INTRODUCTION

Our knowledge on drug effects and safety in the paediatric population is inadequate despite the fact that children (0-18 yr) compose 20% of the total population. As a consequence, pharmacological treatment in children and adolescents is often performed off-label; that is, the drug is prescribed outside the approved Summary of Product Characteristics (SmPC) and thus with inadequate scientific support.1-3 Some studies have indicated that off-label use results in more side effects and is less safe.4,5

Legislation concerning the evaluation of new drugs in the child population before they are approved for use has been in existence in Europe (The Pediatric Regulation) for almost 15 years and even longer in the USA.6 The Medical Products Agency in Sweden has reported that the total number of clinical studies, including paediatric studies, has decreased despite this pan-European legislation.7,8 Even the European Medicines Agency (EMA), in a report covering the first 10 years, found that the number of clinical paediatric studies had not increased and there was still a large unmet need.9

Sweden has now incorporated the UN Convention on the Rights of the Child (UNCRC) in its national legal system, and it became law on January 1, 2020. The convention has 54 articles including the four core principles on non-discrimination, the best interest of the child, the right to life, survival and development and the right to be heard. Moreover, article 24 of UNCRC specifically states that children have the right to the enjoyment of the highest attainable standard of health, and facilities for the treatment of illness and rehabilitation of health. A prerequisite for these aims is that research and development is specifically performed in children and adolescents and by personnel with knowledge about the rights of the child and the perspective of the child. We are of the opinion that clinical...
research in children and adolescents needs to be strengthened in Sweden in order to follow the convention.

In 2014, a systematic evaluation was performed at the Queen Silvia Children’s Hospital, Gothenburg, regarding the needs of clinical researchers within paediatrics. This evaluation indicated that there was a need for support to both academically initiated research and industry-sponsored research (Table 1) and resulted in a proposal to establish the Pediatric Clinical Research Center (PCRC).

The aim of this paper is to describe our experience after the first years since the start of PCRC in 2016 and depict the need for clinical research within the paediatric sector.

2 | PAEDIATRIC CLINICAL RESEARCH

Paediatric clinical research comprises all clinical studies performed in individuals under 18 years of age. Studies in the paediatric population differ in certain important respects from studies in the adult population.

One important difference is the consent procedure where adults personally can consent to participation in studies, while in paediatric studies, consent is obtained from the child’s guardians, most often the parents. However, it is also necessary that the child/adolescent receives information about the study, relevant to the child’s age and level of maturity. A paediatric subject cannot be included in a study against his/her will even if it is the guardian who has the right to provide the legal consent. It should be noted that the consent requirements vary between countries due to national laws and regulations, and that these are not harmonised in Europe. For instance, in Sweden, both parents and the child, if literate, need to sign the consent.

Another important difference between studies in adults and children is that the performance of paediatric studies and treatment provided is often more time-consuming. For example, more time is required in preparation prior blood sampling in children compared to adults. This increases the total time required for a study and directly influences the budget requirements of a paediatric study compared to the same study in an adult population. A large number of study activities and examination procedures are included in some studies. From a child’s perspective, the number of contacts, visits to different clinics and departments, and being subjected to different activities and examinations can be a burden. Moreover, the outcome measures must be adjusted to accommodate children of different ages. Validated paediatric versions of outcome measures regarding quality of life or other instruments assessing health indicators are required. Certain parameters, specific for children and adolescents such as growth and pubertal development, are necessary to assess potential adverse drug reactions specific to developing individuals. Paediatric competency is therefore essential in order to plan, coordinate and implement a clinical study in children and adolescents.

3 | THE PEDIATRIC CLINICAL RESEARCH CENTER

The Pediatric Clinical Research Center (PCRC) was started in order to support and facilitate clinical research at Queen Silvia Children’s hospital at Sahlgrenska University Hospital. Prior to the creation of PCRC, there were already several well-established research groups performing clinical research independently of each other at Queen Silvia’s Children’s Hospital. PCRC was established to complement the healthcare organisation already in existence at Queen Silvia Children’s Hospital with infrastructure, resources and functions that previously were not available for all departments. Activity at PCRC initially started on a small scale, and the initial focus was on the recruitment of staff and starting the first studies under the leadership of PCRC. Creation of a specialised clinical research unit enhanced coordination of resources (research staff, statisticians, equipment and laboratory facilities) between the different already established research groups. Concentrating clinical research activities under the umbrella of PCRC also created a platform where researchers from the various groups meet on a daily basis and can exchange and discuss ideas. PCRC has also a close cooperation with Gothia Forum, the regional node of Sweden’s western healthcare region that cooperates on a national level with Clinical Studies Sweden (a collaboration between Sweden’s six healthcare regions). The Clinical Studies Sweden collaboration is funded and supported by the Swedish Research Council aiming to simplify and develop the work of clinical trials. The creation of PCRC was initially supported by a strategic grant from Sahlgrenska University Hospital for the first 3 years, but it is expected to be self-supported thereafter through income from ongoing studies.

The number of requests to PCRC regarding study inquiries and requests for research support has increased numerically from year 2017 to 2019 from seven (7) to thirty-five (35) and ongoing paediatric clinical studies from two (2) to five (5), and they continue to increase. The total number of included subjects at the hospital has also increased.

Early contact between the sponsor of a study (company or academic researcher) and PCRC is imperative and facilitates the planning of the study. The feasibility of performing the study is assessed from several aspects. The principal investigator (an experienced physician with expertise in the area of the proposed study) performs a medical assessment, and in addition, qualified staff at the PCRC perform a benefit-risk assessment by evaluating important

| TABLE 1 | Identified factors of importance necessary for clinical paediatric research
| Academic research | Industry-sponsored studies |
|-------------------|----------------------------|
| Statistical support | Good Clinical Practice (GCP) |
| Assistance with the budget, study economy | Contracts/agreements, legal support |
| Data management | Economy, budget |
| Management of registers | Administration, monitoring |
| Research staff | Research staff |
aspects of the proposed study including scientific, methodologic (specifically relating to paediatric clinical studies), administrative, economic and logistic aspects. In this assessment, the ability to successfully complete the study and the economic prerequisites must be fulfilled. The scientific value of the proposed study is of greatest importance, and the expertise from PCRC can provide important assistance in choosing the most suitable study design and study protocol modifications early in the process. A benefit-risk assessment, usually defined as ‘the continuous evaluation of the favourable and unfavourable results of a specific treatment to determine whether its benefits outweigh its risks in a specific condition’, is relevant in any clinical trial context but is particularly important in a sensitive population such as children and adolescents. It is also important that the budget analysis is performed in cooperation with the staff from PCRC, who are experienced in clinical paediatric studies, in order to avoid underfinancing the study for the reasons mentioned earlier. The experience available at PCRC is also of value when planning the logistics of performing a clinical study in the paediatric population.

A close cooperation has also been established between the clinical studies specialist functions at PCRC and the medical and nursing expertise available within Queen Silvia Children’s Hospital (Figure 1). Our way of working means that the child’s ordinary doctors and nurses provide medical care and nursing as they already have an established relationship with the child. The research team from PCRC coordinates and is responsible for study-related activities. This form of teamwork between the ordinary caregivers and the research team from PCRC ensures the best possible care and sense of security for the patient, and smooth running of the study and enhances the quality and speed of data collection.

4 | PAEDIATRIC RESEARCH IN A WIDER PERSPECTIVE

Children are generally healthy, and the number of children who fulfill study criteria for a given study is relatively small at most paediatric units in Sweden. Hence, it is necessary to cooperate on regional and national levels as well as on an international level. A recent study demonstrated that physicians and nurses involved in the treatment of children in Sweden calls for research infrastructure to support clinical research and an expanded national collaboration. Such

**FIGURE 1** Overview of the clinical research process at Queen Silvia Children’s Hospital
cooperation is of importance when performing studies in small populations, and therefore, we have allocated resources for cooperation with other centres performing research within the paediatric sector.

Paediatric oncology has an established network of cooperation within the Nordic countries as well as within Europe. A network for clinical paediatric studies, FinPedMed, was started in Finland in 2007 and now has 172 members from different specialties. FinPedMed is financed by an annual grant from the five university clinics in Finland.

SwedPedMed is a network for paediatric clinical studies in Sweden that is currently evolving with the aim to disseminate within Sweden information about paediatric clinical research study proposals and facilitate contact between research groups with a view to cooperation. However as yet, the financing of SwedPedMed has not been solved. SwedPedMed has established a cooperation with FinPedMed and the other Nordic countries within the auspices of NordicPedMed. PCRC has close contact with SwedPedMed, and staff from PCRC are engaged in the reference group of this network.

Pediatric Clinical Research Center has also established cooperation with several European networks working within the field of drug development within the paediatric sector such as the pan-European clinical trial network Connect4Children (https://connect4children.org/) and the European network for paediatric translational research European Paediatric Translational Research Infrastructure (EPTRI, www.eptri.eu).

5 | FUTURE NEEDS

Sweden has recently incorporated the UN Convention on the Rights of the Child (UNCRC) in its national legal system, and it became law on January 1, 2020. There is a need for scientific evidence regarding the treatment of children and adolescents within many areas, and clinical research requires strengthening. Hospital systems are under pressure, and it is difficult to perform clinical studies within routine hospital care without extra resources. In order to solve this problem, the PCRC at Queen Silvia Children’s Hospital has been established as a professional resource with an infrastructure specifically designed for paediatric clinical research. Our experience is that knowledge regarding research concerning pharmaceutical products and medical devices in the paediatric sector is limited amongst the companies involved in this type of research. Clinical studies within the paediatric sector need to be assessed, planned and coordinated by staff with the experience of paediatric research and who are actively engaged in paediatric hospital care.

Historically, individuals under the age of 18 have often been discriminated in terms of medical progress as they have been excluded from studies involving new forms of treatment. At PCRC, new forms of treatment can be evaluated in the clinical setting and participation in such studies provides the medical staff performing the studies with the experience of the latest forms of treatment. In addition, the subjects involved in clinical trials come in contact with the latest forms of treatment before they achieve marketing authorisation. PCRC supports the hospital system and manages ongoing clinical paediatric studies without encroaching on clinical care of patients within the hospital system.

Many of the countries in the European Union as well as the Nordic countries are more advanced than Sweden with regard to the creation and financing of a national infrastructure for clinical paediatric research. It is therefore imperative that Sweden supports the further development of an infrastructure and national network for research in the paediatric sector. In order to achieve this goal, it is necessary to develop a national plan and allow the possibility of children moving when necessary between the different hospital regions in order to participate in studies.

In summary, children and adolescents have the right to modern forms of treatment that have been adequately evaluated in the relevant population and the adoption of the UN Convention on the Rights of the Child (UNCRC) as law in Sweden gives added support. Resources for clinical research within the hospital system have been declining in recent years. Thus, the establishment of a paediatric clinical research centre as well as a national initiative to promote research within the paediatric sector is necessary to strengthen future research within this important area.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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