

MECOR

How to Develop a Research Protocol



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What is an example of a “protocol” in every day life?

- McDonalds, KFC
- Airline pilots
- Car assembly line

What is a *Clinical Protocol*?

An explicit description of steps to be taken in patient care in specified circumstances.

Example of Clinical Protocol: Surgical Check List

- Recent study published in NEJM
- Multicenter study in many countries
- Pre-surgical check list required
- Outcomes were related to adverse post-surgical complications
- Very significant reduction in complications in all centers

What is a *Research* Protocol?

- The written documentation of a study plan.

Why Have a Protocol?

- Without a protocol:
- A study may simply become an unguided exercise in data collection.
- The design is likely to “creep”, that is to change in unintended ways.

What Should be Included in a Protocol?

- Title
- Research questions, objectives
- Significance
- Design: time frame, study design
- Study participants: selection criteria, sampling design, recruitment plan
- Variables: predictor, confounding, outcome
- Statistical issues: hypotheses, sample size, analytic approach

What Should be Included in a Protocol?

- Strengths & weaknesses
- Human subjects
- Organization/administration
- Timeline
- Budget
- *If you can, add a section with preliminary data*

Title

- Should be **clear & descriptive**
- COPD Prevalence and Risk Factors in Three Cities in Nigeria and Namibia

Research Question(s)

- What question(s) will the study address
- A good question should pass the “so what” test!

Study Hypothesis

- The research question should be clear and answerable by yes/no or a number. It should be relevant and address a hypothesis.

What is a Hypothesis?

- A **best guess**

Examples of Research Questions

- Do inhaled corticosteroids in moderate-severe COPD reduce mortality & frequency of exacerbations?
- Does an asthma education program in the context of a children's asthma camp improve asthma control?

Study Questions & Hypothesis using TORCH as example

TORCH:

Question: Does a combination of long-acting beta-agonists and inhaled corticosteroids reduce mortality in COPD?

Hypothesis: A combination of long-acting beta-agonists and inhaled corticosteroids reduces mortality in COPD

Research Questions may be stated as Objectives

- ***Overall objectives*** are an indication of the contribution to be made to biomedical knowledge/theory and public health.
- ***Specific objectives*** are in the form of answerable questions, either yes/no or a number
- Specific objectives are often divided into **Primary & Secondary**

TORCH Study *NEJM 2007; 356:775089*

- **Overall objective:** to evaluate the role of combination of LABA and ICS in management of COPD
- **Primary Specific Objective:** to determine if a combination of LABA & ICS reduces mortality
- **Secondary Specific Objective:** to determine if a combination of LABA & ICS reduces the frequency of exacerbations

Significance

Background and rationale

- Why are these questions important?
- What is the existing knowledge in the area?
- This section cites previous research that is relevant & indicates the problems and what questions remain

Background for TORCH

- COPD 5th leading cause of death worldwide
- Mortality from COPD is increasing
- We don't have any effective treatment that changes the natural history
- Some evidence that ICS reduce mortality & exacerbations but evidence on combo of LABA & ICS is limited

Design

- Describe study design e.g. cross-sectional etc
- Say why you selected that study design.
- There is no such thing as a single “correct” design... hypotheses can be studied by different methods using different designs.
- All research designs represent a compromise dictated by the many practical considerations.
- State the time frame e.g. 3-year, 3-month etc

Design of TORCH

- “We undertook the Towards a Revolution in COPD Health (TORCH) trial, a double-blind, placebo-controlled, randomized, parallel-group study comparing salmeterol plus fluticasone propionate (the combination regimen) with each of the components alone and with placebo over a 3-year period”

NEJM 2007; 356:775089

Methods

- All methods need to be described, even if standard approaches are used.
- Detail provided should be sufficient for replication by others.
- A quality control/quality assurance plan should be specified.

Study Participants

- State selection criteria (inclusion and exclusion)
- Describe sampling design
- Describe recruitment plan

Selection Criteria

Criteria should be explicit and applicable by others.

- Geographic location.
- Time period.
- Demographics: age, sex, other.
- Other selection criteria: Inclusion and exclusion criteria.

Inclusion Criteria for TORCH

- Current or former smokers with at least a 10-yr pack history of smoking
- Men & women aged 40-80 yrs with a diagnosis of COPD
- Pre-BD FEV1 <60% predicted and increase of FEV1 of <10% pred after 400µg albuterol and FEV1.FVC ≤.70

NEJM 2007; 356:775089

Exclusion Criteria: LHS-2

- **medical conditions** precluding corticosteroid use: cataracts, osteoporosis, or adrenal-pituitary axis disease
- **major chronic illnesses** other than COPD: such as cancer, endocrine disease, angina, congestive heart disease, stroke, severe hypertension, insulin-dependent diabetes mellitus, renal failure, or major neuropsychiatric disorder
- **medication use**: systemic or inhaled corticosteroids within the last six months, anti-coagulants, major psychotropic drugs, beta-blockers, nitrates, digitalis, insulin, anti-arrhythmic drugs

Describe Recruitment Plan

- Descriptions should be very explicit and indicate why these plans are likely to work, e.g., show calculations of potentially eligible participants and realistic response rates
- Be realistic and conservative. Unrealistic goals suggest inexperience!

Variables

- Outcome (often called dependent variables)
- Exposure (risk factor, independent variable, predictor)
- Potential confounders (a variable that is **associated** with the predictor variable and is a **cause** of the outcome)
- Methods of data collection & quality control

Methods of Data Collection

- Questionnaires
- Chest x-rays
- Spirometry
- Medical record review
- Sputum culture

Data Collection Methods:

Quality of Life

- The proposed assessment of quality of life will include a combination of generic measures and measures that are specific to COPD. The generic measures which we will use are the 36-item short form of the Rand Medical Outcomes Study or **MOS (SF-36)**, and a simple generic scale, the **Ladder of Life**. The specific measure will be the brief **University of Alabama at Birmingham (UAB) COPD Index** which measures the impact of respiratory symptoms on physical, social, and role functioning.

Methods: Spirometry

- Forced expiratory spirometry will be carried out in accordance with the protocol developed for the LHS. Equipment and software specifically designed for this study is standard across all centers (Spirotech Model 150 Dry Rolling Seal Spirometer). The protocol exceeds quality control and performance standards of the ATS.
- Bronchodilator response is measured as the percent increase in FEV1 10 minutes after two puffs of isoproterenol by MDI with a spacer:
$$\frac{(\text{postbronchodilator FEV1} - \text{pre-bronchodilator FEV1})}{\text{pre-bronchodilator FEV1}} \times 100$$
The post-bronchodilator FEV1 is used to calculate longitudinal change in lung function.

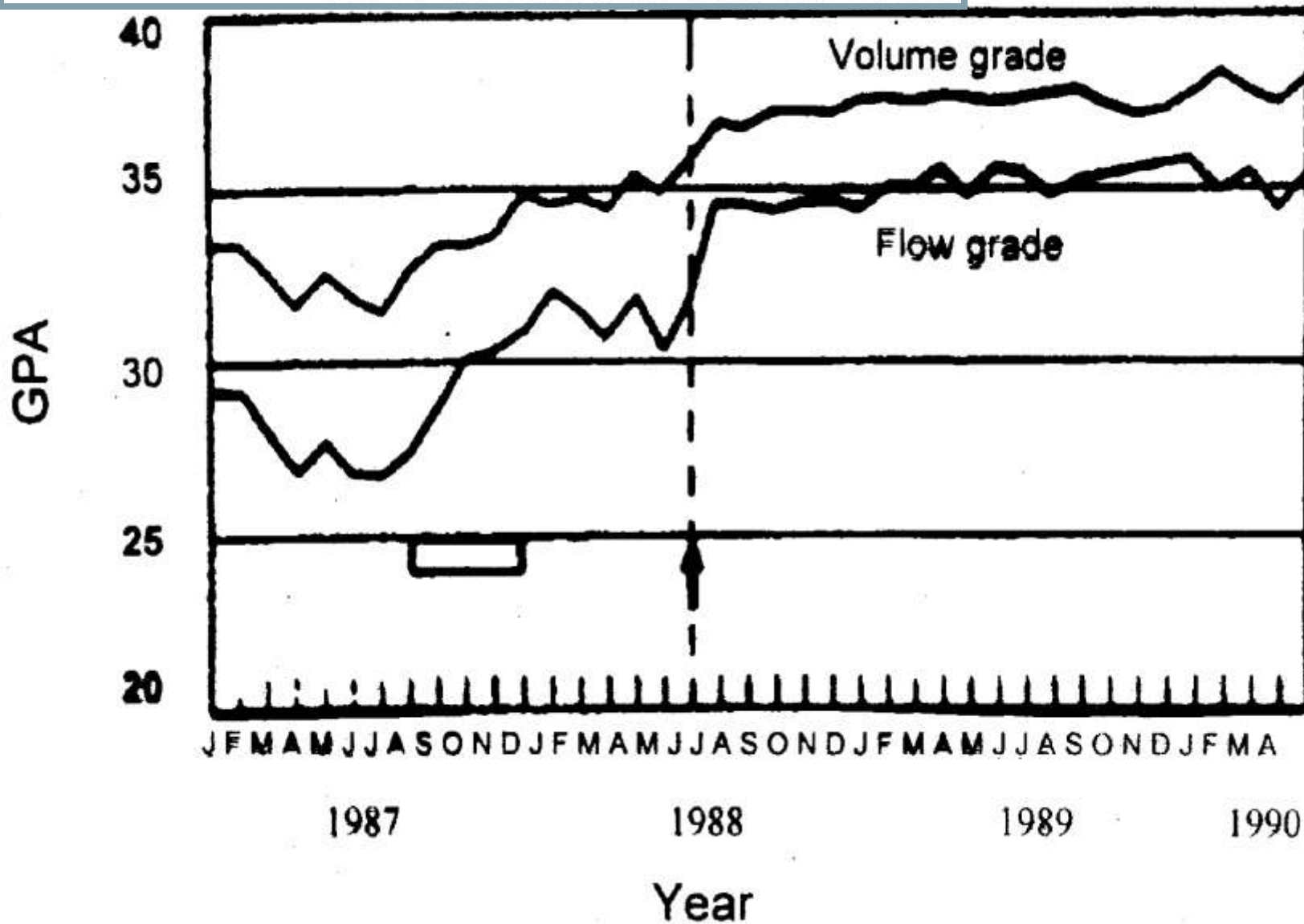
Quality Control IS IMPORTANT!

- Be very explicit. The knowledgeable reader should be able to judge if you know what you are talking about and have experience with the methods you propose to use

Quality Control: Pulmonary Function LHS-2

- Daily 3-Liter calibration and leak checks
- Automated real-time maneuver acceptability and reproducibility cues
- Automated grading of all test sessions
- Central over-reading of a sample of test-sessions
- Monthly quality control grades and remedial actions
- Initial 2-day training and certification of technicians
- Annual site-visits to observe testing procedures
- Annual refresher training courses for technicians

Example of effect of QC in LHS



Statistical Issues

- Hypothesis
- Sample size
- Analytic approach

Sample Size

The basis for determining the sample size should be given, along with documentation of any calculations.

Analytic Methods

- Detail the analytic methods to be used.
- Describe anticipated problems.

FINER Criteria

- **Feasible:** adequate number of participants; technical expertise; affordable in time & money; manageable in scope
- **Interesting:** to the investigator
- **Novel:** Confirms or refutes previous findings; extends previous findings; provides research direction
- **Ethical**
- **Relevant:** To scientific knowledge; clinical & health policy & future research directions

Consent Procedures

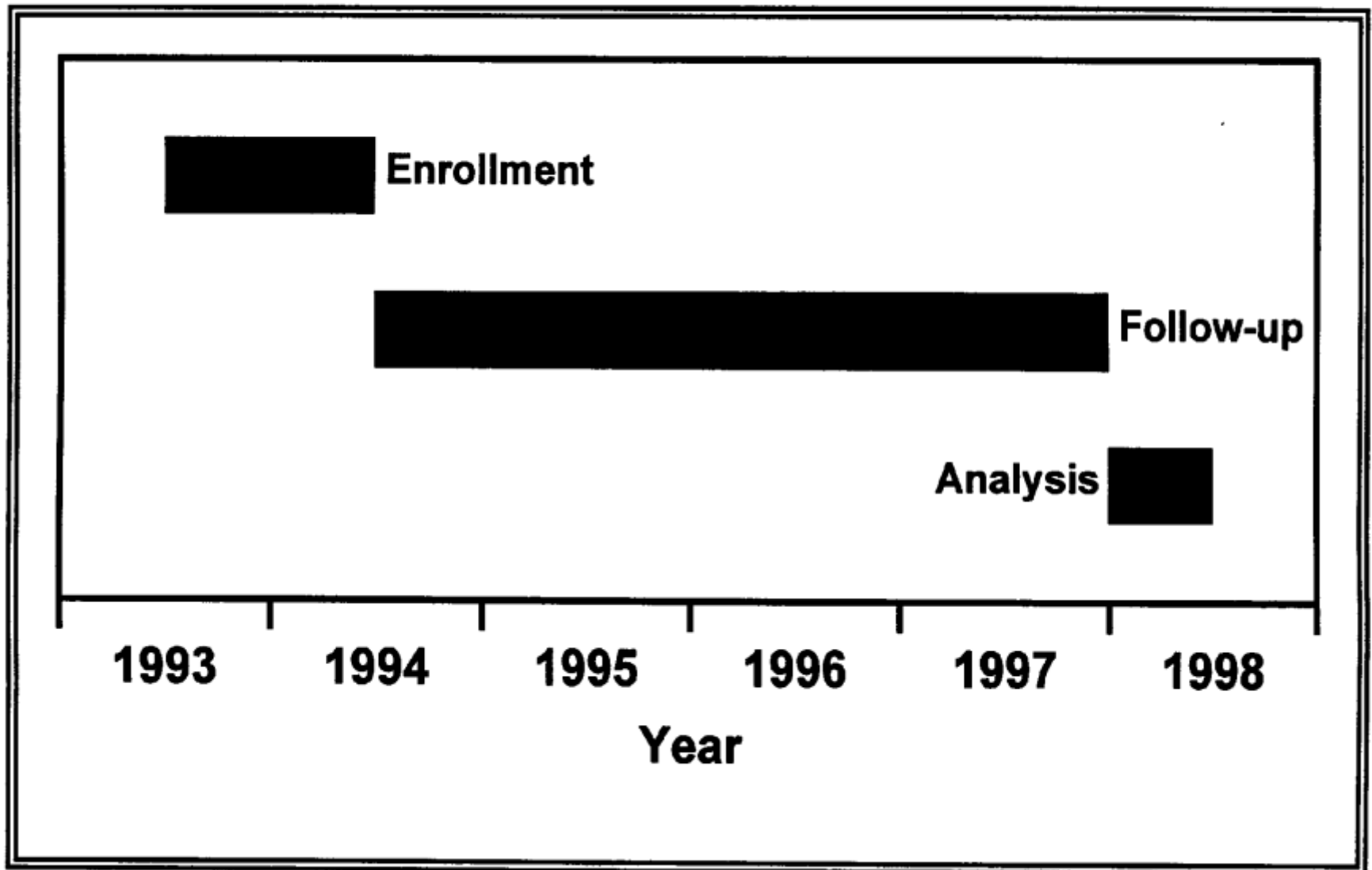
- Advise participants of procedures and purposes (what is expected of them and what will be done)
- Explain how the information will be used and its value to the participant and society
- Discomforts and risks
- Availability of medical treatment and compensation for injury
- Safeguards for maintaining confidentiality
- Right to withdraw without affecting future care
- Name and telephone number of contact person for questions

Timeline

Specify anticipated timing for:

- Steps or phases of research plan of recruitment.
- Screening for participants.
- Initial data collection.
- Follow-up.
- Data analysis.
- Report preparation.

Timetable For The Inhaled Corticosteroid Study



Budget

- Personnel
- Equipment
- Travel
- Materials (eg skin tests, chest X-rays)
- Publication costs

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