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Opinion paper

Challenges in conducting paediatric trials with off-patent drugs

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ABSTRACT

Introduction: For more than two decades several initiatives have emerged to increase recruitment of paediatric patients in drug trials. While trials of newly approved drugs have successfully included paediatric patients in their drug development plan, the collection of safety and efficacy data in paediatric patients treated with off-patent drugs poses a major challenge.

Aim: This paper aims to draw attention to problems and solutions across countries in investigator-initiated trials with off-patent drugs and recommendations for improvement.

Discussion: Off-patent drugs represent a particular challenge when they are included in a paediatric trial; these trials are frequently investigator-initiated and have limited resources, off-patent drugs are used in clinical settings and the trial protocol must accommodate e.g. flexible dosing and specimen sampling schedules, off-patent drugs typically exist in few formulations and concentrations which necessitates special or imported formulations. Paediatric trials are in some countries confined by e.g. consent from both parents, regardless of whether the Investigational Medicinal Product (IMP) is a well-known drug or a new experimental drug.

Conclusion: Facilitation of research in off-patent drugs can improve evidence-based and safe treatment for the paediatric population. The following supportive initiatives are recommended: Harmonised regulatory change that improves the consent process in low risk trials to prevent inadequate recruitment. Pharmaceutical expertise should be prioritized to secure the best choice of IMP and supply. Constant focus on flexibility in design to accommodate a multifaceted paediatric population and ensure that trial protocols fit in well with routine clinical care and family life.

1. Introduction

For more than two decades regulatory frameworks and private-public partnerships have been established to support paediatric drug development in EU and US [1]. These initiatives and guidelines need to be translated into practical ways on how to conduct clinical trials in children. Equally important, reasons for failure or success in clinical trials in children need continuous scrutiny.

While approval of new drugs succeeded to include paediatric patients in the drug development plan, off-patent drugs has never reached same priority, which has resulted in limited scientifically sound safety and efficacy data, enabling the assessment of risk benefit balance in paediatric patients. Lack of data generation is partly due to lack of financial incentives and partly due to few regulatory initiatives, such as The Paediatric Use Marketing Authorisation (PUMA) in EU [2]. The PUMA provides 10-year data exclusivity of a medicinal product already authorized and no longer protected by a patent, when exclusively developed for paediatric use [2].Ten years after the Paediatric Regulation was enacted only two products (Hemangiol® and Buccolam®) were approved [2], however, 20 projects covering off-patent drugs have also

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been funded by the EU Seventh Framework Program for Research in private-public collaborations [3]. Likewise, in the USA a part of the Best Pharmaceuticals for Children Act (BCPA) supports the study of off-patent drugs through the National Institute of Child Health and Human Development. The Pediatric Trials Network, coordinated by the Duke Clinical Research Institute, has enrolled more than 7000 children in studies of more than 70 drugs [4].

Other facilitators of clinical trials are organized networks e.g. The European Network for Paediatric Research at the European Medicine Agency (Enpr-EMA) https://www.ema.europa.eu/en/partners-networks/networks/european-network-paediatric-research-european-medicines-agency-enpr-ema, The Pediatric Trials Network USA (PTN) https://pediatrictrials.org/, Paediatric European Network for Treatment of AIDS and Infectious Disease (PENTA-ID) https://penta-id.org/, European Society for Paediatric Oncology (SIOP Europe) https://siope.eu/encca/ and those initiated by investigators in academia. The latter often includes only one or a few countries and one or a few sites. Some examples are the optimisation of antineoplastic agents in childhood acute lymphoblastic leukaemia, [5,6], or fluconazole prophylaxis and treatment of systemic candidiasis in preterm neonates [7–9].

Managing clinical trials in children requires a business like, structured, and pragmatic approach to accommodate clinical reality, independently of size and complexity of the trial.

The aim of this paper is not to generalise problems in trials with off-patent medicine, but to draw attention to problems and solutions across countries in order to learn from one another. We present guidance to avoid some of the most common pitfalls and provide lesson learned based on experiences from recent clinical trials across all age spans from neonate to adolescents supported by published studies within this field.

2. Discussion

2.1. Resource mapping

Well-designed trials are prerequisite for addressing a clinical important hypothesis. However, its essential to navigate the legal, regulatory and practical aspect of a trial to succeed. In most circumstances, a skilled team of regulatory experts, biostatisticians, operational trial managers, and formulation specialists are not at disposal as opposed to trials run by the pharmaceutical industry. Balancing and mapping the resources available to investigators and the resources necessary for the completion of the trial are recommended before trial initiation. It may come as a surprise to new investigators that some of these steps are quite lengthy and they need to be planned in parallel. Setting up paediatric drug trials is far from a solitary task and often requires multicentre and multinational setups and a broad understanding of country specific regulatory aspects. Outlining resources is also a practical matter of mapping e.g. hospital staff, patient flow, available diagnostics, collection and storage of biological specimens and drug analysis. Available resources and supportive regulatory framework will differ between regions, states, and countries.

Several checklists and templates from Ethics Committees, National Medicines Agencies, the Good Clinical Practice (GCP) units, EMA and Food and Drug Administration (FDA) are freely available to investigators (see Table 1 for useful links). In some countries the GCP units provide free counselling (including protocol review) and monitoring of the investigator-initiated trials. Likewise, the approval and later amendments from e.g. the Danish Medicines Agency and Ethics Committee are free of costs. It is important for regulators to support academic sponsors while keeping the regulatory requirements and quality of 'commercial' and 'non-commercial' trials at the same level [10].

The sample size needs to be justified independent of type of study (pharmacokinetic, pharmacodynamic, bioequivalence or safety). This is one of the key components, and it is also required when applying for grants. It may therefore be challenging to find biostatistical help before funding is finalized when drafting the protocol. However, tutorial resources are available, e.g. the StaR Child Health group [11]. Take into consideration whether subgroups in the study will be too small to obtain statistically sound data analysis.

Table 1
Useful websites.

Resource	Website
1. EMA Europe	https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/scientific-guidelines-paediatrics
2. Consortium Guidance from the FDA	https://www.fda.gov/drugs/development-resources/division-pediatric-and-maternal-health-pediatric-guidances
3. StaR Child Health group	www.starchildhealth.org
4. World Health Organization-	https://www.who.int/ictrp/child/en/
5. Guidance from the International Conference on Harmonization	https://www.ich.org/page/efficacy-guidelines
6. Medicines Agencies	https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human
7. National Ethical Committees	Lepola et al., 2016 [15] provides an overview of websites

This table was inspired by Shakhnovich et al., 2019 [13].

The recruitment stage may be a particular demanding tasks, and can be compared to "marketing", "sales" and "client management" from a business management perspective [12]. Up to 19% of paediatric trials are terminated early, due to difficulties recruiting patients [13]. Incentivizing staff (providing funds for enrolling patients) has been shown to improve patient recruitment [13]. Incentives (e.g. reimbursements, compensations or tokens of appreciation) for trial participants is a practice that varies across continents and countries as well. In an overview article reporting 300 paediatric trials, 14% used incentives mostly in North America and Asia [14], most frequently compensation and tokens of appreciation [14].

2.2. Pragmatic and flexible designs

We recommend the following considerations when designing a trial, to avoid unnecessary obstacles. Although randomized trial is seen as state of the art or the assessment of the effect of any therapeutic intervention, they can be difficult to implement especially in small subpopulations e.g. in extremely preterm neonates and other approaches may be explored. Consider to use adaptive design, which among others allows early stopping, sample size re-estimation and adaptive randomization, sequential design with an a priori of non-fixed sample size or withdrawal design [16,17]. In addition, data from clinical databases and or studies in adults may quantify a priory probability to obtain treatment effect as in Bayesian approach design. The hospital database when available can also determine the number of patients admitted with the diagnose you intend to investigate and the use of the investigational medicinal products (IMP) in a specific age group at the hospital, preferably going back more than two years in time. It is equally important to ensure that the condition being studied occurs and is handled similarly in all age groups proposed in the study and at all sites, keeping in mind that in some countries adolescents may be referred to adult departments. The age definition of adolescents and adults also varies e.g. according to WHO an adolescent is a 10–19 year old [18] while it is a 12–16 year old depending on region according to the FDA [19]. The databases will provide a better overview of the number of patients eligible for the trial and whether additional sites should be included up front. Based on the available resources and eligible patients the design of the trial should take sampling frequency, timing, invasiveness and volume into consideration. For example alternatives to conventional blood sampling (e.g., saliva, urine, dried blood spots) [20,21], minimally invasive sampling, and trial related sampling synchronized with clinical samples could be considered. An important aspect of optimizing the trial design, is to learn from previous studies and incorporate the knowledge into the new study.

Lessons learned: study population and design

The PARASHUTE study (EudraCT: 2017-002724-25) investigated long-term safety with paracetamol in neonates of treatment of three days and above [22]. Before initiation a chart-review of 200 patients in one Neonatal Intensive Care Unit (NICU) revealed that approximately 10% were treated with paracetamol intravenously and 5% orally for more than 72 h. This NICU had approximately 1000 admitted patients yearly. With an expected attrition rate of up to 50%, the study would need to run for 24 months in order to obtain the intended sample size [22]. Therefore, it was a priori decided to include a second site. In the same study the protocol specified samples was flexible in order to accommodate routine laboratory samples to avoid unnecessary heel pricks. This requires funding and training of dedicated research staff. It is a prerequisite that the research staff is part of the department and know all routine procedures. Especially, when conducting trials in children, endurance can suffer greatly if patients and parents have to interface routinely with new research staff [23].

In the CYTONOX trial (EudraCT: 2014-004554-34) microdosing of midazolam was used, as an inherently safe sub-pharmacology dose, to investigate the pharmacokinetics of the liver microsomal enzymes cytochrome P450 family (CYP3A4) in obese and non-obese children. However, it turned out that the analysis was not sensitive enough to quantify the metabolites of the parent drug. Thus whenever using microdosing as a probe remember to confirm the lower limit of quantification before applying this method into the trial [24,25].

2.3. Supply chain and choice of medicinal product

The supply and choice of IMP and possibly placebo are often major challenges [26]. End-to-end pharmaceutical supply chain including manufacturers, distributors, health systems, and pharmacies needs to be considered. Especially in off-patent drug trials with limited choices in terms of concentrations and formulations and access to placebo formulations. Problems with availability of the IMP increase the costs of the trial and may prolong the trial. Resources to satisfy the requirements for IMP are often inadequate in hospital pharmacies and the costs of the services are high [10]. For placebo-controlled trials not conducted with a partner in the pharmaceutical industry, the placebo production is limited and the costs are often as high as for commercial organizations [10]. In the UK, a unit is dedicated to give pharmaceutical support to investigator initiated trials and advice from experts is much needed [26]. Moreover, in some instances marketed drugs provided from hospital supplies are exempted from the requirements for labelling and accountability (even if not in the licensed indications) [10]. This can diminish costs and paperwork in the trial, if the medicine administration follows normal routine and do not need separate accountancy. The procedure in trials with new medicines is comprehensive, covering age appropriate dosage forms, excipients, acceptability, delivery devices, volumes and frequency, preparation procedures and wastage. All aspects need to be addressed for the off-patent drugs as well, trying to find the best IMP for a trial when these drugs were never purposefully developed for children.

Lessons learned: investigational medicinal products

In the POP child study (EudraCT: 2017-003590-33) the initial trial was set up to investigate four different formulations of prednisolone in children with asthma. The study was paused for almost 10 months due to supply chain disruptions of the oro-dispersible tablets imported from France. Initially, a new delivery was expected after seven months. As we neared the promised delivery date all export of the IMP was banned. To proceed, the trial needed to be redesigned including a new randomization scheme and approval of a major amendment by the health authorities. The study also included an extemporaneous formulation (oral solution of prednisolone) due to lack of age appropriate formulations and strength in Denmark. The oral solution had a rather short shelf-life of only 3 months and the costs of buying the IMP increased considerably [27]. This is an enduring problem with fewer marketed formulations in smaller countries [28].

In the trial 'Pharmacokinetics and safety of treatment with paracetamol in children and adults with spinal muscular atrophy and cerebral palsy' EudraCT: 2018-002295-40 where paracetamol metabolism is compared in children with spinal muscular atrophy or cerebral palsy and healthy adults. The oral solution was chosen since weight-based dosing is mandatory and a titratable formulation needed. This requires blinding, repackaging and placebo preparation by the pharmacy and hereby increasing cost.

2.4. Informed consent

The process of obtaining consent is inconsistent across Europe in terms of number of required signatories i.e. one or both parents [15]. In the US this is a federal regulation and similar across states [29]. In general, the trial design should allow scheduled visits with enough time for the parents to consider whether they feel confident to let their child participate in the study and sign the consent form. Not all trial designs allow for scheduled visits especially if the IMP is part of the usual care i.e. an off-patent drug and the potential participants are hospitalized children. Hospitalized children represents the 'burden of disease' however, only a moderate correlation has been shown between clinical trial activity and paediatric burden of disease [2,30]. This necessitates recruitment of hospitalized children which adds a time pressure to the recruitment and consent process which is not adequately considered in the ethical framework. This framework needs to be continually developed and discussed to keep up with the reality and risks of the clinical studies [31,32].

It is unfortunate that the majority of paediatric drug trials in Europe [15] are confined by the same restrictions (e.g. consent from both parents) regardless of whether the IMP is a well-known drug as or a new experimental drug. These limitations seem counterproductive. Even in comparable countries like the Nordic countries, the requirements of consent differ, e.g. Iceland allows trial participation with only one parental signature [15]. Different solutions could be considered when evaluating an? (off-patent) drug trial, e.g. the Ethics Committee could assess trial characteristics (IMP, population, and trial procedures) and grade the trial into different stages of risk e.g. low risk, intermediate and high risk similar to the US. Depending on the risk stage each category should have different regulatory requirements. This was already proposed in 2009 but has failed to be implemented [10]. Thus, the administrative burden remains unchallenged in most European countries. This calls for a harmonised change when the requirements for the consent process are indeed country specific and hinders ethically sound research. The recommeded suppotive initiatives are summarized in Fig. 1.

Lessons learned: informed consent

The POP child study recruited children admitted with asthma exacerbation; in the majority of cases, only one parent was admitted with the child. This caused a difficulty in obtaining consent from both parents (required in Denmark). In the POP child study prednisolone was already prescribed by the attending physician and could not be postponed for hours. By March 2021 83 patients were screened for inclusion in the POP child study, 42 were included and 14 were willing to participate but it was impossible to obtain consent from both parents in the given time span, resulting in inclusion failure of around 17% of eligible patients. We applied for a waiver in this study, since only

Fig. 1. Suggestions to facilitate off-patent drug trials
IMP: investigational Medicinal Product.

already prescribed medicine was administered and only saliva samples were collected. However, this waiver was not granted leading to a prolonged recruitment period.

In the PARASHUTE trial, which recruited neonates treated with paracetamol, it was easier to obtain consent because both parents were often present in the NICU. In addition, inclusion could be postponed 24 h after treatment initiation, creating the essential flexibility for the consent process, allowing a window even though the neonates were hospitalized and needed immediate drug treatment.

3. Conclusion

Clinical trials with off-patent drugs are receiving less attention partly because of lack of economic incentives and few regulatory initiatives to stimulate these trials. Variations in how different countries interpret and implement guidelines and support clinical trials are reflected in the challenges that each investigator face in their trial.

Inadequate sample sizes due to unobtainable consent from both parents in low risk trials prolong and complicate the trials unnecessary in some countries. Regulatory change is warranted in harmonizing or improving the consent process across continents and countries.

Core facilities of professional help in choice and supply of an IMP is necessary in off-patent drug trials in order to choose the best solutions and to keep costs reasonable. Alternative formulations are limited in off-patent drugs even though trial success may depend on age-appropriate formulations.

Constant focus on flexibility in design and development of innovative methods for facilitating trials is necessary to accommodate a multifaceted paediatric population and ensure that trial protocols fit in well with routine clinical care and family life.

Improving the framework for paediatric off-patent drug trials will be possible with regulatory and public support.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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