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Design, conduct and reporting of phase I trials

Bethan Copsey, Ayodele Odutayo, Jonathan Cook, Douglas Altman, Sally Hopewell
Centre for Statistics in Medicine, NDORMS, University of Oxford, UK
Contact: bethan.copsey@csm.ox.ac.uk

Introduction

- Phase I trials involve the early testing of investigational medicines in humans.
- Methodological flaws in phase I trials (e.g. too high a starting dose) may compromise patient safety.
- Poor dissemination of phase I trial results is unethical as safety concerns could impact on design of future trials.
- Objective: To assess the design, conduct and reporting of phase I trial protocols from 19 UK research ethics committees (RECs) in 2012.

Methods

- Duplicate data extraction on intervention, funding, sample size, intention to publish.
  - For first-in-human: dose schedule.
  - For completed trials: date ended, serious adverse events, publications.

Sample

Study sample included 55 phase I trial protocols:

- Almost all drug or vaccine trials (98%)
- Mostly industry funded (84%)
- Median sample size 32 (inter quartile range: 18-56)
- 17 were oncology trials (31%)
- 17 were first-in-human trials (31%)

Conclusions

- Based on our sample, phase I trials were generally safe but dissemination of results was poor.
- Trial registration was common but details were often not made publicly available.
- Recommendations on starting dose and justifying observation time before subsequent dosing were often not followed.

Results

REGISTRATION

- All phase I trials (n=55) were registered.
- Only 39 (71%) were publicly accessible as per EU regulations.

SAFETY

- Of the 13 first-in-human trials of biological agents, 8 (57%) did not address the MABEL* or PAD** for calculating the starting dose.
- Only one justified the interval of observation between dosing subsequent participants.

*MABEL: minimum anticipated biological effect level
**PAD: pharmacologically active dose

REPORTING

- Of the 39 trials completed by Nov 2016, only 26 (67%) provided an end-of-study report to the REC (median time since completion 3.2 years).
- Six treatment-related serious adverse events (SAEs) occurred across 3 trials.

PUBLICATION

- Of the 39 completed trials, only 17 were published (median 3.2 years since completion).
- Only one of the trials with treatment-related SAEs was published but did not mention the SAEs.

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