Multi-Arm Clinical Trials – Teams within Teams

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Clinical trials are held up as good examples of team science (1) (defined as output-focussed research involving two or more research groups) and this is true. The hub-and-spoke approach of co-ordinating centres liaising with multiple sites both nationally and internationally has proven its worth, and it is also widely acknowledged that a cross-disciplinary approach involving both clinicians and statisticians is required. However, clinical trials are evolving and some aspects of the team approach have not kept pace with the newer designs. The classical 2 arm comparison of standard treatment versus novel therapy may, in some circumstances, still be useful, but in oncology an increasing knowledge of tumour biology, a wider choice of potential therapeutic agents and increasing regulation have led to new trial designs and different ways of working. Platform designs, umbrella or basket trials are increasingly seen (2). They share a common aim to increase efficiency either by evaluating several new treatments or management approaches simultaneously in the same group of patients, or by straddling several tumour sites utilising genetic mutations or other biomarkers to identify groups of patients that are likely to respond to targeted therapies.

The academy of medical sciences (AMS) report entitled “improving recognition of team science contributions in biomedical research careers” (1) encourages research funders, employers and publishers to pro-actively develop processes to recognise individual contributions within large collaborative scientific projects. In particular they recommend that team science grants should phase out the requirement for a “lead or principle investigator” in favour of a list of co-applicants, acknowledging the potential need for an administrative lead role. This is contrary to the definition and responsibilities of a clinical trial chief investigator (CI) as defined by both the Medicines and Healthcare Products Regulatory Agency (MHRA) and International Conference on Harmonization (ICH) Good Clinical Practice guidelines which remain focussed on one individual. For a clinical trial conducted at multiple sites, the CI is defined as the authorised health professional (doctor, dentist, nurse or pharmacist) who takes primary responsibility for the conduct of the trial, whether or not he is an investigator at any particular site. Their responsibilities extend well beyond direct clinical care - for example ensuring adequate resources for a trial, randomization and unblinding, investigational medical product accountability, training of site staff etc. In practice, these are often considered the responsibility of the sponsor or trials unit which may be embedded in a separate institution to the CI.

Platform trials are effectively programmes of work, involving multiple clinical trials, and - once established - potentially run for many years. They are most likely to be initiated by those whose primary role is to design and manage clinical trials, a role that requires both disease-specific and statistical knowledge, as well as practical experience of managing clinical trials. The overarching aim is to improve efficiency, and to evaluate new therapies more quickly and this requires strategic vision, institutional commitment, pre-planning and leadership. Senior project management skills are also required above and beyond those of a traditional trial manager role. As an example, the STAMPEDE trial, a multi-arm trial in locally advanced and metastatic prostate cancer - conceived by Max Parmar, a statistician and trialist - has evaluated a range of therapies from standard chemotherapy agents, repurposed drugs to novel uses of radiation therapy. It has adopted the approach of appointing individual clinical comparison leads, equivalent, at least clinically, to a CI to ensure that appropriate clinical expertise is focussed on the development of new treatment comparisons. It also provides a realistic expectation that the clinical responsibilities associated with the trial can be incorporated within an academic clinical job plan, and allows individual investigators to develop new ideas and subsequently receive appropriate credit.

Basket protocols further increase the complexity of clinical governance within clinical trials. Such studies recruit patients from multiple tumour sites based on specific biomarkers or genetic mutations. Disease-specific knowledge of multiple tumour sites (contrary to the ever increasing tumour site subspecialisation), as well as experience of new targeted agents is required to ensure patient safety within such trials. Whilst clinical trials usually have a trial management group which may include clinicians from different disciplines, the multiple tumour types included in a basket protocol highlights the need for an even wider team approach. Sponsors of clinical trials are familiar with the concept of delegated responsibility, usually from sponsor to national co-

ordinating centre and then to site for many of the administrative aspects of the trial, a similar model for clinical governance particularly within basket protocols may also be required. Figure 1 provides an overview of the multiple teams involved in a hypothetical 4–arm basket trial, highlighting the multiple teams involved and the coordination needed to deliver such projects.

Efforts to encourage team science have been focussed on basic science (with clinical trials, as noted, held up as examples of good practice). Yet the AMS report shows that scientific papers acknowledging that 2 or 3 named authors contributed equally to the leadership of a piece of work are now more common in basic science journals than in clinical journals where the majority of papers will be reports of clinical trials. For authorship there are various models that could be adopted. The International Committee of Medical Journal Editors guidance for authorship includes the requirement for both substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data, as well as drafting the paper or revising it critically for important intellectual content. Long lists of multiple authors acknowledging a range of contributions are feasible, and address some of the concerns relating to the importance of publications for career development. Publishers have been encouraged to record contribution information with the idea that this is then used by individuals to demonstrate significant contributions to major projects to both current and potential employers, as a way of counteracting the importance of key positions in an authorship list. This may work well for some, but academic careers and institutions remain highly competitive, and authorship is likely to remain a key metric for the foreseeable future.

In an era where team science is increasingly recognised, encouraged and applauded, and clinical trials are becoming even more complex, clearer acknowledgement of the roles and responsibilities of all those involved is warranted. One size is unlikely to fit all, as this is a rapidly evolving and adaptive field, so the onus is on those involved in clinical trials to champion the team approach, ensure that credit is fairly apportioned and foster career development.

References:

1. Improving recognition of team science contributions in biomedical research careers. Academy of Medical Sciences Report March 2016
2. Parmar MK, Cafferty FH, Sydes MR, et al. Testing many treatments within a single protocol over 10 years at MRC Clinical Trials Unit at UCL: Multi-arm, multi-stage platform, umbrella and basket protocols. Clin Trials 2017:1740774517725697