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Research governance in placebo-controlled trials: Is the EMA/ICH position consistent in itself and in accordance with the declaration of Helsinki?

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Abstract

The European Medicines Agency and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use are powerful international institutions for the regulation of biomedical research. Although not directly concerned with the ethical aspects of research, both institutions have disseminated position papers on ethical issues relating to the use of placebos in clinical trials. What appears initially to be guidance on the methodology of placebo-controlled trials (with very technical content) clearly has some far-reaching implications for the extent of risk patients can be expected to be subjected to in such trials. On the basis of this guidance, this article questions how much additional harm to patients would be acceptable in placebo-controlled trials in comparison with active-control trials. The article will show that the instruments provided in the guidance are unsuitable, remaining unclear on vital points and thereby leaving patients, researchers and research ethics committees without appropriate direction. In conclusion, placebo-controlled trials urgently need more

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appropriate regulation to ascertain an acceptable level of risk for participating patients in relation to additional harm.

Keywords
EMA, ICH, placebo, research ethics, risk assessment

Introduction

Placebo-controlled clinical trials have been the subject of controversial debate in research ethics and governance communities. This is in part due to the fact that in order to conduct such trials, it is crucial that one arm of study's participants do not receive the active drug, but a placebo, that is, something that looks like the drug but has no pharmacological effect. This means that, if an established treatment for a specific disease already exists, this treatment is withheld from study participants for reasons of scientific/statistic validity. In the case of more severe diseases, this raises questions of ethical acceptability (for an overview, see Figure 1) as well as broader questions of research governance and tortious and criminal liability. Research ethics committees (RECs) that frequently receive proposals for placebo-controlled trials for evaluation and their significant influence in terms of approving or denying such proposals is an example of research governance and regulation in its broadest sense. In some jurisdictions, the legislator has delegated this power to RECs by way of legislation such as, inter alia, the Mental Capacity Act 2005 (sections 30–35) in England and Wales, the Adults with Incapacity (Scotland) Act 2005 (section 51), the Medical Devices Regulations 2002 (England and Wales and Scotland), the Pharmaceuticals Act (Arzneimittelgesetz) in Germany (sections 40, 42) and the German Medical Devices Act (Medizinproduktegesetz, sections 20–22c). This 'privatized' regulation puts significant power into the hands of RECs, bodies that rely heavily on guidance such as that of the EMA and the ICH which we critically appraise in this article.

As an illustration, one of the largest registries for clinical studies, the registry of the U.S. National Institutes of Health, shows some 33,753 entries for (ongoing and completed) trials featuring the keyword 'placebo', within a total of 161,980 registered clinical trials.[1] This would mean a share of just below 21% of registered clinical trials including some kind of placebo aspect. The issue therefore continues to be worthwhile investigating.

1. Available at: www.clinicaltrials.gov; search for "placebo" (accessed 28 February 2014). As the search was for the keyword within the title of the study, this does not necessarily mean that the study was against a placebo. It does, for example, also include studies of the placebo effect. Therefore, the figures represent a proportionate illustration of the prevalence of placebo in the current clinical trial landscape but do not make a claim of accuracy.

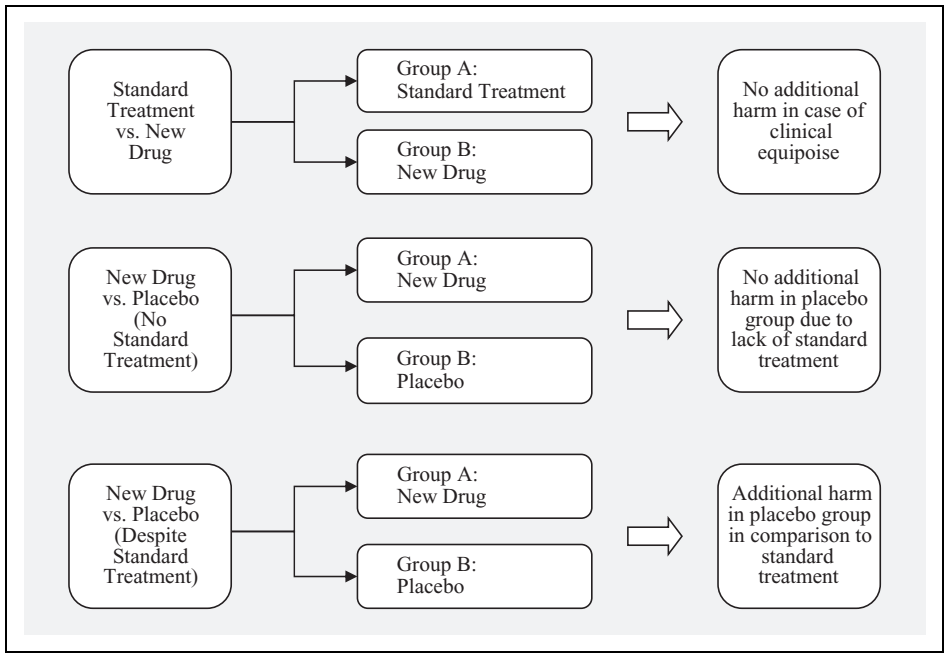

Figure 1. Ethical implications of different study constellations including the use of placebo (two arms only).

In Europe, there are two important institutions for the governance of clinical controlled trials. On the basis of its powers in relation to the granting of centralized marketing authorizations for pharmaceutical products for the European market, the *European Medicines Agency* (EMA) influences the criteria and standards of proof for a drug's efficacy and safety. The *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) issues guidelines on *good clinical practice*, which are a mandatory consideration when planning and evaluating clinical trials. As the name suggests, the original objective of the ICH was the harmonization of the *technical requirements* of clinical trials, not of the *ethical* or *legal* requirements of such trials. Both institutions openly encourage placebo-controlled trials on the basis of a presupposed methodological superiority of such trials in comparison with active-controlled trials. On the basis of the terminology used in this guidance, the result is, at least by implication, the provision of ethical justification mechanisms as a 'bolt-on' to technical guidance.

It is the aim of this article to examine whether the approach contained in the EMA and ICH guidance is (a) consistent in itself and (b) in accordance with the Declaration of Helsinki. This is not only of theoretical relevance for medical ethics, but this has potentially important implications for the day-to-day work of

all institutions that carry responsibility for evaluating clinical studies, especially REC[2] and Data and Safety Monitoring Boards.[3] It is this area in particular which seeks to identify the state of the art on the basis of existing guidance and good practice models to determine the appropriateness (ethical and legal) of proposed research. We will first identify the methodological bases for conducting clinical trials (including any methodological and ethical justification for benchmarking against placebos rather than standard therapy). Second, the beneficial effects of placebo treatments will be discussed to test the concept of placebo for validity in terms of substituting efficient standard therapy. The concepts will then be put in the context of consent and the clinicians' and researchers' duty of care before testing their validity and compliance with the EMA and ICH positions.

Background and methodological questions for the conduct of clinical trials

Montgomery states,[4] 'The most rigorous scientific position is that a comparison against placebo is required for the unequivocal demonstration of the efficacy of a treatment'. In other words, if scientific rigour and certainty are to be achieved, every new treatment should be tested in a placebo-controlled trial environment, independent from an already existing alternative treatment, if any. This is the position Emanuel and Miller[5] call the 'placebo orthodoxy' – the view that it is a *conditio* sine qua non for proof of the efficacy and safety of a drug to test it in a trial against a placebo. Statistics suggest that this demonstrates that a newly developed, active drug is more effective than a placebo rather than to actually show that it is as effective as the standard treatment[5] (also see the work by Miller[6]). The authors give the example that a trial against a standard treatment, which has a response rate of 60%, would require, for unambiguous statistical findings, the participation of two groups of patients with 297 members in each group. In comparison, placebo-controlled trials require merely 48 participants in each group.[7] The paper

2. H.J. Ehni and U. Wiesing, 'Placebos in Klinischen Versuchsreihen. Eine Vergleichende Analyse der Internationalen Richtlinien. [Placebo in Clinical Test Series. A Comparative Analysis of International Guidelines.]', *Ethik in der Medizin* 18 (2006), pp. 223–237.
3. A group of external experts who monitor adverse events and study results at defined time points in the course of a clinical study. With regularly monitoring, the patient safety shall be secured (Cf. EMEA, 2002, para 5.5.2).
4. S.A. 'Montgomery, 'Alternatives to Placebo-Controlled Trials in Psychiatry', *European Neuropsychopharmacology* 9 (1999), p. 267.
5. E.J. Emanuel and F.G. Miller, 'The Ethics of Placebo-Controlled-Trials – A Middle Ground'. *New England Journal of Medicine* 345(12) (2001), pp. 915–919.
6. F.G. Miller, 'The Ethics of Placebo-Controlled Trials', in E.J. Emanuel, Ch. Grady, R.A. Crouch, et al., eds., *The Oxford Textbook of Clinical Research Ethics*. (Oxford: Oxford University Press, 2008), p. 262.
7. Emanuel and Miller, 'A Middle Ground', p. 916.

of Emanuel and Miller met with strong approval by the World Medical Association.[8,9] Although this is a persuasive argument in favour of the conduct of placebo-controlled trials, especially in the case of rare disease conditions where the assembly of a sizeable cohort is significantly more difficult, it is different from the original position that placebo-controlled trials are a *necessary* condition for the proof of efficacy. The placebo-controlled trial is easier to organize, which does not mean that it should be the standard of drug testing when important ethical and legal considerations are at stake. Proponents of placebo-controlled trials also argue that it is the only way to document unknown side effects in comparison with a patient group that does not receive pharmacological treatment,[10] although the comparison of two active drugs can also reveal different profiles of adverse drug effects. Non-inferiority studies with active controls can be argued, in this context, to carry greater informative value.

The methodological position of the EMA,[11] according to the *Position Statement on the Use of Placebo in Clinical Trials with Regard to the Revised Declaration of Helsinki*, seems to be a moderate version of the 'orthodox position' on the use of placebos:

> Although the efficacy of some new medicinal products can be satisfactorily demonstrated without the use of a placebo, for others the judicious use of placebo remains essential to demonstrate their value. Where medicinal products do exist for a given indication, active controlled trials are encouraged provided that a methodologically acceptable demonstration of efficacy and safety can be obtained. However, trials that seek to prove that a new agent and an active control have similar efficacy are inherently less reliable than trials that seek to prove the superiority of the new agent to a comparator, whether inactive or active. Increasing the size of trials does not alleviate this problem.

From the point of view of EMA, trials with active controls (i.e. of a new drug against a standard treatment) are acceptable, but methodologically *inferior* to placebo-controlled studies. Therefore, the definition of the standard of what should be the *normal case* in drug testing is significantly different from the position of the Declaration of Helsinki, which views (as will be outlined below) the active-controlled trial as the standard or *normal case* in drug testing and placebo-controlled trials as a possible exception in narrow circumstances. The vagueness of the language and the requirement of placebo-controlled trials to be *judicious* do little to make clear how the suggested inferiority of active-controlled trials against placebo-controlled trials is explained. It looks very much

8. World Medical Association (WMA): Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Available at: www.wma.net/en/30publications/10policies/b3/ (accessed 30 June 2014).
9. R. Smoak, 'Placebo–Its Action and Place in Health Research Today', *Science and Engineering Ethics* 10(1) (2004), pp. 9–13.
10. Miller, 'Ethics of Placebo-Controlled Trials', p. 262.
11. EMEA/CPMP Position Statement on the Use of Placebo in Clinical Trials with Regard to the Revised Declaration of Helsinki, London, 28 June 2001.

like a transfer of responsibility to those who are told to be *judicious* when using placebo controls.

Finally, even when accepting the methodological superiority of placebo-controlled trials, the question remains whether this satisfies the objective of medicine aimed at human welfare (i.e. to establish safe and effective treatment options for patients). Placebo-controlled trials can only show that using a new drug is better than to use a placebo but not that it is better than the standard treatment. Active-control trials will give exactly the answer which is important in the clinical setting (i.e. whether a new drug is more effective or less effective than what is currently being offered to the patients and what the profile of adverse drug effects is in comparison to this). Therefore, placebo-controlled trials may be methodologically superior from the point of statistics and biometrics but not necessarily from the point of clinical care. We do, of course, at this point have to acknowledge that the friction between research and clinical care positions plays a weighty role in this context.

The 'placebo argument'

There is a common argument which asserts that patients who receive placebos during the course of other medical treatment cannot be said to remain untreated. They may still obtain some therapeutic advantage from their participation in a placebo-controlled study. This argument, which we will call the placebo argument, can be found in two variations in the relevant ICH document (Topic E 10, Choice of Control Group in Clinical Trials).[12] It would exceed the scope of this article to analyse all the implications connected with this argument, but it has some importance for our analysis as it concerns the ethical criticism that patients in a placebo group are deprived of the standard treatment for their condition.[13] We will therefore present a conventional form of the placebo argument which we take from an article by Montgomery[14] and will then make some general remarks on this kind of argument. Montgomery's article explains:

12. ICH, Topic E 10, Choice of Control Group in Clinical Trials, 'The use of placebo control group does not imply that the control group is untreated. In many placebo-controlled trials, the new treatment and placebo are each added to a common standard therapy'.

    'It should also be noted that not all placebos are completely inactive. For example, some vehicle controls used in studies of topical skin preparations may have beneficial activity'. [. . .] 'It should be emphasized that use of a placebo or no-treatment control does not imply that the patient does not get any treatment at all. For example, in an oncology trial, when no active drug is approved, patients in both the placebo or no-treatment group and the test drug group will receive needed palliative treatment, such as analgesics, and best supportive care'.
13. Cf., for example, the following definition of placebo: 'Basically, a placebo is any medical treatment (or component of a medical treatment) that is inactive for the condition being evaluated other than the effect that may result from a person's thinking that he or she may be receiving an active treatment', in R.J.Amdur and C.J. Biddle, 'An Algorithm for Evaluating the Ethics of a Placebo-Controlled Trial', *International Journal of Cancer* 96 (2001), p. 261f.
14. Montgomery, 'Placebo-Controlled Trials'.

> It is apparent from some of the recent discussion of placebo-controlled trials that the nature of placebo is not fully understood. Because placebo is used as a control for an active treatment it is sometimes assumed to be ineffective. In fact the placebo is not merely treatment with an inert substance. Patients who receive a placebo are provided with support and concern; they are reassured by the perception that the complaint or disorder is understood and is being taken seriously.[15]

This seems to be a curious justification of controlled clinical trials in the framework of modern medicine, which predominantly sees itself as based on 'hard science'. It is precisely this paradigm of science which asserts that it is not the emphatic commitment of the physician or the patient's hope and desire for healing which cures her but the drug's active agent. After all, the idea behind conducting pharmacological trials is to determine the efficacy of the active ingredient as accurately as possible, not the side effects triggered by care and attention. The distinction between both modes of treatment, according to this paradigm, is that the pharmacological treatment is supposed to help all patients from a specified group with a described health condition, whilst few who adhere to scientific medicine would say this for a placebo treatment. This is quite reasonable as current trends in medicine, especially in psychiatry in the last 25 years, point in the direction of giving even more credit to pharmacology-based treatments rather than to psychological intervention. Therefore, the message of the statement above does not sit comfortably with modern medicine's self-conception. The message to patients is that they do get something – but the question from the ethical point of view would rather be whether it is not the discipline of medicine which obtains something important and of value from the patients (i.e. the willingness to participate in a treatment which is inadequate according to present therapeutic standards). This raises a significant issue in terms of the balance of fairness between patients and physicians and goes to the issue of fostering a relationship of trust between the scientific community and research participants.

Some considerations concerning the ethical evaluation of placebo-controlled trials

One of the most influential guidance instruments for placebo-controlled trials is the Declaration of Helsinki, which stipulates that such trials only be deployed in cases where there is no established standard treatment for a disease.[16] As the 'note of clarification' to

15. Montgomery, 'Placebo-Controlled Trials', p. 266.
16. The use of placebo is a feature since the Fourth revision of the Declaration at Somerset West, South Africa, in 1996. The First revision from Tokyo 1975 introduced the paragraph with the following wording: 'II.2 The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods. II.3 In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method', in In R.V. Carlson, K.M. Boyd and D.J. Webb, 'The Revision of the Declaration of Helsinki: Past, Present and Future', *British Journal of Clinical Pharmacology* 57(6) (2004), pp. 709f.; H.J.

the relevant paragraph 29 of the Declaration from the year 2002 shows, there was some doubt within the World Medical Association (responsible for the drafting of the Declaration) whether this original principle needed some modification. Critics remarked that, with these modifications, the Declaration of Helsinki could easily become 'a guidance for industries'.[17] The special importance of the Declaration of Helsinki results from the fact that many details of clinical research are not regulated in national law. For example, the German Pharmaceuticals Act (Arzneimittelgesetz) contains not a single mention of the word placebo.[18] (Although, interestingly, The Medicines for Human Use (Clinical Trials) Regulations 2004 (S.I. 1031/2004) do mention placebos (in Part 1, sections 2, 35 and part 2, section 11), if only to ensure that the regulations also apply to them).

Other commentators have suggested that, prior to the clarification note, placebo-controlled trials breaching the requirements of the Declaration of Helsinki were taking place in full view of regulatory bodies.[19] The starting point for the debate was the ethical assessment that placebo-controlled trials are an alternative design for the conduct of studies in cases without an existing standard treatment. Any changes to this standard should lead to careful consideration of the circumstances in which placebo-controlled trials could be acceptable despite there being an established standard therapy. Surprisingly, this does not seem to be the case to a sufficient extent, producing a gap of regulation in this area of clinical research. Whilst the Declaration of Helsinki does not constitute binding law, it has been said – and widely accepted – that it has become the definitive benchmark against which research projects are measured.[20] Therefore, its indirect binding effect (i.e. its regulatory force as a professional guideline for medical research involving humans) is evident. To treat the Declaration as if it were not binding would therefore be to misunderstand its significance in international research governance.

On the basis of Emanuel and Miller, we can frame at least three preconditions for placebo-controlled trials in cases where a standard therapy already exists (Table 1). These preconditions concern:

Ehni and U. Wiesing, 'Die Kontroverse um Placebo-Kontrollen und die Deklaration von Helsinki. [The Controversy Regarding Placebo-Controls and the Declaration of Helsinki.],' in H. J. Ehni and U. Wiesing, eds., *Die Deklaration von Helsinki. Revisionen und Kontroversen*. (Köln: Deutscher Ärzteverlag, 2012), pp. 43–56.

17. C. Kurihara, T. Mitsuishi and J. Nudeshima, 'Crisis of the Declaration of Helsinki becoming a Guidance for industries', *British Medical Journal* 327 (2003), p. 642. Available at: http://www.bmj.com/rapid-response/2011/10/30/crisis-declaration-helsinki-becoming-guidance-industries (accessed 19 August 2014).
18. Which seems consistent in terms of legislators generally tending to avoid enshrining methodological aspects of biomedical conduct which are subject to frequent development and change. Where there is a nexus to potential physical harm to a patient, be it through an act or an omission, the legislator possibly ought to be more forthright.
19. K.J. Rothman and K.B. Michels, 'The Continued Unethical Use of Placebo Controls', *New England Journal of Medicine* 331(6) (1994), pp. 394–398.
20. S.A.M. McLean, 'Regulating Research and Experimentation: A View from the UK', *The Journal of Law, Medicine & Ethics* 32(4) (2004), p. 607.

Table 1. Evaluation of placebo-controlled trials according to the type of treatment, type of disease and type of risk.

	Criteria	Consequences	Ethical implications
Type of treatment	Effective, life-saving and life-prolonging treatment is withheld due to methodology reasons	Significantly increased probability to suffer serious harm in the placebo group	Not acceptable
	No effective treatment available	No additional harm in comparison with the 'normal treatment'	Acceptable with the consent of patients
Type of disease	Serious health conditions	Remains untreated in the placebo group	Not acceptable
	Minor disease	Remains untreated in the placebo group	Acceptable with the consent of patients
Type of risk	Severe medical and physical risks	Will not be prevented in the placebo group	Not acceptable
	Severe psychological and social risks	Will not be prevented in the placebo group	Not acceptable

- the type of treatment;
- the type of disease; and
- the type of risk.

First, the more severe the burden on the research subject, because of the allocation to a placebo group despite the availability of a standard therapy, the less acceptable the use of a placebo-controlled trial seems to be. The decisive issue here is the additional risk of harm that a patient has to accede to because of the methodological rationale behind conducting a placebo-controlled trial (without going into the discussion on what constitutes harm and who decides). If the additional harm in comparison with the active drug and the standard therapy is significantly elevated, conducting such a trial does not seem to be acceptable. This poses the question of possible absolute standards of the conduct of placebo-controlled trials in the case of existing standard therapies. Emanuel and Miller propose the following approach:

> If effective, life-saving, or at least life-prolonging treatment is available, and if patients assigned to receive placebo would be substantially more likely to suffer serious harm than those assigned to receive the investigational drug, a placebo-controlled trial should be prohibited.[21]

This means, that it is not acceptable if a patient in a placebo group is deprived of a life-saving or life-prolonging treatment or the patient has a significantly increased probability to 'suffer serious harm' compared to other patients merely on the basis of

21. Emanuel and Miller, 'A Middle Ground', p. 917.

methodological validity. These demands can be justified by the general principle of non-maleficence and the principle of proportionality, both in medical research and in standards of liability in medical law (expected benefits should outweigh inherent risks for the participants in the study or patients), which can be found in the Declaration of Helsinki,[22] the Belmont Report,[23] the European Convention on Human Rights and Biomedicine[24] and in national legislation on criminal and civil liability for injury. Indeed, it seems (from a medico-legal perspective at least) fairly trite to state that, in the health context, we should not deprive individuals of the means to save their lives.

The second precondition concerns the *type of disease*. Use of placebo treatment instead of an existing standard treatment, can be acceptable in cases of minor diseases but not for serious conditions. This precondition is connected to the principle that the result of an omission can be equivalent to actively doing damage. If the patient is subjected to serious harm during a clinical trial because of the gravity of her untreated condition, this is ethically unacceptable and legally problematic, especially where a clinician was involved in the inclusion of the patient in the trial. Placebo-controlled trials should be limited to patients with minor diseases, where the patient can suffer only minor harm following a withholding of the adequate treatment. In the words of Emanuel and Miller:

22. Declaration of Helsinki (16), 'Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects', in World Medical Association (WMA): Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects (2013). Available at: www.wma.net/en/30publications/10policies/b3/ (accessed 30 June 2014).
23. Belmont Report (section on 'The Nature and Scope of Risks and Benefits'): The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence [. . .] Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight', in National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, The Belmont Report. U.S. Department of Health, Education, and Welfare, 18 April 1979. Available at: www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4178b_09_02_Belmont%20Report.pdf (accessed 30 June 2014).
24. EU Convention on Human Rights and Biomedicine (Article 16, Protection of persons undergoing research): 'Research on a person may only be undertaken if all the following conditions are met: [. . .] ii the risks which may be incurred by that person are not disproportionate to the potential benefits of the research; [. . .]' in Council of Europe 1997: Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Available at: conventions.coe.int/Treaty/en/Treaties/Html/164.htm (accessed 30 June 2014).

> [. . .] advocates of active controls should agree that for ailments that are not serious, if there is only a minimal chance that patients randomly assigned to receive placebo will suffer harm or even severe discomfort, the use of placebo controls is ethical.[25]

In this context, a further aspect should be considered. In many cases, upon being assigned to a placebo group, the subject's treatment with the conventional treatment which she has received up to that point is stopped and a placebo is given *instead*. In much the same way as, in medico-legal terms, 'active' and 'passive' euthanasia are discussed, the distinction between withdrawing active treatment in favour of a placebo (to the manifest detriment of the patient/subject) and omitting to start a subject on an active treatment in favour of a placebo (to the possible detriment of the patient/subject) needs to be reflected. In the latter case, there is only a problem of evidence subjectively relieving the researchers of blame rather than an objective reduction in potential harm.

Third, *the risk assessment* in placebo-controlled trials should avoid focusing only on medical risks (mortality and prolonged morbidity), at the expense of considering psychological and social risks. Montgomery writes in relation to psychiatric clinical studies, 'where there is risk to life a placebo-controlled study is difficult to undertake'.[26] Given the criteria mentioned above, it is not only 'difficult to undertake' but simply inadmissible. Montgomery continues to argue that even 'very severe or suicidal patients can be included in placebo-controlled studies, when some measures to reduce the risk are undertaken.[27] Therefore, the only kind of risk that seems to be relevant from Montgomery's point of view is the patient's death due to the omission of an adequate treatment. This is at odds with fundamental considerations in medical ethics, where there is a frequent effort to include less extreme but equally important risks into the evaluation of medical intervention. Emanuel and Miller report a very similar observation:

> In arguing for placebo-controlled trials of antidepressants, Temple and Ellenberg suggest that the only relevant harm is depression-induced suicide. Psychological and social harms caused by depression – such as mental anguish, loss of employment, and disruption of relationships – are either not considered or dismissed. Yet psychological and social harms are invoked to justify the value of the research. This is contradictory. In evaluating the risk-benefit ratio, psychological and social harms must be addressed.[28]

It can be argued that there is a frequent tendency to focus on organic problems and neglect connected personal, psychological and social problems. These issues clearly have an equally important influence on the patient's life and her 'pursuit of happiness' and should be included in the evaluation of inherent risks and benefits. Non-medical problems can be produced by the omission of a standard therapy in the course of a placebo-controlled trial and the study is, in this case, the certain cause of the patient's problems.

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25. Emanuel and Miller, 'A Middle Ground', p. 917.
26. Montgomery, 'Placebo-Controlled Trials', p. 267.
27. Montgomery, 'Placebo-Controlled Trials', p. 268.
28. Emanuel and Miller, 'A Middle Ground', p. 915.

Taking the three preconditions together, the result is an approach that permits placebo-controlled trials in cases where it is necessary for methodological reasons but limits the inherent risks for participating patients in experiencing additional harm to a defensible level.

Consent and duty of care issues

A fundamental problem in relation to placebo-controlled trials is that of obtaining sufficient consent to heal the illegality of a detrimental intervention. Such consent can hardly be given effectively if the patient is left in the dark about the exact type and quality of the treatment he/she is about to receive. Further questions arise where the course of a disease progresses unchecked due to a placebo treatment, administered to an unwitting patient. An additional dilemma is encountered in the setting of a 'double-blind' placebo-controlled study,[29] where the researchers themselves are unable to ascertain whether they are providing the research subject with state of the art treatment, a potentially noxious drug or just an ineffective sugar pill. Both cases revolve around knowledge or lack thereof. The research subject needs to be sufficiently and specifically informed in order to give valid, informed consent to the treatment. In order to sustain the placebo-controlled trial, the research subjects must consent to the experimental treatment with the caveat that – if they are apportioned to the control group – they may receive a placebo, though this raises the legitimate question of whether the patient ought to *know* that she is in the placebo group or merely be put in a position to be able to *suspect* so for the purposes of fully informed consent. The inclusion of the patient in the study does not release the 'physician as researcher' from his duty of care and the obligation of non-maleficence towards his patients. At the same time, we acknowledge that the legislatively touted standard of informed consent in many jurisdictions seems closer to wishful thinking than an achievable gold standard.

The physician–researcher has to take responsibility, morally and legally, for the well-being of his/her patient. In the case of placebo-controlled trials – where a conventional therapy is available – he/she willingly participates in an activity where a number of his/her patients are deprived of treatment they would benefit from. The threshold between 'treating physician' and 'researcher' is all too often quickly crossed, and the act of crossing is, more often than not, trivialized. This is exactly why researchers should have well-defined criteria to judge what extent of additional harm is acceptable for participants. The assumption that the relationship is not one of 'doctor–patient' but one of 'researcher–subject' disregards the motivation of the subject in the research. In a situation where an actual medical condition exists in the placebo group, the motivation of the subjects taking part in the study is presumably largely the desire to be cured and to obtain the best possible medical treatment. The risk of ending up in a placebo group is

29. Double-blind placebo-controlled study: A methodological measure in clinical studies to minimize the expectations of participants and physicians/researchers regarding the positive effects of the study drug. It is unknown for the participant and the physician, whether the placebo or the active drug is administered, the study is therefore 'blinded'.

something the participant therefore has to calculate into the general risk potential of the therapy. At the same time, the research participant is entitled to expect that the researchers will, to the best of their ability, prevent harm from occurring. In essence, the mechanism of apportioning patient cohorts to different arms of the study might therefore already constitute additional risk before the activity or inactivity of the administered treatment comes into play.[30]

The ethical problem with the EMA/ICH position

The paragraph from the EMA position paper,[31] which explicitly deals with medical ethics, reads as follows:

> There are a number of conditions that govern and restrict the use of placebo in order to avoid unethical use. First and foremost, the period during which a placebo is administered must not entail any additional risk of irreversible harm to the patient. Also, the patient included in the trial, or his/her legal representative, must receive and understand appropriate information on the trial, and give informed written consent. The patient's right to withdraw at any time, but still receive conventional treatment must be respected. It is acknowledged that un-ethical abuses of placebo in trials of medicinal products may occur in any country, and this potential for abuse should be eliminated. Similar ethical standards should be applied in trials performed in the European Union as well as in foreign countries.[32]

Those who regularly conduct ethical assessments of clinical trials will see that the majority of the criteria that are cited by EMA apply to all clinical trials. Therefore, it is unclear which 'un-ethical abuses of placebo in trials' are referred to because the position paper itself remains largely silent on what such abuses could be. The last sentence is particularly enigmatic and begs the question of why such standards 'should' be similar in foreign and European Union (EU) countries. Is it because of universal human rights, which should be equally protected all over the world? Or is it because of more liberal research regulations in foreign countries, which should also apply in the countries of the EU? The only sentence that mentions

30. Cf. the legal discussion on physician and hospital liability, especially, *Corrigan v. Methodist Hosp.* [1994], 158 F.R.D. 70, 73 (E.D. Pa. 1994). See also S. Fraser, 'Hospital Liability: Drawing a Fine Line with Informed Consent in Today's Evolving Health Care Arena', *Indiana Health Law Review* 1 (2004), pp. 253–278.
31. The EMA still refers in its latest publications to this position paper and the ICH Topic E 10 *Note for Guidance (. . .)* as the decisive documents (Cf. EMA Reflection Paper on the Need for Active Control in Therapeutic Areas where Use of Placebo Is Deemed Ethical and One or more Established Medicines Are Available. London 2011). In a way, in the current reflection paper from 2011, the demands for placebo-controlled trials are even extended, because it is now recommended to add also a placebo arm to studies which would normally carried out without placebo (because established medicines are already available).
32. EMEA/CPMP Position Statement on the Use of Placebo in Clinical Trials with Regard to the Revised Declaration of Helsinki, London, 28 June 2001.

placebo-specific criteria is the second one, which demands that a placebo-controlled trial should not produce 'any additional risk of irreversible harm to the patient'. This phrasing resembles the ICH Topic E 10 *Note for Guidance on Choice of Control Group in Clinical Trials*:

> When a new treatment is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new treatment to placebo. Use of a placebo control may raise problems of ethics, acceptability, and feasibility, however, when an effective treatment is available for the condition under study in a proposed trial. In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control.[33]

The first sentence of this quote is an example of the EMA/ICH position distorting the current ethical standards on the use of placebos. The position is not that it is 'no problem' to use a placebo when there is no known standard therapy but that the use of a placebo is under some circumstances 'acceptable' in studies where no current proven intervention exists (see paragraph (33) of the Declaration of Helsinki). Even the (intensively criticised) note of clarification, which was added to the Declaration in 2002 on placebo-controlled research,[34] remarked that 'extreme care must be taken in making use of a placebo-controlled trial' – so it seems to be rather ambitious to rephrase this position into the message of the first sentence of the quote above that there 'is usually no ethical problem'. The text also contains an outline of the conditions under which placebo-controlled trials are no longer acceptable (i.e. in cases of 'serious harm, such as death or irreversible morbidity in the study population'). The ICH would, for example, therefore tolerate the following study:

> In the case of a severe and harmful disease where a successful standard treatment is known, patients can – for methodological reasons – be included in a placebo-controlled trial, although the responsible study physician expects a high risk of severe, but reversible suffering due to the omission of an adequate treatment for the patients in the study's placebo group.

The patient's suffering could easily be prevented by designing a study that tests the new drug against an active control – the already established standard treatment. From our point of view, this position goes too far in accepting the possibility of severe suffering of the patients. We will demonstrate in the next section that even the ICH document in question contains some indications that the criteria for the conduct of placebo-controlled trials should be construed much more narrowly.

33. ICH Topic E 10: Choice of Control Group in Clinical Trials. (CPMP/ICH/364/96) EMEA 2001, at p. 16.
34. Ehni and Wiesing, 'Die Kontroverse', p. 47.

Consistency of the EMA/ICH position

The ICH Topic E 10 *Choice of Control Group in Clinical Trials* gives the following example regarding the case of a placebo-controlled study design instead of an existing standard therapy:

> For example, a short term placebo-controlled trial of a new antihypertensive agent in patients with mild essential hypertension and no end-organ disease might be considered generally acceptable, while a longer trial, or one that included sicker patients, probably would not be.[35]

Interestingly, this example rather fits in with the first two of the criteria given by Emanuel and Miller than with the ICH's own definition of when the use of placebo is admissible (serious harm, such as death or irreversible morbidity).

Therefore, the EMA/ICH position is inconsistent in itself due to the clinical examples provided which fail to align with the papers' own definitions of the acceptability of placebo-controlled clinical trials. If one takes the EMA/ICH position seriously, even a longer trial involving a more severe form of hypertension would fit perfectly into the definition – if 'death or irreversible morbidity' could be excluded, for example, in the case of patients suffering a stroke. There is a second example in ICH Topic E 10 that sheds light on how much additional suffering is acceptable for the patients in the placebo group. In the case of hypertensive disease, the question was the 'reversibility' of damage caused by the placebo treatment. In the second example, the discussion is broadened to include additional suffering for patients in the placebo group during the trial:

> For example, in an oncology trial, when no active drug is approved, patients in both the placebo or no-treatment group and the test drug group will receive needed palliative treatment, such as analgesics, and best supportive care. Many placebo-controlled trials are conducted as add-on trials, where all patients receive a specified standard therapy or therapy left to the choice of the treating physician or institution.[36]

The reference to 'add-on studies' is misleading in this context. One of the objectives of ICH Topic E 10 is to show that the pure placebo-controlled trial is – measured on the statistical findings concerning safety and efficacy – methodologically superior and more reliable than a study against an active drug. However, an 'add-on study' does not fulfil these methodological criteria of the 'most rigorous scientific position' as outlined above, because it always has an influence on the study findings through the administration of the basic medication which is given to both patient groups. Second, the reference to palliative care obscures the fact that there should be additional measurements taken for the protection of patients in the placebo group. On top of the question of whether there is really no existing standard medication or at least a therapeutic alternative to a placebo,

35. ICH Topic E 10: Choice of Control Group in Clinical Trials. (CPMP/ICH/364/96) EMEA 2001, at p. 16.
36. Emanuel and Miller, 'A Middle Ground'.

some safety measures should be included to provide for the possibility that the new treatment turns out to be beneficial for all patients. Otherwise, the patients in the placebo group may experience unnecessary harm when they are deprived of the new drug and given the placebo treatment instead.

Another significant point is that the use of palliative measures and pain reduction is not necessary according to the definition of permissible placebo-controlled trials given by the ICH. The definition only demands the prevention of death or irreversible morbidity but not the prevention of pain and nausea for patients in the placebo group. This fact illuminates the inadequacy of the description and underlines the inconsistency of the definition with the clinical examples, which start out with a much narrower area with higher patient protection. In contrast to the examples, the clause requiring the prevention of death or irreversible morbidity is only the description of the most extreme case which should be excluded from guidelines for the regulation of placebo-controlled trials. The EMA/ICH position on the conduct of placebo-controlled trials should be reformulated so as to provide a more appropriate level of guidance.

Compliance with the Declaration of Helsinki

A number of stipulations in the EMA/ICH documents seem to quietly turn the Declaration's original position on its head and to present placebo-controlled trials not as a possible exception but as the state of the art in the field of clinical research. We will show that this is incompatible with the wider aims of the Declaration (independent of the Declaration's different versions) as well as with the sections that are explicitly concerned with placebo-controlled trials.

First, there are more general principles such as the Declaration's paragraph 8, which demands that the individual patient's rights and interests are superior in medical research to any considerations of scientific (and methodological) issues.[37] In the case of placebo-controlled trials with an existing standard therapy, this means that methodological necessities *do not justify* serious (or possibly any other) restrictions on the patient's subjective well-being. This stipulation alone already highlights a significant normative departure from the guidance provided by EMA and ICH.

Second, there are considerations concerning the balancing of risks and benefits such as paragraph 16, mentioned above.[38] The scientific achievements that can be realized by conducting a placebo-controlled study design have to be balanced against and outweigh the harm experienced by the participating patients.

Finally, there is paragraph 33, which deals specifically with conducting placebo-controlled clinical trials. The paragraph's first sentence represents the paramount ethical position of the past decades ('The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention, . . . '),[39] whilst

37. ICH Topic E 10: Choice of Control Group in Clinical Trials. (CPMP/ICH/364/96) EMEA 2001, at p. 16.
38. World Medical Association (WMA): Declaration of Helsinki (2013). Available at: www.wma.net/en/30publications/10policies/b3/ (accessed 30 June 2014).
39. WMA, Op. cit.

the following exclusions were inserted due to the placebo-friendly paradigm shift in the Declaration's more recent versions:

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention, is necessary to determine the efficacy or safety of an intervention;
- and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
- Extreme care must be taken to avoid abuse of this option.[40]

Paragraph 33 therefore excludes 'additional risks of serious or irreversible harm' due to scientific and methodological reasons (fully in accordance with the preceding paragraphs) of the Declaration. As a consequence of a placebo-controlled study design, only minor and reversible harm is therefore acceptable – a result comparable to the findings of Emanuel and Miller mentioned above. The differences to the EMA/ICH position are plain. The two decisive definitions of this position concerning placebo-controlled trials are that:

a. 'the period during which a placebo is administered must not entail any *additional risk of irreversible harm* to the patient' (EMA)[41]; and
b. the use of placebo should 'generally' not take place 'in cases where an available treatment is known *to prevent serious harm, such as death or irreversible morbidity* in the study population [. . .]' (ICH, emphasis by the authors).[42]

A comparison of (a) to paragraph 33 of the Declaration of Helsinki shows that the authors of the EMA omit the word 'serious' with the result that not only are circumstances which carry a risk of 'irreversible' damage excluded by their position paper but serious harm (as long as it can be reversed) would in principle be acceptable. As outlined, this phrasing is not that does not facilitate adequate risk reduction in placebo-controlled trials. In the case of (b), the reference to death or irreversible morbidity by the ICH does not match up to the Declaration of Helsinki's stipulation to avoid additional risks of serious or irreversible harm. The EMA/ICH position is clearly not in accordance with the Declaration of Helsinki – even in the weaker, revised version after the year 2002 – and does not

40. WMA, Op. cit.
41. EMA Reflection Paper on the Need for Active Control in Therapeutic Areas Where Use of Placebo Is Deemed Ethical and One or More Established Medicines Are Available. London 2011.
42. ICH Topic E 10: Choice of Control Group in Clinical Trials. (CPMP/ICH/364/96) EMEA 2001.

sufficiently guarantee an acceptable level of risk control for patients who participate in placebo-controlled trials.

Conclusions

The discrepancies described above lead to a number of pressing questions, namely, which document and which position should be binding or more persuasive for the researchers (who plan) and the RECs (which evaluate), clinical studies? A situation emerges where two different sets of criteria for acceptable placebo-controlled studies exist and scientists can pick and mix – which is clearly undesirable. How homogenous, in fact, is the level of additional risk which patients are exposed to during the conduct of placebo-controlled trials? Miller[43] concludes that there is 'a lack of consistent guidance on the use of placebo-controlled trials in the extant regulations and codes of ethics'. It is understandable that bureaucratic institutions such as the EMA or the ICH, primarily responsible for the technical regulation of clinical research, act according to the principles which they consider to be central to the achievement of good science. However, it is a confusion of competencies when institutions that are primarily engaged with the *technical* aspects of the approval and registration of drugs at the same time attempt to resolve fundamental *ethical* and *medico-legal* questions.

The later qualification of the original position of the Declaration of Helsinki may be understandable from the point of view of methodological purity, but the external 'updating' of the Declaration by authors with insufficient understanding of ethical issues can produce serious harm for patients and considerable confusion among the users of ethical guidelines. The wording of the note of clarification in the 2002 version and the further development of the Declaration demonstrate serious deficiencies in the international guidance governing this important and relevant area of clinical research. From our point of view, the problem is not to be found on the conceptual level but rather on the institutional level (i.e. which organization has sufficient competence to decide which level of risk are acceptable for patients included in placebo-controlled trials).

Straddling the divide between providing the best possible care to all patients and furthering the progress of research to provide better possible care to future patients is riddled with acute ethical dilemmas, which can nonetheless be resolved. A clearer, less abstract position by the relevant bodies and a more detailed description of when the use of placebo-controlled trials is permissible will aid the development of a sensible system and assist RECs in evaluating placebo-controlled trials in a predictable fashion. The international scientific community would do well not wait too long before issuing general and comprehensible guidance for this important ethical problem.

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43. Miller, 'Ethics of Placebo-Controlled Trials', p. 264.