British Heart Foundation

Clinical Study Guidelines (Interventional)

Please provide a brief description of your interventional clinical study, based on the headings below:

1. Study design
Describe the study design including whether the trial will be placebo controlled, methods of randomisation, allocation concealment, masking, types of analysis (intention to treat, per protocol).

2. Study population
Describe the inclusion and exclusion criteria. Describe any relevant details about how the study population will be selected e.g. after a run-in period.

3. Proposed interventions
Include a description of both experimental and control/comparator interventions.
Note the dose and duration of administration of the intervention(s). If you are trialling a complex intervention, please refer to MRC Guidance about developing and evaluating complex interventions.

4. Outcome measures
Describe primary and secondary outcomes measures. Explain how the outcomes will be reliably measured and at what timepoints. Explain if and how the outcome measures will be adjudicated.

5. Follow up
Provide details of frequency and duration of follow up, and methods to avoid losses to follow up. Provide details of any anticipated problems with compliance and explain how these will be dealt with.

6. Study setting
Describe the clinical setting in which participants will be identified and invited to participate (e.g. general practice, hospital outpatients, ambulance service users).

7. Power calculations and sample size calculations
Provide a proposed sample size, describing the event rate (which should be based on contemporary data) and explaining how it was estimated. Give a detailed justification for the event rate, estimated effect size, power and type 1 error rate. If there are known adverse effects leading to non-adherence, this will need to be taken into consideration when calculating sample size.

- BHF would usually expect a high value, definitive trial to be designed with 90% power.
- When estimating effect size, bear in mind that for a binary clinical outcome most treatments have at best moderate effects (e.g. a 15-20% relative risk reduction). An effect estimate larger than this will need careful justification. (Note: since the results of systematic reviews of small trials are known to overestimate effect size, such studies are not generally suitable for determining the likely effect size of a treatment in a new trial).
- Where sample size requirements exceed the capacity of the UK, the BHF encourages applicants to consider seeking international collaboration.
- If the study involves international centres, please make it clear if the study is powered on the UK arm alone or on the total number of participants across all countries.

8. Planned subgroup analysis
Describe any planned subgroup analysis, including any sex/gender stratified analysis. If you are not planning to perform a sex/gender stratified analysis, please justify why not.

9. Bias

Identify potential sources of bias and explain the methods used for protecting against such bias. If the trial is not placebo controlled, explain how you will avoid the potential for bias (e.g. perhaps by using patient registries to identify outcomes).

10. Planned data/statistical analysis

Describe how you plan to analyse the data you have collected. Depending on your study design and methodology, you may need to explain what quantitative statistical methods you plan to use, your methods for qualitative data analysis, and your approach to combining data from multiple methods or sources.

Note: If the study involves international centres, explain the arrangements for data management between countries. Explain how data will be shared and who will be responsible for the analysis.

11. Potential risks and hazards

Outline the potential risks to participants and how they are being minimised.

12. Early stopping

Outline the plans in place for early stopping of the trial.

13. Recruitment strategy and study delivery

Describe how recruitment will be organised and the time period over which it will take place, including the number and location of recruiting sites. We usually expect applicants to include a 'Vanguard phase'' in an application for a high value clinical trial, with full funding contingent on satisfactory milestones being reached within the vanguard phase (see section 15).

Note: If international sites are involved, state the location of these sites, the number of participants to be recruited at each site, and give details of the proposed UK and international recruitment targets. It should be clear what proportion of total participants are expected to be recruited from the UK.
If recruitment has already commenced at some sites/locations, provide details of the latest recruitment figures for these sites versus recruitment targets.

14. Including people from under-represented groups

- Describe the demographics of the population that is affected by the condition being studied or that needs the healthcare intervention (e.g. age, sex/gender, ethnicity).
- Explain the strategies you will use to recruit a diverse group of participants that represents the population affected by the condition or needing the healthcare intervention, and how your recruitment and retention methods will engage with under-represented groups.
- You may find it useful to refer to guidance linked within BHF's policy on diversity in research design.

15. Vanguard phase

BHF would usually expect an application for a large, multicentre clinical trial to include a 'Vanguard' phase, to establish trial deliverability, with full funding contingent on satisfactory milestones being reached within the Vanguard phase. **The Vanguard phase should begin with activation of the grant.**

You may find the following articles helpful when configuring the Vanguard phase:

- BMJ Open: Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies
- Trials: Progression criteria in trials with an internal pilot: an audit of publicly funded randomised controlled trials.

If you are not planning to conduct a Vanguard phase, please justify why not.

If you are planning to conduct a Vanguard phase, please provide information on the Vanguard phase in one of the formats below:

UK trial

Total sample size: x participants
Duration of recruitment for the total sample size: x months

Vanguard phase targets:

- **Target recruitment number for the Vanguard phase**: x participants (% of the total sample size)
- **Target number of sites open and recruiting at the end of the Vanguard phase:** x sites (% of the planned total number of sites)
- **Proposed length of Vanguard phase:** x months (x months set up [if included], x months recruitment, % of the recruitment time for the total sample size)

Vanguard phase stop/go milestone/s:

- **Proposed date of the stop/go milestone**: Please specify clearly the time when the stop/go milestone will be reviewed (e.g. x months after the start of recruitment [opening of the first site to recruitment], and x months after the grant start date)
- Set out the progression criteria that will be used to determine whether the milestone has been met successfully and indicate whether the study can progress to the main phase. The progression criteria should usually include (but not be restricted to) the criteria in the table below.
- If the measures in the table are not appropriate for your study, please specify others and fully justify your choice.
- As well as recruitment, the Vanguard phase may also collate important compliance information (e.g. compliance to randomisation allocation, treatment protocol, procedures, follow-up data) which may also form part of the progression criteria to the main trial.

Stop/go milestone progression criteria	Red	Amber	Green
Total number of participants recruited (% of Vanguard target)	<n <x%	n-n x-x%	>n 100%
Number of sites opened (% of Vanguard target)	<n <x%	n-n x-x%	>n 100%
Recruitment rate/site/month	n-n	>n	n-n

We would usually expect the RAG rating to be defined along the lines below:

- Red: <50% Vanguard target – discuss trial viability with the TSC and BHF, consider early termination
- Amber: 51-90% – discuss trial viability and possible remediation plan with the TSC and BHF
- Green: 100% – pass milestone, progress to main trial

Funding envelope for the Vanguard phase: State the total cost for the UK Vanguard phase (% of the total cost requested from the BHF for the trial). This should match the total cost provided in the Vanguard/Internal Pilot Phase Costs table in the Funding/Support Requested section of the online application form

Multinational trial (UK arm of international trial, or a UK-led international trial)

Summary of the trial sample size and recruitment duration:

- **Total sample size for the whole trial:** x participants
- **Total sample size for the UK arm:** x participants

- **Duration of recruitment for the whole trial:** x months
- **Duration of recruitment for the UK arm:** x months

UK Vanguard phase target figures:

- **Target recruitment number for the UK Vanguard phase:** x UK participants (% of the UK arm total sample size)
- **Target number of sites open and recruiting at the end of the UK Vanguard phase:** x UK sites (% of the UK arm total sites)
- **Proposed length of the Vanguard phase:** x months (x months set up [if included], x months recruitment, % of the total recruitment time for the UK trial

The UK Vanguard phase should also include target figures for international recruitment:

- **Target international recruitment for Vanguard phase:** x participants (% of total international sample size)
- **Target number of international sites open and recruiting at the end of the UK Vanguard phase:** x sites (% of planned total number of international sites

UK Vanguard phase stop/go milestone(s):

- **Proposed date of the stop/go milestone:** Please specify clearly the time when the stop/go milestone will be reviewed (e.g. x months after the start of recruitment [opening of the first UK site to recruitment], and x months after the BHF grant start date)
- Set out the criteria that will be used to determine whether the milestone has been met successfully and indicate whether the study can progress to the main phase. The progression criteria should usually include (but not be restricted to) the criteria in the table below.
- If the measures in the table are not appropriate for your study, please specify others and fully justify your choice.
- As well as recruitment, the Vanguard phase may also collate important compliance information (e.g. compliance to randomisation allocation, treatment protocol, procedures, follow-up data) which may also form part of the progression criteria to the main trial.
- The stop/go milestone criteria for the UK Vanguard phase should take into account the performance of the international trial. If there are formal progression milestones for the international trial, explain how the UK milestone and RAG ratings will be combined with the international trial milestones and RAG ratings in any stop/go decision.

	Stop/go milestone progression criteria	Red	Amber	Green
UK	Total number of participants recruited (% of Vanguard target)	<n <x%	n-n x-x%	>n 100%
	Number of sites opened (% of Vanguard target)	<n <x%	n-n x-x%	>n 100%
	Recruitment rate/site/month	n-n	>n	n-n
	Number of sites opened	<n	n-n	>n
International trial	Total number of participants recruited (% of Vanguard target)	<n <x%	n-n x-x%	>n 100%

We would usually expect the RAG rating to be defined along the lines below:

- Red: <50% Vanguard target – discuss trial viability with the UK TSC, international steering committee and BHF, consider early termination
- Amber: 51-90% target – discuss trial viability and possible remediation plan with the UK TSC, international steering committee and BHF
- Green: 100% – pass milestone, progress to main trial phase

Funding envelope for the UK Vanguard phase: State the total cost for the UK Vanguard phase (% of the total cost requested from the BHF for the trial). This should match the total cost provided in the Vanguard/Internal Pilot Phase Costs table in the Funding/Support Requested section of the online application form

16. Evidence of deliverability

Explain how you have assessed the feasibility of delivering the study and provide evidence that the planned recruitment rate is achievable. Please include the following information:

- The proposed number of participants and centres
- The total number of participants available from which the trial population may be drawn. This should include details of the contemporary incidence or prevalence rates for the condition (whichever is relevant) and how you have identified these rates
- Referral volumes and the likely proportion of eligible patients
- The process for identifying potentially eligible participants
- The proportion of potentially eligible participants who will fulfil the inclusion/exclusion criteria
- Estimated consent rates
- Estimated attrition and drop-out rates

Give details of any pilot/feasibility studies to establish study methods and numbers of available participants, and any pilot work demonstrating that planned recruitment targets can be achieved and that the study can be successfully delivered.

Provide evidence of the existence of equipoise for the study question, the numbers of sites (including internationally, where relevant) that have given 'in principle' agreement to collaborate, and contemporary event rates.

17. Competing studies

Provide details of ongoing studies that are competing for the same group of participants or whose results may affect recruitment.

18. Study management and governance

Explain briefly how the study will be managed and the name of the registered clinical trials unit managing the study. The role of the UK clinical trials unit should be clearly outlined.

For an international trial, explain how the trial will be managed across countries, including the role of any international coordinating centre or international data coordinating centre. Explain how the UK clinical trials unit will interact with any international co-ordinating centre or data coordinating centre, if relevant.

A Trial Steering Committee (TSC) should be set up for all multicentre studies. If you have assembled a TSC, list the proposed members of the TSC and their job titles. Otherwise, please state your intention to set up a TSC if the study is funded. Please read our guidance about setting up a TSC.

The Sponsor should complete a risk assessment to determine the need for a DMC. If you have assembled a DMC, please list the proposed members of the DMC and their job titles. Otherwise, please state your intention to set up a DMC if the study is funded. If there is no intention to set up a DMC, please justify why not. Please read our guidance about setting up a DMC.

Note: If the study includes international centres, please outline the arrangements for overarching organisation and management of the study across the collaborating countries, including the name of the overall study lead and UK lead. State who will be the overall international sponsor for the study, and whether there will be distributed country level sponsors. Explain how the trial committee structures (TSC, DMC) will operate across the whole study.

19. Trials registration

We require that all applications for funding for clinical trials should be registered on the ISCRTN database (BHF's preferred registry) or another appropriate database, and that summary results from your clinical trial should be made publicly available on the trial registry within 12 months of primary study completion (defined as the last data collection time point for the last subject for the primary outcome measure). We will request the registry ID as part of annual reporting. Please read our guidance about trial registration and reporting of results.

20. Data management

Provide a brief data management plan for the study, including information about:

- Where trial data will be stored in the short, medium and long term.
- The type of data to be shared after completion of the trial and when it will be shared. *Example: a fully anonymised version of the dataset used for analysis with individual participant data and a data dictionary will be available for other researchers to apply to use 1 year after publication.*
- Details of the process for data release.
  Example: Written proposals will be assessed by members of the trial steering committee and a decision made about the appropriateness of the use of data. A data sharing agreement will be put in place before any data are shared.

It should be clear how trial data will be made more widely available, while maintaining the confidentiality and privacy of trial participants, respecting the terms of consent of participants, and avoiding identification of participants.

The BHF expects researchers to follow the guidance in Good Practice Principles for Sharing Individual Participant Data from Publicly Funded Clinical Trials. The sharing of data must be consistent with relevant legal, ethical and regulatory frameworks.

21. Project timetable

Provide a narrative timeline and a Gantt chart for the trial.

Please note that the grant can only be activated once ethical approval is obtained. Any work that takes place prior to ethical approval will need to take place prior to grant activation (and should be noted and marked as such in the written timeline and on the Gantt chart).

Written timeline

Outline the main stages of the trial and the expected duration of each. Include time for:

- Securing ethics and regulatory approval and any other activities planned to take place prior to grant activation
- Vanguard phase:
  - Time for site set up and other activities taking place after grant activation, but before commencement of Vanguard phase recruitment (if relevant)
  - Vanguard phase recruitment
  - Time of Vanguard phase milestone
- Main phase recruitment
- Follow up
- Data analysis and any other activities prior to end of grant

Gantt chart

The Gantt chart should be consistent with the written timeline and key milestones set out in the application. **Please include set up time and make it clear what activities will take place prior to activation of the grant**. Clearly mark key milestones, e.g.

- Activities taking place prior to grant activation
- **Grant activation date**

- Commencement of the Vanguard phase (which should coincide with grant activation)
- Commencement of Vanguard phase recruitment (if not coincident with grant activation)
- Time of stop/go Vanguard milestone review
- Commencement of the main trial if Vanguard progression milestone is met
- Analysis time.

Note: If the application is for the UK arm of an international trial, please also include a Gantt chart for the overall international trial to indicate how the UK trial timelines relate to the international trial.

22. Flow diagram

Please include a flow diagram (single-side of A4) for submission with your application form. This should illustrate the study design and the flow of participants through the study. Key information to convey includes the timing of all study activity, starting from initial eligibility, screening, randomisation and each study visit through to long term follow up. Applicants should describe complex interventions and controls accurately and in full within their diagram. If proposing a randomised controlled trial, we advise that you refer to the CONSORT statement website for guidance.