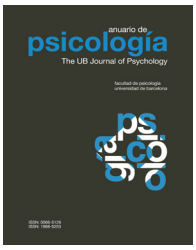
Anuario de Psicología (2017) **47**, 130–139

anuario de psicología
The UB Journal of Psychology
www.elsevier.es/anpsic



THEMATIC REVIEW

Setting-up a clinical trial: Some methodological recommendations

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Received 21 April 2017; accepted 23 December 2017
Available online 21 February 2018

KEYWORDS
Clinical trials;
Methodology;
Guidelines;
Psychometrics;
Statistics

Abstract Well-designed clinical trials are the gold standard for evidence-based research and for the assessment of the effectiveness of a clinical intervention. Methodological guidelines are available from various sources, such as textbook, funding applications and institutional guidelines. Nevertheless, a high number of published trials still lack methodological rigor, decreasing their utility, quality and scientific validity. In this article, we aim at providing some methodological recommendations for the development and report of a clinical trial, including the definition and recruitment of the sample, the basic study designs, randomization, blindness, data analysis and data report. Finally, we will discuss some of the most important ethical issues.

PALABRAS CLAVE
Ensayos clínicos;
Metodología;
Directrices;
Psicometría;
Estadística

Creación de un ensayo clínico: algunas sugerencias metodológicas

Resumen Los ensayos clínicos bien diseñados son el estándar por excelencia para la investigación basada en la evidencia y para la evaluación de la eficacia de una intervención clínica. Las directrices metodológicas se encuentran disponibles en varias fuentes, tales como libros de texto, solicitudes de financiamiento y directrices institucionales. Sin embargo, un gran número de ensayos publicados todavía carecen de rigor metodológico, disminuyendo su utilidad, calidad y validez científica. En este artículo, nuestro objetivo es proporcionar algunas recomendaciones metodológicas para el desarrollo e informe de un ensayo clínico, incluyendo la definición y selección de la muestra, los diseños básicos de estudio, la aleatorización, el cegamiento, el análisis y el reporte de datos. Finalmente, discutiremos algunas de las consideraciones éticas más importantes.

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https://doi.org/10.1016/j.anpsic.2017.12.001

Introduction

Clinical trials (CTs) are prospective studies that aims at investigating the effects and value of a new intervention on a specific population, over a defined period. The intervention can be of different nature (like medical, pharmacological or behavioral) and can have either preventive, therapeutic or diagnostic purposes.

When adequately designed, performed and reported, CTs are the gold standard for evidence-based research (Moher, Schulz, Altman, & Group, 2001). For these reasons, all trials should meet some important methodological criteria (Moher et al., 2001): Lack of procedural rigor may lead to biased results, which are difficult to consider valid, generalizable and reliable (Juni, Altman, & Egger, 2001).

Every year, dozens of CTs are published; by the way, up to 50% of them show important methodological deficiencies (Chan & Altman, 2005). The same negative trend has been observed in the psychological field (Michie et al., 2011; Stinson, McGrath, & Yamada, 2003). Aiming at improving the quality of reports, an international group of clinicians, statisticians, epidemiologists and biomedical editors have created the CONSORT (CONsolidated Standards Of Reporting Trials) statement, which consists of a checklist and a flow diagram for reporting CTs (Begg et al., 1996). Subsequently to the original version, some revisions have been published: The last revision dates back to 2010 (Schulz, Altman, Moher, & Group, 2010), Other than providing a methodological systematization, the CONSORT statement constitutes a valid tool that allows readers to be able to evaluate by their own the quality of a CT. Nevertheless, many behavioral investigators have not completely adopted these guidelines (Bonell, Oakley, Hargreaves, Strange, & Rees, 2006; Stinson et al., 2003), considering them not fully adequate for the investigation of social and psychological interventions (Mayo-Wilson, 2007). For instance, explicit guidelines related to external validity and process evaluations are still missing (Armstrong et al., 2008; Prescott et al., 1999). For these reasons, more specific guidelines have been created: An attempt in this direction are JARS (Journal Article Reporting Standards), developed by the American Psychological Association (APA) (Publications & Communications Board Working Group on Journal Article Reporting, 2008), or the CONsolidated Standard Of Reporting Trials – Social and Psychological Interventions (CONSORT-SPI), which is being developed by the Centre for Evidence Based Intervention at the University of Oxford, the Centre for Outcomes Research and Effectiveness at University College London, and the Institute of Child Care Research at Queen's University Belfast, in association with the CONSORT Group (Montgomery et al., 2013).

Every well-designed CT requires a protocol, a written agreement where the key points of the study are exposed. Importantly, all protocols should be defined before the beginning of the trial and they should be not modified anymore in the subsequent phases.

The main topics that every protocol should address are listed in Table 1 (Friedman, Furberg, DeMets, Reboussin, & Granger, 1998). Starting from this scheme, the main phases of the development, application and results' reporting of a CT will be discussed in the next paragraphs. The reported methodological recommendations are based on a synthesis of the existing guidelines identified in literature.

Table 1 Schematic key points of a clinical protocol.

Background of the study	- Rationale - Previous literature
Objectives	- Research questions and response variables - Subgroup hypothesis - Adverse effects
Design of the study	- Study population - Sample size assumptions and estimates - Enrollment of participants - Interventions - Follow up visit description and schedule - Ascertainment of response variables - Safety assessment - Data analysis - Termination policy
Organization	- Participating investigators - Study administration
Appendices	- Definitions of eligibility criteria - Definitions of response variables - Informed consent form

Adapted from (Friedman et al., 1998).

Background, research questions and response variables

First of all, it is important to be clear and explicit about the rational of the study and to ensure that there is consistency between the theoretical stance and the developed protocol (Twining, Heller, Nussbaum, & Tsai, 2016). The definition of the theoretical background includes the analysis of literature and the explanation of the scientific background, in order to examine and compare what investigators have already pointed out on the same topic.

In this early planning phase, investigators should define what the experimental study wants to give an answer to, namely defining the research questions.

Research questions are the fundamental core of every research study and they should be selected and defined in advance, being as specific as possible. The primary question is the most important issue the study wants to answer to and it is typically a test of the effect of a specific intervention (Ellimoottil, Vijan, & Flanigan, 2015): The entire CT is then developed based on it. On the other hand, secondary questions are subordinate questions and they are usually related to the primary question. They can be differentiated in two categories: (1) secondary questions in which the response variable is different than the one of the primary question and (2) secondary questions that are related to subgroup hypotheses. Finally, investigators may also define some ancillary questions that, even if not directly related to the implemented intervention, could be addressed by the outcomes of the trial.