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PROPOSAL OF GUIDELINE FOR CLINICAL TRIAL PROTOCOLS WITH HERBAL DRUGS

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SUMMARY

Cuba has extensive experience about herbal drugs, however only a few products get to the clinical phase of drug development. Our objective was to design new guidelines for clinical trials with herbal drugs.

A detailed bibliographic search about regulatory aspects about clinical trials in Cuba and the world was done for development of the guideline. The guideline's proposed format includes: 1) Index, including the classification of the content. 2) Summary, 3) Fifteen chapters, related to the clinical trials. The guideline also propose the inclusion of annexes.

A new guideline containing 15 chapters allows for writing more clear and detailed clinical trial protocols. The guideline contains the information required to guide the research staff who is interested in the validation of herbal drugs pharmacological activations from the perspective of clinical trials.

KEY WORDS: Herbal drugs. Clinical trial. Guía clínica

RESUMEN Cuba tiene experiencia extensa sobre plantas medicinales, aunque solo algunos productos llegan a una fase clínica del desarrollo. Nuestro objetivo fué diseñar una nueva guía para ensayos clínicos con plantas medicinales.

Hemos realizado una detallada búsqueda bibliográfica sobre aspectos reguladores de ensayos clínicos en Cuba y el resto del mundo para el desarrollo de la guía. El formato propuesto de la guía incluye: 1) Índice, incluyendo la clasificación de los contenidos. 2) Resumen, 3) Quince capítulos, relacionados con los ensayos clínicos. La guía también propone la inclusión de anexos.

La nueva guía que contiene 15 capítulos que orientan la redacción de protocolos de ensayos clínicos más claros y más detallados. La guía contiene la información requerida para orientar al personal investigador interesado en la validación de la actividad farmacológica de las plantas medicinales desde la perspectiva de los ensayos clínicos.

PALABRAS CLAVE: Herboristeria. Ensayos Clínicos. Protocolos

BACKGROUND

In 1998 the editors of the New England Journal of Medicine declared: "It is time that the scientific community stops the free walking in alternative medicine"¹. This statement was based on the fact that few scientific publications in this field. From that moment, practitioners and researchers specialized in alternative medicine initiate the defense of their discipline by publication of clinical investigations. During the past few years, medicinal plants and herbal drugs have occupied a relevant position not only in the developing world but also in the industrialized nations²⁻³. There is evidence that the adequate use of these products may help to improve the health of the population. For that reason it is necessary the development of an adequate guideline for performing clinical trials with these products.

The World Health Organization (WHO) considers that to telling the difference between myth and reality is essential. These two aspects are closely linked in traditional medicine, and thus researchers should be able to determine which practices and products are valid and which ones are worthless and dangerous using the scientific methods employed by modern medicine. The WHO promotes the search for evidence by means of adequate methods based on the principles of safety, efficacy and quality⁴. The implementation of regulations that guarantee these principles in one of the goals of the drug regulatory agencies⁵.

The phase of clinical development of a new drug is extremely important and requires careful attention. It is necessary the implementation of safe and efficient methodologies to measure if the product can be used for its main goal, solving a health problem. It is also necessary that the scientific and technical personnel working on this field has adequate qualification in the area.

There is a critical step in the process of developing a new drug involves a series of studies to be fulfilled before the presentation of the product for registration of the product.

The requirements for a synthesized molecule of which its efficacy and adverse effects are unknown, should not be the same that botanical products that are been used in different countries in its traditional form of administration⁶⁻⁷. This does not mean that we should limite evaluation of the safety and efficacy of a plant to popular wisdom. Each component may contain several biological activity substances with the potential of causing undesirable effects, some of which could remain unnoticed in a inappropriately designed investigation. Undesirable effects presenting a high incidence rate could be noticed by the population, but the long term effects could go undetected even for well trained observers. That is why the regulatory agencies established procedures for authorization of clinical trials. Regulatory agencies have the responsibility of ruling and controlling the new drug investigation process; supervising the use of the correct methodology and the appropriate interpretation of the results, and avoiding biased conclusions.

In Cuba, many studies with herbal drugs have been carried out, however few of them reach the clinical phase of drug development. Taking into account this situation we decided to propose guidelines for the design of herbal drug clinical trials protocols, and to discuss the updated Cuban regulations in this type of research.

MATERIALS AND METHODS

The guidelines for designing herbal drug clinical trial protocols was drawn up after the complexation of a careful bibliographical revision about the regulatory aspects for clinical trials in Cuba and the world. Other available methodological guidelines were consulted⁸⁻¹⁰.

The following aspects were includes in the guidelines:

1. An index to organize the content
2. A summary of the protocol
3. Fifteen chapters including the fundamental aspects in the designing of an herbal drug clinical trial protocol.

The guidelines also propose the inclusion of annexes.

In order to facilitate the use of the guidelines and to obtain a well organized final protocol, the chapters also include a corresponding subheading.

The documentation required for the registration file and the requirements for registration for human use are also included.

RESULTS

The new guidelines for preparing herbal drug clinical trial protocols includes the following information:

Index: It was done taking into account a total of 15 chapters and subheading. Summary: It contains the synthesis of why, what for, and how the study is done, including the objectives of the trials, its design (size of the sample, masking, randomization, study and control group, length of the investigation), the characteristics of the population that will be studied (illness or condition to be treated and most relevant aspects of the criteria of inclusion and exclusion), ethical considerations, statistical analysis plan, practical considerations and legal aspects.

I- General Information: It is presented in 10 subheadings that included: title, of the clinical trial, coordinating unit, promoting center, scientific committee, leading researcher, monitor, project manager, person in charge of data handling, person in charge of statistical analysis, and institutional review board.

II- Introduction: It is divided into two items

- 1) basic data of the health problem itself and its context. This includes a brief description of the problem that requires a therapeutic solution, and
- 2) justification of the proposed study, including the pre-clinical studies (toxicology and experimental pharmacology) carried out and the available clinical experience.

III- Objectives: It explains how to formulate the objectives (general and specific) and the hypothesis of the study.

IV- Medical Deontology: The ethical considerations of the trial are presented in two sections: General ethical considerations of the investigation, and informed consent.

V- General Conception: The most relevant aspects to be considered in the design of the clinical trial are described

VI- Subject selection: The characteristics of the subjects to be included in the clinical trials are described.

VII- Treatment: The following considerations are established: Pattern of group treatment dose and administration procedures.

VIII- Adverse Events: The procedures for the identification and description of the adverse events that might occur during the trial, as well as the categories used to report the intensity and causality of these events are established.

IX- Response assessment: The necessary variables to assess and measure the outcomes of the treatment (effect/effectiveness and safety) are specified

X- Collecting and handling of data: This chapter provides information about the use of forms to record the information of the trial: notebook for the collecting of data (detailing each module), informed consent form, included/not included record, subject's identification and outcomes record.

XI- Statistics: The following subheadings are included: sample size, including the number of subjects required, and statistical analysis plan.

XII- Calendar: A detailed schedule for the study is included.

XIII- Practical considerations: It contains the aspects related to the implementation of the study once the protocol was approved, as well as other considerations about the organization of workshops, and the duties and responsibilities of the involved parts.

XIV- Resources and legal aspects: The required human and material resources are described. The legal and regulating requirements for the clinical trial (authorization and approval by the sanitary authorities, ethic committed and institutional review board) are included.

XV- Bibliographic References: The updated list of all the bibliographic material consulted in the elaboration of the clinical trial protocol is included.

XVI- Annexes: The annexes will be numbered according to the order they are cited including a title that briefly describes its content and characteristics of the herbal drug used. The following document should also be included: subject form, initial assessment form, periodic assessment form, adverse reaction and concomitant effects, final assessment form, approval letter from the group of expert (natural and traditional medicine department), approval letter from the institutional review board, data collecting notebook, statistical analysis plan, program for monitoring and audit.

Once the protocol is prepared following all the necessary steps, the researchers should present a written request to the Cuban Advisory Committee for Medicinal Plant Research (This committee belongs to the scientific and Technical Division of the Public Health Ministry), The written request should contain the final reports of the 4 fundamental preclinical studies: pharmacognostic, pharmacology, toxicology, and pharmaceutical forms. An agrotechnical report may also be present. If any of these studies was published, a copy should also be included.

The first three parts of the registration request should be presented to the Regulatory Agency before starting the study in humans:

- 1) managing information,
- 2) biological, pharmaceutical and chemical information and
- 3) preclinical information about experimental pharmacology and toxicology including long term studies.

Once the groups of experts has analysed the document and decided the phase of clinical trial that should be carried out, the Coordination Department for Clinical Trials (CENCEC) together with the national net of coordination will be in charge of all the arrangements to get the approval from institutional scientific council and institutional review board.

The 2 remaining stages of the 5 established by the Center for State Control of Drug Quality (CECMED) should be presented for a definitive registration of an herbal.

4) Clinical Information: The clinical study done with the result obtained in accordance with the clinical trial protocol should be presented. As many outcomes from clinical trials as therapeutical actions need to be validated will be include, as well as the bibliographical information about other clinical trial that confirm the proposed pharmacological actions, photocopies of original articles or reference of clinical trials carried out, documented knowledge about the use of a natural drug for a given pathology defining the length of the treatment obtained according to experimentation.(11)

5) Complementary information of the product: An informative sheet containing all the necessary data about the use of the product will be presented as well as the format of the labels and containers with the provided information, listing in the label the active ingredient with its common and scientific names.

DISCUSSION

The different subdivisions in the form of chapter and subheadings included in the guidelines facilitate the organization of all the necessary

considerations for the protocol design. The guidelines contains the information that researches in this field need for validation of the natural products' pharmacological activity by means of clinical trials.

It's very important to develop the investigations according the international requires, if we try to obtain natural products with efficacy, safety and quality, and the use of the guidelines helps to obtain this purpose. For another hand, the use of the guidelines makes more simple the procedures to the regulatory agencies because all the information that they need will be presented in a logical sequence and including all the aspects that they need to evaluate the studies.

In our opinion, the guidelines may represent an important instrument in the investigation of medicinal plants field, and the general use will be a relevant contribution to the scientific activity.

CONCLUSION:

A new guidelines proposal for herbal drug clinical trial protocols is proposed. It contains the most updated methodology and shows the level of documentation requirement needed for the clinical assessment of these products.

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Nowadays, medicinal plants are more and more used worldwide and frequently there is no clinical information, in contrast to synthetic or semi-synthetic drugs, produced by the pharmaceutical industry. No matter how the drug is made –synthesized in a laboratory, extracted from a medicinal plant or a part of the plant.

We should demand equal quality for both types of drugs: a medicinal plant or the newest drug brought up by the pharmaceutical industry. That requires investigation and serious clinical trials with medicinal plants (as if they were a synthetic drug). But there is almost nothing to patent, so the pharmaceutical industry is not interested in investigations which they are not going to obtain any benefit from.

That is the reason why these investigations are being made in universities and institutions. The authors suggest a complete guide to develop clinical trials with medicinal plants, which are quite similar to the ones used to synthesize new molecules.

The guide is excellent, but it would be necessary to encourage the pharmaceutical industry to finance and take part in the investigations, to make drugs from medicinal plants available for anyone and as effective and secure as a synthetic drug is.

Comment of the reviewer Beatriz Cuevas Ruiz MD, PhD. Complejo Asistencial de Burgos. Burgos. Spain.

The fundamental basis of traditional medicine is the clinical trial and other types of studies that provide evidence based medicine. This enables the scientific method to be applied to our daily medical practice and implies that the use of drugs is safe. Current legislation helps to ensure the safe use of effective drugs.

These requirements must be extrapolated to include so-called alternative medicine and as such, all herbal medicine products must be subjected to research studies to guarantee their suitability and safety as medical treatment.

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