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

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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 está 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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{14} and to the fact that not all treatments operate in the same way.\textsuperscript{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?\textsuperscript{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 2. Classification of trials by sequenced objectives

<table>
<thead>
<tr>
<th>Type of trial</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Exploratory trial</td>
<td>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.</td>
</tr>
<tr>
<td>2. Confirmatory trial</td>
<td>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.</td>
</tr>
<tr>
<td>3. Therapeutic use trial</td>
<td>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.</td>
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</table>

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).8-11,19,20,23 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...
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 patients 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.

**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) in intervention; avoiding researchers to predict or have influence on this process and avoiding a “selection bias”. There are different randomization methods according to the design, sampling size and objectives of each trial, which are described in Table 5.

**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. In this way, a central part of the RCTs is implementing a strategy according to the objectives of the study and based on the approach of the design.

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. 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. The second one is the “protocol analysis”, in which only those that fulfilled the protocol throughout the study are considered in the results (Table 6). On the other hand, RCTs may have two types of results comparison: superiority and non-inferior-

| 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 patients 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”. |
Conducting randomized controlled clinical trials (RCT) for addictive disorder’s interventions

Table 5. Most common randomization methods

<table>
<thead>
<tr>
<th>Randomization method</th>
<th>Description</th>
<th>Example</th>
</tr>
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<tbody>
<tr>
<td>Simple randomization</td>
<td>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.</td>
<td></td>
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<tr>
<td>Balanced-block randomization</td>
<td>This method is used with the purpose of ensuring a balance in the number of patients assigned to each study intervention. It is a variation of any of the aforementioned randomization methods, except that in these cases the probability of intervention assignment is increased for individuals with certain characteristics.</td>
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<tr>
<td>Stratified randomization</td>
<td>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 &quot;strata&quot; according to the possible values of each identified variable that has a predictive power (or a potential as confounder), generating a list of combinations among the strata of all variables that will constitute &quot;stratum&quot;. Then, a simple or balanced-block allocation of the intervention for each group of patients included in each &quot;stratum&quot;. 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.</td>
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<tr>
<td>Dynamic randomization</td>
<td>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 &quot;balanced&quot; or &quot;adjusted&quot; 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.</td>
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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.

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
   - 2. BABB
   - 3. ABAB
   - 4. BABA
   - 5. ABBA
   - 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.

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.
- Patients with psychiatric comorbidity + patients without psychiatric comorbidity.
- Patients with main consumption.
- Patients without main consumption.
- Patients with psychiatric comorbidity + patients without psychiatric comorbidity.
- Patients with main consumption.
- Patients without main consumption.
- Patients with main consumption.

III. A simple randomization is independently performed on each "stratum".

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.
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. 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 (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. 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. 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.

![Figure 2. Consideraciones estadísticas en un ensayo clínico controlado.](image)

**Table 6. Clinical Trial Interpretation**

<table>
<thead>
<tr>
<th>Method</th>
<th>&quot;Intention-to-Treat&quot; Principle</th>
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<tbody>
<tr>
<td>Description</td>
<td>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).</td>
</tr>
<tr>
<td>Advantages</td>
<td>It keeps comparability among the intervention groups.</td>
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<td></td>
<td>It minimizes the bias in the study results, since the size of the sampling, defined previously, is not affected.</td>
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<td></td>
<td>By considering all randomized participants it avoids favoring any of the intervention groups.</td>
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<td></td>
<td>It provides a conservative estimate of the treatment effect.</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>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.</td>
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<thead>
<tr>
<th>&quot;Analysis by Protocol&quot;</th>
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<tbody>
<tr>
<td>Description</td>
<td>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).</td>
</tr>
<tr>
<td>Advantages</td>
<td>This method facilitates that a treatment has additional efficacy.</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Sometimes adherence to protocol during the study may be directly related to the allocated intervention, which may cause an important bias in the results.</td>
</tr>
</tbody>
</table>
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. Therefore, the standardization of the maneuver constitutes a crucial element. There are at least three elements to guarantee the integrity of therapies in RCTs: intervention manual, training and supervision. 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), and implies the definition of the critical elements of the new treatment. 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.

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. 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

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**Table 7. Results by type of comparison**

<table>
<thead>
<tr>
<th>Type of Comparison</th>
<th>Description</th>
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<tbody>
<tr>
<td>Superiority of studies</td>
<td>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.</td>
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<tr>
<td>Non-Inferiority studies</td>
<td>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.</td>
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**Table 8. Analysis of results**

<table>
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<tr>
<th>Description</th>
<th>Usefulness</th>
<th>Usefulness</th>
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<tbody>
<tr>
<td>Baseline Analysis</td>
<td>It is the first analysis of the variables carried out after the randomization of the participants in the different treatment groups.</td>
<td>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.</td>
</tr>
<tr>
<td>Middle Analysis</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Final Analysis</td>
<td>It is conducted once the trial is finished and a definitive analysis of the results is about to be performed.</td>
<td>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.</td>
</tr>
</tbody>
</table>
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.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

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Serious Adverse Events</td>
<td>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.</td>
</tr>
<tr>
<td>Regular Adverse Events</td>
<td>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.</td>
</tr>
<tr>
<td>Special Interest Events</td>
<td>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.</td>
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</tbody>
</table>

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.56–57

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.38–64 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.63–64 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
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-
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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.

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 |

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.

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Declaration of conflict interest: None