Ethical issues in naturalistic versus controlled trials

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Ethical core issues in research with human subjects are related to informed consent and risk-benefit assessment. This is valid for all types of studies. However, there has been much greater focus of ethical considerations on controlled clinical trials than on naturalistic trials, probably because the former are interventional in nature and may have unknown and perhaps severe somatic risks, whereas naturalistic studies seem not to intervene but only to observe, and therefore are assumed to have fewer or almost no risks. However, there are also ethical implications in naturalistic trials, although their weight is differently accentuated, more with potential, more with potential psychological burdens of the observational procedures and more with potential physical risks in interventional trials. This will be elaborated with examples of placebo-controlled trials and of incidental findings in screenings, of marketing influences on observational studies, and of psychological burdens by survey interviews. The ethical implications will be analyzed within a more general framework. Finally, recommendations will be offered.

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Ethical core issues in research with human subjects are related to risk-benefit assessment and informed consent. This is valid for all types of studies. However, at least in former times, there was a much greater focus of ethical considerations on controlled clinical trials than on naturalistic trials. A major reason could have been that controlled clinical trials that aim at the efficacy and safety of a new (therapeutic or diagnostic) intervention may have unknown and perhaps severe somatic risks, whereas naturalistic studies seem not to intervene, but only to observe and analyze phenomena in a population or in data of routinely recorded findings, and thereby are assumed to have almost no risks. At least the weight of ethical implications is differently accentuated, more with potential physical risks in the former, and with potential psychological consequences of the observational procedures and confidentiality of recorded data in the latter. Whereas controlled trials have clearly established procedures including the obligation to obtain a vote from the competent ethics committee (EC) or institutional review board (IRB), naturalistic trials are performed by a much broader set of various procedures, for many of which and in some countries the consultation of an EC is not obligatory but at best only recommended, although selection of participants and application of questionnaires and interviews are interventions in their lives with potential psychological consequences.[1]

The following examples of controlled as well as of naturalistic trials will demonstrate the need for a thorough ethical evaluation of the risk-benefit assessment and of

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informed consent in order to protect the participant with regard to the ethical principles respect for his or her autonomy, welfare, nonmaleficence, and confidentiality.

Examples

Controlled clinical trials

Controlled clinical trials, especially in the form which up to now has been the gold standard, ie, the double-blind randomized controlled clinical trial (RCCT) are research studies for the proof of efficacy and safety of a new intervention. Objective influences on the outcome of a specific intervention are controlled by randomizing the allocation of research subjects to the index group and to the control group, and subjective influences by blinding the patient and—if necessary—the researcher (double-blinding). However, the more the sample of research subjects is selected according to strong inclusion and exclusion criteria, the less the generalizability of results will be. Therefore, the result of the same intervention in nonselected samples from routine practice may differ, and justifies additional trials under naturalistic conditions.
Two controversially debated ethical issues are placebo-controlled trials and the "therapeutic misconception."

Placebo-controlled trials

The revision of article 29 of the Helsinki Declaration in 2000 and its "Note of Clarification" in 2002 on the use of placebo controls in cases of an existing standard treatment provoked a heated controversy between advocates of an "active control orthodoxy" as opposed to those of a "placebo orthodoxy." [2] The former argue that withholding a proven standard therapy is unethical and violates the ethical principle of nonmaleficence, whereas the latter defend the position that placebo controls are necessary to evidence the efficacy of a new intervention in cases, in which the efficacy of an established standard treatment is supplied only by historical and clinical experience. The discussion was intensified a decade ago also by the usage of purely placebo-controlled RCCTs in patients with schizophrenia, and resulted in the operationalization of a set of criteria for an ethically acceptable use of placebos in controlled trials of patients for whom a standard therapy is available.[3] Further pro arguments are high placebo rates in the field of indication, a high risk of side effects of the standard treatment, or its efficacy on only single symptoms.[4,5] Particularly controversial was the debate about placebo controls in depression: whereas some argue for their indispensability[6,7] in order to avoid ostensible evidence by equivalence with an inefficient standard treatment, others are convinced of the efficacy of antidepressant drugs, especially in severe depression.[8,9] Efficacy is less evident in mild depression. Therefore, placebo-controlled trials in depressed patients may be considered only: (i) if the objective of the trial cannot be achieved by any other design, eg, by a trial of superiority with a standard treatment as comparator[10]; (ii) in patients with mild depression, eg, in samples from which all patients with severe depression with high risks, for example, suicidality, or with intense individual suffering are excluded; (iii) if the placebo control is added onto a standard treatment; (iv) if the patient is fully informed and competent to give consent.[11]
The ethical consequences are that researchers as well as ECs[12] are obliged to assess comprehensively the risk:benefit ratio in order to establish whether the advantage of the placebo application is greater than its risks. They must examine precisely the pros and cons of the study (eg, "me-too-trials," noninferiority or superiority trials),[10] and the definition of the clinical conditions of the study sample (eg, severe or mild depression, therapy resistance). They must guarantee that the research patient will be informed clearly and comprehensively and has the capacity to consent.

Therapeutic misconception

Ethically important is a patient's misconception of research as care, ie, "to confuse the design and conduct of research with personalised medical care." [13] This situation was labelled 25 years ago "therapeutic misconception" (TM).[14] Recently this concept has been controversially discussed. It was suggested that the term TM supports the "assumption that clinical trial participation disadvantages research participants as compared with receiving standard medical care"[13] as well as the reproach that some of its newer interpretations "exaggerate the distinction between research and treatment." [15] But such statements were clearly repudiated by the inventors of the term, who stated:

> Our concerns about TM's impact on informed consent do not derive from the belief that research subjects have

> poorer outcomes than persons receiving ordinary clinical care. Rather, we believe that subjects with TM cannot give an adequate informed consent to research participation, which harms their dignitary interests and their abilities to make meaningful decisions. …In the absence of empirical studies on the steps required to dispel TM and the impact of such procedures on subject recruitment, it is premature to surrender to the belief that TM must be widely tolerated in clinical research.[16] An investigation by these latter authors resulted in the conclusion that "subjects often sign consents to participate in clinical trials with only the most modest appreciation of the risks and disadvantages of participation." [17]

The ethical consequence is the necessity to be sure that patients as potential research participants have understood the differences between clinical research trials and clinical care.

Naturalistic trials

Naturalistic trials are either prospective "noninterventional" observational studies of phenomena, eg, real-world events or conditions, or retrospective analyses of existing data from other studies, eg, follow-ups of treated patients, or routinely documented basic data. Prototypes are cohort studies or case-control studies as well as screenings or surveys.

In general naturalistic trials have no individual benefit but do have potential risks, mainly psychic burdens such as worries or stigmatization by (i) the selection of cases, eg, family members in genetic risk studies with regard to information and consent; (ii) the method of observation and assessment, eg, by interview with intimate questions; (iii) data confidentiality, eg, in epidemiological studies; (iv) "interventions" in marketing trials called "observational or utilization studies."

Major ethical aspects are: method and content of information for consent, data confidentiality; dealing with incidental findings.

Observational trials

Up to the 1990s, such studies, mainly postmarketing studies of newly licensed drugs, had a questionable reputation because they were often misused as a marketing instrument: physicians were offered money for observing the effects of a new drug that they were supposed to prescribe—mainly with meaningless results. However, observational studies without such distorting influence and with a scientifically based methodology[18] may yield valuable additional knowledge to the results of controlled clinical trials.[19] The aims of such trials could be to gain knowledge about: (i) prescribing behaviors, etc; (ii) undesirable drug effects of routinely administered drugs under real-world conditions, eg, interactions with other drugs in multimedicated patients with chronic diseases; (iii) the course of the treatment.[18]

According to the recommendations of the German Federal Institute for Drugs and Medicinal Products[18] the nonintervention of an observational study is characterized by the separation of the inclusion of patients into the study from the prior decision on the treatment that will follow usual medical practice. Scientifically sound prospective observational trials should use systematic and standardized observations and a schedule for data analysis laid down prior to the observations. Observational studies are not clinical trials, and the researcher is not obliged to apply for the vote of an EC. However, he or she is advised to consult an EC, and is obliged to do so if he or she uses procedures beyond the mere routine treatment, eg, a specific questionnaire. Also additional information to the usual information of a patient for his/her consent to treatment should be given, at least regarding the fact that the patient will be included in a study and about the confidentiality of his or her recorded data according to data protection laws.

Screening procedures and the problem of incidental findings

Screenings almost always result in unexpected incidental findings. A currently highly debated example is that of incidental findings with magnetic resonance imaging (MRI): increasing breadth of applications of brain MRI in healthy, ie, asymptomatic people for various reasons such as research, occupational or clinical screening, or commercially for reassurance of good health[20] yielded clinically significant incidental findings in 2% to 3%; these were primarily neoplastic or vascular in nature.[21] These evidence-based data provoke questions: how to deal with incidental findings in banked data and how to interpret individual findings that fall outside a normative range yielded by group-averaged functional images, and particularly how to deal with such findings towards "study participants, patients and consumers to enable

them to navigate through the labyrinth of information about incidental findings in research, clinical care, and the rapidly evolving industry of personalized medicine." "Information available online to the self-guided user is noisy and unreliable." Therefore, "the professional community has the duty to ensure that rational decisions can be made," especially because such findings "might become a part of a person's life. Questions about anticipating and managing such finding must be explicitly and systematically encouraged."[20]

Until now neither the law nor governmental regulations as well as ECs offer clear guidance to researchers on handling unexpected findings[22,23] and a frame for participants to contextualize their expectations.[24] However, there seems to be agreement that before screening procedures for research studies the potential research subject should be informed about the possibility of an incidental finding and how to deal with it. We preferred to obtain the consent of the research participant that we might inform his/her practitioner about unexpected and perhaps clinically relevant findings, because the practitioner—knowing the patient and his/her context —is better equipped to judge the clinical significance of the finding and how to convey the information to the subject.[25] This is particularly valid if the researcher is not a clinician or has no specific competence, eg, in evaluating functional MRI images. If the potential research subject refuses to have such information transmitted to his/her practitioner or if he/she has no physician at all, the information about the possibility of an unexpected finding and its potential and perhaps severe consequences for the individual's life (Kerr 1995, cited in refs 26,27) must be given explicitly and in detail, in order to enable the subject to make a rational decision. If an incidental finding of potential clinical relevance is discovered, the subject should be advised to consult a physician as soon as possible. A comprehensive analysis of handling incidental findings in brain imaging has resulted in a range of options, examples of key points, and practical guidelines.[28] An early example of a detailed information procedure, particularly explicit information prior to testing and psychological counseling before and after the test, has been elaborated for genetic screening for Huntington's disease,[29] and then for all genetic testing,[30] and will get much more importance with the rapidly evolving availability of affordable genetic testing of the whole genome ("the $1000 genome").

Surveys

Surveys on psychiatric morbidity in a population must consider possible psychological risks by the mode of contacting and questioning the participants or by the content of questionnaires, eg, intimate questions, but also how to deal with difficult findings such as demand for help, illegal behavior, or child abuse.[1] Major precautions must be implemented to protect confidentiality, ie, anonymization and safeguarding of data according to data protection laws and guidelines, eg, European standards on confidentiality and privacy in Healthcare 2006.[31]

Ethical implications

These examples have demonstrated the ethical significance of risk-benefit-assessment in order to avoid a violation of the ethical principle of nonmaleficence and the importance of adequate information of potential study participants in order to enable them to make rational decisions, ie, to respect the ethical principle of self-determination. Both core components of ethical implications of research with human beings will be discussed now in a more general framework, but with specific reference to research interventions in mentally ill patients, and particularly in those who are incompetent to provide consent. Clinical research is understood as an intervention in human beings that aims by scientific methods systematically to achieve supraindividual knowledge, and thereby goes beyond the individual benefit of the participating person. Such research intervention is ethically acceptable only: (i) if its risk:benefit ratio is acceptable, and (ii) if the informed consent is valid.

Risk:benefit ratio

Proportionality of the risk:benefit ratio

This ethical core requirement of a clinical research intervention means that the relationship between its potential benefits and risks is reasonable and justified and does not violate good practice. Without these preconditions a research intervention is not permissible, even if competent probands consent to participate in the research intervention. On the other hand, even risky interventions or those without a potential direct individual benefit may be ethically justified if competent persons consent, eg, in phase I trials in healthy people, and particularly in nat-

uralistic trials. However, it is difficult to find an acceptable balanced relationship[32] in cases with only a future or no direct potential individual benefit but with potential risks such as objective physical risks or psychological burdens. "Risk-benefit ratios often cannot be calculated, even roughly." [33] The final report of the US National Advisory Bioethics Commission (NABC) stated in 2001: "An IRB may approve a research proposal only if it judges that the risks are reasonable in relation to potential benefits. This judgement may be an IRB's single most important and difficult determination, because it ensures that when research participants voluntarily consent to participate in a research study, they are offered a "reasonable choice" (cited from ref 23). Unfortunately, as the NBAC notes: "current regulations do not further elaborate how risks and potential benefits are to be assessed, and little additional guidance is available to IRBs." [34] Furthermore, there exist discrepancies between guidelines: whereas this NABC report states that risks must be reasonable in relation to potential benefits, others demand absolute limits for risks such as potential irreversible damage or death, and no more than minimal risks in incompetent research participants.

Due to the difficulties of judgement Research Ethics Committees (RECs) tend to avoid such in-depth evaluation of the risk-benefit relationship and focus on other aspects of the study, such as the consent process as Simonsen found out in his 3-year observational study of Swedish RECs.[32] This may be especially the case in naturalistic trials with at best minor benefits such as rewarding altruistic feelings of participants by serving others or the social good but with some generally unexpected potential burdens or even risks. A careful evaluation implies a clear understanding of the uncertainties in establishing (i) potential benefits and (ii) potential risks and/or burdens and/or inconvenience for the participating individual as well as for other present or future patients (social value),

Benefits and risks

Both benefits and risks must be considered on the individual as well as on the social level.

Social benefit

The aim of research with human beings in the field of mental health is scientifically based knowledge with the final objective of improving the treatment and care of ill people (in the best case successfully also for the participating individuals), either directly by controlled trials or indirectly by naturalistic, eg, epidemiological trials for the planning of services or case-control trials for knowledge of risk factors for disorders. The important social value of this objective is evidenced directly or indirectly by legal norms such as laws and guidelines, eg, the German social law (SGB V) provides that insurance companies are permitted to pay only for medical interventions with established economic efficacy and advisability, and correspondingly physicians are obliged to prescribe only indicated, effective, and economical interventions. Consequently it is a societal demand to prove scientifically the "efficacy" (or "effectiveness" under conditions of clinical routine or in practice), and the "efficiency" of medical interventions, ie, the relationship of therapeutic effectiveness to its costs, both medically in terms of side effects and risks and economically in terms of financial burdens. This societal demand must be, of course, fairly balanced with the protection of the individual research participant against risks, burdens, and inconvenience, particularly in vulnerable individuals.

Individual benefit

However, due to the legally founded conviction in liberal Western societies that no human being is obliged to sacrifice him- or herself for the community ("In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests."—§6, Declaration of Helsinki/Seoul 2008) the practice of clinical research is dominated not by the social value of clinical research but by the impression of *individual benefits* of the participating research subjects such as:

- Gaining a better intervention that is more effective, acts more rapidly, or has fewer side effects than the existing standard intervention
- Satisfying his or her altruistic feelings of solidarity with other ill people[35]
- Earning money[36] or other privileges.

Further motivational factors are a feedback about one's own illness and its status, feeling autonomous and self-determined and the wish for other people to have a better understanding of one's own mental state.

Particularly with incompetent patients with mental illness the motivation of their caregivers and guardians is

important; this has been shown in research interventions that aim to improve the ill person's quality of life and/or to lessen the burden for the caregiver.[37,38]

Risks, burdens, and inconvenience

If an individual participates in a necessary and legally required research study for the best of all, of course, this individual must be protected against risks and burdens of the research intervention. A variety of normative regulations prescribes the content, extent, and mode of this protection of research participants against risks.
The heading of "risk" comprises: (i) objective threats to the individual proband, eg, undesirable side effects of the intervention; prolongation of suffering or worsening of the disorder due to the withholding of a specific treatment in a placebo-control group; and in a broader sense also dispositions for undesirable effects, eg, pharmacogenetic or allergic dispositions or those that are related to noncompliant personalities, as well as (ii) subjective burdens and inconvenience, eg, by overly rigorous research procedures or a feared risk such as stigmatization, particularly in depressed patients and drug abusers, which may demotivate potential research participants.
Risks and side effects of an intervention are objectifiable effects in contrast to burdens and inconvenience, which are much more of a subjective, individual specific character. Therefore, the researcher should explore specifically or should at least be aware of the research participant's potential individual sensitivity to both physical and psychic burdens that are specifically related to the intervention.
However, risks for society should also be considered, eg, the progression of hitherto untreatable conditions, or if research interventions do not precisely follow the regulatory requirements and thereby lead to incidents and undermine the necessary trust of the public; this may prolong or even prevent the recruitment of individuals for research interventions that aim for the gain of needed knowledge.

Standards of benefits and risks

These can be determined more precisely only in reference to a factor such as reduction of symptoms or suffering or an increase in the quality of life. *Individual* benefit may comprise the improvement of welfare or well-being as well as the best interest of the research participant, ie, both subjectively experienced benefits and objective benefits seen from outside. *Social* benefit is related to the gain of knowledge.
The reduction or increase of more complex concepts such as suffering or the quality of life are clearly more difficult to be operationalized as a requirement for the assessment of the size of a benefit. Terms such as the "prospect" of benefit, or a "direct," "important," or "significant" benefit for the participating research subject or the gain of "essential" knowledge are not clearly defined or—as undetermined terms of law— not definable at all and thereby open for subjective interpretations.[39,40]
Standards comprise, among other aspects, strength and limits. Strength of risks is described by a broad range of grading terms such as "without the danger of impairment", minimal risk, minor increase of minimal risk, "not insignificant risks", "serious risk to health", "possible irreversible damages," risks of unacceptable dimensions." [41]
Absolute upper *limits* of risks for research participants are irreversible impairments and death. Standard limits for research with incompetent patients are no more than "minimal risk," "minor increase of minimal risk" and "direct prospective benefit," [42,43] terms which are under discussion.

Assessment of the risk:benefit relationship

The assessment of the strength and probability of potential risks and burdens as well as of potential benefits and particularly their relationship to each other is the crucial step in evaluating the acceptability of a research intervention. It is filled with uncertainties (and difficulties in conveying its result to the potential research participant)[40,42]: "accordingly, the estimation of the reasonableness of a risk:benefit ratio depends upon normative values and conventions."
Thereby, different standards for the evaluation have been developed, as is evidenced by a recent controversy between representatives of the "equipoise" standard (eg, ref 44) and those of a "net-risks-test." [43,45]

Validation of the risk:benefit ratio

With regard to the uncertainties of risk-benefit estimates, a safe validation of consent should be observed by a three-step evaluation of the requirement of acceptability of potential risks and burdens in relation to the expected benefits of a research intervention:

1. First the *researcher* must give reasons for considering the relationship of risks and burdens of his or her planned research intervention as acceptable, ie, as reasonable and justified.
2. Then the *Research Ethics Committee (REC)* must evaluate this relationship with regard to legal and ethical norms and professional expertise, and should give reasons—at least in research studies with vulnerable subjects—not only for refusal but also in case of acceptance of the research application and particularly of the ethical considerations of the applying researcher.
3. Finally the potential *research participant* or his or her legal guardian must evaluate the institutionally approved acceptable relationship of potential risks, burdens, and inconvenience to the expected benefits of the research study with regard to his or her personal idiosyncrasies, interests, and values, and in case of his or her individual acceptability of the relationship he or she may consent to participate.

Informed consent

All medical interventions in human beings must be authorized personally by the concerned individual. This is particularly important for a research intervention because it is aimed not only for the benefit of the individual but also or even only at the benefit of others. This is much less regulated in naturalistic studies, although they offer no or at best minor individual benefit but potentially considerable risks, eg, with unexpected incidental findings.

Therefore, the basic precondition for research with human beings is their voluntary and valid informed consent. However, the voluntariness may be jeopardized by conditions such as imprisonment, poverty, or personal dependency, and the validity may be impaired by insufficient information, its inadequate understanding, or incapability of making decisions. Populations with such risk factors are called vulnerable populations. Mentally ill persons are a vulnerable population. Their specific vulnerability is given by the risk that their competence to consent may be impaired or does not exist at all. In such conditions they are at risk to be used without authorization for other than their own benefit. This may also happen in naturalistic studies, eg, in those that include children, but in general participants of such studies are healthy adults with competence to consent. Nevertheless, the researcher and the design of the study should be aware of the possible incapacity of potential participants in order to deal with it.

The underlying concept of informed consent is that the consenting research participant makes the objective of the research intervention his or her own. However, practice is more or less distant from this concept, particularly with incompetent patients, eg, with minors or mentally ill people.

Assessment of capacity to consent

Details and open questions of the informed consent process are eg, embedding it into the development of the physician-patient-relationship and improving the patient's capacity to understand and to consent, particularly the assessment of the capacity.[39] Recently a broad range of instruments for a standardized assessment of the capacity to consent has been developed, but up to now its application is limited by a restricted practicability or unproven validity or specific indications for only some dimensions of the capacity to consent.[46,47] Some of them focus not only on understanding information but also on both intentional and emotional influences on the capacity to consent, and on attitudes of relatives and caregivers as well as personal dependency on them. Even if the capacity to consent is impaired, the researcher should try to obtain at least an assent as an expression of respect for the patient and as a trust-building measure, whereas a dissent of an incompetent patient must be respected in any case. Particularly patients who are in remission from an episode of mental illness and/or who have regained the capacity to consent, as well as patients in early stages of a progressive neurodegenerative disease but still with the capacity to consent should be encouraged and empowered to develop an advance directive for medical interventions in situations to be expected in the future, eg, relapses/recurrences or the worsening of the illness, in which their capacity to consent may be impaired. If possible and acceptable with regard to the value profile of the patient he/she should be asked to include a statement on a possible participation in a research project in this advance directive.[48]

Information on the risk:benefit ratio of the research intervention to the potential research participant (or his authorized guardian) is a core requirement of obtaining a valid consent.

Recommendations

1. Ethical questions of research with human subjects must be answered not only for controlled trials but also for naturalistic trials as well. They are related to risk-benefit-assessment and to informed consent.
2. Informing the patient is not only a legal requirement but much more a chance to develop trust. (The patient who is armed with information, who wants to ask questions, should be seen as an asset in the process of care and not an impediment to it." (Donaldson, cited in ref 49). It needs time and should be considered in planning the research study. In particular, vulnerable research participants should be empowered at least to assent to the research procedure besides the substituted informed consent by authorized persons.
3. Mentally ill patients with still maintained (eg, in neurodegenerative diseases) or regained capacity to consent after an illness episode should be encouraged to develop an advance directive for medical interventions including a possible participation in a research project.
4. Assessment of competence to consent is needed to be sure of the validity of consent. However, there is still a lack of both scientifically proven and practicable standardized tests which should be overcome by further research.
5. Consent should be related to the relevant matter in question. Occasionally it will be considered also to relate the threshold for acceptance of the competence to consent to the risk of an intervention. In practice this may be a valid consideration in order to avoid an uncritical consent of a patient to a risky intervention. However, it requires a more differentiated risk-benefit estimation in research: the possible benefit of increasing the threshold of acceptance the competence to consent for the protection of the research participant is opposed by the possible risk that his/her guardian authorized due to his/her supposed incompetence will consent to an intervention with a greater risk than that to which the competent patient would have been consented. In such a case it should be examined whether the authorized guardian orients his/her decision exclusively by the presumed will of the patient.
6. Benefits and risks are undetermined terms of law, and should be determined explicitly as clearly as possible in each specific research design.
7. With regard to the uncertainties of risk-benefit estimates a safe validation of consent should be observed by a three-step evaluation (researcher, REC, patient) of it.
8. Researchers should be educated systematically on the ethical implications of clinical research. In October 2009 a workshop of the European Science Foundation made clear that "there is an urgent need to develop consistent education in conduct of research (RCR)."[50] All regulations should be observed thoroughly in order not to lose the trust of both the research participant and the public in research, which is a basic requirement of successful recruitment of vulnerable individuals. ❑

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Temas éticos en estudios naturalísticos versus estudios controlados

Los temas éticos centrales en la investigación con sujetos humanos son el consentimiento informado y la evaluación del riesgo-beneficio. Esto es válido para todos los tipos de estudio. Sin embargo, las consideraciones éticas han tenido un mayor foco de atención en los ensayos clínicos controlados que en los ensayos naturalísticos, probablemente porque los primeros constituyen intervenciones en el organismo y pueden tener riesgos somáticos desconocidos e incluso graves, mientras que los estudios naturalísticos parecen no intervenir sino que sólo observan y por lo tanto se asume que tienen menos o casi ningún riesgo. Pero, también hay consecuencias éticas en los ensayos naturalísticos, aunque su ponderación se acentúa de manera diferente; tienen más peso los potenciales riesgos físicos en los ensayos con intervenciones y más peso las potenciales cargas psicológicas en los procedimientos observacionales. Estos aspectos serán presentados a partir de ejemplos de ensayos placebo-controlados y de hallazgos incidentales en los tamizajes, de influencias del marketing en los estudios observacionales, y de las cargas psicológicas en las entrevistas de investigación. Las consecuencias éticas serán analizadas en un marco mucho más general. Finalmente se entregarán algunas recomendaciones.

Questions éthiques dans les études naturalistes versus *contrôlées*

Les principales questions éthiques de la recherche chez l'homme sont liées au consentement éclairé et à l'évaluation du rapport bénéfices/risques, et ceci pour tous les types d'études. Néanmoins, les études cliniques contrôlées ont plus soulevé de considérations éthiques que les études naturalistes, probablement parce que les premières sont de nature interventionnelle et peuvent comporter des risques somatiques inconnus et peut-être sévères ; en revanche, les études naturalistes semblent seulement observer sans intervenir et donc ne comporter que peu ou pas de risques. Les études naturalistes ont cependant des implications éthiques, bien que différemment pondérées : les risques physiques potentiels sont plus importants dans les études interventionnelles alors que les risques psychologiques le sont dans les procédures observationnelles. Ces considérations seront illustrées dans cet article par des exemples d'études contrôlées contre placebo et de résultats fortuits dans les dépistages, des exemples d'influence commerciales sur les études observationnelles et de charges psychologiques dans les études d'enquête menées au moyen d'entretiens. Les implications éthiques seront analysées dans un cadre plus général et enfin, des recommandations seront proposées.

18. Empfehlungen des Bundesinstituts für Arzneimittel und Medizinprodukte und des Paul-Ehrlich-Instituts zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen vom 7. Juli 2010. Available at: http://bjp.rcpsych.org/cgi/citmgr?gca=bjprcpsych/188/6/504. 2010. Accessed 4.11.2010.

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