P220

An assessment of the design and dissemination of phase I clinical trials: where can we improve?

Bethan Copsey[1], Ayodele Odutayo[2], Jonathan Cook[2], Susan Dutton[2], Douglas Altman[2], Sally Hopewell[2]
[1]University of Oxford; [2]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford
Correspondence: Bethan Copsey
Trials 2017, **18(Suppl 1):**P220

Background
Phase I trials involve the early testing of investigational medicines in humans in order to assess their safety, tolerability and pharmacokinetics. Questionable design and conduct of phase I trials has led to long-term morbidity and mortality. There is limited information publicly available regarding how these trials are conducted, monitored and disseminated. A systematic methodological review of the ethical submission for phase I trials was carried out to address this gap.
Methods
A representative sample (n = 426) of clinical trial protocols that received ethical approval by the UK Health Research Authority (HRA) in 2012. We extracted details related to study design and methods from the protocols on phase I studies. Additionally, information on serious adverse events (SAEs) from submitted clinical study reports (CSRs) and searched for publications (by April 2016) of the completed trials was collated. Findings were narratively summarised.
Results
Of the 426 HRA-approved trial protocols, 54 were phase I trials (17 oncology; 37 non-oncology). Forty-five (83%) were industry funded and 17 (31%) were first-in-human studies. All trials were registered in a trial registry, although registry details were publicly available for only 21; as per EU regulations. Across the included studies there were 869 participants; the median sample size was 27 (interquartile range 18 to 41).
Of the first-in-human studies, 13 specified an observation period between administration of the study drug to the first and subsequent participants. Only one study provided justification for this observation period. Thirteen first-in-human studies used biological agents but only 5 of 13 used the MABEL (minimum anticipated biological effect level) for calculating the starting dose or justified not doing so.
Of the 54 phase I trials, 32 have been completed and 24 submitted CSRs to the HRA as of April 2016. No deaths occurred but 11 SAEs were reported, of which 3 were deemed potentially related to the study treatment. All treatment-related SAEs occurred in non-oncology trials.
After a median 2.7 years since completion, only 3 of the 32 fully completed phase I trials have been published and only 10 of these 32 trials have a publicly accessible trial registry entry. None of the trials with SAEs have been published.
Discussion
These findings suggest that phase I trials are generally safe, however there are important opportunities to improve the design, conduct and dissemination of these studies. Methodological gaps exist which should be addressed when planning phase I trials, particularly for dose escalation studies. Much greater transparency through the public registration and dissemination of findings from phase I trials is needed to improve the safety and conduct of future studies.

P221

Practical sample size re-estimation of propensity score analysis for prospective study

Naoki Ishizuka[1], Takeharu Yamanaka[2], Noriko Tanaka[3]
[1]Cancer Institute Hospital; [2]Yokohama City University; [3]National Center for Global Health and Medicine
Correspondence: Naoki Ishizuka
Trials 2017, **18(Suppl 1):**P221

Background
Sample size must be determined when one start any prospective study regardless of it is intervention or observational. The recent popularity of propensity score rapidly increases its application in prospective observational studies with time-to-endpoint in various areas including cancer or cardiovascular disease and some would expect it as an alternative of confirmatory trials. However, a limited number of papers have discussed sample size calculation. We proposed practical sample size re-estimation in mid-course of the study. The approach provides not only statistical power but also the incorporating with interim analysis which have to adjust type I error.
Background
There is a couple of issues in practice. One of issues is that it depends on the distribution of propensity score. The score is usually estimated by logistic regression. However, it is not easy to assume prior to commencing the study. Another one is that some factor which has association with treatment selection but is not correlated with endpoint decrease the precision of confidence interval for the estimate of treatment effect. As result, it leads to decreasing statistical power of test as previous report warned. However, identifying these factors to be excluded would contradict the nature of propensity score analysis which collects data not to miss confounding factors as much as possible. Furthermore simple stratified analysis, ex Cox regression, is enough if it is possible to identify these factors in advance.
Methods
We assume the situation that one would assess the new treatment compared to the standard one. Calculate the sample size tentatively if one assumes alpha level, power and an effect size delta. If time to event is a primary endpoint, expected number of events is determined by the method of Schoenfeld and the variation. Estimate propensity score when the sample size or the number of events reaches tentative sample size or expected number of events. Use stratified logistic or stratified Cox model to estimate the parameter of the effect size. Calculate the inflation coefficient - Which is defined as follows = (Observed Standard Error)^2/(1/(_1 × _2 × D)) where _1,_2 are the fractions of each treatment group and D is the tentative expected number events for time to event. =(Observed Standard Error)^2/(Assumed Variance) for binary endpoint. Calculate the target sample size or the number of events as a product of inflation coefficient - and tentative sample size or the number of events. Do the interim analysis ad Information time as 1 if one would like to plan. If the interim analysis is not significant or one has not done it, do the final analysis.
Results
The operational characteristics concerning the statistical power for various scenarios in which there is no correlation between the factor of treatment choice and endpoint were examined by the simulation study. The result guaranteed the statistical power as planned.
Conclusions
Our approach keeps the statistical power without any assumption of propensity score including the distribution and the correlation between the endpoint and the factors of the treatment choice.

P222

Evaluating personalised treatment recommendations using randomised controlled trials

Matthias Pierce, Richard Emsley
University of Manchester
Correspondence: Matthias Pierce
Trials 2017, **18(Suppl 1):**P222

Objective
To explain, demonstrate and compare methods for evaluating personalised treatment recommendations using a standard, two-arm, parallel randomised controlled trial.
Background
The modern paradigm of stratified medicine (also termed personalised or precision medicine) seeks to move beyond a one-size-fits all approach, that treats patient populations as a whole, towards one that identifies patient strata with different disease pathways or responses to treatment. A major aspect of stratified medicine is to provide personalised treatment recommendations (PTR'S): an algorithm