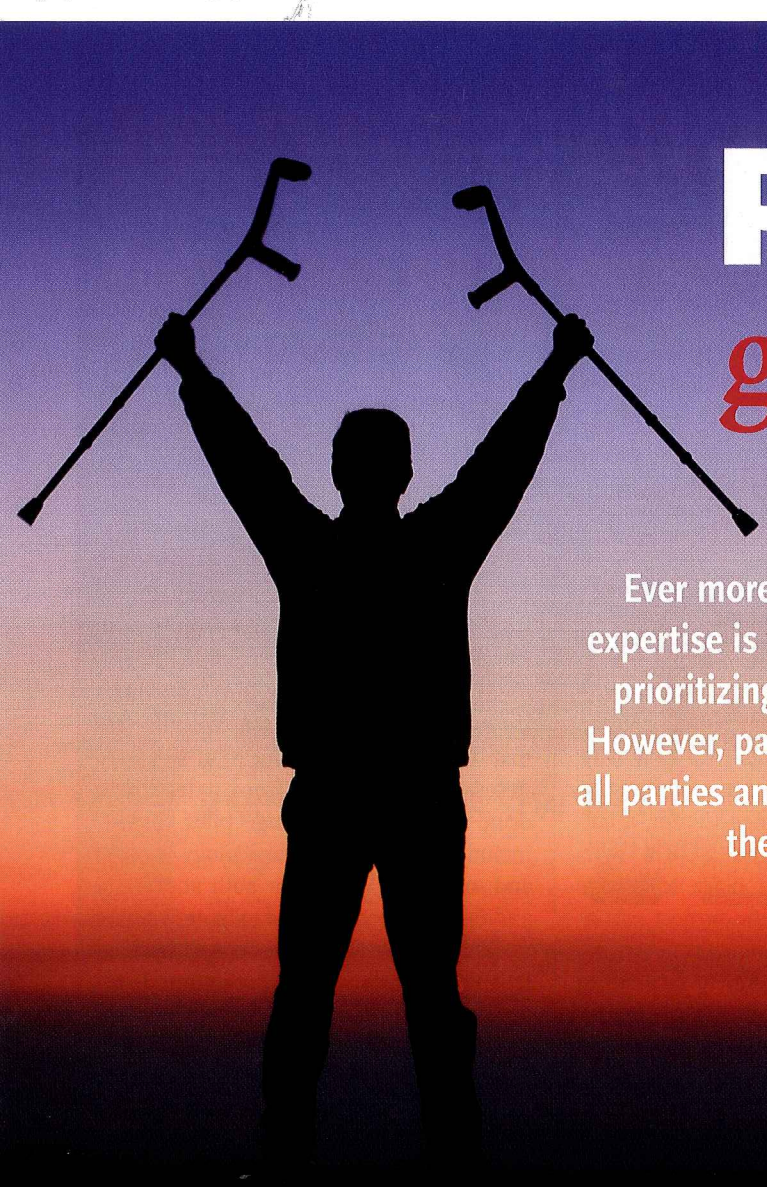


Patients *gain ground*

Ever more often the usual stakeholders agree that patient expertise is valuable for drug development and approval, from prioritizing research topics to assessing clinical endpoints. However, patient participation takes a great deal of effort from all parties and the results vary from none or minor successes to the flywheel effect it has had for Duchenne.

MARTINE SEGERS

What is the relevance of a six-minute walk test as a clinical endpoint for Duchenne boys when they are already wheelchair dependent? Elizabeth Vroom, president of the Duchenne Parent Project, travelled to the European Medicines Agency (EMA) in London to ask the regulators this question and to show them films of patients with Duchenne muscular dystrophy in which the patients reveal what capabilities they most fear losing.

Vroom wants to prevent candidate drugs from being thrown out when the patients who use them do not pass the six-minute walk test even though the drugs could be slowing down the progression of the disease. In London Vroom advocated that a drug which enables these boys to keep using their laptops and the steering mechanisms on their wheelchairs for a much longer period could make a huge difference in their lives over time and is worth approving in future.

> 'The introduction of patient participation is an irreversible process'

Consulting patients in all phases of drug development and approval is on the agenda of more and more organizations in the Netherlands. At this year's edition of the FIGON Dutch Medicines Days, for example, patient representatives will be 'dating' researchers. Furthermore, ZonMW is actively promoting patient consultation. The Dutch *top sector plan* for Life Sciences and Health emphasizes the importance of patient participation, especially as far as prioritizing which medical innovations are needed most, as was advocated earlier this year by the *Gezondheidsraad*, is concerned.

PRIORITIES

In reality, researchers, drug developers and regulators are sometimes of two minds concerning patient participation: they wonder whether they should invest time and energy in contact with patients without knowing upfront whether it will really bring them useful information. "In my opinion, however, the introduction of patient participation is an irreversible process," states Tineke Abma, professor of client participation in elderly care at the VU University Medical Centre.

Quality of life aspects are one of the

main issues that patients bring to the table, providing researchers input for their research and for more relevant clinical endpoints. Abma: "These disorders include the terrible itch caused by burns, and fatigue as one of rheumatism patients' main problems." Other examples are the long-term side-effects of chemotherapy that survivors of breast cancer experience every day. The impact of these problems is often obvious for patients. They would, however, not have been high on the priority list of drug developers and regulators if patients or their parents had not been involved.

STRESSFUL VISIT

"Inviting patients to tell their stories in a committee meeting at EMA influences the general trend of thought of the other committee members. That is one of the main contributions of patient representatives," according to Pauline Evers, staff member at the Dutch Federation of Cancer patient organizations (NFK). On behalf of the European patient network EGAN, she is one of the three European patient representatives at the Committee on orphan medicinal products of EMA, although not a patient or the parent of a patient herself.

"It is difficult to pinpoint tangible results. Committee members starting to think more in terms of patient orientation, however, does lead to granting the orphan drug status more often to drugs that do not offer prolongation of life expectancy, but do bring major contributions to the patients' quality of life. For example, this status was granted to a candidate drug for combating acute angio-oedema that patients themselves can administer, at school or at work, preventing a stressful hospital visit to get an injection of another drug that prevents the dangerous effects of rapid facial swelling."

There are more examples of patients' influence. If rheumatism patients had not talked about their fatigue problems during the Omeract conferences, at which scientists try to reach consensus concerning clinical endpoints, fatigue would not have been an important topic. It is now. Scientists are developing and validating measurements methods to include fatigue as one of the clinical endpoints.

"We would not have taken sleeping disorders into consideration in our mouse research on the Angelman syndrome if the parents had not convinced us of the need to do so," Prof. Ype Elgersma of Erasmus MC points out, to cite another example. Not being able to get a good night's sleep turned out to be a huge problem for families with a child with this syndrome. While trying to unravel the molecular mechanism behind this neuro-genetic disorder by knocking out candidate genes in mice, he therefore decided to look at the effects on not only cognitive aspects and epilepsy, but also on sleep behaviour.

'In the cancer field we are lagging behind'

Some patient organizations, especially in the field of rare diseases, even set up their own worldwide biobank and patient database. "When an interesting candidate drug has been found, the existence of such collections helps the industry to set up a clinical trial faster and to include patients more easily," affirms Cees Smit, a patient advocate for over 40 years who received an honorary doctorate from the University of Amsterdam in 2003. "This way a patient organization can speed up drug development by already setting up an infrastructure for a clinical trial, even when at that moment no candidate drug is available as yet."

A good example is the Pompe survey of the International Pompe Association and Erasmus MC, in which they characterized the disease as precisely as possible. Later on this served as input for the design of the phase 3 study of alglucosidase alfa, brand name Myozyme. It has also paved the way for the drug's approval because the patients could quantify the benefits of the new medicine more precisely, according to Smit.

SHORTER TIMELINE

The well-known Duchenne story also illustrates how patient involvement in drug development can make a difference. Starting 15 years ago with a roadmap and a fundraising plan for 40 million dollars, the United Parent Projects Muscular Dystrophy has put Duchenne research on the map, according to Cor Oosterwijk. He is director of VSOP, a Dutch collaboration of 65 patient and parent organizations. These Duchenne parents decided not to spend their money locally, but to fund only the best research proposals in the world. One of the results was the promising exon-skipping therapy, which is now in phase 3 of its clinical trials. With this therapy, the Dutch start-up company Prosensa and its partner GSK hope to alter Duchenne into a much milder neuromuscular disease, known as Becker muscular dystrophy.

"Such success stories inspire other patient organizations to become actively involved if they are not satisfied with the current progress concerning drug development for their disease," Smit points out. "They show that patients are capable of moving the drug development process forward to a shorter timeline and faster approval."

The power of patient advocacy groups involved in several rare diseases is that they themselves have taken the initiative to bring all parties together, according to Evers. "Patients, whose only interest is


PHOTO: ©ISTOCKPHOTO.COM/DAMIR CUDIC

Prof. Ype Elgersma: 'We would not have taken sleeping disorders into consideration in our mouse research on the Angelman syndrome if the parents had not convinced us of the need to do so.'

their own health, can more easily stimulate stakeholders to really work together. Any other party involved might have a hidden agenda."

SIDE-EFFECTS

"In the field of rare diseases, cooperation between drug developers and patients and their parents is already a matter of course," says Evers. "In the cancer field we are lagging behind, just making the first steps in bringing patients, regulators, physicians and industry together. As a patient representative, it is difficult to get started in this field. For heaven's sake, who do you contact first when there are 500 companies involved in developing cancer treatments?"

Moreover, the advantage of including a patient's view is also less clear in cancer research, says Evers. "Everybody, including patients, agrees that getting rid of the tumour is the main priority in drug development, and that side effects are acceptable when survival is at stake. Quality of life seems to be less important at first glance, but one thing patients did ask the regulators for is to pay more attention to the long-term side effects."

"It is possible that not all consultations require patient involvement. Purely technical discussions on clinical trial design, for example, do not need patient input," Evers concludes after taking part as a patient representative in a European Healthcare Innovation Leadership Network pilot project that aimed to consult all stakeholders during the whole process of drug development for a breast cancer drug.

CONFIDENTIALITY AGREEMENT

For judging research proposals in the field of cancer, patient participation still has to prove its added value. Evers is curious whether a KWF pilot, for which thirty patients will receive special training to enhance their skills in this area, will demonstrate added value. She is involved in this pilot: "Patients need to review the clinical study proposals, completing a checklist with criteria relevant from a patient perspective. I would have preferred them to be at the committee meeting in person, because they can have more direct influence. But this is a good first step."

The European Union is a frontrunner in this regard, according to Oosterwijk. EMA takes patient participation very seriously. The European Commission also asks for patient participation in research proposals for the Framework Programme increasingly more often. The EU funded project Patient Partner developed guide books for patient organizations as well as for industry. "These include advice on how to develop sustainable and ethically sound relationships between the pharmaceutical industry and patient organizations when they want to discuss confidential pre-clinical research," says Oosterwijk. "One of the recommendations is, for example, to carefully record the expectations from both sides." In continuation of this project, an approximately 10-million euro IMI project called European Patients' Academy on Therapeutic Innovation will start in 2012. Nearly all major European patient organizations will participate in it to interact with industry in the field of therapeutic innovation and to empower European patients and their organizations for that task.

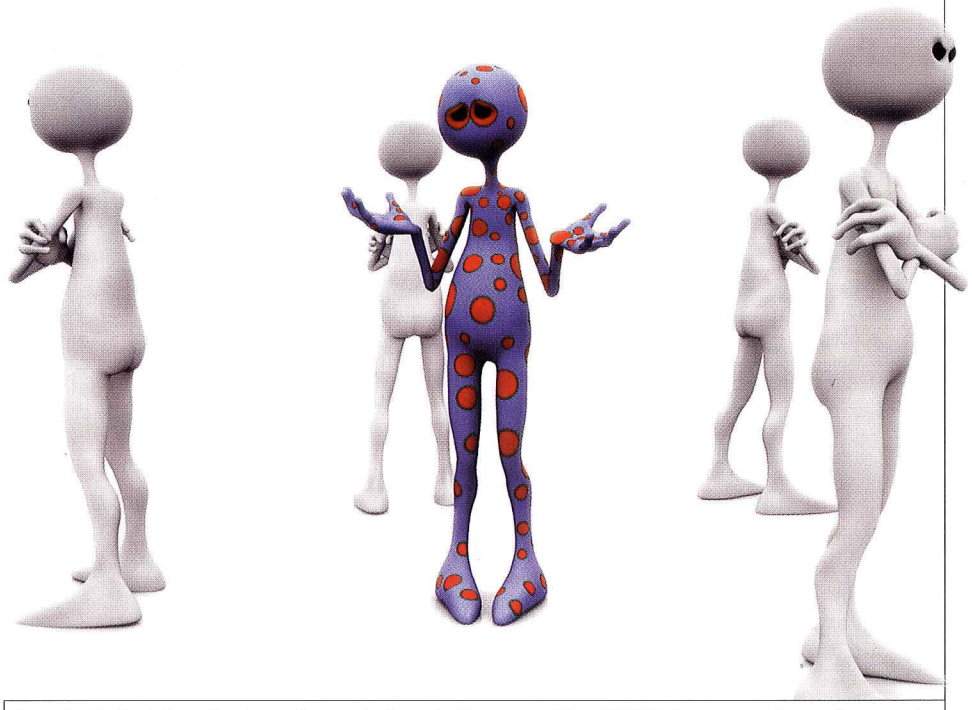
'METC's should not be allowed to decide without patient consultation'

In the Netherlands, however, patients are not allowed to participate in the approval process for clinical trials, for which local and central ethical committees are responsible. Oosterwijk: "Current civil representatives in so-called METCs are not patient representatives, whereas that would be much better since they could bring in a network of patient organizations. He or she could consult the relevant patient organization, for example, to find out what invasive procedures patients would be willing to undergo for a specific clinical trial, or to review the patient information leaflet. Another option for organizing patient participation at this level is that METCs are obliged to ask advice of the proper patient organizations themselves. With clear procedures on all sides and a proper (digital) infrastructure, this will not delay the ethical approval process."

MANIPULATION

"An METC should not be allowed to decide without patient consultation," concludes Oosterwijk. Evers and Smit could not agree more. According to them, the resistance to patient participation at the METC and CCMO level is a lost opportunity. Smit: "In my opinion, not listening to patients at all, as in the case of the CCMO, is a worse form of manipulation than the pressure from industry that patient organizations sometimes experience."

At the Date2Innovate meeting on October 4th during the FIGON Dutch Medicines Days, patient representatives and researchers and developers can 'date' to exchange information and enhance cooperation (www.date2innovate.nl).



Cees Smit: 'Not listening to patients at all, as in the case of the CCMO, is a worse form of manipulation than the pressure from industry that patient organizations sometimes experience.'