination to NHSBT, is also planned.

Data collected in the STRIDES/NIHR Bioresource will be analysed separately from the main trial principal outcomes paper.

5. Overall analysis strategy

Principles
Intention-to-treat analyses will be used, comparing interventions as randomised and including data from all donors attending the donation sites during the trial, unless the donor opted-out.

Principal analyses will concern assessment of the main effects of interventions based on outcomes aggregated at the site level (i.e. unit of randomisation). Tests of interaction will assess whether results differ between pre-specified subgroups.

Subsidiary analyses will be done using individual level data with allowance for clustering of observations by site. Multiple testing will be taken into account when interpreting results other than the principal analyses (see **section 12**). The trial will be reported according to CONSORT guidelines.

End-of-trial analyses
Primary analyses will calculate odds ratios for the main effects of interventions using a binomial generalised linear mixed model fitted to the aggregate number of primary outcomes recorded in each 9-month period by site with denominator as the number of donations recorded by site-period. In accordance with NHSBT practice, a donation constitutes a complete donation or a partial donation. Other attendances not leading to a donation, such as a failed venepuncture, do not count as no blood has been taken and the donor can return quickly.

Key secondary analyses related to the primary outcome will include assessment of interactions of interventions and possible variation of the intervention main effects by period and baseline characteristics.

Analyses of the secondary outcomes will follow the same approach as for the primary outcome.

6. Descriptive analyses

The STRIDES trial protocol paper describes the recruitment and trial procedures in detail, and will be referenced. The current principal outcomes paper will provide further details on:

- Baseline characteristics by randomised group and period, for example: age, sex, pre-baseline 2-year events history aggregated at site level (VVR rates, blood donations, deferral rates) and site type (fixed or mobile). Results will be presented as mean (SD) or number (%). No statistical testing of differences between groups will be undertaken.
- Flow of donors through the trial after randomisation, as a CONSORT diagram, including number of attendances, donations, and completeness of the primary and secondary outcomes data.

7. Primary outcome

There is one primary outcome:

- The number of in-session VVRs with loss of consciousness (abbreviated AE_ONS_VV2MORE).

These results will be presented as n (%) per donation in each randomised group, and odds ratio (95% CI) for the main effect of each intervention (i.e. as compared to no intervention).

8. Secondary outcomes

The following four secondary outcomes will be analysed in the principal outcomes paper:

- All in-session VVRs with and without loss of consciousness (AE_ONS_VV1MORE).
- All delayed VVRs with and without loss of consciousness after leaving the venue (AE_DEL_VV1MORE).
- Delayed VVRs with loss of consciousness (AE_DEL_VV2MORE)
- Any in-session non-VVR adverse events or reactions (AE_ONS_NONVVR), specifically: bruising and rebleed.

The statistical analysis and presentation of the secondary outcomes will be the same as for the primary outcome.

9. Descriptive analyses of outcomes

Some additional outcome data may be presented, probably graphically, but without statistical testing. This includes:

- Primary and secondary outcomes event rates by geographic region, month and year of attendance, to assess possible impact of operational changes during the COVID-19 pandemic.
- Primary and secondary outcomes event rates by age group and sex, to assess possible impact of COVID-19 pandemic.

10. Baseline covariate adjustment

Analyses will be presented first unadjusted, and then adjusted for baseline prognostic variables that were considered for balancing at randomisation (i.e. historical VVR rates, total numbers of donors bled, and type of site) plus dummy variables for the four nine-month periods of intervention and a random effect for site.

For the subsidiary analyses using individual participant data, a missing indicator method will be used for categorical baseline variables with missing data, so that all data can be included [1].

11. Subgroups

Subgroup analyses will be carried out only for the primary outcome by assessing statistical interactions in three hypothesis groups: First, assessing pair-wise interactions between interventions; second, assessing interactions between interventions and period; and third, assessing interactions between interventions with significant main effects and selected baseline characteristics.

Continuous baseline characteristics will be analysed as linear terms in the regression models, but results presented in groups as specified below.

The subgroups to be compared will be:

Interventions

- Pairwise interactions between four interventions: AMT*PSY, AMT*ISO, AMT*CHA, PSY*ISO, PSY*CHA, ISO*CHA.

Periods

- According to four nine-month periods: categorical period variable, with three-degrees of freedom of test interaction for each intervention.

Site-level characteristics

- According to site historical VVR rate: linear in regression models, but presented by tertiles.
- According to site type: fixed centre vs. mobile team.
- According to site size (assessed by number of two-year donations): linear in regression models, but presented by tertiles.

Individual level characteristics

- According to age: linear in regression models, but presented as <50 vs. 50+ years.
- According to sex: male vs. female.

12. False positive rates

The P-values presented will not be adjusted for multiplicity, but interpretation needs to take into account the multiple statistical tests that have been performed.

- There is one primary outcome, thus $P<0.05$ would be considered appropriate for assessing significance of the main effects of four interventions jointly. Further testing of each intervention separately would consider $p<0.0125$ (i.e. 0.05/4) as providing strong evidence, and otherwise suggestive if $p<0.05$.

- There are 4 secondary outcomes, which suggests considering only $p<0.0125$ (i.e. 0.05/4) as providing significant evidence of intervention main effects with regards to secondary outcomes.
- For the tests of pair-wise interactions between interventions, there 6 interactions, which were also allowed for in the trial design. This suggests considering $p < 0.008$ (i.e. 0.05/6) as providing significant evidence of interaction of interventions.
- For the tests of interactions with baseline characteristics, if 1 intervention is assessed, there are 5 interactions. This suggests considering only $P<0.002$ (i.e. 0.01/5) as providing significant evidence of differences in trends between subgroups.

Interpretation of results will also take account of internal consistency across outcomes, as well as clinical plausibility based on prior evidence.

13. Missing data

Data are expected to be >98% complete for the principal trial outcomes assessed at blood donation sessions. Data on blood biomarkers and questionnaires will only be available for participants who consent to join the STRIDES/NIHR Bioresource. These data will not be analysed in the principal outcomes paper and approaches to handle missing data in this subset of participants will be detailed in a future analysis plan for these data.

14. Proposed tables and figures

The above analyses would lead to the following tables and figures in the paper. Some could be supplementary material.

- Table 1: Baseline characteristics
- Figure 1: CONSORT diagram
- Table 2: Primary outcome, unadjusted and adjusted
- Figure 2: Primary outcome
- Table 3: Secondary outcomes, unadjusted and adjusted
- Figure 3: Secondary outcomes
- Figure(s): Descriptive outcomes
- Figure(s): Subgroup findings for primary outcomes

15. References

1. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomised trials. *Statistics in Medicine* 2005; **24**: 993-1007.