Providing Australian children and adolescents with equitable access to new and emerging therapies through clinical trials: a call to action

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doi: 10.5694/mja2.52191

Opportunities for children to benefit from novel therapies have increased substantially over the past decade. Change is needed to maximise these opportunities, particularly in the paediatric trial environment. Investment and a coordinated national approach are needed to prevent Australian children falling behind their international peers. There is international recognition that collaborative approaches and strategic investment in paediatric clinical trials reap benefits in terms of access to clinical trials and new therapies. This article exemplifies a multi-state collaboration and presents a united call to action to prioritise paediatric clinical trials, by strategically investing in effective governance and infrastructure, and a shift in culture that embeds clinical trials in the core business of paediatric health care and academic institutions.

Recently, numerous life-changing and life-saving therapies have emerged, with many more in the drug development pipeline (Box 1).[1-4] Phenotypic drug discovery has been revolutionised by advanced methods for pre-clinical screening: disease models using induced pluripotent stem cell technologies, organoids, gene-editing tools and imaging assay technologies.[5] Between 2010 and 2020, 440 innovative drugs were approved for marketing by the United States Food and Drug Administration,[2] including

1 Examples of novel and transformative therapies approved for use in children with rare diseases over the past five years

Condition	Medication	Medication type
Achondroplasia	Vosoritide	Modified recombinant human CNP analogue
Alagille syndrome	Maralixibat	Ileal bile acid transporter inhibitor
B-cell precursor ALL (relapsed or refractory)	Tisagenlecleucel	CD19-directed CAR T-cell therapy
Cyclin-dependent kinase-like 5 deficiency disorder	Ganaxolone	Synthetic modulator of the $GABA_A$ receptor complex
Cystic fibrosis	Ivacaftor	CFTR protein modulator (potentiator)
	Elexacaftor–tezacaftor–ivacaftor	CFTR protein modulator (combination of two correctors and a potentiator)
Duchenne muscular dystrophy	Delandistrogene moxeparvovec-rokl	AAV based gene transfer therapy
Haemophilia A	Emicizumab	Bi-specific mAb against factor IXa and factor X
Heterozygous familial hypercholesterolemia	Inclisiran	siRNA which degrades PCSK9 mRNA
Inherited RPE65 retinopathy	Voretigene neparvovec-rzyl	AAV-based RPE65 gene transfer therapy
Long chain fatty acid oxidation disorders	Triheptanoin	Synthetic medium chain triglyceride
Metachromatic leukodystrophy	Atidarsagene autotemcel	Lentiviral vector encoding the human ARSA gene
Molybdenum cofactor deficiency type A	Fosdenopterin	Synthetic cyclic pyranopterin monophosphate
Neurofibromatosis 1 with symptomatic, inoperable plexiform neurofibroma	Selumetinib	MEK1/MEK2 inhibitor
Porphyria	Givosiran	siRNA against aminolevulinate synthase 1 mRNA
Primary hyperoxaluria type 1	Lumasiran	siRNA against HAOX1
Progressive familial intrahepatic cholestasis	Odevixibat	Selective ileal bile acid transporter inhibitor
Pyruvate kinase deficiency	Mitapivat	Pyruvate kinase activator
Spinal muscular atrophy	Nusinersen	SMN2 splicing modifier (intrathecal)
	Risdiplam	SMN2 splicing modifier (oral)
	Onasemnogene abeparvovec	AAV-based SMN gene therapy
X-linked hypophosphatemia	Burosumab	mAb against FGF-23

AAV = adeno-associated virus; ALL = acute lymphoblastic leukaemia; ARSA = arylsulfatase A; CAR = chimeric antigen receptor; CD19 = cluster of differentiation 19; CFTR = cystic fibrosis transmembrane conductance regulator; CNP = C-type natriuretic peptide; FGF = fibroblast growth factor; GABA = γ-aminobutyric acid; HAOX1 = hydroxyacid oxidase 1; mAB = monoclonal antibody; MEK = mitogen-activated protein kinase; mRNA = messenger ribonucleic acid; PCSK9 = proprotein convertase subtilisin/kexin type 9; RPE65 = retinal pigment epithelium-specific 65 kDa protein; siRNA = small interfering ribonucleic acid; SMN = survival motor neuron. ◆

an increasing number of gene and other advanced therapeutics.[1] New and truly transformative paediatric therapies include highly effective modulator therapy in cystic fibrosis,[6] gene therapies for spinal muscular atrophy,[7] and chimeric antigen receptor T-cell therapy for cancer.[8]

Access to novel therapies through clinical research is increasingly seen as optimal care for children affected by devastating and previously untreatable disease. Many of these diseases are rare, affecting fewer than 5 in 10 000 people.[9] About two million Australians live with a rare disease, most first experienced in childhood. One-third of children affected by a rare disease will not live to see their fifth birthday.[10,11] Children managed at hospitals that support advanced therapeutic trials — including gene therapies — have been able to access potentially transformative therapies years before regulatory approval and subsequent reimbursement make them broadly available. For progressive or life-limiting conditions, this can mean major direct benefit.

Ideally, clinical research should be embedded into clinical practice, as has long been in the case for paediatric oncology. Oncology provides an exemplar for disciplines that can provide effective overarching treatment paradigms that incorporate numerous subsets of very targeted treatment pathways.[12,13] Additionally, while most advanced therapies are currently sponsored by overseas-based pharmaceutical companies, experience in trials provides opportunities to develop research pipelines that enable the development, evaluation and translation of novel Australian therapies.

Nevertheless, considerable challenges to delivering high quality clinical trials in children and adolescents remain (Box 2).[14-17] Internationally, these challenges have led to the development of paediatric clinical trials networks.[18] A Bill is currently before the US House of Representatives, promoting the establishment and maintenance of a paediatric trials network, supported by substantial grant funding from 2024 to 2029.[19]

2 Challenges in delivering high quality clinical trials in children

- Hesitation in involving children in industry-led clinical trials
- Ethical complexity in gaining consent through parent(s) or guardian, and assent from child
- Complexity in organising study visits and procedures affecting multiple family members
- For most paediatric trials, limited number of eligible subjects per site, along with barriers to recruitment and retention
- Mismatch between costs that study sites recover from trials, and the time and resources required:
  - Relatively small per-study costs for low recruiting trials (the majority)
  - Increased time required for multiple study processes including: consent process, involving child and family; patience and support required to minimise distress and burdens to children of interventions and investigations (including play therapy and distraction, or procedural sedation, for minor procedures); and the medical, social and infrastructure needs in catering for children ranging from infants to late adolescence
- The fluctuation in trial activities, in the absence of network collaboration, leading to loss of skills and resources in lulls, needing to be redeveloped with new activities

In Australia, the challenges in delivering clinical trials in children is further compounded by distance, with less concentrated populations and large distances between capitals, and our position outside of the major global regulators, particularly the US Food and Drug Administration and the European Medicines Agency.

A call to action

It is the responsibility of tertiary and quaternary paediatric centres to provide equitable and streamlined access to early phase and emerging treatments for every Australian child affected by disease or disability, regardless of rarity of disease, socio-economic status, or geographical location. This aligns with the articulated objective of Australia's National Strategic Action Plan for Rare Diseases, which aims to enable all Australians to have equitable access to the best available health technology.[20]

This shift away from the traditional separations between clinical care and clinical research into a seamless clinical interface requires reconsideration of the funding models that have previously been utilised for clinical trials. Just as excellent clinical care involves investment beyond a physical bed and staff at the bedside — with resourcing for education, professional development, and capacity building — these same pillars of sustainability are essential in the clinical trials sphere.[21] A thriving and expanding advanced therapeutics service cannot be established by haphazard revenue generated by pharmaceutical company-funded clinical trials alone.

Increased support can ensure: recruitment and retention of expert personnel in both paediatrics and clinical trials; high quality local infrastructure to support novel therapies along with workflow processes, quality assurance and control mechanisms; and adequate staffing and resources to meet site performance and data standards, as recommended prerequisites for high quality trials. This cannot occur without the same support that international networks have received to grow collaborative networks, site infrastructure and resources.[22]

Governance and collaboration

We recommend the development of a national collaborative community of paediatric trials centres, enabling clinicians and researchers to exchange excellence and experience in the strategy and implementation of clinical trials and advanced therapeutics. This will provide an efficient, national approach to paediatric clinical trials and advanced therapeutic delivery that potentiates the health, economic and social impacts for all paediatric hospitals in Australia.

Given the rarity of many paediatric diseases and the complexity of emerging therapies, a national approach for complex trials in paediatrics is imperative. This compliments the priorities identified in the National Strategic Action Plan for Rare Diseases,[20] which promotes the importance of a national rare disease workforce strategy as well as the National Clinical

Trials Governance Framework[21] and is in line with other nationally coordinated approaches such as the National Health Genomics Policy Framework.[23] We have established a collaboration across the Sydney Children's Hospitals Network, the Royal Children's Hospital Melbourne and Murdoch Children's Research Institute campus, Monash Children's Hospital, Queensland Children's Hospital, and university partners, with a view to eventually creating a national network of paediatric clinical trial centres.

The rate at which advanced and targeted therapeutics are moving through scientific pipelines to trials and clinical care requires rapid enhancements in knowledge and skillset. Mapping of expertise allows streamlined access for both industry and referring clinicians. The lessons learnt from a gene replacement therapy in neuromuscular disease will inform implementation of future gene therapy trials. With a collaborative approach, the complications experienced from chimeric antigen receptor T-cell therapy at one centre can provide benefit in managing complications at another. Our collaboration of Australian paediatric trials centres remains informal but has been effective in sharing ideas for best practice, written resources and educational material; however, greater resources and core funding are required to achieve its full potential. The European Union has recognised the importance of such networks and funded a paediatric trials network with a substantial Horizon 2020 grant.[24]

Infrastructure

We recommend the delivery of precision medicine that is transformative and disease specific, by combining and developing world class paradigms and investment in infrastructure.

Paediatric clinical trials, particularly complex and early phase trials, are resource intensive and require highly skilled personnel. The ebb and flow of trial activity with rare diseases leads to difficulty in efficient resource allocation and retention of experienced staff to cater for the complexities in consent, complex trial protocols, and engagement,[15] and an inability to maintain stable infrastructure for complex therapeutic interventions.[17]

Historically, clinical trials have been funded by specific investigator grants or industry. What follows is a stop–start, silo approach to infrastructure. Our recommendation is that all paediatric clinical trials are considered core business and an essential part of the patient care journey, and that costings of overarching infrastructure, at levels that maintain high quality staff recruitment and retention, with ongoing professional development and quality improvement, are quantified and allocated through sustainable and prospective funding. For most disciplines, this involves increased support for multidisciplinary clinical teams who are delivering the clinical care required in complex trials. This is in addition to resourcing the fit-for-purpose clinical trial infrastructure that streamlines clinical trial set-up and conduct. This deliberate and proactive approach to resource mapping for innovative therapies in the clinical trials space contributes to a more seamless approach as these therapies transition from investigational products to approved therapies.

In our experience, funding to support trials is rarely a priority for hospital core funding, with each centre relying heavily on philanthropy, program-specific state government funding, or other sources of funding. These funding sources are intermittent and not guaranteed. This problem is not unique to Australia. Globally, all paediatric trials centres rely on substantial philanthropic, direct or indirect government funding, and support from core hospital funds. While further collaboration between and within centres aims to maximise efficiency, an ongoing secure source of core funding is ultimately required to enable efficient use of infrastructure resources. This could be provided by state or federal government directly (for example, by utilising Commonwealth block funding that currently exists to support national standards across innovation in health care in the form of teaching, training, and research funding) or by acknowledging that clinical trials are core activity and accepting that the costs for running these trials must be incorporated into hospitals' operational budgets.

Culture

We recommend a considered shift in the conversation surrounding paediatric clinical trials, to emphasise the tangible and immediate benefits to patients by allowing access to novel therapies, and by Australia remaining competitive in the international arena.

Although not universal, there has long been an impulse to protect children from the experimental nature of clinical trials. This may be driven by tragedies reported throughout the 20th century impacting young children: elixir sulfanilamide in 1937;[25] sulfisoxazole in 1956;[26] chloramphenicol in 1960;[27] synthetic vitamin K in 1961;[28] thalidomide in 1962;[29] and excipients benzyl alcohol,[30] propylene glycol[31] and polysorbate 80[32] in the early 1980s. Crucially, however, these occurred not as part of a regulated drug development program, but rather before, or outside of, drug regulatory oversight.[33] While robust regulatory oversight of therapeutic drugs was introduced around the world in the 1960s following the thalidomide tragedy,[13] children and adolescents were excluded from the drug development process, with the coining of the term "therapeutic orphans".[34] It was not until the late 1990s that paediatric drug development became part of standard care.[33,35]

This followed the necessary development of an ethical framework for involving children in research from the 1970s;[36] the introduction of pharmacometric techniques to allow increasingly accurate paediatric dose prediction, as well as confirmation using limited blood samples;[37] advances in trial design to minimise risk and burden to children;[38] and crucially, the scientific revolution of paediatric clinical pharmacology.[33] These developments have mapped out an understanding of maturational processes in infants and children that impact drug handling. While any given ethically approved trial must be judged on its merit, the current landscape bears no relationship to the environment

in the 20th century that saw the many therapeutic tragedies.[28,35]

Emphasis on embedding clinical trials into clinical practice has informed the National Clinical Trials Governance Framework, which recommends integration of research into routine health care and the fostering of a research culture in health organisations.[21] This requires forward planning and a realignment that refocuses the needs of the patient and their family at the centre of clinical trials planning. A similar call is made in the National Health Genomics Policy Framework, in which there is a priority to develop a model of person- and family-centred care.[23] Equitable and efficient access to emerging and novel therapies is an essential component of patient-centred care and aids in maintaining the family's trust in the quality and competitiveness of the Australian health care system while facilitating cutting edge training for the next generation of clinicians.

Cultural changes are tangibly linked to shifts in governance priorities. Culture is also informed by experiences and dialogue, and we believe that ongoing and formalised partnerships with patient advocacy groups, such as Rare Voices Australia (https://rarevoices.org.au) and the Childhood Dementia Initiative (https://www.childhooddementia.org), to promote the importance and urgency of complex clinical trials, remains an essential aspect of clinical trial planning. Culture change can also be triggered by changes in legislation, such as the 2002 and 2003 changes to US law, which led to widespread increase in paediatric clinical trials.[33] In Australia, federal agencies such as the Therapeutic Goods Administration and the Pharmaceutical Benefits Advisory Committee play a key role in facilitating Australia's access to novel therapeutics for both trials and the rapid translation of novel therapeutics into practice.

Conclusion

In conclusion, without a change in approach to paediatric clinical trial delivery in Australia, paediatric clinical trials centres are at risk of failing to deliver equitable efficient access to novel treatment options, leaving Australia's paediatric health care system trailing behind other centres internationally. We call for national investment in this space.

Open access: Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

Competing interests: The Murdoch Children's Research Institute and Sydney Children's Hospitals Network have received funding from Roche to aid in building capacity for gene therapy in Australia. All authors' hospitals and/or institutions are active sites for pharmaceutical company-sponsored clinical trials and receive enrolment-based reimbursement on a trial-by-trial basis, but do not receive direct funding for clinical trials capacity or capability building unless stated above.

Provenance: Not commissioned; externally peer reviewed. ■

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