Clinical trials on trial

Arnold G Vulto

It has been 3 years since I wrote an editorial on the topic of uncertainty around new cancer treatments (issue 4 of volume 2009). Has this field progressed in 3 years? I think the answer is both yes and no. Yes because we now have a clearer picture of why cancer drugs can sometimes act differently (usually worse) in real life situations than they seem to in pre-registration clinical trials. No, as due to this, they continue to be overpriced. Drug prices are initially based on pre-registration trials, which often intend to achieve licensing rather than demonstrate added value for the average patient under real life conditions.

At the EAHP 2012 annual conference in Milan several presentations looked at how the traditional drug market seems to be stuck in a dead end street, and that governments—on behalf of patients—increasingly refuse to follow the brutal price settings of companies. Dr Paul Cornes from Wales (UK) made a particularly strong case in a seminar sponsored by the European Generics Association. He talked about the three E's: efficacy ('can it work'), effectiveness ('does it work') and cost-effectiveness = efficiency ('is it worth doing compared with other things we could do with the same money'). He described several examples of NICE-evaluations in which new drugs had no proven overall survival benefit or a very limited life extension. He added that just because a drug is licensed does not imply that it is a wise decision to prescribe it. There is a clear discrepancy between licensing requirements and usability of a drug in practice.

This concept was elaborated on in another congress seminar by Angelo Palozzo from Padova (Italy). He made a case that pre-marketing licensing trials have only limited value in appreciating the added value of a new drug for the everyday patient we see in our hospitals. In Italy hospital pharmacists are involved in an interesting real-life experiment with oncology patient registries. Dispensing and reimbursement of a drug is made dependent on enrolling a patient to a national registry. Via these registries the result of drug treatment can be followed as a real life experiment, allowing pharmaco-economic analysis with subsequent conclusions on the real value of the new drug. On page 397 you can read about the considerable differences they found between the findings in the registry and pre-registration trials.

We also received two commentaries from practicing hospital pharmacists in Germany (Prof Irene Krämer) and Spain (Gerardo Cajaraville and Maria-José Tamés) on the same topic (see page 390 and 394), expressing their concern on the current practice of price setting. This illustrates that hospital pharmacists in different countries are losing patience in this roller coaster pricing game. Their major concern, of course, is unsustainability of healthcare and patients having limited access to effective treatment.

Additionally a recent study of the largest clinical trials database (http://www.clinicaltrials.gov) showed considerable heterogeneity in the reporting of drug trials and the authors question how well many of the trials are suited to guide clinical practice. ClinicalTrials.gov contains data on almost 100 000 trials, (supposedly some 80% of all trials performed worldwide). Califf *et al*[1] express concerns that many trials have an inadequate sample size, or do not include the number of projected participants.

Another concern is that there is usually no independent coordinating investigator in industry sponsored multicentre trials. As a member of an ethical review board it fills me with unease that in such trials each centre might enroll 5–10 patients, or even fewer. A number too small to draw any conclusion on a local scale, and only the industry sponsor has a real overview. I call this black box trials: data are collected locally, but disappear in a big black box from the company sponsoring the trial. I believe that all multicentre trials should be governed by an independent scientific committee with the knowledge and the means to perform an independent statistical analysis on the whole dataset.

Hospital pharmacists play a key role in all drug trials: as members of ethical committees, as dispensing pharmacists or in another capacity. However, are we critical enough? Some weeks ago I was involved in a committee discussion about a placebo controlled phase-III multi-centre registration trial for a new oral oncology drug from a reputable multinational company. On checking the investigational medicinal product dossier we noticed that the placebo and active drug actually had different colours. A double blinded trial? We as pharmacists have to be critical of both trial methodology aswell as the practical aspects.

I am concerned that the gold standard of the controlled trial to assess beyond doubt the qualities of a drug (does it work and is it safe, and in which proportion of patients) is eroding.

- Many trials are flawed in numbers, set-up and design.
- Registration trials are there for lawyers and regulators, and seem to have objectives with limited bearing on clinical practice.
- Once the drug is on the market, the market itself (ie, us, the healthcare system) has to build an assessment system to work out the real value of a drug.

I ask myself the question: where have we gone wrong? We have created an incredibly expensive system of clinical trials that seems to be cracking. How do we safeguard a viable and sustainable drug provision system that will be of benefit to patients, and not just for company shareholders? Given the primary objective of registration trials—a marketing authorisation which will benefit the developing company—they are not a useful tool for assessing an initial price. I hope that this issue's cover story contributes to the awareness of hospital pharmacists and subsequently benefits our patients.

Correspondence to Arnold G Vulto, Editor-in-Chief EJHP Practice and Science, Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam 3015 CE, Netherlands; editor.ejhp@bmjgroup.com

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