

On the Frontiers of Clinical Research Ethics: Adjusting Norms to Progress

En las fronteras de la ética de la investigación clínica: ajustando las normas al progreso

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It is clear that norms may be good, regular or bad. As a consequence of logical regulations and bureaucracy, there is insufficient emphasis and investigation about the bad norms in clinical research and their impact on scientific production in Argentina, particularly about their detrimental effects. Undoubtedly, norms should be evaluated. Some ideas, in line with the letter by Borracci, (1) can reduce the collateral effect of the research ethics committees in the complex scenario of current research.

An experience with a request for approval of trials by the Administración Nacional de Medicamentos Alimentos y Tecnología Médica (ANMAT, National Drug, Food and Medical Technology Administration) demonstrates that some observations made by Borracci can be applied in our environment. For example, the Vigía/CONPRIS protocol (National Ministry of Health) was a pragmatic, randomized controlled pilot clinical trial (RCT) with economic analysis, designed to evaluate an intensive multicomponent medical treatment (conceived as a “Polypill-Plus”) in diabetic patients > 65 years of age with cardiovascular risk at 5 years > 20%. (2) As the research involved randomization of human subjects, the protocol was submitted to the ANMAT for approval; however, it was not authorized as it did not follow the standards of the Good Clinical Practices valid at that moment, (3) and for lack of adherence to ANMAT Regulation 5330/97. (4) The ANMAT was consistent with its regulations; the valid norms excluded this type of study that did not contemplate that design. Thereafter, Yusuf et al. (5) published a study with a similar design and the evidence involved 7,047 patients from 9 clinical trials in 2014. (6) The key point of this opinion article is that standard norms can be inadequate for certain type of investigations.

The effectiveness of a health intervention should be increasingly evaluated. A polypill, for example, is not a new drug but uses approved medications in a

new application of usual drugs to improve the effectiveness in daily practice. In a certain sense, it is a new strategy of multiple pharmacological interventions, with multiple effects in the cardiovascular continuum. Finally, the strategy increases the effectiveness of cardiovascular prevention with consequent better cost-effectiveness. For these and other reasons, the protocol exceeded the taxonomy of studies existing at that moment. This case leads to analyze certain basic concepts of clinical research ethics which is currently under review, and some related methodological evolutions. The aim is not to discuss this case in particular, or the study design or the polypill, (7) which has evolved from the promise to pragmatism, (8) and has been added to the World Health Organization model list of essential medicines, (9) or to criticize the ANMAT. The aim of this article is to illustrate the underlying issue of regulations. Of interest, the same general bioethical issues generated by this protocol occur in developed countries. These topics make us reconsider the ethical bases of the oversight requirements, of the regulations for approval and of the Research Ethics Committees (RECs) but related to some new methods of research in clinical trials. (10) These concepts have a cascade effect toward the public and private regulatory policies of this activity.

The first bioethical distinction must differentiate between research and medical practice. There is a difference between treating patients and making human research in terms of their ethical demands. This distinction is the basis of the Belmont Report, (11) and is widely accepted. (12) The research-treatment distinction justifies the different ethical approach for both medical activities, though they complement and support each other. (13) The ethical norms guiding the oversight of clinical research in humans were the answer to abuses in the dignity of research subjects. The position of the traditional clinical research ethics is reactive to these abuses. The research-treatment

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distinction poses the question about which actions should have obligatory and simultaneous ethical oversight, an oversight that does not occur in daily clinical practice. (14) This ethical oversight may overprotect clinical research subjects and leave research patients in the services unprotected. The conclusion is that the burden of oversight could be reduced (15) leading to a separation from traditional research ethics. (16) For these reasons, it has been argued that not all the randomized controlled trials require informed consent. (10) In the current setting, the research-treatment distinction is more complex, and is less necessary in a certain sense.

The second distinction is between effectiveness and efficacy. (17) Effectiveness is a measure of the benefits and risks from an intervention for a given health problem under usual practice conditions, while efficacy is measured under ideal practice or experimental conditions. The greater complexity of medicine emphasizes the context. (18) A given X intervention (e.g, a drug, a diagnostic method) has a contextual circle of practice made up of many components that interact with the intervention X and produce a significant modification of the effect. If we call the immediate context healthcare systems, the variables of this context define the intervention ($X + s$, where $s =$ services). For example, treatment of hypertension in the emergency department is not the same as treatment of hypertension, in an organized clinic or in the primary healthcare clinic of a poor neighborhood. When the aims of $X + s$ are analyzed, the aims of the services are thus defined, and they must be included in the evaluation.

The third distinction is between the objective of improving healthcare services (the idea of the Learning Healthcare Systems) and improving personal clinical practice. (19) Improving healthcare services means achieving high clinical standards and, at the same time, generating information to improve the results of medical care. This idea is strange for those who regulate clinical research. The way the intervention acts is evaluated, and the purpose of learning is expressly included (with its impacts on benefits of quality and safety for the patients, and goals in efficiency and equity). The efficacy-effectiveness gap and the equity gap are greater in developing and underdeveloped countries. There is a significant effect that has socioeconomic conditions and suggestive evidence. (20) Learning to improve the services is a valid and even imperative bioethical target.

As the ideas of the bioethical foundation are transferred to regulatory instruments, it is necessary to explain the norms that regulate RECs and regulatory agencies. The current position is that regulations must be proactive to extend the benefit (effectiveness), increasing quality, efficiency and equity. This proactive position is important for some reasons: 1) it reduces the potential harm for patients; 2) increases the benefits in health; and 3) increases the value of the interventions (risk-benefit ratio). The three em-

phasized conceptual distinctions are transferred to research environments in the last three methods emphasized. Both sets of arguments, in the bibliography discussed, rest importance to many of the traditional emphasis of the RECs and, at the same time, they emphasize new aspects that are not usually considered. Both problems, general ethics and methods, should be contextualized to the local regulation structure. The ANMAT regulation for clinical research was updated in 2010 in the Regulatory Guideline for Good Clinical Practices in Clinical Pharmacology Studies (ANMAT Regulation 6677/10), but preserves the same denomination for the studies, considering only phase II, phase III and phase IV trials. (21) This regulation has been included in an updated guideline for research in human subjects (ANMAT regulation 1480/2011). (22) Both regulations govern the current conduct of clinical pharmacology studies in Argentina, and are compared with the regulations from other countries. (23) The "polypill", a technology made up of drugs usually used in clinical practice, questions many research topics. In the case considered, the ANMAT Regulation 5330/97, has many aspects that can be discussed. Was it necessary to request ANMAT approval or could that protocol be excluded from approval? Is that study a phase II, phase III or phase IV study? Does it refer to one drug or to many drugs? Is it valid to talk about "drug" or "drug class" indistinctly? How should the informed consent be and who should obtain it? Should a pragmatic randomized controlled study with economic evaluation follow the same criteria of other randomized controlled clinical trials to obtain approval? The taxonomic ambivalence, particularly between phase III and phase IV studies compared with pragmatic trials in general, as these designs have components of the phase III and phase IV studies simultaneously.

Continuing with the observations made by Borracchi, emphasis should be made on the methodological aspects of the general bioethical points previously mentioned, which are scarcely analyzed in our environment, under three main topics: pragmatic randomized controlled trials, complex interventions and comparative investigations. This protocol had these controversial characteristics about methods of clinical trial in the current literature.

Pragmatic randomized controlled trials: RCTs are evolving. (24) Pragmatic RCT (25), also called practical clinical trials, measure effectiveness in routine clinical practice. The importance of these trials is increasing in clinical research. (26) The focus of these studies is their high external validity -they can be generalized- rather than internal validity, (27) and their ability to be extrapolated to clinical practice. (28) Therefore, pragmatic RCTs reflect the heterogeneity of patients in general practice, keep exclusion criteria to a minimum, focus on specific clinical groups that include a wide range of diagnoses, patients are defined by their way of presentation rather than by di-

agnoses, may not use placebo, may not be blinded and must carefully conceal allocation during randomization. (29-31) The aim of the intervention was to solve the effects on many cardiovascular risk factors at the same time. This inclusion criterion is not very restrictive. External validity, frequently ignored, increases as the inclusion of subjects is less defined.

One of the most obvious problems in bioethics is the extension, mode and appropriateness of the informed consent for this type of studies. In the mentioned case, a minimal and practical model of consent was proposed, similar to the one then called “integrated consent model”. (32) There was sufficient uncertainty among the medical community and the individual physician-patient relationship to justify randomization of patients. (33, 34) In this case, the principle of uncertainty among the medical community is adequate; the target was to replace clinical uncertainty with randomization.

Complex interventions: This case fulfilled the criteria of the so called complex interventions, also known as multicomponent interventions. As it happens with this case, complex interventions escape from the standard regulations in clinical research based on randomized controlled clinical trials comparing a drug versus placebo or usual care. The Medical Research Council of the United Kingdom considered and defined complex interventions in 2000, (35) and made a revision in 2006. (36) A complex intervention includes different actors, different actions and different technologies in a single preventive, therapeutic and/or rehabilitation/palliative program. Complex interventions usually contain a number of interacting components, a number of behaviors beneficiaries and actors need to change, a number of organizational levels targeted by the intervention, and a number of health outcomes and require flexibility of the intervention to be performed. They normally assess effectiveness, they are evaluated by several types of pragmatic randomized studies, some of them with economic evaluation, and their regulation has recently been matter of interest. (37) The core issue is that as long as chronic diseases or prevention aspects of medical practice (both conditions present in the epidemic of cardiovascular disease) become the matter of the interventions, complex interventions will be the norm rather than the exception.

Comparative effectiveness research (CER/Real world clinical research): This type of research compares “head-to-head” two or more interventions. (38) They tend to be complex interventions and are frequently evaluated with pragmatic RCTs. Comparative effectiveness research compares the benefits and harms in “real-world settings” (39) and has multiple implications for decision-making in research. (40) This method is associated with the use of electronic health records in clinical research. (41) This protocol was a pragmatic study that did not compare drugs but two “strategies”: the intervention versus usual care.

By definition, it was a pharmacoeconomic model with economic analysis. (42) Therefore, considering only that criterion, it fulfilled the criteria to be included as a phase IV study. The use of the criterion “new therapy” was a complicated matter: if the simultaneous use of drugs could be considered a new therapy was a matter of discussion; it was clearly a new way of indication and a new question about the intervention. The polypill as it has been described was literally a new therapy, but the protocol evaluated the “strategy” of the polypill, but with many single pills; thus, it did not qualify for “new therapy”. The underlying logic of the design was that of comparative effectiveness studies.

The case previously mentioned had the main components of the methodological evolution analyzed by the recent research ethics. Research on medical practice, research on new applications of known technologies, research on the evaluation of complex technologies, research on comparative effectiveness, etc., demands an update of the research ethics committee criteria. High standards of practice should be preserved in the regulations of quality for clinical research with oversight of abuses and risks for patients and populations. However, the undesired effects of the regulations must also be evaluated. The new point is that the validity of these norms are being reevaluated in first-line research centers as the research ethics committees of the United States National Institute of Health. If the current regulations in Argentina were applied, a pragmatic RCT would not be approved and the dilemmas would be the same as those in this protocol.

In summary, the Regulatory Guideline for Good Clinical Practices in Clinical Pharmacology Studies (ANMAT Regulation 6677/2010) and the Guideline for Research in Human Subjects (ANMAT Regulation 1480/2011), as well as the Good Clinical Practices: Document of the Americas (PAHO 2010) should undergo deep bioethical and methodological analysis and revision. The process of review of the regulation should include an explicit mention of a better description of a clinical trial, including pragmatic randomized trials and other less conventional designs, better descriptions of methodology of research in clinical trials and a sub-section of Comparative Research Evaluation, adapting its glossary. Including another topic related with research developed in electronic medical records is mandatory. In this way, the current regulation could be updated and improved to expand clinical research, particularly the one focused on improving effectiveness and sustainability of the healthcare services.

The imperative need of improving research and services for non-communicable diseases is an opportunity to do so. This could develop a vehicle to improve patient care and reduce premature death.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material).

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