Randomized Controlled Trial

A randomized controlled trial (RCT) is a prospective interventional clinical study design, where the intervention is assigned to patients in a random fashion; i.e. in a manner that cannot be predicted. RCTs can be blinded or not, using single, double or further blinding of patients, providers, outcome assessors and statisticians. Double-blinding typically necessitates the use of a placebo.

- ☐ **Background**
  - Explain the research topic to a non-expert
  - Present prior research, evidence and/ or guidelines on the topic, as relevant
  - Explain the rationale for the current study
- ☐ **Study significance**
- ☐ **Objectives and hypothesis**
- ☐ **Study design and hypothesis:**
  Define the study as a RCT, provide the randomization ratio, describe special design feature if relevant (parallel group, individual or cluster-randomization, whether crossover was used), whether single-center or multicenter and the underlying hypothesis (superiority or non-inferiority)
- ☐ **Setting and dates:** Describe the study setting/s and relevant dates
- ☐ **Patients (study population)**
  - Inclusion and exclusion criteria
  - Describe how eligible patients will be identified and how the process of inclusion/ exclusion criteria application
- ☐ **Intervention:**
  Define the study interventions (intervention and control) with sufficient details to allow replication including how and when they will be administered.
    - Address drug, regimen, dose, duration and individuals who will perform the interventions.
    - Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
    - Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

- Relevant concomitant care and interventions that are permitted or prohibited during the trial

- ☐ **Outcome/s**: separate the primary outcome/s from secondary outcomes and always address adverse events among secondary outcomes. A primary outcome should preferably be single. Define the time points for all outcomes assessment
- ☐ **Randomization methods and blinding:**
  - Randomization type: simple, stratified and/or using restriction (e.g. blocks)
  - Randomization sequence generation: describe how a the random sequence will be generated (using excel or other random sequence generator) and how the study interventions will be applied to the random sequence
  - Randomization concealment: describe how the physician/ staff members recruiting the patient and the patient were blinded to the allocation before the patient has been included
  - Blinding: describe whether blinding was used, who was blinded and how blinding was achieved
  - If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
- ☐ **Sample size:**
  - Compute the sample size using methods compatible with the study design (superiority/ non-inferiority), providing all the assumptions used for the calculation (control event rate, effect, non-inferiority margin if relevant).
  - Provide the basis for the sample size assumptions (prior evidence, preliminary results or similar).
  - Define interim analyses and stopping rules, as relevant and consider the sample size adjustment required for these
- ☐ **Study flow:**
  - Describe who will generate the random allocation sequence, who will enrolle participants, and who will assign participants to interventions;
  - Describe recruitment process and strategies for achieving adequate participant enrolment to reach target sample size.
  - Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how.
  - How the intervention will be applied and by whom; and the trial schedule of assessments.

- Describe the methods for patients' follow-up, adherence and outcome assessment.
- Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended.

☐ **Data collection and management:**

- Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
- Describe how data will be collected (software used) and by whom.
- Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols.

☐ **Monitoring**

- Data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; Alternatively, an explanation of why a DMC is not needed
- Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
- Harms- Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

☐ **Biological samples**

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

☐ **Statistical analysis**

- Statistical methods for analyzing primary and secondary outcomes.
- Define planned subgroup analyses
- Methods for any additional analyses (eg, adjusted analyses)

☐ **Ethical considerations**

- IRB approval
- How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

- Financial and other competing interests for principal investigators for the overall trial and each study site
- Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
- Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

☐ **Potential sources of bias:** describe the planned study limitations, potential bias and, if relevant, methods to address these.