Roles of Clinical Research Networks in Pediatric Drug Development

Mark A. Turner, MbChB, PhD[1]; Sabah Attar, PhD[1]; Saskia N. de Wildt, MD, PhD[2,3]; Gilles Vassal, MD, PhD[4]; Laura Mangiarini, PhD[5]; and Carlo Giaquinto, MD, PhD[6]

[1]Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom; [2]Department of Pharmacology and Toxicology, Radboud University, Nijmegen, the Netherlands; [3]Intensive Care and Department of Pediatric Surgery, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands; [4]Department of Clinical Research, Gustave Roussy, Paris-Sud University, Paris, France; [5]Fondazione PENTA onlus, Padova, Italy; and [6]Department of Women's and Children's Health, University of Padova, Padua, Italy

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 pediatric drug development need to be aware of the "big picture." An increasingly important part of this big picture in pediatrics, as in other populations, is the design and conduct of clinical trials in networks. This narrative review provides an overview of the roles of clinical research networks in pediatric drug development. Networks take many forms as specialty networks and geographic networks but work toward common principles, including sharing resources between trials, and using experience with trial conduct to improve trial design. Networks develop standardized 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 programs, including extrapolation and clinical trial simulation. Networks can work across geographic 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 multifunctional platform that promotes the quality and timeliness of clinical drug development. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮)

Key words: integrated drug development, pediatrics, research networks, industry, academia.

INTRODUCTION

Evaluation of new and existing drugs requires collaboration. This is particularly important in pediatrics 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. This article provides a selective, narrative review of the roles of pediatric research networks in pediatric drug development based on the literature and experience of two large speciality networks and two large national networks. To advance the field, we speculate about some opportunities for networks and the implications of those opportunities for network design and practice.

We define a clinical research network as a group of sites with persistent governance arrangements that

Accepted for publication September 6, 2017.
http://dx.doi.org/10.1016/j.clinthera.2017.09.001
0149-2918/$ - see front matter

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. Networks may have other roles, but these roles need to be clearly demarcated from research.

OVERVIEW OF PEDIATRIC RESEARCH NETWORKS

Many pediatric research networks exist. There are 48 members of the European Network of Paediatric Research at the European Medicines Agency, including Canadian and US networks,[2] and >70 pediatric research networks in North America.[3] The Pediatric Trials Network has studied a number of off-patent drugs.[4] A recent addition is the Institute for Advanced Clinical Trials for Children.[5] The Paediatric Trials Network of Australia is under development.[6]

The networks found 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.

Broadly, those networks that form around clinical specialties tend to be driven "bottom up" by clinicians intent on optimizing patient outcomes compared with networks that are geographically organized and working with multiple specialties that tend to be driven "top down" by decision makers intent on system improvement for efficiency and economic gain such as attraction to industry or optimizing the efficiency of publically funded studies. These two networking approaches are not mutually exclusive and, in the ideal world, are highly integrated. Clinical specialty networks bring patients and families as more eager participants in clinical research, a wealth of data (or the on-going ability to get data) on biomarkers and disease stratification, and the ability to assure uniform standards of care on which to conduct trials of new therapies and to rapidly implement new evidence. Through high-profile achievements that influence rate of mortality (childhood cancer)[7] and quality of life (cystic fibrosis, irritable bowel disease),[8,9] the value of clinical specialty networks is increasingly recognized, and steps are being taken to reward clinician engagement in networks (eg, American Board of Pediatrics recertification) and to support networking (in Europe, European Reference Networks, and Innovative Medicines Initiative 2–funded Clinical Research Networks; in the United States, National Institutes of Health [NIH]–sponsored networks). Geographically organized networks address barriers and inefficiencies in the conduct of clinical research such as regulatory and ethics affairs, data management, site function, and personnel qualification and training by working with all specialties. The establishment and harmonization of best practices for these areas is under the control of governments and institutions through legislation, policy, and setting procedures. The approach to effect change is well illustrated by the recent NIH policy on the use of a single institutional review board for multisite research.[10] The outstanding achievements of the English Medicines for Children Research Network to increase participant engagement and attract clinical trials are testament to the importance of high-level bureaucratic commitment[11] that deploys resource to where the patients are and is coupled with a national single ethics committee and institutional approval.[12] The potential tensions between geographic and speciality networks need to be proactively managed with clear expectations and arrangements that allow win–win outcomes.

Networks have found the success that can be achieved through proactive portfolio management, using data sets, operationalizing new technologies, using innovative techniques, encouraging clinical–community partnerships, and improving performance through transparent pursuit of meaningful goals.[13,14]

There are challenges to the network model.[15] 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.

An NIH study in 2006 reported key elements of success, including relevant and well-managed leadership structure, information technology systems, subject recruitment and retention, network administration, education and training, data management, financial policies, and efforts to build sustainability that have been used to evaluate networks[16]; others have reported similar experiences.[17] In addition, our experience has found that the attributes of a good network include processes that are easy to use and predictable, service design that accommodates the needs of each clinical situation while using an efficient core of services that are