


European research networks to facilitate drug research in children

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Paediatric drug development faces several barriers. These include fragmentation of stakeholders and inconsistent processes during the conduct of research. This review summarises recent efforts to overcome these barriers in Europe. Two exemplar initiatives are described. The European Paediatric Translational Research Infrastructure facilitates preclinical research and other work that underpins clinical trials. conect4children facilitates the design and implementation of clinical trials. Both these initiatives listen to the voices of children and their advocates. Coordination of research needs specific effort that supplements work on science, resources and the policy context.

KEYWORDS

drug development, paediatric, research infrastructure

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1 | INTRODUCTION

There is a broad medical need for new, innovative medicines for children. This need is paralleled by the need for a better understanding of products currently used in children due to the widespread use of medicines that have not been tested for safety and efficacy adequately in babies, children and young people. The barriers to research on new and existing medicines include nonclinical issues. Academic research capacities for discovering/early development of new drugs are not linked together. Investigators encounter difficulties when locating collaborators with relevant methodological expertise. Many institutions have relevant equipment, technologies and facilities but there is no forum to facilitate collaboration. There is no way to link bench to bedside outside large pharmaceutical companies. The nonclinical constraints are compounded by issues relating to the design and implementation of clinical trials. Paediatric drug development programmes often require a relatively high number of participants compared to the number of patients with the condition under study, leading to slow recruitment and delayed completion. Each trial has to develop its own network of sites and related processes leading to delays, inefficiencies and poor quality of trials.^{1,2} Furthermore, the lack of input from patients and caregivers in the design of trials may lead to protocols that do not fit the needs of the families, babies, children and young people.³

Experience shows that these barriers can be addressed by utilising a structured approach to research, a research system or infrastructure.⁴⁻⁶ A structured approach overcomes fragmentation of stakeholders, provides a consistent framework for all stages of drug development, speeds up research by using the same systems and processes for each trial, enhances quality, and can ensure that the voices of patients and caregivers are heard.^{7,8} A specific approach for paediatrics is needed because of the impact of ontogeny on drug development, most child health services are hosted in dedicated facilities and provided by specialised staff, and communication with paediatric participants in research requires specific approaches.

The scope of this discussion is illustrated by the structural model of paediatric drug development shown in Figure 1.

- i. Context: sufficient drivers and incentives to make drug development appealing to investors in commercial and public sectors, including a clear path from approvals to market; proportionate regulations.⁵
- ii. Resources: sourcing resources for each project; rational and efficient deployment of resources within organizations to where they can yield most value (taking account of the uncertainties in all drug development).⁵
- iii. Coordination: coordination (avoiding duplication and unnecessary gaps); promoting collaboration (finding researchers, clinicians and experts, and supporting joint working); ensuring the patients and caregivers involvement; clear processes; enhancing quality of trial conduct; handoffs between elements of the pathway including regulatory authorities.

- iv. Science: rigour and stringency; good guidelines and pathways; good techniques leading reliable, repeatable results; coherence across each step of the pathway. The science has been described extensively.⁹⁻¹¹

This paper focuses on the coordination part of this model and discusses 1 approach to structured drug development: Research Networks and Infrastructures. Research Networks and Infrastructures do not address science, resources or context of paediatric drug development. In order to explore the contribution of European research networks/infrastructures to the paediatric research landscape in Europe, this paper aims to:

- i. Identify the current state of the art for European research networks/infrastructures that can facilitate drug research in children.
- ii. Describe 2 exemplars of the development of European research networks/infrastructures.
- iii. Suggest the future state, the situation from 2024 onwards.

2 | EUROPEAN LANDSCAPE

At the start of 2020, the European landscape for paediatric drug research is made up of more than 300 sites that conduct paediatric clinical or preclinical research or research that underpins clinical trials.^{12,13} Many, but not all, sites are organized, to a greater or lesser extent, in national networks, specialty networks, thematic research platforms and transnational networks/infrastructures (target barriers that are shared across multiple stakeholders).¹⁴ National multispecialty paediatric research networks are currently active in 20 countries and since 2018 have been working together to develop consistent contact points and processes to support clinical trials (see below). Specialty networks collaborating with conect4children (c4c) include: PENTA (HIV/AIDS and paediatric infectious diseases) <https://penta-id.org>; PRINTO (paediatric rheumatology) <https://penta-id.org>; Treat-NMD (neuromuscular disorders) <https://treat-nmd.org>; ECFS-CTN (cystic fibrosis) <https://www.ecfs.eu/ctn>; SIOPE (paediatric oncology) <https://siope.eu>; and ENCP (child and adolescent mental health) <https://www.ecnp.eu/research-innovation/ECNP-networks/List-ECNP-Networks/Child-and-adolescent-neuropsychopharmacology>. These networks have grown in response to advocacy by families and professionals. These networks target their activity according to the needs of the disease community and have selective interactions with industry.

EnprEMA is a *network of networks* that acts as a *professional organization* for 51 networks including representatives from industry groups like the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE).¹⁴ EnprEMA facilitates studies in order to increase the availability of medicines for children through precompetitive work, including: paediatric clinical trial preparedness; involving young people and families in the design and conduct of

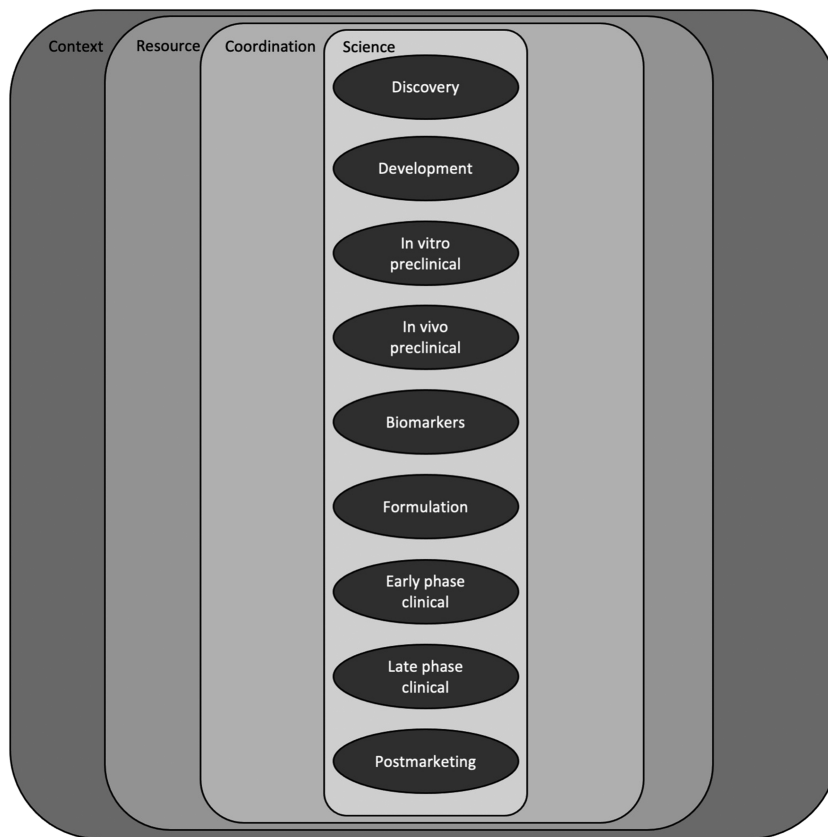


FIGURE 1 Structural model of key elements in paediatric drug development

trials; collaboration with ethics committees; collaboration with paediatric research nurses; informed consent requirements for paediatric clinical trials; and facilitating interactions between the pharmaceutical industry and networks.

Children, young people and caregivers can provide useful input to paediatric drug development.¹⁵ This includes the identification and prioritization of unmet needs for preclinical and clinical research. The earlier that patients and caregivers are involved in clinical studies the better. Their contribution to the co-design of protocols will increase feasibility, reduce time of execution and ensure the measurement of outcomes that can be meaningful for the patients. This applies to studies of natural history, biomarkers, genetics etc., as well as to clinical trials. Their involvement in a clinical trial can include advice about the lay summary of the study and can be extended beyond the marketing authorization, for example in the co-design of the package leaflets or information about safety.

The involvement of minors in research requires the right expertise, methods and resources that need to be available in multiple countries. The European Young People's Advisory Group network (eYPAGnet, <https://www.eypagnet.eu>) coordinates patient and public involvement and engagement (PPIE) activities in paediatric clinical research adopting a collaborative PPIE landscape. There are many patient organisations in Europe. Many of them work on *advocacy* for the needs of patients and families. This is in contrast to patient and public involvement which involves researchers working with patients and the public during clinical trials. Engagement is disseminating information about research. The paediatric PPIE landscape includes

EURORDIS (<https://www.eurordis.org>), VSOP (<https://vsop.nl>), EUPATI (<https://www.patientsacademy.eu>), and EFCNI (<https://www.efcni.org>). eYPAGnet is recognised by EnprEMA and plays a strong role in European Medicines Agency (EMA) activities.¹⁶ eYPAGnet emphasizes the education of young people to ensure that they have the knowledge and skills to play an active role in the design of research. The Young Person's Advisory Group (YPAG) members are young patients and healthy young people. They provide feedback on the views of young people regarding the use of language and terminology within patient documentation and technology applications to be used by patients and their families. YPAG members also comment on protocol design and expectations of the patient.

Despite these initiatives, there is a range of activities, driven by local drivers and incentives, that are not contributing to the bigger picture of paediatric clinical drug research. While some networks are very well-established, many paediatric subspecialties do not have access to a research network. There is limited sharing of experience between the subspecialty networks. Some transnational research infrastructures (RIs) that aim to support specific activities have been established but have not yet worked extensively in paediatrics. Despite significant effort, attempts at coordination remain fragmented. There are no generalised attempts to promote the quality of trials.

Some aspects of paediatric drug development in Europe are consistent across countries in and outside the European Union. The European Union has a unified approach to paediatric drug development that has influenced neighbouring countries. The Paediatric

Regulation has been effective since 2007 and mandates all Sponsors who wish to market a new medicine, or apply for a new indication, a new pharmaceutical form or a new route of administration, to propose a Paediatric Investigation Plan (PIP) to the EMA.^{17,18} The PIP includes preclinical and formulations work, as well as appropriate clinical trials. Not all trials fall under the Paediatric Regulation, especially studies for off-patent medicines, and therefore many trials are done outside a PIP.

3 | RESEARCH NETWORKS/INFRASTRUCTURES

During the past 30 years a number of RIs relevant to health and the life sciences have developed in the European Research Area.¹⁹ The European Strategic Forum for Research Infrastructures (ESFRI) has moderated this process and recommended a rigorous approach to the development of RIs.²⁰ ESFRI was set-up in 2002 by a mandate of the EU Council in June 2001, to support a coherent and strategy-led approach to policy making on RIs in Europe. ESFRI is made up of national correspondents and has facilitated the development of a portfolio of strong infrastructures.

Adapting these recommendations to paediatric drug development, we specify the core characteristics of a research network/infrastructure as: (i) a stable collection of trained staff, health care professionals, experts and organizations to be involved in multiple projects; (ii) independence from individual projects, funders and sponsors; and (iii) work conducted according to standardized and consistent procedures. We distinguish between *users* who have questions or needs, including investigators and sponsors, and *providers* who have services or expertise. Other *stakeholders* include patients and regulatory authorities. Supplementary characteristics include effectiveness (delivers specified outputs from specified inputs to specified quality standards); appropriateness (the network/infrastructure meets the needs of users and providers); efficiency (greatest benefits for the lowest cost, good value); reliability (a consistent record builds trust). We believe that these supplementary characteristics are necessary for the quality, value, and sustainability of a network/infrastructure. Only a European network/infrastructure is able to provide these benefits because an unstructured collection of national and specialty networks would recapitulate the existing fragmented and inefficient structure.

Research networks/infrastructures:

- prepare for user requests by defining processes and identifying and qualifying providers;
- support user requests by brokering collaborations, by sharing information about requests to providers and about providers to users, by troubleshooting during projects;
- depend on personal and institutional relationships that are not specific to individual projects or programmes;
- do work that others do not, that is overcome fragmentation;
- include the perspectives of patients and carers.

We distinguish between *scientific networks* such as PENTA or PRINTO, that are primarily related to specific communities within paediatrics rather than comprehensive and national networks.

Research networks/infrastructures in the sense used here do not:

- initiate research projects (this is done by scientists and organizations with resources);
- sponsor research;
- own the results of studies;
- work as contract research organizations (CROs), with some exceptions.

CROs and academic clinical trial units are task focused for specific sponsors. Some of these tasks will not be done by research networks/infrastructures including providing sites with trial supplies or writing protocols, developing case report forms, hosting trial-related data. European research networks/infrastructures will not provide services such as monitoring, although some national networks support monitoring of academic trials. European research networks/infrastructures are community focused and work on selected issues to overcome fragmentation rather than provide comprehensive support for trials.

To develop a European research network/infrastructure, it is necessary to align the work of each national network/infrastructure and its members. Alignment needs to cover assumptions, strategy, concepts, operations, procedures and processes, terminology, culture, and behaviour. Among these factors, terminology and behaviour are often the most obvious problems. However, we need to focus on each of these factors for success. Alignment involves identifying and co-producing the purposes, goals and the standardized processes (including a shared quality framework). The networks/infrastructures are learning from experience with studies that test their operations and demonstrate the viability of their approaches. This process of alignment takes several years.

4 | CURRENT WORK

European RIs potentially relevant to paediatric drug development are members of CORBEL.¹⁹ These organizations are central to drug development in general; the need for paediatric complementary organizations is recognised by ESFRI.

Two initiatives exemplify the rigorous approach identified by ESFRI, the European Paediatric Translational Research Infrastructure (EPTRI)²¹ and c4c.²² EPTRI is relevant to basic, preclinical and translational research for paediatric medicines since it will provide drug developmental expertise, facilities and methodologies able to account for the related ontogeny variability of the main pharmacologic results including: (i) differences in drug disposition and effect between age groups; (ii) age-related pharmacogenetic changes on diseases target, drug responses and biomarkers; and (iii) strength and forms of medicines responding to paediatric physiology changes during the children growing process.

EPTRI will work in the current landscape to cover a significant gap enhancing technology-driven paediatric research in drug discovery and early development phases to be translated into clinical research and paediatric use of medicines. To do this, EPTRI counts on a community of experts focused on paediatric science from >300 research units allowing the coordination of efforts, standards and methodologies, and providing an open space for researcher to exchange expertise and facilities without barriers.

c4c is relevant to early and late phase clinical trials. c4c will add to the current landscape by supporting sites to setup and conduct trials through coordination by national hubs. National hubs will provide a *national corporate memory* that meets specific needs of Sponsors, Contract Research Organizations, and Academic investigators during trial setup and conduct. Support will include standards for trial conduct, metrics for trial performance, and a quality framework for the work of the network. Education and training will be available to investigators and sites. EPTRI and c4c are currently collaborating through the alignment period and will open to general operations from 2024 onwards. The voices of children and their carers are important for both initiatives: their involvement is described after the initiatives.

EPTRI is performing its preparatory phase of RI development working with service providers organized into Thematic Research Platforms: Medicines Discovery; Developmental Pharmacology; Biomarkers; Formulations. Potential users will approach the EPTRI Central Management Office who will parse the requests for services and identify the most appropriate service providers and regulatory framework. The quality of the services provided will be monitored.

Inputs from potential users will be requests for facilitation of pre-clinical and translational research focused on paediatric medicines discovery and development and to prepare the ground for paediatric clinical trials and medicines use. EPTRI will receive requests relating to the facilitation of: (i) identification and hit screening of new drug targets specific for children's diseases; (ii) research services and advice for nonclinical research to improve preclinical data to be used in paediatric developmental plan; (iii) use of paediatric human/animal samples, tissues and cells to work on the identification, characterization and validation of new biomarkers; and (iv) design and development of appropriate paediatric medicine formulations, tailored for children use in all paediatric ages.

4.1 | Resources

EPTRI is organised as a distributed RI based on the hub and spoke model. A central hub will be based on managers and key experts, ethical and scientific advisory boards, and an access management board in charge to respond transparently to the requests from users. The scientific key resources are represented by >200 research units in 25 countries distributed in the thematic research platforms representing the scientific area of interest for paediatric medicines pre-clinical development.

Outputs will be services that provided to the requesting users to promote and foster innovation in paediatric in the fields of paediatric

medicines discovery; paediatric biomarkers and biosamples, developmental pharmacology, and paediatric medicines formulations.

The users that will get access to the EPTRI services will be: academia and other public research organisations, i.e. preclinical researchers and clinical investigators; pharma industry and biopharma small and medium-sized enterprises; sponsors of new medicines and therapies; contract research organizations; nonprofit research organisations, charities, foundations etc.

The performance and the benefit provided by EPTRI will be objectively evaluated through several key performance indicators including numbers of users, publications/citations, patents/licenses, industrial users and projects with industrial cooperation.

User feedback will allow EPTRI to adapt its services on the basis of the requests.

The EPTRI design phase has been supported by the INFRADEV-01-2017 grant, which has covered the analysis of the potential user community, the outline of a business case and the rationale for the international consortium. The preparation phase is planned from 2021 to 2023 and is expected to be funded through the H2020 funds for integrating activities (INFRAIA-02-2020) which will provide support by accelerating the implementation of EPTRI on European scale. The implementation phase is planned from 2024 to 2027 and is expected to be funded through the European funds dedicated to integrating activities for advanced communities, dedicated to RIs showing an advanced degree of coordination.

The long-term sustainability of EPTRI is also based on the participation (at the time of full operation) of 200 research units providing a financial commitment to support with a defined amount per year the continuous functioning of the EPTRI coordination and national nodes.

c4c is combining preparatory and implementation work as a public-private partnership under Europe's Innovative Medicines Initiative 2 (IMI2) Joint Understanding (<https://www.imi.europa.eu>, Grant Agreement 777,389). The IMI2 c4c project was launched in May 2018 and the IMI2 grand will end in April 2024. To ensure sustainability of the network after the IMI funding period, c4c is currently developing a business model and creating an organizational blueprint for a successor organization, able to maintain and sustain network operations after the end of the IMI2 funding period. The new legal structure will be implemented before the end of the funding period of the current consortium in spring 2024.

This innovative approach allows the pharmaceutical industry and academia to work together precompetitively within a well-defined governance framework. c4c will provide several services: expert advice during planning of paediatric development plans and clinical studies, including the voice of patients and families; clinical trials including facilitation of the use of innovative methods in study design and conduct; support for operational set-up and conduct of paediatric clinical trials from national hubs and networks of sites; and education and training to support the use of the network and broader needs in paediatric drug research.

Due to IMI2 funding rules c4c services can currently only be offered to members of the c4c consortium. This will change after the

end of the IMI funding period. After end of IMI funding (2024), and transfer of network operations to a successor organization, all network services will be available to all kind of sponsors (industry, academia, advocate-driven) and to intermediary organizations such as CROs. We anticipate a mixture of membership dues and fees for service to meet the needs of different users.

As a member of EnprEMA, c4c is ready to work with the EMA and other regulators. Most of the work of c4c relates to specific drugs so that EMA is not able to be a part of the Consortium. EMA provides an external advisor to c4c.

4.2 | Expert advice

4.2.1 | Inputs

Study sponsors, either industry or academia, as well as funders can request for advice on paediatric drug development programs (e.g. PIPs) or individual studies.

4.2.2 | Resources

To support these requests, standing clinical and innovative methodology expert groups (totalling more than 300 individual experts across all paediatric specialties and methodologies) have been set up as well as a network of individual parents and patients and organizations. When requests come in, ad hoc strategic feasibility groups are formed, drawing experts from these groups.

4.2.3 | Outputs

The strategic feasibility meeting reports will be the formal responses to requests, *strategic feasibility*, opinions on topics. These will be

suitable for internal discussion by investigators and Sponsors, and for external discussion with regulators and other stakeholders.

To date, 12 requests have been received from members of the Consortium. The Expert Advice team are also developing *multi-stakeholder meetings* based on the experience of ACCELERATE in paediatric drug development.^{23,24}

4.3 | Clinical trials

Inputs from sponsors and investigators will be clinical trial protocols, as outline or full protocols relating to trials with funding.

Resources are sites organized by national networks, cross-referencing with specialty networks; a Single Point of Contact for sponsors and investigators; coordinating Network Infrastructure Office; clearly defined ways of working with sites, national and specialty networks, and sponsors.

Outputs will be reports on *operational feasibility* at country and site level, consistent support for trial conduct, and facilitation of timely opening and completion of trials.

The work of c4c on trials is being evaluated through studies that test the viability of the network. The academic *proof of viability* studies are shown in Table 1. Industry proof-of-viability studies will be Sponsored by Janssen, Bayer, Novartis and Roche.

4.4 | Education and training

Inputs will be topics that meet clearly defined educational needs in paediatric drug development relating to generic issues (GCP, regulatory affairs) and to specific trials.

Resources will be a comprehensive approach to the development and implementation of courses including an Educational Board, pedagogic expertise, subject experts and portal for deployment of educational activities.

TABLE 1 Academic conect4children proof-of-viability studies

Title of study	Sponsor	Specialty	Nature of trial	Planned sample size	Planned initiation date	Duration
TREOCAPA	INSERM, Paris, France	Neonatology	Phase 3 trial of paracetamol to prevent patent ductus arteriosus	800	October 2020	3.5 y
KD-CAAP	UCL, London, UK	General Paediatrics, cardiology, rheumatology	Phase 3 trial of the effectiveness of adding steroids to standard treatment in children with Kawasaki disease	262	August 2020	3.5 y
cASPerCF	OPBG, Rome, Italy	Pharmacokinetics in cystic fibrosis	Phase 2 trial to assess the dose of posaconazole in children and young people with cystic fibrosis and infection with <i>Aspergillus</i>	130	October 2020	3.5 y

Outputs will be curricula, webinars, interactive sessions and courses that support capability building at national and site level, increased efficiency and increased quality of network operations.

Both EPTRI and c4c work on data interoperability relating to pre-clinical and clinical topics. Both initiatives will contribute to context and policy development by raising public awareness of the need for research about medicines used by babies, children and young people.

Within c4c, eYPAGnet supports discussions about individual projects, is standardizing the training of the young people who advise about drug development and protocols, and is defining common methodologies for patient and public involvement and engagement across different countries. In addition, eYPAGnet is analysing the impact of PPIE in terms of return on investment and return on engagement.

EPTRI and c4c are working with the relevant ESFRI Landmark RIs. EPTRI works with 7 RIs: BBMRI, EATRIS, ELIXIR, EURO-BIO-IMAGING, EU-OPENSREEN, INFRAFRONTIER and INSTRUCT. c4c includes ECRIN and partners in c4c and ECRIN are working on PedCRIN (<https://ecrin.org/projects/pedcrin>), to support the work of ECRIN in paediatrics.

c4c is collaborating closely with the rare disease community, including the European Reference Networks (ERNs, https://ec.europa.eu/health/ern_en), through a joint Steering Group with the European Joint Programme for Rare Diseases (EJP RD, <https://www.ejprarediseases.org>).

c4c, EPTRI and eYPAGnet are working towards the setup of sustainable legal entities. Identifying the roles of the new entities involves collaboration with other groups in Europe including networks in paediatric oncology, rheumatology, HIV/AIDS, neuromuscular disorders and cystic fibrosis as well as the established RIs and EnprEMA. In addition, there are links with similar networks/infrastructures in the USA,^{25,26} Canada²⁷ and Japan. These international collaborations aim to develop a shared approach to paediatric trial delivery based on interoperable networks.

4.5 | The impact of the COVID-19 pandemic

c4c actively mitigated the impact of the COVID-19 pandemic through a comprehensive business continuity plan. The main barriers to the work of c4c were the availability of staff to work on the clinical studies and the effects of lockdown on other staff. This has led to a delay of about 6 months in the initiation of the trials. We anticipate completing the trials within the funding envelope available from IMI. The possibility of remote patient visits was explored but this is not possible for the academic proof of viability studies due to the population (neonates), assessment (echocardiography) and study procedures (sputum production in cystic fibrosis). Some of the sponsors of the trials have explored remote monitoring but some national regulatory authorities limit this approach.

4.6 | Future state

The c4c successor organisation plans to be implemented by 2024 while EPTRI plans to enter in the operational phase at the beginning

of 2025. Once they are operational, studies/research done within c4c and EPTRI will be more likely to be completed to time, to scope and to budget. Quality of trial conduct will be significantly better than outside the networks. Unexpected events will be managed efficiently due to clear expectations of roles and responsibilities and resilience at study and network level (e.g. finding extra sites for clinical studies, finding extra expertise if preclinical studies yield unexpected findings). This will be facilitated by clear specification of inputs and efficient processes that promote high quality outputs. A professionalised and integrated approach to paediatric drug research will be available.

This will contribute to better quality studies completed on time and so to timely completion of PIPs and better information about drugs studied in babies, children and young people. This will lead to an increased number of drugs with licensed paediatric indications and lower the off-label prescribing to this population.

4.7 | Lessons

To facilitate paediatric research, it is necessary to take a step back from science. A formal approach to the development of Research Networks and Infrastructures requires specification, alignment and testing of the work of RIs. This work takes time and attention to detail by people who have dedicated time and resources. We need to move from enthusiastic voluntarism to accountable professionalism while maintaining vision and purpose. We need to start by working thoroughly and then *think lean* to optimise the conduct and sustainability of the Research Networks and Infrastructures. Improved quality of trial conduct needs to be central to the design and implementation of this work.

The risks that may arise during the preparatory and implementation phases include:

- Loss of flexibility for users and providers that adds to their internal burdens but is balanced by reliability of the research networks and infrastructures
- Bureaucracy that is not proportionate to the benefits of working with research networks and infrastructures
- Lack of buy-in from users and providers that could arise from slow, poor-quality or expensive services; poor communication about a useful service; vested interests
- Difficulty for sponsors recognizing the value of successful initiatives and changing their approach to work with successful initiatives

These risks are being actively mitigated by the governance of c4c and EPTRI and by reflective learning from experience. Studies to assess the feasibility of the infrastructures are under way.

5 | CONCLUSION

Networks and RIs will improve the quality and value for money of paediatric drug research in Europe and ensure that projects are patient

centred. Readers can support this work directly through membership of each initiative. In time, readers will be able to act as users of the networks and RIs. Indirect support includes recognizing the need for networks and RIs and working to overcome avoidable barriers.

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COMPETING INTERESTS

All the authors are associated with the c4c project because their employers are Beneficiaries or Third Parties of the c4c consortium. Bonifazi, Ceci, Turner, de Wildt, Rossi, Attar, Claverol, Nefri and Giaquinto are associated with the EPTRI project because their employers are Beneficiaries of the EPTRI Consortium. Cheng is an employee of Johnson and Johnson. Hildebrand is an employee of Bayer AG.

CONTRIBUTORS

M.A. Turner drafted the paper and contributes to the work of c4c and EPTRI. K. Cheng reviewed the paper and contributes to the work of c4c. Saskia de Wildt reviewed the paper and contributes to the work of c4c and EPTRI. H. Hildebrand reviewed the paper and contributes to the work of c4c. S. Attar reviewed the paper and contributes to the work of c4c and EPTRI. P. Rossi reviewed the paper and contributes to the work of c4c. D. Bonifazi reviewed the paper and leads EPTRI. A. Ceci reviewed the paper and contributes to the work of c4c and EPTRI. J. Claverol reviewed the paper and contributes to the work of eYPAGnet, c4c and EPTRI. B. Nafria reviewed the paper and contributes to the work of eYPAGnet, c4c and EPTRI. C. Giaquinto reviewed the paper and contributes to the work of c4c and EPTRI.

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