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The French network of Paediatric Clinical Investigation Centres (CICPs). Assessment of activities over a three year period, 2004–2006

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The network of Paediatric Clinical Investigation Centres (CICPs) consists of eight research centres integrated into teaching hospitals. They collaborate with medical and surgical departments, medico-technical departments, INSERM (Institut National de la Santé et de la Recherche médicale) research units, and university research units. The aims of the network are to conduct paediatric clinical trials and basic scientific research (primarily related to growth and neurosciences) and contribute to technical innovations. The CICP network provides support to investigators, from the study design through the conduct of investigator-initiated or industrially sponsored clinical research protocols. Also, the CICP provides physicians, pharmacists and nurses with specific training in paediatric clinical research. Over a three year period, 369 research protocols have been adopted. These have included 213 clinical trials of medicines. The CICP facilities are specifically designed for the conduct of research in children. In accordance with Good Clinical Practice (GCP) guidelines, the CICP network also supports parents and their children during participation in medical research.

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Introduction

Many drugs prescribed for children are used in an unlicensed or off label manner. The incidence of unlicensed and off-label prescribing depends on the category of the drug and the age of the patient, being higher in critically ill neonates than in older children and lower in general practice than in hospitals[1,2]. It affects children in different European countries where over half of the hospitalised patients received an off label or unlicensed drug prescription[3]. The situation is similar in both the USA and Australia[4,5]. In such situations, the treatment may be ineffective and associated with an increased risk of drug toxicity[6-8].

More randomised controlled trials for medicines in children are required to improve this situation and to provide the evidence base for safe and effective drug prescribing[9]. The evaluation of drugs in children may be difficult for several reasons:

- Ethical concerns[10,11].
- Small numbers of children with a particular disease that makes recruitment for large safety and efficacy studies difficult.
- Practical issues, as relatively few investigators have training and experience in the conduct of clinical trials in paediatric patients.
- Financial and marketing issues.

For all these reasons, the US has taken the initiative in adopting a legislative programme with the goal of stimulating paediatric research[12]. It started with the Pediatric Plan (1994), followed by the Food and Drug Administration Modernization Act (1997), the Pediatric Rule (1998), the Best Pharmaceuticals Act for Children (2002) and the Pediatric Research Equity Act (2003). Following this initiative, the European Union has introduced legislation with the specific goal of stimulating the evaluation and labelling of paediatric medicines[13]. The European Guidance on the Investigation of Medicinal Products in Children and the Memorandum for Paediatric Drugs were unanimously accepted by the European Council in December 2000, and the European Commission was mandated to prepare a regulation. A Consultation document was released on February 2002 entitled "Better Medicines for Children". The European Regulation[14] came into effect on 26th January 2007.

The aims of the European Regulation are to stimulate research and development by the pharmaceutical industry for medicines used by paediatric patients. It provides incentives but also the obligation to consider whether the medicine will be of benefit to children[13,14]. Pharmaceutical companies will need to develop a Paediatric Investigation Plan (PIP) prior to submitting data regarding a new medicinal product for marketing authorisation. The applicant may be granted a 6 month extension of the duration of the patent (for products still covered by a patent) if the PIP is followed and if the product is authorised in all member states regardless of positive or negative outcome of paediatric development[14].

The regulation will hopefully have a positive impact and increase drug evaluation in children by increasing the number of paediatric clinical trials. In this context, the objectives of the paediatric network are to combine the existing strengths in paediatric medicine, clinical pharmacology, data management and biostatistical analysis in order to increase and optimise drug evaluation in children and allow the pharmaceutical industry to perform high level paediatric studies.

Paediatric network

The Clinical Investigation Centres (CICs) are clinical research departments within both INSERM (Institut National de la Santé et de la Recherche médicale) and hospitals. The first one was created in 1992 in the Robert Debré Hospital in Paris. There are now 26 CICs in France. Each of them is located in a teaching hospital under the responsibility of a physician trained in clinical research, working in a research team including nurses and technicians. Different structures are connected to the CICs: the research departments of INSERM that facilitate translational research, epidemiology units, centres for biological investigation, centres for biological research and tissue bank facilities. The network receives financial support from INSERM and hospitals. In addition, pharmaceutical industries, research organisations, and patients' associations, sponsor their own research protocols.

The network of paediatric CICs (CICPs) includes eight centres in France. One of the centres does not have paediatric beds as it is a clinical research centre that has expertise in clinical trials. Most centres have both adult and paediatric research activities and only one centre (Robert Debré Hospital, Paris) is involved solely with paediatric trials. Research activities may be undertaken inside the research centre. In such cases, paediatric patients are either transferred from the clinical ward or attend the research centre as either an inpatient or outpatient. A total of 35 beds dedicated to clinical research are available within the network: four CICPs receive children whatever their age, two CICPs receive children aged six or older and one CICP receives only neonates. In addition, research activities are conducted by the

research team in the clinical wards, primarily for critically ill patients in intensive care, neonatology, bone marrow and organ transplant units. This "delocalised" activity is important in some CICPs such as Nantes or Lyon that conduct predominantly neonatal studies.

The potential to perform paediatric studies within the network is illustrated by the important paediatric activity in the participating hospitals. The number of paediatric beds linked with the network is close to 2,000 and the total number of paediatric inpatients was more than 200,000 in 2004.

Each CICP participates in the different steps required to start and conduct clinical research in children. The medical team participates in the design of the research project, the evaluation of potential recruitment, and the financial requirements[10]. The CICP is responsible for the conduct and implementation of the protocol. It defines the standardised operating procedures required for the trial, organises patient charts and database, and handles blood sampling, sample preparation and dispatching.

The network has the expertise required for paediatric research in the fields of physiology, pathology, paediatric clinical pharmacology, biostatistics, and epidemiology. In addition to the aims of the CICPs, specific objectives of the network include:

- Select the appropriate study design in order to minimise the required number of subjects.
- Promote trials evaluating paediatric formulations for infants and very young children[15].
- Support parents and children when included in a trial (by organising medical care and reducing the stay in hospital, organising visits and appointments when convenient for the parents, and respecting both school time and family life).

Scientific committee

To achieve these goals, the network has established a scientific committee including the doctors from the CICPs, nurses, investigators, invited representatives of INSERM and regional Delegation for Clinical Research (DRC). The committee validated *the charter of the CICPs* in June 2006 and organised the activities of the network. In brief, it states that two centres, in Paris – Robert Debré and Lyon are responsible for coordinating the activities, and organising communications between CICPs. The meetings of the scientific committee are scheduled twice a year in order to organise collaborative projects and answer research calls.

The charter of the CICPs states that:

- The paediatric activity within the CICP is promoted locally and a paediatrician is part of the medical team or at least is identified as paediatric partner of the medical team. Within the network, five centres have a paediatrician as the centre lead.
- All the CICPs are informed by the network of a new study and may participate.
- The study planned in a CICP is evaluated only once by the local technical committee and the conclusions are available for all the centres. In addition, for a given trial, the procedures and financial evaluation are prepared once but validated and accepted by all the other participating centres.
- Specific paediatric procedures are available to the network through the paediatric procedures group working with a representative of each CICP. (As examples, three recent paediatric procedures are dealing with the use of EMLA cream in children, the recommendations for paediatric venepuncture and the procedure to discuss a trial and obtain parental consent).

Research areas

All the protocols ongoing in the network, either single or multicentre, are compiled and analysed each year (at the national or international level). They are classified as drug evaluation trials in the field of clinical pharmacology and therapeutics, or trials in the field of physiology and pathology. Over the past three years, there were approximately half of them in each category (Table 1). They were conducted according to the paediatric procedures validated in the network, even if single centre studies. Protocols were conducted in most of the paediatric subspecialties as presented in Table 2.

Table 1 Research protocols conducted within the CICP network

Year	Total number	Scientific research	Clinical trials involving drugs
2004	107	59	48
2005	136	54	82
2006	126	43	83

Table 2 Areas of drug evaluation

	2004	2005	2006
Oncology/Haematology	15	14	29
Endocrinology/Metabolic	10	20	22
Neurology/Psychiatry	8	20	21
Gastroenterology/Hepatology	11	12	14
Genetics*	–	–	9
Nephrology/Urology	13	14	4
Infections (including HIV)	15	14	3
Others	35	42	24

*considered separately since 2006 only

The new regulation is expected to have a major impact on the research activity of the network in the coming years. In the Robert Debré centre, 516 children were recruited and participated in studies during 2006. Seventy children were followed up in the paediatric department (primarily in neonatology), corresponding to 737 visits.

The network aims to stimulate clinical research for both investigator-initiated and industrially sponsored studies. In our experience, the design, organisation and course of a clinical trial are very different whether the trial is industry or institution-sponsored. In the second case, the whole CICP team is involved, including specialists in paediatric clinical pharmacology, epidemiology and biostatistics who are members of the network. The study design, administration, ethic stages, procedures and organisation of the trial are coordinated in collaboration with the CICP.

By contrast, an industry sponsored trial is usually discussed with the CICP at a later stage when the protocol is already decided. Late contact with the CICP network is an area of concern. Many of the industry sponsored trials are not well designed from a paediatric viewpoint[16]. Modifications and improvement of the design at this stage are very difficult. The role of the network is reduced to conducting the trial, optimising recruitment, and ensuring GCP. In our experience in two recent protocols, patient recruitment was almost impossible, because the inclusion criteria were adapted to the adult population or included invasive procedures not performed in clinical practice in paediatric patients.

Subsequently, it is understandable that feasibility is sometimes difficult to evaluate and the rate of recruitment difficult to maintain. In all the recent studies conducted in France, the recruitment rate was between 60 and 65%; however, this is much higher that the 30% recruitment reported by INSERM when a protocol (either in physiology or pharmacology) does not involve a CICP (unpublished data).

The future of the French CICP network

In the field of paediatric drug evaluation, in addition to the already achieved goals, the objectives of the network are:

- Evaluate the similarities and differences in efficacy, tolerance, and safety of drugs between adults and children.
- Increase the use of appropriate methods for drug evaluation in children with limited numbers of patients (triangular test, Bayesian approaches…).
- Perform population pharmacokinetic and pharmacokinetic/pharmacodynamic studies[17,18].
- Participate in the development and evaluation of drug formulations adapted to children.
- Support and develop research in the areas of physiopathology and translational science.

The network also participates in the education of young investigators in paediatrics by training them in paediatric clinical pharmacology[19] and research at the CICPs. In addition, some of the key investigators are teachers in courses available at national (Master in Clinical Pharmacology University Paris VII), European (Eudipharm)[20] or international level (International Workshops on Paediatric Clinical Trials organised by the Association of Clinical Research Professionals and Paediatric and Perinatal Drug Therapy)[21]. The network will also develop a training programme for nurses and technicians.

The network will strengthen the existing connections with national and European networks. The CICP network participates in specialised national thematic networks, such as the INSERM CICP networks[22]. Similar to the paediatric network, these networks were created in order to participate and optimise clinical research in diabetes, neurology, psychiatry, gastroenterology, hepatology and nutrition in France. Five CICPs are involved in the national

GenDrug network, promoted by INSERM and aiming to investigate the predisposing genetic factors of adverse drug reactions.

Within Europe, clinical research networks already exist and cooperation is required. Some networks are thematic networks while others are infrastructure networks. The PENTA network (Paediatric European Network for the treatment of AIDS)[23], addresses questions on the treatment of children with HIV, and in France, the PENTA trials in children have been conducted in close collaboration with the paediatric CICP network since 2002. Other thematic networks include the Children's Leukaemia Group within EORTC (European Organisation for Research and Treatment of Cancer[24]), PRINTO (Paediatric Rheumatology International Trials Organisation[25]), or the UK Clinical Ethics network[26]. Paediatric infrastructure networks are already set up in Germany – PAED-Net[27] with an organisation very similar to that of the paediatric CICP network. It provides the infrastructure to professionally plan and perform multicentre paediatric studies. Six paediatric units, (Cologne, Freiburg, Heidelberg, Leipzig, Mainz and Muenster) are coordinated by a central office in Mainz and cooperate closely with the children´s hospitals at the respective locations as well as paediatric practices. A national paediatric network already exists in Belgium –Belgian Pediatric Drug Network (BPDN)[28].

With the new Paediatric Regulation coming into effect, it is likely that further collaboration will occur between European investigators and networks. The CICP network and Paed-Net are already part of the European project of Clinical Research Infrastructures Network (ECRIN) aiming to connect national networks of clinical research infrastructures in Europe[29,30].

Conclusion

Both basic scientific research and clinical trials are required in children. The CICP network has been working to develop excellence in paediatric clinical trials, organise efficient infrastructures at national level and promote and optimise the conduct of randomised multicentre studies in children and adolescents. As recommended by the European Commission, and because so few children are involved in clinical trials, a European network connecting paediatric networks existing in many European countries should be built in order to optimise collaborations in the field of drug evaluation in children.

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