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Original Article

Paediatric cardiovascular clinical trials: an analysis of ClinicalTrials.gov and the Food and Drug Administration Pediatric Drug Labeling Database*

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Abstract Recent regulatory initiatives in the United States of America and Europe have transformed the paediatric clinical trials landscape by significantly increasing capital investment and paediatric trial volume. The purpose of this manuscript was to review the impact of these initiatives on the paediatric cardiovascular trials landscape when compared with other paediatric sub-specialties. We also evaluate factors that may have contributed to the success or failure of recent major paediatric cardiovascular trials so as to inform the optimal design and conduct of future trials in the field.

Keywords: Pediatric cardiovascular trials; pediatric exclusivity; heart failure

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CLINICAL TRIALS REPRESENT THE GOLD STANDARD for developing an evidence base in medicine; however, children have historically been under-represented in clinical trials. Consequently, most drugs and devices are used "off-label" in children with their safety, efficacy, and dosing extrapolated from data from adult clinical trials.[1–3] This practice is sub-optimal as children have unique developmental differences that can affect drug metabolism and response, as well as device safety.

Recognising the importance of conducting clinical trials in children, regulatory agencies in Europe and the United States of America have enacted several recent initiatives aimed at stimulating paediatric drug/device development and research.[4–11] Collectively, these initiatives have transformed the paediatric clinical trials landscape with an unprecedented injection of resources and financial capital. With CHD remaining the number one birth defect worldwide, the purpose of this article is to review the impact of these initiatives on the paediatric cardiovascular clinical trials landscape with a focus on ways that we can optimise future trials so as to maximise the return for children with heart disease.

Regulatory initiatives: brief historical overview

Although a comprehensive overview of paediatric drug/device development regulation is beyond the scope of this manuscript, a brief review of recent legislative initiatives will be helpful to better understand the current clinical trials landscape. Figure 1 summarises initiatives from the past 2 decades designed to encourage paediatric trials in the United States of America and Europe. Landmark initiatives include the 1998 "Pediatric Exclusivity" provision, the 2002 Best Pharmaceuticals for Children's Act, the 2003 Pediatric Research Equity Act, and the 2007 Paediatric Regulation. Collectively, they have established regulatory mandates, incentives, and oversight mechanisms designed to advance the paediatric evidence base. These efforts have been tremendously successful. In the United States of America, >480 paediatric trials enrolling >175,000 study patients have been conducted over the past decade with similar recent successes documented in Europe.[12–14] From a financial

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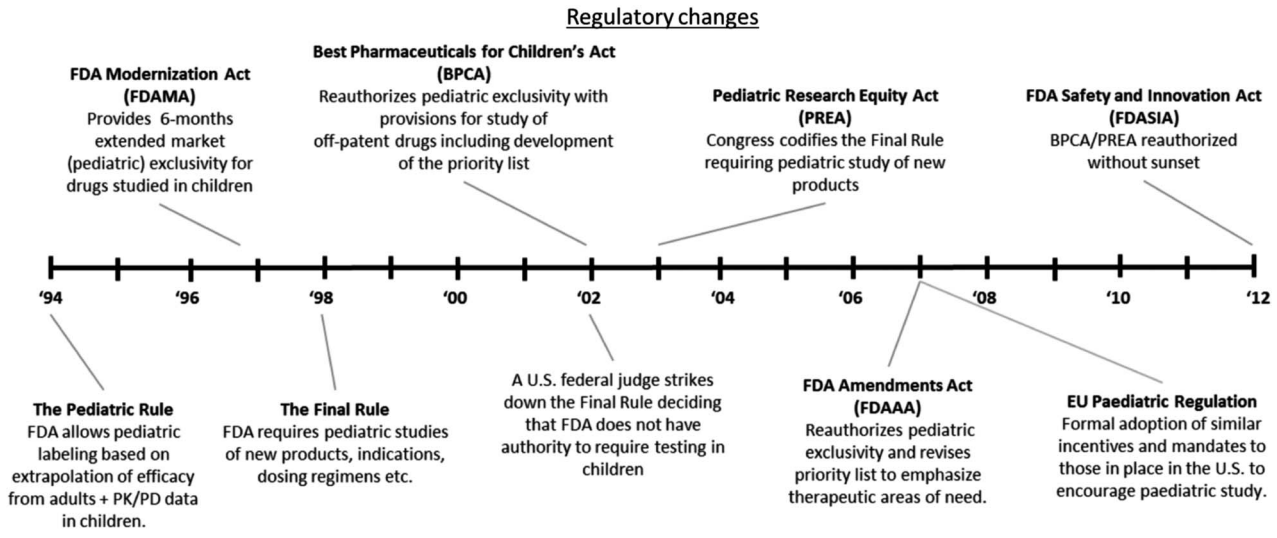

Figure 1.
Time line depicting recent regulatory initiatives to encourage paediatric drug study in the United States and Europe.

standpoint, these trials have injected an enormous amount of capital into paediatric research. Li et al estimated costs for a subset of trials conducted under the auspices of the Pediatric Exclusivity provision between 2002 and 2004.[15] The median cost to the sponsor to conduct the required paediatric drug studies was $12.34 million (with a range from $5.13 to 43.80 million). Despite this upfront expense, the economic return from patent extension – the principal financial incentive for study sponsors – is typically well worth the investment with an estimated median net economic benefit of $134 million (with a range from – $8.9 to +$507 million) for the nine products studied.[15] Not surprisingly, after decades of inaction, the pharmaceutical industry has now enthusiastically embraced paediatric drug study with an almost sixfold increase in the average annual number of trials conducted in children to evaluate drug safety.[16–18]

Measuring our successes and failures

With such significant changes in the paediatric clinical trials landscape, we sought to evaluate progress within the field of paediatric cardiology. How does our trial infrastructure and volume compare with our adult colleagues or with other paediatric sub-specialties? What types of trials are we conducting? What are the important drivers of trial design and conduct, and, most importantly, are we optimally advancing the evidence base in paediatric cardiology? To address these questions, we will focus on the US clinical trials landscape as the US Congress has established several mechanisms to evaluate progress. First, was the creation of a clinical trials registry: ClinicalTrials.gov is a searchable database that was mandated by Congress under the 1997 Food and Drug Administration Modernization Act and was made publically available in February of 2000.[19,20] ClinicalTrials.gov includes information on trial design, study cohort, outcome measures, trial timeline, and, more recently, trial results. In 2005, the International Committee of Medical Journal Editors began requiring trial registration as a condition for publication, and in 2007 the US Congress began requiring registration of all clinical trials conducted in the United States of America.[9,21] These actions have greatly increased trial registration; there are now >180,000 registered trials on ClinicalTrials.gov (Fig 2). A second mechanism to evaluate progress in paediatric cardiovascular clinical trials is the US Food and Drug Administration's "New Pediatric Labeling Information Database".[22] This public database was mandated by Congress in 2007, and it includes a listing of all trials conducted under the auspices of recent legislative efforts, as well as the reviews of these trials and the associated labelling changes. Together, ClinicalTrials.gov and the Pediatric Labeling Information Database include a wealth of information that can provide important insights into paediatric cardiovascular trials and their outcomes.

ClinicalTrials.gov

Numerous publications have used the ClinicalTrials.gov database to evaluate the clinical trials landscape. Califf et al evaluated adult cardiovascular trials in comparison with oncology and mental health trials.[23] Over a 3-year span from October, 2007 to September, 2010, 3437 adult cardiovascular trials were registered. Significantly, US National Institutes of Health-sponsored trials performed substantially

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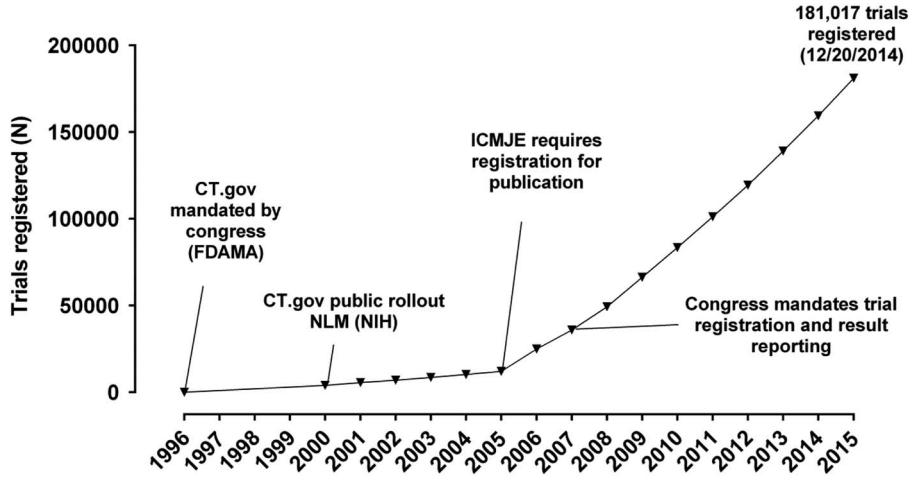

Figure 2.
Clinical trials registered on ClinicalTrials.gov and associated milestones. FDAMA = The Food and Drug Administration Modernization Act; ICMJE = International Committee of Medical Journal Editors; NIH = National Institutes of Health; NLM = National Library of Medicine.

better across all trial quality metrics when compared with industry or other sponsor sources. In a follow-up to this assessment, Pasquali et al evaluated the paediatric clinical trials landscape.[16] In this analysis, which spanned from July, 2005 until September, 2010, 5035 trials restricted to children and adolescents (aged <18 years) were registered. Paediatric trials were dominated by infectious disease trials, which comprised ~23% of all registered trials (Fig 3). Other paediatric specialties with a relatively larger volume included the following: mental health/psychiatry (~13%), neurology/anaesthesia/pain (~11%), pulmonary (~10%), endocrine/metabolic (~10%), and gastrointestinal/nutrition (~7.5%). In comparison, paediatric cardiology trials represented a relatively small subset of the overall trial landscape (~4.5%); the only sub-specialties with significantly fewer trials were haematology, dermatology, and nephrology.

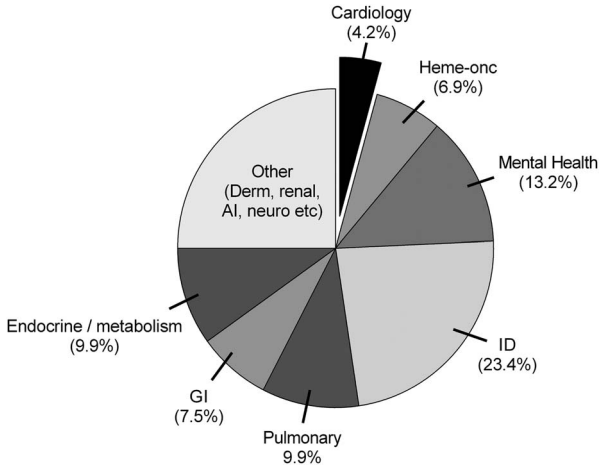

Figure 3.
Paediatric trials registered on ClinicalTrials.gov (September, 2005–October, 2010). AI = allergy/immunology; GI = gastroenterology; ID = infectious diseases.

Paediatric cardiovascular trials registered on ClinicalTrials.gov

Using the same database as Pasquali and Califf, we evaluated the subset of paediatric cardiovascular trials.[17] Overall, 213 paediatric cardiovascular trials (aged <18 years) were registered between September, 2005 and October, 2010. After manual review, we identified an additional 71 trials that also included adult patients (age ⩾ 18 years) but that we judged to have a primary paediatric cardiovascular focus, examples include the US Medtronic Melody valve trial and the Pediatric Heart Network trial of losartan versus atenolol for Marfan syndrome. Paediatric cardiovascular trials had a median (interquartile range) trial enrolment of 65 (36, 186) patients and only four registered trials had a projected enrolment of >1000 study patients. The median trial duration was 2.2 (interquartile range: 1.4, 3.3) years. Overall, 68% of trials used a drug/biologic intervention, 12% were device interventions, and 10% were behavioural interventions.

In terms of specific trial focus, collectively, hypertension, dyslipidaemia, obesity, and pulmonary hypertension trials comprised >40% of all trials (Fig 4). These trial subsets also appeared to dominate funding priorities; hypertension and obesity trials represented 61% of all National Institutes of Health-funded trials, whereas hypertension, pulmonary hypertension, and dyslipidaemia trials accounted for

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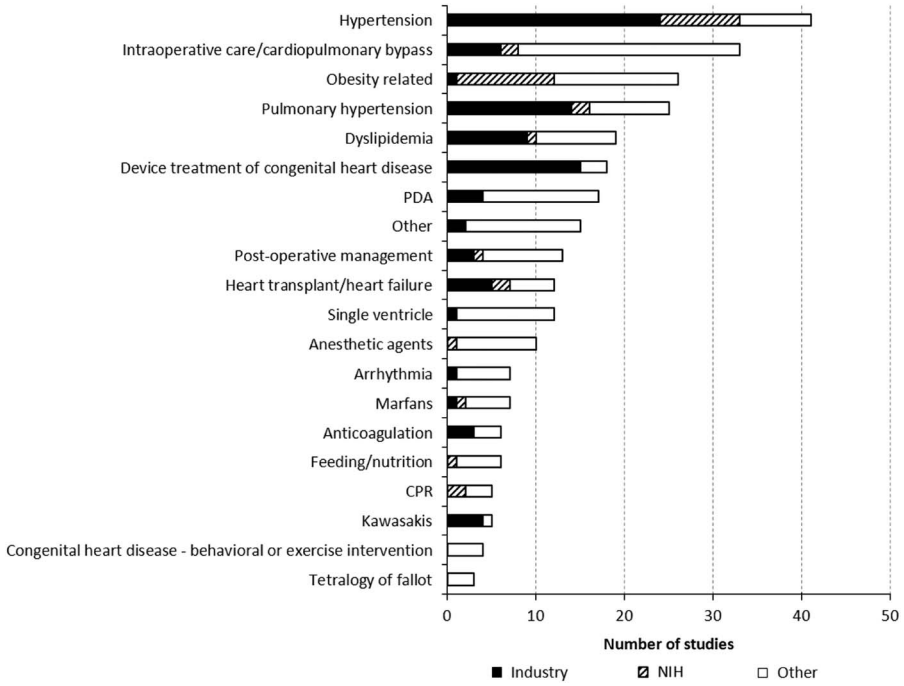

Figure 4.
Paediatric cardiovascular trial focus and funding sources. NIH = national institutes of health; PDA = patent ductus arteriosus; CPR = cardiopulmonary resuscitation.

49% of all industry-funded trials. Device trials accounted for an additional 15% of industry-sponsored trials. Overall, 44% of all registered paediatric cardiovascular trials identified had industry or National Institutes of Health sponsorship. Over a 3-year span (September, 2007–October, 2010), 24 paediatric cardiovascular trials were sponsored by the US National Institutes of Health and 69 were sponsored by the industry. In contrast, over the same time period, 295 adult cardiovascular trials and 149 paediatric mental health trials were sponsored by the National Institutes of Health, and 2365 adult cardiovascular trials and 708 paediatric infectious disease trials were sponsored by the industry. Importantly, paediatric cardiovascular trials generally did well in terms of quality metrics with 75% reporting randomisation, 51% using blinding, and 54% reporting the use of a data monitoring committee. Similar to adult trials, the most important factor associated with the conduct of a high-quality trial, with a randomised and blinded design, was sponsorship by the US National Institutes of Health – multivariable odds ratio, 1.9 [95% CI, 1.5–2.4] when compared with industry sponsorship.[17]

Heart failure trials

With the primary focus on paediatric heart failure and heart transplant at the 2015 Daicoff summit, we subsequently used the search terms "heart failure" or "heart transplant" to interrogate ClinicalTrials.gov for all paediatric trials (enrolling patients aged <18 years). These trials were downloaded and manually reviewed to identify trials with a primary paediatric cardiovascular focus. A search from 1 July, 2005 to 1 January, 2015 yielded 212 trials; however, the majority were excluded due to a primary adult focus or because the trials were withdrawn or terminated. We identified only 10 active (n = 6) or completed (n = 4) paediatric heart failure/heart transplant trials in this 10-year period. These trials are summarised in Table 1. The 10 trials were sponsored by the industry (n = 8) or the National Institutes of Health (n = 2); nine represent drug trials including five with a safety end point and five with a pharmacokinetic end point. Only two of the drug trials assessed efficacy end points and both were National Institutes of Health-sponsored trials: the Pediatric Heart Network Infant Single Ventricle trial and a National Institutes of Health-sponsored trial of diltiazem in patients aged between 5 years and 39 years with early signs of hypertrophic cardiomyopathy. Furthermore, one trial, the EXCORÂ® Pediatric Ventricular Assist Device trial, was an industry-sponsored trial with a safety and pseudo-efficacy end point, compared with historical controls. For these 10 trials, trial enrolment ranged from 10 to 230 patients with only two enrolling >100 patients. Of the four completed trials, listed completion dates ranged from January, 2006 to September, 2013.

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Table 1. Paediatric heart failure or heart transplant trials registered on ClinicalTrials.gov 2005–2014.

Trial (CT.gov ID)	Sponsor	n	Intervention	Patient population	Primary outcome	Design	Start–completion date	Trial status/ results
Infant Single Ventricle trial (NCT00113087)	NIH (PHN)	230	Enalapril	Infants (<45 days) with single ventricle	Weight for age z-score	RCT	08/2003–06/2008	Completed, no change in primary outcome
Safety of twice daily carvedilol – extension of previous carvedilol trial (NCT00129363)	Industry	75	Carvedilol	Children (<18 years) with systemic ventricular systolic dysfunction	Safety events	Open label	01/2002–01/2006	Completed, not published
EXCOR® paediatric ventricular assist device (NCT00583661)	Industry	48	Ventricular assist device	Children < 17 years with heart failure requiring circulatory support	Safety and probable benefit	Open label	12/2007–12/2011	Completed, improved survival versus historical controls
Valgancyclovir PK (NCT01165580)	Industry	17	Valgancyclovir	Paediatric heart transplant recipient <4 months	PK	Open label	05/2011–09/2013	Completed, not published
Daclizumab for Prevention of allograft rejection in pediatric heart transplant (NCT00284531)	Industry	10	Daclizumab	Patients (<18 years) undergoing a first cardiac allograft transplant	PK and safety	Open label	10/2003	No status update, not published
Treatment of pre-clinical hypertrophic cardiomyopathy with diltiazem (NCT00319982)	NIH	50	Diltiazem	Patients (5–39 years) with pre-clinical hypertrophic cardiomyopathy	Diastolic function (Echo)	RCT	01/2006–12/2013	Completed, not published
Pharmacokinetics of tacrolimus in paediatric allograft recipients converted from PrografÂ® to AdvagrafÂ® (NCT01294020)	Industry	72	Tacrolimus	Children (5–16 years) s/p solid organ transplant	PK/safety	Open label	05/2011	Enrolling
Pharmacokinetics of children receiving Modigraf following solid organ transplantation (NCT01371331)	Industry	60	Tacrolimus	Children up to 12 years with liver, kidney, or heart transplant	PK	Open label	06/2011	Enrolling
A paediatric, open, follow-up study with modigraf (NCT01371344)	Industry	60	Tacrolimus	Children up to 12 years with liver, kidney, or heart transplant	Safety	Open label	06/2011	Enrolling
Pharmacokinetics & safety of serelaxin in children with acute heart failure (NCT02151383)	Industry	36	Seralexin	Children (<18 years) hospitalised with acute heart failure	PK/Safety	Open label	09/2014	Enrolling

NIH (PHN) = National Institutes of Health (Pediatric Heart Network); PK = pharmacokinetics; RCT = randomised control trial

Despite all the trials being completed for over a year, only two of these trials have published results identified on ClinicalTrials.gov or Pubmed.

The Food and Drug Administration Pediatric Drug Labeling Database

ClinicalTrials.gov provides a meaningful overview of the clinical trials landscape; however, a major limitation is that it is difficult to use this database to assess the impact of trials on the overall evidence base. Although there is no perfect metric for evaluating this outcome, changes to the drug label represent a reasonable surrogate of new evidence. The US Food and Drug Administration Labeling database tracks labelling changes for paediatric drugs.[22] As of 14 November, 2014, the drug database documented 489 studies that have been completed for paediatric agents. Of these, 28 (5.1%) represent cardiovascular agents including 16 anti-hypertensive agents and eight lipid-lowering agents including seven statins. The remaining four drugs are carvedilol, sildenafil, sotalol, and clopidogrel (Table 2). All the eight lipid-lowering agents have been studied for heterozygous familial hypercholesterolaemia in adolescents and all have resulted in a new labelled indication for the drug – that is, have demonstrated efficacy. The anti-hypertensive trials have led to 10 new labelled indications (63% success rate). None of the remaining four drugs have demonstrated efficacy in the

Table 2. Cardiovascular drugs with studies performed for paediatric exclusivity that have resulted in labelling changes.

					New paediatric information on drug label				
Drug name, trade (generic)	Indication studied	Trial "N"	Safety extension phase	Label date	PK	Dose	Safety	Liquid suspension	Efficacy demonstrated
Betapace (sotalol)	Arrhythmia	25	–	10/2001	+	+	+	+	Not evaluated
Vasotec (enalapril)	Hypertension	110	–	02/2001	+	+	+	+	Yes
Monopril (fosinopril)	Hypertension	252	+1 year	05/2003	+	+	+	–	No
Prinivil (lisinopril)	Hypertension	115	–	05/2003	+	+	+	+	Yes (6–16 years)
Zestril (lisinopril)	Hypertension	115	–	07/2003	+	+	+	+	Yes (6–16 years)
Norvasc (amlodipine)	Hypertension	268	–	01/2004	+	+	+	–	No
Lotensin (benazepril)	Hypertension	144	–	03/2004	+	–	+	+	No
Cozaar (losartan)	Hypertension	177	–	03/2004	+	+	+	+	Yes (6–16 years)
Avapro (irbesartan)	Hypertension	*	–	03/2006	–	–	–	–	No
Diovan (valsartan)	Hypertension	351	–	11/2007	+	+	+	+	Yes
Inspira (eplerenone)	Hypertension	304	+1 year	01/2008	+	–	+	–	No
Atacand (candesartan)	Hypertension	333	+1 year	10/2009	+	+	+	+	Yes
Benicar (olmesartan)	Hypertension	302	–	02/2010	+	+	+	+	Yes (>6 years)
Corlopam (fenoldopam)	Hypertension	77	–	04/2004	+	+	+	–	Yes
Nitropress (Na nitroprusside)	Hypertension	266	–	11/2013	+	+	+	–	Yes
Toprol XL (metoprolol)	Hypertension	144	–	11/2013	+	–	+	–	No
Mevacor (lovastatin)	Heterozygous familial hypercholesterolaemia	180	+48 weeks	02/2002	–	+	+	–	Yes (10–17 years)
Lipitor (atorvastatin)	Heterozygous familial hypercholesterolaemia	187	+1 year	10/2002	–	+	+	–	Yes (10–17 years)
Pravachol (pravastatin)	Heterozygous familial hypercholesterolaemia	214	+2 years	10/2002	–	+	+	–	Yes (8–18 years)
Zocor (simvastatin)	Heterozygous familial hypercholesterolaemia	175	+48 weeks	10/2002	–	+	+	–	Yes (10–17 years)
Lescol (fluvastatin)	Heterozygous familial hypercholesterolaemia	114	+2 years	04/2006	–	+	+	–	Yes (10–16 years)
Zetia and vytorin (ezetimibe ± simvastatin)	Heterozygous familial hypercholesterolaemia	248	+33 weeks	06/2008	–	+	+	–	Yes (10–17 years)
Welchol (colesevelam)	Heterozygous familial hypercholesterolaemia	194	+29 weeks	10/2009	–	+	+	+	Yes (10–17 years)
Crestor (rosuvastatin)	Heterozygous familial hypercholesterolaemia	176	+1 year	10/2009	–	+	+	–	Yes (10–17 years)
Revatio (sildenafil)	Pulmonary arterial hypertension	184	+2 years	08/2012	–	–	+	+	No
Plavix (clopidogrel)	Prevention of shunt thrombosis	1006	–	05/2011	–	–	–	–	No
Coreg (carvedilol)	Heart failure	161	+8 months	02/2007	–	–	+	–	No

*Irbesartan trials remain unpublished and details are not readily available

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paediatric trials; three were negative trials, whereas the sotalol trial[24,25] did not evaluate an efficacy end point, instead focussing on drug kinetics.

What can we learn from the negative trials?

- *Hypertension trials:* In an insightful analysis, Benjamin et al found that the successful hypertension trials used large differences in the dose ranges of the drugs studied (20- to 32-fold), with little or no overlap between low, medium, and high doses, whereas failed trials used overlapping dose ranges, which made it more difficult to detect a dose–response effect.[26] Successful trials also provided paediatric formulations and used diastolic blood pressure, which tends to demonstrate less variability than systolic blood pressure, as the primary study end point.
- *Carvedilol:* These studies failed to demonstrate improved outcomes in children with cardiomyopathy with either low- or high-dose carvedilol when compared with placebo.[27] The investigators noted several important factors that may have contributed to the negative trial outcome and they can serve as valuable lessons for future trials: relative to adults, patients – particularly younger patients – with heart failure had a higher than anticipated rate of spontaneous improvement. As a result, the trial was relatively underpowered; the study end point was a composite heart failure outcome with three levels of assessment – improved, no change, worsened. Assessing three levels requires more power and compounded the noted problems with sample size; there were several signals suggesting a mixed response: children with a systemic right ventricle demonstrated a trend towards worsening function with carvedilol, whereas those with a single left ventricle demonstrated a trend towards improvement, and younger children were more likely to improve than older children; and, finally, relative to adults, children demonstrated more rapid drug clearance and consequently trough concentrations of carvedilol were relatively lower. Taken together, the findings from this trial are often viewed as inconclusive in patients with a systemic left ventricle. A show of hands at the Daicoff summit suggested that most heart failure providers still use carvedilol off-label in children with left heart failure.
- *Sildenafil:* These trials have been the source of much debate in the paediatric literature. Initial pharmacokinetics trials were completed, but to our knowledge the data have not been published in the medical literature and are available only through the Food and Drug Administration's clinical pharmacology reviews.[28] The initial efficacy trial did not demonstrate improved exercise tolerance when comparing low-dose sildenafil with placebo in children with pulmonary hypertension.[29] In the long-term extension trial, children randomised to high-dose sildenafil had increased mortality when compared with low-dose sildenafil.[29,30] Similar to carvedilol, there was a mixed signal with worse outcomes in children with idiopathic pulmonary hypertension when compared with those with CHD-associated pulmonary hypertension, and the increased mortality effect seen primarily in older children. The European Medicines Agency interpreted the trial results in the context of historically poor outcomes for children with pulmonary hypertension, noting that children receiving low-dose sildenafil had improved survival when compared with historical controls.[31] They approved low-dose sildenafil for the treatment of paediatric pulmonary hypertension. In contrast, the Food and Drug Administration did not approve any dose of sildenafil and went one step further by placing a safety warning on the drug label.[32]
- *Clopidogrel:* This trial evaluated clopidogrel in addition to standard therapy – aspirin for 87% of trial patients – for the prevention of shunt thrombosis and associated morbidity in neonates and infants with a systemic-to-pulmonary artery shunt.[33] There was no additive benefit with clopidogrel, and therefore there is no paediatric indication for the use of clopidogrel in children; however, the drug label specifically notes that the negative study may reflect that the majority of study patients were receiving concomitant aspirin therapy.

Conclusions

When analysed together, ClinicalTrials.gov and the Food and Drug Administration Labeling Information Database provide important insights into the paediatric clinical trials landscape.

First, it is clear that paediatric cardiovascular trials are relatively under-represented; this is the case when compared with adult cardiovascular trials and also with other paediatric sub-specialties registered on ClinicalTrials.gov. This is also reflected in the Food and Drug Administration paediatric labelling database where only 28/489 listed agents represent cardiovascular agents. In comparison, the labelling database lists studies that have been performed for 31 anti-asthmatic agents, 32 anti-histamines, 16 agents to treat gastro-oesophageal reflux disease, 20 stimulant or non-stimulant attention deficit-hyperactivity disorder agents, and 11 anti-acne agents. The relative lack of paediatric cardiovascular studies is also

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reflected in the relative paucity of both United States National Institutes of Health-funded and industry-funded trials. Of note, National Institutes of Health-funded trials are consistently the highest quality and highest impact trials; however, in a 5-year period there were only 13 National Institutes of Health-funded paediatric cardiovascular trials that did not focus on either obesity or hypertension. Strategies are needed to increase funding and also the overall volume of paediatric cardiovascular trials, particularly larger trials focussed on efficacy end points.

Second, the focus of paediatric cardiovascular trials appears to be driven by the financial incentive structure, which does not always align perfectly with the actual need within the field. This conclusion stems from the fact that the Food and Drug Administration typically requires a minimum of two to three trials in order to satisfy paediatric exclusivity requirements – for example, a pharmacokinetics trial, short-term efficacy trial, and a longer-term safety extension. Therefore, it is reasonable to assume that many of the trials of anti-hypertensive agents registered on ClinicalTrials.gov represent trials being completed for 1 of the 14 different anti-hypertensive agents that have gained patent extension under the exclusivity programme. It is likely that the same logic can be applied to the dyslipidaemia and perhaps also to the pulmonary hypertension trials. It is certainly beneficial that we now have five angiotensin receptor blockers labelled for paediatric hypertension and seven different statins for familial heterozygous hypercholesterolaemia; however, there might have been greater child health benefit if only one or two agents in each drug class were studied for these specific indications and the other agents perhaps could have been evaluated in other important patient populations. As an example, one needs to only consider paediatric heart failure or heart transplantation. These patients typically require an arsenal of medications, yet our evaluation of ClinicalTrials.gov indicates that very few trials over the past 8 years have focussed specifically on these high-risk patient cohorts; one could easily rationalise a trial of an anti-hypertensive agent or lipid-lowering agent in the heart transplant patient population. Moreover, three trials for paediatric exclusivity have been completed to evaluate transplant rejection agents; however, all three have been performed in kidney transplant recipients and none have included heart transplant recipients.

Finally, there are patterns that emerge when evaluating outcomes of our trials. Our experiences with the hypertension trials have demonstrated the value of child-centric dosing strategies, including the use of weight-based dosing and the use of liquid formulations for younger children.[26] Successful trials in our field have focussed on homogeneous patient populations with more restrictive age ranges – for example, all the dyslipidaemia trials (100% success rate) enrolled adolescents with familial heterozygous hypercholesterolaemia. Similarly, the successful hypertension trials have typically performed separate trials in the 1–6 versus 6–17 year age ranges. In contrast, interpretation of the carvedilol and sildenafil trials was significantly hampered by differing effects in the heterogeneous diagnostic cohorts and when comparing younger patients with older patients. The carvedilol trial also demonstrated the value of preliminary pharmacokinetic data to optimise trial drug dosing, as well as the importance of pilot data in children – not extrapolated from adults – to guide power calculations. Looking forward, further work is needed to evaluate optimal outcome measures, particularly for heart failure trials where outcomes are inherently difficult to ascertain. Adult trials have recently considered the global rank end point, a mechanism for increasing power by considering the full range of different outcomes – death, transplant, clinical worsening, re-hospitalisation, etc. This may be something to consider in children, given the inherent difficulties studying these relatively rare conditions.[34]

In conclusion, recent legislative initiatives have led to a complete metamorphosis in the paediatric clinical trials landscape. Clinical trials represent the best means to improve outcomes for our patients, and it is critical that we continue to evaluate ways to improve the emphasis, infrastructure, and processes of existing clinical trials. Although significant advances have been made to date in paediatric hypertension and hyperlipidaemia, in order to improve the health of children with heart disease, future studies should focus on these processes for children with heart failure, CHD, and pulmonary hypertension.

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