**Abstract**

The evaluation of drugs that are used in children has been neglected historically but is now well-established as an essential part of clinical drug development. The increase in pediatric activity among industry, and other sectors, has highlighted the importance of joint working. All participants in drug development need to be aware of the “big picture”. An increasingly important part of this big picture in paediatrics, as in other populations, is the design and conduct clinical trials in networks. This review provides an overview of the roles of clinical research networks in pediatric drug development. Networks take many forms but work to common principles including sharing resources between trials and using experience with trial conduct to improve trial design. Networks develop standardised processes for trial conduct (including performance management) that increase the speed and predictability of trial conduct while reducing burdens on sites, Sponsors and intermediaries. Networks can provide validated, real-world information about natural history, participant distribution and standards of care to inform planning of development programmes, including extrapolation and clinical trial simulation. Networks can work across geographical and jurisdictional barriers to promote global interoperability of drug development. Networks support participant-centrality. Networks offer an opportunity to develop relationships with investigators, sites and methodological experts that span pre-competitive foundations for drug development and specific products. Sustainable networks benefit all stakeholders by providing a multi-functional platform that promotes the quality and timeliness of clinical drug development.

**Introduction**

Evaluation of new and existing drugs requires collaboration. This is particularly important in paediatrics because children with specific conditions are rare, even though the overall burden arising from ill-health in children is large. This is coupled with the inefficiency in clinical research, particularly clinical trials, that is common in all therapeutic areas (1). Networks have been identified as one way to overcome inefficiencies in clinical research. Working in networks requires specialists in one area, such as pharmacometrics, to be aware of the broader picture.

This paper reviews the roles of clinical research networks in the delivery of paediatric drug development, illustrating the context in which specialists contribute to the complete spectrum of clinical drug development. We define a clinical research network as a group of sites with persistent governance arrangements that is involved in the delivery of clinical studies (including observational and interventional). Delivery includes the implementation of studies and design of studies. This may or may not involve leading or sponsoring studies. Ideally, experience with implementation of studies influences the design of subsequent studies. Networks may have other roles but these roles need to be clearly demarcated from research.

**Overview of paediatric research networks**

Many paediatric research networks exist. There are forty eight members of the European Network of Paediatric Research at the European Medicines Agency (EnprEMA) including Canadian and US networks [2] and more than 70 pediatric research networks in North America [3]. The Pediatric Trials Network (PTN) has studied a number of off-patent drugs [4]. A recent addition is the Institute for Advanced Clinical Trials for Children (iACT) [5]. The Paediatric Trials Network of Australia (PTNA) is under development [6].

The networks demonstrate a wide variety of structures and levels of activity with different organizational and funding models. Some are based around clinical specialties, others are geographically organized working with multiple specialties. There are some common features. Effective networks develop a learning organization and optimize performance. Support across multiple studies within single specialties is effective. Generic support that works across multiple specialties is feasible and is attractive to network funders because it provides the best return on investment in networks.

Recent advances have demonstrated the success that can be achieved through proactive portfolio management, utilising datasets, operationalising new technologies, utilising innovative techniques, encouraging clinical-community partnerships, and improving performance through transparent pursuit of meaningful goals [7] [8].

Challenges to the network model exist [9]. Amalgamation of organizations or adoption of identical procedures is less important than adopting processes and standards that allow multiple organizations to work effectively on the same project.

The attributes of a good network include: processes that are easy to use and predictable; service design accommodates the needs of each clinical situation while using an efficient core of services that are deployed in multiple settings; networks meet the needs of multiple stakeholders for timely, high quality, consistent completion of trials; capacity building at site level as well as network level. Individual networks have many but not all of these attributes. The paediatric clinical trials enterprise, and availability of information about medicines for children can be improved by sharing existing good practice and developing synergies that reduce barriers to entry for new trials and for countries and clinical specialties that do not yet have effective research infrastructure.

**Efficient Implementation of studies**

Good implementation is necessary for the delivery of all studies, irrespective of design. Children, young people and their families want rapid availability of new and improved drugs, as do study funders.

Pinch points for the rapid conduct of studies include:

* Site identification
* Site opening
* Time from opening to First patient first visit (FPFV)
* Time to meet recruitment target
* Time to complete study
* Participant retention and completion of all study assessments

These mainly relate to events in individual sites but these delays can be reduced by good planning by the Sponsor (or their delegates such as Contract Research Organizations). Good practice with regards to trial implementation has been defined but not universally applied [10] [11]. Active performance management of trials includes tracking of recruitment at site level, frequent communication with site PIs and Study Coordinators to identify ways to improve recruitment, remote monitoring of data collection, following missed visits up with the site to confirm the reason but focused attention on site selection strategies tailored specifically to address the target population required for the protocol is equally important [12]). All of these issues are generic to clinical trials and can be managed by staff with generic skills.

Sites have a learning curve that can be expedited by sharing good practice, having clear standards for site management and by having core staff who work with all trials.

Most work at sites can be done by “generic” staff who contribute to many clinical studies and clinical areas. Specialists in clinical areas can make the most of their time-limited investment in trials by working on those tasks that only they can address. Sites that work in networks can benefit from rapid dissemination of information about trials, a structured approach to good practice and economies of scale from marketing and negotiations with Sponsors and other funders. Table 1 shows key functions in trial implementation and how networks can make a positive impact on these. Networks can provide and identify good practice and apply it across a range of studies [13] [14].

Good practice includes the utilisation of contracts and costing templates that have been used in paediatrics. Efforts to improve consent/assent of people who are recruited to clinical trials (study participants) are underway [15] [16]. Each Sponsor, trial or site can handle these separately. However, autonomy comes at a cost to the Sponsor and to the sites – inconsistency and repeated specification of similar documents adds time to trial implementation and increases regulatory and compliance risks – so that pre-competitive collaboration is beneficial to all parties. Sites can work independently with internal siloes and fragmentation across countries and specialties. Quite often site independence is promoted by quality assurance and risk management procedures that focus on the risks to the site rather than the benefits of joint working. In addition, localised benefits (such as control over staff and budgets at departmental level) provide short-term benefits to key individuals that reinforce fragmentation between sites. Networks can overcome these problems and facilitate improved trial efficiency by providing supplementary assurances and additional benefits to key individuals and the institution as a whole. See Figure 1.

Issues specific to paediatrics include implications for trial conduct and design of growth and development. Most of these issues can be managed effectively at the site level by deploying staff with skills in, and experience of, paediatrics across paediatric subspecialties. A few paediatric subspecialties are so distinct that they need specialised research staff (e.g. child and adolescent mental health and neonates). Other subspecialties may need specialised research staff according to the volume or complexity of work (e.g. paediatric oncology).

**Optimal design of studies**

The evaluation of medicines in children involves developing a dossier of information that enables decisions about market authorisation, pricing and policy, and clinical choices about individual children – different decisions require different enabling information [17]; Turner and Hirschfeld this issue). Clinical studies, including randomised clinical trials (RCTs), require many adaptations to the specifics of the target population, the intervention and the role of the study in a programme of research. Furthermore, standard trial designs may not always be possible, appropriate or efficient in the development of new drugs or repurposing of old drugs for the small study populations in paediatrics. Alternative and innovative approaches to clinical trial design in small populations can overcome the limits related to small samples and to the acceptability of the trial. There are advantages of these innovative approaches to clinical trials design. In practice however, many factors such as protocol approval, limited knowledge of methodology, lack of in-depth understanding of child physiology, psychology, the social embedding of children hinder the use of innovative methods [18]. Optimal trial design requires clinical input and methodological input.

Evidence-based research is also important to design and conduct trials that will make a real difference to children's health [19]. Standards and guidelines have been recommended on most aspects of undertaking paediatric clinical trials [20]. The implementation however remains variable. Clinical trial networks should enable and facilitate the implementation of good practice [21].

To tackle these multiple factors there is a need to improve the inputs to study design.

Expert groups can inform the development of information that contributes to trial design and interpret that information (since information will need to be adapted to specific trials and will always be imperfect). Determinants of the value of expert groups include their past experience of trials and their familiarity with regulatory processes. Expert advice will always include judgments but judgments can be optimised by using best-available information about the clinical context or relevant methodologies. Best available information can be enhanced through experience and underpinning data. Good judgments benefit from understanding the nature of the study and adapting the advice to the context of the study (regulatory vs clinical vs policy making). Judgments relating to marketing authorisation need be based on understanding regulatory procedures. Judgments related to policy about medicines use and availability need to reflect the policy goals and procedures of reimbursement and health technology assessments.

*Clinical input to design and feasibility*

Trial design depends on understanding the clinical context of the trial: “trial designs, no matter how novel, will only be as good as the knowledge that underlies them [22]”. Trial conduct, and the quality of information yielded by the study, will be impaired if variability in disease expression or progression are not recognised and accounted for in the design of the trial. Furthermore, biomarkers that are not specific for diagnosis or prognosis will reduce the precision of the study results. The views of the patient community on the burden of disease should inform outcomes, particularly patient-reported outcomes. Thus, the likelihood of trials yielding useful information can be improved by developing a sound awareness of natural history, biomarkers and impact on the patient community (including families). Information about the clinical context is not proprietary to individual Sponsors but needs to be develop in a trusted, verifiable pre-competitive space that Sponsors, regulators and investigators can access equally. Independent clinical research networks are ideal for this. Similarly, the views of children, young people and their families need to be collated in a way that avoids undue pressures and conflicts of interests. Independent groups that support advocacy are required. In both cases transparency about funding is essential.

Incorporating information and expertise is crucial through evidence-based feasibility. We propose a roadmap for increasing the quality of inputs to design through clinical expert groups. See Table 2.

Experienced specialty groups have developed a range of ways to optimise their advice, including multi-stakeholder meetings that incorporate regulators, Sponsors, patient advocates and investigators [23] [24]. Population registries which provide large and representative study samples with high-quality data that can be used to generate information and evidence, as well as to inform clinical decision making. Such networks provide improved outcomes in primary care practice as well as care for chronic paediatric diseases, perinatal care, by providing the social, scientific, and technical infrastructure and data for multiple types of research [8].

*Methodology expert groups*

Advice by methodology expert groups covers disease-independent aspects of study design such as selection of key study features. This requires experts in biostatistics, pharmacometrics, data management, apps and devices. Examples include the application of pharmacokinetics and pharmacodynamics to optimal sampling regimens and timing of study assessments [25].

The capability of methodology expert groups can be developed. The simplest methodological advice involves a description of a method and contributions to the application of the methods, e.g. by writing or commenting on a draft protocol. Extra value is generated by comparisons between the performance of different methods, preferably based on objective criteria. One approach to comparing methods is clinical trial simulation. Simulation cannot indicate which method is best, they can de-risk the decisions and sometimes validate assumptions and indicate key knowledge gaps [26] [27]. Some methodologies are well-adapted to children and expert groups can give balanced opinions based on careful evaluation of the strengths and weaknesses of each study design. Other methodologies are novel or have not been adapted to children in which case expert judgment is needed. Expert groups also need to contribute to regulatory policy, for example through drafting white papers or contributing to regulatory consultations.

**Opportunities for networks**

Using these tools, networks have a number of opportunities to contribute to excellent research performance and, ultimately, to improving patient care through: global interoperability; leveraging existing data; strategic alliances between stakeholders; developing research through relationships as well as data; and ultimately, sustainability.

1. Global interoperability

Some conditions need global recruitment pools to address the small sample sizes in children. There has been progress in developing statistical methods and collaborative specialist multi-national groups and clinical trials networks that pool their data and resources [28] [29] [30] [31] [32]. In principle learning from these networks can be extended to other specialities. Economies of scale will arise from pooling efforts between specialties, within regulatory regions and across regulatory regions. Network processes need to balance flexibility for country/institution specific policies and consistency of process for the sponsors and trialists.

The operational implications of work towards global interoperability are the need for constant communication and clarity of purpose and process coupled with the flexibility that is needed to make the most of existing structures.

1. Leverage existing knowledge held by clinical networks and other groups

As noted above, knowledge and experience about medicines and natural history is a crucial aspect of medicines development which can inform study designs and contribute to research priority discussions with sponsors and policy makers. Many clinical research networks own relevant data or have relationships with other data owners. Clinical research networks can develop and manage the fora that bridge between relevant stakeholders.

The operational implications with respect to shared work about data are that networks should: collect and curate data in a way that allows secondary use; develop standards that promote data sharing; build links with people that hold and use data; develop standard legal and policy approaches to data ownership and privacy taking account of the specific needs of children.

1. Strategic alliances between stakeholders

Currently, strategic collaboration is not a consistent feature of paediatric research. Most paediatric research involves Sponsors maximising recruitment for each trial while minimising costs to each site. Conversely, individual sites currently focus on maximising income per trial without considering the bigger picture. There is a widespread perception that adequate resources are not provided to sites to run clinical trials. On the other hand, the clinical research community does not deliver information needed to advance drug development: the paediatric research community is not reliable or predictable. Clinical research networks need to develop strategic alliances to maximise impact and resources. Key elements of a strategic alliance include cooperation that is long-term work together that is based on optimising outcomes rather than maximising the benefits arising from each interaction.

These deficiencies can be overcome by developing strategic alliances between Sponsors and networks. Alliances would provide fair rewards to sites and networks that overcome bottlenecks in trial design and implementation. Sites and networks would provide Sponsors with assurances that the alliance is a good investment. Effective alliances promote efficiency, provide a more comprehensive basis for adapting to changing circumstances, and spread risk. All parties need a good reason to join because working in an alliance will disrupt their current ways of working. Setting up an alliance between experienced networks is more difficult: experienced networks potentially have fewer opportunities to benefit and more legacy procedures to disrupt.

Confidence in an alliance can be enhanced by processes and standards that promote predictable outcomes (what some have termed control mechanisms). Control mechanisms will be more effective if partners trust each other. The literature suggests that there are three key control mechanisms in strategic alliances: goal setting and monitoring; structural specifications and monitoring; organizational culture blending. There are four key techniques in building trust: communication; fairness and equity; mutual adaptation; risk-taking. All of these mechanisms and techniques work better when they are done across sites rather than in fragmented ways such as when multiple specialities in a site maintain parallel ways of working.

Operational implications for networks interested in developing strategic alliances are to look at the long-term, to compromise on processes that are not mission-critical, to develop a culture that cuts across specialties, and to base an alliance on values such as equity, culture and transparency.

Relationships with patient advocacy groups are essential during paediatric drug development. Children and young people can make substantial contributions if they are educated appropriately and supported people with relevant expertise.

1. Developing research through relationships as well as data

Resilient alliances can improve the current, fragmented situation. Currently, most drug development plans are prepared as an isolated procedure using standardised approaches and metrics. Frequently, the quantitative estimates of sample size etc. are inaccurate leading to inefficiencies as plans are adjusted. Furthermore, the low level of trust between Sponsors and regulators (and intermediary organizations and sites) makes the necessary adjustments onerous and rooted in process rather than clinical reality. If consistent relationships are built between stakeholders then the same results can be obtained with less burden on the stakeholders.

1. Sustainability

At present a limited number of networks are sustainable. Network sustainability requires continued access to resources that are not bound to specific projects and are not limited by time. Aspects of sustainability that need to be addressed include: willingness to host the network by sites; availability of staff with appropriate skills and enthusiasm; sufficient resources to maintain the network. Maintaining the willingness of sites to be part of the network depends on evidence about the utility of participation in clinical trials (to participants and the institution), ensuring that reasonable costs are met, and demonstrating that network participation maximises benefits while minimising the costs that the site has to bear. Maintaining the engagement of relevant staff means ensuring they have relevant skills that can be updated and developed, minimising the burdens of trial conduct that fall to staff with other responsibilities and demonstrating that the network promotes their personal goals while minimising the effort needed to meet those goals. Resources that maintain the network can be financial or in-kind. In either case the holder of the resource required by the network needs to be informed about the return on their investment and persuaded that that return helps them meet their strategic goals. Many academics are used to working on projects with well-defined outputs. Networks need to build on project outputs to construct capabilities and knowledge that deliver useful outcomes that ensure stakeholders experience benefits, and that it is put at benefit for future research. Networks need to provide quantifiable evidence about the benefits derived from the functions described in Table 1 and add predictability and quality. Networks add value by providing benefits at less cost than the alternative of fragmented inconsistency. However, it is problematic for networks to identify the value they add because the costs met by study funders and Sponsors are not transparent. Networks can define their benefits more easily than they can demonstrate reduced costs. Nevertheless, networks need to market their work effectively.

Operational implications with respect to sustainability include: the development of a sound business model that will attract resources. Existing funding models include combinations of governmental funding, in-kind contributions from pharmaceutical companies, membership fees for institutions, and charge per activity undertaken. Networks should start by looking beyond their own views about their capabilities and focus on the needs of people who provide the resources (sites, staff and institutions) – in addition to the needs of study participants.

**Conclusions**

Although many national, international and specialty specific networks exist, several issues hamper the consolidation in successful networks such as the establishment of governance models, infrastructure, geographical boundaries, resource and sustainability. We have described the roles of clinical research networks in the current paediatric research environment. To address these issues, components of a network have been described which utilise portfolio management and expert advisory groups. Clinical research networks provide infrastructure that can be used by multiple studies: the optimal return on investment for all stakeholders comes from sharing infrastructure across as many specialties as possible. The optimal way forward will involve developing alliances and relationships between stakeholders that promote sustainable, high quality data collection about medicines used in children.

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Table and Figure captions

Table 1. The roles of clinical research networks in clinical trial functions that promote efficiency, data quality and timely study completion

Table 2. Improving the quality of clinical advice

This table provides a framework to identify the which level of advice a clinical advisory group is able to give.

As time goes by specialties are able to move to the right for some of the rows depending on availability of funds and the enthusiasm of the clinical community. The further to the right a specialty is the more likely its input will be sought early in the development of drug development plans or protocols

Figure Caption

Figure 1. The roles of networks in promoting clinical trial efficiency.

The figure illustrates the contributions of networks to reducing the resources needed to conduct clinical trials. Clinical trials can be conducted by isolated sites that come together for each trial. Alternatively, with a modest investment sites can develop ways of working that can be used in multiple trials. Local barriers can require some extra resource initially (time, money) but once deployed shared ways of working can reinforce collaboration.