Risk proportionate approach to pediatric clinical trials: the legal requirements, challenges, and the way forward under the EU Clinical Trial Regulation

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Abstract

Background

It is now widely accepted that there is a need for safety and efficacy data on medicines used in children. In the European Union (EU), legislation has provided the necessary framework obligating and incentivizing pharmaceutical companies to carry out appropriate pediatric research to support the development of new medicines. This change in research culture, that medicines used in children should be appropriately researched in children, has also led to the recognition of the importance of investigator-initiated clinical trials in furthering medical knowledge on the off-label use of authorized medicines for which pediatric data are often limited. However, medicines regulatory authorities of EU countries have largely adopted a uniform approach to the regulation of both industry-sponsored and investigator-initiated trials, and in doing so, have added disproportionate burden to the conduct of pediatric clinical trials investigating authorized medicines.

Case studies

Two European multinational pediatric clinical trials funded by the conect4children consortium are presented to provide a comparative insight into past challenges and to illustrate how the new framework provided by the European Clinical Trials Regulation (No 536/2014) addresses these barriers in practice.

Conclusions

The European Clinical Trials Regulation gives a strong impetus to a risk-proportionate approach and offers a path for more efficient delivery of investigator-initiated pediatric clinical trials.

Keywords: Clinical Trials Directive, Clinical Trials Regulation, Pediatric investigator-initiated trial, Risk proportionate approach

Introduction

The Clinical Trials Regulation (EU) No 536/2014 ("Regulation") was formally implemented in the European Union (EU) on 31 January 2022.[1] It repeals the EU Clinical Trials Directive (EC) No. 2001/20/EC ("Directive") and associated country specific laws,[2] providing identical rules for conducting clinical trials throughout the EU.[1] A key goal of the Regulation is to drive efficiency through harmonization of clinical trials requirements with the aims to foster innovation and research while helping avoid unnecessary duplication and reducing delays in the process. Moreover, the Regulation introduces a concept of "low-intervention clinical trials" and brings a more explicit risk-proportionate approach to trial management and operations,[1] a change that has long been advocated by those engaged in investigator-initiated research.[3] The extent to which it can do so depends on how the Regulation is applied by researchers, but most importantly, sponsors and medicines regulatory authorities. In this context, this article aims to raise awareness of these new risk-adapted provisions with a focus on investigational medicinal product (IMP) requirements. Two multinational clinical trials funded by the conect4children consortium (a public-private funded collaborative network for European clinical trials for children) are presented to provide a comparative insight into past challenges and to illustrate how the Regulation offers a framework to address these barriers in practice.[4,5]

Historical perspectives

Since its implementation in 2004, the now replaced Directive has drawn heavy criticisms from all stakeholders, including patient groups, industry, and academic researchers, for its bureaucracy, resultant delays, and the increased costs it imposes for conducting clinical trials.[3,6–10] Despite the intention to create a harmonized framework and setting out the goals for clinical drug research across the EU, the divergence in the transposition of the Directive into country specific laws and the consequent differences in definitions and specific practical

requirements (e.g., labelling requirements, function of ethics committees) between countries have resulted in enormous increase in administrative burden for researchers, delays in trial initiation, and sometimes trial failure.[3,6–11] Moreover, irrespective of the risk added by the research as compared to usual care, countries have in general adopted a uniform "one size fits all" regulatory approach to both industry-sponsored trials of new medicines and investigator-initiated trials (IITs) of authorized medicinal products.[6,12] The consequences of which are illustrated by Knaapena and colleagues who reported that the IMP-related costs accounted for 23% of the total trial budget in the Antibiotics versus Primary Appendectomy in Children trial where the cost of amoxicillin/clavulanic-acid as an open-label IMP, used within its licensed indication and dosage, was at least seven times more than the cost of using routine hospital stock.[8]

The imposition of highly demanding, costly, and unnecessarily prohibitive regulatory requirements has been criticized as placing significantly disproportionate burden in the execution of IITs, and often cited as the key reason for the substantial decrease in the number of IITs.[9,13] In contrast to industry sponsored trials, which largely evaluate new medicines with unknown safety profiles, a notable proportion of IITs generally pose no or minimal additional safety risk to participants because they evaluate a medicine product that is covered by a marketing authorization with quality, safety and efficacy already fully assessed in the course of marketing authorization procedures. For these trials, the damaging effects of the Directive are apparent without any evidence for benefit or avoided harm that can be attributed to the Directive.[8,14]

Pediatric investigator-initiated trials

Evidence generated by IITs complements those from industry-sponsored trials and provides a valuable contribution towards improving healthcare. Due to the historical exclusion of

children from clinical drug trials, and the general lack of commercial interest to invest in research of off-patent drugs,[15] IITs play a particularly important role in furthering medical knowledge to guide pediatric prescribing practices. The off-label use of medicines in pediatrics is widespread, with survey data suggesting figures that are often above 50%.[16]

A significant proportion of pediatric IITs concerns medicinal products that are already authorized or are used off-label in a manner consistent with established clinical practice. As such, trial participants are exposed to no additional risk compared to routine clinical care with respect to the intervention, and understandably this has led to widespread calls for the adoption of a risk-proportionate approach which would allow a better balance between patient safety, data quality, and maximizing time and cost effectiveness.[3] Moreover, due to the inherent challenge of having a relatively small population from which to recruit from per site,[17] multinational clinical trials are necessary for many pediatric diseases and conditions,[18] and thus it is important for reform and further harmonization of legislations across borders.

Risk proportionate approach

The Regulation and the EU Commission expert group recommendation on *Risk proportionate approaches in clinical trials* bring a strong emphasis on appropriate and proportionate requirements on trial design and conduct.[1,12] It formally establishes a new clinical trial sub-category of "*low intervention clinical trials*".[1] These clinical trials (Table 1) are defined as trials posing a minimal additional safety risk or burden to participants compared to normal clinical practice, and for these trials, the Regulation sets out areas for potential risk adaptation including dossier requirements, informed consent, safety reporting, monitoring, contents of the trial master file, and insurance coverage.[1,12] Of particular importance is that the Regulation allows risk adaptations to be applied to any type of clinical trial based on

appropriate risk identification and evaluation, thereby encouraging sponsors to develop more systematic and risk-based approaches to all clinical trial activities.[1,12]

Labelling and traceability of IMPs are two further areas for potential risk adaptation. For IMP which "*have already been placed on the market as an authorised medicinal product*" in the EU, a general rule of "*no additional labelling*" could be applied for clinical trials that do not involve the blinding of the label.[1] The Regulation simply requires labelling to be "*in accordance with Title V of Directive 2001/83/EC,*[1] which essentially translates to labelling in line with normal practice. It is important to note that this risk adapted provision is not limited to "*low intervention clinical trials*" and may be applied more widely provided the IMP is covered by a marketing authorization in the EU.[1] Similarly, taking into account whether the IMP is an authorized medicinal product, and whether the clinical trial is a low-intervention clinical trial, the Regulation also provides the possibility of using routine medical and pharmacy records or other source documents to demonstrate IMP traceability and accountability.[1,12]

Labelling and traceability of investigational medicinal products

The purpose of IMP labelling is to enable clear identification of the IMP, the trial, and the investigator, and to ensure the safety of the participants by facilitating the correct use of the IMP. It also provides a mean for traceability to ensure the safety of the participants in case of incidents or product recalls, and the reliability and robustness of the data generated in the clinical trial. Compliance with IMP labelling and traceability is a legal requirement for all clinical trials conducted in the EU and many other countries,[1,19,20] where failure to demonstrate compliance is in breach of good clinical and manufacturing practice. For EU countries, the requirements are set out in Article 51, Chapter X, and Annex VI of the

Regulation and the Detailed Commission guidelines of good manufacturing practice for IMP for human use.[1,21]

An important point to note is that the labelling of IMP falls within the legal definition of manufacturing.[1] In clinical trials, the increased complexity in operations associated with randomization, blinding, and consequent packaging and labelling designs thus requires manufacturers to be specifically authorized for IMP related activities, unless otherwise exempt.[1,21] The granting of this authorization is managed by each EU country, where holders of authorization are required to demonstrate compliance with Good Manufacturing Practice.

Case studies

At the time of this article, cASPerCF (EudraCT Number: 2019-004511-31) and KD-CAAP (ISRCTN71987471) are two ongoing pediatric IITs involving 16 EU countries and the United Kingdom (regulated under the same Directive at the time of trial set up).[5] The cASPerCF trial investigates the pharmacokinetics of posaconazole in children with cystic fibrosis and *Aspergillus* infection. KD-CAAP is a randomized trial of prednisolone plus standard of care (intravenous immunoglobulin), versus standard of care alone for the prevention of heart complications in children with Kawasaki disease. With an open label design, both trials were able to use authorized posaconazole and prednisolone products, respectively, without the need for bespoke manufacturing or re-packaging.

cASPerCF

For the cASPerCF trial, despite the presence of clear identification and traceability information (e.g., name, batch number and expiry date) on authorized posaconazole products, full compliance with clinical trial labelling requirements was required under the Directive.[2] IMP procurement and labelling activities were contracted to a central authorized

manufacturer as it was not possible to discern whether all potential sites hold the required authorization to perform clinical trial labelling. With a multinational trial like cASPerCF, the preferred option is often to use booklet labels to accommodate the different languages, as otherwise, the alternative of country specific labelling would hugely reduce flexibility in supply logistics. Patient recruitment rates are rarely predictable, and the re-labelling operation to reallocate IMPs between countries would often require more time and cost to deliver. However, the use of multilingual booklet labels necessitates the coordination of label text translations, and delay in labelling is not uncommon as labelling activity can only be initiated once all country specific translations have been finalized. Accordingly, should recruitment be slower than expected, the work involved in expanding the number of research sites to other countries would require significant re-work.

A further challenge with a centralized IMP supply model is balancing supply against unused stock whether this be expired products at the manufacturer or unused stock held at sites. For trials of high-cost drugs such as posaconazole (~ € 2,800 per box of 96 tablets), the issue of unused stock simply cannot be afforded especially in the context of a publicly funded trial. The success of a centralized IMP supply model thus requires careful planning as well as resources to ensure continuous oversight by experienced personnel. For cASPerCF, the research team weighed up the risks and cost-implications of various options facilitated by the support of the c4c consortium. A distribution model with smaller and frequent shipments was chosen, though this needed to be carefully balanced against the costly temperature-controlled shipping of IMPs to each site.

As illustrated by the cASPerCF trial, the IMP labelling requirement can have considerable resource, regulatory, and cost implications on IMP supply chain logistics.[22] Under the Regulation, an assessment of "*no additional labelling*" would be an option for the cASPerCF

trial as the IMP fulfils the criteria of "*already been placed on the market as an authorised medicinal product*" in the EU and "*do not involve the blinding of the label*".[1] It would be feasible to use authorized posaconazole products from routine supply chain; this would obviate the need for a central authorized manufacturer to perform clinical trial labelling, booklet labels, and temperature-controlled IMP shipping which translates to a cost saving of over tens of thousands of euros as well as the many hours saved in administrative burden. As each site could make supply to participants from their routine inventories (i.e., from the hospital pharmacy) and label in line with normal practice, this approach would allow greater flexibility in inventory control as the challenge of centrally balancing drug availability against stock wastage is minimized. Considering these downstream implications, the risk-adapted provision on labelling is thus an important framework for researchers and sponsors to understand and appropriately apply.

KD-CAAP

In contrast, the KD-CAAP trial opted for the use of routine stock from hospital pharmacy at the outset, but the divergent application of the Directive meant that the research team faced a different set of challenges with the first hurdle of navigating through the different national laws and guidelines. A risk-adapted approach to labelling was approved by the UK medicines regulatory authority which permitted pharmacy at research sites to source and label authorized prednisolone products as per routine practice without having to hold specific IMP manufacturing authorization or to include additional clinical trial label content. On the other hand, there were countries with no exemptions in place, while others have made provisions for reduced label content but would still require additional labelling to be performed. It is difficult to comprehend how clinical trial labelling requirements would provide additional safeguards to trial participants compared to routine practice which already include clear

dosing instructions, patient details, and information that enable clear identification and traceability of the product.

The logistics of labelling and completion of IMP accountability documentation, particularly with respect to enabling out-of-hours patient recruitment, raised another set of practical questions, and it was not always easy to decipher the country specific regulatory requirements from local operational practices. The disparities between countries thus led to laborious discussions with each site, making the conduct of the trial unnecessarily complex and contributing to months of delays in trial initiation.

Applying the same risk assessment as the cASPerCF trial, the risk-adapted provision on IMP labelling could equally be applied to the KD-CAAP trial where the direct applicability of the Regulation would avoid the variation in practice seen under the Directive. The use of routinely maintained pharmacy and clinical documentation to demonstrate IMP traceability may also be justified on the basis that it is an open-label trial of an authorized medicinal product from routine hospital pharmacy stock and taking into account that normal prescribing practice and documentation apply.[12] As such, these steps toward greater pragmatism and alignment with routine practice should allow research sites to support trials with minimum additional operational burden, where it is expected that these less burdensome requirements would positively impact on the conduct of clinical trials.

Implementation and challenges

Risk proportionate approaches in clinical trials are particularly welcomed in pediatrics as investigating off-label uses of authorized medicinal products remains a research priority. The direct applicability of the Regulation, removing the need for interpretation of individual country specific law, is also expected to positively impact on the planning and conduct of

multinational pediatric clinical trials. However, some concerns remain over the scope of what is meant by "*the use of the IMPs is evidence-based and supported by published scientific evidence"*,[8] since such a statement is open to interpretation which might impact implementation for "*low-intervention clinical trials"*. It is recognized that interpretation of *"evidence-based"* may vary among different researchers and medicines regulatory authorities, but the Regulation is inclusive of the risk proportionate principles in that "*published scientific evidence"* includes "*high quality data published in scientific journal articles, as well as national, regional or institutional treatment protocols, health technology assessment reports or other appropriate evidence"*.[1] Moreover, the Regulation acknowledges potential variation in practice between countries, and specifically sets out that the country where the use is evidence-based should be proposed as the "*reporting Member State*" for assessing the clinical trial application.[1] Nonetheless, the principle of a risk proportionate approach has not been implemented in most EU countries, and its application in practice may still present practical challenges. Thus, the impact of the risk-based provisions remains to be seen.

Wider perspective

While the focus of this article is on pediatric IITs, the assessment of "*low-intervention clinical trials*" could equally be applied to industry-sponsored clinical trials. Both industry and academic sponsors should thus familiarize themselves with the Regulation and associated guidance. It is worth reiterating that the principle of risk proportionality is not only limited to IMP management; the Regulation's provision for risk adaptation may be applied to any type of clinical trial, taking into consideration trial specific characteristics. It is also noteworthy that while other countries have not explicitly categorized what the Regulation has defined as a "*low-intervention clinical trial*", the global movement towards a risk proportionate approach is evident in guidance developed by groups such as the Organization for Economic

co-operation and Development,[23] the US Food and Drugs Administration,[24] and the TransCelerate group.[25] As the EU lead the way in the implementation of risk proportionate approaches in clinical trials, medicines regulatory authorities and investigators in other settings will likely be guided by how effective the Regulation proves in practice.

Concluding remarks

The Regulation gives a strong impetus to a risk-based approach to clinical trial implementation with respect to IMP management, and as such, offers a path for more efficient delivery of pediatric IITs. However, its implementation in practice will inevitably requires national medicines regulatory authorities, sponsors, and researchers to effectively apply these provisions, and there remains a risk of variation in the interpretation of "low-intervention clinical trials". Medicines regulatory authorities are recommended to provide examples of trials in which such risk-based provisions can be applied to enable researchers and sponsors to relate the Regulation requirements in the context of their own healthcare setting as well as to facilitate discussions to ensure consistencies in implementation in practice. Furthermore, experience from multidisciplinary and multisectoral European research networks such as the c4c consortium, European Paediatric Translational Research Infrastructure, European Network of Excellence for Paediatric Research (TEDDY) and others, can facilitate researchers through shared learning and support efficient trial implementation to facilitate the application of the Regulation to its full potential and stimulate greater research in children in the EU.

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Table 1: Definition of 'Low-intervention clinical trial'[1]

'*Low-intervention clinical trial'* *means a clinical trial which fulfils* ***all*** *of the following conditions:* ***(a)*** *the investigational medicinal products, excluding placebos, are authorised.* ***(b)*** *according to the protocol of the clinical trial, (i)the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned.* ***(c)*** *the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.*