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Pragmatic trials can be designed as optimal medical care: principles and methods of care trials

Jean Raymond[a,*], Tim E. Darsaut[b], Douglas G. Altman[c]

[a]*Department of Radiology, Centre hospitalier de l'Université de Montréal (CHUM), Notre-Dame Hospital, 1560 Sherbrooke East, Pavilion Simard, Suite Z12909, Montreal, Quebec, Canada H2L 4M1*

[b]*Division of Neurosurgery, Department of Surgery, Mackenzie Health Sciences Centre, University of Alberta Hospital, 8440 112th Street, Edmonton, Alberta, Canada T6G 2B7*

[c]*Centre for Statistics in Medicine, University of Oxford, Botnar Research Centre, Windmill Road, Oxford, UK OX3 7LD*

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Abstract

Objectives: The way clinical research and care are currently separated encourages the practice of unverifiable medicine. Some pragmatic trials can be designed (1) to guide proper medical conduct in the presence of uncertainty and (2) to govern the distinction between unvalidated and validated care.

Methods: Care trials are simple randomized trials integrated into a practice they regulate in the interest of present patients. The fundamental principle guiding the design of a care trial is the protection of the patient being offered medical care that has not yet been validated. Selection criteria are inclusive, to assist most current patients confronted with the problem. The trial entails no extra tests or risks beyond what is proven beneficial. Endpoints are pre-defined, simple, valuable and resistant to bias. Follow-up visits and tests are routine. Data is collected in simple case-report forms.

Results: Care trials protect present patients from both unverifiable medicine and research performed for extraneous interests. They provide prudent care when evidence is lacking. They should not be obstructed by the need for separate funding, or by bureaucracy.

Conclusion: Care trials can identify which medical alternative should be standard therapy. In the meantime, they provide optimal care in the presence of uncertainty. © 2014 Elsevier Inc. All rights reserved.

Keywords: Clinical trials; Methodology; Research ethics; Clinical practice; Pragmatic trials; Evidence-based medicine

1. Introduction

The most urgent problem of modern medicine is how can patients be treated in a transparent, prudent, and verifiable manner? This question applies to any intervention, whether it is a screening test [1], a change in diagnostic criteria [2], an imaging study [3], preventive care [4], the use of new devices [5], surgical innovations [6], or even prognostic studies if they impact on decision making [7]. What these interventions have in common is an action, an intrusion into the lives of vulnerable individuals. Such intrusions must be justified if they are to be prescribed with authority by trustworthy physicians. The justification for an action carried out on a patient must be the reliable demonstration that, in general, it leads to better outcomes. But how can a medical action be justified before it has been shown to be beneficial? This article proposes care trials, pragmatic trials used as patient care, as the best possible solution to this problem.

Three great barriers must be addressed. First, the current research care dichotomy must be revised. A prevailing view conceives clinical research as an enterprise dedicated to gain knowledge for the benefit of future patients. This view misses the normative role research methods can play immediately, in guiding medical actions and simultaneously providing the best possible care to patients given the uncertainty. When current care includes interventions that have yet to be proven beneficial, proper research methods must be brought into the sphere of care. Patients need a distinction between validated care (care confirmed to be beneficial by rigorous research) and clinical care research (care in the process of being evaluated). The fundamental ethical principle underlying the practice we propose is that physicians

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* Corresponding author. Tel.: +1 514 890-8000 ext. 27235; fax: +1 514 412-7621.

E-mail address: jean.raymond@umontreal.ca (J. Raymond).

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What is new?

- The current research/care demarcation should be revised.
- Optimal medical care continuously needs evaluation and revision.
- Some trials can be designed to (1) regulate unvalidated actions within medical care and (2) demarcate validated from unvalidated care
- Verifiable medicine can be practiced when care and care research are conjugated.

should either (1) provide validated care and refrain from using tests or treatments that have never been validated because they may be harmful or (2) offer promising interventions only within declared research, designed in the interests of those same patients needing care.

Care trials may play a dual role in this program: they are the test that an intervention must pass to qualify as validated care; in the meantime, care trials are the rational and ethical means to care for patients despite the shortcomings of our knowledge regarding what to do. In this context, the trial must be designed for the interests of the present patient in such a fashion as to address a number of ethical concerns, such as the notion that the patient is being used for the benefit of science [8], the therapeutic obligation (the notion that clinicians should offer the treatment they prefer) [9], and the therapeutic misconception (the notion that patients falsely believe they are being cared for when they are research subjects) [10]. With a proper trial design, these concerns can be addressed.

A second great barrier is practical: the financial, bureaucratic, and organizational obstacles to trials which view care, no matter how poorly justified, as a necessity, whereas research is a luxury [4]. It may be unrealistic to expect that all currently practiced unvalidated interventions will be trialed. However, if proper trials can be conducted to evaluate and limit unverified care, these obstacles should be removed.

The third and perhaps greatest barrier is cultural. Outside research, physicians and patients are led to believe that a single best treatment can be found in each particular case, even in the absence of evidence [4]. Uncontrolled interventions are used on a large scale, perpetuating a practice based on dogma, belief, custom, or fashion. This barrier can perhaps be addressed by reconstructing the ethical role that trial methods play in guiding conduct, by exposing how the design makes the trial optimal care. This cultural obstacle may slowly abate as care trials become customary. To make them realistic and accessible, their review and implementation must be simple and timely. If they are to be prioritized by patients, physicians, and institutions as optimal care, they must satisfy some criteria. To help research ethics committees identify the protocols that qualify as care trials, a checklist is provided along the CONSORT guidelines (Table 1) [11,12]. Trial characteristics can also be displayed in a graphic form inspired from the pragmatic-explanatory continuum indicator summary [13], to readily identify trials that entail extra tests, risks, or costs (Fig. 1). Perhaps unsurprisingly, the end result resembles a pragmatic trial [13–16]. This means there is no conflict between what is best for the patient and what will be the best way to judge the value of medical interventions. All pragmatic trials are not care trials, however. While pragmatic trials are designed to gain knowledge to inform decisions, care trials primarily guide clinical actions although knowledge remains lacking. The label remains important to emphasize the protection of present patients in need of care, which necessitates (1) methods that may affect usual care and (2) rules that ensure that the trial will not be devalued in favor of other interests (such as collecting interesting scientific observations). If the trial meets these criteria, competition for research funding, waiting for extra personnel or for contracts between institutions can only harm patients. The ultimate goal is to practice a verifiable medicine that patients can trust.

2. Study design and setting

2.1. What are care trials for?

Care trials have a dual role. First, they offer optimal care in the presence of uncertainty (to protect *each* present patient). Patients and physicians are frequently confronted with an unresolved clinical dilemma. Clinical judgment may suggest that a test or treatment, standard or new, is preferred, but the belief that the intervention is beneficial remains an untested hypothesis; there is nearly always an alternative that has previously been validated. If not, doing nothing may be a prudent option. The primary purpose of care trials is to protect patients from unverifiable medicine. Unvalidated care cannot be prescribed as standard care. Somehow the unknown, the uncertain, and the potential harm that may result to the patient must be integrated with the medical act the doctor is proposing. This is how the trial protects present patients: it fosters a practice that promises a desirable end and it simultaneously protects the same patients from false promises. How is that possible? By using randomized allocation of treatments. In the context of uncertainty, science and ethics demand the same truth-seeking, life-saving measures, and trial methods become rules of proper medical conduct to prevent error and morbidity.

Second, care trials test yet-to-be validated care (to protect *all* patients). They provide prudent boundaries for the use of care that has not yet been proven beneficial. The two roles of a care trial are logically articulated: Before an intervention is validated, it cannot be offered as standard care but only as an investigational option—openly admitting that this is care research. The unvalidated practice is restricted to use within the trial. When a new intervention

Table 1. Key design features of a care trial

Section	Item	Description
Title	1	Is the trial identified as a care trial?
Background and Objectives	2	Should emphasize the clinical dilemma justifying the use of a care trial. Is the trial to provide optimal care in the context of uncertainty? In general care trials should evaluate the clinical value of a yet-to-be-validated medical intervention.
Methods	3	Trial Design: Is randomization part of the design?
	4	Patients: Are all or most patients in need of care, for whom proposed treatments are appropriate, eligible to participate? Exclusions should be justified.
	5	Interventions: Are proposed interventions appropriate to the care of patients? No restriction required by protocol should have preponderance over clinical care. Clinicians can always escape protocol specifications for the safety of patients.
	6	Outcomes: Are outcomes fully defined? There should be no extra test or visit beyond what is necessary for the care of the patient.
	7	Number of patients: The number of patients required to test the primary hypothesis, proposed interim analyses and stopping guidelines (for harm or for clear superiority) that will be used by the Data Safety and Monitoring Board for assuring the safety of participants should be pre-specified.
	8–10	Randomization: In general treatment should be assigned by random allocation of 2 appropriate alternative courses of action, to assess which is preferable.
	11	Blinding is encouraged, at least for judging clinical endpoints.
Note: Items 12–22 unchanged from Zwarenstein et al. [12]		
Other items	23	Is the trial registered? Registration number and name of registry.
	24	Is the full protocol publicly available or published?
	25	Sources of funding must be revealed (Institutions are encouraged to participate even when there is no monetary compensation).
	26	Is there any research-related cost?
	27	Are case report forms as simple as possible?

has been convincingly evaluated, the verdict impacts on medical practice: the new practice replaces the old (if better) or is stopped (if harmful). Even if at the end of a care trial the answer remains unclear, at least participants have limited the potential harm associated with unverified medical practice. Care trials are the way to care for patients, keeping in mind that a scientific verdict awaits.

2.2. Protocol

2.2.1. Background and purpose

Science, ethics, and care cannot be separated. They are reconciled in the care research question. In the nonscientific language of the patient: "Am I more likely to do better with course of action A or B?" Clinicians intend to do good; they may have a preference for unvalidated action A, but a medicine based on results rather than on intentions must question the very beliefs behind the intervention and verify that good intentions translate into good outcomes. Starting from this vague basis, scientific methods are introduced to guide clinical actions and prevent errors in the performance and evaluation of care. The most prudent action in this context is to offer option A that requires confirmation only as an alternative to the next best previously validated option (B), in a 1:1 allocated randomized trial. This is how the trial can protect each individual patient. The question will be refined (by defining A, B, and "to do better") to elaborate the "primary" hypothesis which determines how many patients can be offered the target intervention before the trial comes to a verdict. This fixes limits within which unvalidated interventions will be practiced.

2.2.2. Design

Care trials are simple, pragmatic, randomized, multicenter trials integrated into clinical care. They are randomized because if patients and physicians are tempted to use the intervention, they recognize that medicine based on intuition or clinical judgment alone has erred before, an alternative course of action nearly always exists, and the only way to protect patients from risks of unvalidated care is with openly admitted care research. They are multicenter because patients and physicians from multiple institutions want access to promising interventions, but they should only be used within trials. Care trials are all-inclusive, because the trial is a framework to protect patients. They are simple because it is the care itself which is being evaluated; fastidious monitoring and rigid protocols should be avoided. Outcomes are simple, considered important by patients, and resistant to bias. They are monitored by an independent Data Satefy and Monitoring Board, because at some point, one alternative may be judged to be convincingly better.

2.2.3. Participants

To whom should participation be offered? The quick answer is "All patients, as long as they are eligible for the management options being compared." This emphasis on access for all patients contrasts with common approaches focused on a successful trial, which typically restrict access to a narrowly defined subset of participants. With that philosophy, research is the priority and patients are the raw material that needs to be sieved to decrease variability, increase "signal-to-noise ratio," decrease

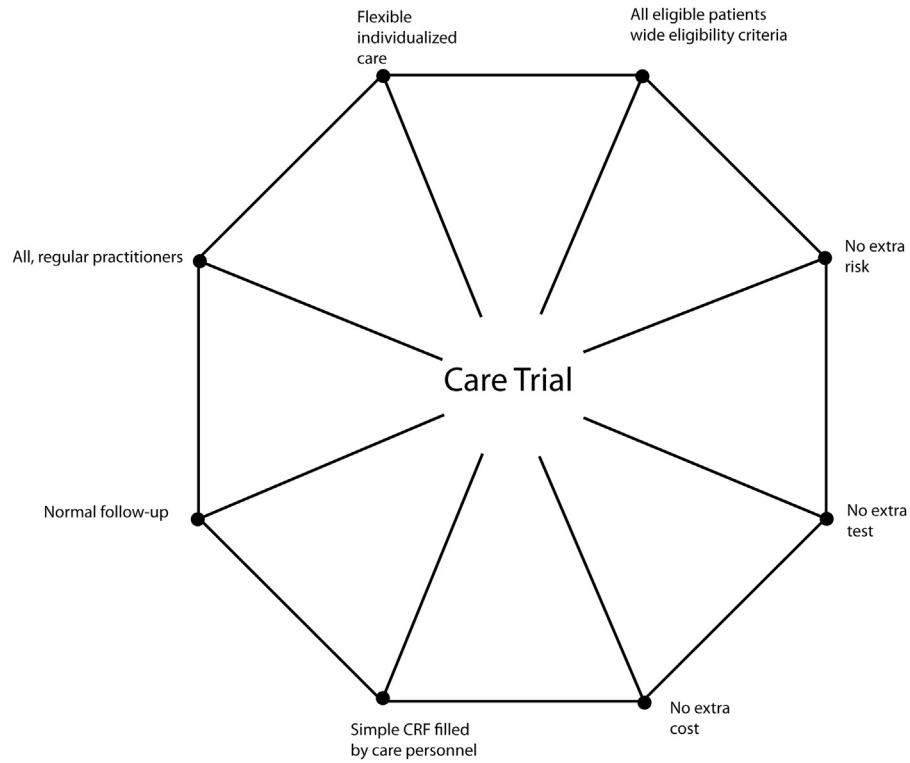

Fig. 1. Graphic display of CT characteristics (inspired by the pragmatic-explanatory continuum indicator summary [13], we have not retained the item ''analyses''; when performed at the end of the trial, they do not affect the care of the present patient).

''sample size'' and costs, and increase the ''feasibility'' and success of trials. But rarely do we really know for whom treatments will be beneficial. In care trials, it is patient care that is the priority; care is appraised at the same time it is prudently offered. If there are reasons to suspect that the outcome may differ for particular subgroups, they may be analyzed separately, but there is no reason to fail to protect these vulnerable patients by using restrictive selection criteria. The same goes for the ''moving target'' problem, an excuse for delaying randomized control trials that were finally able to identify interventions as harmful only after decades of uncontrolled use [17,18]. It is essential that trials of innovative care include the very first patients, to protect them from physician learning curves, evolving technologies or indications. It is always possible to predefine analyses that will exclude the first ''*n*'' patients from each center, but there is no reason to leave all these initial patients unprotected from unverified care outside the trial.

2.2.4. Outcomes

The primary outcome, explicitly detailed in advance, attempts to capture in *one judgment* the notion of success regarding what is of outstanding importance to patients and physicians. In general, it should not be a surrogate end point. Ideally, it is meaningful and evident to everyone, as well as resistant to bias.

Secondary outcomes should preferably not require tests or procedures that are not part of routine care. If extra tests are necessary for a particular intervention, they should not be imposed on patients within the comparison group.

2.2.5. Interventions

Care trials include (at least) two management options, both appropriate for the care of the patient. A favored intervention that has yet to be validated is one arm of a comparison. The comparator, then, is the best validated alternative. When no validated option exists, the comparator may be a placebo or conservative management. When there are multiple ''standard'' alternatives, the choice can be left to the clinical judgment of the physician. More complex designs are beyond the scope of this article [15]. Importantly, clinicians remain responsible for the health of each patient. Protocols must be flexible to promote the best possible individual care.

2.2.6. Randomization

Randomization, for the sake of the patient, is essential. It balances risks and prevents acting on unreliable beliefs, opting for preferences based on simplistic maxims or on values falsely associated with one option (ie, a less-invasive approach that turns out to be more risky). The allocation ratio (1:1) avoids any suggestion that the promising intervention is likely to be better than the validated alternative. Randomization is also essential for an unbiased comparison of interventions.

2.2.7. Masking

Admittedly, trial methods may affect the way care is provided. They serve ethical rules that guide clinical actions in the presence of uncertainty. They may well change the way clinical actions are performed, not only for scientific validity but for the protection of present patients from errors for the entire duration of the care episode. Whenever possible, masked treatment assignment helps physicians and patients accept that an alternative to the ''preferred'' option is possible. Blinding may assure equal quality of care during follow-up.

Unbiased outcome evaluation requires masking. Masking test results may be indicated when yet-to-be validated tests may trigger risky biopsies or interventions. It is difficult to ignore the test (even if it has never been validated as accurate) and difficult not to have a test result influence actions, even with full knowledge that test results can mislead. Placebos may be indicated when no therapy has been validated before. These measures prevent jumping to conclusions and the temptation to resort to more radical alternatives, when patients and physicians may falsely believe ''there is nothing to lose.''

2.2.8. Feasibility

Care trials have so far been described in general terms, because they are applicable to all clinical contexts of uncertainty. Each application will require specific adjustments. But care trials are not optional—they are necessary if we want to practice corrigible medicine. Thus feasibility, the expectation of reaching a resolution of the uncertainty, is an important but secondary consideration [19]. Meta-analytic methods could be prospectively planned to combine results of underpowered care trials, but as long as the yet-to-be-proven care is provided somewhere, it should be provided within a trial.

2.2.9. Equipoise

Equipoise, conceived as a condition to render randomization ethically acceptable [20], has no place in care trials. The notion often reintroduces the very unjustified beliefs that require testing and promotes the use of unvalidated treatments without control.

2.2.10. Implementation

Data collection should be limited to parsimonious outcomes collected with minimal effort during standard visits. Then, there is no need for additional personnel or for compensating participating centers [19]. Time-consuming contracts between institutions are inappropriate. Ethics Research Committee review of care trial protocols should be free of charge. There is no reason for care trials to compete with one another for funding, but peer review remains desirable. Limited financial support may be needed for a Web-based platform, centralized randomization and data collection, to cover the costs of monitoring a random sample or the totality of the data, and for expert analyses. In future, these expenses, so modest compared with the uncontrolled costs of unverifiable medicine, may very well be considered as health care expenses. Care trials should be monitored by benevolent individuals, following the DAMOCLES framework [21].

3. Results

3.1. Potential health care examples

The care trial concept has yet to be developed, adapted, and thoroughly tested in real medical practice. Care trials could, for one thing, be the optimal way to introduce new tests or interventions. The first real-life application of this concept, in our relatively small field, is the FIAT trial, which was designed to ''provide a prudent, controlled clinical context for the use of flow diversion (FD), a promising but as-yet unproven treatment option for patients with difficult intracranial aneurysms'' [5]. The sole inclusion criterion is ''Any patient with an aneurysm in whom FD is being considered for use by the treating clinician.'' There are only four exclusion criteria: absolute contraindications to endovascular treatment, anesthesia, or antiplatelet therapy, and inability to obtain informed consent. Patients are allocated 1:1 to FD or to the ''best standard treatment'' (BST), selected by the treating physician between aneurysm clipping, parent vessel occlusion, aneurysm coiling or stent-assisted coiling, and observation [5]. Patients can also be entered in a registry when the treating physician believes there is no other treatment alternative. Treatments (FD or BST) are administered according to local expertise and clinical judgment. Follow-ups are routine and simple case report forms can be completed online by care personnel. The trial does not entail extra test or costs. The trial is ongoing without financial support, having recruited 53 patients as of February 2014 in three Canadian centers. A similar care trial design is currently used to offer thrombectomy in acute stroke (EASI trial). Once they are widely practiced, care trials may help control overdiagnosis and iatrogenia, by curtailing the common practice of using promising tests or treatments as care before they have been shown beneficial. Care trials can address this issue not only in our field but also for questions of greater scope that have regularly resurfaced in the past, such as the merit of screening mammography, prostate-specific antigen testing, or the changes in diagnostic thresholds, for example, in gestational diabetes. Care trials have the potential to promote verifiable medicine in real time. They could change the way medicine is practiced and taught.

4. Discussion

Conventional trials are conceived to gain knowledge of causal mechanisms (explanatory trials) or of efficiency of treatment options (pragmatic trials). The knowledge that is gained is intended to help decision making regarding

Table 2. Key similarities and differences between pragmatic and care trials

Characteristic	Pragmatic trials[a]	Care trials
Similarities		
Question	Effectiveness: Does the intervention work when used in normal practice?	Same
Setting	Normal practice	Same
Participants	Little or no selection beyond the clinical indication of interest	All patients eligible for the target and alternative interventions
Intervention	Applied flexibly as it would be in normal practice	Same
Comparator	Usual care, with usual variation; applied as it would be in normal practice	Validated alternatives or observation if none exists
Outcomes	Directly relevant to participants, funders, communities and health care practitioners	Directly relevant to patients and physicians
Relevance to practice	Direct: the trial is designed to meet the needs of those making decisions about treatment options in the setting in which the intervention will be implemented	Immediate: the trial is designed to meet the needs of current patients, to offer promising but unvalidated care in a controlled fashion; results are secondary, but crucial to eventually adopt intervention as validated care
Differences		
Goal	Inform decision about treatment	Practise verifiable medicine Control the use of unvalidated interventions
Design	When planning their trial, trialists should consider whether a trial's design matches the needs of those who will use the results	When planning their trial, clinicians should consider whether a trial's design protects current patients in need of care
Attitude	No prescription; the explanatory-pragmatic distinctions are conceived as a multidimensional continuum	Prescriptive; only use unvalidated interventions within the trial AND Do not impose 'research' on current patients for the benefit of others

[a] Characteristics of pragmatic trials selected to show similarities were taken from references [12,13].

future patients. This emphasis on knowledge leaves many current patients subject to either unvalidated case-by-case care or research designed for the benefit of future patients. Care trials resemble pragmatic trials [13–16], but it is the immediate care-oriented dimension which renders them fundamentally different (Table 2). The results of pragmatic trials help users choose between options for care [16]. Trials integrated within care, at low cost, using routine health records, have also been described, but they typically limit comparisons to active treatments or compare options for which patients have no preference [22,23].

Care trials are prescriptive. They provide rules of medical conduct in the presence of uncertainty, ways to autonomously control medical actions before reliable knowledge becomes available. Once widely accepted, they can speed up the acquisition of reliable knowledge and the provision of optimal care.

Not all pragmatic designs meet care trial criteria. For example, the CURES trial, comparing surgical and endovascular treatments of intracranial aneurysms, is pragmatic but not strictly a care trial, because neither treatment options has been proven beneficial as compared with observation [24]. In contrast to most pragmatic trials, masking and placebos which may interfere with "usual care" may be used in care trials to protect patients from errors, biases, and misleading information. Care trials are not optional. They are a duty for physicians if they wish to offer optimal medical care. Because it is impossible to fulfill that duty without the means to do so, care trials should be promoted by regulation and health care organizations [25]. By controlling the use of well-intended but unvalidated interventions within care, care trials can improve health care efficiency. Although not designed for cost containment, they may ultimately be the ethical way to control the huge costs of unverifiable medicine.

5. Conclusion

Care trials can help to identify which medical alternative should be the standard therapy. In the meantime, they provide optimal care in the presence of uncertainty.

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