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Current perspective

Clinical trials for children with cancer in Europe – Still a long way from harmonisation: A report from SIOP Europe

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ABSTRACT

Clinical trials for children with cancer have been particularly hard hit by the introduction of the EU Clinical Trials Directive in 2004. Largely investigator-led and lacking in commercial sponsorship, they have struggled to find the resources necessary to comply with the complex bureaucracy. These rare diseases require multinational participation to permit appropriately powered clinical trials to be undertaken. Differences in interpretation of the Directive by national regulatory authorities have had a disproportionate effect on trials in children, highlighted by differences in what is deemed an 'investigational medicinal product' when paediatric use of an old drug is outside its licensed indication. Insurance costs have increased a 100-fold with no increase in actual risk between consecutive trials from the same study group. Issues raised at the recent conference held to reappraise the operation of the Directive are summarised to emphasise the particular issues for trials in children with cancer.

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1. Introduction

Randomised phase III clinical trials for children newly diagnosed with cancer have been the bedrock of progress in Western societies for nearly 40 years. The result is that nowadays approximately 75% of children newly diagnosed with cancer can expect to be cured of their condition using tried and tested drugs with well recognised efficacy and side-effect profiles.¹ This enviable position in these rare diseases is largely due to the high rates of participation in clinical trials in the past. As the total number of cases of most types of childhood cancer is less than 100 per year in the average European country, successful trials require multinational collaboration and a high level of acceptance by patients.² This has been made possible by the long-established practice for clinicians caring for children with cancer to work together through national networks and multinational tumour-specific working groups

to design and implement investigator-led trials. Until recently, over 70% of children newly diagnosed with cancer in most Western European countries would enter a national or international phase III clinical trial.³ However, the availability of clinical trials to children with cancer in Europe is now threatened as investigator-led, non-commercial trials struggle to find the resources necessary to comply with the EU Clinical Trials Directive 2001/20/EC (EU CTD).⁴⁻⁷

Much has been written about the impact of the EU CTD on the conduct of non-commercial trials in Europe.⁵⁻⁷ The overall aims of the directive were laudable, to standardise the regulation and quality of trials and ensure patient safety. However, it is well recognised that the effect on the ground has been to greatly slow the opening of trials, without any noticeable improvement in patient safety, which already had a good track record in trials in this sector. The EU CTD has had a disproportionately negative impact on trials in childhood cancer. This is

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because nearly all trials require international participation in order to achieve necessary recruitment. Also, if one applies the strictest definition of an investigational medicinal product (IMP), then the majority of drugs used in children with cancer should be so declared as their use in children is not usually specified in the marketing authorisation. Specific aspects, such as the requirement for a single European trial sponsor, have created serious difficulties in the conduct of international trials, both within the EU and for collaborations with cooperative groups outside of the EU. These factors mean that virtually any trial for children with cancer is bureaucratically complex and hence requires additional resources to comply with the regulations, over and above those required to run a clinical trial within a single national group.

2. Key issues for paediatric cancer trials in relation to the EU CTD

The obstacles to smooth and efficient conduct of clinical trials in children with cancer can be discussed under the following headings. These were identified from a survey undertaken by SIOF (Société Internationale D'oncologie Pédiatrique) Europe of the clinical trial groups and national childhood cancer

organisations running multinational clinical trials in Europe. Many issues apply equally to the majority of investigator-led multinational clinical trials in all age groups (Table 1).

2.1. Definition of an interventional clinical trial

The majority of childhood cancers have 'standard of care' treatment regimens that are widely accepted at an international level. These use cytotoxic medicines outside of their licensed indications, as there are often no approvals in place for use in this age group. Such 'off label' drug use together with variable national interpretation in whether defined treatment strategies linked to clinical data collection constitute 'research' have led to wide variations in what is deemed an 'interventional' clinical trial between countries. The therapeutic question is often one of fine tuning the risk stratification to assign patients to one of several 'standard of care' treatment arms of differing intensity, each with a track record and well established side-effect profile in this age group. Often the main questions are to ensure that the children are accurately staged, that response assessment is performed in a standardised fashion and that relapse and survival are promptly and fully documented. Provided the appropriate

Table 1 – Key issues for paediatric cancer trials in relation to the EU CTD

Issue	Experience of European paediatric study groups running investigator-led ('non-commercial') trials in childhood cancers
Definition of an interventional clinical trial	'Standard of care' regimens often include medicines used 'off label' Variation in acceptance by national regulatory authorities of such use as 'background medicine' or whether it falls outside the definition of an 'interventional clinical trial'
Sponsorship	National variation in whether a single European sponsor is required or a national co-sponsorship arrangement is accepted Complex contractual negotiations required between partners
Insurance and Indemnity	Large variation in costs and in whether 'no fault' indemnity is required Insurance costs increased 100-fold with no perceptible change in risks between consecutive trials of the same study group Premiums may be paid by fundraising efforts of childhood cancer parents' associations
Definition of an IMP	Hugely variable for use of old drugs with no or limited paediatric information in their marketing authorisations IMP definition has major impact on bureaucracy of pharmaco-vigilance
Pharmaco-vigilance	Hugely bureaucratic with no noticeable improvement in patient safety (which was in any case very good in childhood cancer trials) National variation in onward reporting requirements for SUSARs when drug is used in more than one trial Inconsistency in inspection findings of regulatory processes for the same trial
Sponsor obligation to provide free drug	Large national variations in how this is absorbed into national health insurance schemes or whether this must be paid for by sponsor Required for IMPs, whose definition is also variable
Drug formulations adapted for children	Lack of appropriate formulations for young children for many oral anti-cancer drugs Strict definition of 'manufacturing' excludes young children from some clinical trials when no appropriate formulation exists
Ethical considerations	Ethical committees need appropriate expertise to evaluate appropriateness of new drug trials in children Timelines to receive the 'single' national ethical approval highly variable Institutions have created other hurdles to opening a trial, variably labelled 'R & D' approval

ethical approval and patient consent are obtained, some countries (e.g. France, Italy) do not consider these 'treatment optimisation' studies to be clinical trials whilst others do (e.g. UK). Hence the cost and bureaucracy of running the same study can vary widely across Europe and even prohibit some countries from participating in the latest 'trial' of the study group of which they are a long standing member. It is essential that ways are found to minimise the bureaucratic workload of running such trials and to maximise participation. If they are to be classified as clinical trials, then the investigators need to work with the regulators to agree to a sensible definition of what are considered the investigational medicinal products (IMPs) to reduce the requirements for expedited reporting of adverse events that are well recognised and expected with current treatment regimens.

2.2. Sponsorship

The EU CTD mandates that each trial must have a sponsor who has overall responsibility for the running of the trial, quality of the data and pharmaco-vigilance.⁴ The sponsor may delegate some or all of these responsibilities to other parties provided clearly defined agreements are in place. There remains a lack of harmonisation across the EU as to how this requirement for a sponsor is interpreted for participation in a multinational study. Some countries (e.g. France, UK and Italy) only require that national sponsorship arrangements are in place and do not insist that a single European sponsor has oversight of the running of the trial in their country. Other countries such as Germany require that there must be one legal entity that assumes overall responsibility for the trial in all participating countries, though accepting that co-sponsorship agreements may be drawn up with national sponsors in each country. This difference in approach has seriously impeded the development of several multinational paediatric clinical trials in the last few years. These trials generally have a university or public research institution as their sponsor. Such institutions are understandably reluctant to assume overall responsibility for children being treated in other countries, where they have no knowledge of the national health care system or the liabilities covered for patients treated within it.

There is inevitably an additional perceived risk by the sponsor when they are approached to take on responsibility for clinical research in children. This may be particularly true for sponsors of early phase clinical trials, where competent children and adolescents with relapsed cancer find it difficult to access new agents that are freely available to those aged 18 years and above. One way to improve this access in a timely fashion might be to encourage sponsors to include competent children and adolescents with high risk relapsed or refractory cancers into open phase I trials once the adult experience has established a maximum tolerated or feasible dose for agents with a low toxicity profile. Such an approach could be particularly pertinent for the newer targeted agents where the mechanism of action is purported to be known and a validated pharmaco-dynamic end-point is available. In such trials, there should be no ethical or scientific barrier to including children and adolescents for whose tumour types there are pre-clinical data to suggest involvement of the particular pathway.

2.3. Insurance and indemnity

The EU CTD requires that the sponsor provides insurance for patients taking part in clinical trials. It is not specified that this needs to be 'no-fault' insurance, hence in some countries, no additional insurance is required for patients taking part in clinical trials sponsored within the infrastructure of the national health service. However, many countries require specific insurance policies for patients participating in clinical trials. The cost of these is highly variable, for example in France, the insurance premium for the current SIOF Wilms tumour trial is €5.5 per patient whereas the premium for patients with rhabdomyosarcoma participating in the current European paediatric soft tissue sarcoma group (EpSSG RMS 2004) trial is €117 per patient, compared to €1.2 per patient in the previous SIOF malignant mesenchymal tumours (MMT 95) trial. The Swiss Paediatric Oncology Group currently pays the equivalent of €77 per patient in any trial. The German Cancer Society is developing criteria to formulate various risk levels with different premiums for each study, in the range of €50–100 per patient. In many countries, these insurance premiums are paid for by charitable funds raised by parents' associations; this seems an unnecessary use of their fundraising efforts.

It is essential that the requirement for liability insurance should take account of the level of risk involved in the clinical trial *per se* rather than the toxicity of the overall treatment, which may be largely deemed 'background treatment' that would be given to all patients with that diagnosis, regardless of trial participation. There should also be no absolute requirement for liability insurance for out-of-patent medicines used 'off label' in the paediatric setting, where such use is well established as part of standard practice.

2.4. Definition of an investigational medicinal product (IMP)

The definition of a drug as an IMP has a major impact on the regulatory requirements and hence bureaucratic burden and expense of a trial. Pharmacy handling of the drug (labelling and traceability) and the need for expedited reporting for pharmaco-vigilance are all defined by the EU CTD and its guidance documents. It is therefore a cause for great concern that the recent European Commission 'Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in clinical trials' published in 2007⁸ makes no mention of the special case of children enrolled in clinical trials, where what could be considered 'background treatment' often includes drugs used for an unauthorised indication. This omission ensures the persistence of national variation in what is defined as an IMP even within the same clinical trial protocol by different national regulatory authorities. These inconsistencies are further compounded by national variation in the requirements for trial-specific labelling of IMPs and permission to use generic drugs supplied from different sources in accordance with each institution's normal suppliers. Finally, the requirement by every national regulatory authority for an IMP dossier has led to unnecessary duplication of effort and long delays.

Regulators should recognise that many of the drugs or treatment combinations used in phase III clinical trials in childhood cancer are long established, with well documented side-effects and safety profiles, even though the individual drugs may be used outside of their licensed indication because there is no, or very limited, paediatric data in their marketing authorisation. The guidance on definition of an IMP should take this into account and provide unambiguous examples of the circumstances where off label use of 'old' drugs in children could be considered as a non-IMP. Also, consideration should be given to providing examples where a waiver to any requirement for trial-specific labelling of IMPs could be given. Even the reduced labelling requirements for marketed products described in Annex 13 of the European Commissions guidelines on Good Manufacturing Practice create barriers to children with cancer participating in clinical trials. The specialist treatment centre for many children with cancer is often far from their home. Some components of many treatment protocols can be delivered by the child's local hospital staff, working under the direction of the centre. However if trial-specific labelling is required, many centres have found that the only workable system in the face of hard-pressed pharmacy staff is to restrict the drugs that can be given in this 'shared care' setting and insist on families returning more frequently to the specialist centre. Of course, children receiving the same treatment but not enrolled in the trial may continue to receive the same medication from their local hospital in the usual way. The additional travel costs and disruption to family life and schooling could be a major disincentive to families participating in clinical trials.

2.5. Drug costs

The requirement for the sponsor to provide the IMP free of charge can be problematic in investigator-led trials without a commercial sponsor or partner. Treatment within the trial is usually available free or at minimal cost to patients within their national health service. However, if there is no mechanism to reimburse the hospital for the costs of relatively expensive but already licensed drugs, this creates a major disincentive for institutions to agree to participate in such trials.

2.6. Pharmaco-vigilance

The introduction of the EU CTD has undoubtedly led to improved structures and systems for pharmaco-vigilance in investigator-led trials in many countries. Whilst we welcome this, it has led to an enormous increase in the bureaucracy and expense of monitoring clinical trials in childhood cancer that have been performed safely in the past with much lower levels of monitoring. The standard treatments for childhood cancer have multiple side-effects which are often serious but expected. Investigators have perhaps been rather slow to react to the need to clearly define in the protocol 'expectedness' of events and to specify which of the more common toxicities can be exempt from expedited reporting as a serious adverse event (SAE) and simply captured on the case report form. However, even with meticulous attention to protocol design, there is still a disproportionate bureaucratic burden for childhood cancer trials.

First, the strictest definition of an IMP as a 'product used for an unauthorised indication'⁸ could be and, indeed, often is interpreted to include many of the drugs that would be considered 'background medication' in a trial in adults, simply because their use in children is not a licensed indication. Second, the lack of paediatric dose and schedule information in the summary of product characteristics (SmPC) means additional work for the investigators in providing an acceptable IMP dossier to the regulators. Third, the reduced labelling requirements for IMPs defined by the EU CTD and Annex 13 only apply to 'marketed drugs used on patients with the same characteristics as those covered by the indication specified in the MA'. Again, this excludes many drugs commonly used 'off label' in childhood cancer simply because no paediatric studies were ever done to support a paediatric licensed indication. When these challenges are added to the national variability in safety reporting requirements, the end result is a massive information overload of largely irrelevant data. A prime example is the requirement in Germany that all investigators are made aware of SUSARs from other trials investigating the same IMP. The effect on the EURAMOS randomised trial of pegylated alpha-interferon as maintenance therapy in osteosarcoma was that in the first 10 months of the trial, tens of thousands of pages of often irrelevant information on SUSARs were being distributed throughout Germany.⁹ A similar paper cascade has been described in adult cancer trials.¹⁰ This is likely to mask the truly important, unexpected rare toxicity whose recognition is the purpose of all this regulation.

The multi-centre and multinational nature of most childhood cancer trials demands a high level of administrative oversight. This is costly in terms of the personnel required at study sites to maintain complex trial master files and document all amendments, however minor. Multi-centre trials expose variation in the conduct of inspections, with inconsistencies even found within a single national competent authority as to whether the same 'error' is deemed a critical finding or not.

2.7. Formulations adapted for children

Some drugs that are commonly used in childhood cancers have no oral formulation suitable for the young children affected by the disease. In the past, many centres have used a variety of techniques to administer tablets to small children (e.g. crushing of tablets into liquids or semi-solids). However, such manipulations are now deemed 'manufacture' and no longer permitted under current regulations for drugs used in clinical trials. Clearly, it is unsatisfactory that proper formulations of some essential drugs are not yet available, with good data on bioavailability. However, the current application of the EU CTD means that children with cancer who are unable to swallow tablets or capsules are now denied the opportunity to participate in some clinical trials. They will still receive the same treatment as is offered by the standard arm of the trial, as this will be the accepted best standard of care. This creates the absurd situation where tablets can be administered legally at home by the parents making whatever 'formulation' they decide, whereas the preparation of the medicine by a skilled hospital pharmacist is not permitted.

Although the financial incentive for industry to develop suitable formulations is modest, there is now some encourag-

ing progress in developing liquid forms of the drugs used in maintenance therapy for acute lymphoblastic leukaemia, for example, However, regulators should be realistic and recognise that there is not going to be a suitable GMP standard product available immediately for every oral drug that is known to be effective in treating children with cancer (e.g. cis-retinoic capsules for neuroblastoma). There should be a constructive dialogue between regulators and paediatric oncologists to decide whether it would be appropriate for some interim approval or amnesty to be put in place to permit the continued participation in clinical trials of children requiring these formulations, prior to a permanent solution being found to address these needs.

2.8. Ethical considerations in children

Clinical trials in children require additional consideration due to the inability to obtain informed consent from the patients themselves. The European Commission's recently published guidance on this topic recommends that all ethics committees reviewing protocols should have appropriate paediatric expertise and that ethics committees specialised in paediatrics could be considered for evaluation of trial protocols that are complex or in serious diseases.¹¹ The need for the latter is clearly demonstrated by the widely differing approach to the approval of phase I trials in children with cancer. Until very recently, ethics committees in The Netherlands took the view that it is 'unethical' to perform phase I trials in children. This attitude fails to recognise the particular needs of children with life-threatening diseases such as cancer. Even quite young children may have become 'expert' in their own treatment options if they have lived through several rounds of treatment for relapse. They may welcome the opportunity to be enrolled in a trial of a new agent, particularly if it has low toxicity in early experience in adults.

Obtaining ethical approval for multinational paediatric trials requires additional time and effort. There are national differences in the requirements for written information and assent at various ages. Some countries require signed consent from both parents for participation of their child in clinical research.

Variation in national implementation of the EU CTDs requirement for a single ethical opinion per member state for multi-centre trials was a major discussion point at a recent conference on the operation of the directive.¹² In Germany, a typical paediatric cancer trial must be commented on by over 50 local committees before the 'single' ethical opinion is arrived at. Some countries that appear to have complied with the single ethical opinion for a clinical trial have simply replaced the institutional control with another layer of bureaucracy variably labelled as 'Research and Development' approval.

2.9. Other issues specific to clinical trials in children

Very long-term follow-up of 20 years or more may be required to identify the final risk-benefit of certain cytotoxic drugs, e.g. risk of cardiotoxicity and impact on fertility. The need to capture such data adds additional expense. Such

long-term data storage may also require additional bureaucracy to ensure compliance with national data protection laws.

3. The way forward

The bureaucratic workload of trial activation is much too high for rare diseases like childhood cancer, where individual treatment centres may see only a few cases per tumour type per year. The European study groups who run multinational childhood cancer clinical trials therefore welcome the opportunity to reappraise the content and implementation of the EU CTD afforded by the European Commission – EMEA conference held in October 2007.¹² Recurring themes emerged from this conference for all types of clinical trials, whether the sponsor is from industry or academia. For multinational trials, the benefit of a single application system for clinical trial authorisation is clear. This could either be through a centralised procedure or by mutual recognition, whereby the clinical trial application is managed by a single competent authority rather than up to 27 national competent authorities. Such an approach has already been suggested for first in man studies and would avoid duplication of protocol and IMP dossier review, reduce the administrative burden and could strengthen expertise in rare diseases.

There is an urgent need to reappraise how the responsibilities of the sponsor are implemented. Consideration should be given to providing the necessary support at a European and/or national level to allow academic institutions or governmental research bodies to feel comfortable with taking on the role of European sponsor for investigator-led trials. This is a particular issue for trials involving children, where the perceived risk to the sponsor is felt to be greater than for trials in adults. A system is needed to limit the responsibilities of the sponsor to assure that the appropriate organisational structure is put in place with national representatives, each of whom confirms that their centre/national group's participation complies with national laws, and for timely communications with all partners of relevant information required by regulatory authorities for safe conduct of the trial. In this way, the coordinating sponsor does not assume direct responsibility for patients treated in other countries, but would be in a position (in conjunction with the trial steering committee) to recommend intervention if there were concerns about the conduct of the trial at an institutional or national level.

Any further adaption of regulatory requirements should be based on the risk of the trial rather than on what category of researcher initiated the trial. The current approach to allow 'specific modalities' for non-commercial trials and mandating that such trials cannot be used for registration purposes implies that there are two levels of quality. Surely the aim of the EU CTD was to standardise quality. If the regulations for clinical trials are to differ in any regard, this should be based on a thorough risk assessment.

The introduction of the paediatric regulation, discussed by Gilles Vassal in this issue,¹³ should encourage industry to seek to work with established paediatric networks to implement the required paediatric investigation plans. However, the full evaluation of the place of new drugs in the front line treat-

ment of children with cancer will require many years of research and many investigator-led clinical trials. These must be supported and made feasible within the resources of academic networks. Initiatives such as the liaison office project initiated by the EORTC, to provide a platform to assist with regulatory compliance at a national level, are required to facilitate multinational trials. Such an approach needs Europe-wide engagement by governments and health services to support the number of investigator-led clinical trials that are required to ensure timely progress in childhood cancer care in Europe.

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