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Review

Ethical approval for multicentre clinical trials in children: contrasting systems in three European countries

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Abstract

Pan-European collaboration in studies of novel therapies and treatment strategies in childhood cancer is playing an increasing role in the attempt to improve cure rates. Differences in the systems of various countries with regard to drug control and ethical issues may lead to problems and delays. This applies in particular to phase I/II studies in children where the ethical considerations may be complex. In this review, the systems in three large countries—UK, France and Germany—are reviewed and current moves within the European Community towards a more standard approach are discussed. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Childhood cancer; Ethical approval; Phase I/II studies; European collaboration

1. Introduction

In order to make further advances in the cure rate of cancer in children, well designed and executed studies of novel therapies and strategies are essential. Even in the commoner tumours, insufficient patients will be recruited in a single European country for phase III trials that are adequately powered to provide reliable results. Phase II studies involving several disease types were common in the past, but the information gained from these was limited and often no conclusion could be drawn about the likely efficacy in any specific disease type. Single disease phase II studies even in the relatively common tumour types such as rhabdomyosarcoma, neuroblastoma or Ewing's sarcoma, must be carried out at a national or international level. Phase I studies are often limited centre collaborations, but in the field of paediatric oncology may take long periods to complete. It is therefore clear that international collaboration is essential.

Over the past 5 years, there has been increasing co-operation between the United Kingdom Children's Cancer Study Group (UKCCSG) and the French Society of Paediatric Oncology (SFOP) in the area of investigational chemotherapy. The New Agents group of the UKCCSG and the Phase II/Pharmacology group of the SFOP have been involved in joint phase II (temozolomide, CPT11) and phase I (daunoXome) trials. Other European collaborations have included phase III trials in Ewing's sarcoma, rhabdomyosarcoma, Wilms' tumour, osteosarcoma, non-Hodgkin's lymphoma and neuroblastoma. It is advantageous to have an understanding of the system, procedures and constraints existing in different countries and, in particular, those involved in obtaining ethical approval for such clinical trials. At present, these vary widely and will influence patient entry, the nature of study monitoring, provision of insurance cover and may cause a delay in starting trials. With phase I/II studies, there may be particular barriers to co-operation due to differences in attitudes or legislation on ethical and drug control issues.

In this review, we outline the systems for ethical approval in three large European countries, namely the United Kingdom, France and Germany.

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2. United Kingdom System (See Fig. 1)

Up until 1997, the system of ethical approval for clinical trials was based entirely on local research ethics committees (LRECs). These varied widely with regard to composition, internal structure and frequency of meetings. They might cover only one institution, such as a large academic teaching hospital, where the committee considered only projects within its own walls or, alternatively, have had a more regional remit covering several different hospitals or institutions. Inevitably, the former were inclined to be more streamlined, meeting frequently and often with a more specialised composition. For example, in a dedicated cancer research institution, there would be major input from cancer experts, whereas the larger regional committees would have to cover research in many different disciplines. With the latter turn around time of projects could be slow, taking up to a year for approval to be obtained. With the increase in large multicentre trials, it became clear that it would be more efficient if such trials were considered by a central body, involving relevant experts in the subject. Any trial that involves five or more institutions must now be submitted for central review. Since October 1997, the Multicentre Research Ethics Committee (MREC) system for approval has been mandatory in the UK. Once the study is approved by MREC the only change that can be requested by the Local Regional Ethics Committee are those related to local factors.

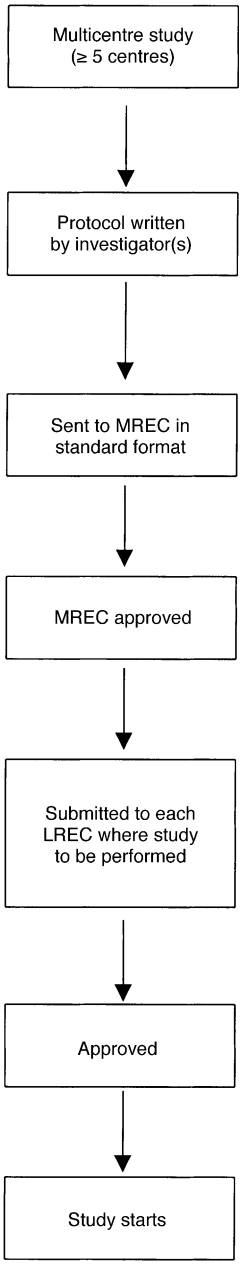

Fig. 1. UK system: average time from initial submission to start is approximately 10–12 weeks. MREC, Multicentre Research Ethics Committee; LREC, Local Research Ethics Committee.

2.1. MREC structure

There are 10 MRECs in the UK, one in each of the eight English National Health Service Regions, one in Wales and one in Scotland. Northern Ireland does not have its own MREC as it was decided that it would be rare for several institutions to be involved in any project. In this event, one of the English MREC's handles the submission. Health service guidelines require that the MREC has the following composition:

Lay persons (minimum four and at least a third of the membership and no more than six), hospital/community consultants (minimum four), general practitioners (minimum two), nurses/midwives (minimum two), a clinical pharmacologist or pharmacist, a professional allied to medicine, an epidemiologist or public health physician, a statistician and an expert in qualitative research.

The MREC compositions should have a broad range of experience and expertise and reflect a mix of gender, age and ethnic background drawn from across the region. The health professionals should include those occupied chiefly in active clinical care, as well as those experienced in clinical investigation and research. Simultaneous membership of LREC and MREC is allowed.

The MREC appointments mechanism is set up in each region and is an open procedure with vacancies advertised in the press. Suggestions are also invited from the LRECs and Community Health Councils. Candidates are shortlisted and interviewed by a panel comprising Regional Office representatives and an LREC representative. The regional director of Research and Development, who is appointed by central government and who is responsible for co-ordinating NHS funded clinical research in each region, is not involved. MREC members are appointed for a period of three to five years and membership may be renewed once. An

application for ethical approval for a study is made to the MREC of the region in which the principal researcher is based.

If one MREC is particularly busy, it may decide to pass a protocol on to another MREC in order to try and speed up the procedure. A limited number of studies, usually a maximum of 10, are considered at each meeting. The lead researcher for the study does not generally have to be present when the study is considered, but may be requested to attend under certain circumstances. This may lead to an early resolution of queries. Some queries raised by the committee may be responded to in writing and approved by the Chairman's actions without resubmission to MREC. If only four UK centres are involved along with additional centres outside the UK, only LRECs need be involved. If a study is already underway with less than five participating centres and more UK centres are needed, the study must be submitted for MREC approval. The committee is entitled to refuse approval for the study to be expanded despite previous LREC approval. In this event, it is up to the LREC to consider their position in the light of the reservation expressed by MREC and decide whether the study can proceed in each of the original centres. This has occurred in the case of a phase I trial in childhood cancer where the MREC's view on the principles applied to dose finding studies in children differed from those of the original LRECs (which were attached to specialised cancer centres). In this case, the study proceeded in the original centres without further centres becoming involved.

Agreement has recently been reached that all MREC proposals for the UKCCSG can be prepared centrally and submitted to a single MREC. This enables expertise to be acquired regarding the particular problems associated with childhood cancer research.

Once a protocol has been passed by the MREC, it is then considered by the LREC. It is not necessary for the full LREC to consider the proposal but, instead, a small executive subcommittee is established by each LREC. This committee can be as large as the LREC feels appropriate, but the quorum must be two members—the chairman's action alone is not adequate. Once a MREC approved submission has been received, the LREC executive sub-committee must meet to consider the protocol within 2 weeks. It may or may not be necessary for the local researcher to attend. The decision of the sub-committee does not have to be ratified by the full LREC and the project can start immediately, provided that the local NHS management has given permission. This is usually obtained from the local Director of Research and Development acting on behalf of the Chief Executive of the hospital.

The issues that are considered by the LREC subcommittee are the suitability of the investigator, the local conditions, the suitability of the subjects and the information sheets. It must ensure that the local researcher has the competence and facilities to carry out the research and that there are no concerns about the local clinical environment. It also considers whether the local population is an appropriate one for the study and if, for example, the same subjects are being used inappropriately for more than one study. No changes can be made to the consent forms and information sheets with regard to ethical aspects. The LREC simply ensures the accuracy of local contact addresses and numbers and that languages other than English are not required. In essence, therefore, the LREC only considers entirely local factors.

The MREC have issued detailed guidelines for patient information sheets which are fully compliant with the International Committee on Harmonisation (ICH)/ Good Clinical Practice Guidelines for the Conduct of Trials Involving the Participation of Human Subjects. These relate to the responsibilities, composition, functions, operation and records of an Independent Ethics Committee/Independent Review Board adopted by the Commission of the European Union (1997).

3. Outline of the system in France (see Fig. 2)

Up to December 1988, clinical trials were allowed nationally without any legal obligations for those involved in the planning and funding. In parallel with the establishment of ethical committees and Institutional Review Boards outside of France, some large institutions had set up internal structures, but these were generally more scientific than ethical or directed solely towards the protection of patients undergoing clinical trials.

In 1980, the pharmaceutical companies requested a specific law concerning the use of healthy volunteers and this resulted in Law Number 881138 of 20 December 1988 relating to individuals undergoing biomedical research. Also known as the Huriet-Serusclat Law, it contains two key concepts, that of 'Protection of Persons' and of 'Direct Benefit'. The individual or corporate body who initiates biomedical research involving human subjects is referred to as the 'sponsor'. The person(s) who themselves direct and monitor the carrying out of research are referred to as the 'investigators'. Where several persons or corporate bodies initiate the same research project they may designate one person or corporate body to be the sponsor of the research and carry out the corresponding obligations pursuant to the provisions of this code. Where the sponsor of a research project entrusts its carrying out to several investigators he is to designate one of them as the co-ordinating investigator.

The 'Loi-Huriet' provides clear directives regarding recruitment to trials which elsewhere are less formally covered by ethical practice guidelines. No biomedical

research may be conducted on human subjects if: it is not based on the latest scientific knowledge and on sufficient pre-clinical testing; if the foreseeable risk to the persons undergoing the research is out of proportion with the expected benefit for the persons or with the interest of such research, or if it does not aim to further scientific knowledge in man and the methods are not likely to improve his condition.

However, research that does not have a direct benefit to the individual is permitted if the following three conditions are satisfied:

1. Where such research presents no serious foreseeable risk to their health
2. If it is of value to persons of the same age, with comparable illness or handicap characteristics
3. If it cannot be conducted otherwise.

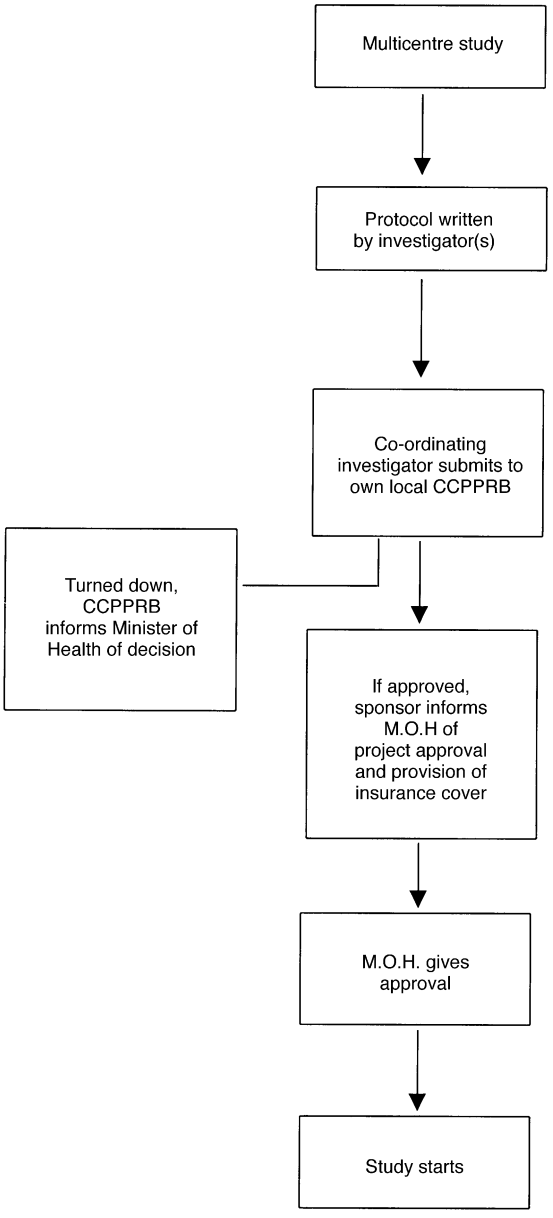

Fig. 2. French system: average time from initial submission to start in approximately 8–10 weeks. MOH, Minister of Health; CCPPRB, Committee for Protection of Persons in Biomedical Research.

3.1. Administrative aspects

In each region of France, the Minister of Health authorises one or, if necessary, several consultative committees for the protection of persons in biomedical research (CCPPRB). The minister designates the number necessary in each region which reflects the number of research institutions. These committees have jurisdiction within the region where they sit and they exercise their task with complete independence. The committees are composed in such a way as to ensure a diversity of expertise in the biomedical field and with respect to ethical, social, psychological and legal questions. Each is composed of 12 members named by the government representatives in each region by random selection from amongst persons nominated by a variety of authorities and organisations.

Members of the committees are legally bound to strict secrecy over information regarding the nature of research, the persons organising it, those whose consent has been obtained and the products, objects or methods tested. Any person not independent of the sponsor and the investigator in the research concerned may not participate in the process of deliberation. The operating costs of the committees are financed by revenue obtained from the sponsors for each project submitted. This amount is fixed by the Minister for Health. The minister may withdraw accreditation from a committee if its independence, composition and functioning conditions necessary to carry out its mission under the best possible conditions are no longer satisfied.

Before conducting research, investigators are required to submit the project to the CCPPRB located in the region where the research activity will take place. Where there are several investigators, a single co-ordinating investigator submits the project to a committee located in the region where he/she carries out research.

The committee gives an opinion on the conditions necessary to ensure the validity of the research. This includes the protection of the subjects, information statement how consent is obtained, the general relevance of the project, the appropriateness of the means used, and the qualifications of the investigator. The committee immediately informs the Minister of Health of any opinion against the carrying out of a research project.

Before a project is undertaken, the sponsor sends a letter of intent to the Minister of Health describing the essential details of the research, together with the opinion of the committee consulted. This opinion does not relieve the minister of the responsibility of the final decision. Where the CCPPRB decision has been against

the project if there is no reply from the minister within 3 months the research could, in theory, go ahead, but this is unlikely in practice.

With regard to medico-legal indemnity, insurance is mandatory and must be demonstrated to the Minister of Health before a study commences.

No person may consent to several simultaneous biomedical research projects without direct benefit to the individual. For each research project which has no benefit to the individual, the experimental protocol submitted to the CCPPRB sets an exclusion period during which the person undergoing such research may not participate in another research project without direct individual benefit. The duration of this period varies according to the nature of the research. To ensure the application of this provision, the Department of Health sets up and manages a national database.

4. Outline of the system in Germany (see Fig. 3)

4.1. Legal basis

In Germany, the obligation to obtain independent ethics approval for clinical trials and biomedical research is subject to various legal provisions that reflect the idiosyncrasies of the German federal system.

At the national level, transactions involving medicine, and especially drug testing, are subject to the German Drug Law (AMG). In §40 Section 1 No. 8 AMG, this law states that the approval of the ethics committee of the co-ordinating investigator is necessary to implement a clinical trial. Each co-ordinating investigator must submit the study protocol and relevant documents (insurance of test persons, informed consent, etc.) to the appropriate local ethics committee for deliberation regarding legal and ethical questions and approval. After approval, the co-ordinating investigator has to register a drug trial at the Federal Institute for Drugs and Medical Devices (BfArM) as the national authority as well as at regional authorities, and the trial can then be activated.

Regulations concerning medical practice (Heilberufsgesetz) are governed at the level of the several federal states of the Federal Republic of Germany. At this regional level, the Board of Physicians Code of Medical Conduct (§15M-Berufsordnung) requires each participating investigator to submit biomedical research to an appropriate local ethics committee for consultation.

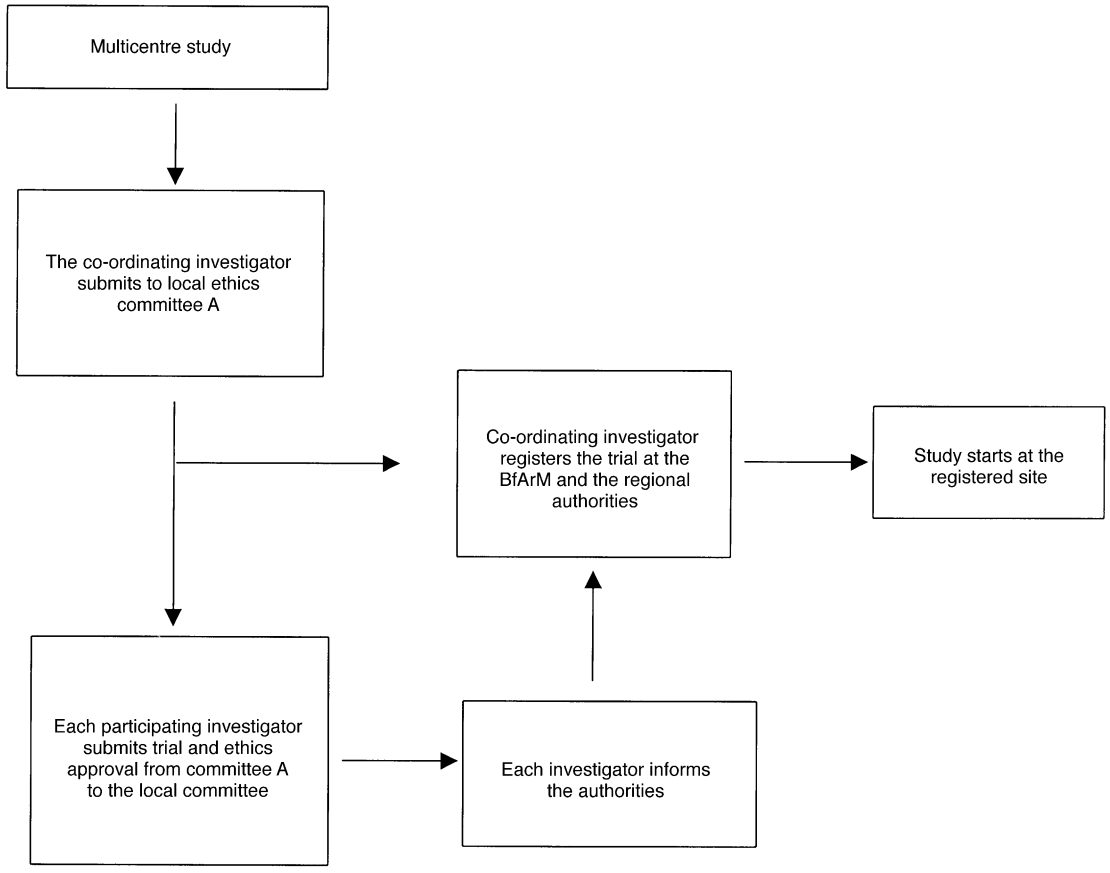

Fig. 3. German system: average time from initial submission to start in approximately 10–14 weeks. BfArM, Federal Institute for Drugs and Medical Devices.

4.2. Ethics Committees

These may be established at the regional physician's boards, at university hospitals or larger medical centres. Rules of procedure, names and curriculum vitae (CVs), including qualification and addresses of the members of the ethics committee, must be accessible to the applicants. The composition of the committees is in accordance with international requirements (ICH-GCP 32. Compositions, functions and operations), but not regulated definitively or uniformly. The federal association of ethics committees recommends a minimum of four physicians and one lawyer.

Most of the German ethics committees request the applicant to answer a list of pertinent questions to better describe and comment on the essential aspects of the project. This is in addition to, or instead of, any trial protocols or other documents prepared for the study proper.

Normally, the co-ordinating investigator is invited to discuss the clinical trial with the members of the ethics committee. Many applicants feel that ethics issues increasingly yield to legal considerations. Statements of the ethics committee focus on the assessment of the consent form, the question of insurance coverage for test subjects in drug trials, and the general classification of the project according to criteria and special conditions laid down by law.

The provisions of federal law put no restrictions on the regional regulations. As a consequence, the approval by the ethics committee granted to the co-ordinating investigator has to be complemented by regional votes regarding each and every participating investigator, taking into consideration local conditions of the research site. Currently, there are more than 50 ethics committees working who may all be involved in the approval process of paediatric multicentre studies, which means that for each nationwide treatment protocol (phase III study) roughly 100 researchers may have to apply for independent approval.

There is theoretically no need for the local ethics committee to re-appraise the clinical trials, they could recognise the decision of the responsible ethics committee. In a multicentre trial, all participating investigators can state their willingness to adopt the advice of the co-ordinating investigator's ethics committee. They then inform their own local ethics committee of the approval of the clinical trial and ask for recognition of this approval in writing. The clinical trial can begin in each region separately when an approval in writing is obtained and the regulatory authorities have been informed. However, this procedure of mutual recognition is accepted only in some regions in Germany, but not in general. Unfortunately, many regional committees currently do not agree with this procedure and the local ethics committee insist on re-appraisal of the clinical trial for their own regions which complicates the whole procedure unnecessarily, leading to an increased administrative burden, loss of time and an increase in expense.

In the past, ethics committees involved often had their own special requests, e.g changes in patient information and informed consent to include more detailed information, question on insurance coverage or a request for alternative ways of anonymising the clinical data. This led to delays in implementing the clinical trial in their region.

The statement from the ethics committee, which has to be provided in writing, is limited to the legal and ethical admissibility of the project, but does not include an evaluation of its scientific relevance. The statement does, however, include an assessment of the institution where the research will be carried out regarding conditions according to ICH-GCP guidelines at an administrative and staff level.

Depending on the research question (animal tests, radiopharmaceuticals, radiotherapy, data protection, laws concerning genetic engineering, protection of embryos, etc.), various other laws and regulations may also be applicable.

The ethics criteria rest on the Declaration of Helsinki (www.wits.ac.za/bioethics/helsinki.htm) the guidelines laid down in the Nuremberg Physicians' Code, and the European Convention on Human Rights and Biomedicine.

Investigators who conduct multicentre clinical trials in the field of paediatric oncology, for example, will regularly be confronted with the question of whether those trials do constitute 'clinical trials' (biomedical research) or drug trials (according to the AMG). Ethics committees tend to regard any scientifically evaluated systematic use of drugs outside approved indications, age range and dosage as drug trials. The ensuing requirements for trial organisation need to observe the legal limits originally imposed on drug manufacturers to regulate the approval of newly developed drugs. These often cannot be met by paediatric research groups who are also responsible for providing scientifically monitored care to patients on a nationwide basis.

Due to the large number of regional ethics committees and the fact that there are no uniform rules regulating mutual approval between ethics committees, the administrative burden, time consumed and financial expense involved in passing large multicentre studies is immense. There may even be conflicting votes, different local requirements for the informed consent forms or other variations within multicentre trials.

As a consequence of the political discussion about clinical research and of the need to implement the Directive 2001/20/EC of the European Parliament and of the Council into national law, the willingness to follow the procedure of mutual recognition has increased

and the working party of the ethics committees in Germany has initiated activities to standardise the procedure of ethical approval of the different committees.

5. Discussion

This review reveals major differences in the approach to obtaining ethical approval for multicentre studies. The situation in Germany resembles that which previously existed in the UK, with a cumbersome approach requiring multiple detailed submissions. Moreover, the ethics committees are more concerned with issues similar to those involved in drug approval and regulation rather than the ethics of biomedical studies in humans.

The system in France rests on a more rigid legal basis than that of the UK and also directly involves government officials. There is, however, no need to submit on multiple occasions, local considerations being less emphasised than in the UK. Because of the need for resubmission to local ethics committees in the UK even after MREC approval has been achieved, there is a potential for delay due to lack of expertise or understanding of the issues relating to the studies in children with cancer.

This research area is fraught with potential ethical problems [1,2] and guidelines regarding research involving children have been issued by the UK Royal College of Paediatrics and Child Health [3] and the Medical Research Council (www.mrc.ac.uk/ethics_b.html). Some of the problems faced in the design and execution of phase I trials in children have been reviewed both by the UKCCSG and by a combined representative group from the UKCCSG, the American Children's Cancer Group and the American Paediatric Oncology Group [4,5].

Regional or national multicentre committees are unlikely to include individuals with combined experience in both paediatric and cancer research. Consideration of projects, either by paediatricians alone or adult oncologists, can lead to problems. In the UK, it has become clear that MRECs in different regions may have very different attitudes to apparently similar issues. This has ranged from the need to seek ethical approval for single arm 'standard therapy' studies to the nature of informed consent for the storage of routine diagnostic tissue for future research studies.

It is inevitable that there will be a move towards a commoner approach to ethical approval across the European Community. A directive from the European Parliament and of the Council in April 2001 has been published [6]. In this document, a number of definitions are presented covering clinical trial, multicentre clinical trial, non-interventional trial, investigation of medicinal product, sponsor, investigator, subject, informed consent and ethics committee. The latter is defined as "an independent body in a Member State consisting of health care professionals and non-medical members whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection by, amongst other things, expressing an opinion of the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent".

It emphasises the need to pay specific attention to clinical trials involving children and the importance of such trials to improve the treatment available to this age group. To quote, "children represent a vulnerable population with developmental, physiological and psychological differences from adults, which makes age and development related research important for their benefit. Medicinal products including vaccines for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid out."

With regard to clinical trials on minors, it is specified that the Ethics Committee must have specific paediatric expertise or take advice in clinical, ethical and psychosocial problems in the field of paediatrics.

It is suggested that there should be a maximum of 60 days from the date of receipt of valid application for the committee to give its opinion to the applicant and the competent authority in the Member State concerned.

For multicentre clinical trials limited to the territory of a single Member State, Member States shall establish a procedure providing, not withstanding the number of Ethics Committees, for the adoption of a single opinion for that Member State. In the case of multicentre clinical trials carried out in more than one Member State simultaneously, a single opinion shall be given for each Member State concerned by the clinical trials.

Adherence to this directive and a more standardised approach in seeking ethical approval for clinical research in children across the European Community would facilitate collaboration in the execution of phase I/II and III studies on which future progress depends.

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