

WRITING THE CLINICAL STUDY PROTOCOL

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Practical tips on how to write a protocol

- **Write the synopsis first**, most if not all content of the synopsis will be included in the study protocol
- **Have ready a summary of** objectives, endpoints, study population, age-group, sample size, study design, study duration, study procedures, visits, number of sites, country/countries (Clinical Development Plan),
- According the country/site you can anticipate some issues related to control group/ICF/feasability of study design

Protocol: Introduction (1)

- Background Information
- Disease, causative agent and epidemiology
 - Summary data of Non-Clinical Studies for IPs
 - Summary data of Clinical Studies for IPs
 - Investigational Product(s)
- Rationale of the study

What's the Research Question?

What is the study hypothesis and design as derived from the clinical development plan?

“The primary objectives of any study should be clear and explicitly stated” E8-ICH- General Considerations for Clinical Trials-

How to proceed: practical approach

- Define the **primary objective** and clearly write it down
 - To demonstrate non-inferior immunogenicity of Nice-to-Be Vaccine as compared to the licensed Wonder Vaccine in 6-25 years old subjects in Indonesia
 - To describe the tolerability and safety of Nice-to-Be Vaccine and the licensed Wonder Vaccine in Vietnam
 - To evaluate the efficacy of For-Ever-Young vs placebo in 2-15 years old subjects in Asia

How to proceed: practical approach

- Define the **secondary objectives** and clearly write all of them
- Discriminate between **objectives and endpoints**

Objectives \neq endpoints (2)

- **Primary Objective:**

- To compare the immunogenicity of a single dose of the PsA-TT vaccine with that of the Men A component of the PsACWY vaccine at 28 days after vaccination.

- **Primary Endpoint**

- The percentage of subjects who show a seroconversion for anti-Meningococcal Polysaccharide A (MenPsA) antibodies, i.e. a 4-fold increase in post-immunization serum titer with respect to pre-immunization serum titer, at 28 days after a single vaccine dose, as measured by rSBA assay.

- Example

http://www.nejm.org/doi/suppl/10.1056/NEJMoa1003812/suppl_file/nejmoa1003812_protocol.pdf

Study Design (3)

- **Description of study design**
 - objective, population, study age-group, randomization, blinding, dose and vaccination schedule, controlled or placebo arm, selection of control vaccine, study duration, safety and immunogenicity evaluation
- **Justification of study design**
 - Alternative study design, feasibility issues, accessible population etc etc
- **Primary and Secondary Endpoints definition**

Study population (4)

- ❖ **Target population**
 - ❖ Study sites, age-group, gender, recruitment, individual study duration
- ❖ **Selection and withdrawal criteria**
 - ❖ Exclusion/inclusion criteria
- ❖ **Premature discontinuation criteria**
 - ❖ For individual subjects (AEs, assumption of concomitant prohibited medications etc)
 - ❖ Usually subjects are excluded from study procedures with the exception of safety follow-up

Study procedure (5)

- Screening and screen failure
- Informed consent process/Assent process
- Contraception and pregnancy
- Laboratory testing
- Biological sample retention and destruction (if any)
- Subject's materials/questionnaires (if any)
- Visit procedures
- Early withdrawal procedure
- Study visit schedule

Study Vaccines (6)

- Rationale for dose selection, Vaccines, Preparation and administration, Precautions, Packaging, labeling, and storage of IPs
- Method of Assigning Subjects to Vaccination Groups, randomization and blinding, emergency unblinding
- Clinical study supply, dispensing, and accountability
- Permitted and not permitted concomitant medication/treatment

Endpoints assessment (7)

- **Safety**

- Methods for safety assessment, Subject's diary cards, assessment by the investigator,
- Severity grade for solicited AE (local and systemic post-immunization reactions, unsolicited Aes, duration of assessment)

- **Immunogenicity**

- Blood draws, blood quantity, serum separation, e tc
- Assay methodology and labs details

Safety Considerations (8)

- **Definitions**
 - Adverse Events
 - Serious Adverse Events
- **Reporting/Recording of AEs and SAEs**
 - Detailed reporting and time of SAEs, PV, SAEs Follow-up, treatment and relationship
- **Independent Data Monitoring Committee (if any)**

Statistical Considerations and Analysis Plan (9)

- Study conduct considerations
- Definition of analysis sets
 - ITT, PP, sub-group
- Assessment endpoints
 - primary and secondary
- Analysis methods
- Analysis plan
 - Demographic characteristics, safety, immunogenicity, efficacy

Quality Control and Quality Assurance (10)

- Pre-study documentation
- Monitoring
- Data management and processing
- Data handling and records keeping
 - CRF
 - Record Retention
- Study and site closure
- Protocol Violation/ Deviation
- Audits and inspections

Regulatory and Ethical Requirements (11)

- Regulatory Authority Approval
- Institutional Review Boards/Ethics Committees
- Subject Information, Informed Consent and Assent
- Notification of Primary Care Physician
- Investigator Reporting Requirements
- Record Retention

Administrative Matters (12)

❖ Amendments

❖ Publication Policy

❖ Insurance for Injury

Conclusion:final tips

- Need SOP on how to write a protocol and a template
- Need a leading author but writing a protocol is a team effort
- Use your own protocol template
- Always re-elaborate and check the standard sections as may not be applicable to any protocol you write
- Use a simple ready-to-understand language
- Use tables as they are easy to understand
- Ask for review and suggestion

Good Luck!



Thank You