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WHY DO WE TAKE CARE OF OTHERS? IN CLINICAL RESEARCH

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INTRODUCTION

The ultimate goal of clinical research is to improve patient care.

Patients and their diseases are the object (the “circumstances”) of our work as physicians and clinical investigators, and the source of our knowledge, and this knowledge requires a method. In clinical research three methods are commonly applied: observation (case report), retrospective review and analysis (data searching and “mining”) and prospective hypothesis testing (clinical trial). The first method has been the most commonly utilized in the past and has resulted in the discovery of several diseases linked to the name of the physicians who first observed and described them (Alois Alzheimer, Harvey Cushing, Thomas Hodgkin, for instance), the second method is frequently adopted in epidemiological research, and the third has gained popularity over the last few decades with increased methodological sophistication, as it largely forms the basis of evidence-based medicine. Yet each of these methods requires a fundamental openness in front of the object being studied: as Louis Pasteur has been quoted saying: “When observation is concerned, chance favors only the prepared mind” pointing to the need for an awareness in the investigator that is far from cold, detached indifference or disengagement.

THE PATIENT

Clinical research, particularly in therapeutic research, involves five different phases with different goals: (1)

- a- Phase 0: introduced recently and limited to the administration of very low amounts of investigational treatments (“micro-doses”), aiming at the elucidation of a pharmacologic and/or pharmacodynamic effect (2)
- b- Phase I: traditionally considered to be the first experiment in humans, usually involving the administration of escalating doses of investigational treatments, aiming at the definition of optimal dose and schedule
- c- Phase II: usually conducted in patients with a well defined disease or stage of disease, aiming at determining the efficacy and the safety of a new treatment
- d- Phase III: usually a comparative experiment, often randomized, often blinded or double- blinded, aiming at assessing the worth of a new treatment in reference to an established standard of care
- e- Phase IV: conducted after a new treatment has been established, in order to further refine properties as long-term effects or improvement on its delivery.

In clinical research phase 0 and I are normally conducted in healthy volunteers, although in certain diseases where particularly potent medications are utilized, such as solid tumors and

hematological malignancies, patients are involved from the very beginning of the clinical investigation process. This has raised some ethical questioning, as phase 0 studies do not have a therapeutic intent. (3) Usually for these patients, as well as for those participating in phase II trials, a standard of care has either previously failed or simply does not exist. For phase III and IV trials, however, an established standard of care would usually be available.

Thus, what would entice a human being to accept or to seek entry into a clinical trial? Interestingly, for neither healthy volunteers nor patients is humanitarian altruism the main reason. Whereas for healthy volunteers financial rewards clearly play a role, for patients it is the fulfillment of a personal need of a different nature that is determinant. This need is a complex mix of desire for an answer to insufficiently met medical needs and of hope for the future, often relying upon scientific progress, both of which are clearly based upon trust in the physician and the healthcare provider.

Because of this strong dependence of the patient on the clinician/investigator, the patient is in an obviously vulnerable position, and thus clinical research is amongst the most strictly regulated of professional activities. Not only are technical aspects of a clinical trial subject to rules that are strictly applied, monitored and audited by both institutional and regulatory authorities (in the US the Code of Federal Regulations) but the ethical conduct of human experimentation, even when technical rules are adhered to, is strictly enforced by institutional and regulatory authorities, as generally stipulated by the 1964 Declaration of Helsinki.

Unfortunately this added layer of control has proven necessary since technical feasibility alone cannot form the basis of research, and multiple abuses have occurred when the separation of science from its application has been accepted indiscriminately. The most infamous examples recorded are those of Nazi medicine in Europe and of the so-called “Tuskegee experiment” in the US in the mid of the last century but, unfortunately, there have been additional incidents in the more recent history of American medicine.

Indeed, in addition to the tightening of regulations, recent years have seen an increased involvement from patient groups, their families and supporters in advocating to governments, academia and the public the interest of funding, organizing and regulating research in particular diseases. The advocacy community has been able to introduce mechanisms of support for clinical research that have been alternative or complementary to the regular channels, fostering flexibility and innovation but maintaining the integrity of scientific scrutiny.

THE CLINICAL INVESTIGATOR

The term clinical research implies the utilization of a scientific, rational method, which requires competence. Competence is necessary: it might not be sufficient, but it is certainly necessary. We should never underestimate the need to study, which is the need to ask questions, the need to honestly and critically review the data, the evidence, and the information available to us as clinical investigators and healthcare providers.

Exactly because of this it becomes evident that science alone is not adequate to address all the questions that human suffering poses to both the patient and the investigator: thinking solely in terms of “unmet medical needs” as opposed to “needs” may indeed prove to be too limiting. When science is thought to be the only answer to the learning process, it may risk becoming an idol for both the patient and the clinical investigator. And when science fails to provide an adequate answer (unfortunately this is often the reality in serious and/ or life threatening diseases), other idols can be introduced to replace it. Manipulations are possible in both cases, including unnecessary therapeutic aggressiveness proposed by the physician and/or sought by the patient or the family on one side, or resorting to unproven remedies or even quackery on the other side. It is remarkable that, in the US only, the sector of “nutraceuticals” – vitamins, herbal remedies and other various forms of poorly regulated and often unproven if not harmful remedies – has increased in the last few years to a multi-billion dollar business. (4)

On the physician side, the pitfalls of science can generate a passive, nihilistic approach to patient treatment: providing the treatment the patients or their families request or sticking to approved guidelines, but not asking the question of what is the most adequate or appropriate treatment for the individual patient. It is remarkable that, in the field of oncology, in the US less than 10% of adult patients are enrolled in clinical trials, as if there were no need to advance our knowledge in cancer or improve its treatment.

To be clear: every patient is entitled to receive a standard of care (that is: the best available treatment for that patient). However, when a standard of care does exist and it has been approved by regulatory health authorities or codified by medical guidelines, this does not automatically eliminate the need for an appropriate relationship between the physician and the patient. If medical practice were to be limited to the application of treatment guidelines or protocols only, an important part of the need raised by the experience of disease will not be addressed. In the era of personalized medicine, every patient is entitled to it with an horizon that exceeds genomic characteristics. (5)

We, as physicians, are treating human beings and not only their diseases.

Thus, what would motivate a physician to become a clinical investigator? As we discussed in the case of the patient, altruism might constitute one of the motivations, at least initially. But relying only on a humanitarian approach, no matter how heroic, has been proven unsustainable in a medical practice environment that burdens the physician with a large volume of other tasks, mostly of administrative nature. Many great figures of the past and recent history of medicine have proven this point.

Academic recognition, including the psychological and financial aspects of career progression, is another powerful motivator. Yet, the current directions taken by the health care system seem to privilege aspects such as effectiveness and efficiency over innovation, as proven by the reduction of support for clinical research that has occurred worldwide in the last few years.

The inadequacy of current treatments in many diseases is certainly a real motivation, sustained, as in the case of the patient, by reliance upon science and, ultimately, hope (i.e. hope for a better future medical practice). In this sense, the desire for truth and the desire to discover something

new (“different”) constitute a critical link between the patient and the physician needs. In fact, it is remarkable that several similarities exist between the motivations of the patient and of the caregiver in participating in clinical research. As it is true that, as a human being, the clinical investigator might very well sooner or later become a patient, all these motivations can converge even more.

CONCLUSION

If what we know is what we learn from our patients and their diseases, then it should be clear that there should not be a separation between the practice of medicine and clinical research. If what is at stake is the whole human experience of the patient, then what equally matters is the whole human experience of the caregiver.

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