Planning Your Protocol

Protocol Navigation/Protocol Development Program (PN/PDP) supporting NIAID

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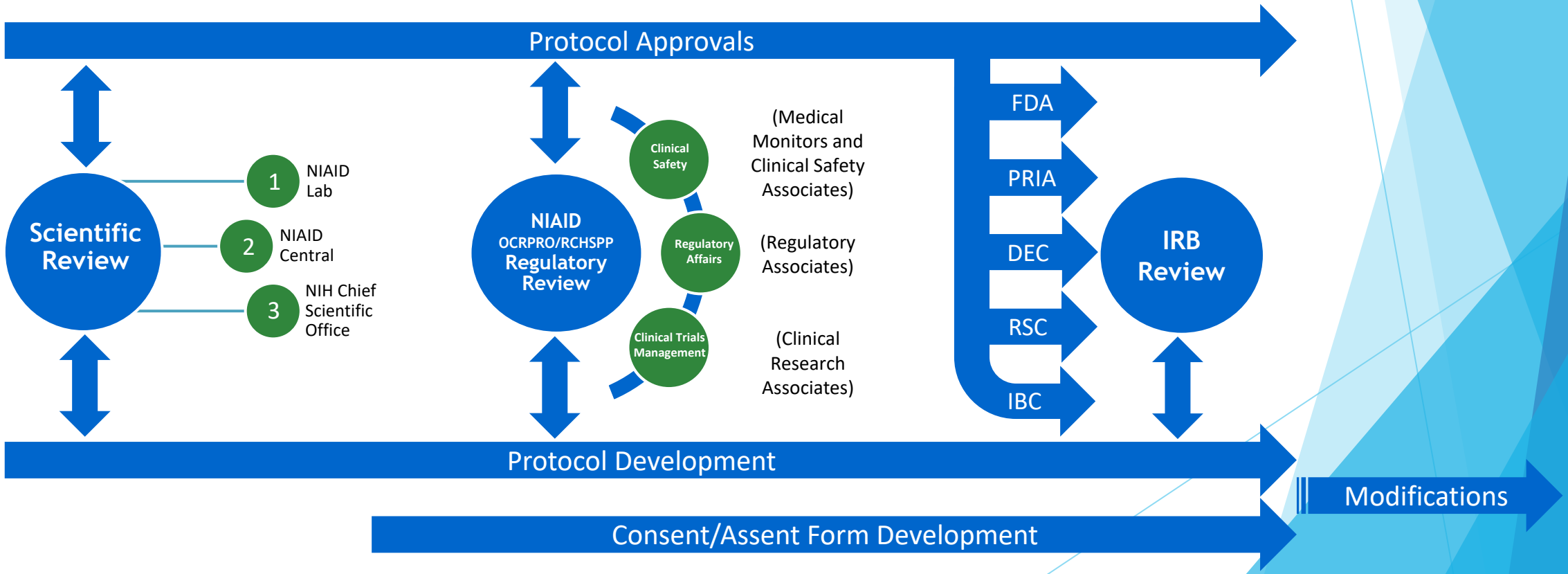
Objectives

1. Describe the content of key clinical research protocol sections and the implications for study implementation
2. Discuss study planning and implications for protocol development and initial approval



What is a Protocol?

- Structured document containing sections providing essential details addressing relevant aspects of, and requirements for, human subjects research
  - Recipe to direct research activities
  - Needed to ensure compliance with research plan
  - A style guide may be used for consistency (eg, American Medical Association Manual of Style)
- Key sections of a clinical research protocol
  - Background/rationale/hypothesis
  - Design/study intervention
  - Objectives/endpoints
  - Procedures/schedule
  - Safety
  - Risks/benefits
  - Population
  - Statistical considerations
  - Human subjects protections/ regulatory and operational considerations

Study Types

- Clinical trial
  - Drugs
  - Biologics
    - Any virus, serum, toxin, or analogous product
  - Devices
- Observational/natural history
- Other (repository, secondary research, PK/PD)
- Study type determines
  - Specific focus of protocol
  - Details of protocol
  - Templates that may apply

45 CFR 46.111 Criteria for IRB Approval of Research

- In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:
  - Risks to subjects are minimized:
    - By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and
    - Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
  - Risks to subjects are reasonable in relation to anticipated benefits and the importance of the knowledge that may reasonably be expected to result.
  - Selection of subjects is equitable.
  - When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Study Design

- Overview of the main study design
  - Natural history vs interventional
  - Prospective vs retrospective
  - Placebo controlled
  - Randomized
  - Blinded
- Overall description of what will happen in the study

Objectives & Endpoints

- Objectives should be clear statements of each individual goal of the study
- Endpoints are usually matched to objectives and show what will be collected or assessed to address the objective

Defining the Study Population

- Eligibility (inclusion/exclusion) criteria are determined by
  - What you want your population to look like based on your rationale and objectives
  - Study-related risks
    - Investigational agent
    - Research procedures
- Considerations
  - What are the demographics/characteristics of the target population?
  - Is there a specific sub-group that would be especially vulnerable to risks of the study drug or research procedures?
  - Are there any strict study requirements subjects must comply with?
  - Does the study involve vulnerable populations?
  - Are any inclusion and exclusion criteria duplicative?

Schedule of Activities

- Detail what evaluations are needed and at what time points
  - Which research procedures must be performed to meet objectives/endpoints
  - Safety issues to consider at certain time points based on the risks
  - Visit windows should be specified
- Considerations
  - How and when is the study agent administered?
  - What data should be collected and when based on the objectives/endpoints?
  - What is the known toxicity profile of the study agent?
  - May any study visits occur remotely?
  - Are the study requirements reasonable for participants, or overly burdensome?
  - Is the site able to perform required evaluations, including laboratory capacity?

Study Assessments & Procedures

- Describe each assessment/procedure
  - How it is performed/what it involves
  - Do not repeat schedule information that is already provided in the Schedule of Activities
  - Standard procedures may not need to be described in detail
- Considerations
  - Are there any deviations from standard procedures that should be described in detail?
  - Are there any special handling requirements that must be followed?
  - Will the participant be asked to complete any procedures (eg, questionnaires)?

Schedule of Activities vs. Study Assessments & Procedures

- Schedule of Activities
  - Table format
  - Focused on exact timepoints for each procedure
  - Footnotes can provide additional information critical for performing procedures appropriately

- Study Assessments and Procedures
  - Text format
  - Focused on detailed description of what each study procedure involves/how it is performed rather than when

Procedure/Evaluation	Screening (days -14 to -1)	Baseline (day 0)	Days 1-5	Days 14, 21, 28 (windows ±1 day)	Weeks 8, 16, 24 (windows ±3 days)
Clinical Procedures					
Informed consent[1]	X				
Physical exam	X	X	Daily (pre- and post-dose)	X	X
Medical and medication history	X	X	Daily (pre-dose)	X	X
Blood collection	X	X	Daily (pre- and post-dose)	X	X
IV catheter insertion/check		X	Daily patency check (pre-dose)		
Randomization		X			
Vital signs		X	Daily[2]	X	X
Study agent infusion			Daily[3]		
AE assessment			Daily (post-dose)	X	X
Laboratory Evaluations					
Urine pregnancy test	X	X	Daily (pre-dose)[4]	X	X
Viral PCR	X	X	Day 5 only (post-dose)	X	X
Liver function tests	X	X	Daily (pre- and post-dose)	X	X
Hepatitis testing	X				
CBC with differential	X	X	Daily (pre- and post-dose)	X	X
Chemistries[5]		X	Daily (pre- and post-dose)	X	X

[1]Informed consent will be obtained prior to initiating any study procedures.
[2]Vital signs will be assessed approximately 30 minutes prior to and 15, 30, and 60 minutes after the start of the infusion.
[3]After completion of the pre-dose procedures and review of laboratory test results, study agent will be infused over 1 hour. Subject should be monitored carefully during the infusion for signs of infusion reaction.
[4]Must be confirmed negative prior to study agent infusion.
[5]Sodium, potassium, chloride, bicarbonate, creatinine, glucose, estimated glomerular filtration rate.

Study Intervention/Agent

- Describe study intervention/study agent
  - Properties/mechanism of action
  - Dosing and administration
    - Dose adjustments/escalations/modifications
  - Preparation, storage, accountability
  - Randomization, blinding
  - Compliance with study agent administration
- Considerations
  - Source of information
    - Investigator's brochure (investigational agent)
    - Package insert/prescribing information (approved agent)
    - Pharmacy manual
  - Placebo

Risks & Benefits

- Risks of study participation to participants
  - Intervention
  - Procedure
  - Pregnancy
  - Other risks, as applicable (eg, confidentiality, psychological, social, economic)
  - Risk mediation, as applicable
- Benefits
  - Individual participant
  - Others
- Risk/benefit assessment
  - Risks should be reasonable in relation to benefits

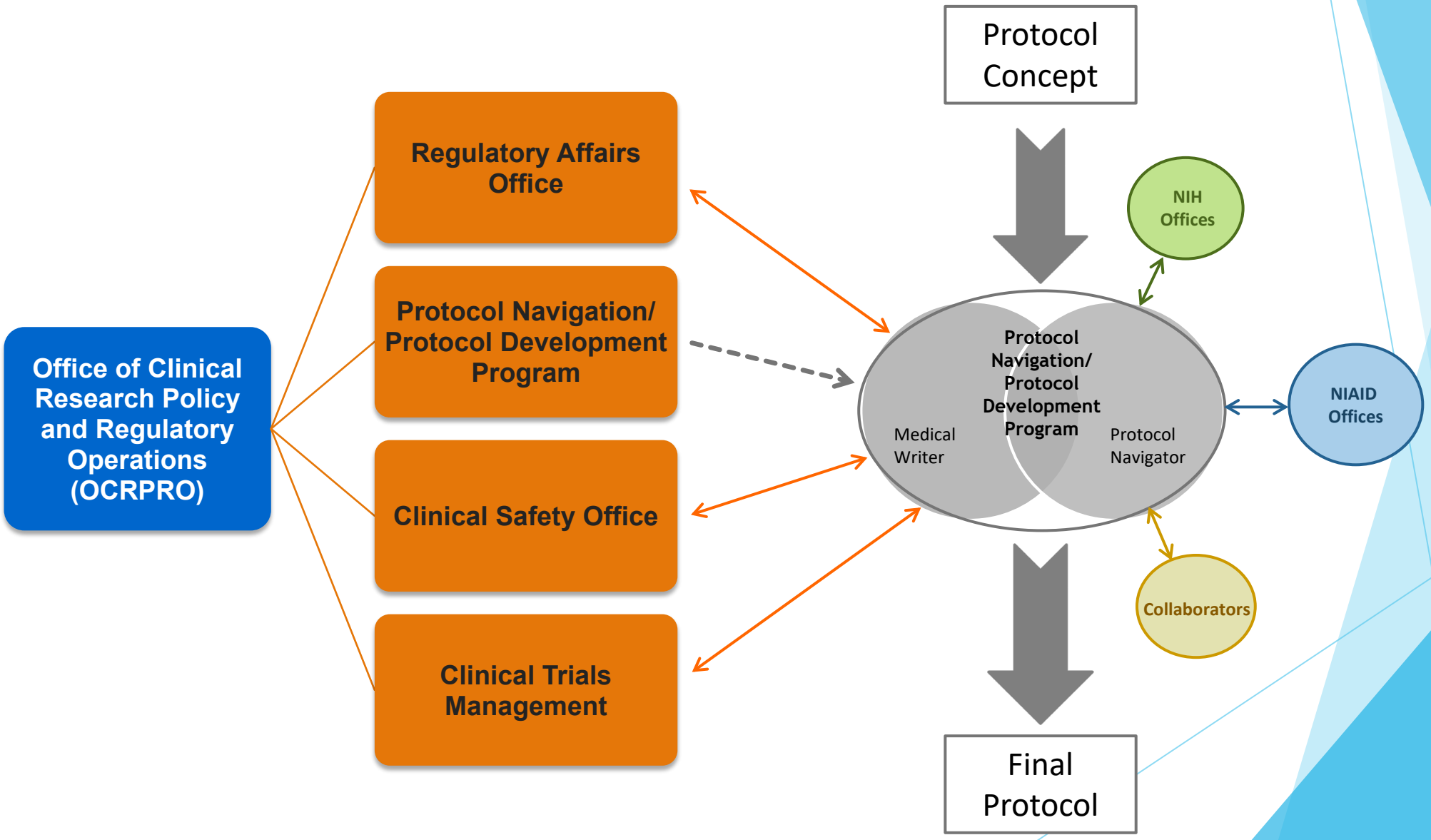
Intervention Discontinuation & Subject Withdrawal

- Describe criteria for discontinuing study intervention(s) and withdrawing participants
  - Pausing rules
  - Halting rules
  - Describe conditions under which study activities may resume
  - Reasons that subjects may be withdrawn by investigator
- Considerations
  - Will subjects remain in the study if study intervention(s) were discontinued?
  - Are there assessments that should be completed if a participant withdraws early?
  - Will withdrawn subjects be replaced?

Safety

- Define events
  - Assessment
  - Toxicity grading scale
  - Causality
  - Record keeping
- Describe safety reporting timelines and responsibilities
- Considerations
  - Information known about study agent and population
  - Institutional or sponsor requirements
  - Pausing/halting rules
  - Blinding and unblinding procedures
  - Additional oversight committees

Protocol Navigation Office

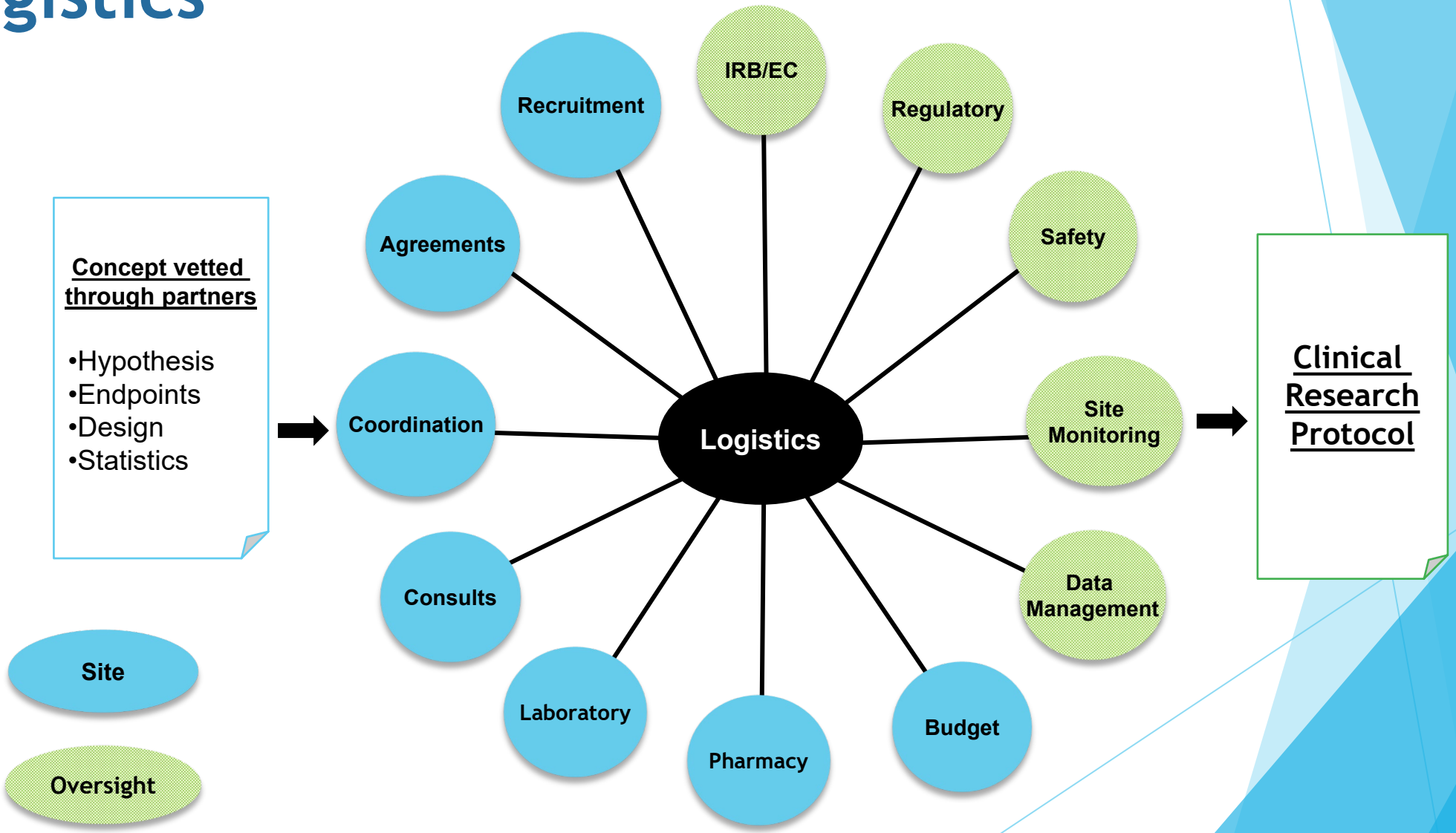


General Logistical Coordination

During the initial meeting the following is discussed with the key decision makers from the study team:

- Discuss concept/protocol
- Required components of submissions
- Estimated timelines

Complexity of Protocol Development Logistics



Study Planning

- Sponsor
- Regulatory
- Statistician
- Agreements
- Recruitment
- Sites
- Safety oversight

Think about materials needing to be prepped at this stage:

- Pre-IND
- IND/IDE
- Exemptions (21CFR312.2(b))
- IB/Package Insert
- CTA/CRADA/MTA
- Remuneration/Reimbursement
- Recruitment and screening guidelines
- Use of 3rd party vendors
- Multi-site
- International site
- IRB of Record
- DSMB vs SMC

- Site Prep
- Ancillary submissions
- PROTRAK
- FDA prep

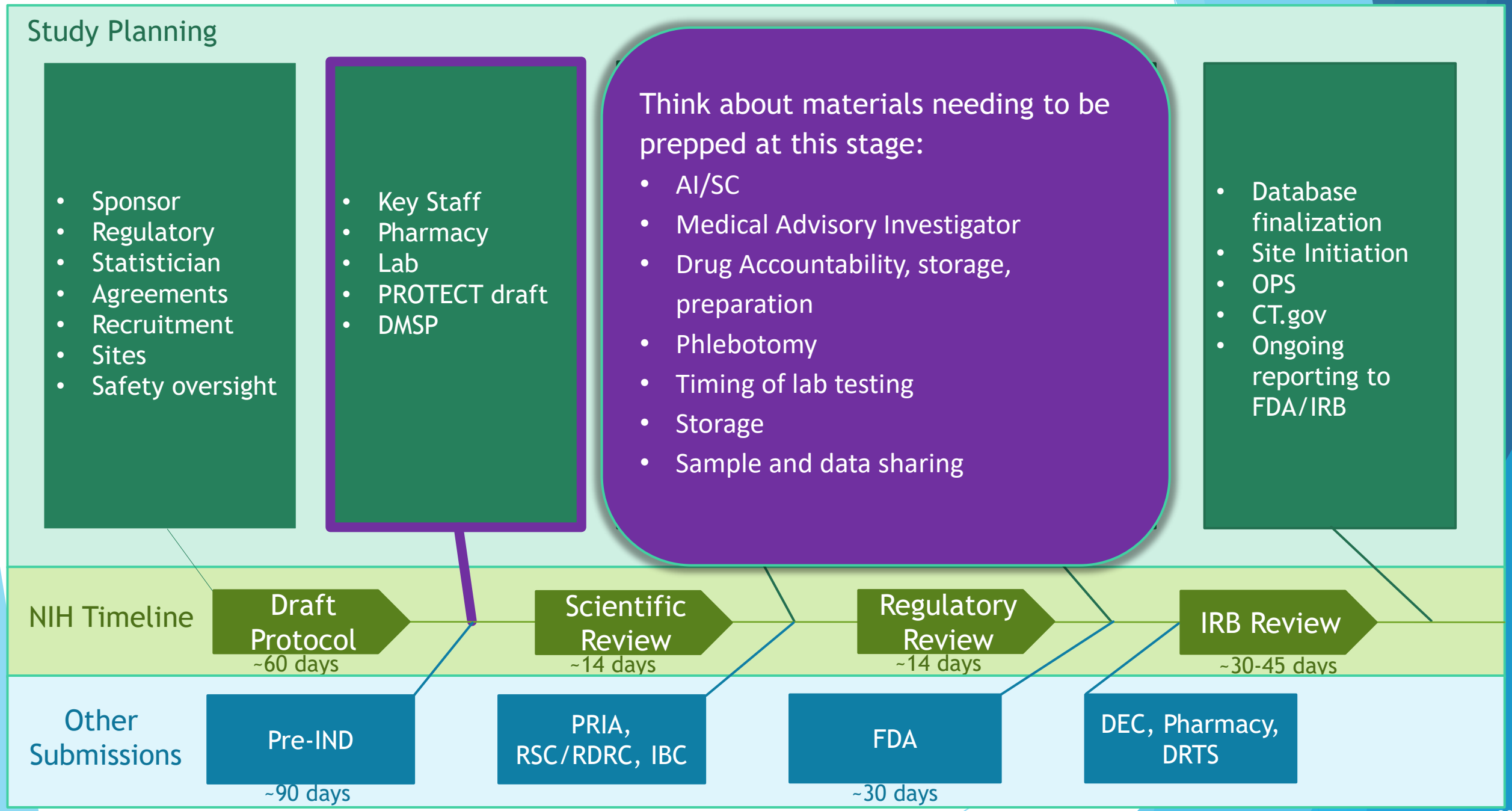
- Database finalization
- Site Initiation
- OPS
- CT.gov
- Ongoing reporting to FDA/IRB

NIH Timeline

Draft Protocol	Scientific Review	Regulatory Review	IRB Review
~60 days	~14 days	~14 days	~30-45 days

Other Submissions

Pre-IND	PRIA, RSC/RDRC, IBC	FDA	DEC, Pharmacy, DRTS
~90 days		~30 days	


Study Planning
Sponsor
Regulatory
Statistician
Agreements
Recruitment
Sites
Safety oversight
Key Staff
Pharmacy
Lab
PROTECT draft
DMSP
Think about materials needing to be prepped at this stage:
AI/SC
Medical Advisory Investigator
Drug Accountability, storage, preparation
Phlebotomy
Timing of lab testing
Storage
Sample and data sharing
Database finalization
Site Initiation
OPS
CT.gov
Ongoing reporting to FDA/IRB
NIH Timeline
Draft Protocol
~60 days
Scientific Review
~14 days
Regulatory Review
~14 days
IRB Review
~30-45 days
Other Submissions
Pre-IND
~90 days
PRIA, RSC/RDRC, IBC
FDA
~30 days
DEC, Pharmacy, DRTS

Study Planning

Think about materials needing to be prepped at this stage:

- Data Management
- Questionnaires
- REDCap
- CRFs

- ICFs/assents
- Database
- Ancillary submissions
- Recruitment materials

- Site Prep
- Ancillary submissions
- PROTRAK
- FDA prep

- Database finalization
- Site Initiation
- OPS
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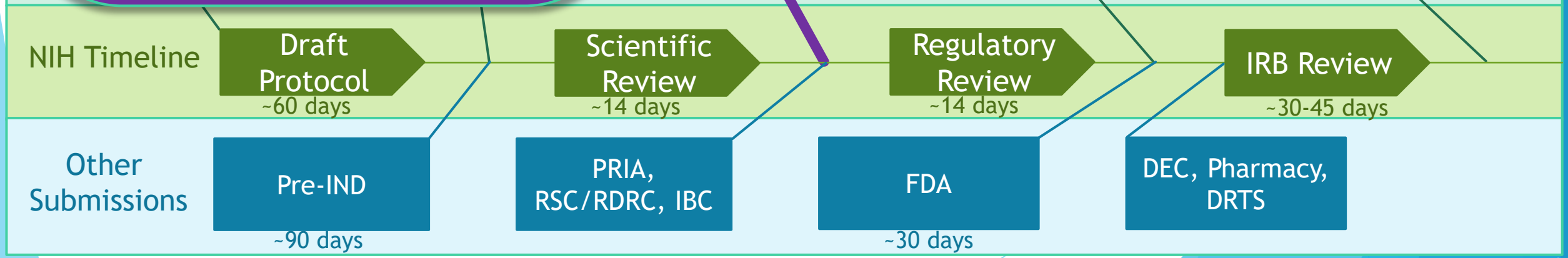
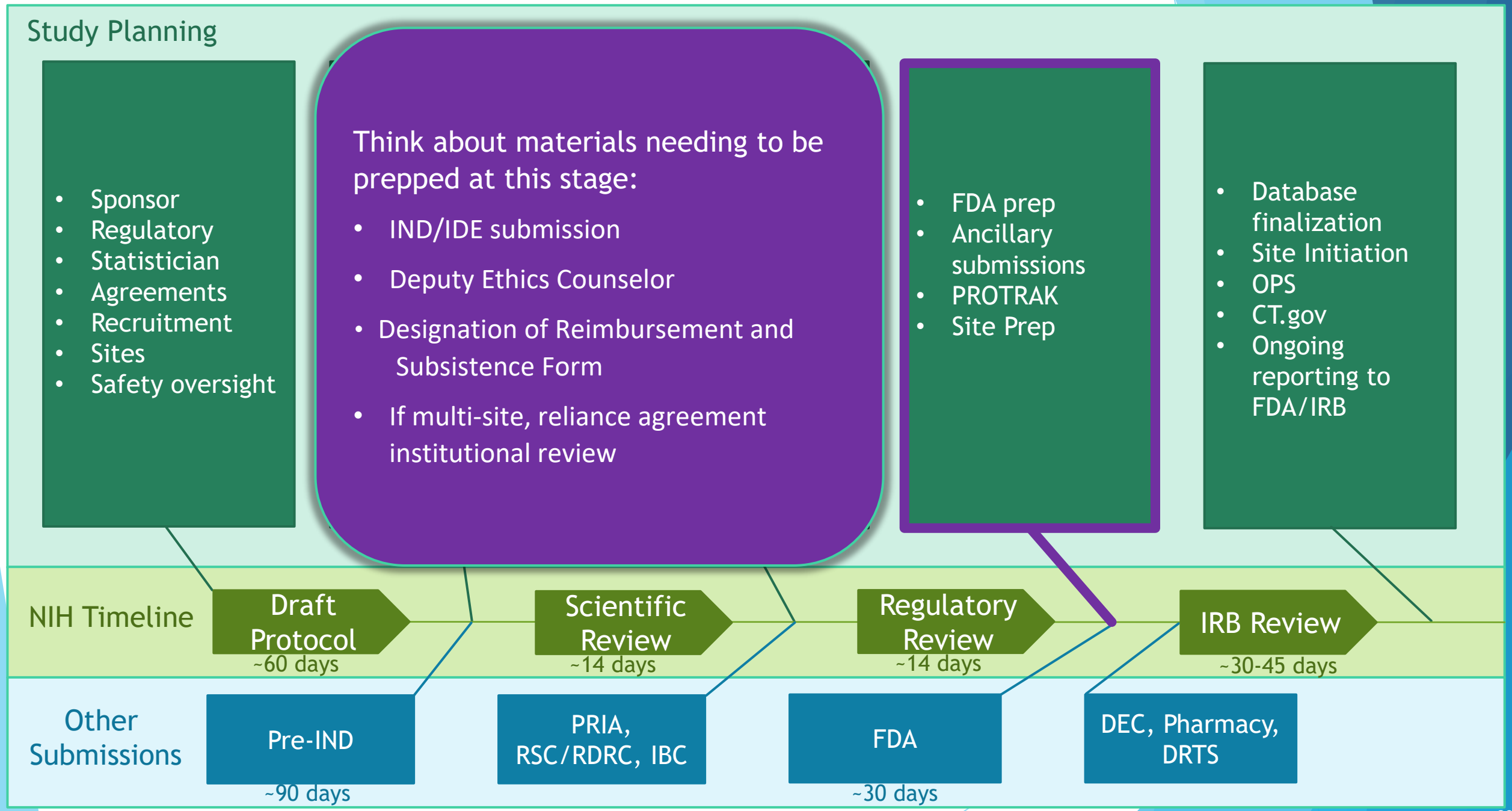



Study Planning
Sponsor
Regulatory
Statistician
Agreements
Recruitment
Sites
Safety oversight
Think about materials needing to be prepped at this stage:
IND/IDE submission
Deputy Ethics Counselor
Designation of Reimbursement and Subsistence Form
If multi-site, reliance agreement institutional review
FDA prep
Ancillary submissions
PROTRAK
Site Prep
Database finalization
Site Initiation
OPS
CT.gov
Ongoing reporting to FDA/IRB
NIH Timeline
Draft Protocol
~60 days
Scientific Review
~14 days
Regulatory Review
~14 days
IRB Review
~30-45 days
Other Submissions
Pre-IND
~90 days
PRIA, RSC/RDRC, IBC
FDA
~30 days
DEC, Pharmacy, DRTS

Study Planning

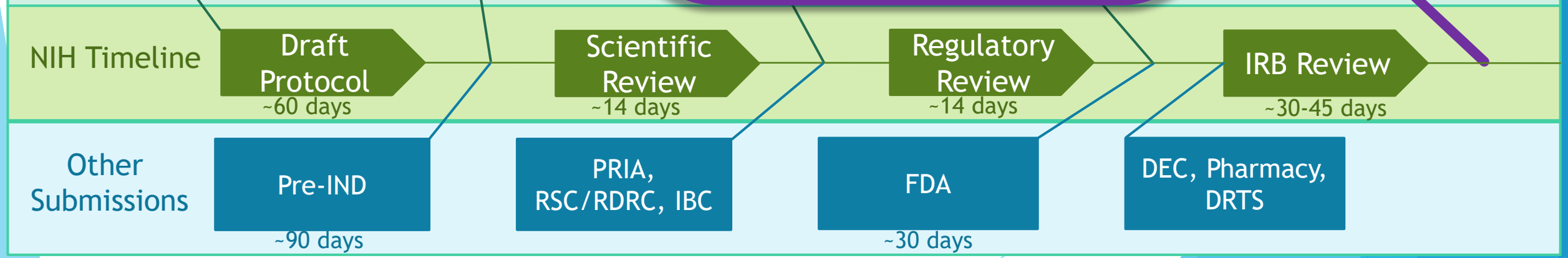
- Sponsor
- Regulatory
- Statistician
- Agreements
- Recruitment
- Sites
- Safety oversight

- Key Staff
- Pharmacy
- Lab
- PROTECT draft
- DMSP

Think about materials needing to be prepped at this stage:

- Stamped consents/assents
- Protocol training
- Site activation
- Order sets and flowsheets
- Regulatory binder

- Database finalization
- Site Initiation
- OPS
- CT.gov
- Ongoing reporting to FDA/IRB

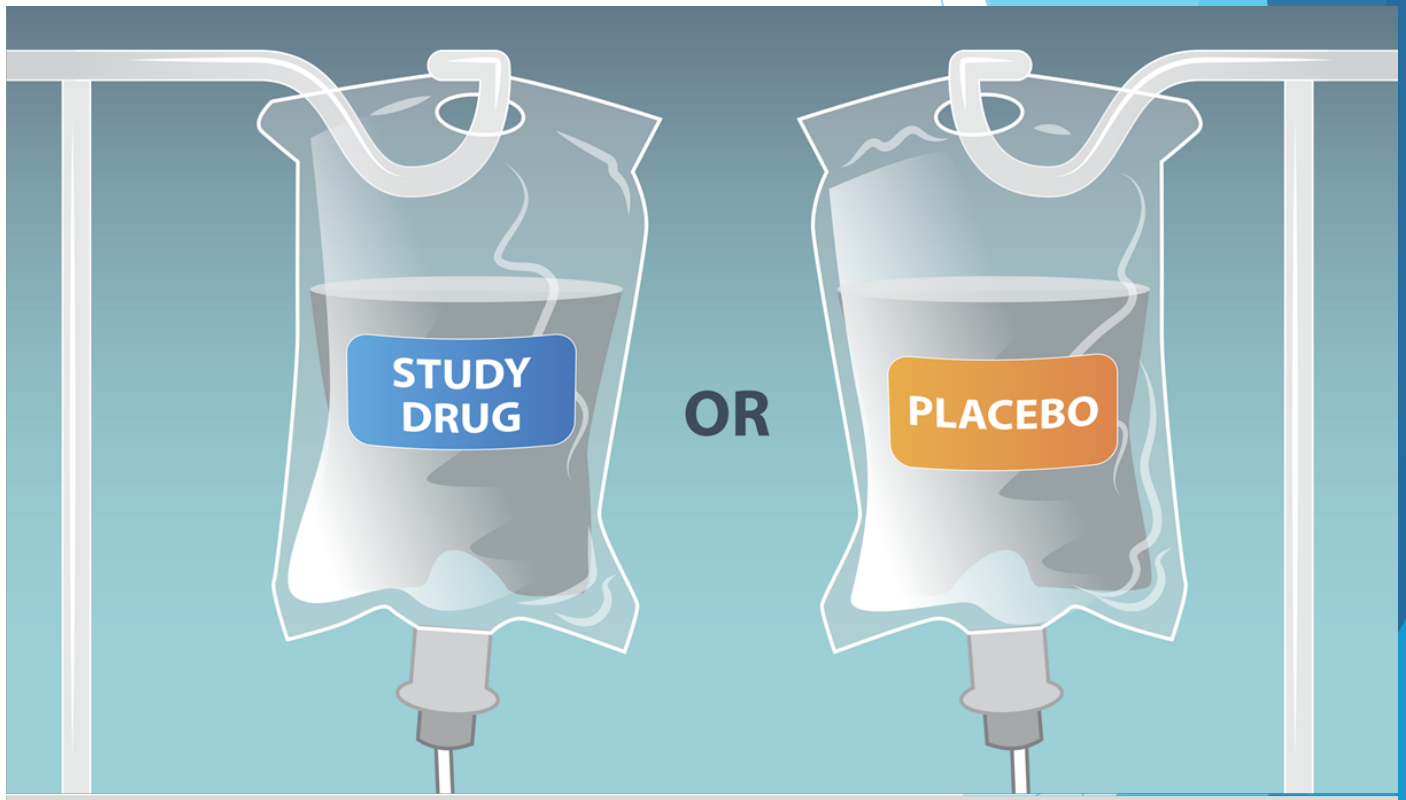


Lessons Learned

- Communication is key
- Track input from multiple simultaneous reviewers.
- Manage study design and endpoints based on resources available at the time.
- Draft the protocol well in advance considering transmission seasons.
- Intervene when reviews or sign-offs are taking longer than expected.
- Use flipbooks to facilitate consent discussions.

Flipbooks & Informed Consent

- Use flipbooks to augment the informed consent process discussion.
- Research concepts may be new to the population being enrolled.
  - Relay complex research themes using illustrations and short, simple text.
  - Incorporate local context and community opinions.
  - Translate into the local language.
  - Note: obtain approvals from IRBs and Ethics Boards for the site-specific flipbooks.

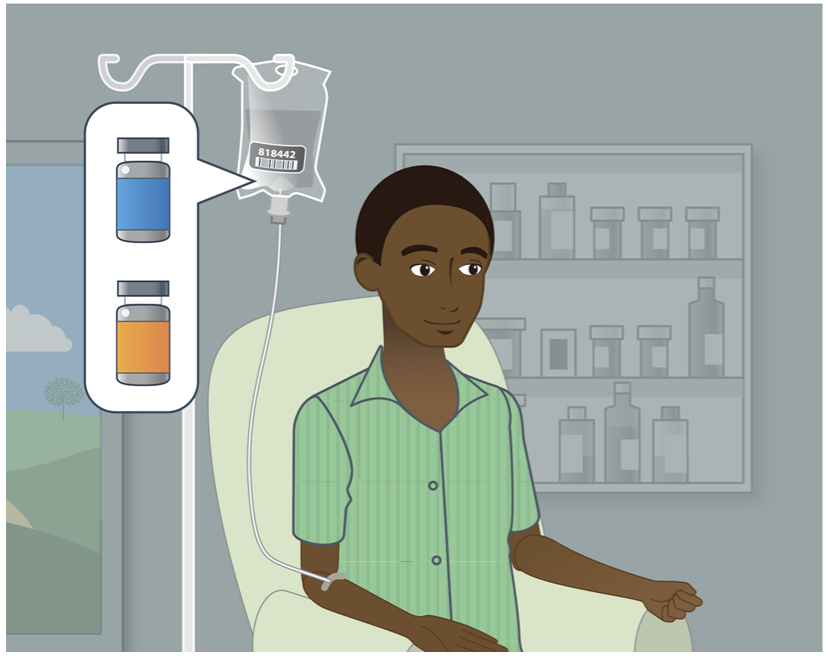


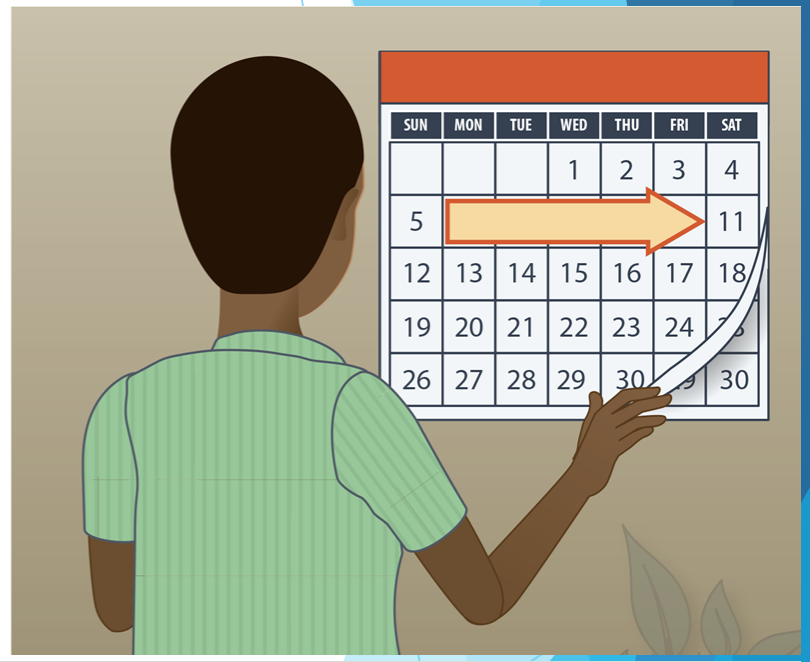
What drug is being studied?

We are studying a drug called ST-1017. This drug has been studied in animals and in a small number of people. We hope that ST-1017 will help get rid of the Jumba virus that is left inside the body. It is given as an infusion. This means it is given through a plastic tube that is put into a vein in the arm. To find out if ST-1017 (the study drug) works, we need to compare it to something that does not have the drug in it. So some people on this study will get a solution called a placebo. The placebo is a liquid that looks like the study drug but does not have the drug in it. Using a placebo is common in research studies. The placebo is also given as an infusion.

Flipbooks & Informed Consent

- Several countries continue to use flipbooks.
  - In Liberia, flipbook pages were posted in the “information room” and the informed consent process involved two parts:
    - Part 1: group overview
    - Part 2: one-on-one meeting





What does the study involve?

If you qualify for the study and decide to join, you will get 1 infusion every day for 5 days in a row. The infusion will be either study drug or placebo, depending on what group you are in. The infusion takes about 1 hour and will be done in the clinic. We will watch you closely for side effects during the infusion and for 1 hour after the infusion. On each of these 5 days, we will also take some blood. We will ask you for a semen sample on one of the days that you get an infusion.

After you finish the study infusions, you will come back to the clinic 3 times during the first month and then 3 more times over 5 months. During the clinic visits, we will ask how you are feeling and if you have been sick. We will also ask for a semen sample and take a blood sample at each visit for research and safety tests.

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- Stacy Kopka and Tracey Miller, Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research

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