E17. How to overcome the hurdles of running a clinical trial?

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Keywords: Investigator initiated studies; Study protocol preparation; Data collection; Monitoring; Statistical analysis; Publication

The following recommendations are based on the authors experience in conducting large scale, multicentre, investigator-initiated phase III/IV breast cancer trials in Germany. Experience and recommendations might differ for smaller, mono-centric trials, registration trials, or other diseases and countries. The recommendations are directed to clinical scientists who are planning to run independently a large scale clinical trial.

Preparation of the protocol

- Try to describe aims and objectives in a clear and precise way.
  - define objectives and endpoints exactly and differentiate between the two
  - prepare a study outline including objectives, endpoints, eligibility criteria, treatment plan, and sample size calculation
- Keep the protocol concise and simple!
  - one aim is better than several aims
  - two arm trials are easier to understand and to conduct for you, the sites and patients. For more sophisticated trial designs highly experienced staff and sites are required
  - each data-item to collect should be questioned if it is really necessary. A guideline for selection might be to collect only items which you consider to include in the final publication
  - inclusion criteria should be as wide as possible (do only exclude patients that are not in the broad focus of the treatment or have contra-indications), otherwise recruitment will be unnecessarily slow
  - do not ask for unnecessary examinations that are not routine practise at the sites (they will otherwise not be done at all or not done correctly)
- Ask for all case report form (CRF) pages with baseline parameters already at registration of the individual patients. This is the time point when this information is most present at the sites. Sites are highly motivated as they want to get the patient into the trial; this might drop later.
- Important baseline characteristics should be used as stratification parameters. As the monthly overview on the trial's conduct is usually extracted from the randomisation data base, this data will usually then be available and provides you with a good and highly actual impression about the trial population
- Establish and meet a steering committee when the protocol is almost final. Discuss main protocol contents (objectives, endpoints, in/exclusion criteria, treatment, treatment modification) and come to a consented version (diminishes the risk of mistakes, improves the identification of the committee members with the protocol)
- Identify dedicated colleagues to become members of the independent data monitoring committee. You might need their experience and input if medical problems arise throughout the trial's conduct
- Do not underestimate the amount of time you will need to conduct the trial. This is crucial! If you do not have sufficient time resources the trial might not succeed

Study initiation

- Independency can only be obtained if you own and control the data base
- Hire sufficient dedicated and experienced staff that are in charge only(!) for this study. One (non-medical) project manager should be fully in charge of the trial
- The optimal situation is to have data centre, monitoring and biometrician in house. An alternative is to hire a contract research organisation (CRO). Problems with CROs might be that:
  - other trials have higher priority,
  - control of the trial conduct is less intense,
  - SOPs being used by the CRO are either prepared for registration trials (too detailed) or not specific to the requirements of your trial
  - consider collaboration with an established collaborative study group; here, these problems might be less.
- Data capturing should be very quick (max. 1 week)! Reporting system on completeness of documented and monitored data is crucial, monthly report is optimal (in the pre-analysis phase even weekly)
- Focus data verification (= on-site monitoring) on the primary and secondary endpoints, as those will be included in the publication. 100% source data verification is not required for an investigator initiated trial
- Select the right centres
  - based on previous collaboration,

  - do not believe in recruiting capacity given by centres (investigators usually over-estimate their recruiting potential, and infrastructure and staff at the site might change throughout the trial)
  - regulatory documents should be processed quickly, local review board should work efficiently especially in those centres where you want to start first
- Do applications to authorities, ethic committees, review boards, and if possible, in parallel
- GANTT charts are helpful for managing the trial
- Always have a plan 'B' in mind in case a vote comes back negative or is delayed

Performance

- Check recruitment per site monthly
- Have 4–8 weekly meetings with all staff involved including pharmaceutical company representatives
- Provide actual trial status, trial specific information to the sites, e.g. by preparation of a newsletter every 3 months or more frequent
- Have regular personal contract with sites, ask for difficulties with trial conduct, frequent reasons for ineligibility (consider protocol amendment early)
- Close inactive sites early (sites with only one patient are time consuming and costly)
- Prepare the Clinical Study Report simultaneously during study conduct (to collect the necessary information later is very time consuming, staff might have changed and information is lost; collection of all requested information is done prospectively and therefore more complete)
- Review study protocol every 6 months, changes might become necessary due to upcoming new data

Analysis

- A statistical analysis plan (SAP) should be prepared in parallel with the CRF (so parameters will be asked in a way the statistician can use them, missing parameters will be identified at an early stage)
- The statistician should look in the data base regularly. He should do test analyses repeatedly, checking data for completeness and validity. Systematic errors of investigators or monitors can be detected and corrected during the study conduct. Incorrect values not detected by the monitors can be identified and corrected early

Publication

- Start preparation of the first draft early (i.e. before start of analysis)
- New available data from other trials might lead to changes of the SAP
- Prepare second draft simultaneously with first conference presentation, include comments and advices of the audience in your manuscript
- Restrict publication on predefined primary and secondary endpoints, as these are of the highest evidence level. Do not dilute your message by a retrospectively created hypothesis.

Conflict of interest statement

None declared.