MASTERplans
Maximizing SLE Therapeutic Potential by Application of Novel and Systematic Approaches

PLANS Management Group

14th February 2018 15.00 – 16.00 by teleconference

Meeting to discuss Lessons Learnt from PLANS

Purpose of meeting: to identify any useful learning points to pass on to future projects and studies.

The issues raised in the meeting are first grouped thematically, followed by recommendations.

ISSUES

The themes discussed were:

1. Study design during development of the grant application

- PLANS was 'bolted on' at some point during development of the grant. 'WS 2-4' should have been a discrete work strand with its own lead, so that it had structure with clear responsibilities and adequate resources.
- The study protocol was drafted after the grant had been awarded. Therefore the study design was not mature at the point of grant submission and many logistical issues had not been thought through, resulting in:
    - The amount and complexity of the work being under-estimated, leading to the timeline not being realistic for what was to be achieved;
    - What would be involved in operationalising the plan not being clear, so there were very significant shortfalls in resourcing for study set-up and for sample processing.
    - The feasibility of recruiting enough patients was not adequately assessed (see below).
- The collated finances for MASTERPLANS were not shared with the grant applicants, so partners could not assist in identifying holes in the budget.

2. Study feasibility

- The expectation of recruiting patients to PLANS at approximately 50% of the rate of recruitment to BILAG-BR was highly optimistic:
    - Recruitment plans were not discussed with research nurses during the study design.
    - BILAG-BR is less complex operationally for hospitals.

    - Recruitment to the BILAG-BR biologics arm is boosted by NHS England prescribing guidelines requiring patients to be enrolled in BILAG-BR.
- Clinicians in the Project Steering Group (PSG) who had experience of BILAG-BR did not challenge the feasibility calculations.
- Clinicians also did not challenge the feasibility of doing the biopsies, especially the extra core in the renal biopsy, which was originally perceived as routine.
- SLE is a rare disease and the inclusion / exclusion criteria reduced the pool of potential recruits further.
- The SLE population is very heterogeneous. The RITUXILUP study showed that the number of patients screened to recruit a patient is disproportionately high compared with other diseases.
- The number of patients available was necessarily small as they had to be ill enough to flare but not too ill to take on the demands of the study.

3. Attractiveness to sites

- Because the study would generate very few patients per site and low CRN accruals, it was not attractive to clinicians or R&D departments.
- Observational studies in general are not funded well enough to be attractive.
- The large number of follow-up visits was unattractive because CRN funding basically pays for research nurses to recruit patients.
- PLANS was as complex as a CTIMP, but was not a CTIMP. The complexity was under-estimated, resulting in PLANS taking more time than anticipated.
    - Site set-up involved local PIs in more work than anticipated, especially where liaison with other departments was needed, e.g. planning for how skin samples would be taken and if necessary, stored over the weekend.
    - The time necessary for non-research-intensive sites to complete scoring for multiple instruments was significant.

4. MASTERPLANS resourcing during study setup

- MASTERPLANS would have benefited from a full time study coordinator and a full time senior technician being available to the project from the beginning. The Project Manager attempted to cover these roles, resulting in accumulating delays.
- The project relied too much on people whose primary allegiance lay elsewhere (e.g. technicians / laboratory staff funded by other projects donating time to MASTERPLANS).

5. Research nurse involvement

- Opportunities to involve research nurses in the study design and operationalisation were missed. This could have resulted in issues being picked up before the study opened.

6. Complexity – samples / hubs

- Sample collection arrangements were complicated (despite simplifying so far as possible).
    - Complexity led to delays in setting up sample processing processes, which delayed the opening of sites.
    - Complexity of processes in conjunction with slow recruitment meant that sites had to 'relearn' what to do for each participant.

7. Lead centre

- The lead centre for studies very often generates the majority of the participants. Slow recruitment at the lead centre could have raised warning bells sooner.

8. Approvals

- There were some generic problems common to all studies:
    - Slow processing of R&D approvals at certain sites.
        - R&D departments being under-resourced.
        - Costings being checked more rigorously than formerly.
        - Prioritisation of high value industry studies; followed by studies (e.g. questionnaire studies) with low effort and high numbers of patients, giving high CRN accruals.
    - The two part REC / HRA approval process has not noticeably shortened the R&D approval process, and the HRA part of the process has added an additional hurdle.
- The start of R&D Capability and Capacity was actively delayed at some sites owing to research nurse shortages having an upfront effect on Capability and Capacity.

9. Governance and decision-making

- There were issues in PSG around in depth engagement with PLANS and willingness to speak out.
- The PSG could have caught some of the issues during the design phase. The protocol was circulated for comment, and EV gave several presentations on the plan, but received very little input.
- The PSG did not react quickly enough to low recruitment. It took some months to accept there was a problem to be addressed and to make a decision on the renal issue.
- Partners were protective of their own budgets and did not release money to employ the study coordinator, despite being warned of the possible consequences.
- The PLANS Management Group was helpful in providing more focus than was possible in PSG and actively making recommendations. However, time was lost waiting for the next PSG.
- As an example of good practice, the restructuring plan describes the date at which a decision on how to proceed will be taken and the nature of that decision, if recruitment is below a certain number on that date.

10. Strategy for dealing with low recruitment

The effect of feasibility not having been adequately assessed led to many centres beyond those originally envisaged being opened to enhance recruitment. Most of these could provide less than 5 patients, 2 – 3 patients in many cases. The meeting agreed that the effort involved in opening such sites was excessive compared with the potential benefit.

11. Weather

We were unfortunate that the very dull summer of 2017 resulted in much fewer SLE flares than normally expected. Summer would be expected to be the key time for recruiting skin patients in particular.

RECOMMENDATIONS

Domain	Recommendation

Study design
Feasibility
Complexity
	• Start work on the grant application as soon as possible and take a long run at the study design, in order that logistical aspects and financing can be properly thought through
	  ○ NB start work on the MASTERPLANS follow-on clinical trial soon.
	• Design simple, well-focused studies, focusing on a small number of centres that have the right sort of patients.
	• Invest effort in assessing feasibility.
	  ○ Consider the inclusion / exclusion criteria very carefully
	  ○ Involve research nurses in the group designing the study.
	  ○ Consider breaking down the study into a small prototype with around 20 patients at a few sites, to inform the design of the main study.
	  ○ Build in time for problems over which the study team has no control, e.g. delays in approvals, weather.
	• Take input from the assessment of recruitment feasibility to consider how long the study needs to be.
	• In thinking about length of study, apply a pragmatic end point determined by what is achievable in a 'reasonable' time frame – perhaps based on the degree of confidence in the result (Bayesian logic).
	• Aim at around eight centres, ideally all represented in the Consortium.
	• Where the design of the study permits, use PIC centres to refer patients.

Sites	• Aim to have a research nurse or study coordinator dedicated solely to recruitment.
Governance	• A specific group should be charged with looking after the operational aspects of studies, including monitoring and recruitment issues, e.g. the PLANS Management Group. • Consideration should be given to where decisions on change of direction of the study would reside. • Build this into committee responsibilities specified decision dates and proposed actions to be taken for recruitment below specified targets.