On Your Doorstep

Paediatric trials have become considerably more common due to regulatory and government efforts to increase the paediatric pharmacopoeia. Home clinical trial visits in particular are part of an increasingly patient-centric healthcare movement

Dr Graham Wylie at MRN

Paediatric trials not only present a huge challenge – both scientifically and ethically – they are also exceptionally demanding from a logistic perspective. After several false starts, the market is gaining traction with 'the FDA rule' finalised in 1998 – essentially requiring all new products to undertake paediatric registration.

Global Metrics

It has been a turbulent decade in the clinical trial environment – as it has in other sectors – driven by the global recession, which had a profound effect on R&D investment. Pharma R&D growth in terms of spend dropped from historical figures of 12-14% per annum into negative figures for the first time in living memory. Many predictions indicate growth may not recover to beyond 5% per annum anytime soon or, indeed, ever.

Figure 1 shows that in total, the number of clinical trials initiated between 2006 and 2014 has grown by only 7%. Looking specifically at the paediatric market, this has in fact fared even worse, showing a decline of -1.5% in the number of trials taking place from 2006 to 2014. However, the make-up of the paediatric clinical trial pipeline has changed considerably. When looking specifically at rare diseases in paediatrics, there has been a 94% growth in the number of trials initiated in the same period.

Across the entire R&D pipeline, the number of indications has grown by 12%, outstripped by a growth in paediatric indications of 31%. This is the result of, one assumes, a sharp shift towards cost control in pharmaceutical and biotech companies' R&D budgets, resulting in their investment being spread over a much larger set of indications, many of which are rare or orphan types.

Figures 2 and 3 throw a bit more light on these trends. Figure 2 (page 40) shows that in 2006, of the top 10 indications initiated, 60% were infectious diseases and 20% were psychiatric indications – with only 10% being rare diseases (diphtheria prophylaxis). Figure 3 (page 41) implies that by 2014, the basic therapeutic areas had shifted slightly to 50% infectious disease and 30% psychiatric indications, due to the entry of paediatric bipolar disease into the list. More importantly, it also shows that three of the top 10 paediatric indications had become rare diseases – duchenne muscular dystrophy, meningococcal infections and diptheria prophylaxis – ranking fifth, sixth and seventh respectively. It can also be seen that the top 10 rare diseases in 2014 were 50% gene defects and 30% infectious disease.

This indicates that the pattern of research in paediatric indications is evolving away from traditional concepts of childhood disease into the newer and, perhaps, more contentious areas of psychiatry, and within the rare disease category, gene defects are now predominating. It seems clear from these metrics that the regulatory push to increase the paediatric pharmacopoeia is working. However, sociologically, the types of mainstream conditions being addressed may be controversial – attention deficit (hyperactivity) disorder (ADD/ADHD),

Figure 1: Number of trials initiated each year between 2006 and 2014 showing annual and overall growth

Trials initiated	2006	2007	2008	2009	2010	2011	2012	2013	2014	Growth 2006-2014	Total initiated
Pure paediatric clinical trials	270	261 -3.3%	241 -7.7%	278 15.4%	265 -4.7%	301 13.6%	244 -18.9%	260 6.6%	266 2.3%	-1.5%	2,386
Rare disease paediatric clinical trials	33	38 15.2%	49 28.9%	48 -2%	40 -16.7%	68 70%	60 -11.8%	52 -13.3%	64 23.1%	93.9%	452
Total clinical trials market	4,370	4,680 7.1%	4,947 5.7%	5,023 1.5%	4,834 -3.8%	4,862 0.6%	4,537 -6.7%	4,450 -1.9%	4,679 5.1%	7.1%	42,382

Source: EvaluatePharma® analysis

Figure 2: Top 10 paediatric indications and trials initiated in 2006

Top 10 paediatric indications in 2006		Trials initiated in 2006
1	Asthma	16
2	Diphteria prophylaxis	13
3	ADD/ADHD	12
4	Hepatitis B prophylaxis	11
5	Pneumococcal infection prophylaxis	9
6	Influenza	8
7	Gastro-oesophageal reflux disease	8
8	Autism spectrum disorders	7
9	Malaria treatment	7
10	Measles prophylaxis	7

Source: EvaluatePharma® analysis

depression, human papilloma virus (which only enters the lists in 2015, so is not reported here) all challenge societies' attitudes to the normal mental and sexual behaviour of children. Perhaps this is inevitable as this process redefines childhood disease by making therapies available, throwing a medical spotlight on where challenges exist – which society may struggle to accept.

The heightened interest in paediatric clinical trials has manifested itself in challenging and complex pieces of work. In particular, they have required long patient visits for multiple pharmacokinetic blood sampling in the earlier phases of clinical research, or the home administration of complex biologicals as subcutaneous injections or infusions. The specialist nature of these trials, in addition to the fragile patient population, has meant that home clinical trial support is an invaluable resource for paediatric clinical trials.

As for paediatric studies in indications that are not rare, or do not require parenteral investigational medicinal product (IMP) administration, the trends are less obvious. In 2014, more than 4,660 trials were initiated, with just over 5% being paediatric. The numbers are too small to observe whether these studies are as yet increasing their utilisation of in-home clinical trial visits.

Study Results

Research attempted to find out why clinical trial sponsors use home healthcare services. Using the definition of 'patient-centric' as any element of a trial that is designed to appeal to patients in order to make it easier for them to take part in the study, these reasons can be analysed as follows:

- To improve recruitment and retention of patients in trials. Providing the option to be seen at home recognises that the patients have a choice to participate in clinical studies. Giving patients the opportunity to undertake some significant elements of the trial in their own home is intuitively attractive to them, and will thus make it easier for them to consent to join and more likely to remain in the trial

- It is expected the drug will be administered in the home when marketed. This is a scientific objective, but derives directly from a marketing patient-centric objective. One way a biopharma company can make their product more desirable when on the market is to make it suitable for use in the home, and so it is logical for them to research it in the same environment

- To make the lives of the patients better in return for participating in the research. Some companies seem to simply want to reduce the impact of the trial on the patient to enhance the relationship they have with them, which they see as important and worth investment in its own right

- To allow access to patients who would otherwise find it hard to participate. Some companies want to broaden access to their research products, and find these services are a good way of promoting access to patients who would otherwise struggle to participate, and thus gain access to more experimental medicines

Patient-Centric Approach

Children need care in the home to prevent them from losing time in school, and to allow their parents to continue working, so everyone can lead as normal a life as possible. They also need to be treated, where possible, in a way that allows them to feel 'normal' without multiple visits to the hospital.

There are specific considerations in home healthcare in paediatric trials. For one, an enhanced model is needed due to stronger bonds between the treating doctors, their teams, the child and their family. Home healthcare introduces another party into this complex set of inter-relationships, which all the stakeholders view as critically important. This leads to greater demands on the home healthcare providers than in standard

Figure 3: Top 10 indications by number of clinical trials in paediatric indications and in paediatric rare disease indications, showing the total number of trials initiated between 2006 and 2014 inclusive and the number initiated in 2014

Top paediatric rare disease indications 2014		Total trials 2006-2014	Trials initiated in 2014
1	Duchenne muscular dystrophy	24	7
2	Meningococcal infections	66	6
3	Diphteria prophylaxis	61	4
4	Haemophilia, general	6	3
5	Spinal muscular atrophy	10	3
6	Meningitis	37	2
7	Pulmonary hypertension	16	2
8	Haemophilia A	16	2
9	Hyponatraemia	3	2
10	Sanfilippo syndrome (Mucopolysaccaridosis III)	3	2

Top paediatric indications 2014		Total trials 2006-2014	Trials initiated in 2014
1	Influenza	96	10
2	Autism spectrum disorders	47	9
3	ADD/ADHD	98	8
4	Asthma	91	7
5	Duchenne muscular dystrophy	24	7
6	Meningococcal infections	66	6
7	Diphteria prophylaxis	61	4
8	Haemophilus influenza type b prophylaxis	26	4
9	Rotaviral gastroenteritis	37	4
10	Bipolar disorder	21	4

Source: EvaluatePharma® analysis

models, particularly in terms of error rates and the quality of communication. The sources of error in home healthcare can be, for example, the inability to find a nurse near the patient with availability in their schedule; a visit interrupted by weather or traffic; the nurse being unwell; a fault in the equipment; disruption in the investigational medicinal product cold chain; or a failure in venepuncture or cannulation.

Personalised Touch

In today's world, anything is possible: more intense models of nursing care than those mentioned for paediatric studies can be operated in highly complex trials in adults; full-time employed nurses can be utilised, who work internationally to support a specific clinical trial, and are permanently 'on call' for the trial in whatever trial site or patient location is required; staff may provide patient care where their licence permits, but in other countries or states, they simply train and advise local site staff on the trial-specific elements of very complex studies, or maintain highly complex equipment to reduce variability in the trial.

The paediatric R&D clinical trial pipeline is changing, showing significant growth in the number and proportion of rare diseases and products that require parenteral administration. Analysis shows there is significant demand for home healthcare services in such studies, simultaneously creating more complex demands on the service provider, as the objectives of the sponsor and site focus more on the patient experience.

It is predicted that high-intensity and basic home trial support models will be increasingly applied to paediatric trials in the future, as patient experience becomes an ever-more important factor.

About the author

Dr Graham Wylie is Chief Executive Officer at MRN, and has more than 25 years' experience in the pharmaceutical industry working for Pfizer, Parexel and Healthcare at Home. He was also named as one of the most influential leaders in the pharmaceutical industry by PharmaVOICE 100 in 2014. Graham joined Healthcare at Home in 2005 to set up their trial division and led the management buy-out to create MRN in 2006.

Email: enquires@themrn.co.uk