

# 6

## Clinical trials in children

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### **Ethics and recruitment issues**

Evidence-based medicine and healthcare are the pillar of optimal medical care. However, there are deficits in our understanding of the quality and efficacy of paediatric therapies, many of which are based on anecdotal data and evidence. Over 50% of medicines used in children are not licensed for use either for the disease states or for the age group. The extrapolation of adult data on medicinal products for the child population is inappropriate, which makes age- and development-related research particularly important. The need to develop medicines in children, whether it is a novel agent or an existing agent in need of pharmacokinetic study, necessitates testing on children. The promise of making drugs safer for children increases the potential for harm to children who serve as research participants. Sometimes it is difficult, if not impossible, to quantify the risk. Without knowing the nature of future risks, to what extent can permission be given to child participation in clinical research? Researchers need to consider the ethical issues of conducting clinical trials in children, not only on a theoretical level, but also on a practical level in the form of ethical approval and statutory requirements.

The most commonly performed clinical trials evaluate new medical therapies on patients in strictly scientifically controlled settings. The purpose of such trials is to determine whether one or more treatment options are safe, effective and better than current standard care. Controlled trials require a higher standard of consent than treating patients unsystematically. Ethically, it is more justifiable to conduct controlled trials than treatments based on anecdotal evidence, as the controlled trial is more likely to clarify the efficacy and safety of a new treatment and its adverse effects.

Patients enrolled in clinical trials are more likely to be benefited by the 'inclusion effect' (Lantos, 1999). Babies who received placebo in a

placebo-controlled trial of antithrombin therapy in neonatal respiratory distress syndrome, for example, had a significantly shorter mean duration of ventilation than non-randomised babies. This could be explained by the more vigorous observations and monitoring as prescribed by the protocol.

Beauchamp and Childress (2001) advocate four principles – autonomy, beneficence, non-maleficence and justice – to form the basis of bioethics discussion. However, in paediatric research, the model of ‘best interests of the child’ sets a paradigm of a combination of parental consent and assents by the child as advocated in the Belmont Report (1978) in the USA.

Clinical research in the UK is governed by statutory requirements in the form of the EU Directive (2001/20/EC) on Good Clinical Practice (GCP), ethical principles (Declaration of Helsinki), the Research Governance Framework for Health and Social Care (Department of Health, 2005) and the duty of care in the National Health Service (NHS), the high professional and ethical standards that most care professionals and researchers uphold.

### **Declaration of Helsinki**

In 1964, the World Medical Association established a statement of ethical principles to provide guidance to physicians and other participants in biomedical research involving humans. It was developed to correct the perceived deficiencies in the Nuremberg Code, especially on physician-led research with patients. The Declaration governs international research ethics and defines rules for ‘research combined with clinical care’ and ‘non-therapeutic research’. The Declaration of Helsinki was revised in 1975, 1983, 1989 and 1996 and is the basis for GCP used today. A summarised version of the Declaration of Helsinki is shown in Table 6.1.

The Declaration of Helsinki has considerable influence in the field of ethics in biomedical research and forms the basis of GCP and subsequent legislation in European Economic Area (EEA) countries. The latest EU GCP Directive (2005/28/EC) has specified the use of the 1996 version of the Declaration.

### **History of good clinical practice**

Good clinical practice (GCP) is a formal approach to the procedures applied to various stages of clinical trials. A summary of the history of

**Table 6.1** Summary of the Declaration of Helsinki 1996**I. Basic principles**

1. Biomedical research must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. Protocols should be clear and reviewed independently and must conform to the laws and regulations of the country in which the research experiment is performed.
3. Medical research should be conducted by scientifically qualified persons and supervised by a clinical qualified person.
4. Biomedical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject and his or her integrity must always be respected.
7. Predictable risk and investigation should cease if the hazards are found to outweigh the potential benefits.
8. Accuracy of the results and reports should only be accepted when research is conducted in accordance with the principles laid down in this Declaration.
9. Subjects must be adequately informed of the aim, methods, benefits and potential risks of the study and the discomfort it may entail. Subjects should be informed of their right to refuse to participate and the right to withdraw at any time.
10. Patients should not give consent under duress or be influenced by the dependent relationship with physicians.
11. Informed consent should be obtained from legal guardians for minors and mentally incapable adults; if possible, minors should give assent.
12. The research protocol should always contain a statement of the ethical considerations and compliance with the Declaration.

**II. Medical research combined with professional care (clinical research)**

1. A physician must be free to use a new diagnostic and therapeutic measure, if it offers hope of saving life, reestablishing health or alleviating suffering of the patient.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. Every patient, including the control group, should receive the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.
5. If the informed consent is not taken, the specific reasons should be stated in the protocol and be approved by an independent committee.
6. The physician can combine medical research with professional care. Medical research is justified by its potential diagnostic or therapeutic value for the patient.

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**Table 6.1** Continued**III. Non-therapeutic biomedical research involving human subjects (non-clinical biomedical research)**

1. In the purely scientific application, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his or her or their judgement it may, if continued, be harmful to the individual.
4. In research on humans, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

the development of GCP legislation and guidelines is shown in Table 6.2. GCP is an international standard governing the design, conduct, recording and reporting of clinical trials. It has gestated through years of accidents in the history of medicines and violation of human rights in the name of biomedical research. In 1947 through the Nuremberg Code, the principle of informed consent was established. The Code was the result of the unethical clinical experiments conducted with war prisoners during World War II. The thalidomide incidents in the late 1950s and early 1960s led to the formation of the Committee of the Safety of Medicines in 1964 in the UK and the requirement for the licensing of medicinal products was issued by the EU (65/65/EC) for all the member states. In response, the UK Government issued the Medicinal Act in 1968 and the Good Manufacturing Practice (GMP) Inspectorate was set up.

In 1975 an EU Directive (75/318/EEC) required each member state to ensure the submission of safety and efficacy for marketing authorisation. Good laboratory practice (GLP) became the principle of non-clinical testing on pharmaceutical products and the requirement of a GCP standard in conducting clinical trials. It stated that 'all phases of clinical investigation, including bioavailability and bioequivalence studies shall be designed, implemented and reported in accordance of GCP' (75/318/EEC, B.1.1).

In July 1991, the European Commission published the Enforcement of the EEC Note for Guidance: 'Good Clinical Practice for Trials on Medicinal Products in the European Community'. This enforcement was setting into operation GCP guidelines that were, however, not yet legally binding at that time. Directive 91/507/EEC was published to modify the annex to Council Directive 75/318/EEC. By this enforcement

**Table 6.2** History of good clinical practice (GCP) and related legislation and directives

<i>Year</i>	<i>Event</i>	<i>Comment</i>
1947	Nuremberg Code	Principle of informed consent
1964 (revised 1975, 1983, 1989, 1996)	Declaration of Helsinki	
1965	65/65/EC	Licensing of medicinal product
1968	Medicinal Act	
1975	75/318/EEC	Safety and efficacy requirement for marketing authorisation. GLP became the principle of non-clinical testing
1991	91/507/EEC	GCP in EEC
1997	CPMP/ICH/135/95	ICH GCP published by Committee for Proprietary Medicinal Products
2001	2001/20 EC	EU Clinical Trial Directive
2001	2001/83/EC (part 4, B1)	Community code on medicinal product, requirement of GCP in conducting clinical trials
2003	2003/63/EC	Amendment on 2001/83/EC. Part 1, 5.2.c defines holding period of essential clinical trials document
2003	2003/94/EC	GMP requirements for IMP
2003	EUDRACT	EUDRACT database guidance note
2003	Annex 13	Manufacture of IMPs
2004	2004/27/EC (13)	GCP requirement for clinical trials outside the EEA
2004	SI 2004/1031	The Medicines for Human Use (Clinical Trials) Regulation's 2004
2005	2005/28/EC	Guidelines for GCP
2006	SI 2006/1928	The Medicines for Human Use (Clinical Trials) Amendment Regulation's 2006

EEA, European Economic Area; GLP, good laboratory practice; GMP, good manufacturing practice; ICH, International Conference on Harmonisation; IMP, investigational medicinal product; SI, statutory instruments.

the European member states were obliged to bring into force the laws, regulations and administrative provisions necessary to comply with the Directive that requests – besides others – all clinical trials to be designed, implemented and recorded in accordance with GCP.

In 1996 the International Conference on Harmonisation (ICH) issued a guideline for GCP (E6) (ICH, 1996). This was instigated by the desire to promote international consensus on mutual recognition of

clinical trials and marketing authorisation procedure. This was adopted by the Committee for Proprietary Medicinal Products (CPMP, now CHMP) and formally accepted as the standard in the EU in 1997, replacing the previous EU GCP guideline.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001, on the approximation of the laws, regulations and administrative provisions of the member states, relates to the implementation of GCP in the conduct of clinical trials on medicinal products for human use. The community code relating to medicinal products for human use (2001/83/EC) was amended in 2003 (2003/63/EC), stipulating that clinical trials data used for marketing authorisation applications in the EU are required to be conducted in accordance with GCP.

The year 2003 saw the launch of the European Clinical Trials (EudraCT) Database (<https://eudract.emea.eu.int/eudract/index.do>). The database is interfaced with the Eudravigilance Clinical Trial Module (EVCTM), and is used to facilitate communication on clinical trials between authorities in the oversight of clinical trials and investigational medicinal product development, and to provide for enhanced protection of clinical trial participants receiving investigational medicinal products.

In the UK SI 2004 1031 was implemented, incorporating into British law the requirement of the EU Directive 2001/20/EC. Finally the EU-issued Directive 2005/28/EC, which lays down principles and detailed guidelines for GCP in investigational medicinal products for human use and the requirements for authorisation of the manufacturing of investigational medicinal products, required member states to implement it into law by 29 January 2006. In the UK, the GCP Directive was implemented in August 2006.

### **Implication of the legislation**

The development of GCP from an international guideline to a statutory requirement has caused upheaval in academic research. Before the legislation, academic research involving already marketed products and not intended to generate results for marketing authorisation purpose was exempt from these rules. Now, however, all research involving humans and investigational medicinal products is covered by the legislation, and publicly funded clinical trials must fulfil the same requirements as their commercial counterparts. It is the responsibility of the sponsor to ensure that clinical trials are designed, conducted, recorded and reported in accordance with GCP standards.

To comply with the new legislation the sponsor needs to develop a set of standard operation procedures (SOPs) to cover all areas of trial activities. A quality system should be in place to ensure record-keeping and verification of data entry or extraction of data from the case report form (CRF), capture adverse events (AEs), serious adverse events (SAEs) and unexpected serious adverse reactions (SUSARs) and report in an expedited manner data transfer from source data to database and archiving of the source data for audit purpose. GCP and trial specific training should be carried out and recorded in a timely manner.

### **Ethics committee**

An ethics committee is an independent body constituted of medical/scientific professionals and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of humans involved in a trial. It provides public assurance of that protection by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants.

In the UK, the United Kingdom Ethics Committees Authority (UKECA) is responsible for establishing, recognising and monitoring ethics committees. The Authority may establish ethics committees to act for the entire UK or for each area of the UK and the description or class of clinical trial in relation to which it may act. The categories are listed in Table 6.3.

Clinical trials of medicinal products for gene therapy are subject to separate arrangements for ethical review. Applications relating to such trials should be submitted to the Gene Therapy Advisory

**Table 6.3** Types of ethics committee in the UK

<i>Types of ethic committees</i>	<i>Expertise</i>
1	Phase I clinical trials of medicinal products in healthy volunteers throughout the UK
2	Investigational medicinal products (other than phase I trials in healthy volunteers) to take place only at sites within an area defined by the geographical remit of their own appointing authority
3	As in type 2 but at any site in the UK

Committee (GTAC), which is recognised as a specialist committee by UKECA under the Clinical Trials Regulations.

The 'main research ethics committee (REC)' is the REC that undertakes the ethical review of an application. All subsequent amendments should be reviewed by the main REC. An application for ethical review of a research study should be made by the chief investigator for that study. Applications may not be submitted by the sponsor(s) on behalf of the chief investigator. Only one application for ethical review should be submitted in relation to any research protocol to be conducted within the UK. In the case of international studies, an application must be made to an ethics committee in the UK, whether or not the study has a favourable ethical opinion from a committee outside the UK and whether or not it has started outside the UK. Trials of medicinal products that are 'non-interventional' are not classified as clinical trials of an investigational medicinal product (CTIMPs) and do not require review by a recognised REC. If in doubt about the classification of a trial, it is the responsibility of the chief investigator or sponsor to seek authoritative advice from the Medicines and Healthcare products Regulatory Agency (MHRA).

Under the clinical trials regulations, an REC is required to give an ethical opinion on an application relating to a CTIMP within 60 calendar days of the receipt of a valid application. Where the REC considers that further information is required in order to give an opinion, the REC may make one request in writing for further information from the applicant. The period of 60 days will be suspended pending receipt of this information.

Where a study involves certain types of research procedure, the suitability of each site or sites at which the research is to be conducted requires 'site-specific assessment' (SSA). The SSA is not a separate ethical review, but forms part of the single ethical review of the research. Where there is no objection on site-specific grounds, a site may be approved as part of the favourable ethical opinion given by the main REC. When submitting an application, the chief investigator should declare if in his or her opinion the research does not require SSA at any research site. Where such a declaration is made, this should be considered by the main REC at the meeting at which the application is ethically reviewed.

### **Non-therapeutic research**

The Royal College of Paediatrics and Child Health guidelines (2000) indicate that a research procedure that is not intended directly to benefit

the child is not necessarily either unethical or illegal. Research work can offer valuable training that may improve the quality of doctors' clinical practice. However, research that could equally well be done on adults should never be done on children. Non-therapeutic research on children should not carry greater than minimal risk of harm. Second, the risks posed by non-therapeutic procedures should be proportional to the knowledge that may reasonably be expected to be gained.

Some research based on observation, collating information from notes and tests already performed for therapeutic purposes, may be permissible without consent because it does not involve direct contact with the child. Researchers must be careful in this matter and consult the Central Office for Research Ethics Committees (COREC) to ascertain this requirement. Non-therapeutic research can be validly consented only when the research can be reasonably said not to go against the child's interests. Even though it is not legally required, research should seek assent from school-age children and should always ensure that the child does not object.

### **Informed consent**

The informed consent process is the foundation of any ethical research. Researchers should have a clear understanding of the process on a theoretical and practical level to conduct ethics studies, to improve parents'/patients' understanding and expectation, and to improve recruitment rates.

Article 3 of 2005/28/EC stipulates that clinical trials shall be conducted in accordance with the Declaration of Helsinki on ethical principles for medical research involving humans adopted by the General Assembly at the World Medical Association in 1996. Principle 9 states that:

In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time.

In other words, the participant should have adequate knowledge and understanding to participate in research, whether it is diagnostic, therapeutic or a preventive intervention. The understanding includes why the research is being done, what will be done during the trial and for how long, what risks are involved, what, if any, benefit can be expected from the trial and, more importantly, what other interventions are available.

The participant also has the right to leave the trial at any time without giving the reason and without giving up their legal rights. Informed consent should be documented by means of a signed, dated, informed consent form, preferably witnessed by a third party who is not part of the clinical trial team.

The purpose of informed consent is to ensure that individuals have control over whether or not to enrol in clinical research and to ensure that they participate only when the research is consistent with their values, interests and preferences. The decision of an individual should be rational, free, voluntary and uncoerced. Children who are unable to make their own decisions also have interests and values. Their preferences and values may be unknown or unknowable. In such cases, research proxy is used to determine whether to enrol them in clinical research.

In the case of minors, Principle 11 of the Declaration of Helsinki stipulates that 'permission from the responsible relative replaces that of the subject in accordance with national legislation'. SI 2004 1031 Schedule 1 Part 4.1 stipulates that a person with parental responsibility can give informed consent on behalf of a minor. Mothers always have parental responsibility. Unmarried fathers do not automatically have parental responsibility for their children. An unmarried father can acquire parental responsibility by: applying for and getting a residence order or parental responsibility order; making a parental responsibility agreement (in a set procedure) with the mother; being appointed the child's guardian (once the appointment takes effect); or subsequently marrying the mother of the child. A step-parent may acquire parental responsibility by obtaining a Residence Order or adopting the child. The different regulations, directives and standards on informed consent for minors are compared in Table 6.4.

### *The informed consent process*

Some have argued that the informed consent process for complex clinical trials can give rise to misunderstanding and feelings of powerlessness, especially for those who are poorly educated and emotionally stressed (Mason, 1997). There is also a tendency for some doctors to avoid the consent issue because they want to 'protect' the patient. In one recent report about the Continuous Negative Extrathoracic Pressure (CNEP) trial, doctors were said to have 'sold' a trial to patients as a 'kinder, gentler treatment' without telling them that they were participating in a clinical trial (Smith, 2000).

**Table 6.4** Informed consent requirements of various guidelines, directives and regulations for minors participating in clinical research

<i>Requirements</i>	<i>SI 2004 1031<sup>a</sup></i>	<i>Directive 2001/20/EC<sup>b</sup></i>	<i>ICH GCP E6 1997<sup>c</sup></i>	<i>Declaration of Helsinki 1996<sup>d</sup></i>
A legal representative for the minor must have an interview with the investigator and has been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted	Schedule 1, part 4.1		4.8.5	9
The legal representative has been informed of the right to withdraw the minor from the trial at any time	Schedule 1 Part 4.3	Article 4.a	4.8.10	9
The legal representative has given his or her informed consent	Schedule 1 Part 4.4	Article 4.a	4.8.5	11
The minor has received information according to his or her capacity for understanding from staff with experience with minors, the trial's risk and its benefits	Schedule 1 Part 4.6	Article 4.b	4.8.12	
A minor who is capable of forming an opinion must give assent to the trial and can withdraw at any time	Schedule 1 Part 4.7	Article 4.c	4.8.12	11
The clinical trial relates directly to a clinical condition from which the minor suffers or is of such a nature that it can be carried out only on minors	Schedule 1 Part 4.9			
Some direct benefit is to be obtained	Schedule 1 Part 4.10	Article 4.e		
The corresponding scientific guidelines of the European Medicines Agency are followed	Schedule 1 Part 4.12	Article 4.f		
The clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the minor's stage of development	Schedule 1 Part 4.14	Article 4.g		
The Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychological problems in the field of paediatrics, has endorsed the protocol		Article 4.h		
The interests of the patient always prevail over those of science and society	Schedule 1 Part 4.16	Article 4.i	2.3	5

<sup>a</sup>SI 2004 1031 The Medicines for Human Use (Clinical Trials) Regulation 2004.<sup>b</sup>EC/2001/20 Official Journal L121, 1/5/2001 pp. 34–44.<sup>c</sup>ICH E6 1997 GCPM/ICH/13.5/95.<sup>d</sup>Declaration of Helsinki 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996.

Parents do not always remember that they have given consent to a study. A small proportion of parents (2.5%) in the Euricon study could not remember being asked to give consent (Mason and Allmark, 2000), and, in another study, the figure was as high as 12% (Stenson *et al.*, 2004). Some parents do not think that there is adequate discussion of alternatives to proposed novel treatments and the scope of the research protocol. This is a common issue with paediatric oncology trials where most treatments are protocol driven (Kupst *et al.*, 2003).

One study found that a high proportion (25%) of parents felt obliged to participate (van Stuijvenberg *et al.*, 1998). This may be due to a feeling of being dependent on the investigator or the hospital. Parents who feel obliged to consent are classed as having failed the informed consent procedure, because they have not truly given informed consent.

Parents may experience guilt for not making the right decision, especially when a baby dies. The process may coerce people into participating or they may be influenced by the desire for a particular treatment that is unavailable in normal circumstance. In neonatal research, the mother may be exhausted or with impaired cognitive function due to a sedative or analgesia. Their worry is exasperated by the admission of uncertainty that leads to the research in the first place. The post-trial interview of parents whose children had undergone the UK extracorporeal membrane oxygenation (ECMO) trial expresses their sense of fear and haste when they were approached by the researchers. They were also angry and distressed when their babies were randomised to conventional treatment (Snowdon *et al.*, 1997).

Researchers should understand the dynamic of parental thought processes. Ample time and sufficient but not overwhelming information should be given to parents to decide whether to allow their children to take part in the study. They should see the giving of informed consent as a process, not as an event; regular updates and reinforcement increase parental understanding and facilitate continuous participation.

### *Assent and age*

Parental consent will probably be invalid if it is given against the child's interests.

It is completely inappropriate to insist on the taking of blood for non-therapeutic reasons if a child indicates either significant unwillingness before the start or significant stress during the procedure.

At what patient age should the researcher ask for assent? The ICH

does not yield any answers; the phrase 'if capable' does not give us any guidance. In reality, there is no such benchmark for minimal chronological age, but it depends on the perceived maturity and the degree of understanding (Rossi *et al.*, 2003). Some suggest that researchers should give more weight to parental consent in therapeutic research but even more to a child's dissent for non-therapeutic research (Barfield and Church, 2005). The law in the UK concerning research on children has never been clearly established. The law requires a child who has 'sufficient understanding and intelligence to understand what is proposed' to give consent (*Gillick v West Norfolk* 1985).

Researchers should engage young children by providing them with information appropriate to their level of understanding. Young children with long-term illnesses have a better understanding of their conditions and the concept of research than their older counterparts who have little exposure to a hospital environment or medical research. Despite parental consent, researchers should respect the will of the children when they decline to take part in a study.

#### *Consent process in emergency*

In the case of an emergency, and when the person with parental responsibility is not contactable prior to the inclusion of the participant in the trial, a legal representative for the minor can give informed consent. In the UK, that will be someone other than the person involved in the conduct of the trial, who by virtue of his or her relationship with that minor is suitable to act as a legal representative for the purposes of the trial and is available and willing to act for those purposes. When no such person is available, a doctor who is primarily responsible for the medical treatment provided to the child, and is not connected to the clinical trial, can act as a professional representative. It is possible, however, that it would still be unlawful if the research were not expected to benefit the child in question.

Fast decision-making is crucial in an emergency; it has been argued that reasonable understanding and voluntariness are likely to be severely compromised (Hewlett, 1996; Manning, 2000). In many neonatal scenarios such as resuscitation, surfactant treatment, modes of respiratory support, treatment of seizures, little time is available for parents to decide participation in clinical trials.

There are alternative approaches that avoid taking consent (Modi, 1994). For example, researchers can discuss the study with parents antenatally. Then when the child is born and is eligible for the study, the

parents are asked whether they would like to opt out of the research. If there is no objection, their babies will be automatically enrolled in the study. Support for such an approach comes from studies that demonstrate that a significant minority of parents would prefer to have their doctor advise them on whether to include their baby in neonatal research than have to decide themselves (Zupancic *et al.*, 1997). The downside is that it may override the autonomy of the parents, but this can be mitigated by continuous communication and information sharing and consents for non-therapeutics and non-urgent research should still be sought (Manning, 2000).

Presumed consent is another option where antenatal consent is sought from parents (Morley, 1997). It is particularly useful in situations where obtaining conventional consent is impractical. It should be supplemented by informing parents as soon as possible and obtaining 'continuous consent' while the baby is still in the trial. The criticism of such an approach is that parents may pay little heed to trial information given antenatally, assuming that their baby is unlikely to be affected.

It has been argued that the opting-out processes would protect vulnerable and deprived families who are less capable of understanding the rationale of the research and consent processes and are likely to give consent and participate in research. The opt-out process will allow these families to participate and reduce selection bias, thus producing more generalisable conclusions and being more equitable (Rogers *et al.*, 1998; Manning, 2000). However, the legality of such approaches in drug trials needs to be explored in view of the latest regulations. Moreover, it has been demonstrated that 83% of parents who consented did not want to forego the consent process, and only 8% of the respondents were unhappy about giving consent (Stenson *et al.*, 2004). In one post-trial interview, 98% of parents with babies in a neonatal intensive care unit wanted to decide and did not want doctors or nurses to decide (Morley, 2004).

### *Parental understanding of randomisation*

The prerequisite for an ethical randomised control trial is that it provides no certain benefit to the individual patients and in fact could harm the child as the result of potential side effects. Research is justified when there is no convincing ground that any patient would be advantaged or disadvantaged if allocated to one treatment arm over the others (Freedman, 1987a). It has been shown that research participants often fail to understand that their treatment has been selected at random

(Edwards *et al.*, 1998). For example, 74% of the patients attending an oncology clinic thought that their doctor would ensure that they received the best treatment offered in randomised clinical trial (Ellis *et al.*, 1999). Again, in the ECMO study, some parents believed that randomisation meant rationing access or a solution to difficult clinical decision-making (Snowdon *et al.*, 1997). In contrast, 88% of parents were aware that their children might receive a placebo in a double-blind study of ibuprofen in the prevention of recurrent febrile seizures (van Stuijvenberg *et al.*, 1998). These diverse observations may be attributed to differences in the complexity and nature of the studies, educational background and the state of mind of the parents.

For the very reason that public understanding is low, some researchers suggest using 'by chance' or 'by the flip of a coin' instead (Waggoner and Mayo, 1995). COREC guidelines suggest that the phrase 'The groups are selected by a computer which has no information about the individual' should be used (COREC, 2006). A more solid approach to ascertain participants' understanding is to allow them to demonstrate explicit understanding by giving a verbal definition of randomisation.

#### *Methods to improve the informed consent process*

The deficiency in patients' understanding of the consent process is apparent; many have called for investigators and institutions to take action to improve research participants' understanding (Lavori *et al.*, 1999; Siminoff, 2003). A systematic review has shown that five main categories of interventions have been used (Flory and Emanuel, 2004). These include multimedia, enhanced consent forms, extended discussion and test/feedback. In 12 trials, multimedia interventions, including video or computer presentation, failed to improve research participants' understanding. Multimedia may be a way to standardise disclosure but it does not add much to the standard disclosure procedure.

Improved presentation in consent forms such as changing the format, font size and adding graphics had little effect, but a shortened form and the removal of irrelevant information did have a significant improvement. When designing a patient information leaflet it should be remembered that quantitative information is often difficult for the general public to understand (Schwartz *et al.*, 1997). Probabilistic language troubles many individuals, and parents and clinicians prefer to use relative rather than absolute terms in assessing risks and benefits (Forrow *et al.*, 1992). Researchers should use simple words, avoiding medical jargon, and sentences should be short (Tarnowski *et al.*, 1990).

Extended discussion between staff and research participants and the test/feedback approach had a significant impact on understanding. But the use of small sample sizes and methodological flaws may not provide enough evidence to support their validity. The rationale of using these approaches is that active engagement and responsiveness to the individual participants of research may improve understanding. The informed consent process is not merely reading and signing a form, but it is a continuous dialogue and takes place over time.

### *Enrolling patients in multiple trials*

Many ethics committees consider it inappropriate for patients to be asked to consent to join more than one study. It is not uncommon for patients with childhood leukaemia to be approached for numerous studies looking at different initial regimens, genetic studies for the family or the disease cells, or psychosocial studies looking at how families cope with long-term illness. The argument for involving certain patients in several studies is that some diseases, such as cystinosis or urea cycle defects, are very rare and it is impossible to recruit all the sufferers in the world. To restrict such patients will result in fewer interventions being evaluated (Brocklehurst, 1994) and treating patients without assessing the risks and benefits of a certain treatment is equally unethical. The counter-argument is that the extra blood samples and visits required by the study procedures create an unnecessary burden on families who are barely able to cope with their diseases. This is more so when the outcome of the studies may not be beneficial to the participants.

In a survey of parents with preterm infants in the neonatal intensive care unit (NICU) who had been asked to join two or more studies, 58% were willing for their baby to be in three or more studies (Morley *et al.*, 2005). Parents are willing to help other children with similar conditions even though they know that their own children may not benefit from the study. Researchers should exercise their judgement to decide the appropriateness of using the same patient population for different studies. They need to ask: Is this patient population over-researched? Can we make use of a different patient group?

### *Enrolling children in phase I studies*

Phase I studies are usually avoided in paediatrics because the risk to a child is more than minimal. The chance of having a significant clinical

response is minimal and it is questionable whether parents are ethically suitable to give permission for their child to be enrolled in such a study. It has been argued that in a palliative care situation, where all possible treatment has failed, it is ethically justifiable to enrol a child into a phase I study if the chance of benefit from the new agent is comparable to that of palliative care or continuation of failed therapy (Barfield and Church, 2005). One would need to justify the extra suffering that may have been incurred with the new therapy, but a well-designed trial can mitigate this (Kodish, 2003).

### *Factors affecting informed consent*

Parents have different reasons for allowing their children to participate in clinical research. A researcher should understand these factors and take them into account in trial design and parent/patient education. The aim is to improve the recruitment rate, on the one hand, and parents'/patients' satisfaction, on the other. Less well-informed parents may misconstrue that their child will get better treatment or will get a novel treatment in a randomised trial and will be disappointed when the result or randomisation does not correspond to their perception. Fundamentally, such a misunderstanding threatens their ability to make an informed choice.

Most studies on parental perception have been carried out within 72 hours of research participation decisions (Zupancic *et al.*, 1997; Hoehn *et al.*, 2005); others are retrospective or prospective questionnaire studies (van Stuijvenberg *et al.*, 1998). Factors that influence parental decisions are societal benefit, personal benefit, risk perception and perceived lack of harm. The logistic factors that influence parental perception of risks are the amount of information given, the trust in the institution and the time required for the decision-making. Parents who perceived benefit, either personal or societal, were more likely to participate than if they perceived risk (Tait *et al.*, 2004; Hoehn *et al.*, 2005). Societal benefit is the most frequently cited reason for participation in clinical research. Parents with a critically ill child have an altruistic view to help future children in similar conditions (Langley *et al.*, 1998; van Stuijvenberg *et al.*, 1998; Schmidt *et al.*, 1999; Mason and Allmark, 2000; Hoehn *et al.*, 2005).

Personal benefit was another common reason. A retrospective survey and prospective interview of parents with children in NICUs has shown that 34–43% of parents had chosen to participate because they believed that their child would get better care in the study (Burgess *et al.*,

2003). Potential benefit may be in the form of increased understanding about their child's disease (Rothmier *et al.*, 2003).

The major factor that influences parental decisions is the perceived risk of the research. It is important to distinguish the risks perceived when considering participation from the risk appreciated while participating in the study. In one study, 74% of parents when asked about hypothetical enrolment of their newborn into a clinical trial refused to participate because of the perceived risk of side effects and the unproved efficacy of the trial medication (Autret *et al.*, 1993). Even the perception of minor risk such as painful procedures may sway parents' choice on participation (Langley *et al.*, 1998).

Those who chose to participate in a research study perceived that there was no risk of harm associated with participation. Parental age affects perceptions of risk: parents who were older (over 30 years) assessed the risks as significantly lower than their younger counterparts (Tait *et al.*, 2004). Furthermore, those who had experience of participation in clinical research had a more positive outlook than those did not have research experience. Sociological factors may have some influence on parental participation in clinical studies. One study has indicated that parents with a higher socioeconomic status and more social support were less motivated to contribute to medical research (Harth and Thong, 1990).

Individuals have different needs of cognition. Parents who perceived that they had been given too much or too little information assessed the risks and benefits more negatively than those who believed they had received just the right amount of information (Tait *et al.*, 2004).

Parents who perceived that they have insufficient time or privacy to make a decision tend to assess the risk and benefit in a more negative light (Hoehn *et al.*, 2005). This is partly a result of stress; parents who were anxious were more likely to decline their child's participation (Tait *et al.*, 2003). This would explain why parents are more likely to give consent in an inpatient setting than in an outpatient preoperative setting (Tait *et al.*, 1998), where there was little time and lack of privacy to ponder the issue. Every effort should be made to provide information in an unhurried manner to alleviate anxiety.

Trust is another important factor affecting the perception of risk by parents. Those who had more trust in the medical system tended to have a more positive outlook on research studies. It is not surprising to discover that individuals from ethnic minorities have less trust in research and the medical establishment and are less likely to take part in clinical research (Corbie-Smith *et al.*, 1999; Shavers and Burmeister, 2002).

### *Application of ethics*

For most researchers, the ethics approval process is a daunting path. The successful ethics application starts with a well-written protocol and document control. ICH E6 Section 6 recommends a list of topics that are fundamental for most research (ICH, 1996). A well-written protocol following a template such as background, trial objective, trial design, end-point, statistics and ethics will make the completion of an ethics application form effortless.

All versions of protocols should be version controlled, tracked and retained. The final version should be peer reviewed, approved and signed by the chief investigator. All related documentation, such as patient information sheet (PIS) and informed consent form (ICF) should be version controlled and clearly defined in the ethics application. The ICF should refer to the correct version of the PIS. The ICF should be written in easily understandable language with minimal use of technical terms or languages. Different versions of ICFs should be prepared for parents and for participants with different levels of understanding; usually these are grouped into teenage, older and young children. All other related materials such as letters to GPs, advertising material or questionnaires should also be version controlled or at least have a reference date.

The next step is to identify the sponsor as defined in the Research Governance Framework (Department of Health, 2005) and SI 2004 1031. The identity of the sponsor is required for both the ethics application and EudraCT database. All drug trials should register with the EudraCT database. Where the trial has co-sponsors, these should be identified. The MHRA algorithm (MHRA, 2006) will enable researchers to decide whether the trial is under UK regulation.

The first stage in the EudraCT registration process is to obtain an authenticated security code; this is followed by the EudraCT number and then clinical trial application. The EudraCT database enables the regulatory agency to have an oversight of clinical trials with investigational medicinal products. Once registered, the EudraCT number can be entered in the ethics application and the EudraCT forms can be printed out for clinical trial authorisation (CTA) from the MHRA.

The ethics application form can be downloaded or accessed online from the COREC website. The researcher should put his or her application through the central allocation system with an appropriate REC if the proposed project is a clinical trial of investigational medicinal products (CTIMP), or is likely to take place in more than one domain. For non-CTIMP trials that are conducted within one domain, the

researcher has the option of approaching the local research ethics committee directly. A domain is an area covered by a strategic health authority (England), a health board (Scotland), a regional office of the NHS Wales Department or the whole of Northern Ireland. Once a validation letter is received by the chief investigator from the main REC, a site-specific assessment for the suitability of the investigation, site and facilities may be submitted to a relevant REC by the principal investigator.

### **Types of paediatric clinical trials**

Researchers need to justify the need to conduct the study concerned. The need of the investigation should be weighed against the prevalence of the condition to be treated, the seriousness of the condition, the availability of alternative treatments, the novelty of the compound, uniqueness of the conditions in paediatrics, the age ranges of the children, unique safety concerns in paediatrics and the unique requirement of paediatric formulations that serve the needs of the population.

### **Paediatric formulation**

The lack of suitable formulations in paediatrics has been highlighted by various authors in various countries ('t Jong *et al.*, 2004; Chui *et al.*, 2005; Nunn and Williams, 2005). The suitability includes palatability, appropriate strength and dose volume, flavour and colours and route. Young children cannot swallow tablets, and liquids, suspensions, chewable tablets and suppositories may be needed for children of different age groups.

The concentrations of licensed medications may be too high, necessitating further manipulation in the form of dilution with an excipient. However, when the concentration is low, the dose volume may be too large for some children. The excipients in many liquid formulations may not be suitable for selected patient groups. For example, the propylene glycol content in amprevir liquid formulation makes it unsuitable for children under 4 years of age. Severe delayed-onset hypersensitivity reaction was associated with formulation of amoxicillin liquid; the reaction may have been caused by the excipient (Chopra *et al.*, 1989). Sweeteners, dyes and other excipients may cause adverse reactions and should be identified and restricted in paediatric formulations (Kumar *et al.*, 1996). Some clinical studies have been directed to ascertain the effect of drug concentration and frequency of

administration on target organs. For example, in one study mercaptamine drops 0.11% and 0.3% were administered at hourly and 6-hourly intervals, respectively, to ascertain whether a high concentration would reduce the need for frequent administration of the eye drops (MacDonald *et al.*, 1990).

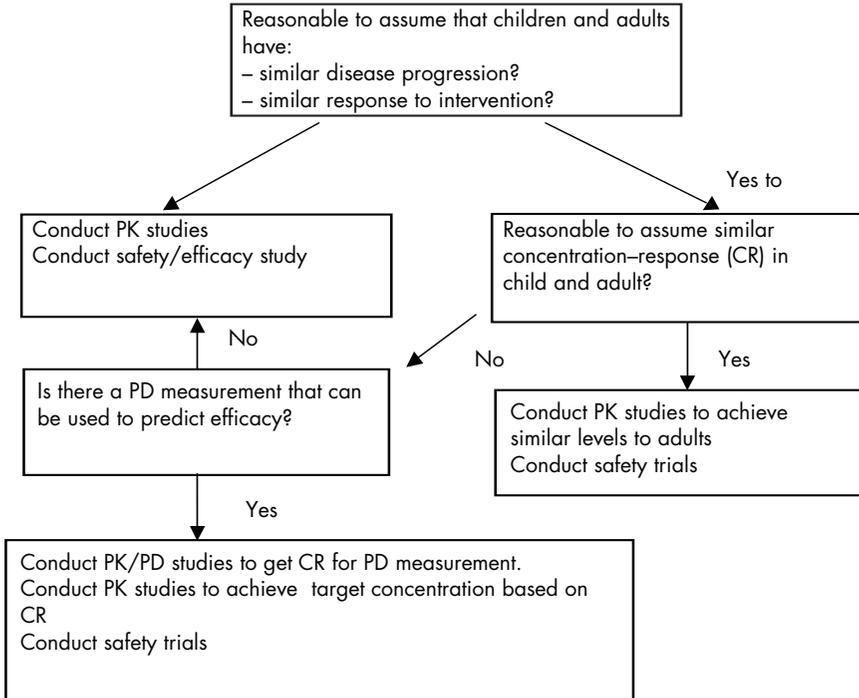
### Pharmacokinetic study

Pharmacokinetic studies are performed to support formulation developments and to determine pharmacokinetic parameters in different age groups to support dosing recommendations (E11) (ICH, 2000). They are generally conducted in children with a disease, which may lead to higher inter-individual variability than in adult health volunteers, although the data reflect clinical use better.

Single-dose pharmacokinetic studies may provide sufficient information for dosage selection in medicinal product that exhibit linear pharmacokinetics. Medicinal products that exhibit non-linearity in absorption, distribution and elimination may require steady-state studies. Such an approach has been used to assess the pharmacokinetics of an extemporaneously prepared sotalol syrup formulation in neonates, infants, and younger and older children. Scheduled blood samples were taken over a 36-hour time interval following dose administration (Saul *et al.*, 2001).

Children are not usually subject to dose escalation studies similar to those carried out in adult populations; an extrapolation approach has been proposed to estimate paediatric dosages (Johnson, 2005). The use of such methods depends on the question to be answered, the availability of patients, and the practical and ethical problems in obtaining blood samples.

The use of population pharmacokinetics and a sparse sampling approach allow each patient to contribute as few as two to four observations at predetermined times to an overall population. Use of the area under the curve (AUC) will minimise the number of samples required from each patient. Population models allow researchers to assess and quantify potential sources of variability in exposure and response in the target population. Population pharmacokinetics seeks to discover which measurable pathophysiological factors cause changes in the dose–concentration relationship and to what degree, so that the appropriate dosage can be recommended. The pharmacokinetic–pharmacodynamic approach has been used to assess sotalol syrup formulations (Shi *et al.*, 2001). Ten blood samples were taken from



**Figure 6.1** Paediatric study decision tree. PK, pharmacokinetics; PD, pharmacodynamics.

children with supraventricular or ventricular tachyarrhythmia following a single dose of sotalol, and doses were escalated over 3 days with an 8-hourly dosing. The data analysis used the NONMEM computer software program to obtain the population pharmacokinetic (PK) and pharmacodynamic (PD) parameter estimates.

A decision tree has been designed by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (Figure 6.1). Where there is similar disease progression and response to intervention and the PK/PD relationship of a drug is similar between adults and children, only PK studies and safety studies are recommended for bridging and dose determination.

### Efficacy studies

When efficacy data from an adult study cannot be extrapolated to the targeted group of children, efficacy studies are required. This may

necessitate developing, validating and employing different end-points for specific age groups. Study design for clinical trials has been covered elsewhere. The methodology for an efficacy study is similar to that in adult studies; what is different is the variety of presentations in children that are not found in adults.

Disodium pamidronate is licensed for use in Paget's disease and osteolytic lesions and bone pain in multiple myeloma and breast cancer in adults, but it has also been used in a variety of paediatric conditions: bone pain in Gaucher's disease (Ostlere *et al.*, 1991), osteogenesis imperfecta (Pizones *et al.*, 2005), mucopolipidosis type III (Robinson *et al.*, 2002), McCune–Albright syndrome (Matarazzo *et al.*, 2002), malignant hypercalcaemia in childhood cancer (Kerdudo *et al.*, 2005) and juvenile spondyloarthropathies (Bukulmez and Colbert, 2002). Therefore a number of efficacy studies for disodium pamidronate are required to ascertain the efficacy for the disease concerned. The differences in the pathology of the diseases may require different dosage and administration regimens.

Research is needed to improve the delivery of drugs in children, either to enhance compliance via the route of choice or to identify alternative routes where the normal route of administration is unavailable or associated with severe side effects. The efficacy of administering ketamine and midazolam orally, rectally and intravenously to children receiving invasive procedures has been compared (Ozdemir *et al.*, 2004). It was found that the alternatives routes were equally effective. The use of other routes may mitigate the usual prolonged sedation and psychedelic effects of intravenous administration of ketamine/midazolam in children.

The quick onset and wearing off of sedation is advantageous in short procedures. For example, the intranasal and oral routes of midazolam have been compared (Lee-Kim *et al.*, 2004) and, although no difference in efficacy was found, the intranasal formulation had a quicker onset of action and a shorter duration of action than the oral preparation.

Occasionally, studies are carried out to target drugs direct to the site of action, thus reducing the exposure of other organs to the drugs. Oral and intravesical administrations of oxybutynin were compared in children with bladder dysfunction. The intravesical route produced a high plasma concentration, and was well tolerated and efficacious. A lack of significant systematic side effects observed in patients receiving oxybutynin via the intravesical route was attributed to the lack of metabolite commonly generated by the oral route. These studies demonstrate that the mode of administration affects the mechanism of action,

side effects, pharmacokinetics and metabolism of oxybutynin (Massad *et al.*, 1992; Amark *et al.*, 1998).

### Safety studies

Age-appropriate, normal laboratory values and clinical measurements should be used in adverse event reporting. Children with developing systems may respond differently to mature adults; some adverse events and drug interactions that occur in children may not be identified in adult studies. The effects of medicinal products on long-term growth and development may not be apparent, therefore long-term surveillance data may be needed to ascertain possible effects. Many established treatments in paediatrics have been conducted for a number of years, and the efficacy of such treatments has never been in doubt in the expert's mind. The use of morphine in neonate analgesia, for example, is a well-established treatment and no one would doubt that the drug does not work in such patient groups. Similarly, drugs such as sodium benzoate and phenylbutyrate have been used for more than 25 years for urea cycle defects, and diazoxide and chlorothiazide combination is a standard regimen for hyperinsulinism in neonates.

On the other hand, certain drugs have gone through the fast-track process and, at the time of authorisation, information on the safety of these medications has been limited, especially for children. In such cases non-interventional observations such as cohort or case-control studies could be a valuable tool to evaluate adverse events.

Safety studies fall into three categories, designed to demonstrate safety, detect new safety issues and evaluate known safety issues.

### Cohort study

A cohort study is a prospective analysis of a population with a particular disease. Participants who are exposed to the study drug and those who are not on treatment are followed for a period of time and observed for development of the disease or result. Information on exposure is known throughout the follow-up period for each patient. The classic example is the use of anthracycline in childhood cancer. A long-term, non-interventional, observational follow-up of 607 children has shown that 5% of patients develop clinical cardiac failure 15 years after treatment. The risk increases with the increase in cumulative doses (Kremer *et al.*, 2001). Once a treatment is associated with certain toxicities, researchers can look at ways to minimise the effect. The relationship

between the cardiotoxicity of anthracycline and its method of administration has been carried out in 44 children (Gupta *et al.*, 2003). A mean of 7 years after the end of therapy, there were no statistically significant differences between those receiving bolus injections and those receiving infusions.

A patient might be exposed to a drug at one time point but not at another. This is particularly important for metabolic diseases, where the progression of the disease should be monitored over a long period and patients should be monitored pre- and post-treatment. Incidence rates can be calculated from the population exposure. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events.

Bias may be introduced into cohort studies when there is a loss to follow-up or when comparator groups are not well matched for potentially confounding factors. When sufficient numbers of patients exist, the data can be stratified to target a specific population. Cohort studies can be perceived as more ethically acceptable than placebo-controlled clinical trials, since a potentially beneficial treatment is not withheld from the participants, and cohort studies can be less expensive to conduct than randomised controlled trials. A longitudinal study is a cohort study with only one group, called the 'inception cohort'. Longitudinal studies are useful for following individuals with chronic diseases. Cohort studies can take a long time to complete when targeting rare diseases or diseases that take a long time to manifest.

### *Case-control studies*

A case-control study is a retrospective analysis; it is generally easier to administer than a cohort study. Cases of diseases or events are identified. Controls and patients exposed to the treatment are selected from the source population. The exposure status of the two groups is compared using the odds ratio, an estimate of relative risk of exposure and non-exposure. Case-control studies are less expensive than cohort studies, but provide weaker empirical evidence than well-executed cohort studies. These studies are useful for identifying the relationship between drug treatments with one specific rare adverse event, or for identifying risk factors for adverse events. Risk factors can include renal and hepatic insufficiency that might modify the risk profile.

In a nested case-control study control sampling is density based; the control series represents the person-time distribution series in the source population. This means that the data about the cases and controls

used in the study are nested within, or taken from, a cohort study. A cohort study collects data from every single individual from a predefined cohort with similar characteristics such as sex or year of birth. On top of that nested case–control study the control matches the duration of cohort membership within a certain time period. The control is randomly selected from the cohort, to a fixed multiple (e.g. 20 controls for each case). This methodology has been used recently to measure the risk of fatal and non-fatal self-harm in patients with first-episode depression receiving selective serotonin uptake inhibitors (SSRIs) and tricyclic antidepressants (Martinez *et al.*, 2005).

Case–control studies are best for studying rare adverse events that take a long time to develop. A disadvantage of this type of study is that it is based on memory and recall, which can be biased, as well as on medical records, which can be incomplete.

### **Trial designs for rare diseases**

Clinical trials should be scientifically sound. Any trial that may not test the underlying hypotheses are unethical and may expose the patients to the risk and burdens without yielding any meaningful results (Altman, 1980; Freeman, 1987b). Randomised, placebo-controlled clinical trials provide the best study result with the least number of patients. When calculating the sample size, the investigator takes into account the expected variability of the outcomes and the chosen probability of type I error. Clinical trials for rare diseases may require a long enrolment period to achieve a sufficiently large sample size to produce meaningful results.

Rare diseases with a frequency of 1 in 10 000 will require 600 participants on each arm to demonstrate an intervention that would reduce the mortality rate from 40% to 30% with a  $p$  value of 0.05. A sample size of 12 million would be required to produce 600 participants (Lilford *et al.*, 1995). A long enrolment period is either impractical or meaningless because new procedures, new agents, improved diagnoses and better understanding of the disease may be developed during the intervening period. A clinical trial of itraconazole for the prevention of chronic granulomatous disease, for example, took 10 years to enroll just 39 patients (Gallin *et al.*, 2003). Alternative approaches such as open protocol, open label, crossover designs and meta-analyses have been used to overcome the shortcomings of traditional design.

**Open protocol design**

Open protocol design has been used in the investigation of mercaptamine for nephropathic cystinosis and sodium phenylbutyrate for urea cycle defects. All eligible patients were given the drugs. The two drugs had been approved as orphan products in the USA. The evaluation of the data was difficult and included anecdotal evidence. As many patients were already on the drug, it was very difficult to conduct any other type of study.

**Open label trials**

Unlike the open protocol design, open label trials can be controlled. The greatest limitation of open trials is the lack of standard features of clinical trials such as placebo controls, randomisation and blinding of raters. Difficulty still remains in the evaluation of the efficacy of the drug, but they do provide important information regarding the safety use of drugs.

**Historical control**

Patients with rare, life-threatening diseases have limited life expectancy, and the use of placebo-controlled studies may be seen by such patients as unethical because they may be withheld from a possible cure. The use of historical controls can circumvent the issues of lack of sample size and the use of placebo. However, interpreting the result of such studies may be difficult. The absence of a placebo control group and factors affecting placebo treatment response often do not remain static over time, making comparisons of recent studies with earlier studies problematic. Historical control trials may take longer, because end-points are controlled against what is historically known. The disease must be well differentiated, with steady and rapid progress.

**Bayesian designed trials**

Bayesian designed trials provide probabilities of treatment effects that apply directly to the next patient who is similar to those treated in any completed or ongoing trial. This approach provides probabilities that can be used in formal decision analysis.

These probabilities are calculated on the basis of the observed data and a prior distribution of probabilities. The results of many small trials are insignificant, and many will say that the treatment is still unproven. However, any small improvement will bring prior equipoised belief in

the direction of benefit. One could argue that a decision taken from a posterior belief that incorporates evidence from a randomised controlled trial, however insignificant, is more likely to be correct than a decision based simply on a prior belief with no evidence to support it (Lilford, 1995).

The design could reduce time and cost, providing greater incentives for pharmaceutical and biotechnology companies to become involved. And with more experimental therapies to be tried, more people will be able to participate in clinical trials in the future.

Whenever a patient's response can be evaluated before the enrolment of subsequent patients, different designs can be used. In the 'play the winner' design, a participant is assigned to one treatment and if the outcome is successful then the next participant is assigned to the same treatment (Zelen, 1969). On the other hand, if the treatment is a failure, the next participant will be treated with another treatment. The limitation is that the response may be delayed or may not be available when the next participant arrives.

### **Crossover design**

Crossover design may help to reduce the sample size while providing enough power to validate the result. Patients receive the two study treatments sequentially and are evaluated for a response after each treatment. Provided that there is no period of carryover effects and drop-outs, crossover studies can match the power of traditional designs. However, the validity of this design is based on the assumptions mentioned above that are relatively difficult to achieve in a clinical setting. The treatment effect must be realised immediately after it is initiated and lost immediately on cessation. This condition may be fulfilled in short-acting compounds such as cytokines but not in long-acting compounds such as the use of Lorenzo oil in adrenaleukodystrophy. Similarly the end-points must be clearly defined and measurable, and the symptoms must manifest in a short latency period. Otherwise they could occur after cessation of one treatment and after the next treatment is commenced.

Another limitation of the crossover design is the lack of long-term safety data. Patients switch from one therapy to another and the evaluation period tends to be short. The use of such a design may be more equitable to research participants. Every participant will have a chance to receive the new treatment, whereas, in the traditional design, only half the patients actually receive it.

## Surrogate end-point

Surrogate end-points may be used in rare diseases where the study of the true end-point is impossible. A surrogate end-point or marker is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end-point that measures directly how a patient feels, functions or survives. Changes induced by a therapy on a surrogate end-point are expected to reflect changes in a clinically meaningful end-point. The changes in surrogate response variables are likely to occur before a clinical event, so less time is needed for a trial. A surrogate end-point can be a legal basis for drug approval in many countries.

For life-threatening diseases, the speed in determining the benefit effect of a treatment is crucial. Surrogate end-points such as CD4 count and viral load are routinely used as markers for antiretroviral treatment. Similarly, in Gaucher's disease, ferritin is a marker for disease progression. However, in some patients, the association between the surrogate marker and disease progression might not be apparent. In orphan drug studies using Lorenzo oil for adrenoleukodystrophy, the reduction in serum long-chain fatty acids is not closely associated with a reduction in disease progress. A surrogate end-point must be validated (Prentice, 1989). For a surrogate end-point to be an effective substitute for clinical outcome, the effects of the intervention on the surrogate must reliably predict the overall effect on the clinical outcome (i.e there should be a strong, independent, consistent association between the surrogate end-point and the clinical end-point).

Some workers have suggested that the use of a surrogate end-point as a sole determinant of efficacy should be used only in phase II studies (Fleming and DeMets, 1996). The surrogate end-points in some incidences do not predict the true clinical effects of interventions. This is because a surrogate end-point might not involve the same pathophysiological process that results in the clinical outcome. Even when it does, some disease pathways are probably causally related to the clinical outcome and not related to the surrogate end-point. The most plausible explanation is usually that the intervention has unintended mechanisms of action that are independent of the disease process.

Researchers need to ensure that the cost savings for not measuring clinical events is not negated by the cost for extra equipment and tests for surrogate markers. They also need to consider whether the result generated is acceptable to scientific and regulatory communities and the safety data are sufficient from a smaller sample size.

### Underpowered studies

Meta-analysis may make small studies meaningful by providing a means to combine the results with those of other similar studies to enable estimates of an intervention's efficacy. Small trials may not be able to test a hypothesis, but they may provide valuable information of treatment effects using confidence intervals (Edwards *et al.*, 1997). Similarly, others argue that a sample size that results in a  $p$  value of 0.1 can be informative and decisions have to be made; even where there is no trial evidence, a little unbiased evidence is better than none. A study might have only limited ability to detect an effect, but participants should be allowed to make an autonomous decision.

Some argue that meta-analysis is meaningful only when researchers explicitly plan the study such that a prospective meta-analysis is possible. Research carries burdens in addition to those encountered in clinical context, such as extra follow-up visits, investigations and discomforts. These burdens cannot be justified by potential benefits to participants, but only by their ability to increase the value of the knowledge to be gained.

The general criticism of alternative trial designs is that the confidence intervals for the estimate of the magnitude of the treatment effect may be wide. The counter-argument is that, when traditionally powered studies fail to produce definite results, the new treatment can still be adopted and additional long-term safety and efficacy data might be gained (Lagakos, 2003).

At a logistic level, the prevalence of rare diseases and the geographical dispersion of such patients have made multicentre studies unavoidable. The investigation of botulism immunoglobulin involved 59 study sites and 120 patients (Haffner, 1998). The enormity of coordinating a trial of such scale is a challenge to many investigator-led researches. The requirement for a single sponsor that is responsible for multinational, multicentre trials, as stipulated by the EU Directive, provides another hindrance.

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