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Practicalities and ethics of running clinical trials in paediatric oncology — the UK experience

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1. Introduction

The conduct of clinical trials in the area of paediatric oncology presents many organisational and ethical challenges. In the first part of this review, the conduct of clinical trials in relation to national organisations such as the United Kingdom Children's Cancer Study Group (UKCCSG), methodological difficulties such as central review, legislation, general ethical considerations and the impact of current guidelines on individual treatment centres will be outlined. In the second part of this review, methodological and specific ethical considerations for the conduct of the phase I, phase II and phase III trials in paediatric oncology will be discussed, with emphasis on early clinical trials. Finally, the possible impact of future legislation on new therapies will be highlighted.

2. Cancer trials, legislation and ethical considerations

Internationally, various organisational models exist for the coordination of national and international trials in paediatric oncology. These are often separate for leukaemias and solid tumours, and the different phases of drug or protocol development. Within the United Kingdom, for example, leukaemia trials are the remit of the Medical Research Council supported Clinical Trials Services Unit in Oxford, while the UKCCSG is responsible for trials in solid tumours.

For trials involving the UKCCSG, these are coordinated through the UKCCSG Data Centre in Leicester, located within the University. This has advantages, of independence, and disadvantages of a lack of direct clinical contact, although this is overcome through strong links with the individual tumour working groups. An alternative model, as observed in France, sees trials coordinated from centres where the lead investigator is based. The establishment and maintenance of a 'permanent' structure, such as the UKCCSG Data Centre is not the cheapest option. It has the advantage, however, that not only are all clinical trials (phases I, II and III) coordinated from the Data Centre, but also the administration and management of the national group, as well as cancer registration from all 22 UKCCSG treatment centres.

In the United States, the formation of national clinical trials organisations such as the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) over the last 40 years has seen the cancer-related mortality associated with childhood cancer fall from 80 to 20% [1]. Indeed CCG- and POG-related studies accounted for 22% of the total number of entries to National Cancer Institute (NCI) cooperative group total in 1994. Moreover, the CCG, POG and other tumour-specific groups have recently merged to form the Children's Oncology Group (COG). The increasing complexity of clinical trials is reflected in the range of trials activity conducted by organisations such as the CCG, where phase I–III, biological, psychological, supportive care and epidemiological studies all form part of the CCG portfolio of studies. Indeed, the clinical trials activity of the co-operative children's cancer groups was responsible for one-quarter of the total NCI Division of Cancer Treatment budget in 1994 [1]. Similarly, the nature of the organisation within the UK is designed to ensure maximum centre support for nationally approved protocols, and also optimum entry into clinical trials. Ascertainment of potential and actual trial patients can be achieved by comparison with patient registration in centres.

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Small patient numbers in childhood cancer, and increasing subdivision by clinical and now biological prognostic factors, mean that it is not always possible to carry out randomised trials. Most trials will be multicentre and increasingly now also international. The latter can add to the complexity of the initial discussions, the need for significant compromises at national level, and greatly extend the length of time to the study opening. For example, the time taken from development of a concept to recruitment of the first patient is likely to take between 2 and 3 years for many studies. Indeed, effective international collaboration takes time to develop, and the balance between adding centres to boost patient numbers and applying some form of centre accreditation must be considered. The criteria for centres are likely to vary according to the phase of the trial. For phase I, it is vital that the centres are able to meet the very strict protocol and rapid reporting demands, as well as compulsory participation in pharmacokinetic studies, and compliance with the requirements of study monitoring. In the UK, the presence of a research nurse is considered essential if these demands are to be met satisfactorily. However trial coordination is organised, close collaboration between clinicians and data managers/statisticians is essential, as is standardisation of processes (patient registration, randomisation, data collection, checking and entry, follow-up, central review, analysis and, finally, publication). Essential and appropriate procedures must be in place to ensure that patient confidentiality is not compromised.

Prior to the advent, via the pharmaceutical industry, of Good Clinical Practice (GCP) Guidelines, the conduct of clinical trials was largely unregulated [2]. Although devised originally for trials involving regulatory submissions, the general principles of GCP have now been widely embraced. Codes of Conduct, Standard Operating Procedures and audit trails are now commonplace. Monitoring and Source Data Verification is not routinely carried out for all phases of trials, although it is standard for phase I. The costs of this, where studies are not supported by pharmaceutical companies, are generally prohibitive. The pros and cons of GCP are widely debated, with opinion ranging from: a good framework for the overall conduct of clinical trials to unworkable bureaucracy overwhelming the whole trial process. With plans to enshrine the principles of GCP into European and then national law, incorporation of GCP into trials will no longer be optional [3].

Trial protocols of today bear little resemblance to those of even just 5 years ago. As they become ever more complex, so the potential for error increases. Arrangements will vary from country to country, but any new protocol is likely to go through a series of stages: national peer review, independent protocol review, approval within institutions and, finally, ethical approval. A recent change in the UK means that now, for any studies involving five centres or more (i.e. most paediatric oncology studies), Multi-Centre Research Ethics Committee (MREC) approval is required prior to local submission for each participating centre. This new system has not been without problems and does appear to have considerably lengthened the ethical approval process. With varying national procedures for ethical approval it is become increasingly difficult to synchronise start times for international collaborative trials. Some streamlining of the process is essential.

The application of general ethical principles such as respect for a person's self-determination, the balance of risk and benefit, and informed consent apply to all areas of clinical study in paediatric oncology. Indeed, informed consent is currently and most commonly viewed as a means of protection of a potentially vulnerable research subject from harm [4]. However, in adult oncology practice the development of increasingly lengthy and unreadable consent sheets have had little or no impact on patient understanding or decision-making in early clinical trials [5]. Moreover, the issue of consent in all aspects of medical research is becoming increasingly complex for paediatric oncology. This has led to a great emphasis on the Parent/Patient Information Sheets in protocols, usually with demands for a range of age-specific sheets. Changes in data protection regulations within the UK (Data Protection Act, 1998) are very specific about the need for explicit consent. There is a danger of this mushrooming out of control, with consent being required for entry to a trial, storage of tumour material for research, consent to use pathology specimens for central review. Debate is currently also underway about the question of consent for cancer registration purposes [6]. Of course, it is vital that patients and their families are fully informed and aware of what they are consenting to, but care needs to be taken to ensure that this does not become unworkable for the treating physician and totally overwhelming for the patients and their families. However, as will be discussed below, there has been very little study of the area of informed consent and other ethical considerations for the conduct of clinical trials for children with cancer in comparison with adult oncology.

Running clinical trials is now both complex and expensive. In order to ensure that the best possible use is made of all the resources, audit systems should be in place through all the stages of the process. The interests of the patient are always paramount and they should be safeguarded by any organisation running clinical trials. Collection of large amounts of patient data in paediatric oncology trials is often justified due to the rarity of the disease, improved chances of survival and lack of knowledge about the long-term effects of the tumour and/or treatment. The 'let's just collect that too' approach must be avoided. The more data collected, the

greater the cost of processing, the more potential for error, and the less likelihood it will ever be fully utilised.

Funding of clinical trials in paediatric oncology is a major issue, with an almost universal reliance on grant and/or charity funding. This may come from grants from the major cancer charities — The Cancer Research Campaign is the main funder of the UKCCSG — through a mixture of programme and project grants, or from smaller charities often set up by individual families. Securing sufficient funds to cover the running costs of national clinical trials activity is a major task, and one which is becoming increasingly diffficult with more and more international trials, and few international funding sources available. Often paediatric oncology trials are in competition for funds with adult trials, involving a large number of patients. In some cases, but usually only in early drug trials supported by pharmaceutical companies, there may be financial reimbursement to centres entering patients into a trial. Whatever funding is obtained, it is important that it is sufficient to cover the entire duration of the trial. A phase III trial is likely to be open to recruitment for at least 5 years, but support for the period post-trial closure, leading to final analysis and publication will also be required.

3. Conduct of phase I trials

Although the majority of children with cancer are now cured of their disease, a significant number have either disease resistant to current therapy, or are unable to tolerate the short- and long-term complications of their treatment. Therefore, phase I trials are needed for both the rational introduction of new therapies into paediatric oncology practice, and the evaluation of combinations of new and established agents. However, adult phase I experience with new agents is not an adequate predictor of the tolerability of a new agent in children [7]. Indeed, internationally agreed guidelines for the conduct of phase I trials in children with cancer have been reported, which describe the determination of the maximum tolerated dose (MTD) which can be taken forward to a phase II efficacy study, and dose-limiting toxicity (DLT) of a new agent or combination [8]. The strict methodology required for phase I studies may serve to highlight the ethical and practical difficulties associated with this stage of clinical development.

Common practice in paediatric phase I trials is to commence with a starting dose that is 80% of the adult MTD. The dose level is generally raised in increments of 25–30%, with children being evaluated in cohorts of three at each dose level for toxicity. A critical aspect of the design of phase I studies is the definition of the DLT and MTD, and strict criteria are applied for toxicity evaluation and eligibility whereby children are required to complete a defined period (usually 1 month) of observation during the first treatment cycle. Indeed, although over 90% of children who have been entered into phase I trials in recent years have been eligible for the evaluation of toxicity [9], this requirement may be more difficult to fulfil for children with leukaemia when compared with children with solid tumours [10]. The severity of toxicities is graded according to the National Cancer Institute Common Toxicity Criteria [11], and the MTD is determined as that dose level in which 0 or 1 children in a cohort of 6 experienced a DLT. In addition, standard criteria for disease response are applied in this clinical setting, and almost all paediatric Phase I studies should investigate the pharmacokinetic behaviour of new agents. Pharmacological studies may identify subgroups of children who are especially susceptible to toxicity by virtue of altered metabolism or elimination, and allow the rational selection of schedules of administration for use in phase II studies [8].

Since the eligibility criteria for entry of children into phase I trials usually demand that they have failed all recognised conventional treatments, this may create a difficulty in reconciling the often natural desire of parents and children themselves to proceed with treatment at any cost, and the need to provide good quality palliative care to children who will, in most cases, die. A recent survey of the perceptions of paediatricans from the UKCCSG and POG with regard to phase I trials in paediatric oncology sought to identify ethical and other considerations inherent in the conduct of these studies, perceived parental and children's motivations, and physician expectations with regard to toxicity and benefit [9]. Overall, respondents felt that parents entered their children for medical benefit, altruism and hope of cure. Medical coercion was not felt to be important. Furthermore, although many respondents felt that children could benefit from medical improvement, feelings of altruism and maintenance of hope, respectively, the chance of cure or complete remission was felt to be very small. Similarly, parents were felt to potentially benefit through altruism and maintenance of hope. Whereas 83% of UKCCSG respondents indicated phase I trials were associated with ethical difficulties, this was a concern for only 48% of POG respondents. The main ethical concerns of respondents were risk of toxicity, consent of the child, unrealistic hope and coercion. However, although the majority of respondents expected a child to have at least a 50% chance of toxicity, the likelihood of life-threatening toxicity was felt to be very small.

Thus, paediatricians from the UKCCSG and POG had largely realistic expectations for toxicity and benefit in relation to phase I studies in paediatric oncology, where literature reviews have identified a 7.9–10% objective response rate compared with a 0.56–0.7% drug-related toxicity for children participating in these

studies [9,12]. Although paediatricians identified altruism, the expectation of medical benefit and psychological factors such as the maintenance of hope as reasons that parents enter their children into phase I studies [9], there have been no studies of the perceptions of children or their parents in this area. In contrast, several adult studies have identified that patients who participate in phase I trials are almost exclusively motivated by the hope of therapeutic benefit [13,14]. Furthermore, the majority of patients were unable to state the research purposes of the trial in which they were participating [13], or whether alternatives to clinical trial participation, including palliative care or non-experimental therapies had been discussed with them [4]. However, cohort-specific consent methodologies are being developed for adult phase I studies, in which an interactive consent process by which patients can become directly involved in the decisions of dose escalation may reduce some of the ethical dilemmas in this area [15]. Therefore, studies are needed to investigate the motivation and perceptions for parents and children with regard to the consent process for phase I trials in paediatric oncology.

In addition to improvements in the understanding of the consent process for phase I trials, future phase I studies in paediatric oncology may be required to embrace methodologies based on the pharmacokinetics and pharmacodynamics of the agents under study. For example, significant antitumour activity has been demonstrated for a phase I study of ifosfamide, carboplatin and etoposide, where a pharmacologically-guided dose escalation for carboplatin has been employed [16]. In addition, continual reassessment methodologies for phase I studies are being developed in the adult cancer setting, and it is hoped that these will minimise the number of patients treated at sub-optimal dose levels [17]. Finally, an action-based methodology may prove an important innovation in phase I trial design, where an end-point of a study may be defined by the biochemical evidence of maximal inhibition of the target enzyme [18].

4. Conduct of phase II trials

Phase II studies are required to determine whether or not a new agent or treatment strategy appears sufficiently active to warrant further study, as determined by objective response rates of 20–30%, but may also further define the toxicity profile and pharmacokinetics of new agents. As with phase I studies, phase II studies in paediatric oncology are conducted on a multi-institutional or group collaborative basis [19]. Phase II trials in paediatric oncology usually follow a two-stage design which allows early termination of studies if the activity level is too low or is adequately high [20].

Many of the ethical issues related to phase II trials of new agents are similar to those discussed above for the conduct of phase I trials. However, the nature of phase II studies may translate into greater therapeutic intent on behalf of an investigator, with the consequence of raising patient or parental expectations [4]. Although this aspect of consent has not been formally studied in the adult or paediatric setting, the overall response rates within the phase II setting are very low for many types of paediatric cancer, which may be an important ethical consideration in obtaining informed parental consent [19].

5. Conduct of phase III trials

Phase III trials compare the efficacy of an experimental therapy with that of a standard or control therapy, and as with earlier clinical studies in paediatric cancer are usually only feasible in a collaborative group or multicentre setting. Phase III clinical trials may usually include a randomisation between treatment arms, and are commonly based on sequential or factorial designs [21]. As with earlier clinical studies in paediatric oncology, phase III clinical trials face several logistical difficulties. This may be exemplified by the example of central pathological review, where misclassification of tumours can result in a reduction in statistical power and inaccurate estimates of median survival [22].

Much of the debate about ethical issues in phase III trials has focused on the issue of equipoise, i.e. the state of genuine uncertainty on the part of a clinical investigator or treating physician toward the comparative merits of the different treatments for cancer [5]. Although simulated trial designs have indicated that the more life-threatening a disease, the less likely subjects were to refuse entry to clinical trials that allowed them to receive experimental therapy [23], this area has not been the subject of specific research in the area of paediatric oncology.

6. Conclusions

Although paediatric oncology represents a remarkable model of organisation and cooperation, there are many areas of difficulty in the conduct of clinical trials in paediatric oncology (Table 1). Due to the relatively small numbers of patients involved, clinical trials in paediatric oncology must maximise the clinical and scientific information gained from their conduct. The ethical considerations for the conduct of clinical trials in paediatric oncology need further study, especially in the areas of parental and patient consent. In order to continue to improve the survival for children with cancer,

Table 1
Overview of conduct, ethical issues and future developments for clinical trials in paediatric oncology

Clinical trials	Definition	Conduct and ethics
Phase I	Determine the MTD and DLT of new agents	• Many ethical difficulties identified by paediatric oncologists •International collaboration, new agents and research in the area of consent is needed
Phase II	Determine the activity of new agents	• Ethical issues not yet studied in paediatric oncology • Funding and international collaboration is essential
Phase III	Determine the efficacy of new treatments compared with standard ones	• Many methodological difficulties common to all stages of clinical trials, including central review, recruitment and length of study • Does 'equipoise' influence the conduct of these studies • Developments in international collaboration and information technology are needed

MTD, maximum tolerated dose; DLT, dose-limiting toxicity.

developments in the area of information technology, international collaboration, chemotherapy standardisation, merging clinical trials with adult groups for diseases such as osteosarcoma, and secure funding to support this and basic science research will be required [1]. However, running clinical trials across national boundaries is not easy: it requires considerable understanding of other cultures, tact, diplomacy and, at times, a willingness to compromise.

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