

How to design and write a clinical research protocol in Cosmetic Dermatology*

Como desenhar e escrever um protocolo de pesquisa clínica em Cosmiatria

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Abstract: Cosmetic Dermatology is a growing subspecialty. High-quality basic science studies have been published; however, few double-blind, randomized controlled clinical trials, which are the major instrument for evidence-based medicine, have been conducted in this area. Clinical research is essential for the discovery of new knowledge, improvement of scientific basis, resolution of challenges, and good clinical practice. Some basic principles for a successful researcher include interest, availability, persistence, and honesty. It is essential to learn how to write a protocol research and to know the international and national regulatory rules. A complete clinical trial protocol should include question, background, objectives, methodology (design, variable description, sample size, randomization, inclusion and exclusion criteria, intervention, efficacy and safety measures, and statistical analysis), consent form, clinical research form, and references. Institutional ethical review board approval and financial support disclosure are necessary. Publication of positive or negative results should be an authors' commitment.

Keywords: Clinical protocols; Clinical trial; Comparative study; Cosmetics; Epidemiologic research design; Research design

Resumo: Cosmiatria é uma sub-especialidade em grande crescimento. Estudos em ciência básica de alta qualidade têm sido publicados; ao contrário, existem poucos estudos clínicos duplo-cegos, randomizados e controlados, que constituem o maior instrumento para medicina baseada em evidência nessa área. A pesquisa clínica é essencial para a descoberta de novos conhecimentos, melhora das bases científicas, solução de desafios e boa prática clínica. Para ser um pesquisador bem sucedido, os princípios básicos são interesse, disponibilidade, persistência e honestidade. É essencial aprender como escrever um protocolo de pesquisa e conhecer as regras regulatórias nacionais e internacionais. Um protocolo de pesquisa clínica completo deve incluir questão, fundamentos, objetivos, metodologia (desenho, descrição das variáveis, tamanho da amostra, randomização, critérios de inclusão e exclusão, intervenção, parâmetros de eficácia e segurança e análise estatística), termo de consentimento livre e esclarecido, ficha clínica e referências. A aprovação do Comitê de Ética em Pesquisa e a declaração do financiamento são imprescindíveis. A publicação de resultados positivos ou negativos deve ser um comprometimento dos autores.

Palavras-chave: Cosméticos; Ensaio clínico; Estudo comparativo; Projetos de pesquisa; Projetos de pesquisa epidemiológica; Protocolos clínicos

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INTRODUCTION

Cosmetic Dermatology is a very exciting subspecialty of increasing interest among dermatologists, researchers, pharmaceutical companies, and the general public. Nevertheless, the greatest number of studies in the medical literature with high methodological quality refers to basic and experimental science and not to clinical studies, which limits generalization of results in clinical practice.

Since cosmetic complaints are due to known physiopathological processes, classical epidemiological approaches are suitable to assess cosmetic endpoints.^{1,2} Randomized controlled clinical trials are the best for determining intervention efficacy in specific situations and are the major instrument for evidence-based medicine.³ It is necessary to accumulate good trials to get solid evidence for better clinical practice.⁴

There is urgency for well designed clinical trials followed by consistent publications in accordance with the CONSORT (Consolidation of Standards for Reporting Trials) Statement and the principles of GCP (Good Clinical Practice) regarding cosmetic dermatology.⁵ Brazilian researchers should also know the guidelines of the Good Clinical Practice: Document of the Americas (*Boas Práticas Clínicas: Documento das Américas* – Portuguese) and the regulatory rules of the Brazilian National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária - ANVISA - Portuguese*).⁶

Information technology has become cheaper, widely accessible and easy to use, playing an important role in the appropriate management of patients. On the other hand, it is essential that clinical trials be critically evaluated and that their limitations be properly understood. If they are improperly designed, their performance becomes unethical, as subjects may be submitted to misguided investigation and interventions, and the results will be meaningless or even erroneous.

The main research aims should be discovering and interpreting new knowledge, exploring subgroups, improving scientific basis, or resolving challenges in clinical practice. Outcomes are expected to confirm, modify, or reject existing knowledge or the efficacy of a therapy or cosmetic procedure. Organized, good-quality research should remain meaningful for a long time and may give rise to new investigations. It also offers opportunity for international collaboration and visibility as well as to get funding sources. Research may influence health system policies and bring benefits to doctors, patients, and the general population.⁷

Investigators' first step is to define a study line or area of interest. Secondly, it is essential to study extensively before elaborating the content of a research protocol. The basic principles for success are interest, availability, persistence, and honesty.

Concerning scientific research, there is no place for fraud. It may not be able to prove or disprove hypotheses, but it always improves knowledge regarding the protocol.^{8,9} Involvement of professionals from various specialties can gather specific expertise and improve research quality.¹⁰

A beginner in research will be faced with the task of writing a clinical trial protocol which should comprise the topics described below (some examples are included) and in chart 1.¹¹⁻¹⁵

HYPOTHESIS OR QUESTION

The hypothesis or question should be original, simple, and logic. The "FINER" criteria - which means feasible, interesting, novel, ethical, and relevant - must be considered. It rises from previous studies in the researcher's area of interest, relevant discussion on scientific events, literature search, curiosity, or innovative mind.

Example: Is oral isotretinoin effective, safe, and superior to sunscreen plus moisturizer in the treatment of photoaging?

INTRODUCTION AND BACKGROUND

An extensive and critical review of the literature is essential to find out some gaps or if another investigator has already studied the same matter. Discussion and feedback from seniors and experts are also helpful. After that, the researcher may maintain, improve, or reject the initial question. Based on a definitive hypothesis, the introduction and background might be written. This section should be concise and strictly related to the subject of investigation and to the questions to be answered.

OBJECTIVES

The study may comprise just one general objective or primary and secondary objectives.

Example:

Primary objective: to evaluate the efficacy and safety of oral isotretinoin as compared to sunscreen plus moisturizer in the treatment of photoaging.

Secondary objective: to evaluate the impact of treatments on quality of life.

METHODOLOGY

It is the most important part for conducting good-quality research and obtaining valid inferences. A complete protocol involving human beings should include design, precise definition of the disease/endpoint, clear description of variables, well-defined inclusion and exclusion criteria, efficacy and safety parameters, sample size calculation and randomization, statistical analysis plan, detailed description of

CHART 1: Schematic structure of a clinical research protocol

	Topic	Example
1	Idea / Hypothesis	Oral isotretinoin can reduce the incidence of actinic keratosis.
2	Bibliographic research	Background and reason for the study
3	Study design	Double-blind, randomized, placebo-controlled, longitudinal study: Group A: Sunscreen + oral isotretinoin. Group B: Sunscreen + oral placebo. Two months of follow-up after cryotherapy (5-second spray of liquid nitrogen) of all actinic keratoses.
4	Diagnosis conception	Actinic keratosis will be defined after clinical evaluation by a boarded dermatologist, not by histopathological analysis, which makes subsequent lesion counting impracticable.
5	Definition of variables	Dependent: Counting actinic keratoses in a standard area; histological expression of proliferative (Ki-67) and apoptotic factors (p53 and Bcl-2). Independent: Treatment group. Potential confounders: Age, skin phototype, sun exposure.
6	Inclusion / Exclusion criteria	Immunocompetent patients older than 50 years, both genders, with up to 30 actinic keratoses on the face and forearms. Those randomized to isotretinoin should be normolipemic and present normal liver function.
7	Sampling	Random sample selection of 50 patients based on an expected reduction of up to 30% in the incidence of actinic keratoses, power of 80%, and alpha 5%.
8	Statistical analysis	Generalized linear mixed model (negative binomial)
9	Chronogram and budget	Time allocated for each phase (table), and calculation of each predictable expense.
10	Ethics committee approval / Funding / Clinical trial registration	Study approved by institutional research ethics committee, financially supported by CNPq and registered at www.ensaioclinicos.gov.br
11	Criteria for discontinuation	Severe adverse effects should lead to study discontinuation

interventions, a chronogram of activities, consent form, clinical research form (CRF), and references.

Endpoint characterization and precise variable description are mandatory and should express the main definitions of each variable in the study, how they will be obtained, presuppositions, techniques, and instruments.¹⁶

Early statistical consultation is essential to determine sample size, standardize variables, and plan data analysis and future data presentation.^{17,18}

In summary, the researcher should clearly state the “PICO” elements (patient, intervention, comparison, and outcome) in this section.

DESIGN

There are many study designs; clinical trials follow the interventional design.

Interventional

The study population is submitted to clinical or surgical therapies or procedures. Therapeutic trials may be designed as the following: placebo-controlled, compared to standard treatment; randomized, not randomized; double-blind, single-blind, open; parallel, cross-over, or cluster allocation. The gold standard design is parallel-group, double-blind, randomized, and controlled with the standard therapy. This is usually referred to as RCT (randomized controlled trial).¹⁹ Open studies and those with associated interventions in just one group of subjects can report positive con-

CHART 2: The most common statistical tests for bivariate data analysis (unpaired data) according to dependent and independent variables

		Dependent Variable				
		Categorical Dicotomic	Quantitative Multinomial	Ordinal	Continuous	Discrete
Independent variable	Dicotomic	Pearson's chi-square;	Pearson's chi-square;	Chi-square for trend	Parametric: Student's t-test	Generalized linear models (Poisson or negative binomial)
		Fisher's exact test	G-test; Residual analysis of contingency table (post hoc)		Non-parametric: Mann-Whitney test	
	Multinomial	Pearson's chi-square;	Pearson's chi-square;	Chi-square for trend	Parametric: ANOVA	Generalized linear models (Poisson or negative binomial)
		G-test; Residual analysis of contingency table (post hoc)	G-test; Residual analysis of contingency table (post hoc)		Non-parametric: Kruskal-Wallis test	
	Ordinal	Chi-square for trend	Chi-square for trend	Chi-square for trend	Parametric: ANOVA	Generalized linear models (Poisson or negative binomial)
				Non-parametric: Jonckheere-Terpstra Test		
Continuous	Binary logistic regression	Multinomial logistic regression	Ordinal logistic regression	-	-	-
Discrete						

clusions, but they have limited value for Evidence-based medicine.^{20,21}

Observational

- Cohort - prospective, historical: a population exposed to the condition under investigation is followed along time and evaluated in determined periods of time.
- Case-control – retrospective: two populations that were or are exposed to a condition are compared in relation to the presence or absence of an outcome under investigation.
- Transversal or cross-sectional: it is a prevalence study; the whole population is analyzed in just one period of time.
- Epidemiological description – case series: it summarizes the characteristics of a population.
 - Descriptive: it reports personal experiences
 - Experimental
 - Example: an interventional, randomized, comparative (parallel groups), prospective, and evaluator-blind clinical trial including 32 healthy women, aged from 40 to 55 years, to evaluate efficacy and safe-

ty of oral isotretinoin (20 mg/day, three times a week, associated with sunscreen plus moisturizer, 22 women) versus the use of sunscreen plus moisturizer (10 women) during three months in the treatment of photoaging.

SAMPLE SIZE CALCULATION, SUBJECT ALLOCATION, AND RANDOMIZATION

There are many formulas to calculate sample size, and randomization lists are available on the Internet. Sample size calculation is inversely proportional to the minimal clinically significant difference between groups and tolerable error of estimation. These parameters should be determined by the investigators and previously discussed with the statistician.^{22,23}

Studies with few subjects may not allow us to detect differences. On the other hand, an excess of subjects may be unnecessarily exposed to investigation, leading to clinically meaningless conclusions. Both are unethical situations.²⁴

Subjects should come from the same population, especially if cultural, ethnical and socioeconomic aspects can interfere with the disease or treatment. Age

CHART 3: The most common statistical tests to bivariate data analysis (paired data) according to dependent and independent variables

Independent variable	Dependent Variable				
	Categorical Dicotomic	Quantitative Multinomial	Ordinal	Continuous	Discrete
Dicotomic	McNemar's test	Generalized mixed models (multinomial)	Generalized mixed models (ordinal data)	Parametric: Student's t-test for paired data Non-parametric: Wilcoxon test	Generalized mixed models (Poisson or negative binomial)
Multinomial	Generalized mixed models (categorical data)	Generalized mixed models (categorical data)	Generalized mixed models (categorical data)	Parametric: ANOVA for repeated measures Non-parametric: Friedman test	Generalized mixed models (Poisson or negative binomial)
Ordinal	Generalized mixed models (categorical data)	Generalized mixed models (categorical data)	Generalized mixed models (categorical data)	Generalized mixed models	Generalized mixed models (Poisson or negative binomial)
Continuous	Generalized mixed models (categorical data)	Generalized mixed models (categorical data)	Generalized mixed models (categorical data)	Parametric: Pearson's correlation coefficient Non-parametric: Spearman's correlation coefficient	

and gender are classical restrictions in homogenizing group responses. Therefore, they should be allocated in a way that each participant has the same chance of being assigned to each group. Non-random subject allocation forms should be discouraged. These forms include casual (convenience-based), snowball, voluntary response, by saturation, and quota sampling. Randomization should eliminate selection bias, create comparable groups, and lend validity to statistical analysis.²⁵

Finally, matching observations (e.g. longitudinal studies, pairing or side-by-side comparisons) require smaller samples, reduce estimation errors, and increase internal comparability among subjects. Longitudinal studies need a long-term follow-up to be useful for clinical practice. Immediate results alone may not demonstrate the real efficacy of the intervention.

EFFICACY AND SAFETY MEASURES

They should be objective and quantitative, as much as possible, and based on the state-of-the-art knowledge about the condition under investigation. It is highly recommended that the same phenomenon be assessed at different endpoints.²¹ Correlation

between the results of each endpoint reinforces the trustworthiness of the effect. Confounders should be carefully considered and also assessed for later adjustment of their effects.

Example:

For results of photoaging treatment: patients' opinion, blind photographic evaluation, non-invasive measures (elasticity, skin surface, hydration, etc), clinical and histological images with quantitative digital analysis.

For adverse events related to oral isotretinoin: report of mucocutaneous or rare side effects, laboratorial tests (liver function, lipid profile, blood count).

STATISTICAL ANALYSIS

It is essential to find real correlations and trends which may or may not be significant and which may or may not imply causation. Every researcher, and even medical practitioners, should have some knowledge of statistical methods and analysis in order to choose the best study design and to interpret data.¹⁴

The study population should be analyzed as intention-to-treat (ITT), modified ITT and per-prot-

col (PP).²⁶ ITT population includes all subjects who used the treatment once or for a period of time and dropped out, whereas PP includes only those who completed the study.

Statistical significance is usually set as a two tailed p-value <0.05 , which means that researchers accept the result of the probability related to the statistical test of less than 5% for conclude that groups are different. Although $p > 0.05$ means insufficient evidence to demonstrate difference, it is not the same as no difference between groups.²⁶

Data structure depends on the characteristics of the variables. Categorical or qualitative variables can be dichotomic (e.g. unhealthy/healthy, male/female), multinomial (e.g. homosexual/bisexual/heterosexual), or ordinal (e.g. Fitzpatrick's phototypes I-IV, Glogau's classification I-III) and should be represented by the percentile of each category. Quantitative variables always have a proportional scale among the values and can be continuous (e.g. age, weigh, height, disease length) or discrete (e.g. counting of cigarettes, number of sunburns). Quantitative data should be tested for normality with the Shapiro-Wilk test. If the distribution is parametric (normal), data should be represented by mean and standard deviation; if not, usually median and interquartile range can be used.²⁷

The choice of which statistical test to use should take into account the nature of the dependent and independent variables, normality of data, and matching. According to these presuppositions, the main tests used are described in charts 2 and 3.

Inter-rater concordance can be assessed using Cohen's (weighed) kappa for 2x2 assessments and using intraclass correlation coefficient (for complete agreement) for 2 or more raters.²⁸ Adjustment of results by confounders is important to explore data, and multivariable analysis is frequently used for that purpose. The selection of co-variables to compound the final model is a debatable subject and is beyond the scope of this text.²⁹

Unpaired data are usually analyzed by multiple logistic regression (categorical dependent variable) or generalized linear models (quantitative dependent variable). Paired data are usually analyzed by generalized mixed models.²⁷

The consent form should be written in simple and popular language. The objective of the study, potential risks, benefits, and detailed procedures should be clearly described. The main researcher's contact should be displayed in case the participants have doubts or want to remove their consent, for instance.³⁰

Chronogram and budget should determine how long each phase of the study will last, calculate each predictable expense, and determine time for disbursement.

The complete protocol should be submitted to the Ethics Committee or Institutional Review Board (IRB). In Brazil, appreciation of the National Council on Ethics in Research (*Conselho Nacional de Etica em Pesquisa - CONEP - Portuguese*) is required in some situations, such as new drug, multicentric and international studies, and research involving native indigenous population, children, and pregnant women.

After ethical approval, financial support may be obtained from governmental foundations, institutes, or pharmaceutical companies. Financial conflicts are minimized by author disclosure and clinical trial registry. Multicentric sponsored studies demonstrate high methodological quality, include a larger sample size, and are more likely to report meaningful results.^{15,31} The ideal situation should be a partnership between university, government, and industry to minimize financial interests in the results.

Afterwards, the study should be added to any online clinical trial record, such as www.clinicaltrials.gov or www.ensaiosclinicos.gov.br. These registers follow a strict process of validation, and a register number is usually requested by medical journals for publication.

At the end of the protocol, authors should inform any potential limitations of the study, drawbacks, and restrictions to generalization of the results. Clear awareness of the study limits strengthens the implications of the conclusions.³²

Attempting to visualize possible final results (using charts and plots) is a useful exercise that allows revising the study structure and data analysis.

Sharing positive or negative results in scientific events as well as their publication are the authors' obligation.³³ Good papers should also follow CONSORT standards, present the question and objectives, state how the sample size was determined, state if confounding factors were considered, and inform which randomization method was used. Statistical tests should be appropriate, interpretation of results and conclusions should be correlated with the initial hypothesis, and possible bias and applicability of findings should be reported.

High impact factor (IF) journals are preferable, as they increase the chance of paper access and citation. Discussions about the real importance of journal IF for clinical practice have been raised in the literature in recent years.³⁴

In conclusion, to be a good researcher and writer, it is essential to read, study, think, and reflect, i.e., to exercise the brain every day. □

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