The WE Study sponsor: St. Olavs University Hospital Norway

St. Olavs Hospital (Trondheim University Hospital) is the sponsor of the WE study funded by the PedCRIN project and it has benefited from PedCRIN services for the expansion of the WE study into other European countries (France and Poland).

St. Olavs Hospital is the University Hospital for Mid-Norway and integrated with NTNU (Norwegian University of Science and Technology in Trondheim). Patient treatment, research and education are integrated functions at this institution.

We had the pleasure to speak to St. Olavs University Hospital about their experience of working as a **sponsor** with PedCRIN.

Could you please summarize the goal of the WE study? What does this trial intend to tackle?

Intramuscular injections of **botulinum toxin A** (BoNT-A) have been a cornerstone in the treatment of **spasticity** for the last 20 years. In Norway, the treatment is now offered to two out of three children with spastic cerebral palsy (CP). However, despite its common use, the **evidence for functional effects is limited** and inconclusive.
The objective of the WE study is to evaluate whether injections with BoNT-A in the calf muscles makes walking easier in children with CP. We hypothesize that injections with BoNT-A in the **calf muscles** will reduce energy cost during walking, improve walking capacity, increase habitual physical activity, reduce pain and improve self-perceived performance and satisfaction.

PedCRIN has received funding from the European Union's Horizon 2020 programme under grant agreement number 731046

Which challenges have emerged when designing the protocol? And during its implementation?

The main challenge when designing the protocol was to **decide on the BoNT-A dosage**. In lack of evidence-based guidelines, the decision of dosage of BoNT-A used in this study is based on one systematic review, one original paper and on two international expert consensus papers. Another challenge was to decide **what would be a clinical significant improvement in ease of walking**. The decision to define a reduction of **10% in energy consumption during a five minutes** walking test as clinically significant was based on knowledge both from basic and clinical science and from our own clinical and scientific experience.

The main challenge during implementation has been **recruitment of study participants**. First, the patient base is small and second, the possibility of receiving placebo may cause some reluctance to participate. However, designing this as a multicenter study, involving first four study sites in Norway would increase the possibility of success. Due to slow recruitment rate, a fifth Norwegian site was included and the study now comprises all heath regions in Norway.

The possibility to include two foreign sites (Poland and France) through the PedCRIN project has also been important in order to reach the planned number of participants. However, despite at present being an international multicenter study involving seven sites, recruitment is still challenging. Approximately one half of the families invited into the study accept to participate. But we are still optimistic; presently we experience an increase in the recruitment rate at several of the participating sites.

Have you taken into account patient experience and participation during this trial?

Yes, we have observed that patients receiving treatment with BoNT-A often experience variable effects. This variation is not only between patients, but also between treatment sessions in the same patient. This was in fact one of the main clinical concerns leading to the design of the study. Patients have not been actively involved during the design process, but the **Norwegian CP association** is represented in the study's **steering committee**. This representation is of considerable value for us.

How many centers are participating in the study? How were these selected?

Seven sites are now part of the WE study. Five are located in Norway, covering all health regions in the country. Since Norway is a small country, the different health regions with its sites cooperate closely in order to improve the rehabilitation management of children and adolescents with CP. Specifically, this cooperation involves the national CP follow-up program **CPOP** and the national **CP Registry of Norway**. All the Norwegian sites are central in this cooperation and most importantly have long and broad experience in treatment with BoNT-A.

In addition to the sites in Norway, two sites, one in **Warsaw** (Poland) and one in **Nice** (France), were invited to participate based on prior research collaboration and collaboration through movement network dedicated movement analysis in children with CP. Cooperation on a large RCT requires a lot of effort by all and a mutual confidence that the study is conducted with high quality. It was therefore important for us as sponsor of the WE study, that we had prior experience and knowledge about the other participating sites.

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As the WE Study sponsor, what are St. Olav's Hospital main duties?

Overall, we are responsible for **managing and funding of the WE study**. Specifically, this includes that ethical, medical, health, scientific, privacy and information security conditions are taken care of in the day-to-day operations. Moreover, it is also our responsibility that the study is conducted in accordance with the approved research protocol and to ensure reporting of deviations of protocol and any unwanted events.

What kind of services did you receive from PedCRIN?

PedCRIN has provided us with management support in the process of including Warsaw and Nice as participating sites in the WE study. **PedCRIN/ECRIN-partners CTUs in the two countries supported a lot of work** related to translations of testing procedures to French, Polish and English, and applications to ethical committees and competent authorities in France and Poland, as well as monitoring of the sites.

Do you think that the trial would have been conducted in other European countries without PedCRIN's support? What is the added value (if any) of working with PedCRIN?

No, and for two reasons. First, although the WE study was fully financed by the regional health authorities in Norway, we did not have the funding for France and Poland. Receiving the **grant from PedCRIN** allowed for completing the preparatory work (translation of documents, communications with national authorities etc.), management and monitoring in the two countries. The national funding in Norway then paid for the IMP and the testing at each visit. Therefore, **it was joint effort**. Secondly, the preparations and management including two foreign countries required expertise and knowledge of the two countries rules and procedures for approval of a clinical study. **Us, as a sponsor, did not have this expertise; therefore the collaboration with PedCRIN was an added value.**

Would you like to work with PedCRIN in future?

Yes, please! Although, the time needed before the first patients could be included in France and Poland, was very long (much longer than we and PedCRIN anticipated, we have learned a lot). Moreover, **the personal collaboration with the ECRIN administration for PedCRIN has been excellent**, but the main take-home message from our study is that complicated studies like the WE study, should probably have **international collaborators** in place before the study starts. The WE study was already ongoing when the first proposal was announced by PedCRIN. We think that the opportunity we got through the collaboration will show to be a decisive action that the study will succeed.

We will therefore include PedCRIN in future applications, although we currently do not have such plans.

We have from the start of the WE study (design and preparations with regard to management) made use of the ECRIN/NorCRIN network; the website and the ECRIN/NorCRIN representative at St. Olavs Hospital. Specifically, standard operating procedures and templates were of great value for us, together with support during the drafting and finalization of the contracts.
After receiving the funding from PedCRIN, **we also had a valuable help from ECRIN European correspondents in France and Norway through the process** of implementing France and Poland in the WE study. This support has been crucial for us.

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