Relevant full text articles were reviewed to identify the type of adaptive methodology applied, if the publication explicitly stated the use of adaptive designs and whether adaptive design methodology was applied prospectively or concurrently.

Results

The databases produced a total of 14544 phase II, phase III, phase II/III cancer trial related articles that were published in 2015. Of which 99/2127 (5%) for the PubMed database, 519/9573 (5%) for the Embase database and 116/2844 (4%) for the Ovid database articles included the search terms related to adaptive design methodology. After the removal of duplicates, 464 articles were remaining. Of the 464 articles, 92 (20%) were full text trial related publications, 261 (56%) were abstracts, 32 (7%) were methodology or review papers and 79 (17%) were not related to the search criteria.

The adaptive design methodology used in over half of the trials (48/92) was applied by performing interim analyses due to safety, efficacy or futility, 21 out of 92 trials incorporated dose escalation methods and 14 out of 92 implemented a two-stage design. The remaining 9 trials applied the following methods: Bayesian adaptive design (3/92), group sequential design (3/92) change in primary endpoint (1/92), seamless phase II to phase III (1/92), multiple adaptive (1/92). Despite using adaptive design methodology, only four trials explicitly stated that it had an adaptive design. There were 89 out of 92 trials that had prospectively planned adaptations, of which two of these also incorporated an ad-hoc interim analysis.

Conclusion

This review has highlighted that adaptive design methodology is rarely explicitly stated and hence supports the argument for needing a set of guidelines to report the adaptive design methodology used in clinical trials. Furthermore specific reporting guidelines will assist in the consistency of reporting and ensure the ease of future identification of trials implementing any prospective or concurrent adaptive design methodology.

1. Hatfield, Isabella. Adaptive designs undertaken in clinical research: a review of registered clinical trials. Trials (2016): 1273–9
2. www.consort-statement.org/consort-2010

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Evidence based evaluation of practice using the ideal-physio framework. A strategic method of evaluating innovation and current practice

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Trials 2017, **18(Suppl 1):**P107

Background

Whilst there have been recent improvements, the practice and profession of physiotherapy (Physical Therapy) has suffered from the uncontrolled introduction and proliferation of treatments which have an inadequate scientific basis, little or poor evaluation, and underexposure to rigorous scientific method. New treatment modalities can be developed and introduced without evidence of efficacy, regulation or governance. There is no requirement to collect prospective data to support any claims or demonstrate efficacy. This approach has resulted in numerous disparate practices which may not stand up to rigorous evaluation or evidence based commissioning.

Description

The IDEAL framework is an established method of formalising the systematic evaluation of innovation (and existing practice) in complex clinical interventions. It has been useful for setting out an internationally based evaluation framework for surgical procedures. This framework lends itself to other complex, non-pharmacological interventions such as Physiotherapy (Physical Therapy). We outline the application of this framework to Physiotherapy (Physical Therapy) in a new IDEAL-Physio framework.

Similarly to IDEAL for surgery, five stages exist; each representing a letter of the acronym.

Stage 1, the Idea phase where formal data collection should begin. This requires quality recording of data using standardised outcome measures. The emphasis is on explanation and description. Stage 2a, the Development phase, is a period of iterative improvement and adjustment with thorough prospective data recording. It focuses on technical details and feasibility. Stage 2b, the onset of formal Exploration evaluation using systematically collected group or cohort data. This stage is a bridge or a pilot to a full RCT. It further refines outcome measures and takes account of learning curves. Stage 3, is a formal comparative Assessment phase of treatment usually involving randomised studies. It involves a full assessment of efficacy. Stage 4; Long term follow up involves monitoring outcome, particularly in long term conditions.

Recommendations

We recommend the use of IDEAL - Physio to help guide and evaluate innovation with the overall strategy of providing better evidence based care and foster innovation in Physiotherapy (Physical Therapy). This paper outlines the principles of IDEAL - Physio and describes its utility in changing practice on a global level.

Keywords: Physical Therapy, Innovation, Evaluation,

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A journey from statistical consultation to funded adaptive trial

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Trials 2017, **18(Suppl 1):**P108

Background

A funding board assessed an application for a Phase 1 three-doses dose escalation trial of a treatment in Crohn's Disease, but disliked the deterministic 3 + 3 design. The principle applicant sought statistical advice which led to an adaptive design with extra doses. Another board disliked this adaptive design and the 3 + 3 was reinstated. The boards jointly requested a three-dose adaptive design which was funded. This incorporated a Phase II stage, and a crossover design to allow placebo-controlled periods in blocked patient pairs. The aim is to describe the use of the adaptive Bayesian Continual Reassessment method available in BCRM Software [1], for designing dose escalation trials.

Methods

There was a consensus to keep the sample size near 20. A 20% target toxicity event rate for the Maximum Tolerated Dose was set, below the 33% relevant in oncology trials. The performance of the 3 + 3 and BCRM methods was assessed through setting a range of likely and unlikely scenarios for the event rates at the 3 doses, followed by simulation (3000 trial repetitions). Primary assessment was the percentage of trials recommending each of the three doses. The 3 + 3 with a sample size of 18 was contrasted with a BCRM of sample size 16 specifying a one-parameter power model and a Gamma prior.

Results

Within the software, we specified five scenarios for the event-rates across doses. For the 'upper dose is just safe' scenario, BCRM outperformed 3 + 3 in discovering the highest dose (72% versus 62%). For the 'upper dose is just unsafe' scenario, the BCRM recommended the upper dose 54% versus 48% times, but 3 + 3 incorrectly recommended the lowest dose more often (22% versus 10%). For the 'all event rates are ascending but lower than the target' scenario, BCRM recommendations across doses were superior (5%,14%,81%) relative to 3 + 3 (34%,35%,31%). For the 'highest dose is unexpectedly high' scenario, both approaches recommended it in just under 10% of simulations. For the 'highest dose is plausibly high' scenario, both approaches recommended it approximately one-third of the time, and BCRM recommended the correct dose more frequently than 3 + 3 (41% versus 30%).

Conclusions

Some funding boards are encouraging of researchers to adopt and exploit the advantages of novel designs. The availability of the BCRM software enabled a range of event-rate scenarios to be examined for a three-dose example with moderate target rate. Across scenarios,