Phase 1 Trials in Israel: Some Considerations

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The prevention and conquest of diseases, mainly those that are infectious, malignant and metabolic, depend to a large extent on the discovery or the synthesis of new compounds. Any new molecule that has the potential to be a better tool in the struggle for health is very welcome. On the other hand, recent history has taught us that the gap between the discovery of the therapeutic potential of a new compound and its actual use in clinical practice is a deep and wide one.

Several compounds that had been very useful in the prevention and treatment of various diseases were later found to cause adverse effects in many people, and their use was subsequently stopped. The most notorious of these drugs was of course thalidomide, which caused exceptionally severe congenital malformations in thousands of infants born to mothers who had used this medication during pregnancy [1]. But there were many other drugs as well [2,3]. The medical community was impressed by the fact that a potential thalidomide disaster had not occurred in the United States. FDA regulations had not allowed the use of thalidomide in the U.S. and thus the results and outcomes of this drug were averted [3]. The lesson drawn then from the thalidomide tragedy was that the approval for use of any new substance mandates a previous thorough investigation. This conclusion in practical terms meant more clinical trials aimed at addressing in depth the issues of toxicity and safety of the new compound. In effect, it also led to more experiments in humans.

Human experimentation has been a very loaded subject since the experiments committed on helpless victims by Nazi doctors and scientists. One of the outcomes of this dark era in the history of medicine was the "Declaration of Helsinki," which was adopted by the eighteenth World Medical Assembly in Helsinki, Finland in June 1964 [4]. It was also amended by this international body several times and was approved by most countries in the world [4]. According to this declaration, "Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects"; and also, "In current medical practice most diagnostic, therapeutic and prophylactic procedures involve hazards. This applies especially to biomedical research" [4]. In the chapter entitled "Basic Principles," it is postulated that "Biomedical research involving human subjects 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" [4]. Furthermore, the Declaration of Helsinki sets out guidelines and directives regarding the rights of patients and volunteers participating in clinical studies. It also includes many other obligations that must be followed by any investigator [4].

The combination of the principles in the Declaration of Helsinki, together with the recent past experience concerning the importance of thorough investigation of any new compound, forged the modern attitude towards clinical trials. In short, the prevailing approach is that clinical trials should be carried out in order to prevent any possible adverse effects of a new compound. However, this is presupposed by two cardinal principals: all participants in these clinical trials must be aware of their rights, and it is the investigator's responsibility to act according to all the rules and regulations relevant to the research project.

These considerations have created the practical method of "drug approval." Drug approval, in turn, is the outcome of a multistep process aimed at the determination of toxicity, safety and efficacy of the suggested new compound [5]. The process is based on the idea that progression from one testing phase to the next is dependent upon attaining the pre-set objectives of each series of studies [6]. The earliest assessment of a compound in humans is called Phase I. Phase I trials are primarily designed to accumulate data on short-term toxicity, safety and pharmacokinetics. In phase I studies the number of participants is small and there is no control group [6,7]. In phase II studies, which are based on the results of phase I, the compound is tested in patients. It is expected that as a result of the clinical trials in this phase the optimal dose and schedule for the medication will be obtained. Phase III trials are designed to measure the efficacy of the medication. Phase IV involves the surveillance of long-term

efficacy and detection of possible rare adverse effects during the post-marketing period [6,7].

Bearing all this information in mind, it is interesting to read the report of Atsmon et al. in this issue of *IMAJ* [7]. Step by step, the reader – who is usually unaware of the tedious process involved in the approval of a new drug – is introduced to this complex area. Though the article focuses on phase I "first to man" trials, much can be learned from it. Important concepts, such as Good Clinical Practice, Good Laboratory Practice, and Standard Operating Procedures, are explained explicitly. The reader is introduced to the details of phase I trials: from the possible pitfalls in recruiting healthy volunteers to the basic requirements of a "phase I unit."

Nonetheless, the basic ethical problems of clinical trials in general and those of phase I in particular have not been completely resolved. According to the Declaration of Helsinki, "…the interests of the subjects must prevail over the interests of science and society" [4]. In accord with this Declaration, the possible effects of phase I trials on quality of life should be assessed. Is this being done anywhere, and can it be done in the long-term?

While many people have claimed that the dictates of the Declaration of Helsinki are too loose and leave too much room for the investigators' initiative, of late other voices are being heard. These are the voices of people demanding revision of the document that they consider to be old- fashioned and outdated for various reasons [8,9].

Another problem is the testing of new anti-cancer drugs. Given for the first time to humans, being phase I trials, for ethical reasons these new drugs are tested not in healthy volunteers but in patients with advanced cancer, thus being Phase II. The expectations of these "volunteers" are far different from those of the healthy people who usually participate in phase I trials. When designing a clinical trial it is absolutely crucial to relate to the ethical issues, considering the participants' particular motivation and expectations [10–12].

There is an ongoing interest in improving the various methodologies of phase I trials. Several improvements are being suggested right now. Their implementation would result in a better validation of the results of phase I trials, better definitions of adverse effects of tested compounds, and a higher level of ethical considerations [13,14].

Judging from the report by Atsmon et al. [7], one may be sure that the new clinical research unit dedicated to phase I clinical trials maintains the highest standards to be expected – both in terms of professional level and ethical obligations. It is indeed an important step promoting clinical research in Israel.

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