An example of problems that arise from clinical trials and how to avoid them

Diane Whitham, **Paul Silcocks**, **William Whitehouse**, **Sheila Hodgson** and **Helen Sammons** explain how their clinical trial became three years overdue and £230,000 over budget, and suggest ways in which this sort of problem could be avoided in future

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£230,000 over budget and three years overdue, we have learnt some valuable lessons from our clinical trial

P3MC is a randomised double-blind, parallel-group placebo-controlled trial of propranolol and pizotifen for prevention of migraine in children aged five to 16 years with frequent migraine referred to secondary care outpatients. It is designed as two two-arm trials, with allocation ratio of 2:1 for each comparison (of propranolol versus placebo and pizotifen versus placebo). From a participant's perspective, therefore, it appears as a single three-arm trial with equal allocation. Because both active trial treatments have been in common clinical use for this indication for over 20 years, the trial does not expose participants to a new therapeutic risk.

The grant for the study was awarded by the Health Technology Assessment Commissioning Board in 2005. Initial delays arose because of changes in staff but, despite these being satisfactorily resolved, further delays and cost escalations have occurred as unintended consequences of seemingly innocuous decisions taken early in the design of the study.

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The problems

An initial problem was that, originally, the study design included only liquid formulations of the medicinal products. The liquid preparation of propranolol contains propylene glycol as a preservative, and a ceiling on the maximum dose was necessary to comply with the World Health Organization's recommended maximum daily intake of 25mg/kg of propylene glycol. Serious concerns were raised by paediatricians that, although the ceiling volume of liquid propranolol (at a concentration of 1mg/ml) of 1ml/kg twice a day would allow normal doses in many participants, many 12 to 16-year-olds would be under-dosed according to the higher dosing regimen used by some experienced paediatricians. This was considered to be a major problem because it could hamper the interpretation of the trial if one or both active drugs were not found to be effective.

The following three alternatives were, therefore, considered by the trial steering committee as possible solutions:

1. Review the data on propylene glycol and the WHO safety recommendation to make sure they apply
2. Seek a liquid propranolol without this constraining concentration of propylene glycol, so that full doses could be used as in the original protocol
3. Investigate the possibility of matching propranolol, pizotifen and placebo tablets for the older age group (12- to 16-year-olds), which would account for approximately 75 per cent of the 450 participants

The second problem was a consequence of a decision to adopt option 3 because commercial manufacturers of these medicines were unwilling to provide matching placebos. At this point, an obvious solution would have been over-encapsulation of a commercially available product, which is the method advocated by the Medicines and Healthcare products Regulatory Agency. However, a methodological decision was taken that this would not be adopted since it was easy intentionally or accidentally to break the blind for the trial.

The manufacture of matching placebos alone by a third party was not feasible because of the complexity of matching the proprietary design, including surface markings,

shape, colour and texture. Consequently, it was necessary for the third party to manufacture bespoke matching generic tablets containing the two active agents as well as the placebo.

The third problem now arose as a consequence of the above decision. Because the formulations were bespoke and did not have a marketing authorisation, an investigational medicinal product dossier for each of the formulations was now required in order to obtain a clinical trial authorisation (CTA) from the MHRA. Although the required quantity of each active ingredient was known, the proportions of fillers and excipients needed to ensure that the placebo and the two active drugs matched in colour, shape, size and taste were unknown. These unknowns had to be determined and included in the IMPD. Moreover, because these were all technically new formulations, standard drug development testing (eg, of disintegration, dissolution, microbiology, etc) was also now required both for the active drugs and for the placebo. These processes all imposed their own time lines.

The fourth problem now appeared and is a catch-22. The third party manufacturer required an order to be placed to justify starting the development work needed for the IMPDs but, to place the order, money had to be released by the HTA to cover the manufacturing costs. However, in order for the project funding to be released by the HTA, all regulatory approvals needed to have been obtained. These approvals included a CTA from the MHRA which, in turn, required the IMPDs for each of the formulations from the manufacturer. After some negotiation, this cycle was broken by the HTA agreeing to release sufficient funds to cover the drug development costs. These four problems alone set the project back at least 26 months.

At this point, the fifth problem became apparent. There were now additional financial consequences. These arose partly because of the time delays, which meant that the original trial budget no longer reflected current costs, but also because the trial now included unlicensed bespoke tablet formulations so that it was now categorised as a phase III trial rather than a phase IV trial. Moreover, in its acceptance letter, the MHRA strongly recommended that "the conduct of stability testing [is] to be run in parallel with the clinical trial to demonstrate the drugs stability over the duration of the trial and ensure the scientific integrity of the study". As a result, the cost of a CTA application increased from a few hundred to a few thousand pounds and additional monies had to be sought from the funder.

The lessons learnt

At the time of writing, the trial was just about to start — now more than three years overdue and £230,000 over its original estimate. Some lessons we have learnt include:

- It is not always efficient or cost-effective to combine two trials into one protocol, but funders' requirements have to be followed.
- Put thought into formulations at the design stage, and involve individuals with pharmacy experience.
- Use a commercially available drug. Discuss early on with the manufacturers that hold the marketing authorisation since they may or may not be willing to manufacture matching placebos.
- Think about blinding. In retrospect (for us), a better option may have been over-encapsulation. Decisions need to be weighed against methodological strength.
- Consider start up times, interim measures and inflation when seeking funding. Saving time also saves money.

By manufacturing bespoke medicines instead of using the existing widely available, well understood and licensed products, we introduced an additional level of complexity within the trial which, with the perfect vision of hindsight, could have been avoided. The consequences have been a hard and costly lesson for us. However, as Rodin said: "Nothing is a waste of time if you use the experience wisely". Next time, we will keep things simple, think ahead and consult widely.