Writing a research protocol in pediatric oncology

Como elaborar um protocolo de pesquisa de oncologia pediátrica

Maryelle Moreira Gamboa, Lauro Gregianin

ABSTRACT

Children are considered an especially vulnerable population in a clinical trial. Specific research regulations in pediatrics focus on the protection from potential risks. Clinical trials in oncology have become an important step for the researchers to discover new drugs, new combinations of known drugs and new methods. This manuscript aimed to help novice researchers to elaborate protocols in pediatric oncology for clinical trials. This guide describes relevant aspects before writing a research protocol and brings a template of research protocol. Moreover, it shows the importance of a well-designed research protocol and its appendices - informed consent and informed assent– in a pediatric oncology study.

Keywords: *Research protocol; pediatric oncology; informed consent and informed assent*

RESUMO

As crianças são consideradas uma população vulnerável em ensaios clínicos. Normas regulatórias específicas de pesquisa clínica em pediatria estão focadas na proteção de riscos potenciais. Os ensaios clínicos em oncologia tornaram-se um passo importante para os pesquisadores descobrirem novas drogas, novas combinações de drogas conhecidas e novas metodologias. O objetivo deste artigo é ajudar os pesquisadores novatos a elaborar protocolos de pesquisa em oncologia pediátrica. Este guia descreve os aspectos relevantes antes de escrever um protocolo de pesquisa e traz um modelo de protocolo de pesquisa. Além disso, mostra a importância de um protocolo de pesquisa bem delineado e seus apêndices – termo de consentimento livre e informado e termo de assentimento - em um estudo de oncologia pediátrica.

Palavras-chave: *Protocolo de pesquisa; oncologia pediátrica; termo de consentimento livre e esclarecido*

Revista HCPA. 2013;33(2):171-177

Pediatric Oncology Unit,
Hospital de Clínicas de Porto Alegre.
Porto Alegre, RS, Brazil.

Contato:
Maryelle Gamboa
maryellelg@hotmail.com
Porto Alegre, RS, Brasil.

Childhood cancer is a rare disease, with some types being almost exclusively seen in children. These cancers compared to adult cancers tend to differ in pathology, clinical signs and symptoms, rate of growth, and response to treatment. Treatment depends on the histological type, localization and stage of cancer, and the child's age. They may include chemotherapy, radiation, surgery or a combination of them. Bone marrow transplantation may be

used to treat children with recurrent/refractory disease. The overall survival of childhood cancer has improved considerably over the last years through advances in diagnostic and therapeutic approaches.

Clinical trials in oncology have an important role to help researchers to test the efficacy of new drugs, new combinations of known drugs and new methods to treat cancer. In 1948, one of the first clinical trials performed in pediatric oncology documented a temporary remission of leukemia in childhood (1). Since then, investigators have developed more effective and less toxic therapies associated to an improved survival (2).

A clinical trial is a scientifically conducted study with the purpose to determine the most effective treatment for a particular disease. The structure of a clinical trial is described in a research protocol, which must be designed through a long review process (3). It describes the objective(s) of the study, the methods used, and the statistical considerations; it also defines the target sample, the testes schedule, procedures, medications, dosages, and the length of the study (4).

The existence of a research protocol allows researchers at multiple institutions (in a multicenter trial) to conduct the study in exactly the same way, so that their data can be combined as though they were all working together.

The aim of this manuscript is to review the main steps of pediatric oncology protocols for clinical trials.

RELEVANT ASPECTS BEFORE WRITING A RESEARCH PROTOCOL

The process of developing a new drug

The process comprises a pre-clinical phase that may include in vitro studies to identify the biochemical characteristics of the agent, pharmacological properties, and toxicity profile; animal models are then used to test the potential therapeutic and toxic effects. The clinical phase is performed in human beings. It takes place only when the previous steps have been completed.

Clinical studies are classified in four phases:

• **Phase I clinical trials** represent the first human testing phase of an investigational drug and is conducted in a small group of health patients, except in case of a clinical trial for patients with cancer or HIV/AIDS. This phase aims to establish the safety and the pharmacokinetics and pharmacodynamic profile of the agent.

• **Phase II clinical trials** are performed with a limited number of patients with a specific tumor to establish the short-term safety and effectiveness of the investigational drug.

• **Phase III clinical trials** are multicentric, controlled, randomized studies performed on large number of patients with a specific disease. In this phase, the effectiveness of the investigational drug is compared to standard therapies and the most frequent adverse events are identified.

• **Phase IV clinical trials** are performed after the investigational drug has been commercialized in order to identify potential rare adverse effects in various populations with long-term use.

The exploratory Investigational New Drug Guidance from the Food and Drug Administration describes a new phase oncology trial called Phase 0 Study (5,6). This new phase may accelerate the process of new oncologic drug development, avoiding larger phase I and II trials for drugs. One of the major objectives of phase 0 trials is to assess and refine a target or biomarker assay and to provide pharmacokinetic and pharmacodynamic data (7,8). Phase 0 trials involve very limited human exposure, small doses, short-term use, and no therapeutic intent (7,8). However, there are controversies about ethical concerns and potential benefits with this type of studies (9).

CLINICAL TRIAL DESIGN

Medical investigations are based on observational and interventional studies design. In an observational study, the investigator observes the subjects and measures their endpoints; no interventions are conducted by the investigator; cohort, cross sectional, and case-control studies are often referred in these studies (10). In an interventional study, subjects are submitted to an intervention. Usually, they compare treated subjects to those who receive no treatment (placebo) or standard treatment. These studies are designed as randomized, double-blind, and placebo/standard-controlled.

ETHICAL AND REGULATORY CONSIDERATIONS

Ethical considerations have been part of the design and conduct of studies with humans for several decades. Research protocols including the

informed consent form should follow the Nuremberg Code (11), Belmont Report (12), Declaration of Helsinki(13), Good Clinical Practice (GCP) Guidance issued by the International Conference on Harmonization (4), and the local law of the country where the study is conducted.

GCP is an international ethical and scientific quality standard guide for designing, conducting, recording, and reporting trials involving human subjects (4). Within GCP, the research protocol and informed consent form must be submitted and approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) prior to enrollment of patients. The purpose of IEC/IRB review is to assure, both in advance and by periodic reviews, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in investigational studies (4). Most of the IEC/IRBs are based at the local investigator's hospital or institution.

The research protocol and informed consent form may be modified at any time for ethical, medical or scientific reasons. Such modifications are documented as an addendum to the research protocol. Most often, an amendment to the research protocol describing all modifications is submitted to the IEC/IRB.

It is the responsibility of the investigator to make a thorough description of the risks associated with the trial to ensure the Ethics Committee is fully aware of the implications of the study for the patients.

STATISTICAL CONSIDERATIONS

The statistical section should clearly outline how the data will be evaluated regarding each objective. The statistical methods for determining the sample size must be defined; the statistical approach to analyze the data must include how the study endpoints will be achieved with a description of the statistical power of the analysis. The size of a trial conducted in children should be as small as possible but large enough to demonstrate the appropriate efficacy with sufficient statistical power.

Many of the methodological aspects of designing a research study and writing the protocol may benefit from the advice of a statistician.

RESEARCH PROTOCOL TEMPLATE

The conduction of any clinical trial requires a well-designed research protocol. The contents of a research protocol should generally include the following topics, but may be adapted for other types. Each country/institution has its own requirements.

1. Title page: protocol title, protocol identifying number and date. Any amendment(s) should also bear the amendment number(s) and date(s). Name, department/affiliation, address, and telephone number(s) of the principal investigator.
2. Table of contents
3. List of abbreviations and definitions of terms
4. Synopsis
5. Introduction and background

5.1 Summary of results of investigational studies (pre-clinical and clinical)

6. Study objectives

6.1 Primary objectives

6.2 Secondary objectives

7 Methods

7.1 Study population

7.2 Details of recruitment process

7.3 Inclusion criteria

7.4 Exclusion criteria

7.5 Discontinuation criteria

7.6 Description of the study phase

7.7 Description of the trial type/design to be conducted (e.g., double-blind, placebo-controlled, parallel design)

7.8 Description of the measures taken to minimize/avoid bias, including (for example): (a) randomization and (b) blinding

7.9 Guidance of the code-breaking of blinding

7.10 Follow-up of patients in treatment and patients withdrawn from treatment

7.11 Overall study design and plan: description

7.12 Concomitant treatments

7.13 Authorized treatments

7.14 Prohibited and/or restricted treatments

7.15 Other restrictions and precautions

7.16 Specimen/laboratory analysis

7.17 Criteria for evaluation

7.17.1 Efficacy assessments (i.e. overall survival, progression-free survival, disease-free survival, time of progression and response rate)

7.17.2 Safety assessments (i.e. adverse events)

8 Treatment

8.1 Investigational drug

8.2 Standard treatment (if applicable)

8.3 Description of dosages, dosages modifications, and route of administration

8.4 Method of treatment assignment, randomization, and/or stratification

8.5 Packaging and labeling
8.6 Handling and dispensing
8.7 Drug accountability
9 Study schedule
10 Statistical and analytical /plans
10.1 Efficacy analyses
10.1.1 Primary endpoint
10.1.2 Secondary endpoints
10.2 Safety analyses
10.3 Interim analyses
10.4 Final analyses
11 Adverse events
11.1 Definitions
11.2 Collecting and reporting non-serious or/ and serious adverse events
11.3 Laboratory test abnormalities
11.4 Overdose
11.5 Pregnancy
11.6 Other safety considerations
12 Adherence to ethical and regulatory considerations
12.1 Good clinical practice
12.2 Institutional review board/independent ethics committee
12.3 Patient information and informed consent form
12.4 Protocol-related regulatory and ethical considerations/issues
13 Administrative considerations
13.1 Compliance
13.1.1 Compliance with the protocol and protocol revisions
13.1.2 Monitoring
13.1.3 Investigational site training
13.2 Records retention
13.2.1 Case report forms
13.2.2 Investigational product records
13.3 Return and destruction of investigational product
14 Study sponsorship and financing
15 Publication policy
16 Translational research data, if applicable
17 References
18 Attachments
18.1 Informed consent and assent forms
18.2 Investigator's brochure
18.3 Performance status scales
18.4 Evaluation scales
18.5 Quality of life questionnaires
18.6 Global schedule

INFORMED CONSENT

Children represent a vulnerable population with developmental, physiological, and psychological differences from adults. Consent and assent forms constitute one of the most important documents and they are required for all aspects of medical care, diagnostic or therapeutic measures of a clinical trial. These forms promote and protect the dignity, privacy, and confidentiality of the child and the family (14,15).

Laws and declarations have viewed patients younger than 18 years as not having the capacity to consent for not being able to fully understand certain issues in the decision process related to taking part on a clinical trial. Parents or legal representatives should act on behalf of them. Once the investigator is assured that parents or a legal representative understand the implications of participating in a study, they have the right to give informed permission (16).

Article 2(j) of the Clinical Trials Directive defines informed consent as follows: "A decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation" (17). The witness referred to in this definition should not be a minor and should be formally independent of the sponsor and the research staff.

The Declaration of Helsinki states the following: "In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever possible the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian"(13).

An informed consent that includes all relevant elements required per local regulations and GCP will be provided to each study patient at screening and before any study related procedure. Study design and method, any potential or possible

hazards, and the patient's right to withdraw from the study at any time will be explained to the patient and parents/legal representative by the investigator (15).

List of items recommended to be described in the informed consent form:

- Title of research project
- Contact of research staff (principal investigator, sub-investigators, and clinical trial coordinators)
- Introduction/purpose of the research
- Protocol design and procedures
- Duration of participation
- Potential risks/benefits
- Alternative treatments or procedures
- Compensatory/expenses
- Confidentiality
- Voluntariness/the right to withdraw
- Publication of results

Baer et al. (15) described recommendations for improving the readability published by the National Cancer Institute, which include:

- Use words that are familiar to the reader
- Define medical terminology
- Reduce sentence and paragraph length
- Sequence content logically
- Highlight important points
- Use a font size of at least 12 points

Dorn et al. (18) showed that emotional factors were more frequently related to understanding research participation than age or cognitive development. If these factors decreased, maybe, children's and adolescent's understanding of the research process might be enhanced. In addition, Chappuy et al (19) assessed the parental understanding and memorization of the consent information. They described that although parents were more likely to better understand about the aims of the study (75%), the risks (70%), the potential benefits to their child (83%), the potential benefits to other children (70%), the right to withdraw (73%), and voluntariness (84%), they were less able to understand about the procedures (44%), the possibility of alternative treatments (53%), and the duration of participation (39%). Considering therefore the variations in the perception of taking part in a clinical trial, increasing efforts must be made to improve the informed consent process by investigators.

INFORMED ASSENT

Assent is different from informed consent. Children are capable of assent when they become able to understand the research in question. This form requires that the minor knows that procedures will be performed and be aware that he/she may withdraw from participation at any time. The withdrawal from the trial will not harm the child and will not affect the treatment. It must be emphasized that after a child withdraws from a trial, the investigator is still responsible for reporting trial-related events. In addition, the investigator needs to assure appropriate treatment and follow-up (20-22).

SAFETY MANAGEMENT

Definitions

- **Adverse event** (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject administered an investigational medication and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with use of an investigational medication, whether or not considered related to the investigational medication.
- **Serious adverse event** (SAE) is any untoward medical occurrence that at any dose results in:

  - death;
  - a life-threatening event;
  - hospitalization or prolongation of existing hospitalization;
  - persistent or significant disability/ incapacity;
  - a congenital abnormal/birth defect;
  - any other medically important condition (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above).

Note that any death, whether due to side effects of the treatment, progressive disease or other causes is considered as a serious adverse event.

DATA COLLECTION AND REPORTING

Following the patient's written consent to participate in the study, all AEs must be collected, including those thought to be associated with research protocol-specified procedures.

All AEs, including those that are serious, are graded according to the Common Terminology Criteria for Adverse Event (CTCAE) (23). Moreover, the casual relationship of an AE to the investigational drug is graded as follows:

- Not related: There is not a reasonable causal relationship to investigational drug administration and the AE.
- Possibly related: There is some evidence suggesting a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
- Probably related: There is evidence suggesting a causal relationship and the influence of other factors is unlikely.
- Definitely related: There is clear evidence suggesting a causal relationship to investigational drug administration and the AE.

The expression "reasonable causal relationship" is meant to convey, in general, that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments suggesting positive causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination or evaluation of a patient. To prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs. The questioning of patients regarding possible occurrence of AEs can be generalized such as "How have you been feeling since your last visit?"

All AEs must be registered in the patient's medical records and in the Case Report Form (CRF). The following information should be reported for each AE: onset, duration, intensity, severity, relationship to investigational drug, action taken, and treatment required.

Reports of all pregnancies and any unexpected SAEs must be communicated as soon as possible to the appropriate IEC/IRB and promptly within 24 hours to Sponsor, if applicable, and within 7 calendar days to Local Health Authorities.

MONITORING ADVERSE EVENTS

Patients having AEs are monitored with relevant clinical assessments and laboratory tests, as determined by the investigator. Any actions taken and follow-up results must be recorded on the appropriate page of the CRF. For all AEs that require the patient to be discontinued from the study, relevant clinical assessments and laboratory tests are repeated as clinically indicated, until final resolution or stabilization of the event(s).

FINAL CONSIDERATIONS

The conduction of clinical trials is a key component for improvements in survival in childhood cancer. Due to the rarity of disease, initiative of cooperative groups and multicenter collaboration allows the accrual of a sufficiently number of patients during a limited period. Following strict, research protocol guidelines and collection of data under quality control assessment represent the main steps for conducting a clinical trial.

A descriptive study (24) assessed the most frequent methodological deficiencies of fifty clinical study protocols. The main deficiencies reported were on statistical analysis (60%), patient selection criteria (48%), choice of sample size (38%), incorrect use of placebo (36%), homogeneity of the groups (34%), concomitant medication (26%), randomization planning (26%), monitoring of adverse events (24%), patients' compliance (24%), and experimental designing (16%). The lack of insurance for the personnel and institutions involved (62%), and inadequacies in the investigators' brochure (52%), and case report forms (40%) were identified.

Finally, a multidisciplinary review team should participate in the designing of pediatric oncology protocols, to make sure it follows the methodological principles to assure quality of a clinical trial.

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Recebido: 20/11/2012
Aceito: 09/04/2013