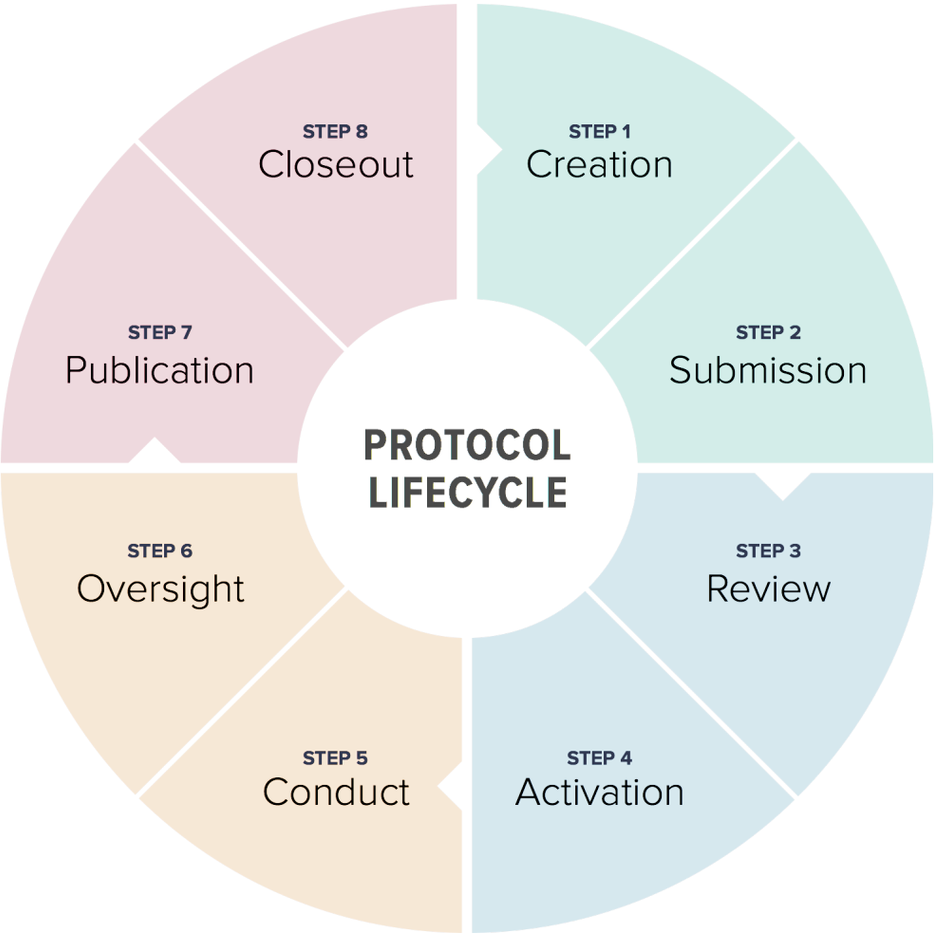
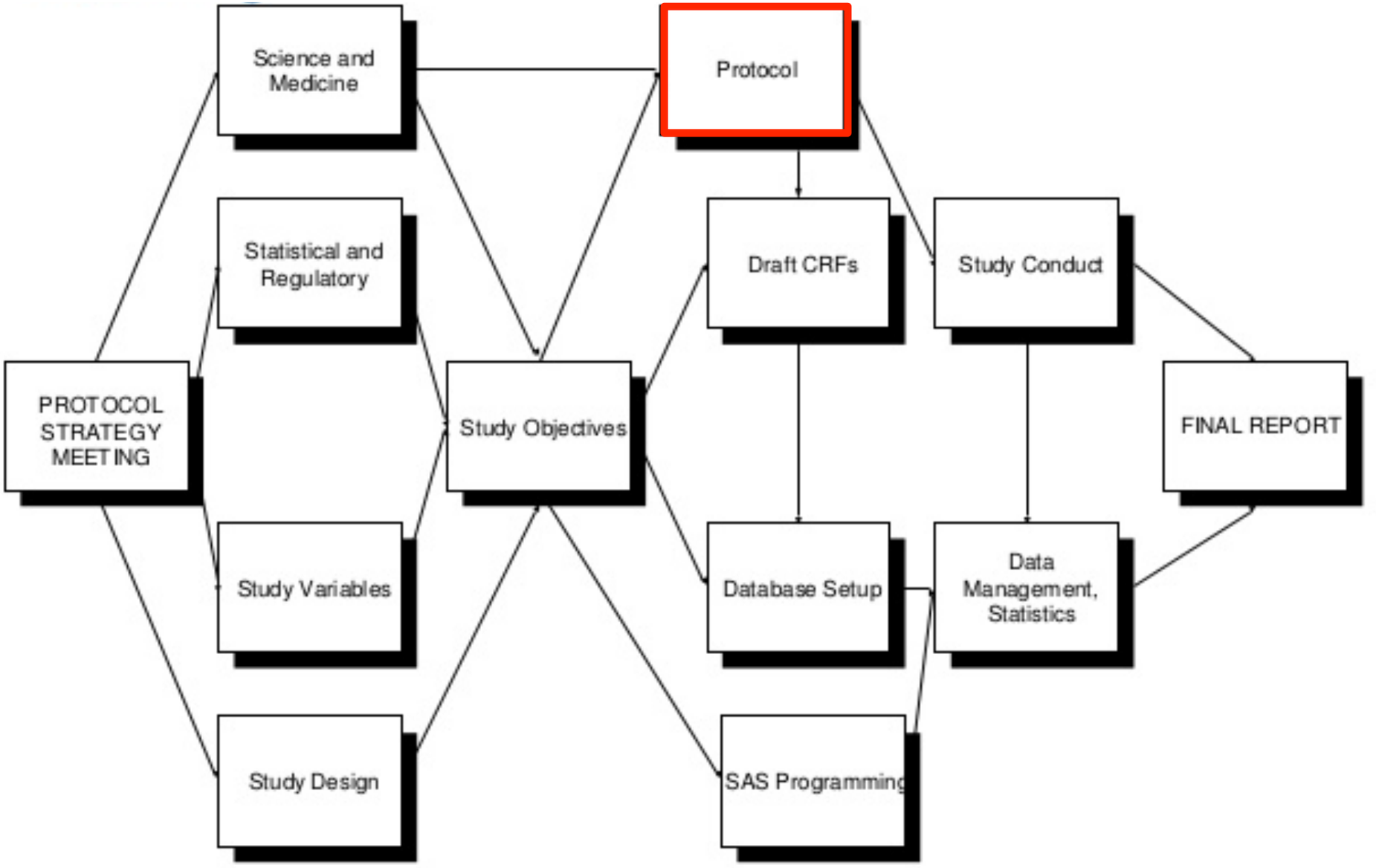
QM

Clinical Trial Protocol Development

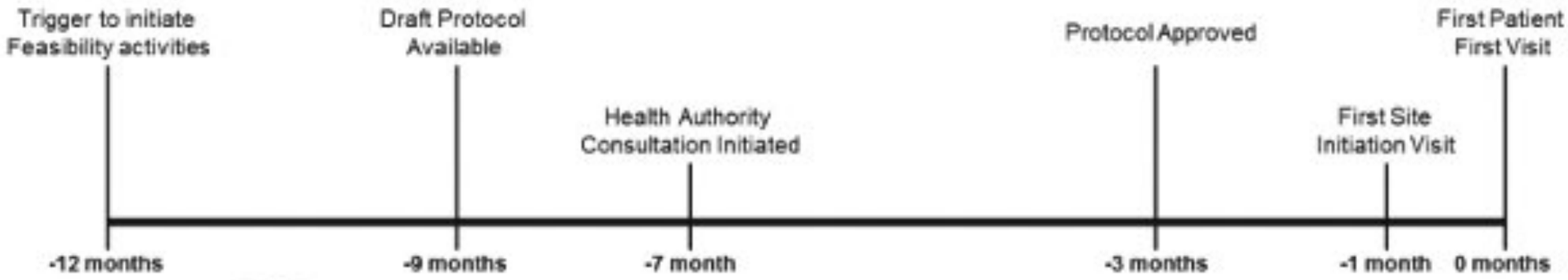


When does the protocol get made?



The Purpose of a Clinical Trial Protocol

- Describe the objectives, design, methods, data analysis, and how to perform the specific trial.
- Provide the background/reason for conducting a study, research questions, and ethical concerns.
- Trial protocols must meet GCP/Ethical standards so they are used for review by the IR
- A ton of stakeholders benefit from the protocol even after the end of the trial



What is in a Clinical Trial Protocol?

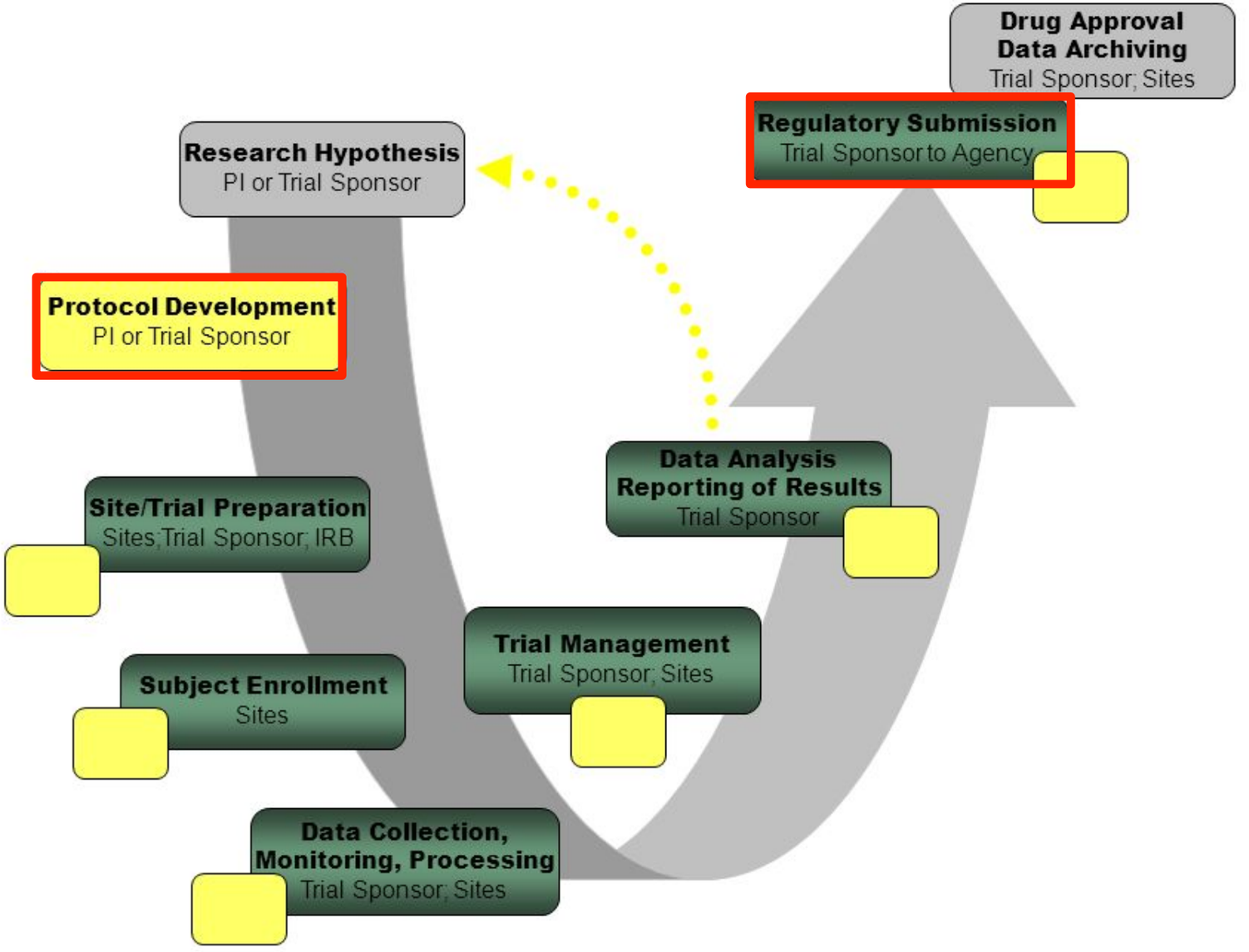
According to the ICH Good Clinical Practice guidelines, a protocol should include the following topics:

- Title Page (General Information)
- Background Information
- Objectives / Purpose/Aim
- Study Design
- Selection and Exclusion of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Adverse Events
- Discontinuation of the Study
- Statistics
- Quality Control and Assurance
- Ethics
- Data handling and Recordkeeping
- Publication Policy
- Project Timetable / Flowchart
- References
- Supplements / Appendices

What is in a Clinical Trial Protocol? Example

1. Title Page
2. Protocol Synopsis
3. Schedule of Assessments
4. Table of Contents
   (a) List of Tables
   (b) List of Figures
5. Introduction
   (a) Background
   (b) Study Rationale
6. Study Objectives
   (a) Primary Objective
   (b) Secondary Objectives
7. Study Endpoints
   (a) Primary Endpoint
   (b) Key Secondary Endpoints
   (c) Other Secondary Endpoints
   (d) Other Endpoints
8. Study Design
   (a) Overview of Study Design
      i. Screening
      ii. Treatment Period
      iii. Follow-up
      iv. Early Discontinuation
      v. Loss to Follow-up
      vi. Data and Safety Monitoring Board
   (b) Rationale for Study Design and Study Drug Regimens
      i. Study Design
      ii. Study Drug Dose and Duration
      iii. Rationale for Study Assessments
9. Study Population
   (a) Inclusion Criteria
   (b) Exclusion Criteria
   (c) Study Restrictions
   (d) Prior and Concomitant Medications and Other Study Restrictions
      i. Prohibited Medications
      ii. Prior and Concomitant Medications
   (e) Removal of Subjects
   (f) Replacement of Subjects
10. Study Drug Administration and Management
   (a) Preparation and Dispensing
   (b) Administration
   (c) Method of Assigning Subjects to Treatment Groups
   (d) Study Drug Interruption
   (e) Dose Modification for Toxicity
   (f) Packaging and Labeling
   (g) Study Drug Supply, Storage, and Handling
   (h) Drug Accountability
   (i) Disposal, Return, or Retention of Unused Drug
   (j) Compliance
   (k) Blinding and Unblinding
      i. Blinding
      ii. Unblinding
11. Assessments
   (a) Timing of Assessments
   (b) Informed Consent/Assent
   (c) Subject and Disease Characteristics
   (d) Efficacy
      i. Primary Endpoint Assessment
      ii. Assessment of Secondary Endpoints
      iii. Assessment of Other Endpoints
   (e) Safety
      i. Adverse Events
      ii. Assessment of Adverse Events
12. Statistical and Analytical Plans
   (a) Sample Size and Power
   (b) Analysis Sets
   (c) Statistical Analysis
      i. General Considerations
      ii. Descriptive Analysis
         A. Subjects
         B. Demographics and Baseline Characteristics
         C. Prior and Concomitant Medications
         D. Study Drug Exposure
         E. Study Drug Compliance
   (d) Efficacy Analysis
      i. Analysis of Primary Outcome
      ii. Analysis of Secondary Outcomes
      iii. Analysis of Other Outcomes
   (e) Safety Analysis
      i. Adverse Events Analysis
   (f) Interim and IDMC Analyses
      i. Interim Analysis
      ii. DSMB Analysis
13. Procedural, Ethical, Regulatory, and Administrative Considerations
   (a) Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting
      i. Adverse Events
         A. Definition of an Adverse Event
         B. Clinically Significant Assessments
         C. Documentation of Adverse Events
         D. Adverse Event Severity
         E. Adverse Event Causality
         F. Study Drug Action Taken
         G. Adverse Event Outcome
         H. Treatment Given
      ii. Serious Adverse Events
         A. Definition of a Serious Adverse Event
         B. Documentation of Serious Adverse Events
         C. Reporting Serious Adverse Events
         D. Expedited Reporting and Investigator Safety Letters
   (b) Administrative Requirements
      i. Ethical Considerations
      ii. Subject Information and Informed Consent
      iii. Investigator Compliance
      iv. Access to Records
      v. Subject Privacy
      vi. Record Retention
      vii. Study Termination
   (c) Data Quality Assurance
   (d) Monitoring
   (e) Electronic Data Capture
   (f) Publications and Clinical Study Report
      i. Publication of Study Results
      ii. Clinical Study Report
14. References
15. Protocol Signature Pages
   (a) Sponsor Signature Page
   (b) Investigator Signature Page

The Clinical Trial Protocol Lifecycle

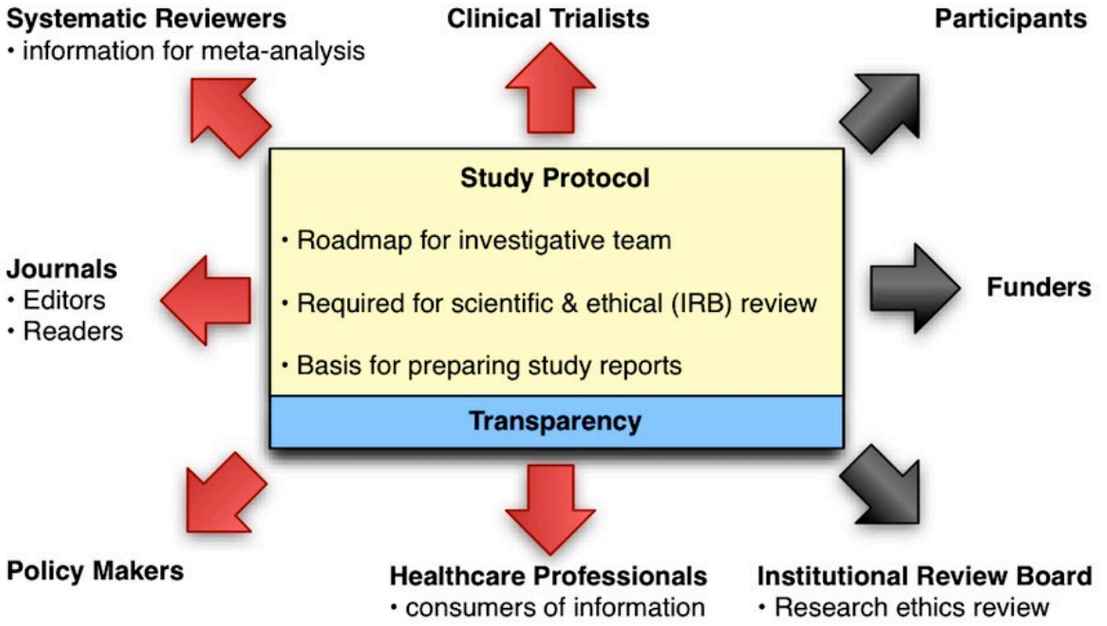


What is a Clinical Trial Protocol?

- The protocol is a document that turns a research question into a study which allows you to answer that question.
- It is important that a protocol is thorough enough to fully instruct the research team in
  1) how to run the study,
  2) to ensure that the outcome of the trial is the ‘right’ answer (i.e. is reliable), and
  3) that the outcome has been obtained ethically and safely.

What will a protocol do?

- A protocol will:
  1. It states the question you want to answer.
  2. It encourages you to plan the project in detail, before you start.
  3. It allows you to see the total process of your project.
  4. It acts as a guide for all personnel involved in the project.
  5. It acts as a ‘reminder’ to you and your supervisor (or co-workers) of the initial structure and aims of the project.
  6. It enables you to monitor the progress of the project.
  7. It is necessary if you need to apply for funding or IRB approval.



Key features of a protocol

- Scientific rationale to justify conduct of the study
- Details sufficient for repetition by other PIs, publication, and inclusion in a meta-analysis;
- Scientifically sound and appropriate study design
- Study population clearly defined (inclusion and exclusion criteria)
- All procedures sufficiently specified such that:
    - Study coordinator can **ensure study visits completed correctly**;
    - Measurements in detail so the data manager can **create case report forms**; and
    - Study team can **perform measurements in a consistent, reproducible manner.**
- Analysis plan and sample size complete, including methods for:
    - **Allocation** assignment and blinding methods;
    - **Blinding** of treatments;
    - Analysis of **primary and secondary endpoints** in sufficient details for scientific review and allow a statistician to repeat the analysis;
    - Sufficient detail for journal publication (compliant with reporting guidelines)
- Cogent and complete **discussion of ethical issues** for IRB/regulatory approval

What is in a Clinical Trial Protocol? - SPIRIT Checklist

Section/item	ItemNo	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

What is in a Clinical Trial Protocol? - SPIRIT Checklist

Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

What is in a Clinical Trial Protocol? - SPIRIT Checklist

Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

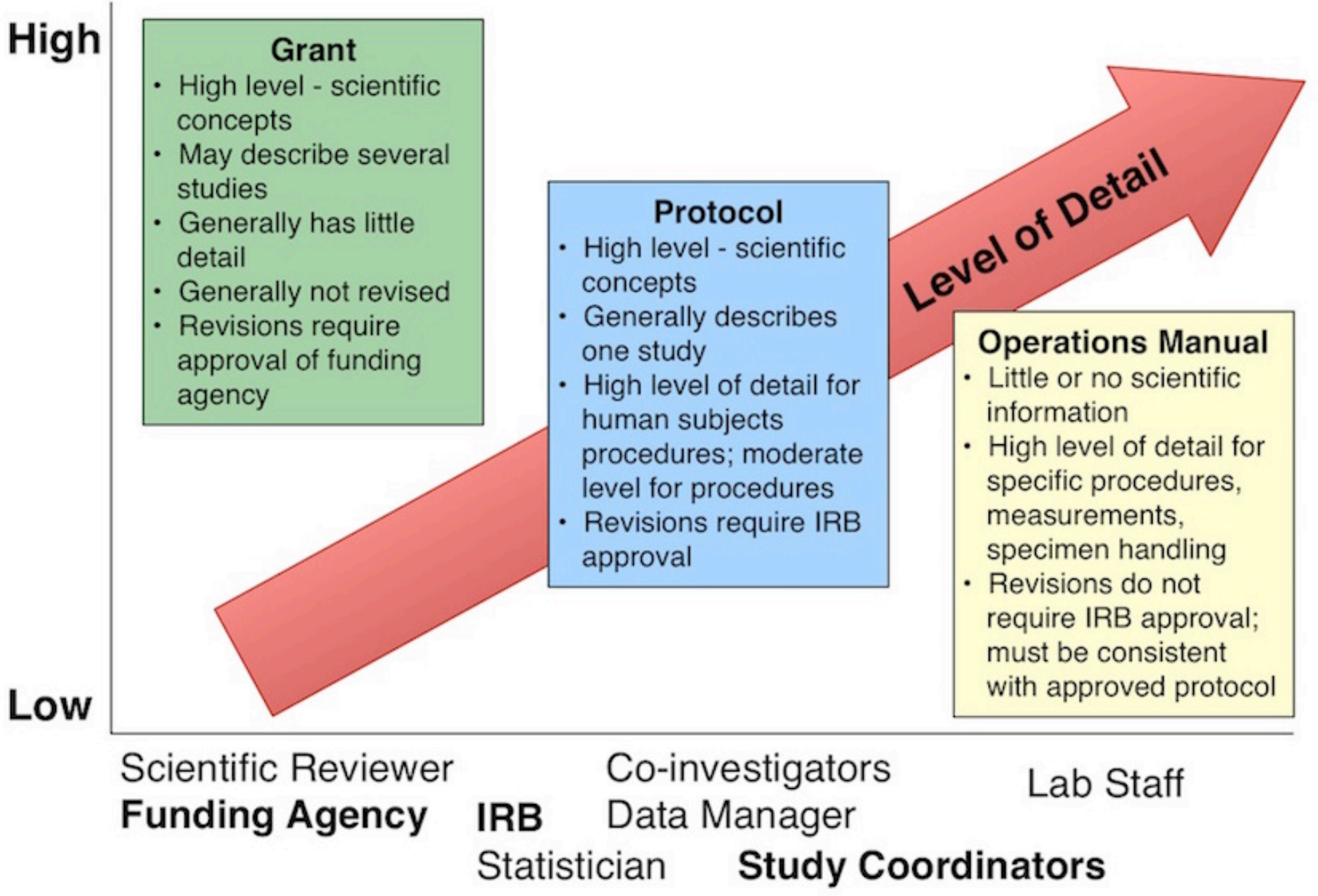
What is in a Clinical Trial Protocol? - SPIRIT Checklist

Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

What is in a Clinical Trial Protocol? - SPIRIT Checklist

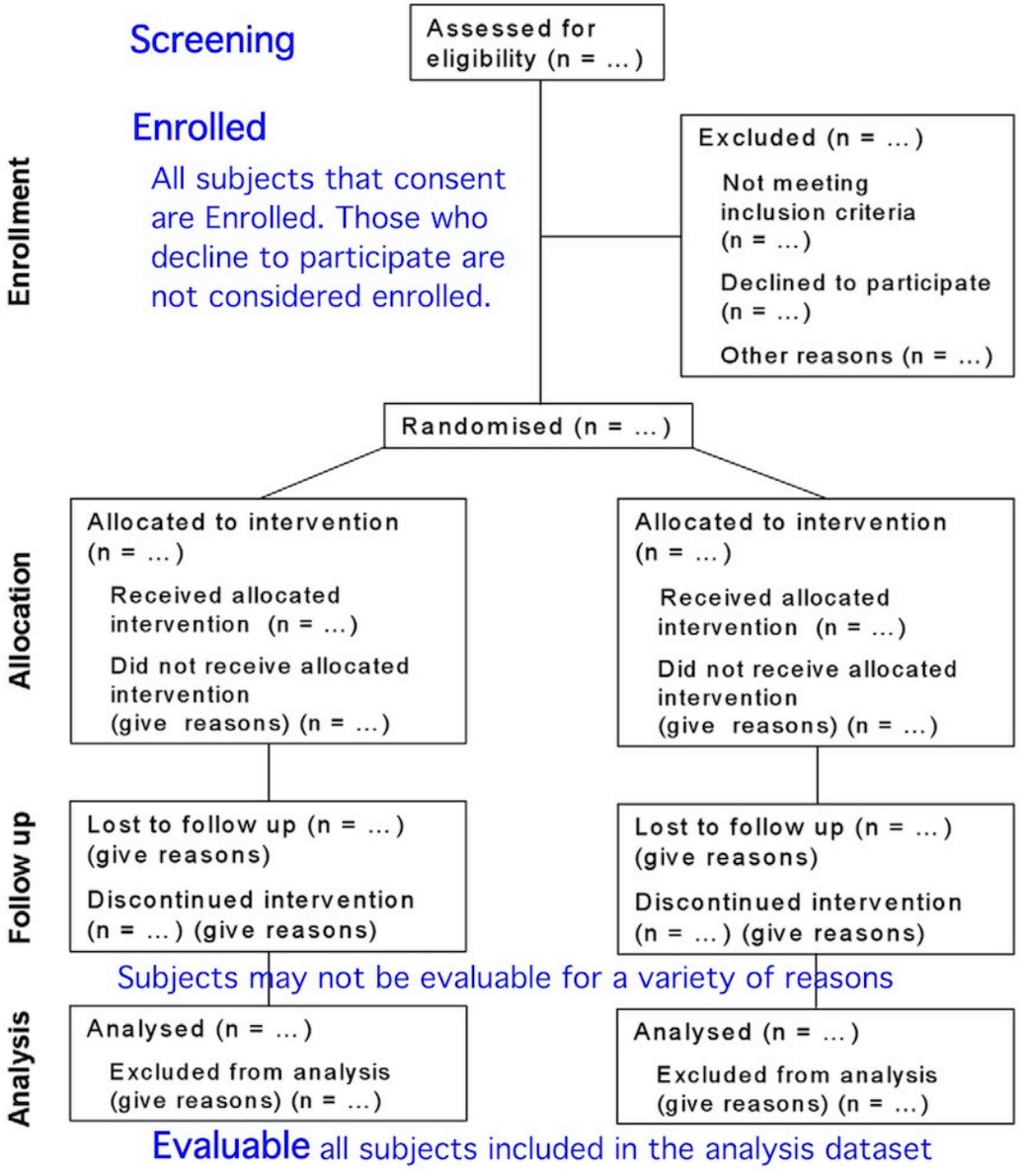
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

Difference between Grant vs. Protocol vs. Operations



Step 1: Screened, Enrolled, and Evaluable

- First estimate the # of subjects you need to screen and factor in eligibility/drop-outs in order to have enough power to prove significant outcomes.
- **Screened: assessed for eligibility** for the study (i.e. **compared patient information against inclusion/exclusion criteria;** may need prior IRB approval, HIPAA Auth, or consent in some cases)
- **Enrolled:** all subjects who have 1) **consented to screening (eligible or not)** OR 2) **met criteria for participation** in the main study (**even if withdrew later on/never got investigational drug**)
- **Evaluable:** all subjects whose **data can be used in the final analysis** data set (patients can be evaluable for some endpoints or all i.e. all 4 samples needed for evaluating PK outcomes vs only 2 samples to evaluate safety outcomes)



Writing A Clinical Trial Protocol

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Writing A Clinical Trial Protocol

National Institutes of Health
Turning Discovery Into Health

Clinical e-Protocol Writing Tool

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CCRPS NEW

Preview | Export | ClinicalTrials.gov | Manage Team | Finalize

Table of Contents

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- Protocol Amendment Summary of Changes Table *
- Statement of Compliance *
- 1 Protocol Summary * >
- 2 Introduction * >
- 3 Objectives and Endpoints *
- 4 Study Design * >
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Protocol Name

CCRPS

Protocol Short Name

CCRPS

Unique Protocol Identification Number (Any unique identifier assigned to the protocol by the sponsor and required for upload into ClinicalTrials.gov. Limit: 30 characters.)

National Clinical Trial (NCT) Identified Number

Principal Investigator

CCRPS

Select study type

What is the name of the entity funding the clinical trial? (Ctrl click to select multiple)

Protocol Preface: Synopsis

- The synopsis is a 1-4 page outline of the study in miniature.
- It enables investigators, study coordinators, IRB reviewers and regulatory personnel and auditors to quickly acquaint themselves with the study.
- The synopsis should be brief. It is not necessary to write complete sentences for many sections, bullet points often suffice.

File Edit View Insert Format Tools Table

Title:	CCRPS	
Study Description:		
Objectives:	Primary Objective:	
	Secondary Objectives:	
Endpoints:	Primary Endpoint:	
	Secondary Endpoints:	
Study Population:		
Phase:		
Description of Sites/Facilities Enrolling Participants:		
Description of Study Intervention:		
Study Duration:		
Participant Duration:		

2.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**	
Title of Protocol: A Comparative, Randomized, Open-Label, Multi-Center, Single Dose Pharmacokinetic, Pharmacodynamic and Safety Study and 25 mg) Between Children, Adolescents, and Adults with Type 2 (Non-Insulin Dependent) Diabetes Mellitus	**IND No.:**	**EudraCT No.:**
Study Number:	**Phase:** 1	

Study Design:

This is a comparative, randomized, open-label, multi-center, single-dose pharmacokinetic (PK), pharmacodynamic (PD), and safety study in which 25 mg will be administered to 36 children and adolescents with type 2 diabetes mellitus (T2DM) and 36 gender- and race-matched adults with T2DM as follows:

- Group 1: 12 subjects aged 10 to <14 years (6 of either sex) with T2DM.
- Group 2: 24 subjects aged 14 to <18 years (12 of either sex) with T2DM.
- Group 3: 36 gender and race matched adults with T2DM to Groups 1 and 2, aged 18 to 65 years, inclusive.

The study consists of a Screening period (Days -28 to Day -2), a Treatment period (Day 1 through Day 4), and a 14-(+/-1) day follow-up phone call. Subjects who satisfy the screening evaluation and the selection criteria defined in Sections 7.1 and 7.2 may be enrolled in the study. Subjects will be admitted into the clinic on (Check-in) Day -1 and will remain confined to the clinic until the evening of Day 2. On Day 1, pediatric subjects will receive a single oral dose of alogliptin 12.5 mg or 25 mg in a fasting state followed by breakfast. On Day 1, all adult subjects will receive alogliptin 25 mg in a fasting state followed by breakfast. Blood and urine samples for PK and PD assessments will be collected from all subjects before dosing and at designated timepoints up to 36 hours after dosing during confinement. Subjects will be discharged from the clinic on Day 2, following collection of the 36-hour PK urine sample. Subjects will return to the clinic for PK blood sample collection and other study procedures in the morning on Day 3 (48 hours postdose) and Day 4 (72 hours postdose). Final Visit procedures will be performed on Day 4.

Objectives:

The objectives of this study are to determine the pharmacokinetic and pharmacodynamic profiles, safety, and tolerability of a single dose of 12.5 mg and 25 mg in subjects with T2DM who are between 10 to 17 years old and adult subjects with T2DM.

Subject Population: Subjects aged 10 to 17 years old with T2DM and adult subjects with T2DM, aged 18 to 65 years, inclusive.

Number of Subjects: 72 (36 pediatric subjects, and 36 adults)	**Number of Sites:** Up to 6 sites in the US
Dose Level(s): 12.5 mg and 25 mg for Pediatric subjects 25 mg for adult subjects	**Route of Administration:** Oral
Duration of Treatment: Single oral dose of alogliptin 12.5 mg or 25 mg	**Period of Evaluation:** Total Study duration: 47 days (including 28-day Screening Period and 14 (+/-1) day follow-up phone call).

Protocol Preface: Synopsis Template

Title:	<Full title>
Study Description:	*Provide a short description of the protocol, including a brief statement of the study hypothesis. This should be only a few sentences in length. A detailed schematic describing all visits and a schedule of assessments should be included in the* ***Schema and Schedule of Activities, Sections 1.2 and 1.3****, respectively.*
Objectives:	*Include the primary and secondary objectives. These objectives should be the same as the objectives contained in the body of the protocol. These align with Primary Purpose in clinicaltrials.gov.*
	<Primary Objective:
	Secondary Objectives: >
Endpoints:	*Include the primary endpoint and secondary endpoints. These endpoints should be the same as the endpoints contained in the body of the protocol. These align with Outcome Measures in clinicaltrials.gov.* <Primary Endpoint: Secondary Endpoints: >
Study Population:	*Specify the sample size, gender, age, demographic group, general health status, and geographic location.*
Phase:	<2 or 3 or N/A> *Phase applies to drugs and biologics.*
Description of Sites/ Facilities Enrolling Participants:	*Provide a brief description of planned facilities/participating sites enrolling participants. Indicate general number (quantity) of sites only and if the study is intended to include sites outside of the United States.*
Description of Study Intervention:	*Describe the study intervention. If the study intervention is a drug or biologic, include dose and route of administration. For devices, provide a description of each important component, ingredient, property and the principle of operation of the device.*
Study Duration:	*Estimated time (in months) from when the study opens to enrollment until completion of data analyses.*
Participant Duration:	*Time (e.g., in months) it will take for each individual participant to complete all participant visits.*

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	INVEGA®
Name of Active Ingredient(s)	paliperidone

Protocol No.: CR010834

Title of Study: A randomized, double-blind, placebo-controlled, parallel-group, dose-response, multicenter stud to evaluate the efficacy and safety of three fixed doses of extended-release paliperidone (3, 6, and 12 mg/day) i the treatment of subjects with acute manic and mixed episodes associated with Bipolar I Disorder

Coordinating Investigator: Andrew Cutler, MD - Florida Clinical Research Center, Bradenton, FL; USA

Publication (Reference): None.

Study Period: 16 February 2006 to 25 June 2007 **Phase of Development:** 3

Objectives: The primary objectives were to demonstrate the efficacy and to assess the safety of 3 different dos of extended-release (ER) paliperidone compared with placebo. The key secondary objective was to assess th effect of paliperidone ER on global functioning compared with placebo. Other objectives were to assess the ons of antimanic clinical response to paliperidone ER, to assess the global improvement in severity of illnes associated with the use of paliperidone ER, to evaluate the impact of paliperidone ER therapy on patient-reporte outcomes (via the Short Form 36 [SF-36]), to assess the impact of paliperidone ER on depressive symptoms an on psychotic symptoms, to explore the pharmacokinetics (PK) of paliperidone ER, to assess the differential effe of the time of study drug administration relative to food intake and the type of meal eaten during the first 6 days study treatment, and to assess the possible relationship of PK to the efficacy and safety of paliperidone ER.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, dose-respons multicenter, efficacy and safety study. The study began with a screening and washout phase of no more tha 7 days during which subjects' current antimanic, mood-stabilizing treatment and other excluded medications we discontinued. Subjects may have been hospitalized at any time during this phase or been followed as outpatient Eligible subjects who completed the washout phase entered a 3-week double-blind treatment phase after balance random assignment to 1 of 4 double-blind study drugs (3, 6, or 12 mg/day of oral paliperidone ER, or placeb once daily). Subjects were hospitalized for at least the first 7 days of double-blind treatment. As early as Day 7 subjects could be discharged and followed as outpatients if they were believed by the investigator to be at n significant risk of violent or suicidal behavior. End-of-study/early-withdrawal assessments were done on Day 2 after the last dose of study drug had been received and PK sampling had been completed, or upon earl withdrawal from the study. A follow-up visit for safety evaluations was scheduled approximately 1 week later.

Number of Subjects (planned and analyzed): The planned sample size was 464 subjects (116 per treatme group). A total of 467 randomized subjects (121 in the placebo group, 112 in the paliperidone ER 3-mg group, 11 in the 6-mg group, and 115 in the 12-mg group) received at least 1 dose and were included in the safety analysi set. A total of 465 subjects (121, 112, 118, and 114, respectively) from the safety analysis set also provide efficacy data and were included in the intent-to-treat (ITT) analysis set.

Diagnosis and Main Criteria for Inclusion: Male and female subjects were eligible for this study if they were 1 to 65 years of age, inclusive; met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteri for Bipolar I Disorder, Most Recent Episode Manic or Mixed (with or without psychotic features); had a history at least 1 documented manic or mixed episode requiring medical treatment within the 3 years before screening and had a total score of at least 20 on the Young Mania Rating Scale (YMRS) at screening and baseline (Day 1).

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER was supplied overencapsulated 3-mg tablets (batch numbers 05A24/F022, 05E23/F022, and 06G03/F022) or 6-mg tablets (bat numbers 05F02/F061 and 06D24/F061). Doses consisted of 2 capsules taken orally once daily.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo (batch numbers 05F03/F02 06B21/F027, and 06F07/F027) was supplied as overencapsulated tablets identical to the paliperidone capsule Doses consisted of 2 capsules taken orally once daily.

Duration of Treatment: The study consisted of a screening and washout phase (up to a maximum of 7 days), 3-week double-blind treatment phase, and a follow-up visit approximately 1 week after the end of double-blin treatment (or early withdrawal).

Criteria for Evaluation:

Efficacy: The following parameters were used to evaluate efficacy: YMRS, Global Assessment of Functioning (GAF), Clinical Global Impression-Bipolar Disorder-Severity of Illness Scale (CGI-BP-S), Positive and Negative Syndrome Scale (PANSS), Sleep Visual Analog Scale (VAS), and SF-36.

Safety: The following parameters were used to evaluate safety: adverse events, clinical laboratory tests, vital signs, weight and body mass index (BMI), ECGs, physical examinations, rating scales for extrapyramidal symptoms, Montgomery-Åsberg Depression Rating Scale (MADRS), and Scale for Suicidal Ideation (SSI).

Pharmacokinetics: Plasma concentrations of paliperidone were determined from blood samples taken at baseline on Day 1, on Days 6 and 21 before study drug administration, and at least 8 hours after study drug administration on Day 6.

Pharmacogenomics: Approximately 10 mL of whole blood was obtained for genetic analysis from subjects who provided specific written informed consent to participate in the genetics portion of the study. No genetic analysis had been performed when this report was written.

Statistical Methods: The change from baseline to end point (last observation carried forward [LOCF]) in YMRS (primary efficacy variable) and GAF (key secondary efficacy variable) was compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment and country as factors and baseline score as a covariate. The closed testing based parallel gatekeeping procedure using Dunnett's test and Bonferroni adjustment was applied to adjust for multiplicity in testing of the 3 doses versus placebo for the primary and key secondary efficacy variables. A similar ANCOVA model was used to analyze the changes in CGI-BP-S, PANSS, Sleep VAS, SF-36, MADRS, and SSI and to compare the YMRS results between paliperidone ER groups without adjustment for multiplicity. A Cochran-Mantel-Haenszel test controlling for country was used to analyze the percentages of YMRS responders (≥50% reduction from baseline in YMRS total score), YMRS remitters (YMRS total score of ≤12 at end point), and subjects who switched to depression (MADRS score ≥18, with an increase from baseline of ≥4, at any 2 consecutive assessments or at the last observation). The remaining efficacy and safety variables were evaluated using descriptive statistics and frequency distributions.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: From baseline to end point, there were decreases in YMRS total scores in all treatment groups, indicating improvement in the severity of manic symptoms. The mean (SD) change was -9.9 (10.22) in the placebo group, -9.6 (11.30) in the paliperidone ER 3-mg group, -11.7 (10.04) in the paliperidone ER 6-mg group, and -13.9 (9.19) in the paliperidone ER 12-mg group. The least-squares mean differences from placebo were +0.3, -1.9, and -4.0, respectively. The improvement in the paliperidone ER 12-mg group reached statistical significance ($p=0.005$) when compared with the placebo group. The paliperidone ER 3-mg and 6-mg groups did not achieve statistical superiority to the placebo group (3 mg: $p=0.992$; 6 mg: $p=0.302$). The improvement from baseline in the paliperidone ER 12-mg group was significantly ($p<0.001$) larger than that in the paliperidone ER 3-mg group but did not differ significantly ($p=0.102$) from that in the paliperidone ER 6-mg group. The onset of therapeutic effect based on the YMRS total score was Day 2 for the 12-mg dose.

There was a significant treatment-by-country interaction for the change in YMRS total score at end point ($p<0.001$). To further explore the interaction, country was categorized as United States vs. non-U.S. All 3 doses were tested using the 2-sided Gail-Simon interaction test. There was insufficient evidence to indicate that the interaction for any of the 3 doses and country was qualitative as indicated by the non-significance ($p\geq0.2499$) of the Gail-Simon test (2-tailed).

The median CGI-BP-S score at baseline was 4 (denoting moderate severity) in all treatment groups. Although the magnitude of the median change from baseline was the same in all 4 treatment groups (-1), there was a statistically significant difference between the paliperidone ER 12-mg group and the placebo group ($p=0.046$). This reflects a noticeably larger decrease from baseline in the percentage of markedly/severely/very severely ill subjects in the paliperidone 12-mg group than in the other groups.

There was improvement in the quality of sleep in each treatment group. The mean (SD) increase from baseline to end point was 8.3 (36.28) in the placebo group, 12.6 (33.25) in the paliperidone ER 3-mg group, 17.6 (30.79) in the paliperidone ER 6-mg group, and 20.6 (33.93) in the paliperidone ER 12-mg group. Statistical superiority to the placebo group was achieved by the 6-mg group ($p=0.034$) and the 12-mg group ($p<0.001$).

There were no significant differences between any paliperidone ER group and the placebo group in the following: change from baseline to end point in the GAF score, percentages of YMRS responders or remitters, PANSS total score, PANSS positive and negative subscales, PANSS Marder factors, daytime drowsiness, or SF-36 results.

SAFETY RESULTS: As shown in the table below, the incidence of treatment-emergent adverse events (TEAEs) increased with increasing paliperidone ER dose. Serious TEAEs were reported at a higher rate in the placebo group than in any of the paliperidone ER groups. The frequency of TEAEs leading to discontinuation was lower in the placebo and paliperidone ER 3-mg groups than in the 6- and 12-mg groups. No subject died during the double-blind phase of the study. One subject who received paliperidone ER 6 mg for 5 days died of unknown causes 1 week after withdrawing consent.

SAFETY RESULTS (CONTINUED):

Overall Summary of Treatment-Emergent Adverse Events During Double-Blind Phase
(Study R076477-BIM-3001: Safety Analysis Set)

	Placebo (N=121) n (%)	PALI ER 3 mg (N=112) n (%)	PALI ER 6 mg (N=119) n (%)	PALI ER 12 mg (N=115) n (%)	Total (N=467) n (%)
TEAE	85 (70)	68 (61)	89 (75)	100 (87)	342 (73)
Possibly related TEAE (a)	49 (40)	45 (40)	64 (54)	68 (59)	226 (48)
TEAE leading to death (b)	0	0	0	0	0
1 or more serious TEAE	10 (8)	4 (4)	5 (4)	5 (4)	24 (5)
TEAE leading to permanent stop	6 (5)	1 (1)	13 (11)	9 (8)	29 (6)

(a) Study drug relationships of possible, probable, and very likely are included in this category.
(b) Subject 605903 who was randomized to the paliperidone ER 6 mg group died 1 week after withdrawing from the study.
tsfae01_t1.rtf generated by tsfae01.sas.

Among the most common TEAEs, i.e., events that occurred in at least 5% of the subjects in any group, the following events occurred in paliperidone ER-treated subjects (total of all dose groups) at an incidence that was ≥3% higher (when calculated to 1 decimal place) than that in the placebo group: headache, somnolence, dizziness, sedation, akathisia, dystonia, and dyspepsia. Headache, somnolence, dizziness, sedation, and dystonia occurred more frequently (≥3% difference, when calculated to 1 decimal place) in the 6- and 12-mg paliperidone ER groups than in the 3-mg group. Mania occurred in placebo-treated subjects at an incidence that was ≥3% higher (when calculated to 1 decimal place) than that in the paliperidone ER-treated subjects (total of all dose groups). Most TEAEs were rated mild or moderate by the investigators.

Mania was the TEAE most commonly reported as serious. Such cases represent subjects who were hospitalized due to exacerbation of their underlying disease. The incidence of serious TEAEs of mania was higher for the placebo group (6%) than for any of the paliperidone ER groups (2% to 3%).

The incidences of EPS-related TEAEs grouped as parkinsonism, hyperkinesia, dystonia, and dyskinesia were higher in the paliperidone ER 12-mg group than in the paliperidone ER 3- and 6-mg groups; the incidences were higher in all 3 paliperidone ER groups than in the placebo group (except for dyskinesia). Distinct events (preferred terms) that occurred more frequently in at least 1 of the paliperidone ER groups than in the placebo group (i.e., ≥3% difference, when calculated to 1 decimal place) were hypertonia, akathisia, and dystonia. The incidences of extrapyramidal disorder, akathisia, dystonia, and dyskinesia were noticeably higher in the paliperidone ER 12-mg group than in the other 2 paliperidone ER groups. Although the 4 treatment groups had similar changes from baseline to end point in EPS rating scale scores, there was a clear dose-related increase in the percentage of subjects who used anticholinergic medications during the study: 9% in the placebo and paliperidone ER 3-mg groups, 13% in the paliperidone ER 6-mg group, and 28% in the paliperidone ER 12-mg group.

There were no clinically relevant changes in vital signs or ECG parameters. Prolactin levels increased in both males and females who received paliperidone ER, as expected. Only 3 subjects in the paliperidone ER groups and 1 subject in the placebo group had treatment-emergent potentially prolactin-related adverse events.

There were slight increases in mean body weight and BMI in all treatment groups from baseline to the end of the study, but the magnitude of the changes was greater in the paliperidone ER groups (increases of 1.1 kg in body weight and 0.4 kg/m^2 in BMI in each group) than in the placebo group (0.2 kg and 0.1 kg/m^2, respectively).

There was no evidence that paliperidone ER increased the risk of subjects switching from mania to depression or developing suicidal ideation.

PHARMACOKINETICS: The median plasma concentrations of paliperidone were dose proportional over the once daily dose range of 3, 6, and 12 mg. The median paliperidone plasma concentrations at 8 hours postdose on Day 6 were comparable between fasted subjects and subjects who had consumed a standard continental or a high-caloric breakfast between 2 hours before and 1 hour after their medication intake.

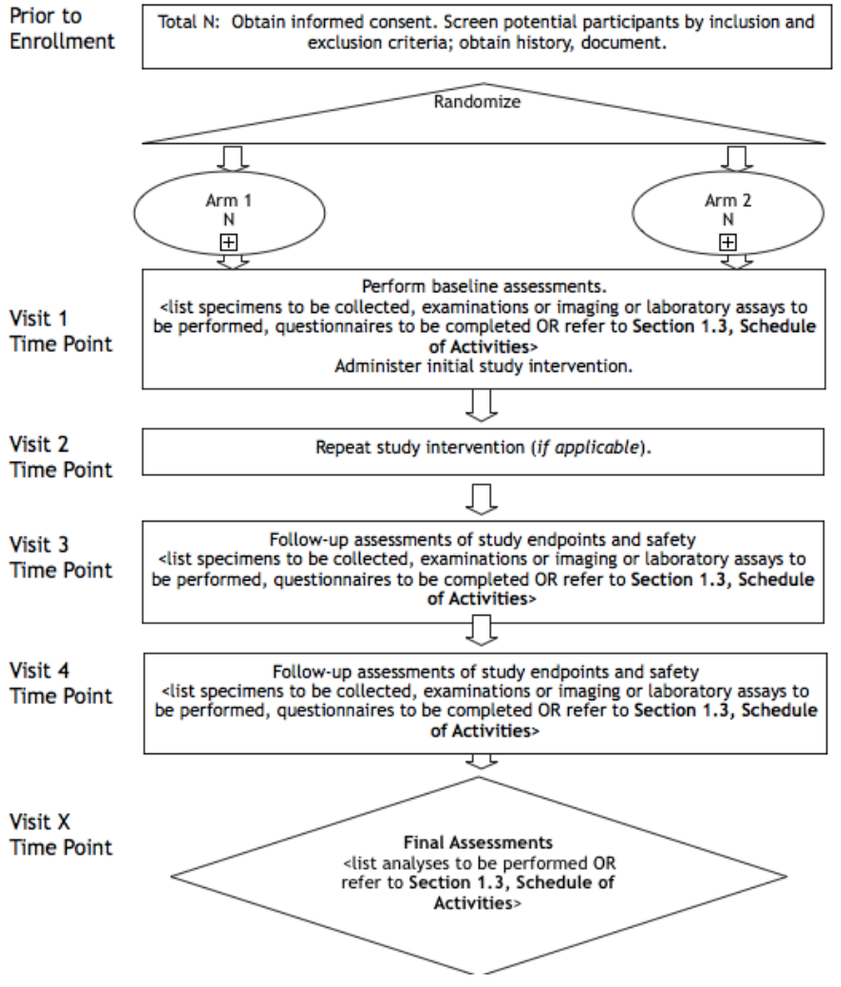
CONCLUSION: Paliperidone ER 12 mg was efficacious in the treatment of subjects with Bipolar I Disorder who were experiencing an acute manic or mixed episode. Specifically, the results of the primary efficacy variable demonstrated statistical superiority of paliperidone ER 12 mg over placebo. Other efficacy variables showed some statistical improvements with the 6- and 12-mg doses, but the results were not consistent across efficacy variables. The overall safety findings were similar to those observed in previous studies with paliperidone ER in schizophrenia, and no new safety signal was detected.

Synopsis Full Example

Protocol Preface: Schema/Flowchart

- When the design is less straightforward, a flow diagram helps explain the groups to which subjects will be assigned and how they will proceed through the trial phases.

***Example #1 Flow diagram** (e.g., randomized controlled trial)*



***Example #2 provided as a guide, customize as needed: Process diagram** (e.g., randomized controlled trial)*

Week/Day (Insert time) Screening

- Total n=x
- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Obtain history, document

Week/Day (Insert time) Randomization

- Intervention Group 1 (n=y)
- Placebo (n=z)

Week/Day (Insert time) Follow-up assessments of study endpoints and safety
Baseline assessments/ Study Intervention

- <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>
- Administer initial dose of study intervention

Week/Day (Insert time)

- <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Week/Day (Insert time) Follow-up assessments of study endpoints and safety

- <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Week/Day (Insert time) End of Study Assessments

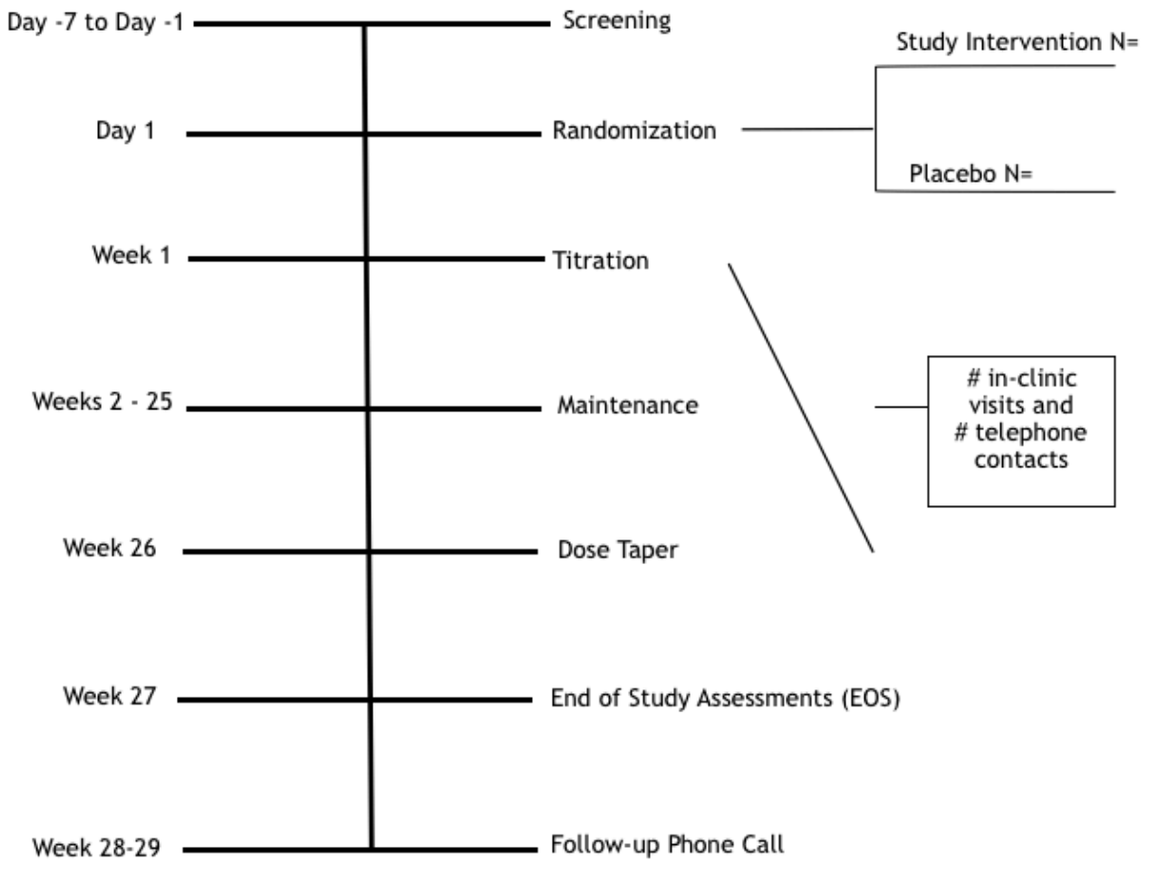
- <List specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

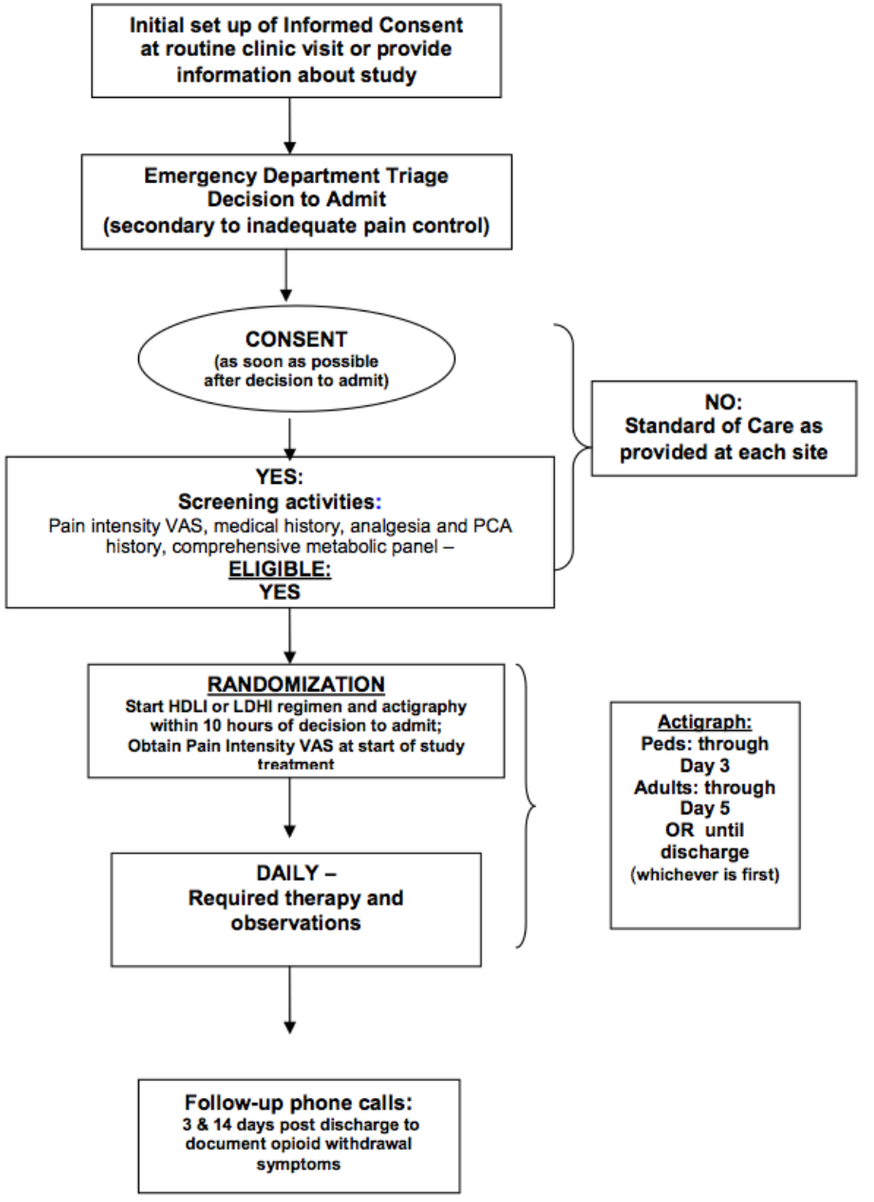
Week/Day (Insert time) Follow-up Telephone Call

- <List questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

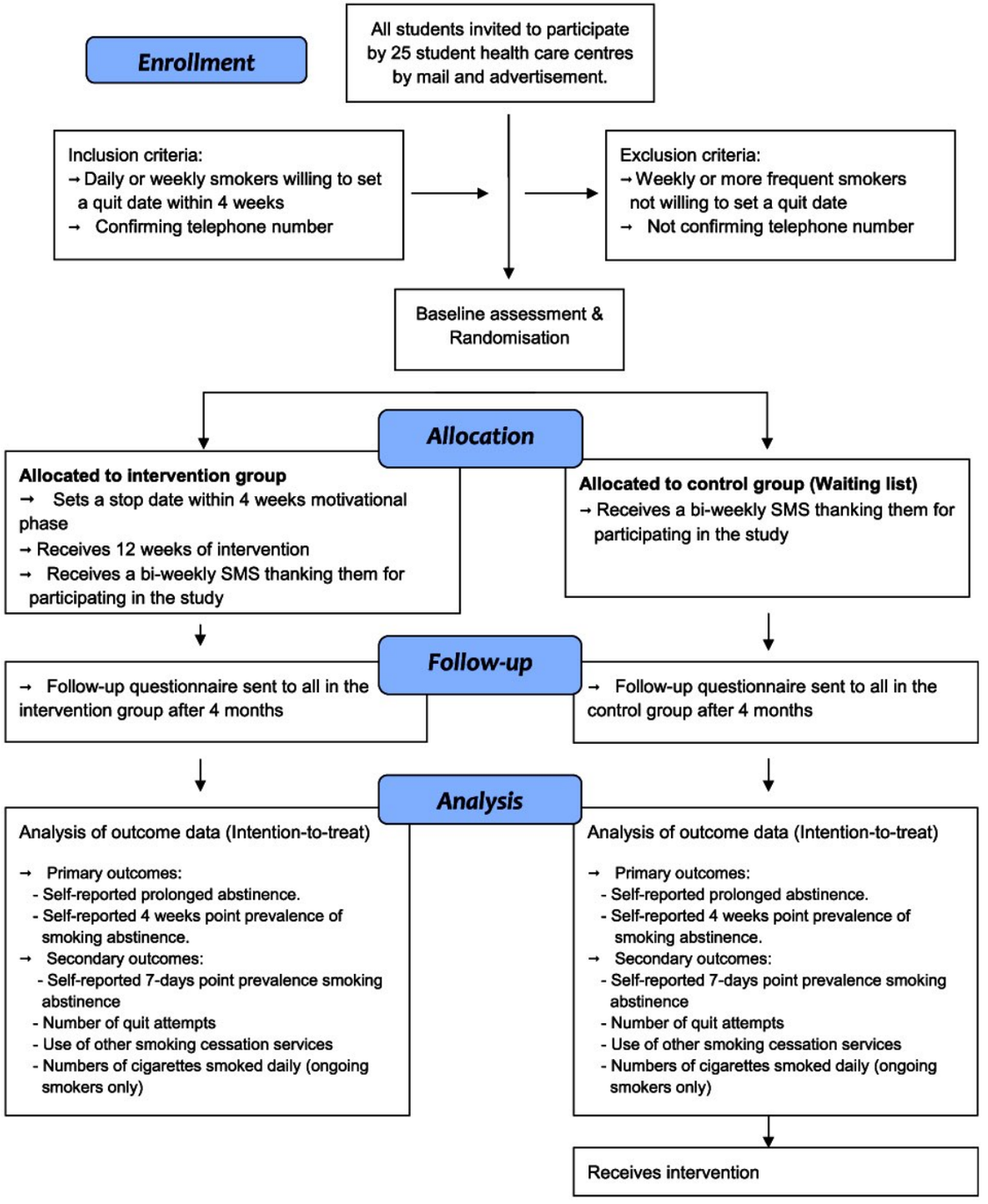
Protocol Preface: Schema Template

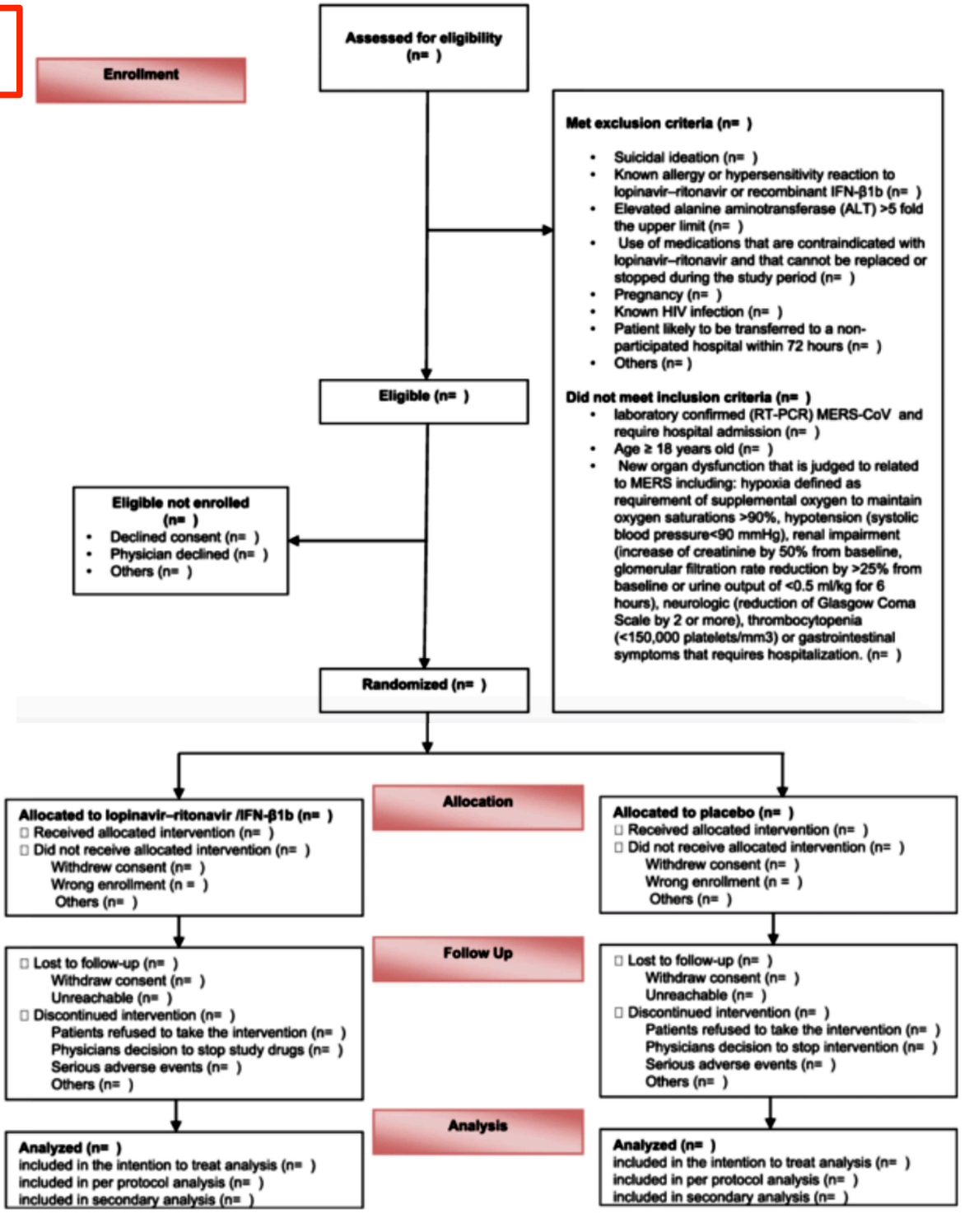
***Example #3 provided as a guide, customize as needed: Timeline diagram** (e.g., randomized controlled trial)*



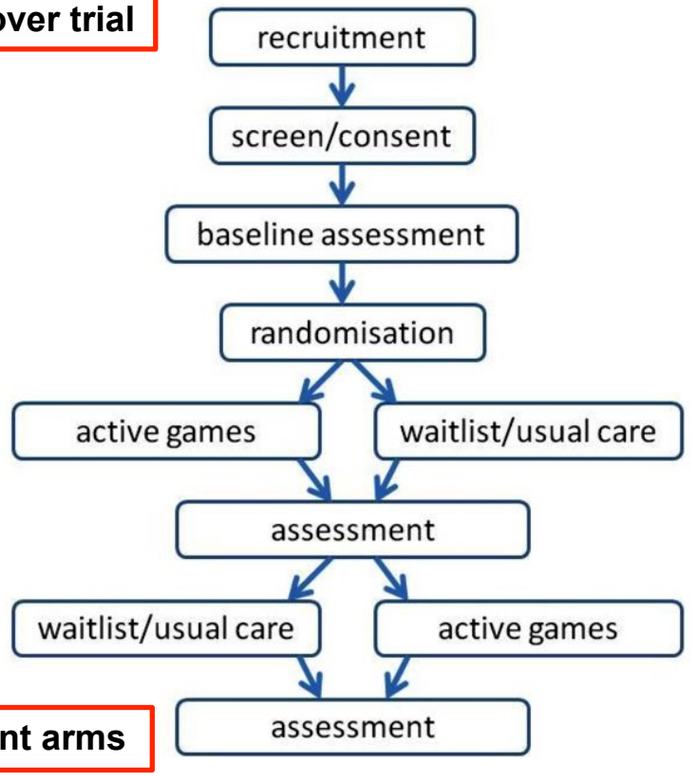


Protocol flowcharts sometimes mimic CONSORT flowcharts
but leave the N value blank since subjects haven't enrolled yet.

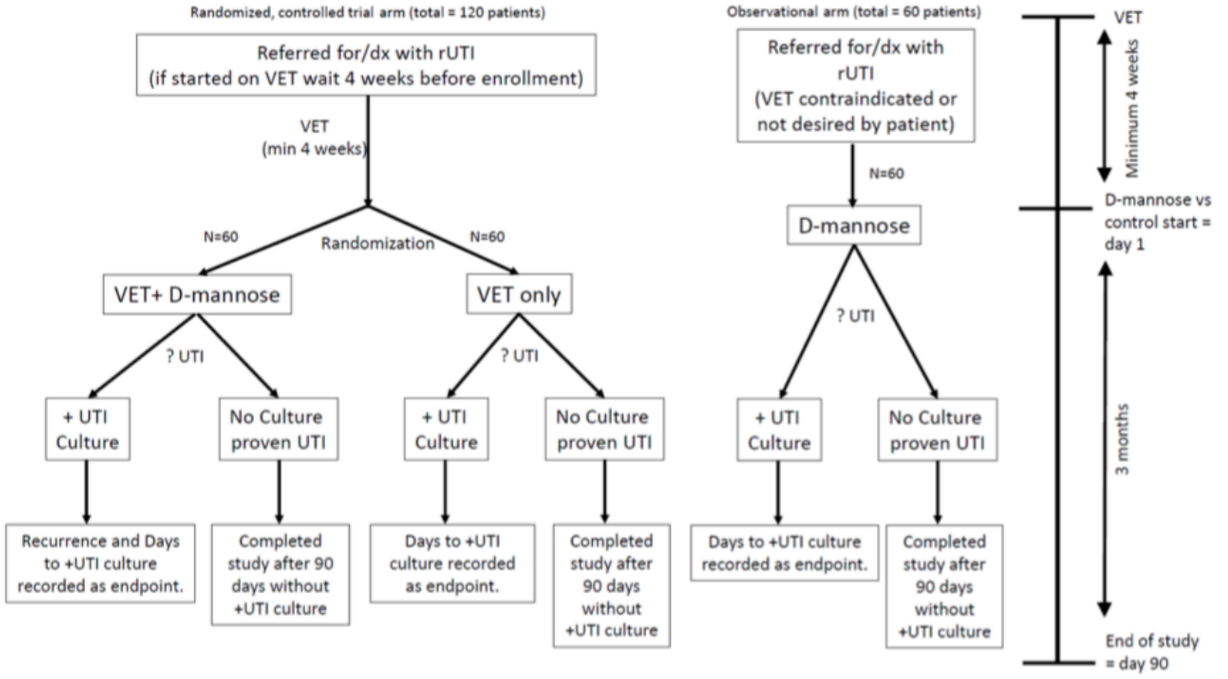




cross-over trial



multiple treatment arms



Exclusion criteria:
-Previous ovarian surgery
- Endocrine dysfunction
- Use of hormone in the past 3 months
-Suspect ovarian malignant tumor
-History of chemotherapy or radiotherapy
-Coagulation disorders
-Pregnancy
-Autoimune desease

Patients ≥18 years of age with unilateral endometrioma

Assessment of elegibility

Inform consent form assessment

SURGERY IN THE FIRST PHASE OF THE MENSTRUAL CYCLE
** ON THE DAY OF THE PROCEDURE BEFORE THE SURGERY*:
- Ultrasound for AFC
- Blood collection for assessment of AMH

** DURING SURGERY:* **RANDOMIZATION**

multiple treatment arms

Bipolar coagulation | Suture | Hemostatic matrix

multiple end-point visits

1 MONTH AFTER SURGERY:
- Ultrasound for AFC
- Blood collection for assessment of AMH

3 MONTHS AFTER SURGERY:
- Ultrasound for AFC
- Blood collection for assessment of AMH

6 MONTHS AFTER SURGERY:
- Ultrasound for AFC
- Blood collection for assessment of AMH

Protocol Preface: Schedule of Activities

- A table listing the study procedures and the timing of procedures helps provide a summary for investigative team members and for reviewers.
- Since the table provides a rapid reference for the timing of all study procedures, this table aids the investigative team maintain a compliant trial.

	STUDY PERIOD								
	Enrolment	Allocation	Treatment (16 weeks)				Follow up		
TIMEPOINT**	$-t_1$	0	t_0			t_1	t_2	t_3	t_4
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
[Pilates intervention]			←	—	—	→			
[Dance intervention]			←	—	—	→			
[Control group]			←	—	—	→			
ASSESSMENTS:									
[Primary outcome - Quality of life]			X			X	X	X	X
[Second outcomes - Psychological variables - Depressive symptoms; Pain; Fatigue; Body image; Self-esteem; Sexual function; Sleep quality]			X			X	X	X	X
[Second outcomes - Physical variables- Cardiorespiratory fitness Lymphedema; Physical activity; Disabilities of the arm; Range of motion; Strength; Flexibility]			X			X	X	X	X

Source: According to SPIRIT 2013 Statement: Defining Standard Protocols Items to Clinical Trials.

Protocol Preface: Schedule of Activities Template

	Screening Day -7 to -1	Enrollment/ Baseline Visit 1	Study Visit 2 Day 7	Study Visit 3 Day 14	Study Visit 4 Day 21	Study Visit 5 Day 28	Study Visit 6 Day 35	Study Visit 7 Day 42	Study Visit 8 Day 49	Study Visit 9 Day 56	Study Visit 10 Day 63	Study Visit 11 Day 70	Study Visit 12 Day 77	Final Study Visit 13 Day 84 +/-1 day
Enrollment														
Informed consent	X													
Demographics	X													
Medical history	X													
Intervention														
Drug Y														
Placebo														
Assessments														
Physical exam (including height and weight)	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
serum chemistry [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [b]	X													
Procedures														
EKG (as indicated)	X													
Adverse event review and evaluation	X	X----------X												X
Radiologic/Imaging assessment	X				X				X					X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Protocol Preface: Schedule of Activities Examples

	STUDY PERIOD				
	ENROLLMENT	ALLOCATION	POST-ALLOCATION		
TIME POINT*	Day -1-0	Surgery (Day 0)	Inpatient	Follow up Clinic visit/telephone	POD 30
ENROLLMENT:					
Eligibility screen	×				
Informed consent	×				
Allocation		×			
INTERVENTIONS:					
ACP+RIVP		×			
ACP+MHCA		×			
ASSESSMENTS:					
Demographic data	×				
Medical history	×				
Concurrent medication	×				
EuroScore II	×				
Blood sample	×		×		
Cannulation site		×			
CPB data		×			
Volume of blood products		×	×		
Mortality			×	×	×
Paralysis			×	×	×
Visceral complications			×	×	×
Cerebrovascular complications			×	×	×
Cardiorespiratory complications			×	×	×
Reoperation			×		
Length of endotracheal intubation			×		
Length of ICU stay			×		
Length of hospital stay			×		
Total hospitalization cost			×		

	Screening	Check-in	Treatment				
			Days			Final Visit/ Early Termination	Unscheduled Visit (a)
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	
Hour after dosing			**0**	**24**	**48**	**72**	
Informed consent/assent/HIPAA authorization (b)	X						
Inclusion/exclusion	X	X					
Medical history/demographics	X						
Concurrent medical conditions	X	X					
Complete physical examination	X	X				X	X
Vital sign measurements (c)	X	X	X	X	X	X	X
Height, weight, and BMI (d)	X	X				X	
12-lead ECG (e)	X	X	X			X	
Clinical laboratory tests (f)	X	X				X	
Fasting C-peptide (g)	X						
Blood glucose monitoring (h)			X	X			
Urine drug, cotinine and alcohol screens	X	X					
Serum Caffeine		X					
Serum pregnancy test (i)	X	X				X	
HBsAg and HCV tests	X						
PK blood sample (j)			**X**	**X**	**X**	**X**	
PD blood sample (k)			X	X			
PK urine sample (l)		X	X	X			
Confinement to clinic (m)		**X**	**X**	**X**			
Prior/concomitant medication assessment	X	X	X	X	X	X	X
Pretreatment/adverse event assessment (n)	X	X	X	X	X	X	X
Study drug administration			X				

Protocol Preface: Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance

ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH	National Institutes of Health
NIH IC	NIH Institute & Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

Protocol Preface: Compliance Statement

STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, ICH E6 and the applicable regulatory requirements.

Example text provided as a guide, customize as needed:

(1) [The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following *(use applicable regulations depending on study location and sponsor requirements; examples follow):*

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- ICH E6

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.]

OR

(2) [The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the <NIH IC> Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.]

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____
Print/Type Name

Signed: _____ Date: _____
Signature

Protocol Preface: Key Roles

1 KEY ROLES

Provide a list of persons, companies, and/or groups serving in key roles in the conduct or oversight of the trial. This should include the sponsor's medical expert for the trial (medical monitor), investigator responsible for conducting the trial (principal investigator (PI)), qualified clinician responsible for the site's clinical decisions (site investigator), and any clinical laboratory(ies) or other institutions involved in the trial. Other key roles may include the NIH point of contact (program director or officer), regulatory specialist, biostatistician, data coordinating center (DCC), data management center, data manager, or industry partner.

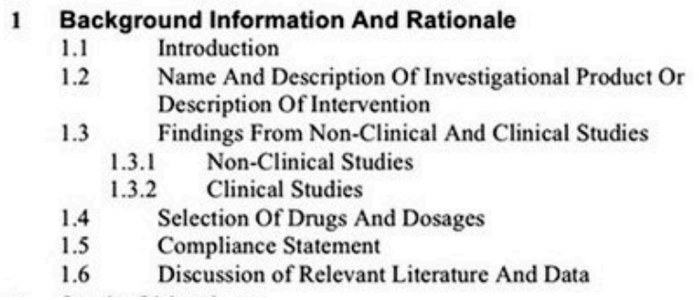
Include the following information for each individual:

Name, degree, title
Institution Name
Address
Phone Number
Email

Investigators:	Multicenter, international, across Mainland China, Taiwan, Republic of Korea and Australia
Coordinating Investigator	Prof. Dr. Minhu Chen Chair, Department of Gastroenterology and Hepatology Vice President The First Affiliated Hospital, Sun Yat-sen University 58 Zhongshan Road, Guangzhou, China
Expert committee	Prof. Dr. Stefan Schreiber Institute for Clinical Molecular Biology University Hospital Schleswig-Holstein Schittenhelmstrasse 12, 24105 Kiel, Germany

Protocol Introduction

- The background and rationale should be no more than 3-5 pages.
- It is appropriate to reference the Investigator's Brochure, the full grant, or 1-3 attached key references from the literature for more detailed information.
- Information about the study intervention, summary of the non-clinical data and clinical data, and a review of the literature are all part of this section.
- If the study involves the administration of a drug or biologic, a justification of the dosage and dosing interval should be provided.
- A compliance statement is included stating research will be conducted in accordance with regulations and hospital and IRB policies.



1 Background Information And Rationale
- 1.1 Introduction
- 1.2 Name And Description Of Investigational Product Or Description Of Intervention
- 1.3 Findings From Non-Clinical And Clinical Studies
  - 1.3.1 Non-Clinical Studies
  - 1.3.2 Clinical Studies
- 1.4 Selection Of Drugs And Dosages
- 1.5 Compliance Statement
- 1.6 Discussion of Relevant Literature And Data

Protocol Introduction: Rationale and Background

1. Study Rationale

State the problem or question (e.g., describe the population, disease, current standard of care, if one exists, and limitations of knowledge or available therapy) and the reason for conducting the clinical trial

2. Background

This section should include:

- A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance
- A summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries, and clinical pharmacology studies
- Discussion of important literature and data that are relevant to the trial and that provide background for the trial (reference citations should be listed in **Section 11, References**)
- Applicable clinical, epidemiological, or public health background or context of the clinical trial
- Importance of the clinical trial and any relevant treatment issues or controversies

Protocol Introduction: Rationale and Background

1 INTRODUCTION

1.1 Background

Interleukin 6 (IL-6) is a pleiotropic cytokine produced by hematopoietic and non-hematopoietic cells, e.g. in response to infection and tissue damage. IL-6 is believed to be a key mediator in diseases such as rheumatoid arthritis (RA), psoriasis and inflammatory bowel disease (IBD; i.e. Crohn's disease and ulcerative colitis [UC]).

IL-6 exerts its multiple biological activities through two main signalling pathways. One is the so-called classic ligand-receptor pathway via membrane-bound IL-6 receptors (IL-6R) present mainly on hepatocytes and certain leukocytes. The second is the *trans*-signalling pathway *via* circulating soluble IL-6R (sIL-6R) originating from proteolytic cleavage of the membrane-bound IL 6R or from alternative splicing (1)(2). While the classic IL-6 signalling is involved in the acute inflammatory response, *trans*-signalling is mainly involved in chronic inflammation and has been shown to prevent disease-promoting mucosal T-cell populations from going into apoptosis. A schematic presentation of the *trans*-signalling pathway of IL-6 is shown in Figure 1.

1.2 Scientific Justification for Conducting the Trial

The safety, tolerability and pharmacokinetic (PK) properties of TJ301 (FE 999301) have been investigated in Germany in two phase 1, single- and multiple-ascending dose clinical studies in healthy and Crohn's disease subjects with up to 4 weeks of weekly intravenous (i.v.) infusion. These studies showed dose-proportional systemic exposure, in the dose range of 0.75 mg to 750 mg, with a mean terminal half-life of approximately 5 days and no apparent dose-dependent trends in the incidence or nature of adverse events. Furthermore, a cohort of patients with quiescent Crohn's disease demonstrated similar systemic exposure to that in healthy subjects, for corresponding doses of 75 mg, 300 mg, and 750 mg in the single-ascending-dose trial.

The purpose of this proof-of-concept trial is to assess the safety, efficacy, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of two different doses of i.v. infusions of TJ301 in patients with active UC. The ability to induce remission of TJ301 will be investigated in the 12-week double-blind treatment period of the study.

1.1 MEDICAL BACKGROUND

Idiopathic Pulmonary Fibrosis (IPF) is a chronic disease of unknown aetiology that is characterized by progressive fibrotic destruction of the lung, resulting in disabling dyspnoea and poor gas exchange. The average life expectancy in IPF patients is 2-3 years.

1.2 DRUG PROFILE

Nintedanib is a small molecule tyrosine kinase inhibitor of the Platelet Derived Growth Factor Receptor (PDGFR) α and β, Fibroblast Growth Factor Receptor (FGFR) 1- 3, and Vascular Endothelial Growth Factor Receptor (VEGFR). Nintedanib binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation, migration, and transformation of fibroblasts, representing essential mechanisms of the IPF pathology. In addition, nintedanib inhibits Flt-3, Lck, Lyn, and Src kinases (U07-1248).

2.1 RATIONALE FOR PERFORMING THE TRIAL

The aim of this extension trial is to provide nintedanib treatment for all patients who have completed one year treatment and the follow up period in the double-blind phase III placebo controlled parent trials (1199.32 and 1199.34), who may have experienced benefit from the study medication and wish to receive treatment.

Protocol Introduction: Risk-Benefit Analysis

3.1.Known Potential Risks

Include a discussion of known potential risks from either clinical or nonclinical studies. If a package insert or device labeling from a licensed or approved product is available, it should be used as the primary source of risk information. If the product is investigational, the IB should be the primary source of the risk information. In addition, relevant published literature can also provide relevant risk information. If the risk profile cannot be described from the package insert, device labeling, or the IB, the risk information discussion will result from published literature and should be included and referenced appropriately.
Describe any physical, psychological, social, legal, economic, or any other risks to participants by participating in the study that the Principal Investigator (PI) foresees, addressing each of the following:

- Immediate risks
- Long-range risks
- If risk is related to proposed procedures included in the protocol, describe alternative procedures that have been considered and explain why alternative procedures are not included

Protocol Introduction: Risk-Benefit Analysis

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[8]	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with possible current clinical COVID-19. All participants are followed for SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers, and COVID-19 illness, including markers of severity.
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic and antibody testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

Protocol Introduction: Risk-Benefit Analysis

3.2.Known Potential Benefits

Include a discussion of known potential benefits from either clinical or nonclinical studies. If a package insert or device labeling from a licensed or approved product is available, it should be used as the primary source of potential benefit information. If the product is investigational, the IB should be the primary source of the potential benefit information. In addition, relevant published literature can also provide potential relevant benefit information. If the potential benefit cannot be described from the package insert, device labeling, or the IB, the potential benefit information discussion will result from published literature and should be included and referenced appropriately.

Describe any physical, psychological, social, legal, or any other potential benefits to individual participants or society in general, as a result of participating in the study, addressing each of the following:

- Immediate potential benefits
- Long-range potential benefits

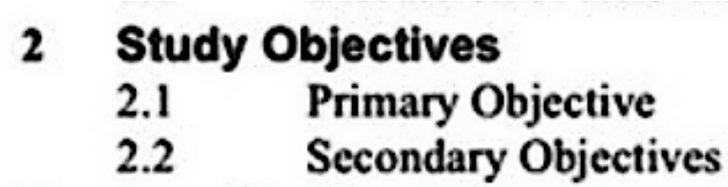
Note that payment to participants, whether as an inducement to participate or as compensation for time and inconvenience, is not considered a “benefit.” Provision of incidental care is also not to be considered a benefit.

3.3.Assessment of Potential Risks and Benefits

Include an assessment of known potential risks and benefits, addressing each of the following:

- Rationale for the necessity of exposing participants to risks and a summary of the ways that risks to participants were minimized in the study design
- Justification as to why the risks of participation in the study outweigh the value of the information to be gained

Protocol: Study Objectives



2 **Study Objectives**
2.1 Primary Objective
2.2 Secondary Objectives

- The study objectives (or aims) should be broken down into **primary and secondary objectives.**
- Objectives need to be **specific to the intervention**
- **-** for a drug, they should **specify the dosage level, route, frequency and duration of administration** and **in a defined population**
- **-** "does the study drug reduce blood pressure when administered twice a day as an oral liquid, at a dose of 50 mg, in children age 6-12 years who have moderate hypertension".
- "The primary objective is to determine (or evaluate) the... (efficacy, pharmacokinetics, safety, etc.)... of the study intervention…"

- The **primary objective** serves as the **basis of the sample size**.
- **Secondary objectives** may be **exploratory** or hypothesis generating and the study may not be powered to achieve these objectives.
- Each **objective** has a corresponding **endpoint** and a corresponding **analysis** plan.
- The endpoints in the IRB's protocol templates are located in the analysis section.
- Some protocols include a table that maps each **objective to its endpoint and corresponding analysis plan.**

Protocol: Study Objectives

3 OBJECTIVES AND PURPOSE

Provide a detailed description of the primary objective and any secondary objectives of the study. An objective is the reason for performing the study in terms of the scientific question to be answered. The primary objective is the main question. This objective generally drives statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing). Secondary objectives are goals that will provide further information on the use of the intervention.

Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., feasibility, acceptability, efficacy, effectiveness, safety) and/or specific purpose (e.g., dose-response, superiority to placebo, effect of an intervention on disease incidence, disease severity, or health behavior).

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 7 days after the last dose • SAEs from Dose 1 to 7 days after the last dose	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	• S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers

6. STUDY OBJECTIVES AND PURPOSE

In patients with mitochondrial myopathy, comparing those receiving [redacted] versus those receiving placebo, the objectives are as follows:

6.1. Primary Objectives

- To evaluate the change in peak work during maximal exercise testing
- To evaluate the safety and tolerability of [redacted]

6.2. Secondary Objective

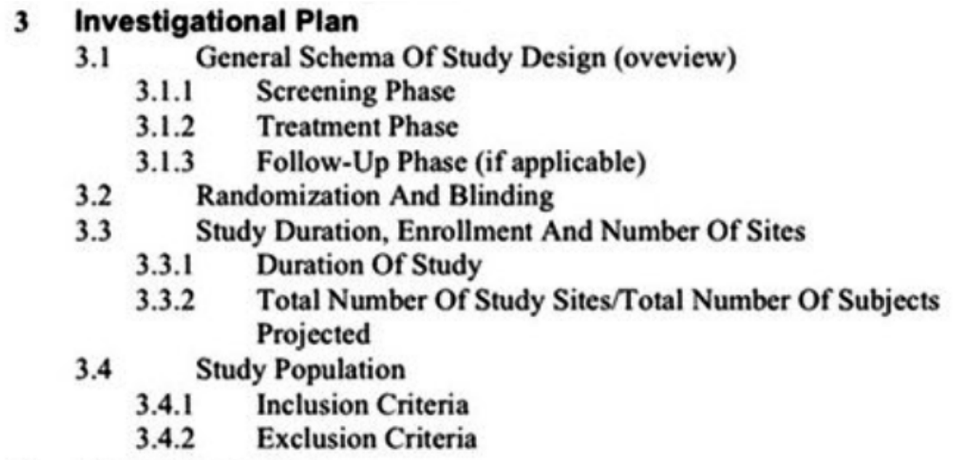
- To evaluate the change in 6-minute walk test (6MWT) distance

6.3. Exploratory Objectives

- To evaluate the change in peak oxygen utilization during maximal exercise testing
- To evaluate the change in peak serum lactate and pyruvate, peak heart rate, and rating of perceived exertion during submaximal exercise testing
- To evaluate the change in Fatigue Severity Scale score
- To evaluate the change in SF-36® Health Survey Update (SF-36) score
- To evaluate change in pharmacodynamic (PD) markers of activity in blood and muscle samples
- To characterize the pharmacokinetics of [redacted] and potential metabolites after oral administration of [redacted] Capsules

Protocol: Study Design/Population

- **General Schema of Study Design:** brief overview of the entire study design including various phases.
- **Randomization and Blinding:** overview including how randomization schedules are generated, who executes the schedule, how the schedule is concealed and the study blinding procedures. Put details in Statistical Analysis Section 9



3 Investigational Plan

- 3.1 General Schema Of Study Design (oveview)
  - 3.1.1 Screening Phase
  - 3.1.2 Treatment Phase
  - 3.1.3 Follow-Up Phase (if applicable)
- 3.2 Randomization And Blinding
- 3.3 Study Duration, Enrollment And Number Of Sites
  - 3.3.1 Duration Of Study
  - 3.3.2 Total Number Of Study Sites/Total Number Of Subjects Projected
- 3.4 Study Population
  - 3.4.1 Inclusion Criteria
  - 3.4.2 Exclusion Criteria

- **Study Duration, Enrollment, # of Sites:** burden on subjects (duration of their participation), study feasibility, and expected sites/subjects.
- **Study Population:** Defines who will take part in the research (mandatory and key for every study, regardless of design) .The **inclusion and exclusion (enrollment) criteria** are included.
- If there are any situations where there might be flexibility in the enrollment criteria, this should be stated explicitly in this section otherwise it is a protocol violation to ever enroll those patients!

3.1.2 Overall Design

This is a multicenter, stratified randomized, double-blind, placebo-controlled phase II study.

The trial includes a Run-in Period (if stable conventional treatment needed), a 4-week Screening Period, a 12-week double-blind Treatment Period, and a Safety Follow-up Period of 3 weeks to Day 105.

3.1.3 Trial Schedule

First patient first visit is planned for Third Quarter 2017 and last patient last visit is planned for First Quarter 2020. The expected total duration of the trial is approximately 2.5 years.

3.2 Planned Number of Patients

In total, 90 patients with active UC at approximately 25-30 investigational sites globally will be enrolled competitively and randomised equally into three arms with TJ301 (two dose levels) or placebo.

3.3 Safety Review Committee

A Safety Review committee (SRC) will be established. The SRC is an expert advisory group commissioned and charged with the responsibility of evaluating, primarily, cumulative safety data at regular intervals. The SRC will review blinded data and provide recommendations to the Sponsor based on their evaluation.

3.4 Discussion of Overall Trial Design

3.4.1 Trial Design

This trial is designed as a randomised, double-blind, placebo-controlled proof-of-concept trial of TJ301. Patients will be on concomitant treatment with stable doses of corticosteroids, or immunomodulators, or 5-ASA/sulfasalazine – all first- or second-line standard of care in UC – for at least the duration of the 12-week Treatment Period (i.e. up to the primary endpoint). Two dose levels of TJ301 will be investigated, and as discussed in Section 3.4.4, modelling of the effect on a PD biomarker, based on PK measurements over a wide range of serum concentrations of TJ301, suggests that the chosen dosages may show a dose-dependent clinical efficacy.

3.4.2 Selection of Endpoints

The prospectively defined primary efficacy endpoint will be a binary endpoint of clinical and endoscopic remission at Week 12, defined as a full Mayo score ≤2, no individual subscore >1, and rectal bleeding subscore = 0. The full Mayo score (range, 0-12; higher score is worse) is based on the clinician's scoring of clinical signs and symptoms, as well as endoscopic scoring of gross colonic mucosal inflammation. While there is no validated scale for scoring the severity of inflammation or clinical symptoms in UC, the Mayo score has been extensively used in earlier clinical trials in UC, and shows a good correlation between the full Mayo score and the clinician-rated components only (partial Mayo score without endoscopy; see Section 7.1.1 for details). The partial Mayo score without endoscopy can be used to accurately predict inflammatory activity, and the evolution of a treatment effect even in the absence of endoscopy.

3.4.3 Blinding

A central, computer-based randomisation procedure is used to eliminate selection bias. To reduce the risk of breaking the blind, IMP thawing and reconstitution will be carried out at the trial site by blinded site personnel, independent of the Investigator and the Sponsor. The appearance of the reconstituted IMP, as well as the infusion volume (290 mL) will be identical for all treatment groups.

3.4.4 Selection of Doses in the Trial

The safety and tolerability of TJ301 have been investigated in phase 1, single- and multiple-ascending dose studies in both healthy subjects and patients with quiescent IBD (Crohn's disease) up to 750 mg without any concern. Pharmacokinetic results indicate dose proportionality in maximal concentration obtained (C_{max}) and overall exposure (AUC) with a terminal half-life of approximately 4.7 days.

3.4.5 Selection and Timing of Dose for Each Patient

During the 12-week Treatment Period, dosing will be infusions every 2 weeks, as administered by trial personnel at the trial site. Dosing is fixed-dose throughout the trial.

3.4.6 Withdrawal Criteria

In addition to the patient's right to withdraw from the trial at any time, as well as withdrawal at the Investigator's discretion as discussed in Section 4.4, the SRC (Section 3.3) will review blinded data, for safety.

3.4.7 Follow-up Procedures

For patients completing the trial, a Safety Follow-up Visit will be scheduled on Day 105 (Week 15). For patients not completing the trial, a Safety Follow-up Visit will be scheduled 35 days (5.8 - 6.6 half-lives of TJ301) after the last dose of IMP.The procedures to be performed during the Safety Follow-up Visit are described in Section 6.3.

Protocol: Study Plan

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

This trial is designed to include adult and elderly male and female outpatients with active, UC. Patients who fulfil all of the inclusion criteria (Section 4.1.1) and none of the exclusion criteria (Section 4.1.2) are eligible for inclusion in the trial.

4.1.1 Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male and female patients 18-70 (inclusive) years of age.
2. Active UC confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy a Screening, with extending > 15-cm past the anal verge from endoscopy.
3. Active UC with a full Mayo score ⩾5 and a rectal bleeding subscore ≥1 at screening.
4. During Day -35 to Day-6 prior to Randomisation, an endoscopy subscore ≥2.
5. Treated with conventional non-biological UC therapy: with corticosteroids stable for at lea weeks prior to Randomization at no more than 20 mg prednisone (or equivalent), and/or w medications containing 5-aminosalicylates (5-ASA) at no less than 2 g 5-ASA per day for least 3 months and stable for at least 4 weeks prior to Randomization, and/or with azathiop (AZA) at no less than 1.5 mg/kg/day or mercaptopurine (6-MP) at no less than 0.75 mg/kg for at least 6 months and stable for at least 6 weeks prior to Randomization.
6. A female subject has been sterilized or has been menopausal, or the subject has no pregnar plan during the trial and voluntarily adopts effective contraceptive measures.
7. The patient is able and willing to comply with the requirements of this trial protocol.
8. The subject should be able to read and write to understand and fill out Patient Diary.
9. Voluntarily signed Informed Consent obtained before any trial-related procedures are performed.

4.1 Trial Population

This trial is designed to include adult and elderly male and female outpatients with active, UC. Patients who fulfil all of the inclusion criteria (Section 4.1.1) and none of the exclusion criteria (Section 4.1.2) are eligible for inclusion in the trial.

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2. Active UC confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy at Screening, with extending > 15-cm past the anal verge from endoscopy.
3. Active UC with a full Mayo score ⩾5 and a rectal bleeding subscore ≥1 at screening.
4. During Day -35 to Day-6 prior to Randomisation, an endoscopy subscore ≥2.
5. Treated with conventional non-biological UC therapy: with corticosteroids stable for at least 2 weeks prior to Randomization at no more than 20 mg prednisone (or equivalent), and/or with medications containing 5-aminosalicylates (5-ASA) at no less than 2 g 5-ASA per day for at least 3 months and stable for at least 4 weeks prior to Randomization, and/or with azathioprine (AZA) at no less than 1.5 mg/kg/day or mercaptopurine (6-MP) at no less than 0.75 mg/kg/day for at least 6 months and stable for at least 6 weeks prior to Randomization.
6. A female subject has been sterilized or has been menopausal, or the subject has no pregnancy plan during the trial and voluntarily adopts effective contraceptive measures.
7. The patient is able and willing to comply with the requirements of this trial protocol.
8. The subject should be able to read and write to understand and fill out Patient Diary.
9. Voluntarily signed Informed Consent obtained before any trial-related procedures are performed.

4.1.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Pregnant or breastfeeding women.
2. Contraindication to colonoscopy or sigmoidoscopy.
3. Allergies to any component of TJ301.
4. History of colostomy, colectomy or partial colectomy.
5. Current diagnosis of inflammatory bowel disease unclassified, Crohn's disease, ischemic colitis, fulminant colitis and/or toxic megacolon, patients with ulcerative colitis limited to the rectum (ulcerative proctitis), infective enteritis, amebic bowel disease and intestinal schistosomiasis.

4.2 Method of Assigning Patients to Treatment Groups

4.2.1 Recruitment

Approximately 25-30 sites will participate in this trial.

Each trial site will require potential patients to undergo a Screening Visit prior to randomisation to a treatment group. Each patient will receive a unique screening number which must be entered in a screening log that must be maintained at each trial site. The screening number will be allocated sequentially in the order in which the patients are screened. The results of each screening should be recorded in the screening log. Selected data for screened patients should also be entered in the electronic case record form (e-CRF), along with the reason for screening failure if the patient is not randomised to treatment.

4.2.2 Randomisation

After all applicable screening assessments have been performed, patients who have met all inclusion criteria and none of the exclusion criteria will be centrally, dynamically, randomly allocated to one of the three groups and will receive a unique computer-generated randomisation number.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

Details of all concomitant medication will be recorded in the e-CRF, along with the main reason for prescription. In addition, prior treatment for UC within 12 months of Visit 1 (Screening) will be recorded.

4.3.2 Prohibited Therapy

Patients will be prohibited from taking any other IMP or undergo any other investigative treatment during the trial from the time the informed consent form is signed through to at least the Follow-up Visit, or any other IMP within 30 days or 5 half-lives prior to Visit 2 (whichever is longer).

The following previous or concomitant medications are disallowed during the trial:

- Immunomodulating/suppressing drugs, including JAK inhibitors (NB: AZA and 6-MP are allowed as per inclusion criteria, see Section 4.1.1).
- Antibiotics, when given as treatment for UC relapse.
- Any biologic drugs.
- Any live (attenuated) vaccines.

4.3.3 Other Restrictions

Patients on stable-dose concomitant treatment for UC at Visit 2 must remain on a stable dose throughout the trial except for patients on corticosteroids; tapering of corticosteroids is allowed at the discretion of the Investigator.

4.4 Withdrawal Criteria

The patients have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the Investigator should record the reason for the patient's withdrawal, if possible. The Investigator also has the right to withdraw patients.

Protocol: Study Plan

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥16 years of age [stratified as ≤55 or >55 years of age]).

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see Section 8.2)

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥16 years of age, stratified as follows: 16 to 55 years or >55 years. It is intended that a minimum of 40% of participants will be in the >55-year stratum. Commencement of each age stratum will be based upon satisfactory post–Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1, respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in Section 8.13, a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

Protocol: Study Plan

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥16 years (Phase 2/3), at randomization.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Informed Consent:

5. Capable of giving personal signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

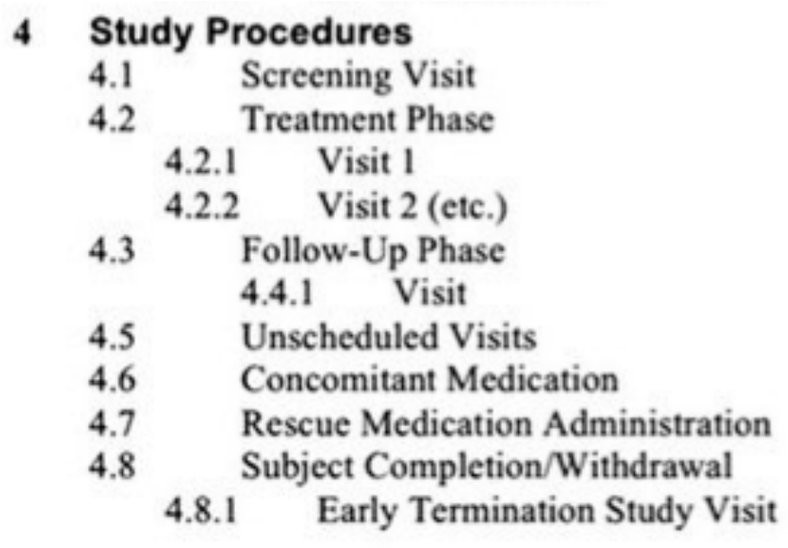
Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for th study.

Protocol: Study Procedures

- This section is a **Visit Schedule** which is visit-by-visit listing of all the procedures that will take place at each visit. If the study will have multiple procedures in one day (e.g. blood draws for a PK study) then the timing of each of these should be included.
- The section on **unscheduled visits** may be applicable when patients are anticipated to require rescue therapy or might need interim care due to chronic illness.
- **Concomitant Medications:** Should list all medications that are permitted or explicitly forbidden during study participation.
- **Withdrawal from Study:** Since subjects can withdraw from participation at any time, the procedures that will be followed to provide for an orderly transition from the research to routine care should be outlined.



4 **Study Procedures**
- 4.1 Screening Visit
- 4.2 Treatment Phase
  - 4.2.1 Visit 1
  - 4.2.2 Visit 2 (etc.)
- 4.3 Follow-Up Phase
  - 4.4.1 Visit
- 4.5 Unscheduled Visits
- 4.6 Concomitant Medication
- 4.7 Rescue Medication Administration
- 4.8 Subject Completion/Withdrawal
  - 4.8.1 Early Termination Study Visit

Protocol: Study Procedures

7.1.1 STUDY SPECIFIC PROCEDURES

All procedures listed here should be specific to the study and not part of standard clinical care.

List and describe all study procedures and evaluations to be done as part of the study. Possible content includes:

- *Medical history (describe what is included for history, e.g., time-frame considerations, whether history will be obtained by interview or from medical records)*
- *Medication history (e.g., describe if a complete medication history is needed, or if only medications currently taken should be included; prescription and over-the-counter medications). Assessment of eligibility should include a review of permitted and prohibited medications.*
- *Physical examination (list the vital signs [including height and weight] and organ systems to be assessed. Address details in the MOP.); if appropriate, discuss what constitutes a targeted physical examination and at what visits it may occur.*
- *Radiographic or other imaging assessments. State the specific imaging required and, as appropriate, provide description of what is entailed to perform the specialized imaging. Details describing how to perform the imaging in a standard fashion may be described in a separate document such as a MOP or SOP.*
- *Biological specimen collection and laboratory evaluations. If biological specimen and laboratory procedures require further detail, they may be described in **Section 7.2 Laboratory Procedures/Evaluations** below, or in a separate document such as a MOP or SOP. At minimum, the biological specimens and purpose should be listed.*
- *A discussion of If the results of any study specific procedures (e.g., radiographic or other imaging or laboratory evaluations) will be provided to participant.*
- *Counseling procedures*
- *Assessment of study agent adherence*
- *Administration of questionnaires or other instruments for patient-reported outcomes, such as a daily diary.*

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Provide a list of reasons participation may be terminated. It may be appropriate to provide distinct discontinuation criteria for participants and cohorts. If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly. Also note that participants may withdraw voluntarily from the study at any time.

Example text provided as a guide, customize as needed:

[Participants are free to withdraw from participation in the study at any time upon request.
An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.]

<Insert text>

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Describe efforts that will be made to continue follow-up of withdrawn or terminated participants or participants who discontinue study agent but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Every effort must be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs). In studies of implantable devices, a discussion should be included of any pertinent information that will be provided to withdrawn or terminated patients (e.g., how to replace batteries, how to obtain replacement parts, who to contact).

*This section should include a discussion of replacement of participants who withdraw or discontinue early, if replacement is allowed. This section should not include a discussion of how these participants will be handled in the analysis of study data. This should be captured in the **Section 10, Statistical Considerations**.*

Protocol: Study Procedures

Day 0 Study Visit:

Day 0 – Administration of study agent (AAV2-hRPE65v2) to the previously, uninjected contralateral eye:
The procedure is expected to occur in approximately 90 minutes; subjects will remain in the hospital overnight. During this time, the subject will remain in the supine position except for meals and bathroom privileges. A patch and eye shield will be put in position over the eye that received the test article; this patch will be removed the next morning. See Appendix 2 for the detailed vector administration procedure. This visit will occur at The Children's Hospital of Philadelphia.

- Vital signs, anesthesia consultation
- Blood tests – clinical labs (~ 3 mL)
- Urinalysis
- A urine pregnancy test will be performed for female subjects ≥ 11 years of age and girls < 11 years who are physically capable of becoming pregnant.
- Fundus photography and/or intraoperative video recording will be performed (while subject is asleep/sedated)
- AE and concomitant medications recording

Follow-up Visits: Follow-up visits will last from one to five hours, depending on which tests are being performed at the particular visit.

Day 1

- Discharge examination, vital signs
- Blood tests – vector shedding (~ 4 mL)
- Tear collection
- Ophthalmic examination
- Optical coherence tomography (OCT)
- Fundus photography
- AE and concomitant medications recording

Day 3 and Subsequent Visits:

Day 3

- Blood tests – vector shedding (~ 4 mL)
- Tear collection
- Ophthalmic examination: Note – if ocular inflammation is present at this visit an additional visit at Day 7 will be included.
- Optical coherence tomography (OCT)
- Fundus photography
- AE and concomitant medications recording

***Week 1**

- Blood tests – immunology studies and vector shedding, if applicable (~ 23 mL)
- Tear collection, if applicable
- AE and concomitant medications recording

Week 2 ± 2 days

- Blood tests – immunology studies (~ 16 mL)
- Tear collection, if applicable
- Ophthalmic examination
- Optical coherence tomography (OCT)
- Fundus photography
- Prednisone discontinued
- Visual/retinal function:
  - Mobility testing
  - Pupillometry
  - Visual acuity tests
  - Visual field tests
  - Full field light sensitivity threshold testing
  - Contrast sensitivity
- AE and concomitant medications recording

Protocol: Study Measures and Evaluations

- The **Study Measurements** should provide the detailed descriptions for how each measurement will be made.
- Mention if patients are **anticipated to require rescue therapy** or might need interim care due to chronic illness.
- Psychological or other measurement scales that will be used should be described.
- Those that have been validated and that are on the **IRB's listing of Validated Instruments** may simply be referenced or otherwise add to appendix/eIRB.
- It is **not necessary to include a copy of the case report form if all of the study measurements are listed** in this section of the protocol.

5 Study Evaluations and Measures

- 5.1 Screening And Baseline Evaluations (Procedures & Measurements)
  - 5.1.1 Physical Exams
  - 5.1.2 Laboratory Tests
  - 5.1.3 Other Procedures
- 5.2 Efficacy Evaluations
  - 5.2.1 Diagnostic Tests, Scales, Measures, Etc.
- 5.3 Pharmacokinetic Evaluation (if applicable)
- 5.4 Safety Evaluations/Measurements

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	• Urine pregnancy test (β-hCG) At screening only: • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Protocol: Study Measures and Evaluations

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. A local NAAT result will be considered acceptable if it was obtained using:

- An FDA-cleared (including Emergency Use Authorization) assay; or
- An assay that is not FDA-cleared but was conducted in a laboratory that is currently CLIA-certified; or
- An assay performed by a laboratory accredited according to the ISO 15189 standard by a national or regional accreditation body.

Serum samples will be obtained for immunogenicity testing at the visits specified in the SoA. The following assays will be performed:

- SARS-CoV-2 neutralization assay
- S1-binding IgG level assay
- RBD-binding IgG level assay
- N-binding antibody assay

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous

Protocol: Study Measures and Evaluations

7.2.1 CLINICAL LABORATORY EVALUATIONS

List all laboratory evaluations to be done as part of the study (e.g., hematology, clinical chemistry, urinalysis, pregnancy testing). Differentiate screening laboratory test(s) from those taken after enrollment. Include specific test components and estimated volume and type of specimens needed for each test. Specify laboratory methods to provide for appropriate longitudinal and cross-sectional comparison (e.g., use of consistent laboratory method throughout study, use of single, central laboratory for multi-site studies). If more than one laboratory will be used, specify which evaluations will be done by each laboratory. In addition, compliance with Clinical Laboratory Improvement Amendments (CLIA) of 1988 should be addressed. If such compliance is not required, a brief discussion should be included explaining why this is the case.

Examples include:

- ***Hematology**: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.*
- ***Biochemistry**: creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST).*
- ***Urinalysis**: dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic evaluation is required.*
- ***Pregnancy test**, usually to be done within 24 hours prior to study intervention and results must*

7.2.2 OTHER ASSAYS OR PROCEDURES

List special assays or procedures required to determine study eligibility or assess the effect of the intervention (e.g., immunology assays, pharmacokinetic studies, images, flow cytometry assays, microarray, DNA sequencing). For research laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. For procedures, provide special instructions or precautions or refer to the study's MOP. If more than one laboratory will be used, specify which assays will be done by each laboratory.

Protocol: Statistical Endpoints and Outcomes

- **Study Endpoints or Outcomes** are study objectives made into explicit statements for comparisons to be made.
- For **each endpoint or outcome**, the trial protocol should define **four components**:
- the specific **measurement variable**, which corresponds to the data collected directly from trial participants (eg all cause mortality);
- the **participant-level analysis metric** (eg, change from baseline, final value, time to event);
- the **method of aggregation** (eg, mean, proportion with score > 2); and
- the specific measurement time point of interest for analysis.
- So…if the objective is to determine the efficacy of Drug A vs. placebo for the treatment of hypertension
- Then…the study endpoint might be the change in the mean (method of aggregation) systolic blood pressure (measurement variable) for Drug A compared to placebo between Visit 1 and Visit 4 (participant analysis metric and time point of interest).

6 Statistical Considerations

- 6.1 Primary Endpoint
- 6.2 Secondary Endpoints
- 6.3 Statistical Methods
  - 6.3.1 Baseline Data
  - 6.3.2 Efficacy Analysis
  - 6.3.3 Safety Analysis
- 6.4 Sample Size And Power
- 6.5 Interim Analysis (if applicable)

5.0 STUDY ENDPOINTS AND EVALUATIONS

5.1 Primary Endpoint

The primary endpoint is the change in the Disposition Index (DI) calculated from data obtained from the frequently sampled IV Glucose Tolerance Test (fs-IVGTT) between baseline and end-of-study (28 days of treatment or earlier in case of discontinuation).

5.2 Secondary Endpoints

Secondary endpoints will include the following:

- The change from baseline at endpoint of sensitivity index (S_i), glucose effectiveness (S_G) and acute insulin response (AIR_g) calculated from IVGTT
- The change from baseline to end of study in fasting glucose, insulin, Hb1Ac, 1,5-anhydroglucitol (1,5-AG) and venous lactate
- The change from baseline to end of study in the Specific Complex I Enzymatic Activity in whole blood
- The change from baseline to end of study in the FARS scale

Protocol: Statistical Sample Size and Power

- When a power calculation is performed the protocol should include the following:
  1. the primary endpoint (outcome);
  2. the values assumed for the outcome in each study group (eg, proportion with event, or mean and standard deviation);
  3. the planned statistical test;
  4. alpha (type 1 error) level;
  5. power (usually at least 80%); and
  6. the calculated sample size per group - both assuming no loss of data and, if relevant, after any inflation for anticipated missing data modified from
- Sample Size section should explain the **why the study is proposing to enroll the specified number of subjects** and not more or fewer

9.2. Sample Size Determination

For Phase 2/3, with assumptions of a true VE of 60% after the last dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true VE >30% with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the

Table 4. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.70	0.91	0.97	>0.99

Protocol: Statistical Analysis Plan

- The IRB will **not approve collection of data without a plan**!
- Get a statistics consult prior to submission
- Deal with all of the sources of bias and for confounding variables.
- If study has interim analysis, then add stopping rules for safety and benefit
- Enough detail that **another statistician unfamiliar with the data set can replicate results.**
- SAP should delineate **populations** (exclusion criteria); **end points; descriptive objectives; testable hypotheses; modifications or derivations of standard variables; statistical methods, including handling of missing data, correlated data, bias, and confounding; subgroups; interactions; and sensitivity analysis.**

Endpoint	Statistical Analysis Methods
Primary efficacy	**Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group 7 days after the last dose. VE will be analyzed using a beta-binomial model. After the above objective is met, the second primary endpoint will be evaluated as below. **Ratio of confirmed COVID-19 illness per 1000 person-years of follow-up in participants with and without evidence of infection before vaccination for the active vaccine group to the placebo group** VE will be estimated by 100 × (1 – IRR), where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group after 7 days after the last dose. VE will be analyzed using a beta-binomial model. The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population. The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population. For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.

Protocol: Statistical Analysis Plan

Table 5. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Table 6. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 7. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

Protocol: Statistical Analysis Plan

10 STATISTICAL CONSIDERATIONS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections should describe the statistical tests and analysis plans for the protocol. They should indicate how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible. Many elements below can be found in ICH Guidance for Industry E9 Statistical Principles for Clinical Trials and the CONSORT statement *which describes standards for improving the quality of reporting randomized controlled trials.*
If a separate SAP will be developed, respective subsections below can be summarized. ***At a minimum, the following subsections should be included in the protocol:***

- ***10.2 Statistical Hypotheses,***
- ***10.3 Analysis Datasets,***
- ***10.4.1 General Approach,***
- ***10.4.2 Analysis of the Primary Efficacy Endpoint(s),***
- ***10.4.3 Analysis of the Secondary Endpoint(s),***
- ***10.4.4 Safety Analyses,***
- ***10.4.6 Baseline Descriptive Statistics,***
- ***10.4.7 Planned Interim Analyses (if applicable),***
- ***10.4.11 Exploratory Analyses, and***
- ***10.5 Determination of Sample Size.***

10.1 STATISTICAL AND ANALYTICAL PLANS

State whether there will be a formal SAP. A formal SAP should be completed prior to database lock and unblinding of the study data. The SAP generally includes additional statistical analysis detail (e.g., more detail of analysis populations, summary of statistical strategies).
<Insert text>

10.2 STATISTICAL HYPOTHESES

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

- Primary Efficacy Endpoint(s):

<Insert text>

- Secondary Efficacy Endpoint(s):

<Insert text>

10.3 ANALYSIS DATASETS

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each). As a guide, this may include, but is not limited to, any or all of the following:

- *Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)*
- *Modified Intention-to-Treat Analysis Dataset (e.g., participants who took at least one dose of investigational product and/or have some particular amount of follow-up outcome data)*
- *Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of investigational product)*
- *Evaluable or Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of treatment according to the underlying scientific model (e.g., participants who took at least 80% of investigational product for 80% of the days within the maintenance period)*
- *Other Datasets*

<Insert text>

10.4 DESCRIPTION OF STATISTICAL METHODS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.
The following subsections should include a description of the planned statistical methods.

10.4.1 GENERAL APPROACH

State the proposed formal design of the study (e.g., two-period crossover, two-by-three factorial parallel group, or case-control). If the design or interventions are complex, reference to ***Schematic of Study Design*** *may be appropriate. As a guide, the following should be addressed, as appropriate:*

- *For descriptive statistics, describe how categorical and continuous data will be presented (e.g., percentages, means with standard deviations, median, range).*
- *For inferential tests, indicate the p-value for statistical significance (Type I error) and whether one or two-tailed.*
- *Indicate whether covariates will be pre-specified in the sections below or later in a SAP.*
- *State whether checks of assumptions (e.g.,normality) underlying statistical procedures will be performed and whether any corrective procedures will be applied (e.g., transformation or nonparametric tests).*

<Insert text>

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For each primary endpoint:

- *Define the measurement or observation and describe how it is calculated, if not readily apparent*
- *Describe the scale (nominal/binary/categorical, ordinal, interval); state if it is measured as a single endpoint/summary measure or repeated measure*
- *Describe the statistical procedure(s) that will be used to analyze the primary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, Analysis of Covariance*

(ANCOVA)). Describe the covariates and factors in the model. Provide your rationale for covariates and how they will be selected to achieve a parsimonious model. If the decision to specify covariates is deferred for the SAP, indicate here.

- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat)*
- *Describe details to check assumptions required for certain types of data (e.g., proportional hazards, transformations or nonparametric tests if non-normal)*
- *Describe the Analysis Set for which the analysis will be conducted, as discussed in **Section 10.3, Analysis Datasets***
- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and loss to follow-up*

Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues ca be described as a group.

<Insert text>

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary endpoint:

- *Define the measurement or observation and describe how it is calculated, if not readily appare*
- *Describe the scale (nominal/binary/categorical, ordinal, interval); state if it is measured as a single endpoint/summary measure or repeated measure.*
- *Describe the statistical procedure(s) that will be used to analyze the secondary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, ANCOVA). Describe the covariates and factors in the model. Provide rationale for covariates and how they will be selected to achieve a parsimonious model. If decision to specify covariates is deferred for the SAP, indicate here.*
- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (LSMEANS) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat).*
- *Describe details to check assumptions required for certain types of data (e.g., proportional hazards, transformations or nonparametric tests if non-normal).*
- *Describe the Analysis Set for which the analysis will be conducted as discussed in **Section 10.3, Analysis Datasets.***
- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and loss to follow-up.*

Note if more than endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.

<Insert text>

10.4.4 SAFETY ANALYSES

*Describe how safety endpoints will be analyzed (e.g., as summary statistics during treatment and/or as change scores from baselines such as shift tables). If your study is evaluating a formal safety endpoint, all of the factors to be included in **Section 10.4.2, Analysis of the Primary Efficacy Endpoint(s)** should b included here. Describe how AEs will be coded (e.g., Medical Dictionary for Regulatory Activities (MedDRA)), calculated (e.g., each AE will be counted once only for a given participant), presented (e.g., severity, frequency, and relationship of AEs to study agent will be presented by System Organ Class (SO and preferred term groupings) and what information will be reported about each AE (e.g., start date, stop date, severity, relationship, outcome, and duration). Also describe how AEs will be ascertained (e.g., adherence and/or PI reported). Adverse events leading to premature discontinuation from the study drug and serious treatment-emergent AEs should be presented either in a table or a listing. The information included here should be consistent with the information contained within **Section 8, Assessment of Safety**.*

<Insert text>

10.4.5 ADHERENCE AND RETENTION ANALYSES

Define how adherence to the protocol (e.g., medication consumption) will be assessed, calculated, and verified (if applicable, e.g., plasma assays). Similarly describe measures and calculations for assessing participation, study retention/loss to follow-up, and frequency of and reasons for discontinuation of the intervention.

<Insert text>

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Intervention groups should be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics. Discuss planned baseline descriptive statistics, indicate whether inferential statistics will be used.

<Insert text>

10.4.7 PLANNED INTERIM ANALYSES

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

Include content in this section if applicable, otherwise note as not-applicable.

The following subsections should describe the types of statistical interim analyses and stopping guidelines (if any) that are proposed, including their timing. Within the two sections below, pre-specify, to the extent possible, the criteria that would prompt an interim review of safety and efficacy data, respectively. Describe who performs the statistical analysis and who reviews the analysis. In addition, discuss whether they are unmasked and how the blinding will be preserved.

10.4.7.1 SAFETY REVIEW

Provide details of the proposed rules for halting study enrollment or study intervention/administration of study product for safety, including whether they pertain to the entire study, specific study arms or participant subgroups, or other components of the study. If statistical rules will be used to halt enrollment into all or a portion of the study, describe the statistical techniques and their operating characteristics, e.g., the probability of stopping under different safety event rates and the associated number of participants that would be enrolled.

State which safety endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed stopping guidelines.

*This section should be consistent with **Section 5.5, Premature Termination or Suspension of Study** and **Section 8.5 Study Halting Rules**.*

<Insert text>

10.4.7.2 EFFICACY REVIEW

*Provide the same information as in **Section 10.4.7.1 Planned Interim Analyses**, but for efficacy endpoints. Also discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.*

If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.

<Insert text>

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Describe how the primary endpoint will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s).

Describe how the secondary endpoint(s) will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s).

<Insert text>

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Include content in this section if applicable, otherwise note as not applicable.

Generally, there should be just one primary endpoint that will provide a clinically relevant, valid and reliable measure of the primary objective. However, if there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.

<Insert text>

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

State whether individual participant data will be listed by measure and time point.

<Insert text>

10.4.11 EXPLORATORY ANALYSES

Exploratory analyses serve as a basis for explaining or supporting findings of primary analyses and for suggesting further hypotheses for later research. These analyses can't be used as confirmatory proof for registration trials. All planned exploratory analyses should be specified in the protocol.

<Insert text>

10.5 SAMPLE SIZE

Include number of participants to recruit, screen, and enroll to meet a goal of evaluable participants for the study. Provide all information needed to validate your calculations, and also to judge the feasibility of enrolling and following the necessary number of participants. In particular, specify all of the following:

- *Outcome measure used for calculations (almost always the primary variable)*
- *Test statistic*
- *Null and alternate hypotheses*
- *Type I error rate (alpha)*
- *Power level (e.g., 80% power)*
- *Assumed event rate for dichotomous outcome (or mean and variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible*
- *Assumed dropout rates, withdrawal, cross-over to other study arms, missing data, etc., also justified*
- *Approach to handling withdrawals and protocol violations, i.e., whether participants will be included in the "intent-to-treat" population*
- *Statistical method used to calculate the sample size, with a reference for it and for any software utilized*
- *Method for adjusting calculations for planned interim analyses, if any (**Section 10.4.7, Planned Interim Analyses**).*

Protocol: Study Drug (or Intervention)

- For drugs: Include details re: **the packaging, dosing, storage and accountability of medications/other interventions.**
- For device or diagnostic test: add essential info of device or the test

7 Study Medication (Adapt for Other Interventions)

7.1 Description

7.1.1 Packaging

7.1.2 Labeling

7.1.3 Dosing

7.1.4 Treatment Compliance And Adherence

7.1.5 Drug Accountability

For non-pharmacologic interventions: Enough detail to replicate study without consulting the PI (see table below for checklist)

Checklist item	Elaboration of Item
Setting	Is it clear where the intervention will be delivered?
Recipient	Is it clear who will receive the intervention, and are all key factors known about the participants?
Provider	Is it clear who will deliver the intervention?
Procedures	Is the procedure (including the sequencing of the technique) of the intervention sufficiently clear to allow replication?
Materials	Are the physical or informational materials used adequately described (and available)?
Intensity	Is the dose, length, duration (exposure) of individual sessions of the intervention clear?
Schedule	Is the schedule (interval, frequency, duration, or timing) of the intervention clear?
Overall	Is the description of the intervention complete?

Protocol: Study Drug (or Intervention)

6.1.1 ACQUISITION

Describe how the study agent and control product will be acquired and shipped to the investigator (e.g., a study agent may be supplied by the manufacturer or IND/IDE sponsor, an approved product may be acquired from the hospital pharmacy).

<Insert text>

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Describe the formulation, appearance, packaging, and labeling of the study agent and control product as supplied. Information in this section can usually be obtained from the IB or the package insert. The package insert may be attached as an appendix to the protocol. This section should include the name of the manufacturer of the study agent and control product. Also, discuss availability of product (e.g., investigational or commercially marketed) and if the product proposed is available for human use in the form, route, dose planned in this trial or if product must be formulated to meet the trial plan.

<Insert text>

6.1.3 PRODUCT STORAGE AND STABILITY

Describe study agent's and control product's storage needs. Include storage requirements and stability (e.g., temperature, humidity, security, and container). Provide additional information regarding stability and expiration time for studies in which multidose vials are utilized (i.e., the seal is broken).

<Insert text>

6.1.4 PREPARATION

Describe the preparation of study agent and control product, including what preparation is required by study staff and/or study participant. Include thawing, diluting, mixing, and reconstitution/preparation instructions, as appropriate. Detailed information may be provided in a separate document such as a Manual of Procedures (MOP) or standard operating procedure (SOP).

<Insert text>

6.1.5 DOSING AND ADMINISTRATION

Describe the procedures for selecting each subject's dose of study agent and control product. The timing of dosing (e.g., time of day, interval) and the relation of dosing to meals should be described. Any specific instructions to study participants about when or how to take the dose(s) should be described. Include any specific instructions or safety precautions for administration of the study agent. Discuss the maximum hold time once thawed/mixed, if appropriate, before administration.

<Insert text>

6.1.6 ROUTE OF ADMINISTRATION

Describe the planned route of administration (e.g., oral, nasal, intramuscular).

<Insert text>

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

State the starting level of the study agent and control product.

If applicable, describe the dose escalation scheme and treatment regimen (using exact dose, rather than percentages). State any minimum period required before a participant's dose might be raised to the next higher dose or dose range.

<Insert text>

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

If applicable, the protocol should state the conditions under which a dose change will be made, particularly in regard to failure to respond or to toxic or untoward changes in stipulated indicators (e.g., white blood cell count in cancer chemotherapy). Address dose modifications for specific abnormal laboratory values of concern or other AEs that are known to be associated with the planned study agent. The protocol must state explicitly the dose-limiting effects that are anticipated. Provide criteria that will be used to determine dose escalations. If a participant is responding positively to treatment, the protocol should specify whether treatment would progress to still higher doses. If appropriate, provide a dose de-escalation schema with treatment modifications. Do not restate reasons for withdrawal of participants. Cross-reference relevant sections, as appropriate.

<Insert text>

6.1.9 DURATION OF THERAPY

Discuss the duration of therapy for each active phase and what duration is the minimum necessary for an "evaluable" participant (should be consistent with ***Section 10, Statistical Considerations*** *and/or Statistical Analysis Plan (SAP)).*

<Insert text>

6.1.10 TRACKING OF DOSE

Discuss what procedures will be in place to monitor dosing and adherence for each participant.

<Insert text>

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

If conducting a study with a device, the following information should be included, otherwise note as not-applicable:

- *Device size(s)*
- *Device model(s)*
- *Device settings and programming (if applicable)*
- *Duration of implant or exposure (if applicable)*
- *Frequency of exposure (if applicable)*

<Insert text>

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Describe plans for how and by whom the study agent(s) will be distributed including participation of a drug repository or pharmacy, frequency of product distribution, amount of product shipped, documentation of adequate and safe handling, and plans for return of unused product.

Protocol: Study Drug (or Intervention)

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s)[a]	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥16 years of age [stratified as ≤55 or >55 years of age]).

6.1.1. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study's SoA. The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Protocol: Safety Management

- **Greater than Minimal Risk Safety Management:** includes the definitions of an adverse event, serious adverse event and summarizes the reporting requirements and timelines.
- **Minimal Risk Safety Management:** When a study is limited to procedures that are not greater than minimal risk, the Safety Management section of the protocol may be simplified

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

SAE Reporting to Pfizer Safety via Vaccines SAE Report Form

- Facsimile transmission of the Vaccines SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccines SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccines SAE Report Form pages within the designated reporting time frames.

Protocol: Safety Management

8 ASSESSMENT OF SAFETY

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The subsections below are intended to highlight the specific assessments related to safety and the aspects of the study which are intended to ensure the safety of trial participants. Consider developing this section in consultation with the study Medical Monitor. Consider the risks of the study agent and other study procedures and the characteristics of the study population (e.g., vulnerable populations such as children). This section should be tailored for specific study characteristics, including but not limited to the following:

- *The study involves an investigational new drug or investigational device*
- *The study involves washout from current medication regimen*
- *The study involves treatment with placebo to population with diagnosed disease*
- *The study requires selection of an appropriate toxicity grading scale*
- *The study involves risks to individuals other than research participants (e.g., household or intimate contacts or communities, study clinicians, pharmacists or interventionists, etc.)*
- *Reporting of certain events (e.g., suspected child abuse or substance abuse) is mandatory because of the study population or study design characteristics*
- *The study is conducted at multiple sites, and will require centralized safety oversight*

In developing the sections below, consider the risks of the study agent. Review and reference the IB, package insert, literature and other sources that describe the study agent. Consider and describe how participant's risk will be minimized in the sections below.

8.1 SPECIFICATION OF SAFETY PARAMETERS

*Reference safety parameters that are study endpoints (**Section 4.2, Study Endpoints**). Include other parameters if not primary/secondary endpoints. Describe safety parameters that will be recorded in the safety reporting system. "Recording" refers to documenting data in the study database. Define what data will require reporting for protection of human subjects.*

<Insert text>

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Provide the definition of an AE being used for the clinical trial. The FDA definition of an AE is used in this template since this template is for phase 2 or 3 IND and IDE studies. For some studies, definitions from the OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events; or ICH E6 definition may be more appropriate.

Example text provided as a guide, customize as needed:

[Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).]

<Insert text>

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Provide the definition of an SAE being used for the clinical trial. The FDA definition of an SAE is used in this template since this template is for phase 2 or 3 IND and IDE studies. Note: The example text provided is from the drug regulations (i.e., (21 CFR 312.32 (a)). There is no definition for SAE in the device regulations. Therefore, investigators should develop an appropriate definition for their study. This definition could include an unanticipated adverse device effect, but an SAE is broader than that definition. According to 21 CFR 812.3(s), an "unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

Example text provided as a guide, customize as needed:

[Serious adverse event or serious suspected adverse reaction. An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.]

<Insert text>

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Provide a definition of an UP. An incident, experience, or outcome that meets the definition of an UP generally will warrant consideration of changes to the protocol or consent in order to protect the safety, welfare, or rights of participants or others. Other UPs may warrant corrective actions at a specific study site. Examples of corrective actions or changes that might need to be considered in response to an UP include:

- *Modification of inclusion or exclusion criteria to mitigate the newly identified risks*
- *Implementation of additional safety monitoring procedures*

- *Suspension of enrollment of new participants or halting of study procedures for enrolled participants*
- *Modification of informed consent documents to include a description of newly recognized risks*
- *Provision of additional information about newly recognized risks to previously enrolled participants.*

Example text provided as a guide, customize as needed:

[OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that ar described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.]

Additional example text, applicable for device protocol:
[This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).]
<Insert text>

8.2 CLASSIFICATION OF AN ADVERSE EVENT

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections will include a discussion of how AEs will be classified.

8.2.1 SEVERITY OF EVENT

All AEs will be assessed by the clinician using a protocol defined grading system. Describe the method o grading an AE for severity. For example, many toxicity tables are available for use and are adaptable to various study designs. Selection of a toxicity table or severity scale should be made in consultation with the Medical Monitor.

Example text provided as a guide, customize as needed:

[For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.]

<Insert text>

8.2.2 RELATIONSHIP TO STUDY AGENT

All AEs will have their relationship to study agent or study participation assessed with a level of specificity appropriate to the study design. Describe the method of determining the relationship of an AE to a study agent. Some protocols may use a binary assessment (related/not related); others may have a scale of relatedness. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors. In a clinical trial, the study agent must always be suspect.

Example text provided as a guide, customize as needed:

[The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

OR

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent

disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

<Insert text>

8.2.3 EXPECTEDNESS

Expected adverse reactions are AEs that are common and known to occur for the study agent being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. Describe the method of determining the expectedness of an AE. Expectedness refers to the awareness of AEs previously observed, not on the basis of what might be anticipated from the properties of the study agent.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the protocol, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Example text provided as a guide, customize as needed:

[<Insert name> will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.]

<Insert text>

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Describe how AEs and SAEs will be identified and followed until resolved or considered stable. Also describe how UPs will be recorded. Specify procedures for recording and follow-up of AEs, SAEs, and UPs that are consistent with the information contained within ***Section 7, Study Procedures and Schedule****, including what assessment tools will be used to monitor AEs. Include duration of follow-up after appearance of events (e.g., 1 week, 2 months).*

An unsolicited AE would occur without any prompting or in response to a general question such as "Have you noticed anything different since you started the study; began the study agent, etc." A solicited AE is one that is specifically solicited such as "Have you noticed any dry mouth since you started the study medication?"

- *Describe which AEs will be collected as solicited events. Plan the reporting and data collection system to avoid double capture (captured both as an unsolicited and a solicited AE).*
- *Describe how unsolicited events will be captured.*
- *Include time period of collection (e.g., Days 0 -28) and note how long SAEs are collected – usually collected through entire study.*

Example text provided as a guide, customize as needed:

[The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]

<Insert text>

8.4 REPORTING PROCEDURES

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

In the following subsections, describe the protocol-specific reporting procedures, including the individual responsible for each step (e.g., PI, DCC, Medical Monitor), which forms should be completed, timeframes for reporting, how reports will be distributed, and what follow-up is required.
Include specific details of reporting procedures for:

- *Deaths and life-threatening events*
- *Other SAEs*
- *Other AEs*
- *Other UPs*

The example text in the following sections may be customized by including IRB-specified reporting time frames or protocol-specific parameters (safety issues) that need to be reported in an expedited fashion, either to the IRB, sponsor, or other regulatory body.

8.4.1 ADVERSE EVENT REPORTING

Describe the AE reporting procedures, including timeframes. Include description and a flow chart of when events are reported to various oversight and regulatory groups, and what study staff are responsible for completing and signing off on the AE reports. Describe who will receive notification of AEs.

<Insert text>

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Describe the SAE reporting procedures, including timeframes. Include description and a flow chart of when events are reported to various oversight and regulatory groups, and what study staff are responsible for completing and signing off on the SAE reports. Describe who will receive notification of SAEs.

Generally, any AE considered serious by the PI or Sub-investigator or which meets the definition of an SAE included in ***Section 8.1.2, Definition of Serious Adverse Event*** *must be submitted on an SAE form to the DCC if one exists for the study. If a study is overseen by a Data and Safety Monitoring Board (DSMB), the DSMB may request to receive real-time notification of all SAEs or only SAEs thought to be related to study agent.*

According to 21 CFR 312.32(c)(1), "the sponsor must notify FDA and all participating investigators...in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting... In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

> *(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);*
> *(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);*
> *(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group."*

Furthermore, according to 21 CFR 312.32(c)(2), "the sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information."

*As noted previously, an unanticipated adverse device effect could be considered an SAE (****Section 8.1.2, Definition of Serious Adverse Event****). For IDE studies, according to 21 CFR 812.150(a)(1), "an investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect." In addition, according to 21 CFR 812.150(b)(1), "A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests."*

Example text provided as a guide, customize as needed:

Example 1, applicable for a drug or biologic protocol:

[The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See **Section 1, Key Roles** for contact information.
- Other SAEs regardless of relationship, will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.
The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.]

OR

Example 2, applicable for device protocol:

[The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in **Section 1, Key Roles**. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.]

<Insert text>

8.4.3 UNANTICIPATED PROBLEM REPORTING

Describe the UP reporting procedures, including timeframes. Include description and a flow chart of when events are reported to various oversight and regulatory groups, and what study staff are responsible for completing and signing off on the UP report forms.

Institutions engaged in human subjects research conducted or supported by Department of Health and Human Services (DHHS) must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)). Furthermore, for research covered by an assurance approved for federal wide use by OHRP, DHHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.

Example text provided as a guide, customize as needed:

[Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.]

Additional example text, applicable for device protocol:
[An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).
<Insert text>

8.4.4 EVENTS OF SPECIAL INTEREST

Include content in this section if applicable, otherwise note as not-applicable.

Describe any other events that merit reporting to the sponsor, study leadership, IRB, and regulatory agencies. For example, in oncology trials, secondary malignancies are often captured.
<Insert text>

8.4.5 REPORTING OF PREGNANCY

Include content in this section if applicable, otherwise note as not-applicable.

State the study's pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to the DCC or NIH, the IND or IDE sponsor, study leadership, IRB, and regulatory agencies. Provide appropriate modifications to study procedures (e.g., discontinuation of treatment while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome).
<Insert text>

8.5 STUDY HALTING RULES

Describe safety findings that would prompt temporary suspension of enrollment and/or study agent until a safety review is convened (either routine or ad hoc). The objective of the safety review is to decide whether the study (or study agent for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group, a particular study site or for the entire study) is a potential outcome of a safety review.

Subsequent review of serious, unexpected, and related AEs by the Medical Monitor, DSMB, IRB, the sponsor(s), or the FDA or relevant local regulatory authorities may also result in suspension of further study agent administration at a site. The FDA and study sponsor(s) retain the authority to suspend additional enrollment and study agent for the entire study, as applicable.

Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

This section should be consistent with ***Section 5.5, Premature Termination or Suspension of Study*** *and* ***Section 10.4.7.1, Safety Review****.*

Example text provided as a guide, customize as needed:

[Administration of study agent will be halted when three grade 3 AEs determined to be "probably related" are reported to the DCC. The DCC will notify the study sponsor and investigators immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the DSMB members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study sponsor/NIH. The study sponsor will inform the FDA of the temporary halt and the disposition of the study.]
<Insert text>

Protocol: Study Administration

- This section enumerates the procedures that will be used to run the research study. Sufficient detail is required to ensure that the research plan will produce valid results.
- **Treatment Assignment:** CONSORT require details of randomization and blinding be reported in sufficient detail to assure that the trial results will be unbiased.
- **Data Collection and Management:** Care in data management is a requirement to assure valid study results.
- **Regulatory and Ethical Considerations:** Identify the areas of risk to human subjects and how the study will minimize those risks
- **Informed consent or pediatric assent:** How to obtain consent, what information will be transferred (consent form, verbal script, video presentation, booklet, etc.), when the consent process will occur, where it will occur and how (in person, by telephone, etc.). Also add waivers (if any) regarding consent.
- **Safety Monitoring Plan:** Early Phase trials may just have PI review AE's vs. Phase 2-4 may have Data Monitoring Committee
- **Payment:** Amount of payment and contingencies

Protocol: Study Administration

13.1 ETHICAL STANDARD

Include in this section the guiding ethical principles being followed by the study.

Example text provided as a guide, customize as needed:

[The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.]

If the study is conducted at international sites, the statement could be as above and/or could reference compliance with the Declaration of Helsinki, Council for International Organizations of Medical Science (CIOMS), International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or another country's ethical policy statement, whichever provides the ***most*** *protection to human subjects.*

<Insert text>

13.2 INSTITUTIONAL REVIEW BOARD

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the US and in other countries, only institutions holding a current US Federal-wide Assurance issued by OHRP may participate.

Example text provided as a guide, customize as needed:

[The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.]

<Insert text>

13.3 INFORMED CONSENT PROCESS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections should describe the procedures for obtaining and documenting informed consent of study participants. State if a separate screening consent will be used. If a separate screening

9 CLINICAL MONITORING

Site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Monitoring refers to the methods used by sponsors of investigational studies, or Contract Research Organizations (CROs) delegated site monitoring responsibilities, to

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Provide details regarding the type(s) of data capture that will be used for the study. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements. Indicate expectations for time for submission of CRFs. Further details should be provided in the MOP.

14.3 PROTOCOL DEVIATIONS

Plans for detecting, reviewing, and reporting deviations from the protocol should be described. A statement should be included to indicate that deviations are not allowed, unless a statement is included in the investigator agreement. Provisions for approval of deviations can be described.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

This section will describe protections for maintaining confidentiality of participant data, including, but not limited to forms, records and samples.

Include procedures for maintaining participant confidentiality, any special data security requirements, and record retention per the sponsor's requirements. Describe who would have access to records, including the investigator and other study staff, the clinical monitor, funding institutions, IND sponsor, representatives of NIH IC, representatives from the IRB, and representatives of the pharmaceutical company supplying product to be tested. In addition, consider inclusion of the following information:

- *Describe whether identifiers will be attached to data/samples, or whether data will be coded or unlinked.*
- *If unlinked or coded, and additional information (e.g., age, ethnicity, sex, diagnosis) is available, discuss whether this might make specific individuals or families identifiable.*
- *If research data/samples will be coded, describe how access to the "key" for the code will be limited. Include description of security measures (password-protected database, locked drawer, other). List names or positions of persons with access to the key.*
- *Include a discussion of the circumstances in which data or samples will be shared with other researchers.*
- *Include a discussion of plans to publish pedigrees, with a description of measures to minimize the chance of identifying specific families.*
- *Describe any situations in which personally identifiable information will be released to third parties.*
- *State who has access to records, data, and samples. Consider if monitors or auditors outside of study investigators will need access.*
- *Discuss any additional features to protect confidentiality (e.g., use of a certificate of confidentiality).*

Protocol: Study Administration

10.6 MEASURES TO MINIMIZE BIAS

No text is to be entered in this section; rather it should be included under the relevant subheadings below.

The following subsections should describe the methods planned to minimize bias.

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

This section should contain a description of enrollment procedures and randomization (if applicable to the study design) and masking procedures. It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that masking or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated but the randomization block sizes should not). It should also include a discussion of the impact of replacement of participants who discontinue early, if allowed, on the statistical analysis/power calculations.

Plans for the maintenance of trial randomization codes and appropriate masking for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unmasking may occur and who may unmask.

Include a discussion of strategies to avoid bias, such as randomization and masking methods, or to decrease variability, such as centralized laboratory assessments. DO NOT include details that might compromise these strategies, such as the size of randomized blocks.

A description of the specific procedures to be used to carry out blinding should be provided (e.g., how bottles will be labeled, use of labels that reveal blind-breakage, sealed code list/envelopes, double dummy techniques).

Sometimes blinding is attempted but is known to be imperfect because of obvious drug effects in some participants (e.g., dry mouth, bradycardia, fever, injection site reactions, changes in laboratory data). Such problems or potential problems should be identified and, if there are plans to assess the magnitude of the problem or manage it, these should be described (e.g., having endpoint measurements carried out by people shielded from information that might reveal treatment assignment).

If the study allows for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Measures taken to ensure that the study agent and placebo are indistinguishable and evidence that they are indistinguishable should be described. Measures to prevent unblinding by laboratory measurements, if used, should be described.

If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained (e.g., use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure and Holter tapes are often read by automated systems that are presumably immune to observer bias). If blinding is considered desirable but not feasible, the reasons and implications should discussed.

<Insert text>

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Include content in this section if applicable, otherwise note as not-applicable.
Provide the criteria for determining the success of blinding.

<Insert text>

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in whic the blind would be broken for an individual or for all participants (e.g., for SAEs). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

<Insert text>

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH IC-sponsored or NIH IC -affiliated study each site will permit authorized representatives of the NIH IC and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance revie audits, and evaluation of the study safety, progress, and data validity. Describe in this section who will have access to records.

Source data are all information, original records of clinical findings, observations, or other activities in clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, pharmacy dispensin records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copi or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to u CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

It is not acceptable for the CRF to be the only record of a patient's participation in the study. This is to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial.

12 QUALITY ASSURANCE AND QUALITY CONTROL

This section will indicate the plans for quality management, the system for assessing the quality of processes within a system. Quality management encompasses quality assurance (QA)[4] and quality control (QC)[5].

Each site, both clinical and laboratory, should have SOPs for quality management that describe:

- *How data will be evaluated for compliance with the protocol, ethical standards, regulatory compliance, and accuracy in relation to source documents.*
- *The documents to be reviewed (e.g., CRFs, clinic notes, product accountability records, specimen tracking logs, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.*
- *Who will be responsible for addressing QA issues (e.g., correcting procedures that are not in compliance with protocol) and QC issues (e.g., correcting errors in data entry).*
- *Staff training methods and how such training will be tracked.*
- *If applicable, calibration exercises conducted prior to and during the study to train examiners and maintain acceptable intra- and inter-examiner agreement.*

*Regular monitoring and an independent audit, if conducted, must be performed according to ICH-GCP. See also **Section 9, Clinical Monitoring**.*

Example text provided as a guide, customize as needed:

[QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.]

Protocol: Publication Policy

- Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
- Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research.
- Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports.
- All parties should adhere to accepted guidelines for ethical reporting.
- Negative and inconclusive as well as positive results must be published or otherwise made publicly available.
- Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication.
- Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

14.4 PUBLICATION AND DATA SHARING POLICY

The publication and authorship policies should be established and clearly outlined in this section. For example, for a study with multiple investigators, this section might state that an Executive Committee will be responsible for developing publication procedures and resolving authorship issues. Please refer to your specific contract grant and/or Clinical Trials Agreements. If details of the publication policy will be described in the study's MOP, refer to it here. The study must comply with the NIH Public Access Policy, the Food and Drug Administration Amendments Act of 2007 (FDAAA), and ClinicalTrials.gov. At the end of the study, the PI will make results of the research available to the research community and public at large. Refer to NIH Grants Policy Statement Section 8.2.

Example text provided as a guide, customize as needed:

[This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

Protocol: References

17 LITERATURE REFERENCES

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is ICMJE. Include citations to product information such as manufacturer's IB, package insert, and device product description.

Examples:

- ***Journal citation***
  Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. J Natl Cancer Inst. 2007 Feb 21;99(4):258-60.
- ***Whole book citation***
  Belitz HD, Grosch W, Schieberle P. Food chemistry. 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.
- ***Chapter in a book citation***
  Riffenburgh RH. Statistics in medicine. 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, Regression and correlation methods; p. 447-86.
- ***Web Site citation***
  Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: http://www.manderson.org/departments/CIMER/.
- ***Electronic Mail citation***
  Backus, Joyce. Physician Internet search behavior: detailed study [Internet]. Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]
- ***References to package insert or investigational brochure or product description***
  Cite date accessed, version number, and source of product information.

Protocols can be amended and revised

APPENDIX

Version	Date	Significant Revisions

Pfizer COVID-19 Vaccine Protocol Table of Contents

TABLE OF CONTENTS

Pfizer COVID-19 Vaccine Protocol Table of Contents

6.1 General Information

E6	Description/Text	Included?	
		Yes	No
6.1.1*	Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).		
6.1.2 *	Name and address of the sponsor and monitor (if other than the sponsor).		
6.1.3	Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.		
6.1.4	Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.		
6.1.5*	Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s). **List any collaborating sites where the study will be performed.*		
6.1.6	Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable) who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).		
6.1.7	Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.		

6.2 Background Information

E6	Description/Text	Included?	
		Yes	No
6.2.1*	Name and description of the investigational product(s).		
6.2.2*	A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.		
6.2.3*	Summary of the known and potential risks and benefits, if any, to human subjects.		
6.2.4*	Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).		
6.2.5	A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).		
6.2.6*	Description of the population to be studied.		
6.2.7*	References to literature and data that are relevant to the trial, and that provide background for the trial.		

6.3 Trial Objectives and Purpose

E6	Description/Text	Included?	
		Yes	No
6.3*	A detailed description of the objectives and the purpose of the trial.		

CLINICAL RESEARCH PROTOCOL CHECKLIST

6.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

E6	Description/Text	Included?	
		Yes	No
6.4.1*	A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.		
6.4.2	A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages. *- Definition of when the subject is considered 'enrolled' (on study).* **Identify any substudies.* **Include a detailed description of number of visits, procedures at each visit, visit windows, and length of study visits for subjects.*		
6.4.3	A description of the measures taken to minimize/avoid bias, including (for example): (a) Randomization, (b) Blinding		
6.4.4*	Drugs, supplements, or biologics: A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s). *Devices: A description of the trial treatment(s) and the device implantation/application, removal. Also include a description of the device specifications, packaging, and labeling of the investigational product(s).*		
6.4.5*	The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.		
6.4.6*	A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial, and entire trial.		
6.4.7*	Accountability procedures for the investigational product(s), including the placebo(s)/sham procedures and comparator(s), if any.		
6.4.8	Maintenance of trial treatment randomization codes and procedures for breaking codes.		
6.4.9	The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.		
6.4.10	If your study is investigator-initiated and multi-site, refer to Section 7 for additional guidance.		

CLINICAL RESEARCH PROTOCOL CHECKLIST

6.5 Selection and Withdrawal of Subjects

E6	Description/Text	Included?	
		Yes	No
	**Subject identification and recruitment methods.*		
6.5.1*	Subject inclusion criteria.		
6.5.2*	Subject exclusion criteria.		
	Describe how the eligibility criteria will be determined • *Information reported by the subject* • *Medical record review* • *Results of screening assessments (e.g. questionnaires, diaries, etc.)*		
6.5.3	Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying: (a) When and how to withdraw subjects from the trial/investigational product treatment. • *What if a subject develops an exclusionary condition?* • *What if a subject begins taking an exclusionary medication?* (b) A detailed description of the study withdrawal procedures, including the type and timing of the data to be collected for withdrawn subjects. (c) Whether and how subjects are to be replaced.		
	(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.		

6.6 Treatment of Subjects

E6	Description/Text	Included?	
		Yes	No
6.6.1*	The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.		
6.6.2*	Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.		
6.6.3	Procedures for monitoring subject compliance.		

6.7 Assessment of Efficacy

E6	Description/Text	Included?	
		Yes	No
6.7.1	Specification of the efficacy parameters.		
6.7.2	Methods and timing for assessing, recording, and analyzing efficacy parameters.		

6.8 Assessment of Safety

E6	Description/Text	Included?	
		Yes	No
6.8.1	Specification of safety parameters.		
6.8.2*	The methods and timing for assessing, recording, and analyzing safety parameters.		
6.8.3*	Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.		
6.8.4	The type and duration of the follow-up of subjects after adverse events.		

6.9 Statistics

E6	Description/Text	Included?	
		Yes	No
6.9.1*	A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).		
6.9.2*	The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.		
6.9.3	The level of significance to be used.		
6.9.4*	Criteria for the termination of the trial.		
6.9.5	Procedure for accounting for missing, unused, and spurious data.		
6.9.6	Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).		
6.9.7	The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluate-able subjects).		

6.10 Direct Access to Source Data/Documents

E6	Description/Text	Included?	
		Yes	No
6.10	The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.		

6.11 Quality Control and Quality Assurance

E6	Description/Text	Included?	
		Yes	No
6.11	A description of the Quality Control and Quality Assurance processes and measures to be taken		

6.12 Ethics

E6	Description/Text	Included?	
		Yes	No
6.12	Description of ethical considerations relating to the trial.		

6.13 Data Handling and Recordkeeping

E6	Description/Text	Included?	
		Yes	No
6.13*	Description of the Data Handling and Record Keeping processes and measures to be taken **Provide information about confidentiality protections, sharing of data, and disposition of data* **Identify information that will be extracted from medical records*		

6.14 Financing and Insurance

E6	Description/Text	Included?	
		Yes	No
6.14	Financing and insurance if not addressed in a separate agreement.		

6.15 Publication Policy

E6	Description/Text	Included?	
		Yes	No
6.15	Publication policy, if not addressed in a separate agreement.		

6.16 Supplements

E6	Description/Text	Included?	
		Yes	No
6.16	*(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guidance for Structure and Content of Clinical Study Reports.)*		

And that's a wrap of the most important document you'll need during the trial.

- Focus on learning the aspects of a protocol and how to read a protocol quickly.
- A CRA must know learn each trial's protocol well in order to properly monitor the trial. Practice reading an interesting protocol (see below for COVID-19 Pfizer vaccine protocol) so you can become more familiar with the layout, language, and important parts.
https://pfe-pfizercom-d8-prod.s3.amazonaws.com/2020-09/C4591001_Clinical_Protocol.pdf