Title
Establishing a Research Network

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Running Title
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Abstract
Multi-centre research provides advantages over single centre research by maximising available patient numbers while providing varied expertise and resources available across different participating investigators and sites. The increased complexity of multi-centre regulatory approvals, communication and study management, can be mitigated by the formation of a research network where multicentre efforts move from ad hoc, single projects to formalized ongoing collaboration. Network research helps prioritize research efforts and importantly fosters the development of a collaborative track record in terms of research expertise, research capacity and grant success. It also has the potential to rapidly change patient care across many hospitals as research results will be more generalizable and definitive. This paper sets out the key elements of network research, its benefits and possible challenges drawing on the example of PREDICT (Paediatric Research in Emergency Departments International Collaborative) an established paediatric emergency research network in Australia and New Zealand.

Keywords: emergency medicine, research, methodology, systems
Introduction

While high level, paradigm shifting research can be conducted in single centre studies, multicentre research has numerous advantages: the availability of larger patient numbers for adequately powered, clinically meaningful results; the ability to address outcomes that are infrequent but serious or where differences are small; the pooling of resources and expertise across sites; and the production of more generalizable results.

Network research is characterised by multicentre research combined with a consistent strategic, longer term approach and efforts to create research capacity and infrastructure. Research methodologies can be continued and refined creating a track record which will likely assist in achieving grant funding success. Ideally paediatric networks should include non-tertiary centres where, depending on subspecialty, the majority of children may be managed. This extension beyond tertiary centres also may include collaborators outside the hospital setting. Participation in network research, through baseline studies highlighting variation in care, networking and communication, and the use of shared research protocols based on current best practice often standardises and improves clinical care across centres.

The Australian Clinical Trials Association (ACTA) is the national peak body for clinical trial networks, coordinating centres and quality registries conducting investigator-initiated clinical trials (https://clinicaltrialsalliance.org.au/about-acta/). It has developed a number of useful resources for network research available on its website. In addition, it has analysed activities critical to success and growth of clinical trials networks (Figure 1). We will draw on these elements throughout this paper.

While a number of paediatric subspecialty research networks have been established in many countries including in Australia and New Zealand (1-4) this paper will use the Paediatric
Research in Emergency Departments International Collaborative (PREDICT) to illustrate typical network issues and their solutions.

**Paediatric Research in Emergency Departments International Collaborative (PREDICT)**
PREDICT was established in 2004 and includes research institutions, healthcare providers and researchers involved in paediatric emergency care across Australia and New Zealand (3). Its goals are to improve the power of paediatric research activities by combining the efforts of individual institutions, to facilitate and coordinate research activities across sites to create a research infrastructure, and to mentor new investigators to improve research skills and develop research projects (www.predict.com.au). While PREDICT started as a collaboration of mainly tertiary centres, 70% of children in Australia and New Zealand are seen in emergency department (EDs) outside of tertiary paediatric hospitals; we have therefore deliberately included investigators from suburban, regional and rural hospitals. PREDICT is also part of a global collaborative of research networks which currently conducts prospective research across more than 200 EDs in 35 countries who together have over 5 million paediatric presentations per annum (5,6).

**The trajectory of network research**
A key benefit of network research is that it can incorporate the full spectrum of research activity from knowledge generation, knowledge synthesis to knowledge translation. Knowledge generating studies include surveys, retrospective and prospective cohort studies and registries, and prospective interventional trials. Existing knowledge and newly gained knowledge can then be synthesized and made useful for clinicians in systematic reviews and guidelines. Without efforts to translate knowledge, change at the frontline takes a considerable time and has been estimated to average 17 years (7). Thus, if the key vision of research networks is to improve clinical care, as with PREDICT, research activity needs to be focused on knowledge translation. Figure 2 shows this trajectory from knowledge generation studies to knowledge translation for
the PREDICT network. PREDICT has undertaken a number of surveys to understand clinician practice (8), retrospective (9), prospective studies (10) and RCTs (11-13). PREDICT has included health economic analysis in all major projects (14,15) and published study protocols (16,17) in addition to registration with relevant bodies (such as trial registration or the registration of a systematic review (18). For key research topics we aim to synthesise what is already known in systematic reviews (18,19). For two research themes with common presentations to both tertiary and non-tertiary EDs, bronchiolitis and head injuries, we have developed bi-national guidelines (20). Recently major efforts have focused on implementation science with expansion of our understanding on how to change practice, through a cluster randomised trial on changing bronchiolitis practice (16), and on how to achieve sustainable practice change.

**Consumer involvement and research prioritisation**

Networks will generally have at least two consumers of their research: the children and families who present to the clinical setting with a certain illness or injury; and the clinicians applying the newfound knowledge in their daily practice. Ideally both groups should be involved in the research from the design phase to the implementation of the findings (Figure 2). For children and families this may occur through disease specific or network specific consumer advocacy groups. For clinicians this may occur through a formal prioritisation process or more informally through the involvement in the steering committee of clinicians from different settings, in particular from sites outside tertiary centres.

To ensure the relevance of research questions and findings and the buy-in of site clinicians assisting with the conduct of the studies, a prioritisation exercise should be undertaken among the network members and the consumers of the research. In PREDICT we conducted such prioritisation using a two stage Delphi survey across network members and site clinicians which led to a prioritised list of topics (21). The availability of these data has proven invaluable in grant
applications - it helps answer the key question of why a certain topic is important. PREDICT members have also conducted disease specific research prioritisation, including both specialist and patients as target audience (22).

Network structure
The basic elements of the network and their relationship need to be defined:

i) Who are the members?
ii) How do they become members?
iii) How is the research steering group formed?
iv) What is the relationship between members and steering group?

Clinicians and researchers with an interest in paediatric emergency medicine research in Australia and New Zealand are eligible for PREDICT membership (Figure 3). Members vote for the executive group, the primary governing body of PREDICT, via an online ballot every second year. Governance within individual research projects is via a steering group which is linked with the executive through at least one executive member.

An alternative model for a structure of a network is a hub and spoke model. This approach has been utilized by other international paediatric networks, e.g. the Pediatric Emergency Care Applied Research Network (PECARN) in the US. It uses a central executive from research hubs based around major research active institutions (tertiary sites). These hubs support spokes of local affiliated sites in the case of PECARN. Within PECARN further infrastructure includes a separate data coordinating centre managing all studies, and standing committees for protocol review and development, quality assurance and safety, feasibility and budget and grant writing and publications (Figure 4).

Network processes
Networks should establish processes for:
i) admission to membership;
ii) elections to the executive;
iii) executive functioning;
iv) project approval;
    a. defining what constitutes a network project (e.g. types of projects, number of sites needed);
    b. delineating the endorsement process by the network executive; and
v) flow from ethics to project publication following network approval.

In PREDICT, projects must be multicentre, defined as ‘involving at least two PREDICT centres’ working collaboratively, for consideration by the executive as a PREDICT project (see Figure 5). The executive reviews all project applications using a “New project template”. Once executive approval is obtained, a study steering group is formed to facilitate collaborative development of the study protocol and ongoing management of the study. One executive member participates as part of the steering group which ensures regular updates to the executive group. In the past the cost of teleconferencing was high; this can now be conducted at minimal or no cost to facilitate communication across institutions. However, regular face to face meetings are invaluable to grow research relationships and address barriers and problems.

Data management
Strategies for data management are a key topic for research networks. For different projects network research leads may be located at different institutions with variable data and biostatistical support, who in turn may prefer different data management programs. Ideally, a network would use a single system for data management to simplify staff and researcher training and create institutional memory. In PREDICT we have found REDcap (23), to be a versatile and easy to use data management tool and data interface and is used for most of our studies. Ideally,
all studies would be housed at a single data centre. In the US PECARN network a federally funded data centre manages all network studies.

**Funding**

The key elements for successful funding applications are a well-developed research question and project proposal; pilot data demonstrating a deep understanding of the issues and the feasibility of the project; and a track record of the applicants for the methodology and the topic. While it is possible to achieve funding success through a brilliant funding application without much background work, generally funding success will require the patient building of a track record through the conduct of the necessary baseline studies – surveys and retrospective chart reviews to understand clinician practice and variation, prospectively collected data to achieve a deep understanding of their limitations as well as a systematic review of the literature. Local grant funding (e.g. hospital charitable foundations, state government funded competitive grants, philanthropic organisations) is particularly valuable to undertake the necessary pilot work and to build local research capacity building. This can then be leveraged to apply for competitive national grants (in Australia the National Health and Medical Research Council [NHMRC] and the Medical Research Futures Fund [MRFF]).

**Capacity building**

Capacity building in a network will depend on the baseline capacity of the constituent parts of the network. Collaborators may already have baseline research training and research higher degrees and sites may already have access to resources such as a trial centre, biostatistics, ethics and health economic support as well as local research education courses and materials. It is useful to undertake at least an informal baseline survey across possible network sites to understand existing expertise and resources. Local professional bodies, colleges, research institutes, universities and other organisations often have freely available resources that
researchers may not be aware of (e.g. RACP and APRN research education materials (https://www.aprn.org.au/resources/how-to-conduct-research/)).

In PREDICT, we have aimed to firstly improve research staff capacity (investigators, trainees and research nurses/coordinators) through annual network-wide standardised research education courses and the development of a 10 part published research education series (24). Secondly we aimed to develop investigators with multicentre capable research higher degrees, in general supervised by network researchers from more than one site. These young researchers represent the next generation of network collaborators. Successful supervision requires academic protected time at affiliated universities and research institutes which in turn often requires sustained effort and lobbying to establish. Successful academic supervision at a distance across sites allows dissemination of research expertise beyond the traditional research strong centres. Other strategies to grow research capacity are the deliberate inclusion of early career researchers in research projects and in the network executive itself. In PREDICT a research higher degree student joins the network executive on a 1-2 year time limited basis.

**Authorship**

One of the important issues to be addressed early on in any multicentre effort is how authorship of joint papers is handled. There are a number of options available for how the by-line reflects co-investigators:

i) listing of all investigators;

ii) listing of the network or working group as the author;

iii) listing of some authors plus the name of the network.

Option i) requires that all authors indeed fulfils authorship criteria; the number of authors that can be listed may also be limited by the target journal. Higher level journals may allow a higher number of authors. Option ii), the listing of a working group was for example used by the Crash 2 investigators (25) with investigators listed in the paper under collaborators and with the collaborator names also PubMed listed. Option iii) can be combined with the PubMed listing of
collaborators. In the PREDICT network we generally aim to include all co-investigators as authors in the by-line of the paper (option i) (10,11). This option has the added advantage of building capacity within team members, as it requires authors to be involved in all aspects of the study to obtain authorship criteria. In a global study across 79 sites on H1N1 we used option iii) with all 101 co-investigators PubMed listed (9).

Problems with multicentre research
Beyond addressing administrative processes and authorship, multicentre research in general, and network research in particular, requires much effort – sustained leadership, interpersonal skills and communication – to maintain enthusiasm and commitment of many investigators and sites over many years. Interests change and site investigators take on new and different roles in studies which may run for years. While there are successful efforts to unify ethics application processes in many institutions through multi-site ethics approvals, overall the complexity and effort required to achieve ethics approvals and multi-institutional legal agreements for even simple chart reviews has dramatically increased. In many jurisdictions it can be difficult to cross the threshold for launching investigator initiated multicentre studies without professional trials staff support from an academic centre, a research institute or staff funded by the network itself. Trials need experienced trial managers and coordinators who acquire understanding how the network works as well as site-specific issues. Considerable effort and resources need to be spent on protocol compliance, regular site visits and processes to ensure verification of source data. Data entry, data queries and data cleaning can be complex and time consuming.

Community and Communication
While it will be advantageous to have some resources to build and maintain a web presence for a network, initially, emailed minutes of network meetings and study specific newsletters will suffice. In PREDICT (www.predict.com.au) we have established a website with information about the network, the network executive, membership, project information and publications. We
also have a password protected members only section containing core study materials such as updated protocols.

We email a monthly network newsletter to all members highlighting studies, recent network events and changes, usually feature a network site or member as well as any new publications, presentations or grants.

While internal communication is critical, the network should aim to reach the wider community of likely consumers of the research results. This may be via relevant subspecialties or societies and their newsletters or existing scientific or educational meetings. PREDICT has established standing links with the Australasian College for Emergency Medicine and Advanced Paediatric Life Support (APLS) Australia where the network routinely present at dedicated sessions of the Annual Scientific meeting and the Paediatric Acute Care conference respectively. PREDICT has also established a link with Don’t Forget the Bubbles, a Free Open Access website and blog. An example of Don’t Forget the Bubbles’ ability to condense complex scientific information into a social media friendly format is shown in Figure 6. These collaborations and relationships have reduced the time from new knowledge generation, e.g. the publication of a randomised controlled trial on paediatric status epilepticus (11), to incorporation of that knowledge into national guidelines and algorithms for APLS Australia and APLS New Zealand to be reduced to less than a year.

Conclusion

Paediatric network research, through formalised ongoing multicentre collaboration, can play a role in achieving definitive, impactful and generalizable research results. It allows the pooling of expertise across sites, the creation of a combined track record and the building of research capacity. The key elements for successful network research are not difficult to establish.
REFERENCES


Figure 1
What makes a network operate successfully? Australian Clinical Trials Association (ACTA).

Used with permission of ACTA.
Figure 2: The trajectory of network projects in PREDICT

Used with permission of Prof Franz Babl, PREDICT.
Figure 3: PREDICT study approval process

- Idea for new research project? What to do....
- Complete the PREDICT New Project Template (2 pages) [http://www.predict.org.au/research-information/research-resources/]
- Request Review by PREDICT EXECUTIVE
  Email the template to the PREDICT Network Co-ordinator who will schedule review at the next appropriate PREDICT Executive meeting (see dates below). Make contact at least 4 weeks prior to the meeting of review and longer for surveys! Also attach any other relevant documents.
- PREDICT Executive reviews the project
  The Executive will give feedback and / or ask for further information
- PREDICT Executive communicates outcome via letter
  Outcomes = Accepted, Further Review Required, Rejected
  Time Frame approximately 2-4 months
- PREDICT Executive member nominated as contact
  If the project is accepted, a PREDICT Executive member will be nominated to be part of the steering group or be sent minutes and provided with regular progress updates.

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Figure 4: 
PREDICT network structure

PERN Pediatric Emergency Research Networks, PEMS Paediatric Emergency Research Networks, NICS National Institute of Clinical Studies, ACTA Australian Clinical Trials Alliance, ACEM Australasian College of Emergency Medicine, GTC.
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Figure 5: PECARN network structure

PECARN Pediatric Emergency Care Applied Research Network, PI principal investigator, HRSA Health Resources and Services Administration, MCHB Maternal and Child Health Bureau, EMSC Emergency Medical Services for Children
Used with permission of Prof Peter Dayan, PECARN network.
Figure 6: Don’t Forget the Bubbles Pictogram to summarize research findings (created by Drs Tessa Davis & Damian Roland)
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