How to read a clinical trial protocol

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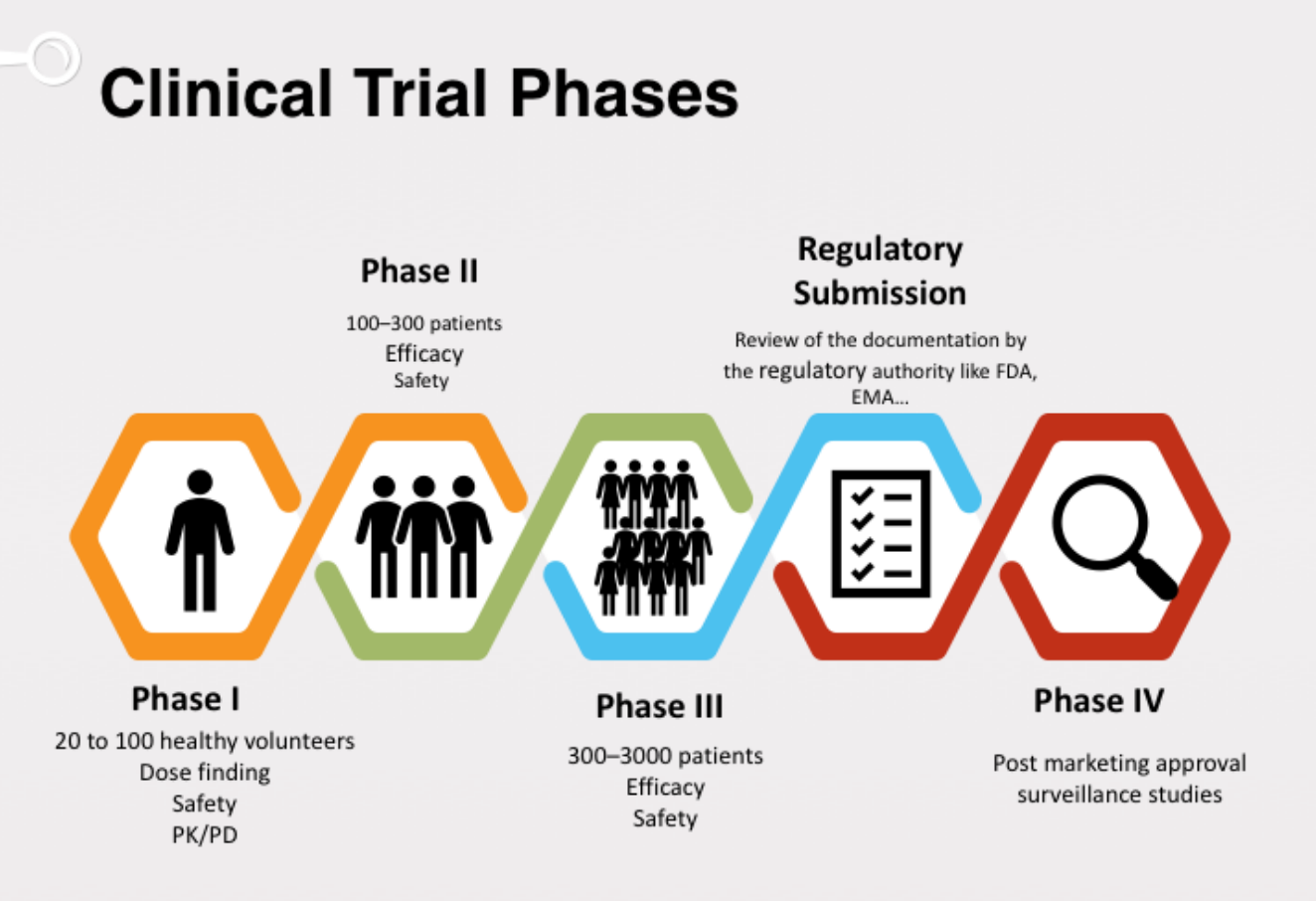
Refresher: phases of clinical trials



What is a clinical trial protocol?

- A clinical trial protocol is a complete written description of, and scientific rationale for, a research activity involving human participants
- The protocol is a guideline and tool for the research team to use when carrying out the study
- Protocols are reviewed by the Institutional Review Board (IRB) to ensure that risks and benefits are reasonable, that informed consent is sought for every individual who participates, and that safety measures are complete.
- Protocols are also submitted to FDA for studies of FDA-regulated products

Some key sections of a protocol

- Title
- Table of contents
- Protocol summary
- Objectives and Endpoints
- Study Design
- Study Population
- Study Intervention
- Study Assessments and Procedures
- Statistics
- Ethics

Study Synopsis

The study synopsis is a *summary* of all the elements of the study:

- **Study objectives**—what do the researchers hope to learn?
- **Study intervention** –drug, or vaccine, or other product— being tested
- **Study population**—characteristics of people who are invited to participate in the study, for example, their age range and health status
- **Schedule of study visits and assessments**—what tests will be done, and how often
- **Safety assessments**—how will safety information be gathered?

Study objectives and endpoints

Objectives: what are the researchers trying to learn?

Example 1: “To assess the antiviral activity of DTG/3TC in antiretroviral naïve HIV-1 infected adolescents.”

Endpoints: what are they measuring?

“The proportion of participants with plasma HIV-1 RNA less than 50 copies/mL at Week 48”

Study Design

- This section describes the different groups, or arms, in the study, and which interventions (products) or controls will be given to each group.
- If the participants are allocated to the different groups by randomization, this is described.

The study design also specifies

- Timing of giving the interventions
- Dose.
- Number of participants in each arm of the trial

Study population

This section describes the people who will be enrolled in the study:

- Age range
- Gender
- Other characteristics

Inclusion and exclusion criteria provide more specifics on who may enroll in the trial

Inclusion and exclusion criteria

Inclusion criteria:

Characteristics we are looking for

Examples:

- In an HIV treatment study, looking for individuals living with HIV
- In a cancer treatment trial, individuals with that particular cancer
- In a vaccine trial, looking for healthy individuals

Exclusion criteria: conditions or characteristics we want to exclude for reasons of scientific validity or safety

Examples:

- Exclude people who have other serious medical conditions (not being studied in the trial)—scientific and safety reasons
- In a vaccine trial, exclude people who have already received a vaccine—scientific reasons

Study intervention

- The study intervention is the drug, vaccine, or other product being tested in the trial
- The product is described, along with the dose that will be used and how it will be administered.

- For example, “In this trial, study treatment will be the fixed dose combination of DTG/3TC, dosage 50mg/300mg, oral, one tablet daily”

Schedule of activities

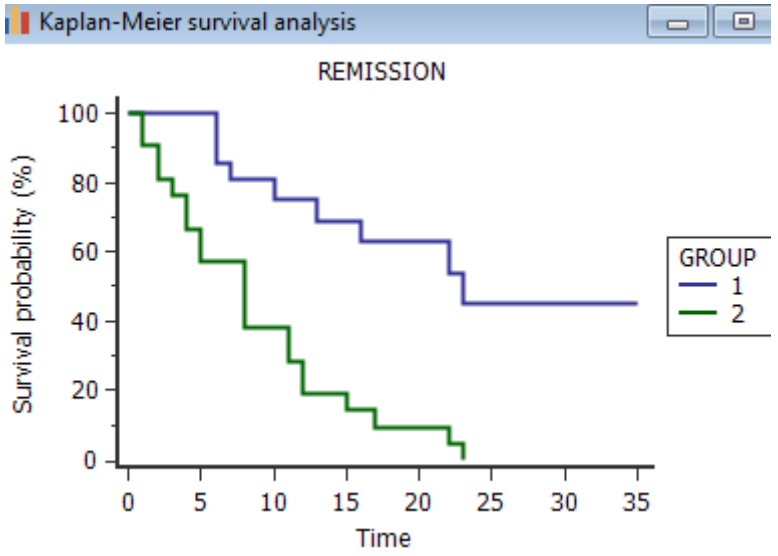
- The schedule of activities describes all the study visits that will take place throughout the entire study
- Often this is presented as a table format
- For each study visit, there are some procedures, such as lab tests, safety assessments, administering the intervention, etc.

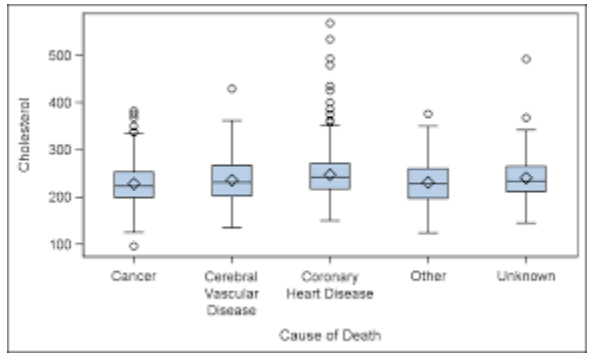
2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening[a]	Treatment Phase (Week)									Extension Phase[b]	
		Baseline / Day 1	1	4	8	12	16	24	36	48	Every 12 weeks after Week 48 through Week 144	Wit
Clinical and Other Assessments												
Written informed consent and assent[e]	X											
Inclusion and exclusion criteria[f]	X	X										
Demography (including year of birth, sex, race, ethnicity)	X											
Medical history (includes substance abuse)[g]	X											
Prior ART/PMTCT history, as applicable	X											
Tanner staging score[h]		X								X	X[h]	
Concurrent medical conditions	X											
Vital signs	X											
HIV risk factors and mode of transmission		X										
CDC HIV-1 classification	X	X										
HIV associated conditions				X	X	X	X	X	X	X	X	

Statistics

- The statistical section of a protocol will give basic information about the data will be analyzed.
- This section also describes how the researchers decided how many people were needed in the trial to enough statistical “power” to answer the research question.





Ethics

- The ethics section describes the researchers' commitment to carry out the study ethically, and describes the research oversight that will take place, i.e., Institutional Review Board (IRB) review.
- This section also describes informed consent, and any other ethical considerations specific to the protocol.
- The details of the informed consent process may be presented in this section, along with provisions for keeping data confidential, and compensation for study participants.

Taking a look at the WRAIR SpFN vaccine clinical trial protocol

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RANGING DOSES OF SARS-COV-2-SPIKE-FERRITIN-NANOPARTICLE (SPFN_1B-06-PL) VACCINE WITH ARMY LIPOSOMAL FORMULATION QS21 (ALFQ) FOR PREVENTION OF COVID-19 IN HEALTHY ADULTS

Protocol Number:	S-20-03; WRAIR #2847, EID030
Compound/Product Number/Name:	SARS-CoV-2-Spike-Ferritin Vaccine 1B06 (SpFN_1B-06-PL) with Army Liposomal Formulation QS21 (ALFQ)
Sponsor:	The Surgeon General, Department of the Army
Sponsor's Representative:	Mark S. Paxton JD, MS US Army Medical Research and Development Command (USAMRDC) 1430 Veterans Drive Fort Detrick, MD 21702-5009 Tel: 301-619-0317 DSN: 343-0317 Fax: 301-619-0197 Email: usarmy.detrick.medcom-usamrmc.mbx.usamrmc-regulatory-affairs@mail.mil
Funding Source	Cooperative Agreement #W81XWH-18-2-0040
Regulatory Agency Identifying Number:	Walter Reed Army Institute of Research Institutional Review Board FWA Number: 00000015 IRB Registration Number: IRB00000794
Clinical Trial Site:	Walter Reed Army Institute of Research Clinical Trials Center 503 Robert Grant Avenue Silver Spring, MD 20910-7500 Tel: 301-319-9660 Email: usarmy.detrick.medcom-wrair.mbx.clinical-trials@mail.mil
Institutional Review Boards (IRBs):	Walter Reed Army Institute of Research Institutional Review Board 503 Robert Grant Avenue Silver Spring, MD 20910-7500

Where to start?
Title of the study

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RANGING DOSES OF SARS-COV-2-SPIKE-FERRITIN NANOPARTICLE (SPFN_1B-06-PL) VACCINE WITH ARMY LIPOSOMAL FORMULATION QS21 (ALFQ) FOR PREVENTION OF COVID-19 IN HEALTHY ADULTS

What's in the title? Part 1

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY

Phase 1 study: assesses safety of the product, small number of participants

Randomized: study participants assigned to active product or placebo by random chance

Placebo-controlled: some participants get active product, participants in control group get placebo

Double-blind: neither the investigators nor the study participants know who got the product or the placebo

What's in the title? Part 2

TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY

Evaluate safety: check for adverse events that might be caused by the product

Tolerability: does the product cause uncomfortable side effects?

Immunogenicity: does the product stimulate the immune system?

What's in the title? Part 3

RANGING DOSES OF SARS-COV-2-SPIKE-FERRITIN NANOPARTICLE (SPFN_1B-06-PL) VACCINE

Ranging doses: several different doses are tested to see which one works best—want to stimulate the immune system a lot, but not cause uncomfortable side effects

SARS-COV-2 Spike Ferritin Nanoparticle (SPFN-1B-06-PL) Vaccine: this means that copies of the spike protein from the COVID-19 virus are attached to a ferritin molecule in a small particle, designed to stimulate the immune system

What's in the title? Part 4

WITH ARMY LIPOSOMAL FORMULATION QS21 (ALFQ)

- This product, **ALFQ**, was developed by WRAIR's own laboratory scientists so it is an Army product
- **ALFQ** is an adjuvant, which is the name for a product given with a vaccine that helps stimulate the immune system to make a stronger response
- **Liposomal formulation** means that the adjuvant has a fatty (lipid) substance as 'packaging' which helps the body process it more effectively

What's in the title? Part 5

FOR PREVENTION OF COVID-19 IN HEALTHY ADULTS

This vaccine is designed to prevent COVID-19

The study population is healthy adults—people over age 18 without significant health problems

Table of contents for the SpFN phase I clinical trial

TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

Table of Contents

Objectives and endpoints

Objective 1

To evaluate the **safety** and **reactogenicity** of 25 µg and 50 µg of **SpFN_1B-06-PL vaccine** given with 0.5 mL ALFQ adjuvant in a total 1.0 mL injection volume

Endpoints associated with Objective 1

- The occurrence and severity of solicited local and systemic AEs* during the 7-day and 28–day follow-up periods after each vaccination.
- The occurrence of SAEs**, NOCMCs,*** and pIMDs from the first vaccination until 1 year after the final vaccination.
- Abnormal WBC, hemoglobin, platelets, ALT, AST, ALP, total bilirubin, and creatinine laboratory values through 14 days following each vaccination. *(these are standard clinical lab tests)*

**AE = Adverse Event*

***SAE = Serious Adverse Event*

****NOCMC = new onset chronic medical condition*

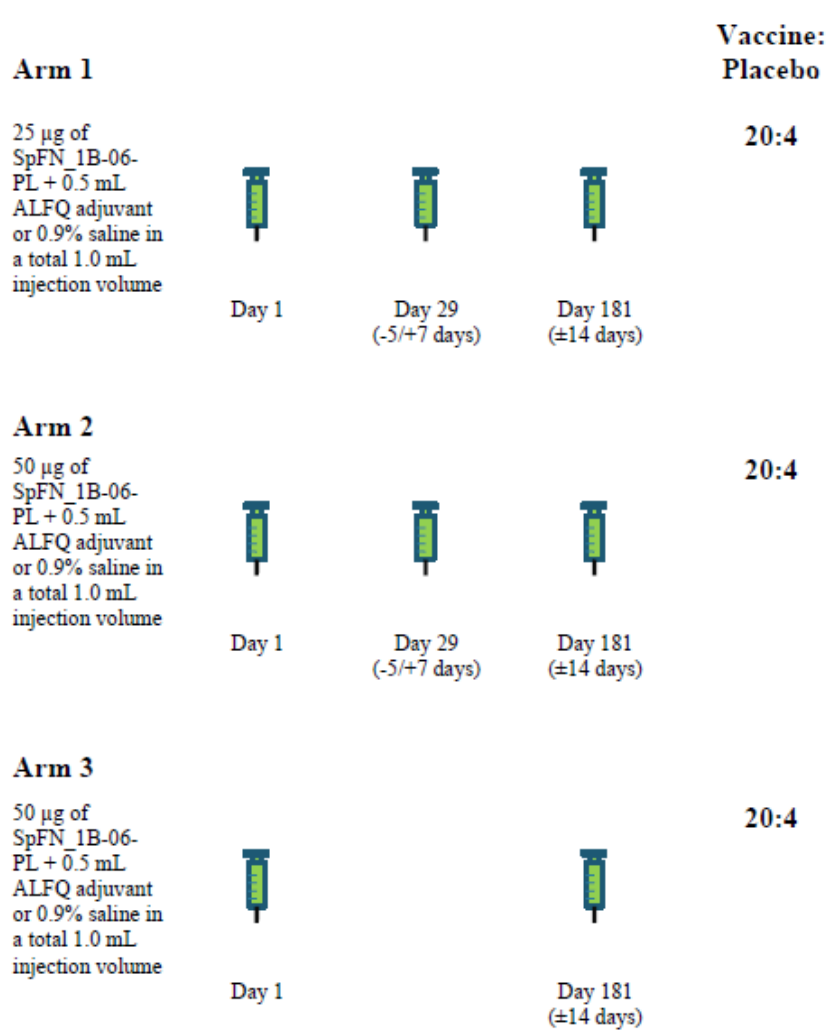
*****pIMD = potential immune-mediated disease*

Study Design

- Arm 1: lower dose of SpFN, 3 doses (day 1, day 29, day 181)
- Arm 2: higher dose of SpFN, 3 doses
- Arm 3: higher dose of SpFN, 2 doses

1.2. Schema

Figure 1: Study Design



Study Population

Potential participants, male and non-pregnant, non-breastfeeding females, ages 18 to 55 healthy volunteers that are not considered to be at high risk for contracting COVID-19, will be recruited from the Greater Washington DC

Metropolitan area.

Inclusion Criteria:

Participants eligible to participate in this study must meet all the following inclusion criteria:

1. Must be a male or non-pregnant, non-breastfeeding female between the ages of 18 and 55 years, inclusive, at the time of enrollment.
2. Must be willing and able to read, sign, and date the informed consent document.
3. Must demonstrate an understanding of the study with a passing score (90% or greater) on the TOU by the third attempt, before study-related procedures are performed.
4. Must be willing and able to comply with study requirements and be available for followup visits for the entire study.
5. Must have the means to be contacted by telephone and/or video for remote follow-up visits as needed.
6. Must have a body mass index (BMI) ≥18.1 kg/m2 and <35.0 kg/m2.
7. Have no previously documented COVID-19/SARS-CoV-2 infection

Study Intervention

- **SpFN_1B-06-PL**

SpFN_1B-06-PL will be provided in a sterile, 2 mL single use vial at 0.7 mL/vial, 90-110 ug/mL

- **ALFQ (QS21) Adjuvant**

ALFQ will be provided in a sterile 3 mL vial at 0.6 mL/vial

- **Sodium chloride, USP, for injection (0.9% NaCl)** *(placebo)*

Normal saline will be provided in a sterile, single-use 10 mL vial

Study Assessments and Procedures: examples

Screening visit

- Study briefing
- Consent form & test of understanding
- Medical history & physical exam
- Concomitant medication review
- Eligibility review
- SARS-CoV-2 exposure risk assessment
- Blood draw
- NP swab *(NP = nasopharyngeal)*
- Urine pregnancy test

Study visit 1

- Study briefing, consent form & test of understanding
- Brief physical exam & medical history update
- Concomitant medication review
- Eligibility review
- SARS-CoV-2 exposure risk assessment
- Urine pregnancy test
- Blood draw

Study visit 1, continued

- NP swab
- Saliva collection
- Randomization
- Vaccine/Placebo Injection 1
- Diary card instruction
- Post-vaccination observation & exam
- SAE/pIMD/SUSAR/MAAE/NOCMC *(review adverse event reporting)*

Schedule of events shows the whole sequence of study visits

1.3. Schedule of Activities

Table 1: Schedule of Events

Study Day	D-60 to D-5	D-14 to D-5	D1	D3 (±1) Call[1]	D8 (±1)	D15 (±2)	D29 (-5/+7)	D32 (±1) Call[1, 2]	D36 (±1) Call[1, 2]	D43 (±2)	D57 (±7)	D181 (±14)	D184 (±1) Call[1]	D188 (±1) Call[1]	D195 (±2)	D209 (±3)	D361 (±14)	D546 (±14)	Final Visit
Tests and Observations	Screen via #2567.07	Screen	Vaccine/ Placebo Injection 1			14d >Dose 1	Arm 1/2: Vaccine/ Placebo Injection 2 Arm 3: No Injection (28d >Dose 1)	Arm 1/2: 3d >Dose 2	Arm 1/2: 7d >Dose 2	Arm 1/2: 14d >Dose 2 Arm 3: 14d >Visit 5	Arm 1/2: 28d >Dose 2 Arm 3: 28d >Visit 5	Arm 1/2: Vaccine/ Placebo Injection 3 Arm 3: Vaccine/ Placebo Injection 2	Arm 1/2: 3d >Dose 3 Arm 3: 3d >Dose 2	Arm 1/2: 7d >Dose 3 Arm 3: 7d >Dose 2	Arm 1/2: 14d >Dose 3 Arm 3: 14d >Dose 2	Arm 1/2: 28d >Dose 3 Arm 3: 28d >Dose 2			
Visit	00	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Week			1	1	1	2	4	4	5	7	8	26	26	27	28	30	51	77	
CLINICAL ASSESSMENTS																			
Briefing, Informed consent, & TOU	X	X	X																
Medical history	X	X	X		X	X	X			X	X	X			X	X	X	X	X
SARS-CoV-2 exposure risk assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion & exclusion	X	X	X				X[2]					X							
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Call visits will be completed by phone or video, depending on the participant's willingness and the video capability of their phone or computer
[2] Arms 1 and 2 only

Statistics

This is a Phase I study to assess the safety, reactogenicity, and immunogenicity of the SpFN_1B-06-PL vaccine along with ALFQ adjuvant in healthy adults, across two or three study injections on either Study Days 1, 29, and 181 (Arms 1 & 2) or Study Days 1 and 181 (Arm 3).

Because this is an early phase study with a limited sample size, most analyses will be descriptive.

However, hypothesis testing will be performed for some endpoints to facilitate decision-making relating to potential follow-up studies.

Ethics

The Institutional Review Board will determine whether the benefits of the protocol are in proportion to the risks. The rights and welfare of the participants will be respected, the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits, the results to be reported will be accurate, participants will give their informed consent and will be competent to do so and not under duress, and all study staff will comply with the ethical principles in 21 CFR Part 50, 32 CFR 219, 45 CFR 46, and the Belmont Principles.

Wrap-up

- Clinical trial protocols are an essential tool for conducting clinical trials.
- Protocols must be accurate, detailed, and complete
- They are used for multiple purposes, including for ethical and regulatory review, as a set of basic guidelines for conducting the trial, and a method to document the researchers' plans
- Protocols are often written in very technical language which makes them difficult to understand
- Becoming familiar with the different sections of the protocol and their significance can help demystify the process.

Questions?