



Research ethics needs fine tuning, not rigidity: how to promote evidence in neglected patient populations by rethinking informed consent

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Received 12 February 2015; revised 28 June 2015; accepted 13 July 2015; online publish-ahead-of-print 29 July 2015

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Introduction

Well-conducted biomedical research tells us how best to act in various clinical situations. In order to do so, ethical and legal rules have been developed over time for optimal study conduct, with special attention to the subjects involved in these studies. This includes asking informed consent before including a person in a clinical trial, and protection of fragile and mentally incompetent individuals by restricting and regulating their participation in biomedical research. Apart from the obvious positive effects, these regulations may also lead to unintended restrictions, and as a result not all relevant patient subgroups are sufficiently included in human clinical research. Consequently, important questions on how to optimally treat certain patient groups remain unanswered.

The objective of this ‘current opinion’ article is to explore how therapeutic scientific research and procedures can be better exploited, to advance clinical expertise and to discuss ethical issues that need to be considered in that context. For that purpose, we reflect on the challenges and consequences of patient selection, studies in acute care setting, and comparison of established therapies, in the final part illustrated by discussing some relevant recent clinical trials.

We all appreciate the fact that biomedical research in humans should be guided by high ethical standards, as outlined in the Declaration of Helsinki,¹ among which informed consent of the subject before participation in a trial. Nevertheless, we propose that, in order to obtain optimal scientific and clinical data, certain study types should not require (pre-study) informed consent, while still guaranteeing patients essential (ethical) rights and safety.

Historical context of ethics in clinical trials

Current Good Clinical Practice rules are strict and defensive, and often demand labour-intensive procedures. This was partly a response to unethical human experiments in the past. Since A. Neisser performed syphilis experiments in 1892 without informing participants that they were enrolled in an experiment,² ethical standards have developed, but have also been overstretched on multiple occasions. Excesses demanded adaptation of prevailing rules, culminating in the Nuremberg Doctors’ Trial in 1947. In addition to it being a trial of the horrible medical experimental crimes that had been committed during World War II, it subsequently resulted in the Code of Nuremberg. This Code defined the 10 most important conditions to which future biomedical research with humans should comply, among which that it is only justified after voluntary consent for participation from the study subject.² The World Medical Association formulated norms and values on biomedical research in humans in the Declaration of Helsinki in 1964.¹

The Declaration of Helsinki used to distinguish therapeutic and non-therapeutic scientific research.¹ Research in which the subject may personally benefit from the intervention is considered *therapeutic*, for instance when two approved therapies are compared. If informed consent is deemed appropriate, but a person is unable to communicate, a proxy can give consent, in the interest of the patient. A study is regarded as *non-therapeutic* if no health-related direct benefit for a specific patient is anticipated, for example when physiological processes are evaluated. Participants of non-therapeutic studies should give informed consent. In principle, a

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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proxy never has the right to take decisions for an incompetent patient concerning non-therapeutic research, as this is not in the direct interest of the patient.

Challenges arise

When trying to comply with all rules and guidelines on conducting biomedical research in humans, several challenges may be faced. For instance, obtaining informed consent of the persons involved can be difficult, due to the age or the mental status of the patients or with severely ill patients who are unable to communicate. Parents give consent for treatment of their children and a proxy decides on behalf of a patient with intellectual disabilities. Moreover, if patients are in need of acute clinical interventions, it may not be feasible to discuss the type of treatments and a randomization procedure. This may lead to underrepresentation of such patient groups in clinical trials. Since these patients may form a substantial part of the patient population in daily practice and are particularly prone to a bad outcome, there may be a serious gap between knowledge obtained in clinical trial populations and knowledge needed for the optimal acute treatment in daily clinical practice.

Trial populations vs. the real world: neglected patient groups

Not all patients who might later be eligible to receive a given treatment are included in studies needed for approval of that treatment. Exclusion criteria in clinical trials serve to yield a homogeneous study population; a first step towards obtaining robust results and registration by regulators (European Medicines Authority, Food and Drug Administration). Patients with multimorbidity and/or polypharmacy are often excluded from clinical trials. Even if for instance elderly patients are included, they may not adequately reflect the target population; trial participants often are in better condition than most people of that age group who visit the clinic in daily practice. Moreover, patients participating in clinical trials may have better clinical outcome than those not enrolled in trials, as a result of better care provided in trial settings. This strongly limits the generalizability of the study results.^{3,4} Fortunately, some research teams acknowledged this data hiatus and have conducted studies to examine treatment of these previously neglected patient groups. Important insights have been obtained in the Hypertension in the Very Elderly Trial⁵ and the 'Pravastatin in elderly individuals at risk of vascular disease' trial.⁶

Patient registries with follow-up data can form another valuable source of real-world information without including patients in clinical trials. Registries may suffer from some inclusion confounding bias. Even if certain clinicians or clinical centres have non-evidence-based preferences for one therapy over another, retrospective comparisons of therapeutic approaches are possible and may be hypothesis generating, as long as treatment decisions and outcomes are properly documented. Registry-based comparative studies are certainly valuable, but can never substitute randomized trials and cannot (timely) provide all information that is currently required in clinical practice.

We propose to place the often rigid division between scientific research and patient care in perspective. Especially in academic hospitals, patient care should be accompanied by critical review and analysis of medical practice and its outcomes. In that context, it should be practically feasible and considered acceptable to do head-to-head comparisons of two *approved* treatments without prior patient consent in case of clinical equipoise, and with similar guideline recommendations. Note that patients should still give consent for the overall treatment strategy. Obviously, the research process may not pose patients at extra risk of harm. This approach can solve the current situation that certain patient groups are neglected in clinical research.

More and easier to conduct prospective randomized trials may be the answer

In addition to registry-based evaluation of therapies, we are in favour of conducting prospective randomized trials. Different randomization protocols can be considered for which informed consent may not always be necessary. Treatment options may be randomized according to time or to medical centre location. In certain conditions, individual patients may even be randomized to different treatment options consecutively, which means that they can serve as their own control. There is only one crucial condition: full transparency for patients and other citizens about a combined treatment-research policy. To this extent, academic health centres may emphasize more clearly that research is part of the care process, including that an individual patient may participate in a research protocol and not be informed until later, provided of course no extra risk of harm is imposed.

In order to keep data storage, randomization, and follow-up affordable and feasible, online (national) systematic registries may play an important role in the future. Scandinavia is taking the lead with, for example, the Thrombus Aspiration in ST-Elevation myocardial infarction (STEMI) in Scandinavia (TASTE) trial. This was a multicentre, prospective, randomized, controlled trial that benefited from the Swedish Coronary Angiography and Angioplasty Registry to blindly evaluate clinical endpoints in STEMI patients randomized to either conventional percutaneous coronary intervention (PCI) or to thrombus aspiration followed by PCI.⁷ Technological developments should be exploited to facilitate better and safe use of anonymized patient data.

For most investigators, the process of randomization is synonymous to the obligation to ask patients for informed consent. However, informed consent may not always be needed in case of a therapeutic study, in which benefit is anticipated for every individual patient. Patients may for example be randomized to one of several already *approved* therapies, especially when they are of similar nature and have similar guideline recommendations. Of course, patients will always be carefully evaluated beforehand to ensure that they are suitable for either intervention. Without the intended study, it remains unknown which treatment is objectively the best and treatment choices are based on subjective judgement. Seen from a patient's perspective, he/she will receive either one of two treatment options somewhat randomly—depending on the

doctor's preferences. In order to get rid of this uncontrollable (doctor's) bias, it would be better to formally randomize this patient. No informed consent is necessary, since no investigation-related discomfort or risk is expected for the patient. But once again: full transparency is a crucial prerequisite.

Moreover, certain (therapeutic) research questions concern urgent situations, in which patients or a proxy is unable to take a well-considered decision. After approval of an ethical review committee, this type of research in which randomization takes place before consent has been obtained, is allowed in urgent care settings. Informed consent to use the clinical data for research purposes can be obtained when the patient is stabilized. Neonatologists conduct studies in this context, for instance to evaluate ventilation conditions in (premature) newborns. Obviously, an obligatory condition for delayed consent is that the research can only be conducted in urgent settings (trauma, neonatal unit, myocardial infarction, and stroke).

Thus, randomization does not automatically imply the obligation to obtain informed consent. Rather what is the alternative for patients who would refuse to give consent? Will their treatment be altered? No. Will they receive alternative treatment? No. The only, clearly non-desirable effect is that data of non-included patients will not be used, and that the lessons thereof will not become available to other clinicians and the patients themselves in the future.

In the last part of this article, we will try to illustrate the above-mentioned points by discussing (recent) clinical trials

Prospectively randomized procedures without prior informed consent: unethical or ground-breaking? A heated debate

Already in the 1990s, the GISSI trials evaluating the effect of intravenous thrombolytic therapy in acute myocardial infarction did not obtain informed consent before randomization. Based on the GISSI and other trials, Tognoni argued that 'the view that informed consent is the most important component of the "ethical" aspects of experimentation is highly misleading'.⁸ The GISSI trials gave more weight to communication than to consent, by informing the patient about his/her inclusion in the trial only once the physician considered it not to be emotionally damaging. The approach focussed on protection of the 'right of the patient not to be exposed to an emotionally burdensome request for informed consent'. The design was approved after considerable ethical review.⁸

Another, more recent illustrative example of a prospective randomized trial was the 'how effective are antithrombotic therapies in primary percutaneous coronary intervention' (HEAT-PPCI) trial. It was unknown which of two approved and commonly used (with similar guideline recommendations) types of adjunctive antithrombotic therapy was best for patients presenting with acute STEMI with an indication to undergo PPCI. Thus, HEAT-PPCI randomized consecutive adults scheduled for angiography in the context of PPCI.⁹ A delayed consent strategy was followed: patients were randomly allocated to periprocedural bivalirudin or unfractionated heparin before undergoing angiography and no attempt was made in this emergency setting to discuss the trial or obtain consent.

Surviving patients or their proxies were approached for formal consent to proceed as trial participants, and to use their data and participate in the 28-day follow-up. This procedure received full ethical approval because two crucial conditions were met: equipoise therapies and acute setting. Furthermore, the national Confidentiality Advisory Group granted approval to include clinical data and outcome measures of patients who died after randomization but before consent could be obtained.

This pragmatic therapeutic study design, in which approved medical interventions for this specific indication were applied, was chosen to specifically address a common limitation of randomized clinical trials, namely to recruit only part of the potential, eligible population and in particular those with a more favourable prognosis. This precludes medical progress for those in greatest need. To improve the generalizability of the study results, they aimed to include every eligible patient entering the catheterization lab for PPCI. This way, also very sick, elderly, or frail patients, or those with low socioeconomic status or from ethnic minorities were included; individuals who are rarely approached for participation in clinical studies. Only four of the 1917 trial participants refused or withdrew their delayed consent, indicating that patients generally agreed with the procedure.⁹ Similarly, most parents give consent for neonatal research after their infants have been enrolled in an acute setting in the delivery room.¹⁰

Despite in our opinion praiseworthy aim and study design, and despite the approval of three separate ethical review committees, HEAT-PPCI raised a heated debate when it was presented at the American College of Cardiology 2014 Scientific Sessions. Received with a hostile attitude by some, and considered positively groundbreaking by others, HEAT-PPCI has sparked an important discussion. In an editorial comment in *The Lancet*,¹¹ David Shaw wrote that the chosen delayed consent strategy may even have been too conservative. Shaw argues 'Consent might not be necessary in some pragmatic comparative effectiveness trials. Despite the tradition of obtaining informed consent for almost all research, some debate surrounds whether patient consent should be sought when both treatments are licensed, consensus is present regarding equipoise, and randomization does not pose any added risk. Outcome data can be used without consent in normal clinical care and audit, and randomization alone does not make consent necessary'.¹¹

Practical solutions: transparency and 'de-juridification'

Rigid application of guidelines on obtaining informed consent may prove counterproductive by limiting the number and representativeness of included patients in a study. Transparency can solve some of the dilemma's surrounding randomization and informed consent. Hospitals have no reason to hide that they perform this kind of studies. On the contrary, this research approach should be appreciated in the context of the obligation of (academic) medical centres not only to provide optimal care but also to monitor quality of care and to advance clinical expertise. As stated in Article 6 of the Declaration of Helsinki: 'Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality'.¹ Special attention and

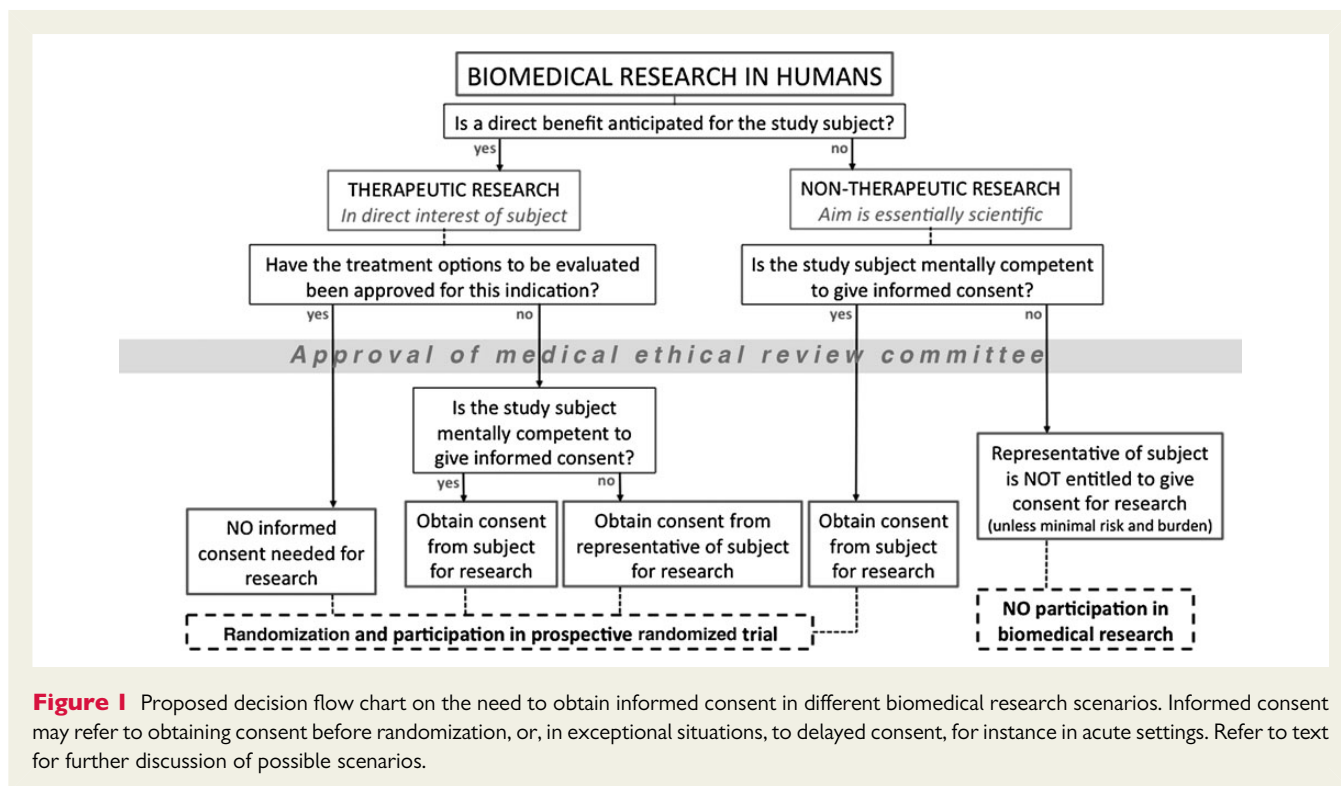


Figure 1 Proposed decision flow chart on the need to obtain informed consent in different biomedical research scenarios. Informed consent may refer to obtaining consent before randomization, or, in exceptional situations, to delayed consent, for instance in acute settings. Refer to text for further discussion of possible scenarios.

explanation about the options should be given to fragile patient groups. Choosing not to ‘bother’ elderly patients with procedures sometimes deemed complicated, maintains the situation in which it is not known how to best treat these patients.

Hence, we advocate a ‘de-juridification’ of the information process between a clinician/researcher and a patient. A clinician should reasonably inform patients. At the same time, a patient should accept that a doctor can propose treatment strategies to his/her best judgement, as long as, to the best of our knowledge, no harm is done to the patient, or the healing process is not delayed. If the treatment to be tested concerns approved similar interventions, it should NOT be necessary to ask patients for consent for the research aspect (see Figure 1). This is a legitimate means to gather clinical experience and insights, and transparency about this type of research contributes to its legitimation. If treatment options have not been approved, informed consent of the patient or a proxy is always needed.

Patients should be aware that they themselves benefit from such learning processes. It is crucial in a healthy society that patients trust their doctors, implying that patients should have some confidence that their doctors are to be trusted. A important role is also played by health organizations and medical institutes, in that they are responsible for creating circumstances that ensure ethical behaviour.

In non-therapeutic study settings, if the study subject does not directly benefit from the intervention, obtaining informed consent is obligatory (see Figure 1). At a practical level, comprehensive patient consent forms can greatly facilitate these processes. These important documents should be readable and contain only a few (1 or 2) pages, rather than a >20 pages long version resembling legal documents that merely deal with shirking liabilities.

Conclusion

We strongly believe that under certain conditions prospective randomized trials can be conducted without asking consent. Of course, adequate trial size and conduct are paramount to obtaining high-quality information. This will facilitate filling gaps in the evidence on treatment of commonly neglected patient groups, by better representing the daily practice population that will receive the therapy. Simplicity and transparency will likely increase the willingness of patients to participate in studies.

We should learn from experience and benefit from clinical data if they were obtained in the general process of providing care. We therefore propose to use a simple paradigm: unless it is clearly unfeasible to do so, when in doubt about the best treatment: randomize with a proper procedure that is as simple as possible and in line with high medical ethical standards!

Conflict of interest: none declared.

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