The WE-study: helping children with cerebral palsy to walk easier

Interview to Prof. Torstein Vik and Siri Merete Brændvik

Torstein Vik, Professor of Paediatrics from the Department of Laboratory Medicine, Children’s and Women’s Health at the Norwegian University of Science and Technology (NTNU), is a specialist in Perinatal and Paediatric Epidemiology. He was the founder of the Norwegian Cerebral Palsy Registry (CPRN), which focuses on cerebral palsy (CP) etiology, clinical picture and co-morbidity. He is the chief investigator of the PedCRIN funded trial the WE-study (Walking Easier with cerebral palsy), a large multinational multicenter pilot trial studying the effects of botulinum toxin-A injections on the walking capacity in children with CP. Physical therapist and researcher Siri Merete Brændvik is the national coordinator of WE study. We recently spoke to both of them about paediatric cerebral palsy, the WE-study and the importance of establishing multinational paediatric clinical trials and research infrastructures.

PedCRIN: In your opinion, why is it important to perform international paediatric clinical trials and what additional value do these have compared to those executed nationally?

TV: Many researchers performing clinical trials with children have experienced, that, even if parents and children are engaged, participants vanish for several reasons. When it comes to children, it is very difficult to have sufficient participants. This is an international well-known problem. In fact, last year, in the international meeting of the American Academy for Cerebral Palsy, there was an instructional course about this issue. In Norway, due to its low population, recruiting people is truly challenging. Therefore, I think that what PedCRIN has initiated is a really good idea. We should try to engage more and more countries to work together and it is really important to include children in these studies because, as you may know, children are
not small adults. Most of the drugs used in children are based on trials and dosages established in adult populations, so this is a crucial task to tackle.

**PedCRIN: Academic trials, unlike commercial trials, often face a lack of funding and adequate infrastructures. In this context, which resources does PedCRIN offer?**

**TV:** They have offered both practical and economic support to include other centres in the study. PedCRIN does not provide funding for research itself but it supports us with other tasks: we have economic support to translate documents, we have access to different clinical and research units, and several formal problems such as contacts between hospitals and insurances were also solved by PedCRIN.

**SB:** We were very lucky because our study was fully funded in Norway by the Regional Health Authorities, so the hospitals themselves pay for this trial. But, as Prof. Vik mentioned, PedCRIN provides many other resources that are essential to perform this trial.

**PedCRIN: Why do you think that we need such infrastructure multinational clinical trials?**

**TV:** We need it in order to get enough participants. In addition, I think that it will be very rewarding to work together with the researchers in Poland and France.

**SB:** After a few months of the start of the WE-study, we realized that this was really a study on drugs. Regarding its license, botulinum toxin had to be treated as if it was a new drug since it was compared with placebo. We had to go through a lot of procedures, forms, approvals, etc. and we could not have done it without the support of NorCRIN (Norwegian Clinical Research Infrastructures Network). They also provided us with some contact here at the hospital in Trondheim. If you wish to do an industry-independent trial at the hospital, you do not have the appropriate infrastructure, but companies do. I think that having this support from PedCRIN is a must.

**PedCRIN: Do non-commercial or academic trials help to improve indications of available treatments and optimize therapies?**

**TV:** I think they help indeed. Ultimately companies work to earn money and they are biased somehow. Doctors and clinical researchers are more trusted when they run studies that are industry-independent. That is inevitable.

**PedCRIN: What is the WE-Study about and what is new about this study?**

**TV:** WE stands for “Walking Easier” and the overall goal is to see if boys and girls who are treated with botulinum toxin-A may ease their walking. We also intend to achieve some secondary but important goals: improve the child’s activity and participation. Children are randomized either to get botulinum toxin injections in their legs or a placebo, which is sodium chloride (common salt). We test energy consumption during walking after these injections.

**SB:** And we additionally look at pain, activity and perceived effect.
TV: There are several new features in this trial, and the main one is how we measure activity. We use small devices called accelerometers that children have to carry for a week and then you can see how active they were before and after the injection. That is very new.

SB: I believe that energy consumptions and some other subjective measures have been used in previous trials but several methods were not properly validated. We use objective and validated measures to study the effect of botulinum toxin. What is also new in our study is that we have a qualitative research approach on a subsample and I do not think this has been done before...

TV: This part of the study is completed through in-depth interviews with the children and their parents, and is performed by a physiotherapist working as a post-doc in the study. We are also planning to search for factors that may explain why some people respond better to the drug and other respond worse. We may not find clear effects between the mean values of the groups (botulinum toxin versus placebo), but this may change when we look at the individual curves. Regardless of the general effect we will look at the effect on the individuals, which is quite new.

PedCRIN: In clinical trials on neuromuscular disorders antiquated scales are often used, which measure the time, the distance... They are not very objective. How do the sensors work in the children and how is the data collected?

SB: We measure accelerations in three planes and convert these accelerations into activity. But this is not straightforward. We get raw accelerations and then we do validation studies trying to link these accelerations to activities during daily life. We extract data from four activities: sitting, lying, standing and walking. The size of the accelerometer is small; it is non-invasive, which is quite innovative as well.

PedCRIN: There are different ages in the study so you expect to see differences among them.

TV: Yes, we hypothesize that the effect will be stronger in the youngest because the walking pattern matures as we grow up.

SB: Older children have altered muscle function and structure, which may affect the effect of Botox.

PedCRIN: For those who do not know anything about this molecule, can you tell me how does botulinum toxin (commonly known as botox) work and what stands for the letter “A”?

TV: Botulinum toxin is produced by a bacterium called Clostridium botulinum. It is an anaerobic bacterium, it lives without oxygen (so-called anaerobic). These bacteria may cause food poisoning and people can die because of the toxin, which interferes with the nervous system. A neurotransmitter called acetylcholine is released from the neurons, the cells of the nervous system, to make the muscle move. Botulinum toxin blocks the effect of acetylcholine, paralyzing the muscle. That is why you may die if you get it in sufficient amounts. There are 8
different serotypes of the toxin. “A” is the most common and it is the one that we use in this treatment.

**PedCRIN**: What are your views for the drug safety and efficacy? What is the message for the people that are not comfortable with the use of a treatment like botulinum toxin?

**TV**: We know that this drug has potential side effects. For instance, adverse effects have been reported when botulinum toxin is injected in the upper limbs or in the cheek to stop salivation in children. In extremely rare occasions there have been records on severe adverse reactions on the lower limbs. Although botulinum toxin has been used for 20 years now, it has not been fully documented yet. That happens with many drugs. I am a paediatric epidemiologist, a researcher, but I am also a doctor, so if patients ultimately come to me worried and anxious because of the potential side effects, I will not try to convince them to be treated.

**SB**: I fully agree.

**TV**: What we are hoping to provide now is the best research-based evidence. So far research evidence in this area is limited. Doctors are relying on clinical experience because they have had very good medical experience, and as they have seen that most of the patients have no problems with Botox, they will surely recommend its use.

**SB**: About efficacy, I assume that the treatment will have an effect on some children but not on all of them. From my experience, there are large variations on the effect. I also think that what Torstein just said really covers what the surgeon here at the hospital thinks. He says that if he has a 5 year-old-child in front him now he has to solve the problems of this child at this very moment. He cannot think about any side effects in 20 years because he has this child here now and he has a problem to solve.

**PedCRIN**: Are there similar studies performed in adult populations? And, if so, in your opinion what would the main difference be in the outcomes when comparing the two groups, adults vs. children?

**TV**: Studies have been performed with adults in Norway and they did not show any measurable effects. The ethical committee asked why we wanted to do this research if it did not seem to work in adults. The answer, of course, was that children are not small adults, that walking pattern matures during childhood and that therefore potential effects of drugs intended to improve walking must be tested in children and adolescents.

**SB**: I am not sure now but I think that the muscle structure is quite different in children and in adults.

**PedCRIN**: When it comes to the action of walking, reducing the energetic cost may be a good point to improve the life of kids. To what extent can we improve their lives?

**TV**: We hope that this treatment will improve children’s activity. Children with CP use a lot of energy; we know that they have high energy consumptions because of their ineffective walking
pattern. After training, for example, they are exhausted. They end up with less energy for other activities, such as activities at school, playing with friends, etc. So we expect that, if they can save some energy by improving walking ability, they will be able to be more active and to take part in more social activities.

SB: One of our main problems was that a clinically relevant cut-off value is not well-defined in the scientific literature. However, some studies assume that 10% could be clinically significant and physiological experts say that every improvement in the energy cost is clinically important. As these children are easily fatigued, energy consumption is an important aspect to improve.

PedCRIN: Now we would like to know more about pain. Are there beneficial synergistic effects of the treatment in reducing musculoskeletal pain in these children?

TV: We expect that less pain will improve activity and participation but I am not sure how much we are able to reduce pain with Botox.

SB: In the Norwegian study in adults with CP they saw pain relief after the injections both in the placebo and the experimental group. They discussed about the reason and they hypothesized that this could be due to a placebo effect. We really do not know what our results would be but it may hopefully have a positive effect on pain relief.

PedCRIN: We are acquainted with a person with CP that does not experience pain derived from his condition, or, at least, he has never complained about the pain. How frequent is it to experience pain for people with CP?

TV: In general, it has been documented that patients with CP as a group report more pain than their peers. However, your example is a good illustration of the differences between population and individual-based statistics. As an individual, pain may not be a problem but as a group... things change. There are reported cases of pain. This may depend on CP subtype and impairments. Patients with more severe CP subtypes, such as the dyskinetic CP and those unable to walk, experience more pain than walkers. But musculoskeletal pain has also been reported among walkers. In another Norwegian study, two thirds of children with CP reported musculoskeletal pain. It will be interesting to see what happens with our group of children.

PedCRIN: How many experts where involved in deciding the inclusion and exclusion criteria of these trials? Was this a difficult task?

TV: At least 10 experts. At first we discussed it here in Trondheim: Siri, another professor and myself. We also discussed it with a famous researcher from Australia. Later, we involved many people, including orthopedic surgeons from hospitals in Northern Norway and in Oslo.

PedCRIN: What is the most satisfying part of working on paediatric clinical trials?

SB: You get involved a lot with the families. Parents are really interested in contributing to research. This is one of the most fascinating things. Although parents do not receive the results in 3 or 4 years or so and maybe these results will not help their child in particular, they
are really interested in helping in research for future treatments. So that is maybe one of the most satisfying parts.

**TV:** We have studied the use of botulinum toxin in Norway and there are big differences between centres. One centre may apply the treatment to 80% of the children and another one to 30% of the children. Our goal is that children do not have to handle more pain than necessary. We hope that we can contribute with more evidence, improving long-term children’s activity and participation.**Helping children is a strong motivation.** It is true that having the injection is painful for them, but when they come here and you test them, they find it exciting and it is very rewarding for us to see how eager they are. I think this is a very special group to study.

**SB:** Yes, yes, they are very special.

**PedCRIN:** How have clinical trials changed the life of children with CP?

**TV:** There are a lot of clinical studies that show improvements in functions with different treatments. If you train motor function, most of the children will show an improvement. The colleague I mentioned from Australia is a leading force in our field and she has studied a large number of interventions. For instance, injection of botulinum toxin in the upper arm to correct elbow extension plus physiotherapy. This improves the angle of the elbow. On children with unilateral CP some treatments force them to not use the healthy hand and it is well documented that this improves the use of the paralyzed hand, which is of course very important to daily life. In rehabilitation of children with CP it is common to ask them or their parents what they want to achieve, set individual goals connected to activity or participation. Again, there is evidence that clinical trials using this method of defining individual goals and trying to achieve them can improve the life of the patients. But those studies are difficult to perform; you cannot do a double-blinded trial, because such treatments cannot be blinded.

**SB:** And you also have this challenge bridging the gap between science and clinical practice, so although you have clinical trials showing effects, implementing this into clinical practice is not straightforward. So that is also an aspect that has to be considered.

**TV:** There are some interventions which maybe painful for the child, for very small children. Practice has shown that we should stop with those interventions... We have a lot to do.
The WE-Study Team: Torstein Vik with some collaborators; from the left, Siri Brændvik, national coordinator in the WE study, Anne Elisabeth Ross Raftemo, neuropaediatrician and PhD student in the WE study, Vik, chief investigator in the WE-study and Sandra Julsen Hollung, responsible for health informatics in the Norwegian CP register.