Specific European Union Aspects on Ethics of Clinical Trials

Peter J. Aggett

Institute of Food Research, Norwich Research Park, Norwich, United Kingdom

All member states of the European Union subscribe to codes of biomedical ethics, including psychological and socioeconomic aspects of such research, and consider it essential for all experimental protocols involving human subjects to be reviewed by independent ethics committees. However, although there is agreement in principle, this cannot yet be represented as a single European perspective on the implementation and policing of ethical review processes (1).

The development of ethical review of experimentation and the acceptance that research needs to be performed on children has followed much the same path in Europe as in North America. Perhaps both started with the traditional professional attitude expressed by Thomas Percival in 1803, when he commented that

It is for the public good, and in the special degree advantageous to the poor (who, being the most numerous class of society, are the greatest beneficiaries of the healing art) that new remedies and new methods of chirurgical treatment should be devised. But in the accomplishment of the salutary purpose, the gentlemen of the faculty should be scrupulously and conscientiously governed by sound reason, just analogy, or well authenticated facts. And no such trials should be instituted without previous consultation of the physicians or surgeons according to the nature of the case. (A.G.M. Campbell, personal communication)

This paternalistic, if not patronizing, attitude to the consent of participants persisted until the mid-1960s, when it was challenged by the publication in the United States of Beecher’s review, “Ethics and clinical research” (2), and, in the United Kingdom, the book Human Guinea Pigs by Pappworth (3).

The degree of professional ambivalence that existed 30 years ago in Britain is exemplified by the minutes of a meeting of the British Paediatric Association’s Academic Board on 7 December 1968; the Chairman presented a paper on the ethics of research investigations in children: “... it was obvious that members could not reach complete agreement on a subject which involved individual ethical practise and it was decided to file the paper and take no further action” (A.G.M. Campbell, personal communication).
The position of those wishing to conduct studies in children had at that time been compromised, particularly with respect to research of no immediate benefit to the subject, by a report of the Medical Research Council (MRC) in 1963 that stated that "In the strict view of the law, parents and guardians of minors cannot give consent on their behalf to any procedures which are of no particular benefit to them and which may cause some risk of harm" (4). This position was essentially endorsed in 1975 by the Department of Health and Social Security, which advised that "the fact that consent has been given by the parent or guardian and that the risk involved is considered negligible will not be sufficient to bring such clinical research investigation within the law as it stands" (5).

The terms "therapeutic" and "nontherapeutic" research came into usage more recently. "Therapeutic research" has been used by the MRC to cover research not only on the treatment of disease but also on its prevention (for example, by vaccination) and on diagnostic procedures; it offers direct and possibly immediate benefit to the participant, whereas with "nontherapeutic research," such benefit is either long delayed or unlikely (4); this type of research would embrace observational work on normal physiology and maturational processes (6), even though such studies could be just as relevant to understanding the prevention and pathogenesis of disease.

The view of the British MRC was based on a strict interpretation of the law and was reiterated by the amended Helsinki Declaration of 1975 (7), which stated that nontherapeutic research can be conducted only on a volunteer basis and that consent on behalf of minors cannot be given by parents or guardians for procedures that are of no benefit to them and might carry risk of harm. Because the guidelines for many national ethics committees focused on the interests and the protection of the individuals participating in studies, it is understandable that they, too, were cautious about allowing nontherapeutic research involving infants and children.

In 1980, the British Paediatric Association published guidelines to aid "ethics committees considering research involving children" (8). These included four basic premises: (a) research is important for the benefit of all children; it should be supported and encouraged, and it should be conducted in an ethical manner; (b) research should never be done on children if the same investigation can be done on adults; (c) research that involves a child and is of no benefit (nontherapeutic research) is not necessarily either unethical or illegal; (d) the degree of benefit resulting from research should be assessed in relation to the risk of disturbance, discomfort, or pain (the "risk/benefit ratio"). Points c and d asserted the position of all those who wished to advance the discipline of child health in the context of a developing human being rather than being constrained by the perspective of practitioners in adult medicine.

The Council for International Organizations of Medical Sciences/World Health Organization published guidelines in 1982 that were intended to encourage and facilitate the setting up of national policies and processes for independent prospective ethical review (1). European countries provided their own guidelines for the conduct of clinical trials, for example, Ireland in 1986, Germany in 1987, and Italy in 1991;
Denmark created a National Ethical Council in 1987, and The Netherlands are establishing a Central Committee on Medical Experimentation to replace an interim committee set up in 1982. In Finland in 1985, the National Board of Health not surprisingly endorsed the Declaration of Helsinki (1). The United Kingdom has produced a variety of guidelines advising on the structure and conduct of local research ethics committees; this system is self-regulatory. In contrast, France in 1988 enacted Loi No. 88-1138 relating to the protection of persons participating in biomedical research (9). This legislation, named the “Loi Huriet” after its sponsor Claude Huriet, set up a Consultative Committee Responsible for the Protection of Persons Participating in Biomedical Research (CCPPBR), whose opinion on studies should be sought. Similarly to the laws of much of the rest of Europe, this law concentrated initially on therapeutic research, but it was made less restrictive in 1990. As well as inspiring, in part, the Convention on the Rights of Children (1990), the Loi Huriet also highlighted the need within the European Union for an agreed framework for ethical review of biomedical research. In February 1990, the Committee of Ministers of the Council of Europe agreed on Recommendation No. R (90) 3, which provided 16 principles on the ethics of medical research (10). These addressed the need for a sound science base; respect for the individual; informed consent; care in the conduct of studies involving children, the mentally ill, pregnant and nursing women, and prisoners; guidelines for emergency situations when the participant is unable to give prior consent; an appreciation of the benefit relative to the risk involved; confidentiality; safety of the research; and ethics review procedures.

To achieve uniformity, the EU Council of Ministers recommended that governments of member states either adopt legislation in conformity with the Recommendation or take measures to ensure its implementation and ensure that its provisions are brought to the knowledge of all relevant persons. These principles will have a considerable impact on research in human beings and on trials in pediatric nutrition, and they have been considered specifically in this context by the French Pediatric Association Committee on Nutrition (9) and, by implication, in the recent United Kingdom guidelines on the “Nutritional Assessment of Infant Formulas,” compiled by the Committee on Medical Aspects of Food and Nutrition Policy (COMA) (11). I briefly review the principles in the EU Recommendation and draw on these reports to comment on its implications.

**EU PRINCIPLE 1**

- Any medical research must be carried out within the framework of a plan and in accordance with the following principles.

A nutritional trial should not necessarily go ahead because it involves no danger or disadvantage for the children involved. If the information to be gained is not novel, or if the scientific basis is unsound, then such a trial would not be justified (see also Principle 11). In short, bad science is unethical (12). The Loi Huriet states that “no biomedical research may be carried out in humans if it is not based on the
latest state of scientific knowledge and on adequate preclinical experiments." For studies in infants, the latter could involve animal models, adults, and older consenting children.

The COMA Working Group suggested that all research should be preceded by a critical systematic review (13) of all relevant existing information as a basis to improve innovation and research and that such a review should subsequently be made publicly available, ideally published (11). This entails aspects of the principles of "evidence-based medicine," and, from the point of view of nontherapeutic research in the nutrition of infants and children, the pooling of data from several published studies should improve the quality of such research and the formulation of research questions and might obviate the need for any further study and avoid unnecessary replication. These considerations alerted the COMA panel to the need for a data base of, and information from, abandoned, incomplete, and unpublished studies.

EU PRINCIPLE 2

- In medical research the interests and well-being of the person undergoing medical research must always prevail over the interests of science and society.
- The risks incurred by a person undergoing medical research must be kept to a minimum. The risks should not be disproportionate to the benefits for that person or the importance of the aims pursued by the research.

This principle presents no challenge to nutritional research involving innovative ingredients and interventions, but it might present difficulties in the clinical evaluation of modifications to infant formulas and feeding products that fall within current guidelines on composition. However, a "new" formula would not always be acceptable simply because its compositional profile fell within national or European specifications. The COMA report, for example, considered that, even within the statutory compositional guidelines for infant formulas, it is possible that variations could be responsible for nutrient interactions that would influence the absorption and metabolism of interacting nutrients. These interactions in a complex material could not be predicted with certainty; examples include interactions between essential trace elements such as iron, zinc, and copper both with each other and with calcium. Similarly, we are not as yet necessarily confident that we have the appropriate balance of levels of protein and energy in formulas within the permitted range. Industrial production processes might have a similar effect on nutritional quality by creating reaction products that limit the utilization of nutrients (11).

A principle of "substantial equivalence" has been developed to assist in safety and nutritional evaluations of new products in proposing that traditional foods, accepted as safe in use, can be used as a basis for the safety assessment and acceptance of novel foods, but the COMA panel held that "further development of this concept would be needed before it could be applied to a complex food matrix such as infant formulas, where the interactions within the food are not fully predictable and the
food is the sole source of nutrition." Similarly, the French Pediatric Association Committee on Nutrition emphasized that clinical trials are needed for both nutritional and safety evaluations of new products (9).

It is debatable whether or not adding approved "substances for nutritional purposes" (for example, nucleotides, taurine, long-chain fatty acids) or a technological modification actually constitutes a "novel food" in the context of European regulations. It is probable that in the context of the COMA report they probably would be regarded as "novel"; even so, there is usually a scientific rationale for such modifications, and this would merit formal evaluation. The COMA noted that "it has been suggested that infant formulas should be assessed as pharmaceuticals with a registered specification of the product and of the processes used in its manufacture." Here again, the vulnerability of infants and their dependence on particular foodstuffs makes it reasonable that there should be some regulation of the composition of such products. This also justifies the view that new emulative products should at least have acceptability and tolerability trials and that, on this basis, the absence of any novel biological and medical knowledge from such trials would not necessarily make them "unethical." These studies should be, nonetheless, appropriately designed and conducted to establish equivalence with comparable products (14,15). Marketing initiatives under the guise of "acceptability studies" in infants should be no more acceptable or ethical than similar studies would be in the assessment of pharmaceutical products (see also EU Principle 11).

In France, acceptability studies are not necessarily legally required, but the French Committee on Nutrition accepted that even if these "clinical trials" were neither absolutely essential for the advancement of knowledge nor mandatory, they would enable some justification of the product and the continuing improvement of products.

The next three principles can be considered together.

**EU PRINCIPLE 3**

- No medical research may be carried out without the informed, free, express, and specific consent of the person undergoing it. Such consent may be freely withdrawn at any phase of the research, and the person undergoing the research should be informed, before being included in it, of his right to withdraw his consent.
- The person who is to undergo medical research should be given information on the purpose of the research and of the methodology of the experimentation. He should also be informed of the foreseeable risks and inconveniences to him of the proposed research. The information should be sufficiently clear and suitably adapted to enable consent to be given or refused in full knowledge of the relevant facts.
- The provisions of this principle should apply also to a legal representative and to a legally incapacitated person having the capacity of understanding, in the situations described in principles 4 and 5.
EU PRINCIPLE 4

• A legally incapacitated person may undergo medical research only where authorized by Principle 5 and if his legal representative, or an authority or an individual authorized or designated under his national law, consents. If the legally incapacitated person is capable of understanding, his consent is also required, and no research may be undertaken if he does not give his consent.

EU PRINCIPLE 5

• A legally incapacitated person may not undergo medical research unless it is expected to produce a direct and significant benefit to his health.
• However, by way of exception, national law may authorize research involving a legally incapacitated person that is not of direct benefit to his health when that person offers no objection, provided that the research is to the benefit of persons in the same category and that the same scientific results cannot be obtained by research on persons who do not belong to this category.

The child’s caregivers and relevant health professionals should be told about the study’s design, and sometimes it might be advantageous to involve parents and other professional carers in pilot studies, study design, and study procedures (16–18). This would also reduce any perceived risk or discomfort arising from disruption of family life or separation of the child from its family. Involving health professionals improves the chances of recruiting participants from sectors of the community that so often include those who would benefit most from nutritional studies in babies and infants and ensure so far as is possible that the participants represent the population for which the product is intended.

The “selection” and recruitment of participants in nutrition studies in children need to be considered in the light of the particular question in mind. If the study has a demanding protocol, for example a metabolic balance, then recruitment should probably take place among children of appropriately educated and motivated parents.

To minimize selection bias in clinical trials, infants should be randomly and blindly allocated to study groups, and it is reasonable to feel that the ideal outcomes in the assessment of products should be those of healthy breast-fed babies. However, it is not practically or ethically acceptable to study groups of infants randomly assigned to or denied breast-feeding. It is debatable whether it is ethically acceptable to involve in a study breast-fed babies who might not derive any benefit from the study. This is really the epitome of nontherapeutic research, but to my knowledge no ethics committee has raised this issue. Nonetheless, data from breast-fed infants (particularly term infants) are needed as a standard for the evaluation of modifications in formulas and for further information about infant development, and so the inclusion of breast-fed babies in studies could be optimally exploited by ensuring that such studies contribute to a reference data base on outcomes in healthy breast-fed infants. This is consonant with the sentiment in the Loi Huriet that “studies without
direct benefit for the individual are permitted [in children] if they present no serious predictable risk to their health, if they are of value for people of the same age with the same disease or handicap, and if they cannot be carried out in any other way” (9).

How much the investigator can properly rely on the consent of the parent or guardian is uncertain in United Kingdom law; the position in France seems to be more explicit and reliable. Consent depends on the information given to the parents, the understanding of the parents or guardians, and, in the ethical context, the voluntary nature of any decision taken. In some instances, the French Pediatric Association felt that it would be important to protect children from the susceptibility of their parents to coercion by virtue of a dependent relationship with the investigator or someone else with a vested interest in the study or from inducement by expenses and the prospect of free food or diapers or both (9). Often such parents, if poorly educated, would not be able to participate reliably in a study and would be unreliable recruits.

The design of readable and understandable consent and information sheets is not easy. Some ethics committees evaluate the reading age required to understand information and consent forms. It seems best to aim for a required reading age of 16, but many initial drafts of forms require a higher degree of literacy, so it is not surprising that 80% of adult patients think that consent forms are to protect the investigators rather than to inform participants (19).

Another means of capitalizing on infant feeding trials has been proposed, in that information derived from such studies could be used further by establishing a means by which the original records, with protection of the participants’ confidentiality (EU Principle 9), could be preserved in anonymized data archives that could subsequently be made publicly available for analysis (13). In the long term, this would allow the possible pooling of data from a number of trials, for example, for the study of long-term effects of early infant nutrition or the detection of adverse effects that would not necessarily be discovered by small studies.

The next two principles need no comment in the context of this chapter.

**EU PRINCIPLE 6**

- Pregnant or nursing women may not undergo medical research in which their health and/or that of the child would not benefit directly unless this research is aimed at benefiting other women and children who are in the same position, and the same scientific results cannot be obtained by research on women who are not pregnant or nursing.

**EU PRINCIPLE 7**

- Patients deprived of liberty may not undergo medical research unless it is expected to produce a direct and significant benefit to their health.
EU PRINCIPLE 8

- In an emergency situation, notwithstanding Principle 3, if a patient is unable to give prior consent, medical research can be carried out only when the following conditions are fulfilled:
  - The research must have been planned to be carried out in the emergency in question;
  - The systematic research plan must have been approved by an ethics committee;
  - The research must be intended for the direct health benefit of the patient.

This has most relevance in clinical nutritional problems and particularly with preterm low-birth-weight neonates. The guidelines are clear. It has been opined that "informed consent from poorly educated parents entering a complex trial in stressful conditions is a sham" (20). Ethics committees have been criticized for not appreciating the practicalities of doing trials in acutely sick newborns by insisting that investigators get the customary consent from parents, who might, however, be too upset to make clear judgments and who are particularly vulnerable to persuasion by investigators. It has been proposed that the Zelen procedure be followed in such circumstances, in that only parents whose infants were being given the novel intervention should be informed of the trial and asked for consent (21). This raises issues that are relevant to quantitative research in infant nutrition in nonacute as well as in acute circumstances.

Principles 9 to 11 cover issues that have been considered elsewhere.

EU PRINCIPLE 9

- Any information of a personal nature obtained during medical research should be treated as confidential.

EU PRINCIPLE 10

- Medical research may not be carried out unless satisfactory evidence as to its safety for the person undergoing research is furnished.

EU PRINCIPLE 11

- Medical research that is not in accordance with scientific criteria in its design and cannot answer the questions posed is unacceptable even if the way it is to be carried out poses no risk to the person undergoing research.

EU PRINCIPLE 12

- Medical research must be carried out under the responsibility of a doctor or person who exercises full clinical responsibility and who possesses appropriate knowledge and qualifications to meet any clinical contingency.
The responsible doctor or other person referred to in the preceding paragraph should enjoy full professional independence and should have the power to stop the research at any time.

The competence and resources of the researchers are crucial to assessing the balance between risk and benefit of studies. In this respect, the Loi Huriet specifies that trials should be conducted "under the direction of a physician with appropriate experience, under material and technical conditions adapted to the trial and compatible with the strict scientific requirements for the safety of the persons participating in it" (9). These are reasonable specifications for the safe conduct of research (EU Principle 10). An absolute need for a physician to be in charge is questionable. Clearly, the expertise of the investigator is crucial to the assessment of the risk/benefit ratio, but the need for a medical qualification has to be gauged against the nature of the study and the risks involved.

To further guarantee or monitor the risk/benefit ratio, the possibility of unpredicted adverse outcomes should be addressed by clinical monitoring of all participants and perhaps by arranging independent scrutiny of study volunteers and of accumulating data, not only for adverse effects but also for beneficial effects, either of which could justify an early termination of the trial. In some circumstances it could be in the investigator's and sponsor's interests to use such a process.

EU PRINCIPLE 13

• Potential subjects of medical research should not be offered any inducement that compromises free consent. Persons undergoing medical research should not gain any financial benefit. However, expenses and any financial loss may be refunded, and in appropriate cases a modest allowance may be given for any inconvenience inherent in the medical research.

• If the person undergoing research is legally incapacitated, his legal representatives should not receive any form of remuneration whatever except for the refund of expenses.

The Committee of Nutrition of the French Pediatric Association was concerned that the selection for studies of children from poorly educated and economically disadvantaged families presented dangers in recruitment and declared that "one can only subscribe to the concept that studies carried out in children from deprived communities and who are not free to decide should be vigorously rejected, except if the disorder or disease to be combated exists only in those communities." One can sympathize totally with this viewpoint, but at the same time it is necessary to appreciate that some studies, such as the nutritional assessment of modifications of infant formulas, might need to be performed on representative populations.

In addition to inducements to participants' parents, the financial basis of studies and potential inducements for the investigators should be declared to ethics committees (22). It has been queried whether or not per capita payments for participation
in pharmaceutical studies are ethically acceptable. In the development of infant formulas, there is a need to use multicenter studies and *pro rata* payments to accelerate the completion of studies. If this form of research funding were to be regarded as unethical, then the development of formulas or work to establish new information on infants and children with specific nutritional metabolic requirements would be seriously hampered.

**EU PRINCIPLE 14**

- Persons undergoing medical research and/or their dependents should be compensated for injury and loss caused by the medical research.
- Where there is no existing system providing compensation for the persons concerned, states should ensure that sufficient guarantees for such compensation are provided.
- Terms and conditions that exclude or limit, in advance, compensation to the victim should be considered to be null and void.

Trials should be covered by a contract between the sponsors and investigators defining the aims, methodology, and conditions of the trial, the outcomes to be expected, and the way the results are to be used. All studies should have adequate indemnity and insurance coverage, and ethics committees would be expected to check this on behalf of the subjects (1). The sponsors and investigators need to be insured, as does any participating health facility. An amendment to the Loi Huriet in 1991 enforced these provisions in France, and that law also makes it clear that the sponsor is responsible for ensuring that the trial conforms with the law (1,9).

**EU PRINCIPLE 15**

- All proposed medical research plans should be the subject of an ethical examination by an independent and multidisciplinary committee.

Ethical examination not only protects the children; it also protects the researcher, the sponsor, and the agency responsible for the location where the research takes place. The work of research ethics committees is increasingly demanding and responsible, and their competence and composition are of considerable concern (23). Most European guidelines expect committees to have a representative range of ages, members of both sexes, some lay members who are not directly associated with the health profession (ideally clergymen, lawyers, philosophers, and so on), a statistician, and members of health professions—certainly family practitioners, clinicians with experience in research, and if possible nurses and community caregivers. Most committees would not necessarily have a pediatrician and would therefore need to seek appropriate expert advice. There is a variable degree of autonomy for committees in EU member states (1), but some have national specialist ethics boards for central
reference or review processes to smooth out variance between committees and to minimize inconsistency, particularly when this affects multicenter studies (24).

Another responsibility befalling ethics committees is to follow up the outcomes of previously approved proposals to ensure that the results are made available publicly (when possible), even if a study is abandoned (25). An applicant's record in this respect should be examined in any new proposal. The view that not to publish or use results is unethical is becoming widely appreciated (26).

EU PRINCIPLE 16

- Any medical research that is unplanned, or contrary to any of the preceding principles, or in any other way contrary to ethics or law, or not in accordance with scientific methods in its design and unable to answer the questions posed should be prohibited or, if it has already begun, stopped or revised, even if it poses no risk to the person(s) undergoing the research.

Pertinent issues arising from this principle have already been discussed. The ability of ethics committees to impose or propose sanctions if the guidelines are violated varies among the European member states. In France, there are penalties for those who transgress the guidelines: provision is made for imprisonment for periods of 6 months to 3 years and for fines of FF12,000 to FF200,000. Elsewhere, moral opprobrium, rejection of work for publication, the displeasure of sponsors, and the possibility of not being able to get any subsequent research proposals approved or funded are considered sufficient disincentives to breaking guidelines. Additionally, anyone who might wish to pursue any miscreants for unethical conduct of clinical trials could initiate legal proceedings on the basis of assault or the breaking of contracts.

REFERENCES

Dr. Perman: Could you comment on the ethics of the sponsor wishing to review a manuscript prior to publication and perhaps engendering some censorship of the data and the nature in which they are going to be reported?

Dr. Aggett: If a study is done according to ethical review, then I think that if the sponsor did wish to exercise interference, it should be referred back to the appropriate ethics committee. In France, the law states that there should be a specified contract between the researcher and the sponsor, and I think this type of contract could actually specify whether or not the company can censor the results. I don’t think any academic institute or research body in the United Kingdom or elsewhere would accept a contract that allowed the sponsor subsequently to exercise interference or censorship.

Dr. Steenhout: I would like to ask a question concerning the independence of the ethics committee. When you submit a protocol to an ethics committee, you must put the name of the investigator and the name of the sponsor. When I see the composition of some ethics committees in Europe, I am apprehensive about their independence. I would like to ask this: don’t you think that the names of the investigator and the sponsor should be withheld from the ethics committee, particularly in view of the fact that such committees may include a philosopher or a priest? And would it not be better if the ethics committee has the right to follow the outcome of the study later, especially in relation to ensuring the publication of all the results, even in the case of negative studies.

Dr. Aggett: Your second question is easier: yes, I think you are right. How one actually implements it, and how one provides the ethics committee with sanctions if data or papers are not published, is another issue. But it is becoming increasingly regarded as unethical not to publish data: results must be publicized in some form or another. When it comes to the independence of the ethics committee, I think there are times when the committee does need to know who is doing the study and to have some idea about the skills of the investigators, and they do also need to know the sponsorship of the studies. I cannot really sense what your anxiety here might be, but I think there are difficulties with the perceived expertise of
ethics committees, and if that is a problem, then the resort that is available in many places now is national central referral committees or, in some cases, professional committees, and by professional, I mean ethics committees for psychiatrists, psychologists, pediatricians, and so on.

Dr. Rey: I am not in favor of a sort of blank proposal by a scientist to an ethics committee. I think that the ethics committee has a duty to discuss the project with the applicant and to try to improve his knowledge of ethics, if necessary, and also to understand fully what are the objectives of the research. As a member of the ethics committee of the Hôpital des Enfants Malades in Paris for many years, we were very pleased to discuss with the applicants the reason why they were proposing a particular piece of research. In France, it is mandatory to consult the ethics committee, but it is not mandatory to follow the opinion of the committee. So, the ethics committee has no right to follow the research afterwards. Finally, I think it is very important for pediatricians to discuss among themselves what ethical rules they should propose to the community. Sometimes, there is no pediatrician in an ethics committee, although it is important to have one when the committee is consulted on research involving children.

Dr. Aggett: I agree with all this. I think it might well be that we are going to see the evolution in due course of specialist ethics committees, committees for pediatric proposals, geriatric proposals, and so on, where people have appropriate expertise and experience in the requirements for the study, can understand the background science, and know whether the study is worthwhile, and then of course, be able to understand better the benefit and risk in the perspective of their own experience and that of the applicants.

Dr. Haschke: I am probably touching a critical issue: validation studies that are carried out by drug companies and infant-food-producing companies are probably unethical because "bad science is unethical." How can we eliminate the need for these validation studies? In the United States, there are clear rules—no validation studies are necessary. But in Europe, it is different: one country might not accept what has been shown in another country. It is even worse in Asia, and there might be also a problem in South America. How can we come to an agreement that we can at least reduce the number of these validation studies?

Dr. Aggett: What do you mean by a validation study?

Dr. Haschke: Once the drug has been tested in a clinical trial and has been found to be effective, it is probably allowed in that country, but in order for it to be marketed in other countries, further studies are required by their respective governments, although the data are already available from an adequate clinical trial. It may be that the companies are doing this for marketing reasons, but it is "bad science."

Dr. Aggett: I agree, that type of validation study is wrong: the science need not necessarily be bad, but it may be, as you imply, repetitious and not needed. Marketing trials, or marketing exercises masquerading as acceptability studies, are probably unethical.

Dr. Guerry: Although I agree with the principle that dictated your answer, I think we have to realize the implications of such an answer. We know that certain countries and certain governments are very protectionist. We also know that many prescribers of drugs or new foods are also protectionist. If we fulfill the rule and don't duplicate studies in other countries, this has at least two consequences and probably many others. If the study has been done in another country, then that means that the children in the protectionist country will not be able to benefit from new drugs or new formulas, and this may be detrimental. If we say, all right, in that circumstance, we will have to do all the research in the protectionist country, this means that scientists in other countries will be deprived of the possibility of doing research.
So, I would like more reflection on this issue. It is not simple, and a fast answer may not be the right one.

_Dr. Aggett_: My answer was an answer to the ethical aspect. I think your position is perfectly understandable from the point of view of the company; the solution, perhaps, lies elsewhere.

_Dr. Lucas_: There is an issue that I would very much like to hear some discussion on from both sides of the Atlantic, and that is to do with the complete reporting of clinical trials. Quite often in an ethically approved trial, a large amount of information is collected, and that is presented very selectively in scientific papers, often to prove a particular point, but the information that isn’t reported is often very important from the point of view of the interpretation by others of the trial results, and it also could be an important basis for future work by other people. Now there would be a case for the complete results of an ethically approved trial being written up somewhere, and the important question here is one of property rights—whether the results of an ethically approved trial are in fact in the public domain, or whether the unpublished results remain the property of the investigators. Do you have any comments on that?

_Dr. Aggett_: We (i.e., Dr. Lucas, our colleagues in the U.K. COMA Panel, and I) have been involved in discussions on just this aspect. My personal view is that if people go to the trouble of collecting all this type of information, then it should be publicly available. If it is sensitive inasmuch as it relates to commercial development of a product, then indeed, there could be a 1-year, 2-year, or 3-year moratorium on this information. But one of the things that the United Kingdom Committee was considering was that it would be advantageous to have all such data deposited in a publicly available data base to which people could have access. We felt that all the data that have been acquired really should be in the public domain, and it should be part of the responsibilities of an ethics committee or review process to ensure that this actually happens by coming back to the investigators 2 or 3 years after the study. The other issue is whether or not one needs to find some way of being able to pool such data to offer the benefits of a much bigger data base for unanticipated benefits or unanticipated adverse effects, either in the 2 or 3 years after the study or, with our current interest, in the long-term effects of infant nutrition, for retrospective exploration, say, in 10, 20, or 30 years’ time. To achieve this, we felt that there could well be an opportunity for basic core protocols to be undertaken giving guidance on how essential data, such as standardized weight, height, and length measurements, should be measured and recorded. In general, I think that once the data are collected, they should be in the public domain.

_Dr. Lozoff_: The comment was made that it is bad science to redo something that has already been done, but in fact, it takes a lot of studies to know something for certain. I was curious about what criteria you had in mind when you said that something was known. To give an example, the trials related to iron deficiency and development have produced different results. If you concluded that the effect was known after the first one, you would never have had the subsequent ones.

_Dr. Aggett_: I think it is the principle that is important. One doesn’t go ahead and replicate a study with all its mistakes. I am sure that if one did look at various intervention studies, one would find anxieties with social class matching groups, how interventions are given, and things like that, and I am sure that one could find ways of benefitting from the previous study to improve on it. I think that is what is happening with the evolution of our understanding of iron intervention. So, I think that with good insight and with the right sort of people looking at the data, the appropriate questions can be generated.

_Dr. Lozoff_: My second question relates to your criterion of the purely breast-fed baby. I am a very strong advocate of breast-feeding, and I have some concern about the basis for
that recommendation. I am aware of only one study on feeding practices that had a worldwide sample of nonindustrialized societies. In that study, one-third of such societies started supplemen-
tary foods before 1 month, one-third started between 1 and 6 months, and only one-third waited until after 6 months (1). So, if you were to establish a criterion of 4 to 6 months of pure breast-feeding, you would not be in harmony with practice in many traditional societies throughout the world.

Dr. Aggett: It sometimes worries me that we are perhaps being tempted to be politically correct in this context. The point that we are trying to make is that to come up with a product that matches human breast milk is not in itself a satisfactory outcome. What we would like to see would be that such a product has the long-term benefits observed in the baby fed predominantly on human breast milk. I don't think we are trying to be too pretentious about the ideal of breast-feeding.

Dr. Aeschlimann: I have to stress the distinction between collective ethics and individual ethics. This is an old debate published about 8 years ago in the British Medical Journal by Stuart Pocock (2), describing trials stopping early because one treatment was showing up as better than another. This was fine as far as individual ethics are concerned, and they stopped the trial, but then, what should the doctor do? The trial was not significant enough, and they continued to use the less-effective treatment. I think that ethics committees must continue to see what happens during the course of a trial and to give clear guidelines on whether to stop or not. Failure to achieve clear results is itself unethical.

Dr. Aggett: It is difficult to comment without knowing either the nature of the condition or the associated variables or even the number of subjects or even if the appropriate outcome is defined for that sort of study. But I agree that there is a risk that on occasions, the null hypothesis might be rejected because of inadequate numbers, and that was the point I was trying to make earlier, that if one has a well-characterized outcome, one should then be able to determine the numbers required to test the hypothesis.

Dr. Roche: In the context of randomized clinical trials, I want to make a heretical suggestion. Many companies producing infant formulas have been conducting clinical trials for years in very large numbers and have large amounts of control data. From an ethical point of view, is there any advantage in these accumulated control data? Can they be used to replace random controls in future clinical trials?

Dr. Aggett: They have not been fed the same product. If the basic formulas have different compositions, then one obviously cannot use the data as a reference.

Dr. Roche: Commonly, they have been collected in a standardized fashion and using the same reference formula. That is not the problem.

Dr. Aggett: It is an interesting suggestion.

Dr. Perman: Dr. Lucas, did you have a comment on the use of controls from previous studies?

Dr. Lucas: My own view is that while the sort of data that you are suggesting would be of immense value as reference data, and really should be available, they could never supplant a randomized clinical trial. The circumstances would always be different—you would never be able to use somebody else's control data to get at causation. So, I think it would be valuable, but it is not a complete answer.

Dr. Uauy: I would like to bring up the issue of double standards. We put all the burden of the ethics of medical acts on research activities, but the uncertainties linked with therapy in everyday practice are actually not subjected to ethical review.

Dr. Aggett: I think there is a lot of truth in that. Our experience is, for example, that something like 60% of the drugs we use are not licensed to be used in pediatric age groups.
I do not know the precise figure. There is a total lack of appropriate study or understanding of these problems.

*Dr. Kauffman:* It turns out that for the past 30 years in the United States, 80% of the drugs marketed have a labeling disclaimer for use in children; that is, only 20% of the drugs are approved for children. I have argued in a number of publications over the past 20 years that this is unethical. What is ethical is to do the studies under carefully controlled clinical trials in children under the purview of ethics committees; what is unethical is to continue this practice in medicine that is perpetuated by our regulatory system under which children are not given the same protection as their adult counterparts. So, I agree with you, it is a major problem.

*Dr. Lucas:* Unfortunately, the problem is one of industrial sponsorship: pediatric pharmacology is not very remunerative, and unless funding came from research bodies, it is very unlikely that clinical trials will be done.

**REFERENCES**