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Harmonising the way to approval

Medical ethics committees are facing a wide range of challenges, including off-label continuation of treatment following clinical trials. A special session during the Dutch Medicine Days will address these issues. Could harmonisation improve the process of obtaining approval for human drug research?

Probably the most important aspect of preparing a clinical trial of a new drug on humans is to get it past the medical ethics committee. Researchers wishing to start research need to prepare a vast amount of paperwork to answer all the questions put to them by the ethics board. What does the drug do? What were the results of the animal tests? What kind of patient groups are required and how are they taken care of? What about the aspect of safety? Do I need a placebo group? What about blinding? Some submissions lack the right answers to these and other questions, others face the problem of having multiple ethics committees to report to, all of them with different demands and preferences – particularly when several countries are involved.

Experts agree that there is need for a thorough discussion. A special session will therefore be held during the FIGON Dutch Medicine Days. 'The session has the working title: Improving content through harmonisation. This means that we want to see ethics approvals being done in a consistent fashion. We need to streamline the whole process', says Gerard Rongen, internist and clinical pharmacologist at the Radboud University Medical Centre (RUMC) and member of the Central Committee on Research Involving Human Subjects (CCMO). He will be leading this DMD session together with Kees Kramers, his colleague at the RUMC and chair of the Dutch Society for Clinical Pharmacology & Biopharmacy (NVKFB).

Accidents

One way to streamline the process of human drug research approval is to have better prepared clinical pharmacologists on medical ethics committees. 'The current problems with ethics committee membership is actually the main rationale behind this session', says Kramers. 'To function properly on an ethics committee, clinical pharmacologists need to be proficient in judging research proposals. They need to go through an investigational brochure – quite a sizeable document – which contains all the data acquired on the product. They need to have the expertise to correctly estimate the risks for the participating patients, etcetera, etcetera.'

Rongen adds: 'What the CCMO in the Netherlands has experienced over the past 5 or 10 years is that it is increasingly difficult to fill positions on ethics committees with capable and experienced clinical pharmacologists. This could form a serious threat to human drug research. There have already been accidents where clinical pharmacologists on ethics committees have misjudged certain studies.'

Examples include the 2016 case of the experimental fatty acid amide hydrolase inhibitor BIA 10-2474, a drug intended to treat a range of medical conditions, including Parkinson's disease. The drug was tested in healthy volunteers, five of whom were hospitalised within days after the fifth dosage; one of them even died. Rongen: 'The initial dosages where much too high and were also repeatedly administered. This could have already been known from early PK-data in humans and the preclinical data, which showed that the risk of accumulation was high, and there were also signs that the target was already blocked completely at a much lower dosage of the drug. It is my strong conviction that if the members of the medical ethics committees had been more capable and experienced this accident could have been prevented.'

'Committee members need to have the right skills'

Starting point

To prevent such tragic accidents in the future, Rongen initiated collaboration between the CCMO and the NVKFB. An

educational programme will be set up to train clinical pharmacologist in regulations and medical ethics issues. Rongen and Kramers feel that the session at the DMD is a good starting point for that. Another reason behind the session is the upcoming change in regulations in 2019 ensuing from the new European directives. 'These will radically change the way medical ethics committees work. It will be more centralised', says Rongen. 'Our first speaker at the session, a representative of the CCMO, will tell us all about the changes, what they mean for the field, and how the Dutch Government and the CCMO are preparing to implement them.'

Another point of focus in the session is the way submissions are prepared by researchers. Academic researchers seem to be faced with much more difficulty in getting their submission approved than those employed by pharmaceutical companies. This is probably because they have less knowledge about what should be set out in their submission documents. 'Now we often see that these documents lack considerations about the risks and reasons why you opt for a particular design', says Rongen. 'We think the preparation of a submission by academic researchers would be greatly improved if they started to discuss their ideas in multidisciplinary groups. Such initiatives are already beginning to take place. Joop van Gerven, the head of CCMO, or one of his collaborators at LUMC will talk about this during the session.'

Elaborate

The industry has its own problems concerning ethics committees. Rongen: 'An important problem in industry-initiated studies is the open-label-extension (OLE)-phase of the study. In this phase the patients taking part in the study that apparently benefit from the treatment are allowed to continue their use of the experimental drug under controlled situations. But there is always a great deal of discussion on medical ethics committees about the appropriateness of OLE-studies. There are various reasons for this. The first is that the drug's risk/benefit balance is not yet known because the study results are still being analysed. Secondly, the OLE-study often lacks a formal research question. And thirdly, the lack of control groups often makes the OLE-phases questionable. An expert from the industry will address this problem during the session. It would be great if we could discuss the pros and cons of OLE-studies and give both ethics committees and the industry an understanding of the position held by both sides.'

'I hope we can come one step closer'

Oncologist and clinical investigator Carla van Herpen of Radboud UMC will give a talk about local approval of human drug research studies. 'After the ethics committees have approved a certain multi-centre study, the participating hospitals still need to endorse that their centre will participate in the study', says Rongen. 'That is done by the board members of the centre. Considerations for this approval are: do we have the right personnel, the right infrastructure, and an adequate number of patients to perform the study? This process can be very elaborate and time-consuming. Van Herpen has ideas on how to perform this process of approval more efficiently. After this lecture, we shall start up a discussion with the audience. By doing so I hope we can come one step closer to harmonising the way to approval.' ●