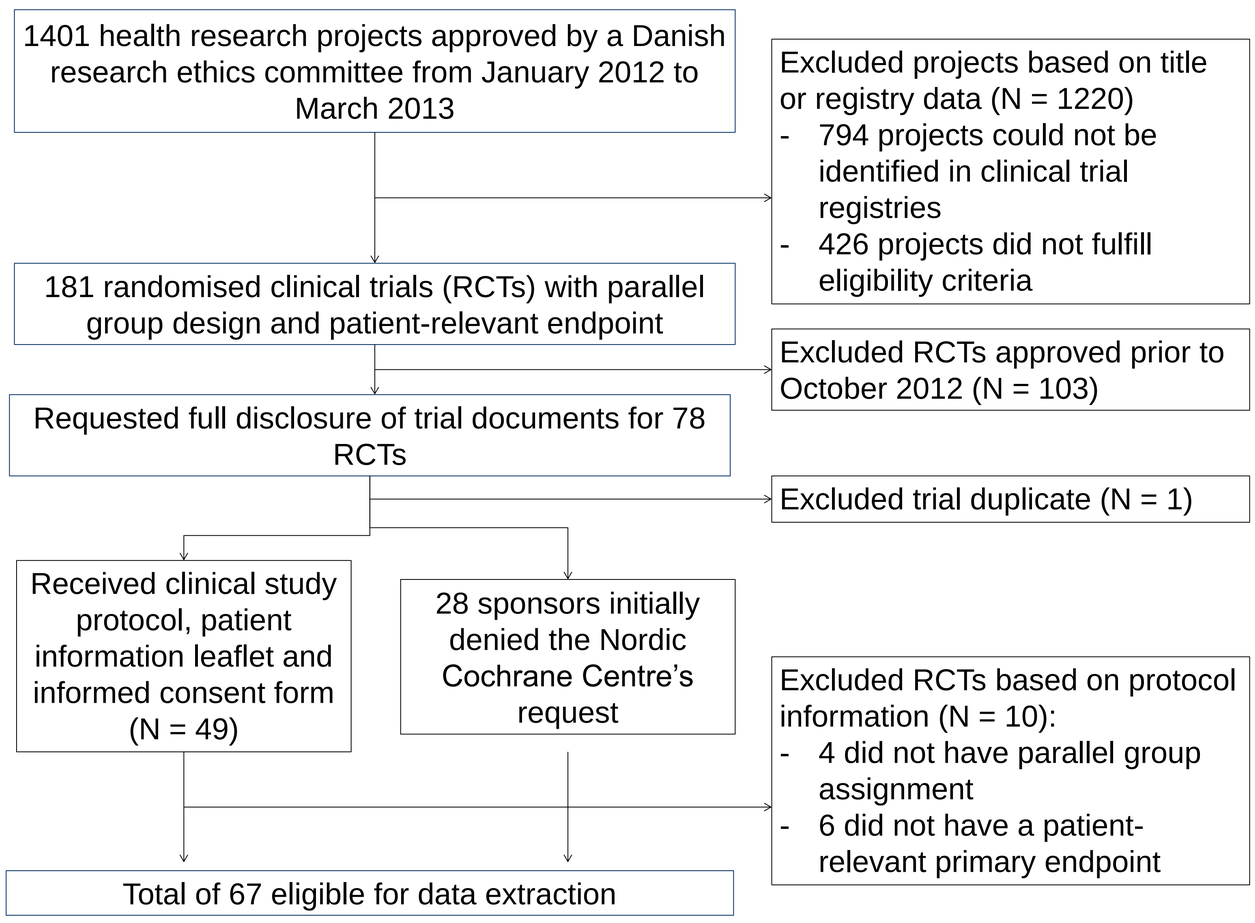
Are earlier trials cited? Review of contemporary clinical study protocols approved by research ethics committees in Denmark

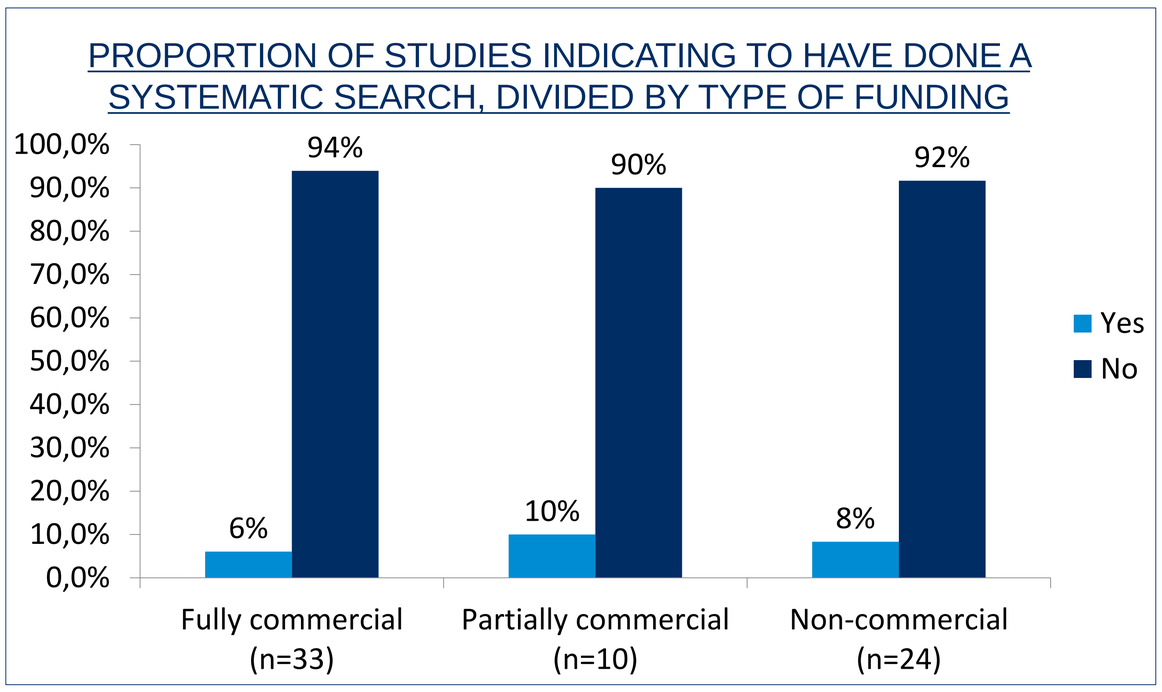
Background

A new trial should always be justified by reference to earlier, similar trials, if any, ideally in the form of a systematic review of such trials. Otherwise trials may be superfluous and patients might risk being allocated to a treatment known to be inferior.

To examine to what extent planned trials were ethically and scientifically justified by existing literature we obtained a cohort of protocols for randomised clinical trials with patient-relevant outcomes approved by an ethics committee in Denmark (October 2012 to March 2013).



FLOWCHART OF RETRIEVAL OF ELIGIBLE PROTOCOLS



Descriptions of search strategies in protocols

We looked at whether protocols mentioned having performed a systematic search, and whether they described their search methods.

Even though we used a very broad definition to judge whether a search had been carried out (simply mentioning a litterature review or a search was enough) only 6 of 67 protocols (9%) indicated having done so.

Use of unethical comparators and lack of valid scientific rationale

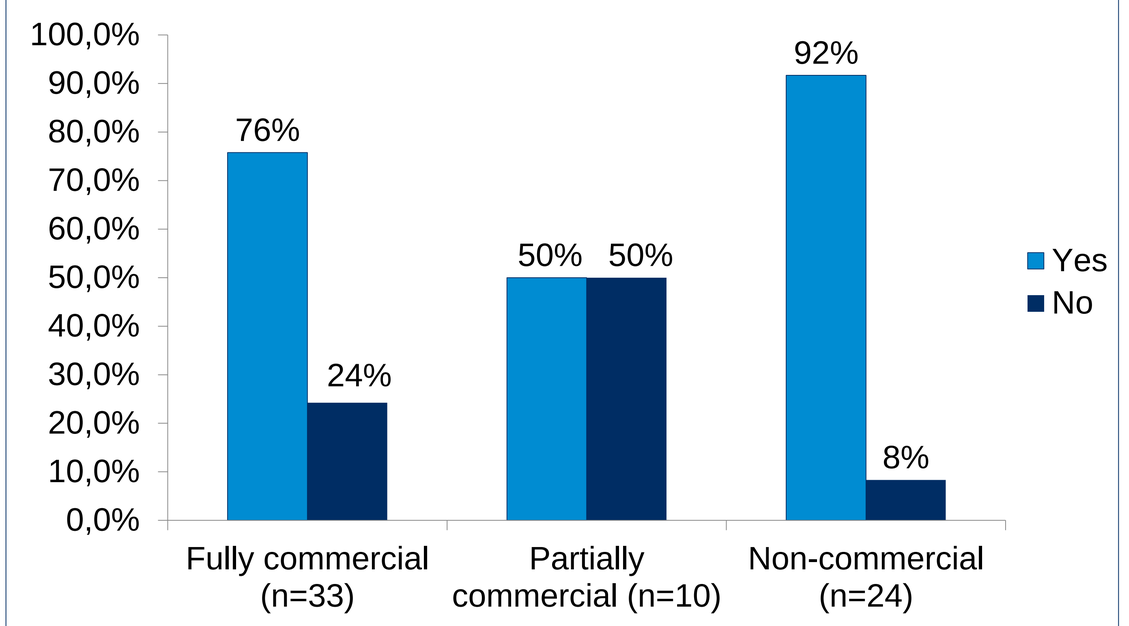
We looked at whether protocols sufficiently justified their choice of comparators and the scientific rationale behind their research questions. We always judged usual care as being ethically acceptable, even though there were examples where usual care was questionable.

Eight out of 67 (12%) protocols used comparators we judged to be unethical, even when not counting studies with questionable usual care.

Eight protocols failed to justify the scientific rationale behind their studies. In total 15 of the 67 (22%) protocols were judged to be unethical, either due to use of unethical comparators, or because of a lack of a scientific rationale behind the study.

EXAMPLES OF UNETHICAL COMPARATORS

- A study used a bare metal stent as comparator, even though the literature search suggested that a drug-coated stent is more effective in reducing revascularisation, which was the primary outcome of the study.
- A study on the effect of Nintendo Wii mediated exercise told the participants in the control group that they could not do any exercise besides what they would normally do, even though the effect of exercise on the primary outcome (quality of life) was well established.
- A study compared an oral form of an intervention with placebo, although the intervention had a documented effect (and should have been given either IV or subcutaneously in the control group)
- Several studies used placebo arms, even though effective interventions existed.



Conclusions

The process of getting access to the protocols in our sample was very cumbersome, as sponsors opposed disclosure for 28 out of 78 (36%) requested protocols. This is especially problematic since our results show that there are ethical issues with relatively many studies. This raises the question whether the ethics committee system in Denmark should scrutinize the protocols in more detail.

Full disclosure of protocols should be the norm, also out of respect for patients as partners in the projects, and it should be a requirement to perform a systematic literature search before a new trial is initialised to avoid patients being given harmful or superfluous interventions.

Paludan-Müller AS, Vive J, Jørgensen KJ, Gøtzsche PC