Pragmatic Clinical Trials in Daily Patient Care and Regulatory Changes

Ensayos clínicos pragmáticos en la atención diaria de los pacientes y cambios regulatorios

Reality is not only exciting, but almost countless
Rodolfo Walsh
(1927-1977)

INTRODUCTION

Randomized clinical trials that form part and are involved in routine clinical care, have the potential of producing highly relevant results, not only for the institution where they were conducted, but also generating information that may be generalized to the entire health care system.

Recently, a group of pragmatic clinical trials have been referred to as "randomized comparative-effectiveness trials". As these trials compare the effects of many treatments currently in use for the same disease, and since there is no scientific evidence about which is the best, these clinical results may guide future decision-making.

What would be the difference between pragmatic clinical trials (such as comparative-effectiveness trials) and trials designed to compare a new or experimental treatment (commonly directed and financed by the pharmaceutical companies) with a control, generally placebo treatment? The difference is that experimental studies are used to establish proof-of-concept, or to elucidate a mechanism of action or establish the efficacy of a new drug.

But the contact with clinical practice should be the place where transformations are produced, because, as the epigraph quoting Rodolfo Walsh's words about reality (which he wrote in Operation massacre or Who killed Rosendo?) says, "reality is not only exciting, but almost countless".

Although there are numerous definitions for "pragmatic clinical trials" (PCTs), some dating several years back, Califf and Sugarman have recently proposed three key attributes for identifying them: 21) an intent to inform decision-makers (patients, clinicians, administrators, and policy-makers), as opposed to elucidating a biological or social mechanism, 2) an intent to enroll a population relevant to the decision in practice and representative of the patients or populations and clinical settings for whom the decision is relevant, and 3) either an intent to: a) streamline procedures and data collection so that the trial can focus on adequate power to inform the clinical and policy decisions targeted by the trial or b) measure a broad range of outcomes.

Given these attributes, a common-sense definition for a pragmatic clinical trial would thus be as follows: "*Designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level.*" (1)

Also: "We think that the current requirements for ethics review should be reconsidered for such trials, in which the risks that can be attributed to the research participants are low."

"Converting naturally observed treatment variation into experimental manipulation challenges the pragmatic goals of comparative effectiveness research by disturbing normal clinical operations... The integration of comparative effectiveness research into clinical practice retains the minimally intrusive effects of observational research while offering the strength provided by the experimental method (including randomization)." (2)

SOME EXAMPLES

A cluster randomized crossover study

Only as an example, we shall comment the pragmatic chlorhexidine bathing trial in the intensive care unit. Noto et al. (3) used a "cluster-randomized crossover" trial to compare normal daily bathing with chlorhexidine bathing in the incidence of infection among 9,340 critically ill patients in intensive care units. Each treatment was performed for a 10-week bathing period, and after a 2-week washout period, the alternate bathing treatment was performed for 10 weeks, three times during the trial.

This is an example of an investigation that was conceived as an institutional quality improvement project and produced results that were generalized to the entire health care system.

It should be noted that this study has significant external validity, as all the patients admitted to intensive care units were enrolled because the institutional review board approved a waiver of informed consent due to the lack of risk of the procedure.

The rate of the composite primary outcome, extracted from the electronic clinical record (central line–associated bloodstream infections, catheter-associated urinary tract infection, ventilator-associated pneumonia and *Clostridium difficile* infection.) was 2.86 per 1000 patient-days during chlorhexidine bath-

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ing and 2.90 per 1000 patient-days during control bathing (p=0.95)

Patient selection and randomization at the clinician's office

To test the feasibility of integrating individually randomized patients, into the practice of general practitioners in the United Kingdom, comparative effectiveness research was performed with the use of a system that was based on electronic history records (EHRs) from the clinician's office: the *Retropo* trial with different statins and the *eLung* trial with different antibiotics. (4)

General practitioners verified *eligibility* and obtained *informed consent* from the patients, and accessed the trial website to register the patients and to obtain the randomly allocated treatment.

The *Retropro* trial compared simvastatin with atorvastatin in patients older than 40 years of age with 20% risk of cardiovascular disease at 10 years for primary prevention. The outcome of cardiovascular disease was obtained from the EHR during the follow-up period.

The eLung trial compared immediate use of antibiotics with deferred use in patients older than 40 years of age who had an acute exacerbation of underlying COPD disease. Clinical outcomes included forced expiratory volume in 1 second and quality of life.

However, the significant workload imposed to the doctors who participated, including filling forms and previous training, determined that only 3.7% and 1.3% of the clinicians in the Retropo and eLung trials, respectively, recruited patients,

The authors concluded:"... The fundamental question is why point-of-care trials are viewed as an activity that requires elaborate governance procedures rather than as quality improvement that is an intrinsic part of routine clinical care." (4)

Pragmatic clinical trial in hospitalized patients by nurses

This trial compared two methods (a sliding scale vs. a weight-based regimen) for determining the dose of subcutaneously administered insulin to be used in hospitalized patients. (5) Selection in the access menu "no preference for insulin regimen" notified the research nurse to obtain informed consent and then treatment was randomly assigned. The primary outcome was length of hospital stay, and the secondary outcome was glycemic control, all of which were ascertained from the EHR database.

WHAT HAVE WE LEARNED IN THE LAST YEARS?

Despite the enthusiasm and willingness of doctors to participate, it is necessary to minimize the time and effort required from clinicians to identify eligible patients and obtain informed consent in order for practice to become a place of learning for its clinical application. This will contribute to successful trials *embedded* in the practice, similarly to the trial with cluster-randomization design in which the consent is waived and all the patients are included, without selection criteria to exclude any patient; undoubtedly, this situation facilitates enrollment.

The use of eligibility criteria, even with the requirement of additional software (beyond the routine EHR application) raises barriers that complicate clinicians' participation. *Embedded* pragmatic clinical trials work best when primary outcomes can be derived from the usual EHR with minimal human input.

The need for outcome ascertainment outside the EHR adds complexity and cost; thus study planners must balance clinical relevance with technical feasibility and cost.

Care providers must be engaged as active partners in delivering treatments in accordance with the protocol after randomization of each patient and defining the objectives of the research as part of the team that designs the study. But they should not be subjected to the complex current regulatory conditions, which inhibit their recruitment, with little or no effect on the safety of patients in clinical trials with very low risk and with drugs or strategies that are used in current care conditions.

"Observational" comparative effectiveness studies, in which different doctors give different alternative treatments for the same disease almost at random, are easier to perform using the EHR. Observational comparative effectiveness studies enhanced by *randomization* provide the necessary evidence for rationale decision-making in clinical practice, reducing the risk of alternative treatments less efficient or even harmful.

Exploiting the full potential of point-of-care methods in the place of patient care includes rethinking and redefining the traditional ethics of "research committees" and regulatory standards, including the informed consent, in this paradigm of low risk research during patient care.

HOW IS RESEARCH DISTINGUISHED FROM TREATMENT?

As we have previously discussed, medical care is focused on an individual patient, to alleviate a person's discomfort or give a medical opinion to that particular patient. On the contrary, the objective of clinical research is to develop knowledge that can be generalized to all patients.

But the difference clinical practice-clinical research is currently vanishing and is no longer so clear. In the United States "the recent and substantial federal investments in comparative effectiveness research, practice-based research networks, and large databases of aggregated health care claim all support strategies to incorporate research questions into clinical settings and activities, generally with fewer constraints or burdens on both health care professionals and patients than traditionally imposed by clinical research."

The Institute of Medicine has called "*learning health care system*, when we approach research clos-

er to clinical practice, building knowledge, development and application into each stage of the health care delivery process. As clinical research and clinical practice move closer to a deliberately integrated system, the distinction between the two is increasingly blurred, although the sharp distinction in United States regulations and research ethics literature remains in place." (6)

The sharp distinction between clinical research and clinical practice has implications for the concepts of ethics in research and the regulatory role of the State that is not only conceptual and moral, but has also effects on daily empirical decisions. The current view of ethical oversight of the "research committees" may lead to overprotection of the rights and interests of patients in some cases of pragmatic trials and to underprotection in other similar situations occurring during clinical practice.

We need a new ethical foundation and its regulation to facilitate both care and research, with ethical oversight that rather than being based on a distinction between research and practice, is commensurate with risk and burden in both realms.

The first United States federal regulation governing research with human subjects appeared in 1974, (7) as a way of addressing public outcries, and included prior institutional review to ensure the research declares the benefit-risk relationship, has an adequate consent process, and a fair system of selecting subjects, but required nothing comparable for clinical practice.

We shall now describe the five characteristics that make a sharp distinction between research and treatments, following the development of Nancy E. Kass et al. (6)

Research is designed to develop generalizable knowledge

The first public use of the term "generalizable knowledge" appears in the Belmont Report, which states that whereas practice "refers to interventions that are designed solely to enhance the well-being of an individual patient… and have a reasonable expectation of success…. research shows an activity designed to test a hypothesis, allows drawing conclusions, and thereby develop or contribute *to generalizable knowledge.*" (8) And, certainly, the subsequent literature on bioethics defines research as an activity devised to produce *generalizable knowledge.*

But health care institutions move increasingly to become integrated systems that simultaneously deliver care to patients and learn the experience of clinical practice. In these integrated institutions, the development of *generalizable knowledge* will be an explicit objective, since at the same time they deliver the care patients need they capture the experience of clinical practice in systematic ways that produce *generalizable knowledge*. In this way, the concept of *generalizable knowledge* blurs the distinction between research and clinical practice.

Let us consider the example of the rapid progress of pediatric oncology over the past decades, which is mainly due to the fact that from its very beginning it was designed to allow a high proportion of children with cancer to be treated under multicenter research protocols considered as the standard of care.

To many patients, even adults, medical care is offered through clinical trials as treatment options that may result in the best available care for their conditions. (9)

Generating *generalizable knowledge* can be a deliberate and integrated aspect of practice, not a set of different maneuvers. The criterion of *generalizable knowledge* cannot be a defining condition to distinguish research from practice.

Research requires systematic investigation

Nowadays, several large health care systems have implemented programs that continuously store data on clinical services and outcomes to improve the quality of care delivered to their own patients.

In this current context, it is futile to try to distinguish a research activity from clinical practice by the concept of collection and *systematic research* of the data.

Research presents less net clinical benefit and greater overall risk

People think that research, in contrast to clinical practice, offers patients both less perspective of net clinical benefit and greater overall risk, which is morally reaffirmed by the Committees on Ethics and Research surveillance. However, when a drug is approved by the FDA in the United States or by the ANMAT in Argentina and is launched into the market, it means that the drug is safe and effective in its proposed use, and the benefits of the drug outweigh the risks.

However, the Institute of Medicine (United States) estimates that more than half of treatments in current use lack adequate evidence of effectiveness, and many surgical and diagnostic procedures extended into practice have little or no prior scientific study. Consequently, many patients in ordinary clinical care are often at risk of having suboptimal outcomes and of being harmed, however inadvertently, as a consequence of inadequate evidence.

We know many therapies that were adopted as standard treatment but that later were shown to be useless or harmful, as incubators with 100% oxygen for premature newborns, postmenopausal estrogens, antiarrhythmic drugs to avoid sudden death, and carotid artery screening, among many others.

Another problem is that conventional randomized clinical trials usually have highly selective inclusion and exclusion criteria that result as efficacy trials, but the population may not represent the general population in terms of age, sex, race and severity of the disease, and their results cannot be generalized because they do not measure the real effect in the population.

These problems in daily medical practice must be constructively compared to the minimal risks and the important benefits of pragmatic clinical research or comparative effectiveness research, which is slightly different from ordinary clinical care and is often directed at ascertaining which of two or more widely used clinical options for the same indication works best for a certain patients.

Although some research studies expose patients to risks or harm, so does standard care.

Research introduces clinically relevant burdens and risks

Another assumption is that research with patients often introduces inconveniences or risks that are unrelated to patients' clinical care needs and that no comparable clinically irrelevant inconveniences or risks are imposed in clinical care outside the research.

However, we have already mentioned the damages produced by treatments previously considered as standard care, and that overutilization of medical services exposes patients to burdens and risks (following the aphorism "less is more") which are not comparable to the clinical benefits they may produce.

Therefore, it remains unclear which clinical practice or clinical research situations impose the highest level of inconveniences and risks on a defined patient.

Research protocols dictate which interventions a patient receives

Another assumption is that in clinical research a patient's clinical management is often determined by a preestablished protocol; however, in clinical practice the use of algorithms or protocols based on practice guidelines is increasingly becoming mandatory.

On many occasions, which intervention any given patient will receive in standard practice can be determined more by the geographic location or by which doctor or hospital they see, than by their individual health characteristics. This contingency is often not recognized.

RETHINKING OUR ETHICAL OVERSIGHT

The distinction between research and clinical practice seems to be faulty to be used as criterion to regulate ethical oversight and for the practical problem of the current regulatory criteria.

Unlike the research context, no third-party oversight is currently required to ensure ethical use of interventions of unproven clinical benefit and unknown risk in clinical practice, generating underprotection on the one side and overprotection on the other side.

We should move from a system of ethical oversight that relies too heavily on the research-practice distinction to another that identifies which activities warrant ethical review and determines when patients are at risk and in need of oversight protection.

We need to identify more efficiently which interventions work, how errors can be reduced, and when interventions or tests should be administered or avoided for groups of patients.

The labels "research" and "practice" that have been placed for three or four decades should no longer be our central moral concern. It is time to create a more balanced and relevant understanding of what matters morally, as health care begins to transform into a system in which learning and clinical practice are properly integrated. (6)

HOW TO BUILD A NEW ETHICAL FRAMEWORK?

As there is no different ethics between "research ethics" and "clinical ethics", Ruth Faden (10) proposes a reference framework with seven principles:

1. Respect the right and dignity of patients.
2. Respect clinical judgments.
3. Provide optimal clinical care to each patient.
4. Avoid imposing nonclinical risks and burdens on patients.
5. Address and reduce health inequalities among population.
6. Conduct responsible continuous learning activities that improve the quality of clinical care and health care systems.
7. Contribute to the common purpose of improving the quality and value of clinical care and health care systems.

The first six obligations fall on investigators, clinicians, health care managers, payers, and purchasers. Patients are responsible for the last obligation.

1. The obligation to respect patients (their rights and dignity)

Respecting autonomy of patients is one of the "rights" in research ethics and clinical ethics, allowing persons to shape the basic course of their lives in line with their values and independent of the control of others. We should assess whether the physician´s activity unduly limits patient choices and the value of those choices.

2. The obligation to respect clinical judgment

When there is uncertainty about the best practices or limited empirical evidence, the importance of respecting clinical judgment in this context is not as rigorous as when there is clear evidence for the clinician or the patient has a defined preference for the different therapeutic options.

3. The obligation to provide optimal care to each patient

This is an unwavering obligation of the health care provider. The risks are morally justified if they are outweighed by the prospect of the corresponding potential or expected clinical benefit.

We should always consider that while some learning activities are likely to increase the prospects for net clinical benefit, others are likely to decrease it.

4. The obligation to avoid imposing nonclinical risks and burdens

Learning activities may also impose burdens beyond

those needed for patients' usual clinical care, such as extra visits to clinical facilities.

5. The obligation to address unjust inequalities

The moral requirements of research are that subject selection be fair and that the distribution of research benefits and burdens be just.

6. The obligation to conduct continuous learning activities that improve the quality of clinical care and health care systems

This obligation makes contribution to learning morally mandatory. It also extends its reach beyond health care professionals to health care institutions, payers, and purchasers. This obligation would be "foundational" for the gradual transformation of health professions and health care institutions into interconnected learning activities.

7. The obligation of patients to contribute to the common purpose of improving the quality and value of clinical care and the health care system

Just as health professionals and organizations have an obligation to learn, patients have an obligation to contribute to, participate in, and otherwise facilitate learning.

This common interest is a shared social purpose with near-universal participation in learning activities, through which patients benefit from the past contributions of other patients whose information has helped advance knowledge and improve care. Nothing would substitute the direct participation and contribution to learning activities.

According to David Hume, "All our obligations to do good to society seem to imply something reciprocal. I receive the benefits of society, and therefore I ought to contribute to its interest." We would have a proportional benefit shared by all, with the moral obligation of sharing the inconveniences and burdens necessary to produce these benefits.

NEW REFERENCE ETHICAL FRAMEWORK

The new ethical framework avoids the moral relevance of the traditional distinction between research and practice and sets a group of moral presumptions in favor of learning, in which health professionals and institutions have an affirmative obligation to contribute to learning activities. This implies changes in oversight policies and practices of current regulations in human subjects and institutional review board systems, including prior review and informed consent.

The new framework provides a moral bond between the first obligation—to respect the rights and dignity of patients—with the seventh obligation, that patients contribute to the common purpose of improving the quality of clinical care and the health care system.

"We are in the early days of a progressive realization of a lofty aspirational goal, but given the harm and uncertainty about clinical effectiveness in health care, efforts to accelerate learning should be given high priority. Now is a good time to lay the ethical foundations of learning in the health care system and start working on its specific moral commitments." (10)

SOME INITIAL DIFFERENT APPROACHES

Several of the NIH Collaborative trials have been performed without express written informed consent because the relevant regulatory requirements for such an approach had been satisfied.

"Workshop participants (*gathered by the NIH*) generally felt the Ottawa Statement was too restrictive in its determination of when it is appropriate to waive or alter informed consent. In particular, the Statement recommends that researchers obtain consent except when '*1) the research is not feasible without a waiver or alteration of consent, and (2) the study interventions and data collection procedures pose no more than minimal risk'*. However, some comparative effectiveness research (which often compares standard-of-care interventions) and quality improvement projects that employ cluster randomization (groups) may pose situations in which obtaining prospective informed consent for particular activities may not seem appropriate. Moreover, requiring consent in these settings may preclude a large number of important and well-designed trials that involve low incremental risk, resulting in interventions being adopted or discontinued without meaningful information regarding their value." (11)

The criteria for waiving or modifying consent in nonemergency settings require that: *"1) the research involves no more than minimal risk to the subjects; 2) the waiver or alteration will not adversely affect the rights or welfare of the subjects; 3) the research could not be practicably carried out without the waiver or alteration; and 4) whenever appropriate, the subjects will be provided with additional pertinent information after participation."* (11)

Of note, the federal regulations of the United States define ''minimal risk'' as ''...the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.''

In evaluating risks and benefits, the institutional review boards should consider only those risks and benefits that may result from the research, differentiating them from those resulting from the therapies patients would receive even though they did not participate in the research.

INVOLVING THE PATIENTS

A dialog was held with 110 members of the public randomly selected in four cities of England and Wales, conducted by the Health Research Authority of the United Kingdom (12) to know the opinion about the development of simplified models of informed consent

for clinical trials of already licensed drugs and other common interventions.

There was in-principle support among the majority of participants to use a simplified patient information form, with communication sheets that do not repeat the information contained on drug pack inserts, assuming that the studies are not blinded.

In view of forthcoming clinical trial regulations allowing for the option of no consent in cluster-designed clinical trials, most people agreed with the use of zero consent in appropriate low risk studies with minimal intervention.

Some participants felt that invasive treatments, for example, those which enter the body in some way (including catheters and intravenous medications), were too invasive to be appropriate for zero consent, while others concluded that if there was genuine uncertainty with licensed medications, then it might be acceptable not to seek consent in these interventional scenarios.

They concluded that: "The dialogue revealed there is strong support for health research as a key part of ensuring there are continuous health improvements. Increasing access to health research participants was supported as a common good." The dialogue also revealed "good support for the process of simplified consent where the research process did not have an impact on the type or quality of the care provided. Reassurances around using zero consent included: using anonymised outcome data, low-risk areas, non-intrusive or non-invasive, genuine lack of knowledge about the best treatment (genuine equipoise), and the patient is unlikely to be aware that there is a different option to the equipment." (12)

CONCLUSIONS

The development of electronic systems helped routine clinical practice become a *learning health care system*, comparing drugs, practices and strategies.

The introduction of pragmatic clinical trials that form part of and are involved in routine clinical care, with the use of the scientific method (which includes randomization to avoid biases), enhances the way of obtaining evidence in the use of different drugs, practices and strategies of routine medical care.

This situation promotes the disappearance of the traditional distinction between research and practice and deserves a revision of the ethical regulations for pragmatic trials.

Research ethics and current regulations in human subjects should not be based on the distinction clinical practice-clinical research. We need a new ethical and regulatory foundation to facilitate both care and research, with ethical oversight that rather than being based on a distinction between research and practice, is commensurate with risk and burden in both realms.

The dialogue with common people demonstrated a strong support for health research as a key part of ensuring there are continuous health improvements.

Almost all the participants supported the use of simplified informed consent forms. Most people agreed with the absence of consent (the use of zero consent) in appropriate low risk studies with minimal intervention.

We are in the early days of a change to understand the uncertainties about clinical effectiveness in health care, giving high priority to efforts accelerating learning.

We have now reached the time to lay the foundations of a new ethical framework for a learning health care system and begin working in a new state regulation.

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