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Pharmacy and formulation support for paediatric clinical trials in England

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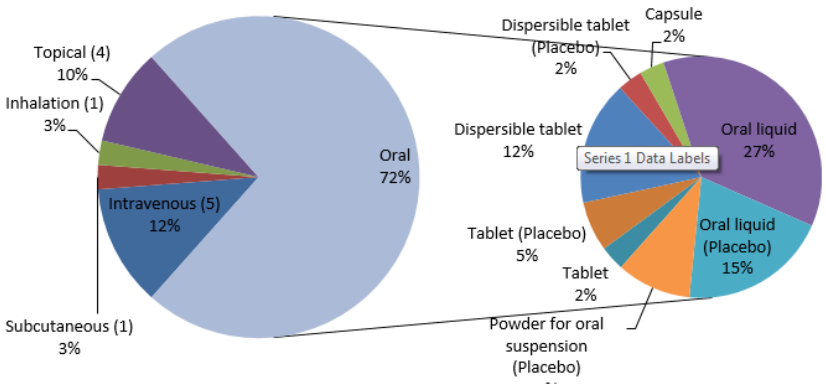
Graphical abstract

Summary of reasons why suitable UK authorised products were not identified for 41/103 products required to support 44 paediatric clinical trials reviewed in this study

Reasons	No. of products
Not available as UK authorised product in any dosage form	2
UK authorised product is not in the required dosage form (and no suitable unlicensed preparation available)	6
UK authorised product is not in the required dosage form (dosage form required is available but as unlicensed product (e.g. "specials", extemporaneous preparation) only)	10
UK authorised product lack dosing flexibility as required for the trial	1
Product is a matching placebo	18
The aim of the study is to test a new drug formulation	3

Pharmaceutical products requiring bespoke manufacture/import



Abstract

Availability and sourcing of investigational drugs for paediatric clinical trials is known to be a challenge for investigator-led clinical trials. The National Institute of Health Research Clinical Research Network: Children (CRN: Children) provides support for formulations and pharmacy related issues to researchers planning and setting up paediatric clinical trials within England. This paper reviews pharmacy and formulation support provided to a consecutive series of investigator-led clinical studies supported by CRN:Children. Case studies are included to describe some of the unique pharmaceutical challenges encountered.

44 trials were reviewed and a total of 103 products were required to support these clinical trials. UK authorised products were suitable for use for 62 of these 103 products. In the remaining 41 cases, 4 could be sourced as an authorised product within the European Union and the remaining 37 required bespoke manufacture. Bespoke manufacture of an investigational drug or placebo is costly. Typical costs for the initial development and testing of a bespoke investigational drug or placebo were in the range of £30,000 - £100,000 per product. The estimated cost for 19 out of 45 trials was available; in summary, the costs on a per patient per day of therapy basis ranged from under £1 to almost £600; short studies involving multiple agents are obviously the most expensive. This range is dependent upon the need for bespoke manufacture and also the number of participants within the trial.

The arrangements for investigational drug supply can greatly affect the study design, regulatory requirements, trial logistics, as well as the total cost of research. As investigational product related activities are often costly, necessitating months of advance

planning, it is imperative that specialist inputs are sought from the very start of the study design and planning process.

Keywords: clinical trial, paediatric, dosage forms, formulation, pharmacy

Introduction

The drive to improve the evidence base for paediatric medicines is underpinned by two major pieces of legislation established in the EU and US (EMA, 2001; FDA, 2013). This commitment to expanding research on medicines for children is similarly supported by academic/clinical researchers, whose increased engagement in investigator-led paediatric clinical trials has given further emphasis on the importance of evidence-based practice in paediatric medicine. Meanwhile, it is widely recognised that paediatric clinical trials are challenging to deliver, and investigator-led trials can be said to be even more so due to inherent resource constraints. The trials and tribulations faced by investigators are overwhelming, and a major challenge is that of the supply of investigational drugs (Lenney et al., 2011; Whitham et al., 2009).

An effective and robust supply of investigational drugs and comparators, that meet the specific requirements of a study, is critical for any clinical trial. The work involved is technically complex, intertwined with regulatory and financial implications. Clinical trials in the UK are governed by statutory requirements in the form of The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), setting out requirements to comply with Good Clinical Practice, and the requirement to manufacture and import clinical trial

medicines to Good Manufacturing Practice standards. Product quality is obviously important as it not only affects patient safety, but can also affect the validity and reliability of the clinical trial results. To ensure quality assurance, clinical trial guidelines from the World Health Organization (WHO, 2005) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (ICH, 1996) require compliance with applicable good manufacturing practices for all investigational drugs and comparators, with many countries legally enforcing such standards.

Poor quality products may include those with no, too little, or too much active drug, and those that degrade with toxic products or contaminants (Newton et al., 2015). The basis of quality also encompasses the concept of bioavailability (Newton et al., 2015). Furthermore, consideration of bioavailability must be extended to take account of drug administration, particularly in the paediatric setting. Our intrinsic clinical practice of manipulating dosage forms that are designed for adults is ill-founded as the effects of such manipulations are often poorly documented (Newton et al., 2015). Splitting tablets can cause dose inaccuracies. Crushing or splitting some tablets, or opening capsules, destroys their release properties and can affect bioavailability. As such, the use of an age appropriate and well characterised dosage form is pertinent to assuring trial data reliability in paediatric clinical trials.

Reporting of formulation information in published paediatric clinical trials has previously been highlighted to be largely inadequate, which may, in part, reflect the lack of appreciation in the trial community of the specificities relating to pharmaceutical formulations (Pandit et al., 2010; Standing et al., 2005). Typically appropriate formulations

were not used or insufficient detail on formulations was reported to ensure that the results can be reproduced in other clinical studies and in clinical practice. The extent of the issue reported in 2005 (Standing et al., 2005) was that 37 (49%) of studies included used a paediatric formulation; only 28 (37%) publications provided adequate information for the formulation to be reproduced accurately, and 20 (26%) did not state the formulation used at all. An update to this review was published in 2010; although an improvement in reporting was anticipated a continuous trend of lack of appropriate reporting of dosage forms used was discovered (Pandit et al., 2010). More recently a review providing more comprehensive evaluation of clinical trial needs for children has been produced, which addresses many aspects of clinical trials, not only those relating to formulations (Van't Hoff and Offringa, 2015).

To facilitate investigators in delivering high quality paediatric clinical trials, the National Institute of Health Research (NIHR) Medicines for Children Research Network (MCRN), currently known as NIHR Clinical Research Network: Children (CRN: Children) (https://www.crn.nihr.ac.uk/children/), established an expert formulation and pharmacy workstream in 2007 to concentrate on paediatric formulation issues. The Pharmacy and Formulation team included 2 paediatric pharmacists and 1 formulation scientist, supporting 14 different Clinical Studies Groups (CSGs) within the CRN: Children covering a wide range of different specialty areas within child health. The CSGs provide, free of charge, expert advice to help researchers develop high quality research proposals. Draft protocol or synopsis can be submitted to CSGs for review at any stage of development. Members of the CSGs (e.g. clinicians, nurses, other healthcare professionals) including the Pharmacy and Formulation team members review the submitted research proposal, and provide advice and comments

directly to the investigator. Following the initial review, the Pharmacy and Formulation team member will continue communication with the respective investigator and provide hands-on support, including, where necessary, securing the drug supply.

In this article, we provide a descriptive analysis of the medicine-related issues identified in setting up paediatric investigator-led clinical trials, and highlight some of the unique pharmaceutical challenges encountered based on a consecutive series of clinical trials where pharmacy and formulations assistance was requested.

Material and methods

A consecutive series of investigator-led clinical trials supported by the CRN: Children, which has a geographical coverage of England, between April 2012 and March 2015 inclusive were reviewed. The review only included trials which were in the planning/ set-up stage and excluded those which opened for patient recruitment prior to April 2012. Paediatric oncology clinical trials were not included in the review as they were outside the remit of CRN: Children and the authors were unable to access the data required to include them in this review. Information on trial design and the characteristics of study drugs were extracted from draft protocols or any documents that were submitted to the CRN: Children. Data on medicine-related issues were extracted from email correspondence (up to 31st May 2015) between investigators and colleagues of the CRN: Children Pharmacy & Formulation group. In order to standardise the results, the different medicine-related issues found in the free text of email correspondence were assigned keywords by two reviewers. A third reviewer was consulted if two reviewers could not reach consensus. The European Directorate for the Quality of Medicines & HealthCare (EDQM) standard terms were used to standardise the

pharmaceutical forms and routes of administration (European Pharmacopoeia Commission, 2014).

Results

Number of types of studies

A total of 45 investigator-led clinical trials were included in the review. Table 1 shows some details about the nature of the studies included.

Study design

In total, 20 (44%) of the studies were open-label trials and 25 (56%) of the studies were blinded. The estimated sample size of the included studies ranged from 10 to 2400 with a median value of 118.

Of the open-label studies, only 5 were single arm trials and the remaining 15 were two-arms trials comparing either different ways (e.g. timing of administration, treatment duration, high dose vs. low dose) of giving the test drug (5 studies), test drug as an addition to standard treatment (3 studies), or test drug against a different treatment (7 studies). Blinded trial design was considered inappropriate for all 15 studies due to inherent physical differences in appearance of comparator drugs and/or the cumbersome nature of the trial for the trial participants should placebo be included in the trial design.

Of the blinded studies, 15 studies were designed so that all site personnel were blinded to treatment allocation. For the remaining 10 studies, open-label as an alternative trial design was considered to be methodologically weak, and the involvement of unblinded site

personnel, either unblinded pharmacist/nurse for drug preparation/administration or independent blinded outcome assessors, was necessary to achieve blinding to assure trial robustness.

Age of participants

Table 2 summarises the age groupings of children involved in the studies, 35 of the studies included more than one age group of children.

Active substances

One trial was excluded from this analysis as it was a study comparing ketogenic diet with any combinations of 20 or more different authorised antiepileptic medicinal products, and thus would have skewed the data significantly. The 44 clinical trials were investigating a total of 58 active substances. Of these, 55 active substances were listed in the British National Formulary for Children (BNFC) (December 2015 update) (Paediatric Formulary Committee, 2015), and available as one or more authorised medicinal products. Two which were not found in the BNFC were listed in Martindale: The Complete Drug Reference (Wisher, 2012), and were also available as one or more authorised medicinal products. The remaining one active substance was in early phase of development and had not been administered to anyone under 18 years of age.

Paediatric formulations

The pharmaceutical formulations included in the studies was of major interest in this review; in total 103 products were required to support 44 clinical trials. UK authorised products were considered suitable for use for 62 of these 103 products. Out of the 62, 29

products would require further central processing (e.g. blinding, clinical trial packaging and labelling by a third party drug manufacturer) or the involvement of unblinded personnel at investigator sites for drug administration.

The route of administration for these formulations was predominantly oral (69/103); with parenteral products being the next most common (27 in total; 20 for intravenous use and 7 for subcutaneous administration) other routes of administration included inhaled products (3); eardrops (2) and topical products to be applied to the skin (2).

In the 41 cases where a suitable UK authorised products could not be identified (see Table 3), bespoke manufacturing or sourcing from other European countries was deemed necessary. Sourcing of a suitable authorised product from EU was possible for 4 of the 41 products, leaving 37 products requiring bespoke manufacture. Table 4 highlights the range of pharmaceutical dosage forms that required bespoke manufacture.

Support from pharmaceutical industry

Eight out of the 14 studies received support from the pharmaceutical industry in the form of the test drug supply at no cost to the researchers. Of these, 2 test drugs were provided in a presentation which needed further labelling and packaging to meet the specificities as required by the clinical trials regulation (EMA, 2001). Eight pharmaceutical companies who produced the study drug under investigation were approached to manufacture matching placebo products and placebo supply agreement was successfully agreed for 4 (19%) products; 3 were zero cost supplies with 1 pharmaceutical company manufacturing the placebo supply at a cost to the researcher. There was one other pharmaceutical company who provided financial support to the researcher to have bespoke placebo manufacturing to

be carried out elsewhere. At the time of review, information on contract and supply agreement negotiations were available for 4 studies, and the time taken to reach an agreement was found to be a minimum of 6 months and up to 15 months in one case.

Cost of investigational drug supply

Estimated costs for investigational drug supplies were available for 19 trials. In summary, the costs on a per participant basis ranged from £95 as the minimum to £6000 as a maximum cost with the median cost per participant being £342. When these are determined as a cost per patient per day of treatment the values range from under £1 to almost £600; short studies involving multiple agents are obviously the most expensive. This range is dependent upon the need for bespoke manufacture and also the number of participants within the trial. Typical costs for the initial development and testing of a bespoke investigational drug or placebo were in the range of £30,000 - £100,000 per product.

Case studies

Figure 1 and 2 outline two case studies to illustrate how integrated formulation and support is required to set up paediatric clinical trials.

Discussion

This review has highlighted that investigational drugs needed to deliver investigator-led paediatric clinical trials cannot easily be met by currently licensed medicinal products on the market. The type of study design has important implications with respect to the study drug supply; it determines the need for blinding, methods of blinding, as well as packaging

configurations of study drugs needed to meet the specific requirements of individual studies. Formulation factors (e.g. appropriateness of dosage form, safety of excipients, stability), sourcing of products and trial packaging are issues which are commonly faced by researchers. Data collected and described provide evidence on the need for integrated formulation and pharmacy support from the early stages of study conception. The age range of participants within the study can affect the type and number of formulations required as this has implications for dosing strategies as well as the appropriateness of medicines for younger children. The range of ages included in the studies is aligned to previous reports where limited research is conducted in the youngest members of the population.

As expected for investigator-led clinical trials, all but one study were investigating off-label use of approved drugs. While many of these drugs, by which we mean the active drug substances, are available as authorised medicinal products, the latter may not always be in a dosage form that can be considered appropriate for paediatric clinical trials. Typically the drugs concerned are not particularly unusual in paediatric practice, however sourcing of non-UK products or bespoke manufacture of new drug dosage forms were considered more appropriate in 38% of the reviewed studies to provide age appropriate formulations for the study. This results in paediatric investigator-led trials being disadvantaged, as significant resources, both financial and time, must be made available for the development of new medicine formulations on top of other drug manufacturing and packaging activities before trials commence.

Among the different reasons, bespoke sourcing/manufacturing of investigational drugs supply was considered necessary even when the drug under investigation can be routinely

sourced as an unlicensed medicinal product. Unlicensed medicinal products are widely used in everyday paediatric clinical practice, and may take the form of extemporaneous products, products made under a specials licence (“Specials”), or imports. “Specials” is a UK term to describe medicines made by facilities with a Manufacturing Licence awarded by the national regulator (MHRA) using GMP standards but without Marketing Authorisation. Specials provide much greater quality assurance than extemporaneously prepared medicines, but while a "Specials" licence provides some confidence in the quality of the product it does not require a formal assessment of product safety or efficacy. The general assumption that these products are appropriate for use in clinical trials is widespread, but the fact is that this is not always the case as they do not always meet the regulatory standards on quality to assure the validity and reliability of the clinical trial results. Unlike an authorised medicinal product, which is made by a standard, reproducible process, and is well characterised in terms of its pharmaceutical and pharmacokinetic properties, this is always absent with extemporaneous products. While “Specials” have greater quality assurance in the manufacturing process than that of extemporaneously prepared products, they too often lack information on bioavailability. A study of captopril investigated the bioavailability of two commonly prescribed unlicensed liquid formulations of captopril found that both products were not bioequivalent to the licensed tablet form, or to each other, and so cannot be assumed to behave similarly in therapeutic use (Girard et al., 2013; Wan et al., 2013). In a clinical trial context, this example illustrates the importance of understanding the formulation of the drug as clinical trial outcome may be very different depending on the product being used. It is this fundamental principle which underpins the requirements of bioequivalence as the legal basis for approving generic copies of drug products. Furthermore, as previously highlighted by others, the reporting of complete pharmaceutical

details in published clinical trial reports is essential to allow post trial application in clinical settings (Pandit et al., 2010; Standing et al., 2005).

The practical consequence in these situations is the need to identify suitable pharmaceutical manufacturers to make the products, and the complexity of this task should not be underestimated. “Specials” manufacturers may appear to be an obvious choice; after all, they are manufacturing these products for everyday clinical use. However, not all will hold the necessary manufacturing licence to manufacture products for clinical trials use. Even for those who hold the appropriate licence, additional *in vitro* studies are likely to be required in order to fully characterise the pharmaceutical properties of these products. Pharmacokinetic studies, as separate or as sub-studies, would also need to be considered to provide supporting bioavailability data (Standing et al., 2005).

Comparative clinical trials were the most common study design in our review, which is not surprising for investigator-led trials. This brings with it the key question of blinding, specifically the ability to blind active comparators and the supply of matching placebo. However, for reasons which have previously been described elsewhere (Wan et al., 2013), it is not always possible to achieve either of them in a satisfactory way. The particular challenge lies in the fact that liquid dosage form, as demonstrated in this data and previous studies, is the most common formulation used in paediatric clinical trials (Pandit et al., 2010; Standing et al., 2005). While this offers dosing flexibility to accommodate weight-based dosing, the pharmaceutical aspects of liquid formulations lead to complex blinding challenges.

Support from pharmaceutical companies can greatly facilitate the delivery of paediatric investigator-led clinical trials. After all, they would have manufactured the investigational drug and placebo for their own marketing authorisation trials, and have all the required technical data on the manufacturing and analytical methods to support clinical trial application. However, the unfortunate reality is that for many pharmaceutical companies, manufacturing on the comparatively limited quantity for independent researchers is simply too difficult to accommodate. Even if supply can be agreed, it is also important to bear in mind that contract negotiations can be lengthy; the divergent needs of the pharmaceutical industry and academic researchers often gave rise to contentious issues surrounding investigational drugs supply and trial protocol designs, which could result in long delays as reported by us and others (Lenney et al., 2011; Whitham et al., 2009).

On the basis of the issues described, it is essential that investigators are supported in sourcing appropriate products for use in paediatric clinical trials. Those involved in the design and development of investigator-led clinical trials are typically unaware of the different factors relating to investigational drugs supply (Girard et al., 2013) and therefore need support and early guidance from individuals with this type of expertise. The European Medicines Agency (EMA) recognises pharmacy and formulation expertise within their Paediatric Committee (PDCO) by virtue of a special working group looking at formulations issues to support pharmaceutical companies in developing new products. However, pharmacists are rarely part of academic/clinical research teams setting up clinical trials.

To the best of our knowledge, this pharmacy and formulations support provided by the CRN: Children is unique, and such collective review of paediatric investigator-led clinical

trials has not been published previously. Those with formulations and research expertise are able to intrinsically examine pharmaceutical aspects along with trial methodology and implementation to enable studies to be delivered using high quality medicinal products. The unique and valued role of pharmacists in multidisciplinary teams has been highlighted in several clinical areas including optimisation of pharmacy content in clinical cancer research protocols (Debruyne et al., 2015; Fairbanks et al., 2007). However, their role in the design and planning of clinical trials can be overlooked, and yet this study demonstrates their value in maximising the likelihood of success of paediatric clinical trials. Informal feedback from investigators to the Pharmacy and Formulations team has been very positive with researchers echoing comments made in previous publications (Lenney et al., 2011; Whitham et al., 2009) where the value of involving pharmacy and formulations expertise early in the trial is acknowledged to be imperative to success.

Conclusions

Despite representing a fundamental step towards evidence-based paediatric practice, the delivery of investigator-led clinical trials in children poses important challenges in relation to investigational drugs supply, partly due to the historical lack of authorised age appropriate formulations for children. The complexity of these challenges is greatly influenced by study designs, which in turn may be limited by the availability of suitable formulations. In undertaking the supply arrangement, considerations should be given to formulation factors, regulatory requirements, trial logistics, as well as the cost of research. Notwithstanding, our experience demonstrates that the majority of these challenges can be appropriately addressed with early pharmacy and formulation experts engagement.

Much work remains to be carried out to address the unmet therapeutic needs in paediatrics, but if the quality of the investigational drugs and comparators being used is not assured, these clinical trials may put patients at risk, conclude with erroneous results, and thus be a major waste of time and public investment. The development of awareness and access to pharmacy and formulations support will aid in the development and delivery of robust high-quality clinical trials in children.

Declaration

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Figure 1: Case study 1 - Identification and sourcing of appropriate investigational drugs

Challenge: Identification of three appropriate products as investigational drugs for oral use in an early phase neonatal clinical trial where no authorised products are currently available.

With our clinical pharmacy knowledge and formulations expertise, the initial proposal of amphotericin, a drug which is not currently authorised for use in this age group, was queried. We proposed using the authorised product nystatin as an alternative. For tobramycin, an assessment was made on a “specials” product which is used clinically sometimes for older children. However, the excipients contained in the product were deemed to be unsuitable for neonates and we proposed the off label use of the authorised nebulised formulation instead. As for colistin, we similarly examined the off-label oral use of the authorised intravenous dosage form. In all cases the excipient load of the products were reviewed to ensure that the products were acceptable for use in neonates as well as considering the practicality of drug administration and the much needed pharmacokinetic component of the study. The study team was presented with full justification for products selection and their associated costs. Taking into account the stage of the research, we supported the study team in selecting products that were “clinical phase appropriate” (Ernest et al., 2012) as well as ensuring that patient safety and results of the clinical trial are unaffected by inadequate quality arising from unsatisfactory products. This enabled the study team to submit robust proposal with appropriate costs for their trial.

Figure 2: Case study 2 - Supply of investigational drugs across multiple sites

Challenge: A study needed to open an additional 20+ sites to support the planned patient recruitment. Lack of expertise within the trial team had implications on the management of the investigational drug supply.

The investigational drug supply was originally planned based on 3 sites, where the supply arrangement was set-up interdependently with the randomisation and stratification scheme. A radical rethink of the entire investigational drug supply chain and pharmacy processes was needed to ensure that recruitment continued within the constraints of limited flexibility in making changes to the overall investigational drug arrangement and trial design. Our effort in re-designing the supply process, creating all required pharmacy documentation, securing local resources to support the study, through to the delivery of individual site initiation visits and transitioning the currently opened sites, was vital in facilitating the timely set up of all participating sites while ensuring all the regulatory requirements were met. The study recruited to time and target, and has now been completed.

Table 1. Key characteristics of clinical studies included in the review

	Frequency
Clinical Specialities (n=45)	
Allergy, Infection and Immunity	7
Anaesthesia, Intensive Care	2
Cardiology	1
Diabetes and Endocrine	2
Gastroenterology, Hepatology and Nutrition	2
General Paediatric	2
Haematology	2
Inherited Metabolic Disorders	1
Neonatal	7
Nephrology	4
Neurosciences	4
Pain	1
Psychiatry	1
Respiratory and Cystic Fibrosis	6
Rheumatology	3

Planned Number of Investigational Sites (n=45)	
Single site	4
2 - 5	20
6 -10	9
11-20	6
21+	6
Geographical Scope (n=45)	
UK Single Centre	4
UK Multi-Centre	37
EU Multi-Centre	4

Table 2. Age of participants and frequency of studies that include each age group

Inclusion age of participants	Frequency of study including this age group
Pre-term	4
0-27 days	7
1-23 months	15
2-11 years	34
12-18 years	20

Table 3. Summary of reasons why suitable UK authorised products were not identified for 41 products

Reasons	No. of products
Not available as UK authorised product in any dosage form	2
UK authorised product is not in the required dosage form (and no suitable unlicensed preparation available)	6
UK authorised product is not in the required dosage form (dosage form required is available but as unlicensed product (e.g. “specials”, extemporaneous preparation) only)	10
UK authorised product lack dosing flexibility as required for the trial	1
Product is a matching placebo	18
The aim of the study is to test a new drug formulation	3

Table 4. Summary of pharmaceutical products requiring bespoke manufacture/import

Route of administration (n=)	Pharmaceutical form	No. of products
Oral (30)	Tablet	1
	Tablet (Placebo)	2
	Dispersible tablet	5
	Dispersible tablet (Placebo)	1
	Capsule	1
	Oral liquid	11
	Oral liquid (Placebo)	6
	Powder for oral suspension (Placebo)	3
Intravenous (5)	Solution for injection/infusion	2
	Solution for injection/infusion (Placebo)	3
Subcutaneous (1)	Solution for injection (Placebo)	1
Inhalation (1)	Inhaler (Placebo)	1
Topical (4)	Ear drop	1
	Ear drop (Placebo)	1
	Topical solution	2