The therapeutic misconseption

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Abstract
The therapeutic misconception has been described as the 'research subjects' unwarranted expectations of obtaining medical benefits by participating in clinical trials. Thus, researchers have found a new conceptual instrument to deny that research ought to be of benefit to subjects involved, once again disregarding the difference between therapeutic and non therapeutic clinical trials. This paper argues that patients involved in research are justified and in fact entitled to expect therapeutic benefits from their participation in research protocols, because the sick should only be recruited for such therapeutic trials as designed to improve their medical condition, and ought never to be involved in non therapeutic research and the risks involved. Insisting that therapeutic expectations research subjects constitute a misguided and erroneous attitude, is an unethical bias when applied to countries with precarious medical services. Subjects with unmet medical needs will willingly participate in research that might be the only way of obtaining badly required medication, an expectation that is obviously understandable and in no way fallacious. These justified expectations will be thwarted in those who randomly fall into the control group, thus delivering an additional argument against the use of placebos.
Keywords**:** Research. Clinical trials as topic. Therapeutic misconception. Therapeutic fallacy. Human experimentation. Research subjects. Moral obligations.

Resumo
A falácia terapêutica
A falácia terapêutica tem servido para negar a legitima esperança de pacientes 'sujeitos da pesquisa' que se incorpora. a estudos clínicos Fase III para obter benefícios clínicos diretos. Esta "falácia" busca ratificar os esforços de pesquisadores em negar a diferença entre *estudos terapêuticos* que beneficiam diretamente os afetados e *estudos não terapêuticos,* que incorporam sujeitos a pesquisas totalmente distanciadas de suas necessidades. Em países com populações pobres, educação e acesso a serviços médicos precários, tenta-se recrutar participantes oferecendo terapias não disponíveis localmente; óbvio abuso das legitimas esperanças destes pacientes em terem acesso às indispensáveis terapias, prometidas pelas pesquisas. Assim, a falácia terapêutica torna-se um modo de justificar a negativa de oferecer benefícios médicos aos recrutados, constituindo viés de transgressão ética, especialmente nos países nos quais o participante não tem expectativa de tratamento. Esta justificada expectativa daqueles que ingressam em estudos clínicos aleatórios constitui argumento adicional contra o uso de placebo.
Palavras-chave: Pesquisa. Ensaios clínicos como assunto. Terapêutica equivocada. Falácia terapêutica. Experimentação humana. Sujeitos de pesquisa. Obrigações morais.

Resumen
La falacia terapéutica
La falacia terapéutica tiene servido para negar la legítima esperanza de pacientes 'sujetos de investigación' que se incorporan a estudios clínicos Fase III para obtener beneficios clínicos directos. Esta "falacia" busca ratificar los esfuerzos de investigadores en negar la diferencia entre *estudios terapéuticos* que benefician directamente los afectados e *estudios no terapéuticos,* que incorporan sujetos a investigaciones totalmente aisladas de sus necesidades. En países con populaciones pobres, precaria educación y acceso a servicios médicos, se intentan reclutar participantes ofreciendo terapias no disponibles localmente; obvio abuso das legítimas esperanzas de estos pacientes de acceder a estas indispensables terapias que les son prometidas al interior de las investigaciones. Así, la falacia terapéutica torna-se un modo de justificar a negativa de ofrecer beneficios médicos a los reclutados constituyendo sesgo de trasgresión ética, especialmente nos países en los cuales el participante no tienen expectativa de tratamiento. Está justificada expectativa de los reclutados que ingresan en estudios clínicos aleatorios es argumento adicional contra el uso de placebo.
Palabras-clave: Investigación. Ensayos clínicos como asunto. Equivocación terapéutica. Falacia terapéutica. Experimentación humana. Sujetos de investigación. Obligaciones morales.

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Bioethics seems to have forgotten that the principle of beneficence is a fundamental pillar of both clinical and research medical ethics, as the *Declaration of Helsinki* insisted, especially in its early versions, being ratified by the Belmont Report and incorporated into the principialist treaty of Georgetown. Neither does an effective presence E. Pellegrino's call to honor the patient´s wellbeing above all other considerations persist: *The rules [of medical practice] describe a theory of goodness being the moral core of medicine and it prescribes action as this theory is professed with dedication to healing* [1].

The undisputed recognition of the therapeutic function of clinical medicine, is becoming less clear as in recent decades the Phase III clinical trials proliferate, with an increasing protagonism of big pharmaceutical companies in the financial sponsorship and the hiring institutions and researchers to develop their protocols, as well as the transfer of investigations to less developed countries where costs are lower and the ethical standards seem to be more lax and easy to evade.

Clinical trials are by definition conducted on people who are sick, the patients, and because they are receiving medical care, therapeutic care is being damaged by being incorporated into Phase III studies. The literature on the "double standard" in biomedical research ethics is abundant, and it is quite alarming to read how an *honest assessment must recognize the profound disagreement between Africans, Europeans, North and South Americans on the issue of the level of care and treatment due to the research subjects in countries with fewer resources* [2].

In a context driven largely by corporate interests and carried out by institutions that sell scientific services, [3] as Contract Research Organization (CRO), profit institutions that commission research, coordinate activities, share interests and are co-owners of promotional companies, by selling educational services and ghostwriting articles, are noted in the debate about biomedical research the best efforts of many bioethics scholars to dispute and limit the benefits in clinical research.

Questioned in these discussions appear the probands compensation, term still infrequently used, but preferable to "research subject" which insinuates the subaltern position where people who take part in clinical trials find themselves, for the inconvenience of their participation. The controversy turns on issues such as due or undue incentives, the question of ancillary therapy that provides medical care beyond that required by research protocol, and the welter of publications which insist that Biomedical research has no obligation to produce benefits for probands.

Informed consent presented to the Ethics Committees emphasize that the recruited participants get no medical benefits for their participation beyond having contributed to the progress of medical science. Among efforts to discredit the obligation to promote medical benefit to the probands, it has been incorporated into the fast and scarce debate the concept of therapeutic misconception.

Regression

Nobody doubts that the fundamental and indispensable objective of medical acts in clinic trials is to assist patients in the healing or mitigation of their diseases. That was why the classical bioethicists insisted that patients should not be subjected to the additional risks of a clinical research, unless the study was related to their disease - therapeutic study - and were given reasonable expectations of medical benefits offered above the routine treatment in progress [4]. Referring to children, P. Ramsey was equally emphatic:

Experimenting with children in ways that are not related to them as patients is a form of a bleached barbarism; excludes the look and neglects the reliance that the child, simply for being a normal, sick, or in the process of dying, placed in us and in the medical care. We should not accept significant moral exceptions to this canon of loyalty toward the child. To suppose that justifiable exceptions will appear in the future, it is, in a sense, to have already forgotten the child [5].

Exceptions undermining the child's trust in the caregivers' benevolent will, appeared effectively leading researchers to develop a true doctrine that denies the difference between therapeutic and non-therapeutic studies, while insisting on distinguishing clinical ethics from research ethics.

Arbitrary distinctions

Much of the confusion arises from the reticence of many researchers to distinguish therapeutic from the non-therapeutic trials. Early versions of the Declaration of Helsinki clearly differentiated between research

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exploring the patient's disease, testing to improve his medical care, and the non-therapeutic research in which the patient enters a protocol that does not have anything to do with the pathology affecting him and, therefore, it does not mean any medical benefit.

Those who dismiss the therapeutic / non-therapeutic distinction proclaim that it is a "conceptual and semantic error", since all research has therapeutic elements as well all medical treatment has the uncertainties of research. First of all, for those who rely on evidence-based medicine, the argument presented is inaccurate and misleading, since every clinician has a clear difference between prescribing and research.

A more differentiated view holds that therapeutic clinical research itself is a form of scientific inquiry, which has the *dual intention of benefiting the patient who is being tested and to collect data of a general nature*[6]; different from *non-therapeutic studies, whose only objective is strictly cognitive driven towards gaining information* [7].

Placing some order in this debate, the distinction between "position of difference" and "position of similarity" has been raised. According to the former, supported by bioethicists related to researchers' interests, *the research and clinical practice are distinct activities with different objectives - research attempts to produce general medical knowledge for the benefit of future patients, whereas the clinical practice attempts to produce therapeutic benefits for the individual patient* [8]. The "position of similarity" argues that research should avoid jeopardizing patient optimal care, since physicians are committed to fulfilling their "therapeutic obligations".

It is reasonable that the randomized clinical trial [RCT] *should be governed by ethical standards appropriate to clinical* research*, which clearly differs from considerations of therapeutic or non-malefic benefits* [9], which is justified because clinical medicine *aims to provide optimal medical treatment for individual patients*, whereas in research, *volunteer patients are at risk of seeing their welfare compromised during scientific research* [9].

Respect for the fiduciary relationship between health caregivers and patients implies the refuse that research ethics replaces clinical ethics, thus recognizing that patients naturally expect to obtain therapeutic benefits when they enter a study [10]. The incorporation of a patient to a clinical research makes him a proband patient, that is, an individual patient that remains sick and requests specific medical care to his condition, as well as becoming either proband included in a study relevant to his disease - therapeutic study - or in a trial that researches issues not related to his medical needs - non-therapeutic research.

The therapeutic fallacy

Early in 1980´s and 1990´s, was introduced into Anglo-Saxon bioethics the concept of "*therapeutic misconception*" - therapeutic fallacy, which quickly entered the language of clinical research ethics, encouraging a series of articles interested in confirming the high frequency of patients involved in clinical trials expecting to receive some medical benefits for their participation[11].

The original description of therapeutic fallacy was based on a study with 13 patients in control and in outpatient treatment for chronic schizophrenia (Project A), two thirds of them receiving medication and "special" or "routine" social training, and the remaining third receiving only medication without a social program support. Project B randomly divided a total of 18 patients suffering from "borderline personality disorders", into three groups receiving either antipsychotics, antidepressants or placebo.

A total of 31 patients were interviewed, who participated in two pharmacological studies. Although thoroughly informed, a good number of these patients claimed "therapeutic intent from research procedures" by participating, an expectation that was considered erroneous and led to the extrapolation of the *therapeutic fallacy* concept and the "suspicion" that most patients entering clinical trials had expectations of medical benefits.

Reviewing this publication, one concludes that the error lies in researchers having described as fallacy what was merely a reasonable expectation: all patients attending the psychiatric service were seeking treatment and, in fact, all but the control group receiving placebo were treated with psychotropic drugs, a significant number also received therapeutic support in the form of social training. It would have been completely incomprehensible that there was *not* any therapeutic expectation.

Authors concluded that their findings have important implications for any effort to undo the therapeutic fallacy, in order to empower patient-subjects to a more accurate risk-benefit assessment. Only very marginally they mentioned that chronic schizophrenics could be particularly susceptible to committing the therapeutic misconception [11].

In addition, being all psychiatric patients, it is difficult to assume that their reasoning was comparable way without more with cognitive characteristics and consideration observed in non-psychiatric patients.

An unprejudiced reading concludes that the small number of people interviewed, all participants in two psychiatric research projects led to build the therapeutic misconception and giving a poorly substantiated generalization. The conclusion from this and other studies of the same academic provenance led to postulate that the research subjects systematically misunderstand the risk / benefit relation when participating in [clinical] studies, because they do not understand the underlying scientific methodology, failing to distinguish treatment from research.

With a little semantic trick, these conclusions mean to validated claim stating that probands are wrong to think that researchers act only in consideration on patient's interests [12] (emphasis added). To think that the study has no other purpose than to benefit the patient would be certainly fallacious, but it is very biased to impute that a patient actually has such a limited belief.

The indeterminacy of therapeutic misconception is exposed by the various interpretations it receives: the "subjects" fail to appreciate the risks and disadvantages of participation that are inherent in the design of an investigation [13] (emphasis in original). According to this interpretation, the therapeutic misconception is not only an unfounded expectation of benefits, but is also a fallacious risk assessment, which has substantially more troubling implications than just frustrated expectation.

The fragile foundation of the therapeutic fallacy produced a variety of meanings, including the suggestion that it is a therapeutic optimism more than a mistake, liable to occur even when the subject has been comprehensively informed and clearly understood the difference between research and medical care [14]. The therapeutic fallacy has been accepted even by those who recognize that the lack of a consistent definition makes it difficult to identify [15].

Origins of the therapeutic "fallacy"

Since its first description, the therapeutic fallacy has been estimated as an error of assessment of probands who presented expectations of medical benefits that had been promised by researchers in order to recruit. Among researchers prevails the view that probands are guilty, as the quote illustrates: reaching *wrong conclusions - the therapeutic misconception, despite the best efforts of the researcher to explain everything fully and with all honesty*[8]. It is the patients who allegedly fail to understand the complexities of a research protocol, as they do not have reasons to expect therapeutic benefits and they ignore that *the only relevant question is perhaps he [the patient] who would like to contribute to the achievement of scientific goals, with all disadvantages and risks that could involve* [16].

There is, therefore, a tendency to suggest therapeutic benefits to obtain informed consent that in some situations goes so far as to deceive the patient in order to gain their willingness to participate[10]. To allow or even encourage the therapeutic fallacy has *ethical* implications not only for being incompatible with a proper informed consent, but it undermines the reliability of scientific research [18].

Therapeutic Expectations

There is empirical evidence to support the view that both healthcare professionals and the lay public, expect from biomedical research some medical benefits for participants. Several surveys and studies confirm that persons perceive that participate in biomedical research generates health benefits to incorporated subjects, and that most patients trust their doctors when they are advised to participate in a clinical trial [19, 20].

Both patients and people involved in clinical research estimate that the participation in a study improve the level of care of probands patient, although this is not necessarily expressed in specific medical benefits[21]. Confirms this commitment the responsibility imputed to researchers to provide ancillary medical care if during the study a patient suffers morbid episodes not related to the study itself [22].

With this background, it is reasonable that patients consent to enter Phase III clinical trials with the justified belief that it will not involve undue risks and reasonable expectations of medical benefit. The confidence in their doctor when they are advised to join the study reinforces the conviction that their illness is best treated when entering a therapeutic trial.

Assessment of benefits/risks

Analysis of Research Bioethics Committees, as well as the informed consent procedure, base their decisions on a balance between the benefits and risks of the proposed research. The voluntary consent takes place *according to the sense of what is good and right and best in light of the situation, the values and the own previous history* of the person who evaluates [23]. Sometimes the patient may be willing to take a high risk of dying if the proposed experiment has some therapeutic expectation, as in the trial of the AbioCor artificial heart [24]. The procedure with informed consent is based precisely on the consideration between expected benefits and possible risks.

Often overlooked that patients are suppressed populations dependent on the medical environment in which they are treated, sensitive to persuasion, and potential victims of subliminal coercion [25]. The informed consent documents have poor ethical credit, which expressly insists that the proband patient will not derive any benefit from their participation, and where participant's consent is a clear sign that he is in a situation of dependency or, at least, feeling like he is.

If the research ethics involving humans discourages recruiting suppressed people, it must restrict the participation of patients only to therapeutic studies, where expectations allow an informed consideration of the benefits to be expected and risks to be accepted. These benefits are real, although uncertain, so that *the patient does not commit any fallacy in consent in light of reasonable therapeutic expectations*.

From a bioethics of protection, the therapeutic fallacy is a strategy to exempt benefic obligations to sponsors and biomedical researchers engaged in disconnecting from any commitment to the probands. Frequent complaints about the lack of availability of patients willing to enter clinical trials, suggest that researchers use to insinuate medical benefits to recruit, but take care to formulated these promises in the informed consent document in order to not documenting commitments that they will not fulfill [26].

Benefits and poor populations

Various reasons have encouraged the transfer of human research from First World countries where studies are conceived, planned and financed, to underdeveloped countries whose populations have socioeconomic problems of access to health care and lack of resources to finance the medications and procedures they require. Often the only hope of access to a therapeutic agent is an entry into a studies protocol that is testing the medicine.

Therapeutic expectations are the reason for admission but, if the study uses control groups with placebo, these expectations are undermined in half of the cases, causing frustration that the researcher seeks to avoid with the negative of health benefits. The patient sees their legitimate hopes unfulfilled are muted with the imputation of having fallen into a therapeutic fallacy. This is another argument against the use of placebo, which not only endangers patients requiring medication, but also destroys the legitimate hope of effective medical help if they enter the study.

When probands are recruited for clinical studies without offering *reasonable expectations of direct therapeutic effects* or by acknowledging that the *expectation of benefits is not robust enough to justify the costs and risks imposed by the study may appeal to altruism is explaining that the decision to participate cannot however be entirely rational because the testing would be contributing to the common wellbeing*[27].

This argument is fallacious and perverse. Fallacious because it assumes that all clinical trials have goals of common wellbeing and, as it happens with the majority, do not obey corporate interests to occupy lucrative niches of the "me too drugs" market. It is perverse because it suggests altruistic attitudes to the poorest link of the research, since researchers, sponsors and scientific institutions are always benefited by clinical trials.

For many reasons, occurs, such as with industry, the scientific off-shoring, moving research to low-income populations with scarce resources and education [28]. These are damaged, violated populations that require therapeutic measures to alleviate their detriments, instead they are classified as "vulnerable" and, as such, are *absolutely or relatively unable to protect their own interests* "because they have" *diminished* capacity or freedom to consent or refrain from consenting [29].

Under these conditions, the informed consent becomes a farce, being understandable that probands have therapeutic expectations or that is easy to convince them they will receive medical benefits then, if this is not met, they are pejoratively dismissed as unjustified therapeutic fallacies.

Final Considerations

The idea of therapeutic misconception was assimilated with more enthusiasm than reflection, described based on studies with feeble foundations, whose results cannot be generalized, serving as argument for both sponsors and as researchers for exemption from the obligation to effectively provide medical benefits. The issue of therapeutic misconception has served to erode the difference between therapeutic and non-therapeutic studies, and to insist that the probands patients are no longer under the protection of clinical ethics, which is replaced by the research ethics that evaluates and protects from risks but does not assume the responsibility of providing medical benefits to the research subjects in whom all attitudes that go clear detriment of the interests and needs of patients and therefore should be dismissed by bioethics.

It is necessary to reactivate the ethical mandate to conduct Phase III clinical trials only in patients only that could benefit from participating and receiving the results of the study. The so-called therapeutic misconception is a rhetoric that allows researchers and sponsors to disavow any obligation to respect medical benefits for probands who are recruited, and to deny all benefit commitments at the end of the research. In nations with scarce resources, it limits access to important medicines, which could not be obtained unless entering a study protocol.

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