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Conceptual clarifications regarding Chilean Act 20850 on public funding of high-cost diseases

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Abstract

In 2015, Chile enacted the 20850 law, providing public funds for rare and costly diseases that demanded high diagnostic and therapeutic expenditures. The law modifies the Chilean Sanitary Code regulation of research with human beings, aiming at the protection of subjects by securing post-investigational medical benefits and insurance coverage for damage imputable to the research they participated in. Due to ambiguous phrasing, a polemic rose for fear that these protective measures applied to all clinical research, although a careful reading of the law in its context clearly suggests that it refers to phase I therapeutic trials. This paper stresses the distinction between compassionate use and genuine phase I/II therapeutic trials aimed at both pharmacodynamics and an intended therapeutic effect for severe and progressive diseases that are therapeutically orphaned, emphasizing the ethical and medical duty of providing post-trial beneficial medication.

Introduction

Chilean law Nº 20850 was enacted under the title "Creation of a systematic financial protection for high cost diagnoses and therapies, and rendering homage to Mr. Luis Ricarte Soto Gallegos". Such a legislation proposing financial protection to patients is more than welcome in a country with severe deficiencies of medical services, one of the world lowest health budgets, lucrative expansion of private medicine that provides technical facilities superior to the public medical system, and where out-of-pocket medical costs take up 40% of family income.

The law focuses on rare diseases –those with very low prevalence-, usually genetically determined, and poor vital prognosis, oncologic conditions that lack effective treatment or are too far advanced to respond to available therapies, and degenerative diseases with progressive bodily dysfunction such as multiple sclerosis and amyotrophic lateral sclerosis.

How the law will work in practice is to be specified by regulations still being elaborated, as yet difficult to evaluate due to its recent and fragmentary implementation, although serious problems in its scope and financing are anticipated.

Being a law intended to financing high costs in healthcare, it surprisingly introduces in the Chilean Sanitary Code a number of norms concerning clinical investigation, included under the heading "On clinical studies of pharmaceutical products and elements of medical use" (Law 2085, Title IX "Modifications of other legal instruments"), which has created an aggressive polemic protesting that biomedical investigations will slow down to a standstill due to the additional costs that will burden stakeholders, sponsors and scientists. The issue relates directly to bioethics in research with human beings, a perspective that has not been extensively debated, leaving, in fact, increasing doubts and uncertainties in these matters.

Evaluation and research

The initial paragraphs of the law refer to "high-cost diagnoses… proven to be useful", and high-cost treatments that are "elements of medical use in diseases that are indispensable for confirmatory diagnosis and treatment", "that have been subject to favorable scientific evaluation of evidence". The intention to finance demonstrated evidence of efficacy, require pertinent instances to evaluate indications and priorities, in order to cover high costs of certain diseases, as analyzed by a "Prioritizing Recommendations Commission" of "recognized capacity, whose members do not include investigators.

Article 15, under Title V, refers to the "continuation of treatments included in the system of financial protection for high cost therapies". Up to this point, the public appears to be receiving financial protection in medical situations that require diagnostic and therapeutic procedures proven to be effective, though highly onerous. Therefore, it is in the public's interest that the selection and prioritization should be carried out with the utmost probity and transparency.

Unexpectedly, the legal text takes a turn to "clinical studies of pharmaceutical products and medical elements to be used in scientific research", at the same acknowledging that this matter has been previously regulated by Law Nº 20120 and Decree Nº 114 (see author's end note). The text of the recent law suggests a new regulation for all clinical studies, thus causing restlessness in view of additional complementary requirements.

In a different interpretation, and given the context of its presentation, the inclusion of regulations concerning clinical research might be referring to trials of experimental procedures and medications for exceptionally severe and progressive diseases that have no treatment. These are known as experimental therapies, featuring exceptional situations that require a specific bioethical debate, the lack of which has generated misleading interpretations charged with more noise that substance. Aiming at a brief review of the current state of the debate on these matters, this paper intends to reach certain clarity in making the distinction between compassionate use of medication, experimental therapies, and other research strategies.

Compassionate use of medications

The term compassionate is employed in medical practice to indicate empathic feelings of health care agents, caused by the misfortunes of patients in their charge [1]. In clinical context, compassionate use refers to a regulated form of dispensing unproven therapies to patients afflicted with progressively invalidating and eventually lethal diseases for which no effective therapies exist.

"Compassionate use of medication refers to individual patients not involved in clinical trials, who receive medication being investigated, including pharmaceutical agents used for indications or conditions other than those authorized, when the physician considers, under his own responsibility, its indispensable use" [2].

Access to a medication that is not registered, nor has been sufficiently studied to determine its risks and efficacy, or is being requested for indications others than those registered, is an extremely complex procedure. Numerous regulations and laws comment, but do not solve, a series of polemic aspects that remain unresolved concerning access, medical indications, costs, insurance, responsibilities, institutional authorization, the will of the title holder to allow access, and the exceptional use of the requested substance.

A most debated issue is the absence of clinical information about risks and therapeutic efficacy, thus questioning the legitimacy of informed consent in uncertainty and the adjudication of responsibility for unexpected toxic effects, including the complexities of insurance to cover possible complications of its use. Debates are kindled regarding the consequences that compassionate use might have on the investigation of the substance, and the distinction between those with scientific background, and alternatives that lack any empirical evidence whatsoever, a notorious example of which has been the use of vitamin 17 as anticancer agent.

The Federal Drug Administration (FDA) has presented four conditions that justify the request for compassionate therapy:

- No satisfactory alternative therapy exists.
- The patient cannot obtain access to the drug by participating in its research
- Potential benefits are justified in spite of potential risks.
- Providing the experimental drug will not interfere with the initiation, development and continuity of its clinical study until completed [3].

The Council for International Organizations of Medical Sciences (CIOMS 2002, currently being revised), requires three conditions for the ethical approval of compassionate therapy: the patient urgently needs treatment, there is scientific evidence of its possible therapeutic efficacy, and no other therapy is known to be effective or superior.

The compassionate therapy request is rarely successful, thus prompting a number of U.S. states to issue a right to try, which has had scant impact because there exists no obligation to comply with this right. Pharmaceutical companies are free to accept or deny access to the requested substance.

Influencing equity of access, all these aspects suggest that the concept of "compassionate therapy" be replaced by the term Extended Access Programs (EAPs) in reference of non-registered substances or procedures to be used outside formal research protocols, thus making a clear distinction from experimental therapeutic studies [4].

The compassionate use has no features or intention of posing as research, it is the plan patients follow when they have not managed to take part in a study protocol that would allow them access to the required medication.

The pharmaceutical industry is wary of developing orphan therapies, such that will be expensive in a small consumer market. To reduce the effects of an orphan therapy, patient initiatives like "Access to Medicine" (http://www.accesstomedicine.co.uk) try to stimulate research in orphan diseases and access to compassionate therapies. "There are many drugs, licensed and unlicensed, for which there is preclinical data, much of which is not in the public domain, supporting their use as potential disease modifying agents in neurodegenerative disease [5].

Experimental therapies

The initial medical intervention of a substance in the human body is known as clinical Phase I, studying healthy individuals to determine relevant data concerning pharmacodynamics (biological behavior of the substance, determination of toxicity levels and establishing the highest tolerable dose that is supposed to be the most effective in further studies. In fact, Phase I is a preclinical trial, designed in such a way that can neither expect nor obtain therapeutically relevant information, for its objective is to gather knowledge that might help advance to clinical studies aimed at the development of therapeutically effective agents.

The therapeutic innocence of Phase 1 studies is not absolute: "The objectives in a classical phase I study are to ascertain ´the metabolic and pharmacologic action of [a single] drug in humans, the side effects associated with increasing doses and, if possible, to gain early evidence of effectiveness´" [6].

The deterioration of oncologic patients that are refractive to available therapies, has legitimated accelerating research of new drugs and their clinical application in Phase I, subject to the regulations of Investigational New Drugs (IND) the therapeutic use in what is acknowledged as Phase I/II. When an experimental therapy protocol is designed, the aim is to go beyond the determination of tolerance levels, since effectiveness is also studied. In other words, Phase I is being contaminated with Phase II aimed at evaluating effectiveness.

The successful social mobilization of HIV/AIDS patients for inclusion in promising therapy studies without being subjected to the rigorous methodologies of randomized controlled trials (RCTs) because the control group would be condemned to the lethally progressive infection, illustrate that Phase I/II are not only cancer studies, for they also apply to other severe and progressive conditions that lack effective therapies [7]. Meta-analysis of Phase I oncology studies indicate that beneficial effects are exceptional and of variably short duration. Furthermore, 90% of all investigated agents are never registered owing to insufficient efficiency. The ethical evaluation of Phase I cancer studies varies from denial of any therapeutic contents, to accept them as an experimental therapeutic intervention that fallaciously is considered to be a non-therapeutic toxicology study.

It is unanimously agreed that Phase I experimental therapy is offered to severely ill patients suffering from progressive worsening where alternative therapies are lacking. In fact, most of these studies deliver some information but the majority has no therapeutic action other than in exceptional cases that may be confounding between causality and randomness: *post hoc ergo propter hoc.* Nevertheless, it is accepted that all participants share a subliminal "cultural-psychological function" tinged with hope for some therapeutic effect [8]. Even though many patients do acknowledge altruistic motivation to participate in Phase I studies, such altruism is less frequent in participating patients with poor prognosis, whose primary motivation continues to be hope for some therapeutic benefit [9].

Gravely ill patients with no therapeutic alternatives insist on taking part in these studies, mostly moved by hope and optimism, in what investigators have labelled the "therapeutic fallacy" [10]. The term is unfortunate, for clinical activities, whether medical care or research, acknowledge that pessimism and hopelessness are deleterious for patients who not only harbor hopes of improvement but also believe in the beneficial effects of a positive attitude [11].

The distinction between therapeutic fallacy and reasonable options of medical benefit is hard to make. However exhaustive and cautious the process of informed consent may be, a discrepancy persists between researchers' reticence and the expectations of patients included as research subjects [12],[13],[14]. Even though patients do record the uncertainties of investigating a drug with possibly high risks and improbable benefits, "it is rational to take a small chance of survival when the alternative is certain death" [5]. "Most of my colleagues [medical oncologists] sympathized and supported patients' hopes by focusing on the promising anticancer effects these had previously demonstrated in animals, and observing, in general terms, that patients in Phase I trials occasionally have had dramatic responses" [8].

Without being at all explicit about, Law 20850 is referring to experimental therapies in which "the patient subject to a clinical trial has the right to receive the substance for as long as it remains therapeutically useful" (Article 111C). The subject consents to these studies knowing fully well the limited possibilities of therapeutic benefit and the uncertain, but probable risks of receiving an exploratory "sanitary product".

The maintenance of post-investigational medical benefits disclosed by genuine experimental therapy protocols is based on two pillars: acknowledging that this type of studies has primarily a therapeutic intention; secondly that, like any clinical investigation, it ought to have local social value focused directly on benefitting the patients under study and, further, for other local or distant patients experimenting the same medical needs.

Bioethics of experimental therapies

The ethics of research with human beings continues to be a much discussed and controversial topic, clearly illustrated by the loss of influence the Declaration of Helsinki has been suffering for over 50 years. The most hotly debated issues have been the use of placebos in clinical research and the commitment to continue beneficial treatments beyond the termination of the research protocol that revealed such benefits. Additionally, debate continues over informed consent, mental competence, the distinction between therapeutic and non-therapeutic clinical trials, vulnerable probands [9]; (the term "proband" is increasingly employed in Spanish and German , rather than participant –which is nonspecific- or subject which has an undertone of dependency) and the differences between clinical practice ethics and clinical research ethics.

In the ethical evaluation of what initially were "Phase I oncologic studies", a number of concepts appear that either *lump* experimental therapies, Phase I studies, trials Phase I/II, and investigational new drugs, or are*split* to specify the genuine *sui generis* feature of experimental therapies understood as Phase I/II. These distinct characteristics, which differentiate these trials from research in less severely advanced clinical situations, are based on patients that are therapeutic orphans with hope that participating in a trial could achieve some medical benefit in terms of palliation or compensation of a severe progressive, eventually fatal disease.

Genuine experimental therapies require a particular bioethical analysis of a dramatic clinical situation where research in possibly beneficial therapies in patients with severe and progressive diseases who will receive an agent as yet not applied in human beings.

Research methods like randomized clinical trials (RCTs) and the use of placebos have no place in these studies. Informed consent reflects the acceptance that an experimental agent will be employed that has unknown and eventually very high toxicity, and that benefits are improbable, though not impossible. Contrary to widespread opinion, such a trial is therapeutic and the patient continues to receive all required clinical care in addition to being protected by the technical and ethical probity of the protocol. "Nevertheless, in designing and approving phase I trials, investigators and institutional review boards (IRBs) must strive to optimize the risk-benefit ratio for participants, while remaining within the constraints imposed by the trials' scientific objectives" [15]. This opinion is valid for usual Phase I studies were searching for therapeutic agents is not the primary motivation, in distinction to trials being carried out in situations that entail patients with severe conditions that accelerate their deterioration and lack any effective therapy. In genuine experimental therapies, possible medical benefits have priority that should not be conditioned by methodological considerations.

Social value of experimental therapies

The social value of science is often dismissed as a vague, ineffable, and resistant to any definition or specifications [16]. Ignoring the social relevance of a trial has allowed many biomedical investigations in general, especially pharmaceutical research, to pursue corporative interests unconcerned with the local needs of the venue where they are performed.

Social value depends on the relevance a study may have to broach problems that the host community needs to solve. Social value ought to be a determining input in the national research policies, especially if public funds are involved in financing, managing and developing clinical studies, clarifying whether the scientific agenda is established by alien and market interests, local scientists or the community which is aware of its own interests and needs [17].

It is widely agreed upon that clinical investigation ought to have social value by generating knowledge that will lead to health improvements. When lacking in social value, research exposes participants to unjustified risks and squandering of resources [18].

The article cited refers to Phase III clinical trials that focus on effectiveness and safety of recommended doses studied in large cohorts of patients, and carried out in "developing nations". Nevertheless, social value that leads to "health improvements" is to be applied in all clinical trials, even more so when investigating experimental therapies that invariable seek benefits to the patients being incorporated, as well as obtaining information that might justify proceeding to Phases II and III to the benefit of future patients.

In the case of experimental therapies, social value includes direct medical benefits to patients participating in the study, including the possible benefits derived for all those sharing the same diagnosis.

The principle of the social value of knowledge (SVK) states that the cognitive value of clinical research results is essential to the moral validity of the study. If the moral legitimacy of a clinical investigation is based on the social value of the knowledge obtained, and this cognitive value is context-dependent, it follows that the moral legitimacy of a study is context-dependent [19].

In other words, the social value of a study is primarily a local value for the host population of which the research subjects are members. Consequently, the SVK should be extended to be a local social value of knowledge (LSVK). Such strategies as off-shoring, the 90:10 resources gap, and the double standard for the ethical evaluation of research protocols, all violate this principle when doing clinical studies in countries that have the double burden of precarious economic development and enormous social inequities.

The most transcendental social value of research is the production of knowledge that will be useful to solve local problems. Clinical studies must, first of all, consider medical benefits for the host population, an aspect that is related but not synonymous with accessibility of post-investigational medical benefits.

A number of clinical trials done in Latin America are not made available in the countries where they were developed. Also, if and when they do reach the local market, their high prices, disproportionate to buying power of those who need them, require out-of-pocket expenditures [20]. In these studies, corporative interests overshadow the diminished local social value, creating an increasingly damaging scissors effect: the lower income nations suffer economic restrictions and reduced social protection, while the pharmaceutical industry continues to obtain exorbitant profits [21].

Discussion

Persons who suffer orphan diseases –rare conditions of poor functional and vital prognosis- which lack demonstrated useful therapies, can only access potential therapeutic agents by way of complex, and often fruitless, petitions for compassionate use. Another form of access is to obtain inclusion in a formal experimental therapy protocol which studies a Phase I agent not previously employed in human beings.

In contrast to Phase I studies in healthy volunteers, experimental therapies are used in patients affected by extremely severe and progressive disease for which no treatment exists, their participation therefore leading to therapeutic expectations, though limited and marked by uncertainty of unwanted and possibly severe secondary effects and complications. In view of this constellation of factors, a possible beneficial effect must be sustained beyond the finalization of the research and for as long as medically indicated. This is proposed in Law 20850, although its phrasing is unclear enough to raise debates that puts to question the protection of these severely diseased patients.

Bioethics of biomedical research has agreed upon that every clinical study ought to be approved by and *ad hoc* committee, that trials must be registered to avoid the silent dismissal of negative results, and that any scientific publication needs to assure the approval of a competent, accredited committee, free from conflicts of interests.

Given their exceptionality, genuine experimental therapy studies require particular ethical analysis and deliberation, validating what the law requires in protection of patients participating in research, stressing the inclusion of sustained beneficial effects obtained through the study, monitored for as long as medically necessary.

Conclusion

The Chilean journalist Ricarte Soto, affected by pulmonary cancer, launched the initiative for legislation aimed at financing high cost medical treatments and medications. Unexpectedly, the law has included extensive paragraphs regulating clinical investigation now explicitly referring to the use of high cost medication, including those not yet proven in human beings (experimental therapies). Pharmaceutical industries, and many researches, have voiced their worries because these regulations implicitly but clearly suggest the extension to all clinical trials of post investigation benefits, the upkeep of medication that may have been found to be effective, and comprehensive insurance of care and compensation for those suffering deleterious effects.

The ambiguous wording and lack of bioethical assistance in the preparation of the law, as well as the feared threat to corporative interests, require clarification of at least three crucial aspects:

1. Bioethics concerned with research with human beings is basically committed to protecting research subjects, especially when they are ailing patients.
2. The speedy research of possibly therapeutic agents when no other treatment for severe diseases exists, presents special bioethical requirements, including the obligation of continuous therapeutic benefits as long as medically indicated.
3. A clear distinction must be emphasized between compassionate therapy (a medical act) and research of experimental therapies (a scientific and medical act).

Although the law emphasizes protection of patients involved in experimental therapies, the legal text lacks clarity and prudence, leading to polemics and discrepancies, as well as uncertainties about the pertinent regulations –as yet in elaboration- to be applied, and the firmness of bioethical protection required.

Just as nationwide legislation, so bioethical reflection and its institutionalization (committees, commissions, rules and norms) need to be contextualized to the social reality of the country, without submitting to regulations and interests that come from other latitudes.

Notes

From the editor

The author originally submitted this article in Spanish and subsequently translated it into English. The Journal has not copyedited the English version.

Author's note

Law 210120 "On scientific research in human beings, and their genome, and the prohibition of human cloning. (Enacted on September 22, 2006. Available at http://bcn.cl/1uxxf Chile, Ministry of Health. Decree Nº. 114. Approves Regulations for Law 20120 22. Available at http://www.leychile.cl/N?i=1032919&f=2012-05-19&p=. Enacted on November 22, 2010.

Conflict of interests

The author has completed the declaration form ICMJE conflicts of interest, and declares he has not received funding for the completion of the report; does not have

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