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Ethics of patient referral in clinical research

Adriel Roitman[1,2], Cecilia Serrano[1,3], Adriana Domínguez[1,4], Leonardo Perelis[1,5], María F. Ossorio[6]

A key aspect of clinical research studies lies in the possibility of recruiting the necessary participants for the project, according to the calculated sample size, to respond to the established objective with the desired precision. Recruitment of participants, is an important –and at the same time critical– step in conducting any research study on human subjects. Without an adequate sample of subjects gathered through ethically valid procedures, research could not be conducted or would lack scientific validity. Therefore, recruitment strategies and methods directly affect the feasibility and quality of the entire research process.

The need to obtain answers quickly and the logic of competition between research centers (sometimes from all over the world) make it necessary the required sample in the shortest possible time to gather. Health institutions that serve a large population usually have no problem complying with this premise.

On the contrary, some research centers are structured for that purpose alone, without serving the target population as health providers. This scheme forces them to use other methods to recruit research participants. Although uncommon in our country, mass publicity is sometimes used to recruit participants, as was the case during the evaluation of COVID-19 vaccines. In other cases, professionals, commonly called “referring physicians”, who usually work in high-demand public hospitals, are used to interest their patients in different investigations. This matter motivates several considerations.

In Argentina, a substantial part of the public health sector has sufficient infrastructure, personnel, and regulations to carry out most research and, simultaneously, to better care for the patients who routinelly entrust their health to them. On the contrary, when a patient is referred for an investigation, they are assisted in a setting that is not the usual for them.

The professionals who assume this “referral” role usually receive a stipend for each patient they refer to the research centers, which is obtained only if the subject is effectively recruited into the study.

It is essential to distinguish between organic and desinterested referral of patients to research studies, and referral that is carried out within the framework of prior agreements and in exchange for financial compensation.

The first situation, where a health professional, knowing the criteria of a study, simply informs their patient the possibility of participating, without expecting anything in return, does not

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[1] Central Research Ethics Committee, Ministry of Health, Gobierno de la Ciudad de Buenos Aires, Argentina; [2] Research Ethics Committee, Clínica y Maternidad Suizo Argentina, Autonomous City of Buenos Aires, Argentina. Research Ethics Committee, Clínica Olivos, Buenos Aires, Argentina; [3] Independent Researcher, Research Career, Center for Social Research (CIS), Ministry of Health, Gobierno de la Ciudad de Buenos Aires, Argentina. Cognitive Neurology, Hospital César Milstein and Ineba, City of Buenos Aires, Argentina; [4] Research Ethics Committee, Hospital General de Agudos A. Zubizarreta, City of Buenos Aires, Argentina;[5] Research Ethics Committee, Hospital General de Agudos J. M. Ramos Mejía, City of Buenos Aires, Argentina. Research Ethics Committee, Buenos Aires, Argentina; [6] Research Ethics Committee, Hospital General de Niños Pedro de Elizalde, City of Buenos Aires, Argentina.

***Correspondence to** María F. Ossorio: mossorio@intramed.net*

raise any significant questions. It is a matter of facilitating access to research transparently and disinterestedly.

However, when there is a link between referring physicians and research institutions, and a financial reward is promised for each referred patient who is actually recruited, critical ethical dilemmas arise that must be carefully evaluated. This type of financial incentive can lead to a bias in the professional's clinical judgment, forcing their patients to participate in studies, violating the principle of autonomy and genuinely informed and voluntary consent. Moreover, these financial arrangements may tempt the referring physician to relax the eligibility criteria to increase the number of "successful" referrals and maximize his income, jeopardizing the scientific validity of the research and the safety of eventual participants. Even if there is no overt intention to manipulate the patient, economic incentives may introduce unconscious biases in evaluating candidates.

As expressed in the *International Ethical Guidelines for Health-Related Research Involving Human Subjects* (CIOMS, 2016)…"a salary or "finder's fee" may lead researchers –intentionally or unintentionally– to interpret the inclusion or exclusion criteria of a study too flexibly, thereby potentially exposing participants to excessive risks or compromising the scientific validity of the research."[1] From a strictly legal point of view, for example, in the City of Buenos Aires, Law 3301 on the Protection of the Rights of Subjects in Health Research contains a direct prohibition "on the use of any incentive to researchers to force, by any means, the inclusion of subjects in research" (art. 5, para. 10). Indeed, this is an impediment closely linked to a specific group of persons, defined by their nature as researchers, without the possibility of extending such prohibition to professionals that are not directly linked to the project. Without explicitly alluding to the referral system, the law prohibits the possibility of forcing the inclusion of subjects in exchange for an incentive.[2]

The above described implies that the payment of fees to health professionals who may detect in their usual practice possible candidates to participate in research does not constitute a behavior contrary to the law in force. However, there are conflicts from the ethical point of view that may require the attention and evaluation of the Research Ethics Committee. By way of example:

- It should be considered that the amount promised does not have to constitute a "recruitment reward." However, it should amount to reasonable compensation in exchange for the physician's additional work in assessing whether a potential candidate meets the criteria for inclusion in a study. Therefore, this payment should be made regardless of whether or not they are actually recruited in the study to limit the possibility of exerting undue influence on their patients.[3]
- The promised fee should not be an "undue inducement" but represent fair market value.

The Research Ethics Committees are tasked with overseen the recruitment processes to ensure the procedure is clear, transparent, and non-coercive. In addition, they have broad powers to ensure that potential referrals do not represent conduct contrary to research ethics by local regulations and international guidelines on the subject.

Clinical research is a fundamental activity for the progress of medicine, and volunteer participation is essential. Dissemination of available research benefits the public and is also of great value.

Paid advertising by physicians to their patients is likely to collide with the fundamental ethical principles of the profession. The American Medical Association (AMA) considers this practice unethical ("Offering or accepting payment for referring patients to research studies -finder's fee- is also unethical") and includes it within fee splitting.[4] Although not in such an explicit way for research, the Argentine Medical Association establishes that fee splitting "is an unethical process."[5] In the specific field of pediatrics, the American Academy of Pediatrics categorically states that this practice is not allowed: "…a monetary finder's fees' or other financial incentives for recruiting or referring children to clinical investigations should be prohibited."[6]

From another approach, verifying eligibility criteria for participants in a study is part of the research. In this line, professionals act as researchers -at least in the role referred to recruitment- and the research regulations must govern their behavior. From this perspective, it can be concluded that, just as the participant is usually informed that a study is sponsored by a pharmaceutical company, the potential participant should know that the physician will be paid for this activity.[7]

Some recruitment and preliminary eligibility assessment activities are performed by personnel external to the core research team, but this does not exempt them from being considered an integral part of the research process. These referring professionals should be regarded as extensions of the research team and, therefore, subject to the same ethical standards and regulations. Otherwise, a loophole is opened to evade ethical controls on critical aspects of the study.

For all these reasons, recruitment processes and all related activities, regardless of who performs them or how they are remunerated, must be unequivocally considered integral components of the overall research process. As such, that activities must be rigorously evaluated, regulated, and monitored by the Research Ethics Committee continuously of the institution where the subject will be contacted.

From what has been said, it is possible to conclude that the ideal way to attract a significant number of research participants outside the main center is the design of multicenter studies or duly established research networks that include different researchers and their institutions. Although it may be more complex from a logistical point of view, this path is undoubtedly more convenient for participants, particularly in populations that are especially sensitive due to the vulnerability of participants, such as in pediatric care areas.

Ultimately, the integrity of clinical research and the well-being of the participants must always be the top priority. Progress in medical science should not be achieved at the expense of patient trust or professional integrity. Therefore, we understand that it is the responsibility of all of us involved in any of the processes or stages of clinical research to ensure that every aspect, from recruitment to publication of results, adheres to the highest ethical standards. Only in this way can we ensure that the pursuit of knowledge truly serves the common good and respects the fundamental dignity of each research participant. ■

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