PRACTICAL ADVICE ON HOW TO WRITE A CLINICAL TRIAL PROTOCOL

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CONFLICT OF INTERESTS

NOTHING TO DECLARE

RANDOMIZED CLINICAL TRIALS

- Well designed and properly executed randomized controlled trials provide the most reliable evidence on the efficacy of health care interventions, but trials with inadequate methods are associated with bias, especially exaggerated treatment effects;

- Biased results from poorly designed and reported trials can mislead decision making in health care at all levels, from treatment decisions for a patient to formulation of national public health policies.

Moher D, et al, CONSORT 2010. *BMJ 2010; 340:c869 doi: 10.1136/bmj.c869*

WHAT IS A CLINICAL TRIAL PROTOCOL?

- The clinical trial protocol is a formal document which serves as the foundation for conducting and reporting the study;

- The protocol reports and defines all aspects of the research, from the scientific to ethical aspects, from the operative to bureaucratic aspects.

CLINICAL TRIAL PROTOCOL

All protocols are substantially divided into two main sections:

- The problem to be investigated
- The method of investigation

CLINICAL TRIAL PROTOCOL

THE PROBLEM TO BE INVESTIGATED:

- Project title;
- Introduction (scientific background, including the literature review and the aim of the study).

THE PROBLEM TO BE INVESTIGATED: PROJECT TITLE

This is one of the most important features of the protocol because it attracts the attention of the potential reader. It is necessary to make it as short and to the point as possible

THE PROJECT TO BE INVESTIGATED: THE PROJECT TITLE

Aprepitant versus dexamethasone for preventing chemotherapy-induced delayed emesis in patients with breast cancer: a randomized double-blind study

THE PROBLEM TO BE INVESTIGATED:
INTRODUCTION AND AIM OF THE STUDY

The reasons for which authors have written the protocol will be discussed in this section. In particular:

- The available treatments for the disease that is the object of the study (state of the art);
- The investigated new treatment (a summary of the data including the reasons for which better results or tolerability are awaited with the new drug);
- The aim of the study.

THE PROBLEM TO BE INVESTIGATED: INTRODUCTION AND RATIONALE

In 2006 dexametasone or aprepitant were recommended for prophylaxis of delayed emesis in breast cancer pts

- Aprepitant was shown superior to ondansetron in a study in which pts receiving it even in the first 24 hours, achieved superior results both on day 1 and on days 2-5 (dependence effect?)

- The aim of the study was to evaluate the role of aprepitant in delayed emesis comparing it with dexamethasone in a superiority study

USEFUL QUESTIONS (WRITING THE INTRODUCTION)

- Will the study answer an important clinical problem (**the relevance of the study)?**
- Is the study original?
- Will the study add something important to the already available knowledge?

CLINICAL TRIAL PROTOCOL

THE METHOD OF INVESTIGATION (the modality in which the study will be done and how the data will be analyzed):

- The patients;
- The type and design of the study;
- Clinical assessment;
- The procedures;
- The statistical analysis (including sample size calculation).

METHODS OF INVESTIGATION: THE PATIENTS

Patient's inclusion and exclusion criteria, the setting (social, economical and cultural environment) and the location (multicenter?) in which the study will be carried out should be reported to allow future readers to assess the generalizability, or external validity, of the study (to whom will the results of the study be extended).

METHODS OF INVESTIGATION: THE PATIENTS

INCLUSION CRITERIA

All consecutive adult chemotherapy-naive pts with breast cancer scheduled to receive, as adjuvant therapy or for metastatic disease, chemotherapy (CT) containing anthracyclines and cyclophosphamide ± fluorouracil

METHODS OF INVESTIGATION: THE PATIENTS

EXCLUSION CRITERIA

- Planned treatments on days 2-4 with other CT agents;
- Presence of nausea and vomiting or use of antiemetic agents during the 24 hrs before CT administration;
- Severe concurrent illness other than neoplasia;
- Other causes of vomiting (GI obstruction, CNS metastases or hypercalcemia);
- Controindication to dexamethasone (active peptic ulcer);
- Concomitant use of corticosteroids, benzodiazepines or radiotherapy.

METHODS OF INVESTIGATION: TYPE OF STUDY

- Considering the available data of the new drug a phase I, II, III or IV study will be planned.

- A phase II study evaluates the activity of the new drug while a phase III study evaluates the efficacy of the new drug. A phase IV study (post- marketing trial) evaluates the efficacy in clinical practice and the short, medium and long- term tolerability of the new drug

METHODS OF INVESTIGATION: STUDY DESIGN

The protocol will describe the design of the trial (for example, as parallel groups, crossover, factorial, superiority, equivalence or non- inferiority design).

STUDY DESIGN

Two experimental designs are the most frequently used in comparative phase III studies:

- Parallel (between subjects) study: pts randomized to receive either the study drug or the comparative treatment during one or several cycles of therapy and the two groups are then compared;

- Crossover (within subjects) study: each patient receives every drug being studied, “crossing-over” from one drug to the next in a predetermined order.

PARALLEL STUDY DESIGN in supportive/palliative care

ADVANTAGES:

possibility to evaluate the persistence of antiemetic efficacy in subsequent cycles

DISADVANTAGES:

Larger number of patients are required to show differences between treatments

CROSSOVER STUDY DESIGN
in supportive/palliative care

ADVANTAGES:

- more powerful (smaller number of patients required);
- possibility to express a preference between treatments;

DISADVANTAGES:

- impossibility to evaluate the persistence of antiemetic activity in subsequent cycles;
- inappropriate if the number of patients lost after first cycle is > 5%

CROSSOVER STUDY DESIGN in supportive/palliative care

DISADVANTAGES:

- necessity to keep the emetic stimulus and the environment unchanged between the two treatments (on the other hand, the sample size may be greater than with a parallel study: the within-patient variability may not be less than the between-patient variability);

- problems of order effects (in relationship to the order in which the antiemetic treatments are administered) and problems of residual effects (in relationship to influence of the previous antiemetic treatment on the subsequent).

CROSSOVER STUDY DESIGN in supportive/palliative care

DISADVANTAGES:

There are ethical and clinical concerns about changing a treatment that has been successful in the first period

THEREFORE,

Due to the disadvantages of the crossover design it has been suggested to use a parallel design in phase III studies of antiemetics.

CROSSOVER STUDY DESIGN in cancer research

- An estimate quarter of randomized controlled trials (22%) used a crossover design

- Crossover trials are statistically suitable for palliative or symptomatic treatment of chronic diseases and for single dose pharmacokinetic/pharmacodinamic studies.

- In cancer research a crossover design is **used widely in a different way in studies that seek to establish basic efficacy of a novel agent**

CROSSOVER STUDY DESIGN in cancer research

- It is planned because the investigators think that trial recruitment will suffer without the promise of a crossover and because they have the sensation of doing the right thing offering the investigational agent to more patients

- This choice is misguided because no studies confirm crossover trials recruit faster and because crossover may undermine a trial's ability to answer a meaningful clinical question (no permitting to reach valid conclusions regarding overall survival benefits of therapies)

CROSSOVER STUDY DESIGN in cancer research

When a trial is incapable of answering a question, it became unethical.

Using a crossover strategy in oncology clinical trials can make trials less ethical, not more

Prasad V, et al. Comtemporary Clin Trial 2014; 37: 167-69

METHODS OF INVESTIGATION: STUDY DESIGN

- In the factorial design participants are assigned to more than one treatment-comparison group, enabling two or more treatments to be evaluated simultaneously.

- The simplest example is the 2 x 2 factorial design where participants are randomly allocated to one of four possible combinations of two treatments (i.e., A and B). This allows the statistical model to conclude from A alone; B alone; both A and B; neither A nor B.

METHODS OF INVESTIGATION: STUDY DESIGN

- A comparative study evaluating soft and subjective endpoint (i. e., fatigue, nausea, pain) should be planned as a double-blind study

- The comparator should be the best available treatment and not the placebo (as suggested sometimes by the regulatory agencies)

METHODS OF INVESTIGATION: STUDY DESIGN

- The antiemetic study will be a multicenter, randomized, double-blind, parallel study comparing aprepitant versus dexamethasone in the prevention of delayed emesis in breast cancer pts

- To avoid a dependence effect all pts will receive the same antiemetic prophylaxis for acute emesis (aprepitant, palonosetron and dexamethasone)

METHODS OF INVESTIGATION: CLINICAL ASSESSMENT

- The primary and the secondary endpoint of the study are described and clearly defined in this section

- The primary endpoint is used to calculate the sample size

ENDPOINT OF CLINICAL TRIALS IN ONCOLOGY

EFFECTS OF THE TREATMENT ON CANCER

- Complete and partial response
- Duration of the response
- Time to progression
- Progression free survival

EFFECT OF THE TREATMENT ON PATIENTS

- Overall survival
- Quality of life

METHODS OF INVESTIGATION: CLINICAL ASSESSMENT

In this section it is necessary to describe any forms or questionnaires which will be used and how the data will be stored and handled

METHODS OF INVESTIGATION: CLINICAL ASSESSMENT

- Pts will fill a diary card for day 1 to 6, in which they will report daily the presence, the intensity, and duration of nausea and the number of vomiting episodes as well as any adverse event and any administered rescue treatment.

- Furthermore, pts will fill out on day 1 (before CT) and 6 (in reference to day 2-5 after CT) the Functional Living Index-Emesis (FLIE) to evaluate the impact of emesis on patient quality of life.

METHODS OF INVESTIGATION: CLINICAL ASSESSMENT

- The primary endpoint of the study is the complete response rate (no vomiting, no rescue treatment) from day 2-5 after CT

- The secondary endpoints on day 2-5 were rate of complete protection (no vomiting, no rescue treatment and no significant nausea), rate of no vomiting, rate of no nausea……

METHODS OF INVESTIGATION: CLINICAL ASSESSMENT

- Detailed information on the interventions intended for each group should be described (e.g., dose, route of administration, duration of administration, when to reduce the doses or interrupt the treatments for adverse events)

- The protocol also gives information about the way in which the patients are randomly allocated to different treatments and describes the stratifications of the pts before the randomization.

METHODS OF INVESTIGATION: CLINICAL ASSESSMENT

- The protocol defines if interim analyses have been planned and when they will be done by an independent data monitoring committee which monitorizes the efficacy and tolerability of the interventions

- Many studies enroll pts for a long period of time, but if a treatment is very or little efficacious the study should be interrupted for ethical reasons.

METHODS OF INVESTIGATION: THE PROCEDURES

- Was protocol approved by ethical committee of each participating center?
- Was informed consent obtained from each patient?
- How was the random assignment performed?
- How was the double-blinding performed?
- How was monitoring organized?
- How were data recorded?
- How was data analysis, interpretation of the results and first draft of the report made?

METHODS OF INVESTIGATION: THE PROCEDURES

- The protocol will be approved by ethical committee of each participating center
- All patients will provide written informed consent
- The random assignment will be performed by the statistician using computer-generated random numbers
- Double-blinding will be performed by a specialized company. Each center will received a block of 10 numbered, already randomly assigned, blinded treatments to use in progressive order

METHODS OF INVESTIGATION: THE PROCEDURES

- Patient case record forms will be reviewed and collected by an independent monitor who will vouch for the accuracy and completeness of the data and will be paid with funds from the Italian Minister of Health

- The data will be recorded on a magnetic device; double-blinding will be removed and the received treatments added to pts files only when data recording is finished

METHODS OF INVESTIGATION: THE PROCEDURES

- The data analysis, interpretation of the results and first draft of the report should be approved by the principal investigators.

- All investigators of the participating centers will contribute to the final manuscript and will agree to submit it for publication.

METHODS OF INVESTIGATION: THE STATISTICAL ANALYSIS

- How has the sample size been calculated?

If the sample size is too small there is a considerable risk that the study may not be sufficiently powerful to detect a difference between the groups, if a true difference exists.

On the other hand, an excess of pts may be unnecessarily exposed to investigation, leading to clinically meaningless conclusions.

Both are unethical situations

METHODS OF INVESTIGATION: SAMPLE SIZE CALCULATION

- The sample size of an antiemetic study must be determined in advance to have the statistical power to detect the smallest difference that would be regarded as clinically important.

- The cut off for clinically meaningful improvement in patient reported outcomes has been suggested as 10% (even for antiemetic studies experts consider a > 10% difference between two treaments clinically important).

METHODS OF INVESTIGATION: SAMPLE SIZE CALCULATION

- Aprepitant on day 2-3 achieved a complete response in 55% of patients submitted to anthracyclines and cyclophosphamide-containing chemotherapy

- We planned a superiority study hypothesizing that dexamethasone increases by 12% the complete response in the delayed phase (from 55% to 67%)

- Fixing a significance level of 5% for a two-sided test able to compare the rates of complete response between the two independent samples, 362 patients per arm were necessary to detect a significant difference with a probability greater than 90%

METHODS OF INVESTIGATION: THE STATISTICAL ANALYSIS

- How will the statistical analysis be carried out?

Every researcher should have some knowledge of statistical methods and analysis in order to choose the best study design and interpret data

The study population should be analyzed as intention-to- treat (all subjects who used the treatment once or for a period of time and dropped out) and per protocol (includes only those who completed the study)

METHODS OF INVESTIGATION: THE STATISTICAL ANALYSIS

- Fisher's exact test will be used to compare the two groups with respect to all endpoints expressed by a binary variable as well as to evaluate the differential safety.

- The Mann-Whitney U-test will be used to compare the two means.

- All tests will be two sided, and a significance level of. 05 will be used

METHODS OF INVESTIGATION: THE STATISTICAL ANALYSIS

- 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% to conclude that groups are different.

- 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.

USEFUL QUESTIONS (WRITING THE METHODS)

- What study has been made?
- Is the design appropriate to answer the clinical question?
- Has a systematic bias been avoided or minimized?
- Was the study large enough and the follow up of adequate duration to obtain believable results?

CLINICAL TRIAL PROTOCOL:

OTHER SECTIONS

- The date of the start and the end of the study (what will be the date of the database closure)

- Ethics

The investigator will conduct the study in compliance with the protocol, current good clinical practices, and all applicable local, state, national, and federal regulatory guidelines and standards of ethics.

CLINICAL TRIAL PROTOCOL:

OTHER SECTIONS

- The publication policy

To avoid disclosures that could jeopardize proprietary rights, the institution and/or the investigator agrees to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts and electronic communications) as detailed in the Clinical Trial Agreement. In accordance with standard editorial and ethical practices, publication of the results of this multi-center trial will be only in its entirety and not as individual center data.

- References

INCOMPLETE AND INACCURATE REPORTING OF CLINICAL TRIALS

- Information on the method used in a trial to assign participants to comparison groups was reported in only 21% of 519 trial reports indexed in PubMed in 2000 and only 34% of 616 reports indexed in 2006.

- Only 45% of trial reports indexed in 2000 and 53% in 2006 defined a primary endpoint and only 27% in 2000 and 45% in 2006 reported a sample size calculation.

Chan AW, Lancet 2005; 365:1159-62

Hopewell S, BMJ. 2010 Mar 23;340:c723. doi: 10.1136/bmj.c723