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Methodological and ethical aspects in conducting randomized controlled clinical trials (RCT) for addictive disorder's interventions

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Original article

SUMMARY

According to epidemiologic reports, the harmful use of alcohol and illicit drugs has been increased among the Mexican population. This use is associated to several risks and issues that affect public health and well-being of the country. This article acknowledges the need for developing treatment models and interventions which therapeutic value is supported by scientific evidence; models that respond to the attention needs of the population affected by substance use in Mexico and that can be generalized in community clinical practice.

In clinical research, randomized controlled clinical trials (RCTs) are the "gold standard" to demonstrate the effect of a therapeutic intervention. An RCT is a prospective study in which the effect, value and safety of one or various experimental interventions are tested against a "control" intervention in human subjects.

Acknowledging that Mexico has a lack of research on addiction treatment complying with all the requirements to be considered as an RCT, this article presents several methodological and ethical considerations that are to be considered for their design and conduction. These considerations include from the establishment of a relevant research question and objectives to adequate study design and development of strategies for data management, statistical analysis, monitoring of interventions, safety monitoring and research quality and protection of human subjects assurance.

Key Words: Substance use disorders, treatment, controlled clinical trials, randomized clinical trials, methodology, ethical aspects.

RESUMEN

Según reportes epidemiológicos, el consumo nocivo de alcohol y drogas ilegales dentro de la población mexicana ha ido en aumento, lo que se asocia a varios riesgos o problemáticas que afectan la salud y bienestar públicos del país. Se reconoce la necesidad de desarrollar modelos de tratamiento e intervenciones cuyo valor terapéutico esté respaldado por la evidencia científica, que respondan a las necesidades de atención de la población afectada por el consumo de sustancias en nuestro país y que puedan generalizarse en la práctica clínica comunitaria.

Dentro de la investigación clínica, el "estándar de oro" para demostrar el efecto de una intervención terapéutica son los ensayos clínicos controlados aleatorizados (ECCA). Un ECCA es un estudio prospectivo en el cual se prueba el efecto, valor y seguridad de una o varias intervenciones experimentales contra una intervención "control" en sujetos humanos.

Reconociendo que en México hay una falta de investigaciones sobre tratamientos para las adicciones que cumplan con todos los requisitos para ser considerados ECCA, en este artículo se presentan distintas consideraciones metodológicas y éticas que deben tomarse en cuenta para su diseño y conducción en la materia; abarcando aspectos que parten desde el establecimiento de una pregunta y objetivos relevantes hasta el diseño adecuado del estudio y el desarrollo de estrategias para la administración de datos, análisis estadístico, monitoreo de las intervenciones, monitoreo de seguridad y aseguramiento de la calidad de la investigación y protección de los sujetos humanos que participan.

Palabras clave: Trastornos por consumo de sustancias, tratamiento, ensayos clínicos controlados, ensayos clínicos aleatorizados, metodología, aspectos éticos.

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INTRODUCTION

Different international reports point out a trend towards an increase, or stabilization, in the prevalence of harmful use of alcohol and drugs in the global and national population.[1,2] Such consumption is associated with several risks and issues significantly affecting public health and well-being such as psychiatric comorbidity, mortality related to chronic diseases, deaths and disabilities from motor vehicle accidents, among others that cause a reduction of quality of life and stability of the population.[3-7] Faced with this scenario, it is of particular importance that interventions devoted to minimize the impact of substance use are reasonably based on the findings of clinical research.[6] Among the principles recommended for substance abuse treatment by the World Health Organization (WHO) and by the United Nations Office on Drugs and Crime (UNODC) it is worth mentioning the development and spreading of treatment models supported by scientific evidence that may be reproducible and sensitive to the different necessities of each patient and of his/her socio-cultural context.[8]

In clinical research, randomized controlled clinical trials (RCTs) are the "gold standard" to assess the effect of an intervention. A clinical trial is a human prospective study in which the effect, value and/or safety of one or various therapeutic interventions are compared against a "control" condition, resembling a control experiment to establish cause-effect relationships.[9,10] In order that a clinical trial may fulfill its purpose it must be designed and conducted according to sound scientific principles and reported properly.[11,12] Different efforts in other countries have been made for conducting clinical trials with scientific rigor in order to assess interventions specialized in addiction treatment—with relative success, giving rise to the spreading of attention models based on evidence to attention community settings.[13] Acknowledging that Mexico has a lack of clinical research on addiction treatment complying with all the requirements and scientific rigor of an RCT, the purpose of this article is to present some methodological and ethical considerations that are to be considered for their design and conduction.

METHODOLOGICAL CONSIDERATIONS

With regard to the type of study

Establishing a proper design in the addiction treatment research implies greater complexity due to the heterogeneity of substance consuming patients[2,8] and to the fact that not all treatments operate in the same way.[15-17] Likewise, other variables related to treatment research and to the addiction clinical practice are to be considered. Such variables may be conceptualized as follows: *In what population? What therapeutic intervention? (On which dose, how long?) Applied by whom? In what scenarios? With what results the intervention is connected to and what are the benefits or advantages that this involves regarding what is already available?*[9,18] Thus, the RCTs may be classified on the basis of a wide range of selection criteria: by type of treatment, design, objective and phase or stage of development of treatment (Figure 1).

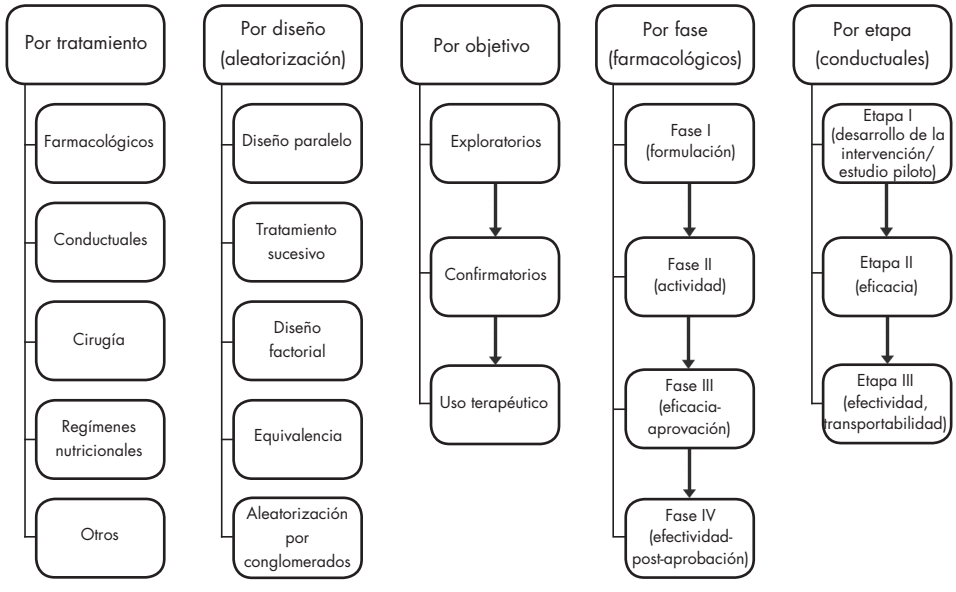

Table 1. Tipos de ensayos clínicos por criterio de clasificación.

With regard to the type of treatment

They can be classified in pharmacologic trials (including vaccines), behavioral therapies, surgery, nutritional diets and other therapeutic mechanisms.[10]

With regard to the design

This classification includes, among other aspects, the way in which the participants are assigned to the interventions.[9,10,19] Each type of trial, according to its design, is described in detail in Table 1.

With regard to the objective

They can be classified according to their objective or to the moment within the clinical development of the intervention in which they are going through (phase or stage). In both classifications a sequential reasoning is established in the development of several clinical trials over a single intervention considering the influence of the previously obtained findings. This sequential differentiation has a descriptive function and does not necessarily imply that a trial must classify its design depending on same, since a single trial may present a design incorporating objectives of several phases or stages simultaneously.[11,19-22] A more detailed description of each type of trial, according to its objective, is presented in Table 2.

Table 1. Classification of trials by type of design

Type of trial	Description
Parallel design	It is the most common design in practice. In this type of trials the participants are assigned to an intervention (either experimental or control intervention) and are observed in parallel fashion for the entire duration of the study to determine differences in the effect of the interventions
Consecutive treatment design	In this type of trials the participants are randomly assigned to different sequences of interventions, in such a way that all receive all study interventions, but in a different sequence.
Factorial design	In these trials all participants are assigned to different combinations of two or more interventions, on the understanding that there is scientific evidence indicating that there is no interaction among them and that both have similar therapeutic effects. Following this design the participants may receive all study interventions, only one of the study interventions, or none (that is to say, exclusively the control treatment or placebo).
Equivalence design	In this type of trials two interventions of similar therapeutic effect are compared in order to prove their therapeutic "equivalence".
Cluster randomization design	In this type of trials numerous groups of participants are randomly assigned to an intervention (i.e. patients in a hospital, or patients of one or more physicians or therapists) instead of being assigned individually.

Table 2. Classification of trials by sequenced objectives

Type of trial	Description
1. Exploratory trial	In this type of trials aspects such as doses or minimal treatment regimen are estimated to achieve a therapeutic effect, the expected clinical outcomes (effect) are established, and possible interactions are observed between the new intervention and other variables of the participants. Also, during these studies the security and initial tolerance to human intervention is estimated.
2. Confirmatory trial	These trials are then conducted to demonstrate or confirm the therapeutic efficacy of the intervention, establish a dose-response ratio, establish the security of the intervention, and provide an appropriate basis to assess the risk-benefit ratio of the intervention so that it may be incorporated to the regular clinical practice.
3. Therapeutic use trial	In these trials the analysis of the risk-benefit ratio and the dose or effective treatment regimen are totally improved and the less common adverse effects are identified.

With regard to the phase of development in pharmacological and behavioral interventions

The pharmacological interventions include four sequential phases ranging from a first experimental test (phase I) in humans, to see its effect, to interaction tests with other available drugs or treatments after demonstrating their therapeutic use (phase IV).[9-11,19,20,23] A more detailed description of each phase is presented in Table 3. Behavioral interventions, together with the pharmacological treatments, have a good cost-effectiveness ratio to reduce consumption, widen time of abstinence and affect other performance areas of patients.[8,24] Onken, Blaine and Battjes (1997) propose a stage research model for behavioral therapies analogous to the pharmacological model that consider three stages described in detail in Table 4.[25,26]

Definition of the study population

Implicit within the formulation of the research question is defining the particular population that will participate in the trial. For this purpose the following questions are put forward: *What patients could receive the therapeutic benefit of the intervention? In what patients the effect of the intervention is more detectable? In what patients the application of the intervention poses a high risk of harm or non-improvement?* And (in some cases), *healthy subjects shall be included in the study?* Answers to these questions will allow defining inclusion

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Table 3. Classification of trials by development phase (Pharmacologic trials)

Type of trial	Description
Phase I	In this phase the management and effects of an experimental intervention are initially tested. Generally, they are conducted on healthy humans and their reaction or how they answer to the intervention is observed (i.e. pharmacodynamics and pharmacokinetics of a drug) to perform initial estimates on their short-term tolerable dose and reliability (or toxicity). They are also known as "formulation" trials.
Phase II	In this phase the minimal dose is determined with a therapeutic effect and the benefits obtained by the intervention in a small group of patients with a specific disorder or particular qualities to which the intervention could be addressed is estimated (i.e. use of maintenance medication in opiate consumers who start treatment). They are also known as "activity" trials.
Phase III	In this phase the intervention is proved in a controlled manner on a wider and diverse population of patients (i.e. with different severity degrees or in different development stages of the disorder) and is compared with a placebo or the regular intervention to demonstrate or confirm its therapeutic efficacy. During this phase a new intervention demonstrates its therapeutic effect; its safety is assessed and, finally, obtains its approval by the applicable regulatory bodies. They are also known as "efficacy" trials.
Phase IV	In this phase trials are conducted to support or optimize the clinical use of the intervention within the previously approved dose or regimen. Generally, in these studies the safety of the long-term intervention is analyzed, its interaction with other interventions (or drugs) or its effect in even larger populations of patients. They are also known as "effectiveness" trials.

Table 4. Classification of trials by development phase in behavioral treatments

Type of study	Description
Stage I	It is the initial stage in which clinical innovation is sought through the study of changes in the behavior expected from patients in the therapy and the definition of unique components and qualities of the intervention having clinical usefulness. During this stage the therapeutic effect of an intervention is tested with the generation of the Intervention Manual, a relevant training plan and an adherence and competence measure in its application that may be used in the next stages. They are also known as "clinical innovation studies".
Stage II	In this stage clinical trials are conducted in a larger sampling of "ideal" patients for the intervention and under highly controlled conditions (with the purpose of ensuring that the therapeutic effect is precisely due to the study intervention). Its purpose is testing the efficiency of an already developed intervention against other treatments or a placebo. They are also known as "Efficacy Studies".
Stage III	This stage is devoted to the preparation of clinical trials focused on studying the effectiveness of an intervention which efficacy has been demonstrated in previous studies, once it is applied in the attention community settings. The research in this stage seeks to answer questions about the interaction among the intervention components and variables present at the attention community settings (i.e. therapists' training needs). The research questions in this phase are about the implementation, acceptability (or adoption), generalizability, transportability and/or cost-benefit ratio of the intervention according to analyze the appropriateness, viability or sustainability of its incorporation to the regular clinical practice. They are also known as "Effectiveness Studies".

and exclusion criteria that must be followed for selecting patients.[9,11,19,23]

TREATMENT RANDOMIZATION

One of the most important aspects in an RCT is the randomized assignation of treatments, because this is a way for assuring that all participants in the study have an equal chance to be assigned to the (experimental or control) intervention; avoiding researchers to predict or have influence on this process and avoiding a "selection bias".[10,11,19,23,27] There are different randomization methods according to the design, sampling size and objectives of each trial, which are described in Table 5.[9-11,19,23,27]

Statistical analysis and interpretation of results

Their application allows minimizing the sources of error in the interpretation of results; therefore, it is essential to systematize the procedures to achieve a valid and reliable result analysis. As part of the statistical considerations that should be taken into account in the development of a randomized clinical trial, there are three essential topics to be developed: 1. the planning of the sampling size, 2. the randomized procedures (explained in the previous section) and 3. the statistical analysis plan.[27] In this way, a central part of the RCTs is implementing a strategy according to the objectives of the study[28,29] and based on the approach of the design.[30]

In addition, within the research protocol the *software* used for the data analysis may be briefly described, appoint the use of preliminary statistical techniques to ensure the compliance of the statistical assumptions or, if they are not complied, look for equivalent tests not having such limitations.[31] For the interpretation of results there are at least two methods: the first one refers to the "intention-to-treat" principle, which considers the inclusion of all randomized participants in the analysis, in order to keep the comparability among the intervention groups;[10,23,30,32] the second one is the "protocol analysis", in which only those that fulfilled the protocol throughout the study are considered in the results[10,30] (Table 6). On the other hand, RCTs may have two types of results comparison: superiority and non-inferior-

Table 5. Most common randomization methods

Randomization method	Description	Example
Simple randomization	It is the simplest form of random and equivalent allocation at any kind of drawing or coin tossing. In practice, this method is seldom used since it may cause an imbalance in the number of patients assigned to each group when the sample is small, or the risk that it generates an accidental bias on the allocation of interventions is very high.	In a trial comparing the effects of an Intervention A with the effects of an Intervention B, a computer randomly-generated number between 1 and 10 is assigned to each participant. • If participant obtains a number between 1 and 5 the Treatment A is assigned. • If participant obtains a number between 6 and 10 the Treatment B is assigned. All participants have a 50% chance of being assigned to one treatment or another.
Balanced-block randomization	This method is used with the purpose of ensuring a balance in the number of patients assigned to each study intervention. Consiste en los siguientes pasos: a. Generating blocks with all possible combinations among the study interventions to which a number is assigned. b. Each block shall be a "sequence" in which the intervention shall be assigned to a determined number of participants. c. Through a draw, a block will be assigned to different groups of participants until completing the sample. This method is widely used in practice. A possible disadvantage is that, if the allocation of interventions is not blind, the "unpredictable" quality of the individual allocation of treatments might be lost within a group.	En un ensayo donde se comparan los efectos de una Intervención A con los de una Intervención B: a. The following 6 blocks of combinations between letters A and B are generated: 1. AABB 3. ABAB 5. ABBA 2. BBAA 4. BABA 6. BAAB b. 4-participant groups are generated. c. Each group of participants is randomly given a number from 1 to 6. If the first group of participants (participants 1-5) obtains a 3, then the interventions in the sequence corresponding to the block 5 (ABAB) are assigned: • Participant 1: Intervention A • Participant 2: Intervention B • Participant 3: Intervention A • Participant 4: Intervention B d. Allocation of numbers from 1 to 6 to the following groups continues randomly until completing the sample.
Stratified randomization	This method is used if researchers have scientific evidence regarding any variable in patients that may have a predictive value on their intervention response (i.e. age, gender, severity of the addiction, time of abstinence, psychiatric comorbidity) in order to ensure a balanced sampling of patients with such variable in all groups. Generally, it is made by determining a number of "strata" according to the possible values of each identified variable that has a predictive power (or a potential as confessor), generating a list of combinations among the strata of all variables that will constitute "substrata". Then, a simple random or balanced-block allocation of the intervention for each group of patients included in each "substratum". In order to carry out this randomized method it is necessary to have a sufficiently extensive participant sampling that make it viable to obtain an equal number of patients with each combination of variables.	In a study the effects of an Intervention A with the effects of an Intervention B are compared with the purpose of diminishing the consumption frequency in the patient. There is evidence that response to treatment may be affected by the following characteristics of the patient: • He/she has a psychiatric comorbidity when starting treatment. • Alcohol is his/her main consumption substance. I. The following two "strata" are generated: 1.a. With psychiatric comorbidity. 1.b. Without psychiatric comorbidity. 2.a. Alcohol as main consumption. 2.b. Alcohol not being main consumption. II. Participants are grouped in the following 4 "substrata". 1.a. Patients with psychiatric comorbidity + 2.a. Alcohol as main consumption. 1.b. Patients without psychiatric comorbidity + 2.a. Alcohol as main consumption. 1.a. Patients with psychiatric comorbidity + 2.b. a. Alcohol not being main consumption. 1.b. Patients without psychiatric comorbidity + 2.b. Alcohol not being main consumption. III. A simple randomization is independently performed on each "substratum".
Dynamic randomization	It is a variation of any of the aforementioned randomized methods, except that in these cases the probability that a participant can be allocated to certain intervention group or other is being "balanced" or "adjusted" according to certain variables (i.e. gender, age) as the intervention groups are formed, with the purpose of ensuring that they are comparable among themselves. It is important to emphasize that, despite this balancing, the researchers who use this method will never be able to predict to what intervention a patient shall be allocated from his/her characteristics and that this method does not ensure that the groups are perfectly balanced.	In a trial comparing the effects of an Intervention A with the effects of an Intervention B it has been decided to perform a randomization in which the chances that a participant is allocated to one group or another will be amended according to the following variables: • Gender (male; female). • Age (between 18 and 36 years; over 37). • Main consumption substance (alcohol; cocaine; marihuana; others). Therefore, if the first randomized patient was a woman, over the age of 36, a marihuana user and was allocated by simple randomization to the Intervention A, then the randomization chances of the following patient with these same characteristics will be changed so that it may be more likely that the Intervention B is allocated.

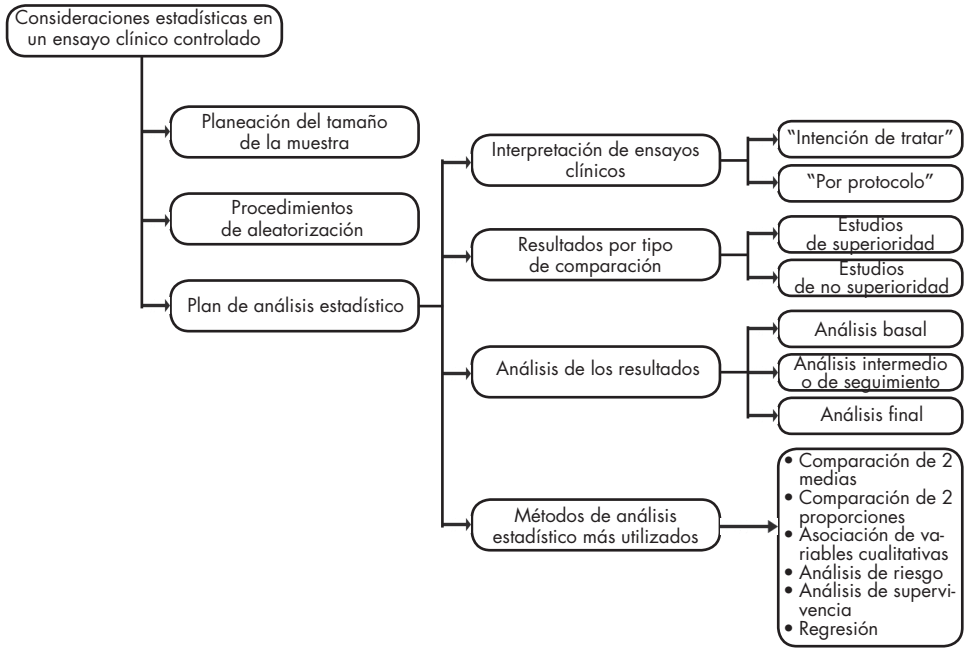

Figura 2. Consideraciones estadísticas en un ensayo clínico controlado.

ity studies. The first ones identify superiority of an intervention in terms of efficiency; the second ones show that the experimental treatment is not worse than the standard treatment. The choose option will depend on the clinical relevance and not on statistics.[10,30] In a randomized controlled clinical trial more than one data analysis is carried out throughout the study; in general they can be divided in three: baseline, middle or follow-up and final analysis. It bears mentioning that each one constitutes an indispensable element for the valid and reliable obtaining of the final results[31] (Table 7).

Clinical or treatment monitoring

A key measure to ensure internal validity in RCTs is to be able to prove that the therapeutic intervention is administered to all participants in *compliance* or *adherence* with their design and avoid the "intervention bias" both in the pharmacologic and behavioral trials.[9,11,33] In pharmacologic trials the compliance or adherence has to be ensured, which implies having a procedure to monitor that all participants receive the correct drug and following the prescribed directions such as blood samples, associated biological markers, monitoring of supplies, counting of pills, self-reporting or records review.[9,11,19,33] The choice of strategy should be based on an analysis of their reliability and usability regarding the design and objectives of the study as well as the particular features of the population of patients and the study intervention.[34]

Table 6. Clinical Trial Interpretation

Method	"Intention-to-Treat" Principle
Description	The data analysis is made by the inclusion of all participants randomized into the study, thus the events that come up throughout such analysis (lack of adherence to treatment, giving up, death, among others) are considered against the allocated treatment (Peduzzi P. et al., 2002; Green S., 2002; Lazcano-Ponce E. et al., 2004; Lazcano-Ponce E. et al., 2009).
Advantages	It keeps comparability among the intervention groups. It minimizes the bias in the study results, since the size of the sampling, defined previously, is not affected. By considering all randomized participants it avoids favoring any of the intervention groups. It provides a conservative estimate of the treatment effect.
Disadvantages	It does not allow obtaining a true assessment of the efficacy of the treatment, but allows a true assessment of the effectiveness of the treatment.
	"Analysis by Protocol"
Description	The analysis of the results only considers the participant subgroup that complies with the protocol throughout the study. This method of analysis should be designed a priori, identifying the criteria to consider the sufficient compliance of the protocol (Lazcano-Ponce E. et al., 2004; Lazcano-Ponce E. et al., 2009).
Advantages	This method facilitates that a treatment has additional efficacy.
Disadvantages	Sometimes adherence to protocol during the study may be directly related to the allocated intervention, which may cause an important bias in the results.

Table 7. Results by type of comparison

Type of Comparison	Description
Superiority of studies	The purpose of this type of comparison studies is to identify the superiority, in terms of efficacy, of an intervention against the placebo or control treatment, either because it clearly produces better results or because shows a dose-response effect.
Non-Inferiority studies	These studies intend to show that the experimental treatment is not worse than the standard treatment. However, to carry out this type of comparison it is essential that the study is conducted with the highest quality, in order to allow identification of significant differences among groups.

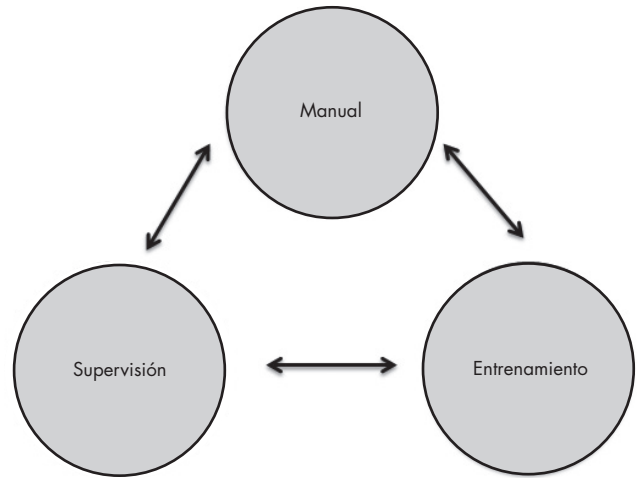

Figura 3. Elementos a considerar dentro del aseguramiento de la integridad de terapias conductuales en ensayos clínicos aleatorizados.

In behavioral interventions the internal validity is affected when there is little or no differentiation among treatments, due to diffuse interventions and to variations in the way that the intervention is conducted.[35] Therefore, the standardization of the maneuver constitutes a crucial element.[36-38] There are at least three elements to guarantee the integrity of therapies in RCTs: intervention manual, training and supervision.[26,37,39,40] The creation of a manual for a new behavioral therapy takes place in the stage I of the behavioral therapies stage model mentioned above (Table 4),[25] and implies the definition of the critical elements of the new treatment.[26,41] Regarding the training there are different challenges to be considered. They include the therapists' previous motivation, interest, experience and education level, the therapeutic approach which they usually perform their practice and the format and duration of the training offered.[42]

Beidas and Kendall (2010) suggest that didactic training without monitoring or evaluation of the subsequent practice of learned skills has little or no effect on the skill and/or adherence of the therapists to the learned maneuver. In this regard, training and supervision turn into two extremely linked processes, since under this viewpoint one learns through workshops and with ongoing supervision and feedback on the work made in the sessions.[40,43-45] Within this style two different approaches are distinguished: *expert-led and train-the-trainer*. In the *train-the-trainer* perspective (Figure 4) an expert trains other therapists in the maneuver and

Table 8. Analysis of results

	Baseline Analysis
Description	It is the first analysis of the variables carried out after the randomization of the participants in the different treatment groups.
Usefulness	Sometimes there are important differences in some main variables, which if not considered could be wrongly attributed to the intervention effect. Therefore, the identification of such variables, through the baseline analysis, allows comparisons controlling such effect by statistical analysis tests, i.e., la covariance.
	Middle Analysis
Description	It is the analysis of variables conducted throughout the study; also called follow-up analysis. One or more middle analyses can be conducted, depending upon the duration of the study.
Usefulness	The middle analysis allows observing the evolution of variables over time, whereby it is possible to establish a clinical and statistical relevance comparing the experimental and control treatment groups. In addition, in the ethical research framework the middle analysis allows identifying preliminary results that may significantly affect participants. Thus, if the experimental treatment is harmful due to unexpected adverse effects, study discontinuation shall be vital or, conversely, in case that the discontinuation is obviously better than control treatment, the study must be discontinued so that the new intervention can be available to all patients suffering from certain illness or disorder.
	Final Analysis
Description	It is conducted once the trial is finished and a definitive analysis of the results is about to be performed.
Usefulness	While the final analysis plan is contained in the research protocol, the contrasts are foreseen and the probability that the differences found are due to chance is lower.

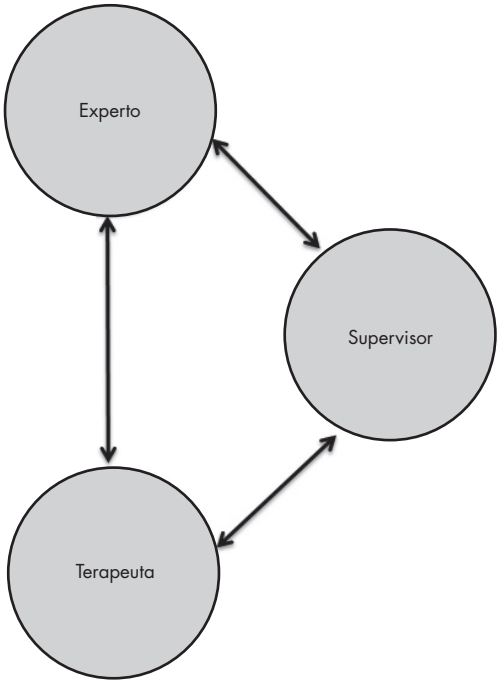

Figura 4. Perspectiva de entrenamiento y supervisión *train the trainer*.

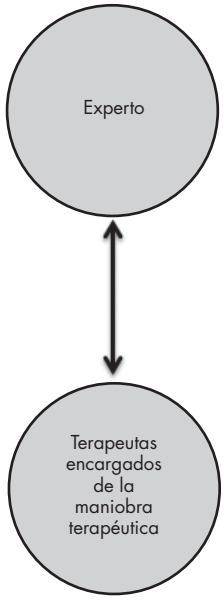

Figura 5. Perspectiva de entrenamiento *expert-led*.

in turn teaches them how to train other persons at their treatment center, holding constant feedback, monitoring and supervision sessions.[46]

In this approach, unlike the *expert-led* (Figure 5), there is the advantage of having an expert who knows the treatment and at the same time has the ability to train and supervise other professionals. Thus, he becomes a supervisor whose practice favors the fidelity for the therapeutic maneuver, and therefore protects the internal validity of the study.[47] Ongoing training, accreditation and supervision are linked to the training and technology transferring process, which results in the spreading and use of maneuvers efficient and effective in real scenarios,[47,48] representing a major challenge in the attention of substance use.[42]

Security monitoring

The evidence that supports the clinical decision for using an intervention over another is constituted in the same dimension both for its demonstrated efficacy and effectiveness and for its possible iatrogenic or undesirable effects, in all patient populations where it could potentially be applied. Therefore, having a data collection mechanism or system regarding all these effects in the participants is a regulatory requirement in the conduction of clinical trials. During an RCT conduction all of these undesired effects are identified as "adverse events".[9,10,49] In the addiction and other mental health disorders treatment patients have a higher risk of developing kidney, heart or respiratory diseases and infections associated with the consumption; as well as accidents, sexual risk behaviors, violent behavior or problems with the law owed to substance abuse; besides an aggravation of the psychiatric symptomatology, or even suicidal behaviors, caused by alcohol or drugs use1,[5,8,15,50,51] or difficulties in family, work or social functioning of the subject.[52]

An RCT performance must include an appropriate plan for the identification, assessment, follow-up and reporting of possible adverse events. The mechanisms or tools used to carry out this safety-monitoring system must be part of the research protocol.[9,52] Table 9 shows a proposal of the different categories of adverse events that are to be identified in an RCT participants.[9] The whole knowledge that researchers have regarding possible risks or adverse events detected and related to the study intervention must be informed to the relevant regulatory authorities (i.e. institutional ethics committees) and, if necessary, to all study participants.

DATA MANAGEMENT

The purpose of the RCT is generating data from which it may be possible to provide an answer to a research question. One of the processes associated with this task is data management, which is a process started prior to recruitment. Its purpose is to assure the quality of the data generated that, at a large extent, depends on the clarity whereby the objectives and the statistical analysis of the study have been defined.[9] The results reported at the end are as good as the quality of the gathered and analyzed data. A "good"

Table 9. Categories of Adverse Events

Category	Description
Serious Adverse Events	They are all adverse events resulting in patient's death, life threat, hospitalization (or unscheduled prolongation of existing hospitalization); causing a persistent, irreversible or significant disability of patient; a congenital disorder or birth defect; or the requirement of medical or psychiatric intervention to avoid any of the previous situations.
Regular Adverse Events	They are all signs, symptoms, or deterioration of preexisting conditions detected in the participant either through self-report, or by clinical results observation or observation made by the interviewer or clinician. These events may vary as for severity or impact on participant's health.
Special Interest Adverse Events	They are all adverse (serious, general or of any severity) events that for the purposes of the protocol shall be especially identified and classified because scientific evidence reviews —or reviews determined by an expert council consulted for this purpose— have proved that they may impact the interpretation of results, or the applicability, of the study intervention. In other words, they may be related to or associated with the study intervention.

result is the one that provides *correct* answers to the questions posed initially; not positive or statistically significant results.[53] The data management plan covers from the design of the Case Report Forms (CRFs) to the data delivery for the statistic analysis. Thus, data need to be continually monitored during the study and during the study as much data as possible are to be gathered.[54]

The introduction of new technologies in the data management process has significantly reduced the errors that were made when gathered through CRFs and substituted by electronic CRFs. Today, the so-called Clinical Data Management Systems (CDMS) are used. Likewise, the inclusion of the Internet allows that the CDMS are available on line, allowing data gathering and/or monitoring in different places and schedules.

ETHIC CONSIDERATIONS

"Equipoise" or principle of uncertainty about treatments

The first ethical implication associated to clinical trials has to do with the random allocation of therapeutic interventions. If the researchers or clinicians who collaborate in recruitment and treatment of patients for a clinical trial have "certainty" about the therapeutic advantages of one intervention over another, they have the ethical obligation to provide the patient with the intervention that has more chances to represent a benefit for him/her.[49,55]

Freedman (1987) has suggested the "*Equipoise*" ethical principle establishing that in order that an RCT can be conducted, the study interventions must be "comparable" among themselves regarding the therapeutic benefit they represent for the patient. This implies that the researchers, while not having control on what therapeutic intervention will be provided to the participants, must be in a state of "genuine uncertainty" about the possible therapeutic benefit the study participant will receive, regardless of the intervention assigned. The last function of the intervention research would be solving such uncertainty.[55-57]

Participants quality and protection plan

Although treatments research is older,[58] it was not until the 20th century XX that the necessity to have standards and regulations was acknowledged in order to ensure the protection of human participants in a research.[9,10,49] Table 10 shows in detail a relationship of the main guides developed for these purposes.[58-64] Every intervention research conveys an important ethical dilemma in the quality of its results, since such results will support a decision of health, both of the participants and of the patients who will potentially be benefited by said decision. In 1990, in a standardization effort conducted by several drug regulatory agencies located in different countries [encompassed within the International Conference on Harmonisation (ICH)], about research with humans, the Good Clinical Practice (GCP) Guidelines were established.[58] Every clinical trial should include the development of a quality monitoring plan where a follow-up of the evolution of the study participant is recorded. The objective of such plan, according to the GCPs, is assuring that: a) the human subjects' rights and well-being are protected, b) the reported data of the study are complete, accurate and verifiable; c) the application of the study is made pursuant to the design and procedures reported by researchers, to the GCPs, and to the applicable regulations.[63,64] An essential point is the constant audit of the trial from its design, planning, execution & analysis and reporting of results in which authorities, sponsors, researchers and collaborators associated with the study must be involved.

Informed consent and confidentiality

In Mexico, the General Health Law, in its Article 20 of the health research regulation, defines informed consent as: "*the written agreement, through which the research subject or, as the case may be, his/her legal representative approves his/her participation in the research, in full awareness of the nature of the implying procedures and risks, with free choice and without any coercion*".[62] The informed consent incorporate the particularities of the subject's participation in the research, and the patient's decision about participating on it is documented.[65] It is the responsibility of the researchers to write it in a clear

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Table 10. Evolution of the applicable regulations

Applicable regulations	Description
Nuremberg Code (1947)	It puts forward and specifies the legitimacy of medical research; as well as the informed consent process and absence of coercion in the participation of subjects.
Declaration of Geneva (1948)	t is a document in which the physician commits himself/herself to conduct an ethical and honorable professional practice.
Declaration of Helsinki (1964)	The World Medical Association published such statement as "ethical principles for medical research involving human subjects, including research on identifiable human material and data." (Introduction, point 1: http://http://www.wma.net/en/30publications/10policies/b3/index.html).
National Research Act (U.S.) (1974)	1979 Belmont Report; three core ethical research principles involving human subjects are identified: respect, beneficence, and justice.
Mexican General Health Law (1983)	Regulations of the general health law in health research (1987).
International Conference on Harmonisation (ICH; agreement among U.S., Japan and the European Union) (1990)	It brings together the regulatory authorities of Europe, Japan and the United States to discuss scientific and technical aspects of pharmaceutical product registration.
Good Clinical Practice (GCP) -Document of the Americas (2005)	According to ICH: "international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subject" (CPMP/ICH/135/95).

and unambiguous manner, following a content structure.[63,64] Table 11 shows a content proposal for the informed consent document according to the General Health Law and the Good Clinical Practices.[62,63]

The participant should receive a duplicate of the signed informed consent document, and the procedure whereby it was obtained should be disclosed.[11,49,62] A clinical research usually deals with personal aspects of participants which handling is sensitive. In the particular case of researches about substance use disorders this information acquires greater sensitivity, since participants are exposed to legal or social consequences if their identity as participants in a clinical trial was disclosed.[49] All information that could identify the participants must be kept strictly confidential. It is essential that —prior to their recruitment— researchers inform participants as well as the relevant regulatory authorities about the procedures to be followed to guarantee the confidentiality of participants and about those cases in which such confidentiality may be limited (i.e. if during the participation a suicide risk is identified in the patient, his/her relatives and responsible clinicians shall be informed so that the patient can be referred to a specialized healthcare).[10,11,49]

DRAFTING A PROTOCOL

The research protocol is a document where researchers make public all considerations taken regarding the execu-

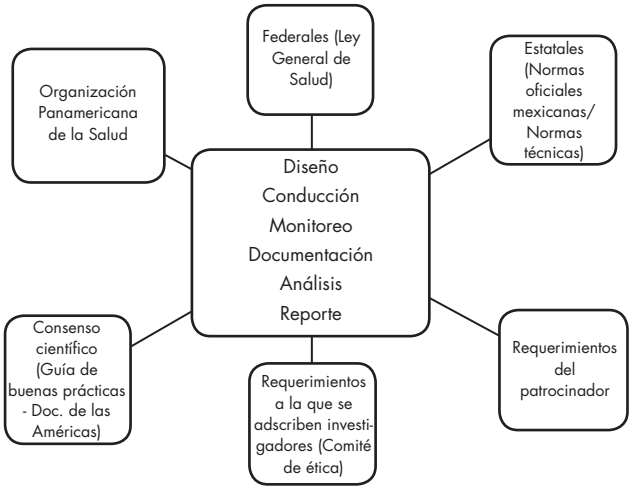

Figura 6. Regulaciones aplicables a los procesos de un ensayo clínico.

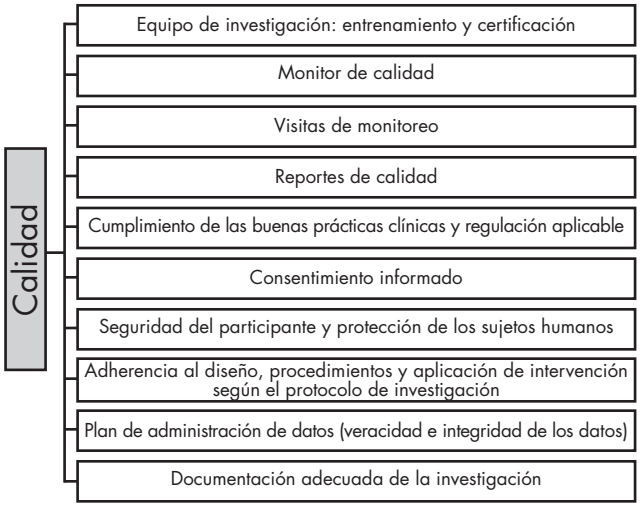

Figura 7. Componentes para asegurar la calidad de la investigación.

Table 11. Content structure proposal for the informed consent document (ICD)

I.	Title of the study
II.	Proposal or objectives of the study
III.	Research procedures
IV.	Possible risks and discomforts
V.	Possible benefits and alternatives
VI.	Possible costs of their participation
VII.	Incentives to be received by their participation (if any); guarantees on their participation confidentiality
VIII.	Right to withdraw
IX.	Deadline of maintenance of records; contact information of researchers
X.	Section to record the signature of: i. participant, or his/her legal representative ii. person who obtains the ICD iii. two witnesses

tion of a RCT for review by the regulatory authorities, sponsors and scientific community in general. Such document shall describe in detail all elements and procedures that will be carried out. Although there is no universal agreement on what a protocol document must contain, since it may vary according to each trial, efforts have been made to offer an standard of the minimum contents that are to be included, such as: background and reasoning of the study, research objectives and question, target population, study interventions, participants recruitment and randomization method, statistical analysis plan and ethical considerations. Additionally, once its effect has been proved the intervention spreading plan and the study management plan may be included.[9-11,27,66]

CONCLUSIONS

In this work we have reviewed, although not thoroughly, the main methodological aspects related to the RCTs when they are used to carry out research projects in the addiction field. We can conclude that these guidelines are the essential foundation to carry out clinical research tasks in this area with a high degree of quality. Thus, the results obtained may be reproduced by other centers or be extended to other health authorities.

Recently, in the Clinical Trials Unit of the Department of Clinical Research of the INPRFM a research project was started with a behavioral intervention in patients with addictions, for which a strict methodological training was necessary. Learning and experience thereof set the standard for this article. Therefore, we consider that its content will help to establish the minimum and essential guidelines for future studies.

REFERENCES

1. **UNODC. World Drug Report 2012. United Nations publication. Sales No. E.12.XI.1**
2. **Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz; Instituto Nacional de Salud Pública; Secretaría de Salud. Encuesta Nacional de Adicciones 2011; México; 2012.**
3. **Secretaria de Salud. Subsecretaría de Prevención y Promoción de la Salud. Dirección General Adjunta de Epidemiología. Dirección de Investigación Operativa Epidemiológica. Sistema de Vigilancia Epidemiológica de las Adicciones (SISVEA). Informe 2009; México; 2009.**
4. **World Health Organization. The Global Burden of Disease: 2004 update. United Nations publication.; 2008.**
5. **Ocampo R., Bojórquez I., Cortés M. Consumo de sustancias y suicidios en México; resultados del Sistema de Vigilancia Epidemiológica de las Adicciones, 1994-2006. Salud Pública Mex; 2009; 51: 306-313.**
6. **WHO, UNODC. Principles of Drug Dependence Treatment: Discussion Paper. United Nations publication 2008.**
7. **Degenhardt L., Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet 2012; 379:55-70.**
8. **Strang J., Babor T., Caulkins, J., Fischer B., Foxcroft D., Humphreys K. Drug policy and the public good: evidence for effective interventions. Lancet 2012; 379: 71-83.**
9. **Friedman LM, Furberg CD, DeMets, DL. Fundamentals of Clinical Trials. 4th. Ed. New York. Springer; 2010.**
10. **Lazcano-Ponce E, Salazar-Martínez E, Gutierrez-Castrellón P, Angeles-Llerenas A, Hernández-Garduño, A. Viramontes, JL. Ensayos clínicos aleatorizados: variantes, métodos de aleatorización, análisis, consideraciones éticas y regulación. Salud Pública Mex; 2004; 46(6): 559-584.**
11. **International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Harmonised Tripartite Guideline: General considerations for Clinical Trials. E8. ICH Harminised Tripartite Guideline; 1997. Obtenido en: www.ich.org.**
12. **Moher D, Shulz K, Altman D. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285(15):1987-1991.**
13. **McLelland, T. Congratularions on the 10-year anniversary of the National Drug Abuse Treatment Clinical Trial Network – Now, what's new for the coming decade?. Journal of Substance Abuse Tretment; 2010; 38(Suppl 1): S1-S3.**
14. **Rojas E, Real T, García-Silberman S, Medina-Mora ME. Revisión sistemática sobre tratamiento de adicciones en México. Salud Mental 2011; 34: 351-365.**
15. **Marín-Navarrete R, Benjet C, Borges G, Eliosa-Hernández A, Nanni-Alvarado R, Ayala-Ledesma, M, Fernández-Mondragón J, Medina-Mora ME. Comorbilidad de los trastornos por consumo de sustancias con otros trastornos psiquiátricos en centros residenciales de ayuda-mutua para la atención de las adicciones (CRAMAA). En prensa.**
16. **Tiet QQ, Mausbach, B. Treatments for patients with dual diagnoses: a review. Alcoholism: Clinical and Experimental Research 2007; 31(4): 513-536.**
17. **Medina-Mora ME, Borges G, Lara-Muñoz C, Benjet C, Blanco-Jaimes J, Fleiz-Bautista C, Villatoro-Velázquez J, Rojas-Guiot E, Zambrano-Ruiz J, Casanova-Rodas L, Aguilar-Gaxiola S. Prevalencia de trastornos mentales y uso de servicios: Resultados de la Encuesta Nacional de Epidemiología Psiquiátrica en México. Salud Mental 2003; 26(4):1-16.**
18. **Carroll K. Dissemination of evidence-based practices: how far we've come, and how much further we've got to go; Addiction 2012; 107: 1031-1033.**
19. **Lees B, Nitsch D, Wang D, Bakhai A. Patient Selection. En: Wang , Bakhai A (eds). Clinical Trials. A Practical Guide to Design, Analysis, and Reporting. Chicago. Remedica; 2006.**
20. **Clarke G. Improving the transition from basic efficacy research to effectiveness research in substance abuse treatment. Journal of Substance Abuse Treatment; 1995; 63(5): 718-725.**

Translation of the original version published in spanish in: Salud Mental 2015, Vol. 36 Issue No. 3.

21. Robbins M, Alonso E, Horigian V, Bachrach K, Burlew K, Carrión I, Hodgkins C, Miller M, Schindler E, VanDeMark , Henderson C, Szapocznik J. Transporting Clinical Research to Community Settings: Designing and Conducting a Multisite Trial of Brief Strategic Family Therapy. Addiction Science & Clinical Practice; 2010; 5(2): 54-61.
22. Hien D, Cohen L, Campbell A. Methodological Innovation to Increase the Utility and Efficiency of Psychotherapy Research for Patients with Co-ocurring Mental Health and Substance Use Disorders. Professional Psychology Research and Practice; 2009; 40(5): 502-509.
23. Green S. Design of Randomized Trials. Epidemiologic Reviews; 2002; 24(1): 4-11.
24. Carroll K, Onken L. Behavioral Therapies for Drug Abuse. American Journal of Psychiatry; 2005; 162: 1452-1460.
25. Onken L, Blaine J, Battjes, R. Behavioral therapy research: A conceptualization of a process. En: Henngler S, Amentos R (eds), Innovative approaches from difficult to treat populations. Rochester, N.Y: University of Rochester Press; 1997.
26. Rounsaville B, Carroll K, Onken L. A Stage Model of Behavioral Therapies Research: Getting Started and Moving on From Stage 1. Clinical Psychology and Social Practice; 2001; 8:133-142.
27. Knatterud GL. Management and Conduct of Randomized Controlled Trials. Epidemiologic Reviews; 2002; 24(1): 12-25.
28. European Medicines Agency (2006) Statistical Principles for Clinical Trials. Recuperado de http://www.emea.eu.int
29. Guillén A., Carreño A., Canal N. (2006) Fases del análisis estadístico de los datos de un estudio. En Guillén A y Crespo R. (Ed.) Métodos estadísticos para enfermería nefrológica. (pp. 247-260) España: Sociedad Española de Enfermería Nefrológica, SEDEN. Recuperado de http://www.revistaseden.org/files/17-CAP 17.pdf
30. Lazcano-Ponce E., Salazar-Martínez E., Gutiérrez-Castrellón P., Ángeles-Llerenas A., Hernández-Garduño A., Viramontes J.L. (2009). Ensayos Clínicos Aleatorizados. En Hernández M. (Ed.). Epidemiología: Diseño y análisis de estudios. (1ª ed., pp.77-119). México: Editorial Médica Panamericana e Instituto Nacional de Salud Pública.
31. Álvarez-Cáceres R. (2005). Ensayos Clínicos: diseño, análisis e interpretación. España: Díaz de Santos.
32. Peduzzi P., Henderson W., Hartigan P., Lavori P. (2002). Analysis of Randomized Controlled Trials. Epidemiol Rev, 1(24), 26-38.
33. Cramer J, Roy A. Burrell A, Fairchild C, Fuldeore M, Ollendorf D, Wong P. Medication Compliance and Persistence: Terminology and Definitions. Value in Health; 2008. 11(1): 44-47.
34. Farmer K. Methods for measuring and monitoring medication adherence in clinical trials and clinical practice. Clinical Therapeutics; 1999; 21(6): 1074-1090.
35. Kazdin AE. Methods of psychotherapy research. En Bongar B, Beutler E (eds.). Comprehensive textbook of psychotherapy: Theory and practice. New York: Oxford University Press.
36. Yeaton, W. H. & Sechrest, L. (1981). Critical dimensions in the choice and maintenance of successful treatments: Strength, integrity, and effectiveness.(Journal of Consulting and Clinical Psychology, 49, 156-167).
37. Carroll K, Martino S, Rousanville B. No Train, No Gain? Clinical Psychology: Science and Practice 2010;17:36-40.
38. Waskow IE. Specification of the technique variable in the NIMH Treatment of Depression Collaborative Research Program. En Williams J, Spitzer R (eds). Psychotherapy research: Where are we and where should we go. New York: Guilford Press;1984.
39. Chambless DL, Hollon SD. Defining empirically supported therapies. Journal of Consulting and Clinical Psychology 1998;66:7–18.
40. Beidas R, Kendall PC. Training therapists in evidence-based practice: A critical review of studies from a systems-contextual perspective. Clinical Psychology: Science and Practice 2010;17: 1–30.
41. Marcus M, Liehr P, Schmitz J, Moeller G, Swank P, Fine M, Cron S, Granmayeh K, Carroll D. Behavioral Therapies Trials: A Case Example. Nurs Res 2007;56(3):210–216.
42. Carroll K, Farentinos C, Ball S, Crits-Christoph P, Libby B, Morgenstern J, Obert J, Polcin D, Woody G. MET meets the real world: design issues and clinical strategies in the Clinical Trials Network. Journal of Substance Abuse Treatment 2002;23:73–80.
43. Miller W, Yahne C, Moyers T, Martínez J, Pirritano M. A Randomized Trial of Methods to Help Clinicians Learn Motivational Interviewing. Journal of Consulting and Clinical Psychology 2004;72:1050–1062.
44. Martino S, Carroll K, Ball S. Teaching, monitoring and evaluating motivational interviewing practice. En Tober G, Raistrick D. (eds). Motivational Dialogue: preparing addiction professionals for motivational interviewing practice. New York: Routledge/Taylor & Francis Group; 2007.
45. Carpenter KM, Cheng WY, Smith JL, Brooks AC, Amrhein PC, Wain RM, Nunes EV. "Old dogs" and new skills: how clinician characteristics relate to motivational interviewing skills before, during, and after training. J Consult Clin Psychol. 2012;80(4):560-573.
46. Martino S, Ball S, Nich C, Canning-Ball M, Rounsaville B, Carroll K. Teaching community program clinicians motivational interviewing using expert and train-the-trainer strategies. Addiction 2010;106:428–441.
47. Amodeo M, Storti S, Larson, M. Moving Empirically Supported Practices to Addiction Treatment Programs: Recruiting Supervisors to Help in Technology Transfer. Substance Use and Misuse 2010;45:968–982.
48. O´Donovan A, Halford W, Walters B. Towards Best Practice Supervision of Clinical Psychology Trainees. Australian Psychologist 2011;46:101–112.
49. Sugarman J. Ethics in the Design and Conduct of Clinical Trials. Epidemiologic Reviews; 2002; 24(1): 54-58.
50. Adrian M, Barry S. Physical and mental health problems associated with the use of alcohol and drugs. Substance Use and Misuse; 2003; 38: 1575-15614.
51. Petry N. Roll J, Runsaville B, Ball S, Stitzer M, Peirce, J, Blaine J, Kirby K, McCarty D, Carroll K. Serious adverse events in randomized psychosocial treatment studies: Safety of Arbitrary Edicts? J Consult Clin Psycol; 2008; 76(6):1076-1082.
52. Horigian V, Robbins M, Dominguez R, Ucha J, Rosa C. Principles for defining adverse events in behavioral intervention research: lessons from a family-focused adolescent drug abuse trial. Clinical Trials; 2010; 7(1): 58-68.
53. McFadden E. Management of Data in Clinical Trials. 2nd. Ed. Hoboken N.J. Wiley Series in Probability and Statistics; 2007.
54. Krishnankutty B, Bellary S, Kumar B, Moodahahu L. Data management in clinical research. Educational Forum; 2012; 44(2): 168-172.
55. Freedman B. Equipoise and the ethics of clinical research. New England Journal of Medicine; 1987; 317(3): 141-154.
56. Ubel P, Silbergleit R. Behavioral equipoise: a way to resolve ethical stalemates in clinical research. The American Journal of Bioethics; 2011; 11(2): 1-8.
57. Weijer C, Shapiro S, Cranley-Glass K, Enkin M. For and Against: Clinical Equipoise and not the uncertainty principle is the moral underpinning of the randomized controlled trial. British Medical Journal; 2000; 321: 756-758.
58. Tribunal Internacional de Núremberg. Código de Núremberg. 1947. Obtenido de: www.bioeticanet.info/documentos/Nuremberg.pdf
59. World Medical Association; WMA Declaration of Geneva. 1948. Obtenido de: http://www.wma.net/en/30publications/10policies/g1/
60. Declaración de Helsinki de la Asociación Médica Internacional. Principios éticos para las investigaciones médicas en seres humanos. Seúl; Asamblea Médica Internacional; 2008. Obtenido en: www.wma.net/es/30publications/10policies/b3/17c_es.pdf
61. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. El Informe Belmont. Principios y Guías éticas para la protección de los sujetos humanos en investigación. EE.UU., 1979. Obtenido en www.bioeticaweb.com/index2.php?option_content&do_pdf=1&id=1060.
62. Reglamento de la Ley General de Salud en materia de Investigacion para la Salud. Título Segundo: de los aspectos éticos de la investigación

en seres humanos. Capítulo 1: Disposiciones generales. 1983. Obtenido en: http://www.salud.gob.mx/unidades/cdi/nom/compi/rlgsmis.html

63. International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice. E6(R1.; 1996. Obtenido en: www.ich.org.

64. Organización Panamericana de la Salud. Grupo de trabajo en Buenas Prácticas Clínicas. Buenas Prácticas Clínicas: Documento de las Américas. Obtenido en www.paho.org/spanish/ad/ths/ev/BPC-doct-esp.doc

65. Mondragón-Barrios L. Ética en la Investigación Psicosocial. Salud Mental; 2007; 30(6): 25-31

66. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013; 158(3):200-207.

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