

COMMENTARY

Care and research concepts should be revised to practice outcome-based medical care

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Accepted 23 May 2019; Published online 14 June 2019

Abstract

Objectives: A central question of medical care ethics is what is “good medical practice?” We will defend the argument that medical ethics must include care research not only to find out what “good” practice will turn out to be in the future once results are available but also to guide practice in the meantime, when no one knows what to do, optimizing patient outcomes in real time.

Study Design and Setting: This work is a summary of our reflections on the barriers to progress we have encountered after many years of implementing small randomized controlled trials in our clinical field, but which are certainly present in other fields as well.

Results: We review nine conceptions regarding care and research that need to be revised if we are to practice outcome-based medical care.

Conclusions: These revisions lead to a reconstruction of the care-research separation, where care research is reintegrated into care using trials specifically designed to offer optimal care in spite of uncertainty, in the best medical interest of participating patients. © 2019 Elsevier Inc. All rights reserved.

Keywords: Care trials; Randomized controlled trials; Learning health care system; Research-care dichotomy; Research ethics; Comparative effectiveness

1. Introduction

Whether commonly used medical tests and interventions actually deliver the good outcomes they promise should be a central concern of clinical medicine. Yet, such questions and their answers have been relegated to clinical research, a separate domain from practice since the Belmont report [1]. Research is constrained by regulation implemented to protect research subjects [2]. In addition,

randomized trials that appraise the merits of medical interventions remain unpopular, even when they address interventions that have never been validated as beneficial [3]. They are often considered incompatible with individualized care. The end result is that trials, considered “unfeasible,” are never conducted, while unverifiable care using the same interventions that should be trialed are practiced on a large scale [4].

Most clinical trials are conceived as scientific tools that can provide future answers to research questions. Care research should rather be conceived as an essential component of medical practice [5], serving the best medical interest of current patients by providing norms of medical conduct when the care of current patients involves serious uncertainty [6]. Consequently, care research should be governed by care ethics. This is a radical departure from the received view. In the present article, we propose to re-examine nine concepts (Figs. 1 and 2) that need to be revised if we want to practice medical care that patients can trust will improve their outcomes, immediately and in the future.

Conflict of interest: The authors declare no conflict of interest.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclaimer: All authors declare that they have no significant financial, professional, or personal interests that might have influenced the performance or presentation of the work described in this article.

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What is new?

Key findings

- To practice outcome-based care, several notions regarding research and care must be revised.
- The research care demarcation cuts at the wrong divide; the appropriate distinction is validated vs. nonvalidated care.

What this adds to what was known?

- RCTs can be designed as best care, where trial participation is in the patient’s best interest.
- Scientific devices such as randomization and blinding can serve ethical functions and protect patients.

What is the implication and what should change now?

- Care and care research should be seamlessly integrated in a learning health system.

1.1. Clinical research is about producing generalizable knowledge

Clinical research aims at producing generalizable knowledge that may inform care for future patients. By contrast, practice aims at benefitting current patients, using interventions that have a reasonable chance of success [1].

Clinical research is too often conceived as an activity concerned with gaining knowledge that may benefit other patients in the future. The emphasis on the future and on knowledge misses the immediate clinical problem: How should patients be cared for in practice when right now

no one really knows what to do? It is not because the “knowledge” is not yet available that any well-intended practice is permissible in the meantime, such as the Belmont definition of practice seems to imply. It is often said that clinical trials should be designed such that their results will impact practice. But why wait for trial results when in truth the uncertainty is serious enough to modify practices immediately? Care trials should be conceived as the prudent way to control the risks of uncertain care actions for the protection of current patients [6]. Whether the trial will come to a scientific verdict (generalizable knowledge) at the end can never be assured up front, but trials can be designed to assure patients they are being offered the best possible chance of a good outcome in the meantime.

Proposed revision: Care research is about guiding uncertain practices in the interests of current patients.

1.2. Research needs to be regulated, whereas practice does not

Research investigates unconfirmed hypotheses about treatments and places subjects at risk. Therefore, it is appropriate to regulate research. By contrast, medical practice rests on interventions of proven benefit and needs no regulations comparable to those governing research [2].

Medical practice is far from being able to “rest on interventions of proven benefit.” Medical practice must be regulated by separating validated from unvalidated interventions. We must first correctly identify the former as “normal” or “validated care,” which can be prescribed (because better outcomes have already been shown), whereas the latter should be regulated (as research currently is regulated; Fig. 2). Unvalidated care should not be practiced in the same way as validated care because benefits

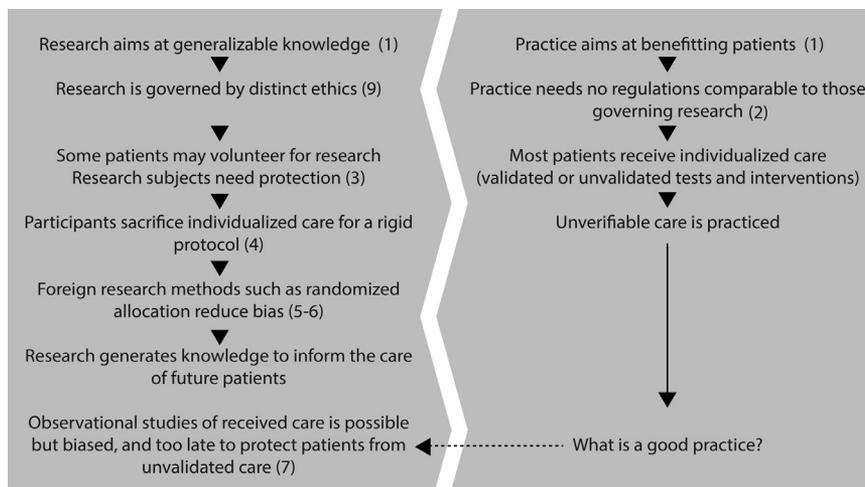


Fig. 1. Care research separated from care. Numbers in parentheses refer to the misconceptions detailed in the text.

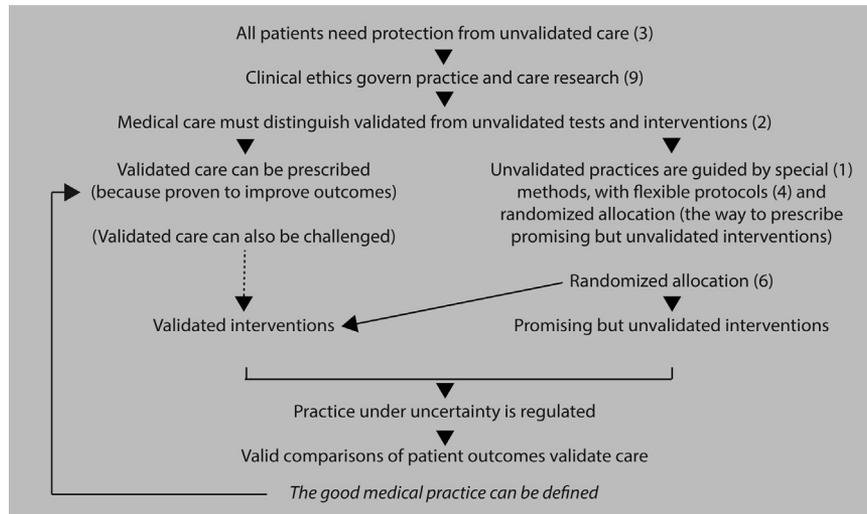


Fig. 2. Care research integrated to care. Numbers in parentheses refer to the revisions detailed in the text.

have yet to be shown. Medical care ethics should prescribe what practical norms should regulate experimental or unvalidated care (care combined with research). This is precisely where both the prevailing view and the research care demarcation detailed in the Belmont report cut at the wrong divide by not identifying yet-to-be validated tests and interventions as research. Currently, enthusiastic expectation of benefit from some unproven test or intervention is admitted as care, while the verification that these actions are actually beneficial belong to the domain of research. The end result is an involuntary encouragement to use tests and interventions that have not been validated as beneficial as care, whereas the trials necessary to verify that they actually do good or harm are obstructed to “protect subjects.” This is misconceived because it is not the research methodology, but the uncontrolled use of experimental tests and interventions themselves that can harm patients.

Proposed revision: Unvalidated tests and interventions must be separated from those which have been validated. Proper care in this context calls for declared care research.

1.3. The patient needs protection when volunteering as a research subject

As things stand, patients need protection when they volunteer for research, but not when the same tests and interventions are provided as care. However, patients do not volunteer to be affected with conditions for which no one really knows what to do (there is no known cure, a controversy regarding treatment options exists, or a promising but yet to be validated test or treatment is available). All patients are vulnerable, they all need care, and they all need protection. Unfortunately, the practical and regulatory obstacles to research, combined with the current research-care separation, encourages patients to receive

and clinicians to practice uncontrolled, unvalidated interventions within care, leaving most patients unprotected because they are not labeled “research subjects.”

Proposed revision: All patients need protection from unvalidated care, which should be practiced within declared care research.

1.4. Research participants sacrifice individualized care for a research protocol

Research participants sacrifice individualized care for the sake of a protocol, which may include procedures that carry risks to participants that are not justified by medical benefits to them [7].

Patients trust their doctor to be able to prescribe the best course of action, given their unique personal histories and preferences. However, in certain circumstances, care choice outside of a research protocol is human experimentation without methods.

Individualized care decisions should concern interventions previously proven to improve outcomes (validated care). Unvalidated care can also be proposed, but within care research, because proposing unvalidated tests and interventions outside research submits patients to risks that are not yet justified by proven medical benefits.

Rigid research protocols are the hallmark of explanatory trials, designed to show if therapy can work in optimal circumstances. By contrast, care research calls for pragmatic trials [8]. If care trials can eventually show whether treatments work in everyday practice, they are primarily designed to guide current practice in the best medical interest of participants [6]. The protocol should be flexible, adaptable to individuals, without extra tests or risks that cannot be justified by medical benefits to them [6].

Proposed revision: Individualized care can be practiced within flexible care research protocols specifically designed for the participants' medical benefit.

1.5. Research uses methods foreign to medical care

Clinical research uses scientific methods such as randomization, masked treatment assignment, and placebo controls that are foreign to medical care [7].

Antiseptic measures before Semmelweis, X-rays before Roentgen, and anesthesia before Morton were at the time methods "foreign to medical care." Some trial methods, until now considered "foreign to medical care", were initially introduced to ensure the internal validity of clinical studies. In care research, trial methods serve important purposes to prevent doctors from jumping to conclusions and protect patients from unproven, potentially erroneous inferences. They are modern clinical devices that can minimize errors and risks in the immediate care of patients. The role randomized allocation of treatment options may play in protecting patients in the presence of serious uncertainty will be elaborated below (Proposed revision 6, *vide infra*). The results of new tests may be masked in order not to bias clinical decisions and actions before they are proven reliable and worthy of such a role. The use of placebo is a powerful means to protect patients from promising (but yet to be shown as harmful) interventions.

Proposed revision: Medical care must learn to use trial methods to guide medical care under uncertainty and protect patients from yet to be validated tests and interventions.

1.6. Randomization is used to reduce bias in comparing treatment outcomes

Randomization is designed to balance groups for valid comparisons at the end of trials.

Randomization is too often conceived as a scientific device serving to make valid comparisons between groups of patients at the end of a trial. The use of randomization is then acceptable on condition that there is genuine uncertainty or "equipose" regarding which option is best. This view misses the protective role randomized allocation of treatment options can play immediately in the care of each patient by controlling the use of unvalidated interventions. In practice, one option is hypothesized superior, but it has not yet been proven beneficial and may turn out to be harmful.

Randomized allocation of treatment options is a "hemiprescription," a way to balance risks and regulate actions when clinical judgment suggests that an unvalidated intervention may be indicated, but it is not yet known that it is indicated. Randomization is perceived as replacing the careful appraisal of unique medical histories with the flipping of a coin. Again, this is mistaken: The clinician must still find out what they believe is best for a particular individual. If the doctor believes it is standard care, they can go ahead and prescribe standard care. But when the doctor believes

that what could be best is the experimental test or treatment, they can only prescribe the trial because the trial is a reminder that the action has not yet been proven beneficial in practice. Thus, the proper clinical choices are not validated vs. unvalidated care; they are validated care vs. care research. If a validated intervention can be prescribed, a promising unvalidated intervention can tentatively be offered as a 50% chance of receiving it, and a 50% chance of being allocated the previously validated intervention.

This is how each patient is protected from prematurely opting for a test or intervention that may lead to worse outcomes than standard care. The intervention will be opened to prescription once it has been proven to lead to better outcomes or alternatively abandoned when shown to be harmful. In the meantime, all patients that are candidates for the unvalidated action will have been given a 50% chance of escaping unnecessary morbidity.

Proposed revision: Randomized allocation of carefully selected treatment options is the prudent way to prescribe an intervention before it has been validated as beneficial.

1.7. Randomized trials can be replaced with observational studies of treatments performed within care

Trials are obstructed by bureaucracy and scarce funding, and randomized allocation of treatment options is poorly accepted in the community. A more feasible alternative is to let patients and physicians remain in the context of care, choosing treatment options according to preferences. Databases and registries will collect outcomes for later analyses that will be adjusted for various decisions, thus replacing trials that are too difficult to conduct.

Patients cannot be exposed to unvalidated treatments akin to how populations are exposed to environmental toxins or infectious agents. If we are looking for ethical guidance in controlling medical practice under uncertainty, the solution cannot be to do just about anything, to intervene as if we knew, and then, without admitting it to current patients, to study outcomes afterward in the hope of benefitting future patients. It is then too late to protect patients from useless or harmful interventions already performed. This is how overdiagnosis and overtreatment can affect patients on a large scale [9]. Care trial methods appropriately differ from standard care because that is precisely how they protect patients from unvalidated practices. Medical care ethics must reserve room and provide guidance within care for practicing unvalidated interventions within trials designed to regulate care in the presence of pervasive uncertainty.

Proposed revision: Observational studies are not an ethical alternative to care trials because only the latter have been designed to practice under uncertainty in the best interest of patients.

1.8. Care research necessitates specific funding and personnel

Confronted with serious uncertainty, we clinicians are enabled to act as if we knew what to do, even when we do not; the budget for doing so is virtually unlimited, in many countries. Alternatively, clinicians can become “investigators” and devote time and resources to compete with one another, writing grant applications for financial support from research institutions, with infrequent success. However, regulating our own ongoing unvalidated practices should not be optional and conditional on winning grants and funding streams. Thus, the design, conduct, and review of care trials should not be conditioned on such competitions. Care trials should be facilitated to make them accessible to patients and care professionals [3].

Should care trials require extra or special “research personnel”? Verifying the outcomes of medical care, standard, or novel should be an integral part of a good medical practice. Most countries spend sufficient funds on health care to reserve a small proportion to support the care trials that can verify the clinical value of unvalidated tests and interventions as they are practiced. Care research should be reintroduced within care where it belongs.

Proposed revision: Care research should be conceived as an integral part of the good medical practice. Accordingly, funding for care research should automatically come with funding for care.

1.9. Research and care are governed by distinct ethical norms

Clinical research should be governed by ethical norms distinctive from those that apply to clinical medicine [10]. “What is a good practice” remains a central question of medical ethics. Medical ethics must not only prescribe ways to determine what a good practice could be in the future but prescribe what a good medical practice is in the meantime. The historical mistake was to attempt to export this question to a separate domain with separate ethics: research. Medical ethics must include norms of conduct when practicing under uncertainty. Here is a sketch of how this could be realized.

All medical interventions are intrusions into the lives of vulnerable individuals. Such intrusions can only be justified by showing interventions lead to better patient outcomes. Thus, patients need outcome-based definitions of what can be prescribed: they need validated care. Unvalidated care, then, is practicing outside that boundary. Medical ethics must provide a prudent way to validate medical tests and interventions and stop harmful practices as soon as possible. Thus, unvalidated care must be regulated and practiced in a special context:

within declared care research. Yet care research must be integrated to care because clinical medicine must provide room for practicing under uncertainty, otherwise clinicians are constrained to always act as if they knew what to do, even when they do not. If validating activities is relegated to research disconnected from care, care is deprived of the means to determine what constitutes good medical care. Care research, integrated into care, should be governed by the same overarching ethical norm of care: to always act in the best medical interest of the patient. This ethical norm needs to be connected, not just in theory, but in actuality, to patient outcomes. This is impossible when care research is separated from care. And the same ethical norm guides the design of trials integrated to care.

Proposed revision: Unvalidated tests and interventions should be governed by norms distinct from those that apply to validated care. Care and care research should be conjugated to practice verifiable care, under the guidance of the overarching principle of clinical care ethics: to always act in the best medical interest of the current patient.

2. Practical implications

The current research regulation may not always be in the interest of patients [11]. It is unclear how much of the current research regulation should change to promote outcome-based medical care and research. Some authors have elaborated a framework justifying the relaxation of some research ethics requirements to develop a “learning health care system” [12]. Multiplying roles and obligations may not be necessary. It has in the past been the source of much confusion. Perhaps, a profound reorganization of institutions and regulations is in order, but this matter needs careful attention and much more work. In practice, we believe progress is possible now, within the current system. The methodology of trials integrated to care can provide verifiable care in the best medical interest of current patients [6].

The nine revisions we have mentioned may provide a clinical framework where unvalidated tests and interventions can be practiced, not as standard care, but within care research, now understood to be an integral part of “good medical care” that should include trials designed to verify the outcome of medical interventions as they are practiced in real time.

CRedit authorship contribution statement

Jean Raymond: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Tim E. Darsaut:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **David Roy:** Conceptualization, Methodology.

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