Extrapolation meets patient-generated data: a happy marriage for paediatric drug development?

Introduction

The EU Paediatric Regulation 1 which came into force in Europe in 2007 was instrumental in changing the ethical mindset of the wider community and the need for clinical trials in children. The majority of stakeholders involved worked to the mantra: “Let’s protect children through research, not from research”.

While the increase in paediatric research and the number of new products with specific paediatric indications can be encouraging, as per the European Commission’s ten years’ report,2 advances in paediatric development have not emerged as rapidly as the early supporters of the Regulation (in particular the authors) would have hoped.

Experience over the past ten years suggests the Regulation works best in areas where the medical needs of adult and paediatric patients overlap.2 Conversely, in diseases that manifest themselves in childhood, major therapeutic advances have failed to materialise to date. A recent cohort study3 demonstrated that after a median follow-up of seven years from approval of paediatric investigation plans (PIPs), only 17% of medicines authorised for adults had completed required paediatric trials, and only 38% of all required paediatric studies were completed. Similarly, in the US in 2015, of the completed paediatric trials at the FDA, 42% had failed to establish either safety or efficacy, leading to an inability to label the product for use in children.4 Parameters that can prevent a paediatric development generating clinical efficacy and safety data are related to developmental changes that may require targeted investigations in specific age or weight groups, different safety considerations, the need for paediatric-specific outcome measures, endpoints or formulations, lack of longitudinal data to define the natural history of the disease or the need to incorporate specific research protection.

In addition, based on an average of 107 first PIP decisions per year for the period 2008–2015, an average of 29 clinical studies were agreed as part of PIPs.

The final report of the study on the economic impact of the Paediatric Regulation by the European Commission not only estimates an average cost per study of €6,831,000 but also due to spillover effects after a period of ten years, a total social return of around €6bn suggesting that, in monetary terms, the benefits of the Paediatric Regulation outweigh the costs.5 Paediatric drug development is indeed expensive, with a small market that limits the return on investment.6 New paradigms in paediatric medicine development are needed and becoming an ethical imperative to ensure the benefits of paediatric regulatory initiatives at EMA and the US FDA can reach the patients and their families. This article explores two different paediatric disease areas and considers how digital tools combined with the extrapolation framework2 can enable drug development for children.

Regulatory framework: is there room for innovation?

The adaptive pathway concept, as highlighted by the work of the Innovative Medicines Initiative (IMI) ADAPT-SMART consortium,8 supported a better use of drug development tools and methods through the current regulatory framework9 in order to foster access to beneficial treatment for the right patient with high unmet medical needs at the earliest appropriate time in the product lifespan in a sustainable fashion, without compromising the usual regulatory standards. While engaging in a multi-stakeholder dialogue, the consortium explored the value of integrating real-world data (RWD) into the regulatory assessments of drugs, a topic also addressed within IMI GET REAL,10 and promoted further beyond Europe, in the US11 and Canada.12 It has been acknowledged that RWD can complement the evidence from randomised clinical trials, support innovative study designs (eg, pragmatic clinical trials) and observational studies, while using digital tools to generate new treatment approaches. As former FDA Commissioner Scott Gottlieb said: “Use of digital technologies can help bring clinical trials to the patient, rather than always requiring the patient to travel to the investigator.” Indeed, a change in the drug development paradigm has occurred where digital technology can help patients participate remotely in a trial while wearable devices are used to monitor patients long term in situations where it was previously either not feasible or ethical.

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KEYWORDS

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ABSTRACT

Strategies to increase the efficiency of medicines development are becoming part of a new paradigm. In paediatric medicine and rare disease particularly, it is now an ethical imperative. In October 2018, the European Medicines Agency (EMA) released its extrapolation reflection paper (EMA/189724/2018), supporting situations where data sources other than clinical trials may prove to be complementary to well-designed, prospective studies that track the standard of care. The importance of data generated from routine clinical practice data is increasing as they give a better perspective of the real-world reality. Technology and innovation are rapidly evolving around us and enabling new means for reporting disease burden and drug value from the patients’ perspective and experience, such as patient-generated data (PGD). In this article we propose case studies as examples for a paradigm shift in the drug development model to ensure that the benefits of paediatric initiatives from the EMA and US FDA can reach the patients and their families.
Nevertheless, the EU and US paediatric legal framework requires approval of a PIP in the EU or similarly a paediatric study plan (PSP) in the US, aimed at ensuring that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population. Regulatory standards for approval of medicines, vaccines and biological products are the same for adult and paediatric patients. In general, approval must be based on evidence obtained from adequate and well-controlled trials, which may not always be feasible or ethical in paediatric drug development, eg, in rare diseases or when extrapolation approaches can be used.

To overcome some of the challenges in paediatric development, but without compromising regulatory standards and ensure timely access to paediatric medicines, the EMA developed a framework for the use of extrapolation approaches in paediatric programmes. The framework promotes context-dependent approaches for how different types of prior knowledge, quantitatively synthesised, could be used to support assumptions or make predictions for treatment effects in a paediatric target population. Additionally, over the past four years, international experts convened to revise the ICH E11 guideline on clinical investigations of medicinal products in paediatric populations in order to address new scientific and technical knowledge advances in paediatric drug development, and reduce the substantial differences between regions in the acceptance of data for global paediatric medicine development programmes. Following the revision of this ICH guideline in 2017, the ICH experts are now focusing on paediatric extrapolation and the EMA framework will certainly help them finalise the new guideline. The EMA extrapolation framework promotes a multidisciplinary approach to integrate the available evidence in order to determine the studies that should be conducted in the target population.

There are, however, several issues that deserve additional attention. Paediatric extrapolation carries inherent risks if any of the assumptions used during extrapolation turn out to be incorrect. Given the variability in individual patient responses, passive adverse event reporting and other factors, erroneous assumptions may not be detected and reported in the clinical setting for years, if at all. The potential impact and the severity of the consequences on paediatric patients will clearly depend on the nature of the erroneous assumptions and the intended use of the drug.

Uncertainties of extrapolation approaches combined with identified reasons for paediatric trial failures, eg, differences in disease course, magnitude of placebo effect, drug dosing, disposition or response, suggest that an improved understanding of the disease course and history may help designing an appropriate paediatric trial which with the use of innovative tools and methods could improve trial success rate.

It is important to note that the EMA extrapolation reflection paper requires mitigating uncertainties and does specify that data sources other than clinical trials can be used to address uncertainties, acknowledging that the value and importance of data generated in routine clinical practice data are increasing. It is acknowledged that patient activity happens outside of the hospital or clinic, beyond the scope of the electronic health record (EHR), and it is becoming evident that information collected directly from highly motivated patients and parents has increasingly understood importance. However, while patients are willing to share this data with their clinicians, few are able to do so due to barriers, such as lack of user-friendly applications, patient portals not having the capabilities to accept patient-generated data (PGD), standalone applications not integrated into clinical information systems or not part of the clinician workflow, and lack of a clear understanding of the privacy and governance of the data. PGD is health-related information created, recorded, or gathered by or from patients, family members or other caregivers to help support and manage disease state. PGD includes, but is not limited to:

- Health-related events/symptoms using videos, photos, voice, scales and free text
- Medication adherence and self-reported side effects/adverse events
- Biometric data (from wearables and sensors)
- Patient-reported outcomes (PROs) and quality-of-life scales

PGD is distinct from data generated in clinical settings and through encounters with healthcare providers in two important ways:

1. Patients, not providers, are responsible for capturing or recording the data
2. Patients decide what data to share, and with which healthcare providers/researchers

Examples include physical activity using wearable devices, medication adherence and mobile PROs (mPRO) using a mobile app. It is important to emphasise that relevant PGDs should be decided in collaboration with patients’ associations. Patient input can help inform the therapeutic context for regulatory review. Patient input also can inform the selection of clinical outcomes, ensure the appropriateness of instruments used to collect trial data, and help ensure that investigations of the effect of treatments are assessing outcomes that are meaningful to patients. If methodologically sound data collection tools are developed and used within clinical trials of an investigational therapy, patient input can provide a direct source of evidence regarding the benefits and risks of a drug. However, the amount of money being invested into innovative drugs and mechanism of action (gene therapy, cell-based therapy, biologics) and the amount of money proportionally invested in developing and validating new endpoints and outcome measures is minuscule – increasing the risk of failing at the last hurdle.

It's this new setting of the digital era, disease registries will also be an instrumental tool to support these innovative study designs. Regulators and industry alike should mandate a disease registry, rather than a drug registry, as a post-marketing obligation. The Qualification of the Cystic Fibrosis Registry is an early sign that this is happening. However, each new orphan drug that is granted with a post-marketing obligation on a company to develop a drug registry for tracking long-term safety and efficacy (in the case of conditional approvals) is merely providing a short-term solution for a long-term pain. The FDA’s recently published “Rare disease: common issues in drug development” for consultation encourages making data from natural history studies publicly available to support and promote rare disease drug development – this cannot be achieved through mandated drug registries managed by one pharmaceutical company.

Meanwhile, the development of decentralised clinical trials (DCTs) using telemedicine and other emerging and novel information technology (IT) services are offering new ways to participate in clinical trials and post-marketing studies. These approaches may provide several advantages such as faster trial participant recruitment and improved trial participant retention, which may reduce missing data, shorten clinical trial timelines, improved data interpretability and increase the diversity of the population enrolled in trials. When there are no acute safety concerns it is also an opportunity for home administration of medicines, which may make the clinical trial experience more patient-centric and less stressful, while being more representative of clinical routine practice.

These potential advantages apply to all disease areas and trials, but offer particular advantages in paediatrics where children find hospital visits to be extremely stressful, and in rare diseases, where patients are limited in number and are geographically dispersed.

Can we turn development challenges into opportunities?

In order to move towards a paradigm shift in global research and development, there are several points to consider when using digital
Duchenne muscular dystrophy (DMD) is a devastating childhood pathology, affecting 1 in 5,000 boys. It is an X-linked disorder caused by mutations in the dystrophin gene and is the most frequent muscular dystrophy in boys. Diagnosis is confirmed by the demonstration of an out-of-frame mutation in the dystrophin gene, sometimes requiring muscle biopsy for confirmation. The disease causes progressive and unyielding muscle weakness frequently identified in the early toddler years when the child begins to miss development motor milestones. Loss of ambulation occurs generally around the age of 12. Survival is up to the third and fourth decade. Glucocorticoid treatment is the main method to help maintain muscle strength and pulmonary function for as long as possible. In 2014, Translarna (ataluren) was granted conditional marketing approval by the EMA and Exondys 51 (eteplirsen) was approved by the FDA in 2017, but the EMA did not approve this product.

In order to tackle this issue, a device based on magneto-inertial technology was developed to capture all movements precisely by sensor technology was developed to capture all movements precisely by sensor technology. This technology was approved by the EMA qualification process. The device is likely to also overcome variations in practice encountered across different centres/countries, which also has a significant impact on global studies.

The Gaucher experience

Gaucher’s disease type I is a rare disease that could be seen as the envy of many other rare diseases, in that not only does it have an effective enzyme replacement therapy which effectively ameliorates disease manifestations, it also has five other licensed products, with different mechanism of action also licensed on the market.

The examples given below look at innovative approaches for two diseases: Duchenne muscular dystrophy (DMD) and Gaucher’s disease.

### The Duchenne muscular dystrophy experience

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The recent regulatory buy-in of this device via the EMA qualification process creates significant momentum in moving towards this direction and an added value in the scope of paediatrics specifically, by reducing the stressful demand of hospital-based tests on children, increasing feasibility of studies and accelerating clinical development.

### Tools: modelling & simulation

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Learning from DMD and Gaucher’s disease

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### Design endpoints through patient involvement and engagement

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### Use of quality source data

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### Can support risk mitigation and reduce risks of study failure

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### Mitigation of uncertainties related to PK, PD, efficacy and safety parameters

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### Tools: modelling & simulation

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### Patient-generated data (PGD) and digital biomarkers can offer a new opportunity including for registries and post-marketing studies

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### Design endpoints through patient involvement and engagement to ensure feasibility and acceptability such as patient-reported outcomes (PROs)

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### Examples of synergies between the EMA extrapolation framework and use of digital tools in paediatric developments

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### Performance during hospital visits (but which depends on the patient's motivation and clinical condition at the precise time of assessment),

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### Monitoring the patient's real life would allow a continuous and completely objective assessment of daily motor activity, and a much more clinically relevant and powerful outcome measure to demonstrate efficacy predictions in DMD clinical trials.

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### In order to tackle this issue, a device based on magneto-inertial technology was developed to capture all movements precisely by sensor measurements and a dedicated algorithm which give precise qualification and quantification of patient activity, in a non-controlled environment.

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### Several variables that are robustly measurable in ambulant patients and clinically relevant in the context of DMD have been identified. These are the 95th percentile of the stride velocity (primary), the median stride velocity, the 95th percentile and the median stride length (secondary), and the distance walked/recorded hour (tertiary). These constitute important outcome measures as clinical endpoint in pivotal studies for ambulant DMD patients.

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### Validated wearable devices presents a significant advantage over the classic 6MWT or clinical scales. It does not rely on patient motivation or subjective assessment and provides continuous monitoring. Thus, it considerably decreases the variability of assessment, which would allow for a smaller number of patients to be included in a study. Using such wearable devices is likely to also overcome variations in practice encountered across different centres/countries, which also has a significant impact on global studies.

- **Can ensure feasibility and acceptability such as patient-reported outcomes (PROs)**

### The recent regulatory buy-in of this device via the EMA qualification process creates significant momentum in moving towards this direction and an added value in the scope of paediatrics specifically, by reducing the stressful demand of hospital-based tests on children, increasing feasibility of studies and accelerating clinical development.

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### Gaucher disease type I is a rare disease that could be seen as the envy of many other rare diseases, in that not only does it have an effective enzyme replacement therapy which effectively ameliorates disease manifestations, it also has five other licensed products, with different mechanism of action also licensed on the market.

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In 2010, the EMA became aware that the three agreed PIPs for type I Gaucher disease were competing for the same patients and specialist recruitment sites, potentially leading to feasibility issues.77 To address this, the agency convened a workshop with the patient group, key opinion leaders and industry partners to explore potential solutions.

As a result, a joint publication with the FDA promoting the concept of a multi-arm, multi-product study design77 was issued in 2014, and revised in 2017, leading to an FDA guideline,28 where, in essence, the competing companies would share the same control group to support feasibility. While such an approach could not be mandated by the regulators either because of timing (some PIPs had already started) or because of competing interests on the part of the companies involved, the approach was broadly presented in the community by regulators and key opinion leaders but not adopted or implemented. Meanwhile two PIPs are still ongoing.

Today, the Gaucher community faces a similar challenge for neuromopathic Gaucher disease – a sub-type which includes the same visceral manifestation of the disease as type I, but also with neurological involvement. Currently there are seven pharmaceutical companies developing innovative therapies for this sub-type, which has a huge unmet need but a small population and heterogeneous disease presentation. In response to this challenge, as well as learning from a feasibility study using a combination of wearable and a paired app downloaded on a patient’s own smartphone, in the UK, the International Gaucher Alliance (IGA) has initiated a project to develop a global disease registry with the three aims: Document the natural history of the disease in a globally harmonised, and interoperable way Support all pharmaceutical companies in their data generation plan to support their individual drug development plans Incorporate real-time PGD as an integral part of the registry to convey disease burden from a patient’s (and carer) perspective

It is hoped that this forward thinking by the IGA will enable and support more innovative and feasible study designs as a total of seven competing pharmaceutical companies have assets on the horizon, bringing hope to patients. Furthermore, the creation of one disease registry rather than a multitude of drug registries will have great value in data analysis.

Conclusion

The EMA, with its paediatric extrapolation framework, has paved the way to optimise paediatric drug development programmes. Extrapolation is a powerful scientific tool that should help streamline paediatric product development. With science rapidly evolving, and the increased use of digital technology, there is the need to revisit the current development paradigm with an open mindset and to move towards a more adaptive paradigm where new technologies complement existing tools and methods. Regulatory guidance on validating digital health tools is now emerging and digital tools operating under a quality management system with a software development lifecycle (SDLC) is well placed to provide compliance assurance to regulators for use in clinical trials.29 Incorporating these with the EMA extrapolation regulatory framework may facilitate a more rapid integration of digital technologies that manages ongoing validation risks and uncertainty. Such tools should not only facilitate patients’ participation and retention in clinical trials and address some of the clinical site capacity issues but also help to generate data that supports the benefit-risk evaluation of any innovative product all along its lifespan. To ensure developments using extrapolation and/or digital technology are fit for purpose, early planning, including early scientific advice is highly recommended to discuss such cases. Early integration of tech, innovation and extrapolation strategies into study designs, as opposed to an after-thought add-on will lead to a greater chance of success.

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