CLINICAL TRIALS IN INFANT NUTRITION

METHODOLOGY, STATISTICS, AND ETHICAL ISSUES

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Preface

The theme of this Workshop is different from that of the previous Nestlé Nutrition Workshops. It does not assess state-of-the-art knowledge in a particular area of nutrition, as in earlier workshops, beginning with maternal nutrition during pregnancy in 1981. Nor does this Workshop deal with a major problem of nutritional pathology in the infant, as was the case, for example, when diabetes or diarrhea were recently Workshop topics.

The original subject of this 40th Nestlé Nutrition Workshop is its examination of the methodological, statistical, and ethical problems of conducting clinical trials in pediatric nutrition. The topics covered included: the legislative framework of the industrialized countries in which trials are conducted; moral obligations in developing countries, in particular where ethics committees have not yet been established; the regulations that the industry must observe in formulating product claims so as not to mislead the consumer and not to discourage breastfeeding; and, finally, the need to adhere to the fundamental ethical principle that is the primacy of protecting the best interest of individual infants and of children at large.

Randomized trials, meta-analyses, multicenter studies—all of these strategies have their advantages and disadvantages, which have been emphasized and discussed at length during this Workshop. It will surprise no one that participants easily accepted randomized controlled trials as the ideal method for the evaluation of nutritional factors that might influence the growth and development of low-birth-weight, full-term, healthy or ill infants.

Incomplete studies and incomplete subjects within the sample are related problems that deserve consideration. The selection of outcome variables is a crucial factor, since it determines the length and complexity of a study. As such, the choice of variables plays a decisive role in the percentage of studies abandoned in mid-course. The longer the study, the more essential is the cooperation of all those involved, in particular, that of the parents or caregivers. Despite their power, crossover studies may also be difficult to complete. They have the disadvantage of obliging participants to submit to two treatments instead of just one. This reduces compliance and increases attrition in the sample. However, there is nothing to prevent those who are less compliant from constituting a subset within a population—quite the contrary. Ignoring those who leave the study, especially those studies designed to evaluate the effects of nutrition on psychomotor development and intellectual performance, would thus be a major potential bias. On the other hand, analyzing the drop-out as a result reflects, to some extent, the acceptability of a treatment and is one way of evaluating its clinical usefulness.

Multicenter clinical trials offer, for their part, a certain number of advantages, in
particular that of obtaining broader patient representation and enhancing the validity of results. However, such studies are generally very time-consuming and demand considerable effort in order to maintain the interest of participating investigators until their conclusion. Problems likely to arise during the study must therefore be anticipated, which presupposes the involvement of all investigators in the protocol planning. However, just as it seems to be essential to involve all investigators in the intellectual process, it is necessary to use specially prepared staff at each site to gather results and perform all practical tasks. When this is not the case, the undertaking is often doomed to failure. One further challenge in multicenter clinical trials is that the standardized protocols may limit the imagination and research questions of individual investigators.

Meta-analyses also pose challenges and these were emphasized during this Workshop. The objective of this statistical approach is to synthesize the results of numerous randomized controlled trials to highlight benefits or drawbacks that trials carried out on smaller numbers of individuals are unable to detect. The basic problem is obviously that of selecting studies that can reasonably be grouped together, since the decision as to whether or not to include a study in the meta-analysis should take only its methodology, and not its results, into account. The major criticism levied against meta-analyses is the difficulty of analyzing all of the studies, including those that have not been published, since negative results have a smaller chance of being published than positive results. Unpublished results could, indeed, contradict those that have been published. This highlights the importance, in the interests of validity, of using tests making it possible to calculate the number of unpublished studies liable to refute evidence drawn from published studies. It is also important, as has been said, to take into consideration in the analysis the fact that some studies conducted among small numbers of individuals evince huge differences—if not for this, they would be insignificant—while others, conducted among large numbers of individuals, show only minimal, if significant, differences.

Various scientific journals have recommended that, whenever justified, appropriate indicators of uncertainties, such as the confidence interval (CI), be used. Despite this, an analysis of publications shows that CIs are used only in exceptional cases, demonstrating that the Vancouver recommendations have little impact on nutritional research at the present time. This observation, which came to the fore during the Workshop, confirmed our belief that it was necessary to clarify the significance of the various tests and to try to demystify the concept of a “significant” value. Statistical significance is often expressed as important, in contrast to an “insignificant” result, which is generally considered to be unimportant. A high percentage of “negative” results is said to be only due to inadequate sample size. However, studies conducted among large numbers of individuals often produce results that are declared to be statistically significant, although differences are so slight that they are meaningless in practical terms.

There are countless biases that we must all be aware of and, if possible, avoid. If we look at data in written publications alone, we can readily see that there is an inverse correlation between sample size and the magnitude of the effects observed;
this is easily explained by the fact that studies conducted among small numbers of individuals must evince huge differences to be significant. Of more interest to Workshop participants, however, and also more serious, is that the decision to submit an article for publication and that of the journal to accept or reject it are linked to the research results; significant results are favored at each stage. Authors apparently play an even more important role than publishers in this form of bias. These publication biases are liable to distort the interpretation of meta-analyses and, more generally, may misconstrue strategies for preventing and treating illness. Thus, profound reflection is necessary in order to try to remedy this source of bias. The idea of a register in which all clinical trials in progress would be recorded prospectively, whether or not they were subsequently published, is one way of achieving this. The prospective registration of studies would enable everyone to know that the study has been conducted, or should have been conducted, and this is the only means of avoiding any selection bias in the register itself.

All of these considerations are not peculiar to the field of clinical trials in pediatric nutrition, but should be borne in mind by those with an interest in it. This is all the more important given that the regulations imposed upon scientists are ever more strict and it will be increasingly necessary to demonstrate the "efficacy" (benefit) and "safety" (risk) of advances in pediatric nutrition. Safety has, to date, commanded less attention than efficacy. As a matter of fact, many participants emphasized that larger numbers of subjects were necessary to verify safety than to test efficacy, as trials conducted on very large samples are necessary to evince an incidence difference for a relatively rare event. This is illustrated perfectly in the discussion concerning the long-term consequences of infant nutrition on neurodevelopment. Indeed, only intervention studies, planned to allow long-term monitoring and having sufficient numbers to evince any undesirable effects, bring satisfactory results. Intervention studies that evaluate long-term effects and the absence of harmful effects must, therefore, be the foundation of public health policy.

It is also helpful to recall that each study raises new questions that modify the way subsequent studies are conceived. This point was illustrated remarkably well by the analysis of environmental factors on mental and motor development in infants. The situation is always more complex than one thinks at first; the approach of most researchers is, more often than not, naïve and simplistic in this respect. Environmental factors can be very different in developing countries than they are in industrialized countries, and the association between a nutritional disorder and poorer development is not necessarily causal. Both outcomes could be the separate results of underdevelopment, poverty, low-level parental education, and unfavorable environment. It is therefore the environment in which the infant lives that must be considered, with attempts to identify those factors that put the infant at risk and those that are most likely to be altered by intervention.

All of this cannot be carried out arbitrarily, without observing a whole series of fundamental principles. These were first stipulated in 1964 in the Declaration of Helsinki and reinforced subsequently on numerous occasions. Today these principles are accepted almost universally. The basic principles that should guide us do not
differ between Europe and North America, even if they have force of law in some
countries and exist only as recommendations or guidelines in others; this is the result
of cultural differences that go far beyond the field of ethics, but which leave its
foundations unshaken. In our opinion, it is interesting to recall these principles and
to analyze the way in which they influence our practice, especially in developing
countries. In fact, the same rules apply throughout the world and every action should
be taken to seek the opinion of a properly constituted local ethics committee. It is
important that investigators working in developing countries are aware of particular
sensitivities in these countries, and are convinced that every infant taking part in
the study, including in the control group, will benefit at some level from participation.
No long-term collaboration is possible if relationships of trust are not built, not only
with those taking part in the study, but with former subjects, so as to obtain their
consent "with hindsight."

Establishing a relationship of trust, including between industry and Nutrition Com-
mittees, is at the heart of this discussion on clinical trials in infant nutrition. Industry
must understand the reasoning of pediatricians and nutritionists, but it must also
assert its point of view when it does not go against basic principles. One of the
difficulties in this respect is knowing just how far industry can go in the messages
it conveys. It was therefore worthwhile recalling existing legislation relating to func-
tional and health claims in the United States, Canada and Europe, as well as the
principles of the Codex Alimentarius, which apply worldwide. The idea that claims
should be authorized, provided that they are not false or misleading, must be the
main idea behind all legislation. But, just as the burden of proof should be incumbent
on industry and not on government, so industry must be allowed sufficient freedom.
To the extent that the benefits claimed are scientifically proven, it would indeed be
detrimental to the entire community, and in particular to infant health, if industry
were unable to make justifiable claims. The purpose of regulations is not to hinder
progress, but to protect consumers and to be of benefit to the population.

The goal of this Workshop is to give future investigators a better understanding
of the methods that are the most appropriate to clinical trials in pediatric nutrition.
We hope that this monograph will serve the pediatric community, which is so keenly
interested in infant nutrition, as well as established and aspiring clinical investigators,
bioSTATisticians, members of ethics committees, and regulatory bodies.

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Foreword

The topic of the 40th Nestlé Nutrition Workshop focused on methodological aspects of clinical research. It deviated from the previous 39 workshops that covered selected topics in the field of clinical pediatrics, pediatric nutrition, and nutrition education. Clinical trials need to be done before medical food, formulas for special target groups, and infant formulas and cereals are newly introduced or substantially revised.

International and national bodies such as the American Academy of Pediatrics or the Committee of the Ministers of the Council of Europe have published principles on the ethics of medical research, which include guidelines for clinical trials. Food companies that produce dietetic products for infants are now challenged to follow these guidelines.

Besides ethical aspects, other aspects of good clinical practice during research need to be observed. No clinical trial without adequate experimental design should be proposed. “Bad science” per se is unethical because infants are unnecessarily exposed to potential risks.

This workshop summarized ethical standards for clinical trials in developing and industrialized countries and focused on adequate experimental design. Our primary goal must be to demonstrate that new or renovated infant food is safe and adequate for the target population. Health claims in the infant food area without convincing clinical support from clinical trials are no longer acceptable. Companies are requested to prove health claims and authorities to monitor their adequacy.

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