Clinical Trials

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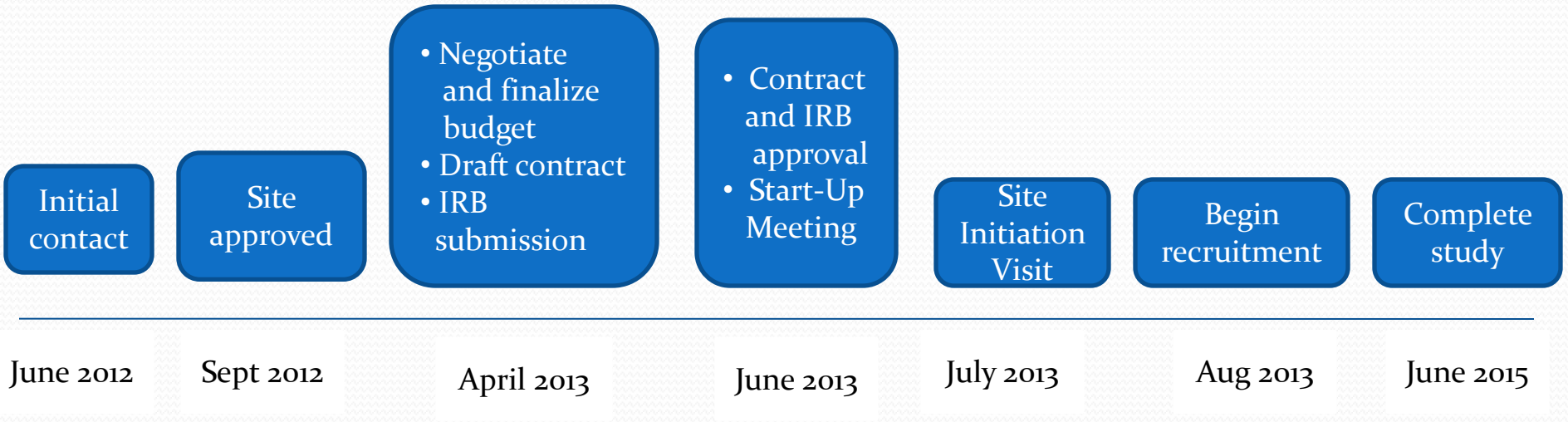
Objectives

- Pre-Study
- Study
- Post-Study

Typical Timeline



Process is often faster if the study is already underway at other sites.

Pre-Study

Initial Inquiry

- Investigator-initiated projects
  - Investigator authors the protocol
  - Not all companies offer funds for investigator-initiated projects
  - Typically limited budgets
  - Company website provides information
- Industry-initiated projects
  - Company (or CRO) initiates contact and provides protocol
  - Pharmaceutical representatives can assist if you are aware of specific studies
- Site Feasibility Questionnaire
  - Investigator and staff experience
  - Patient sample characteristics/feasibility of recruitment

Protocol and Budget Review

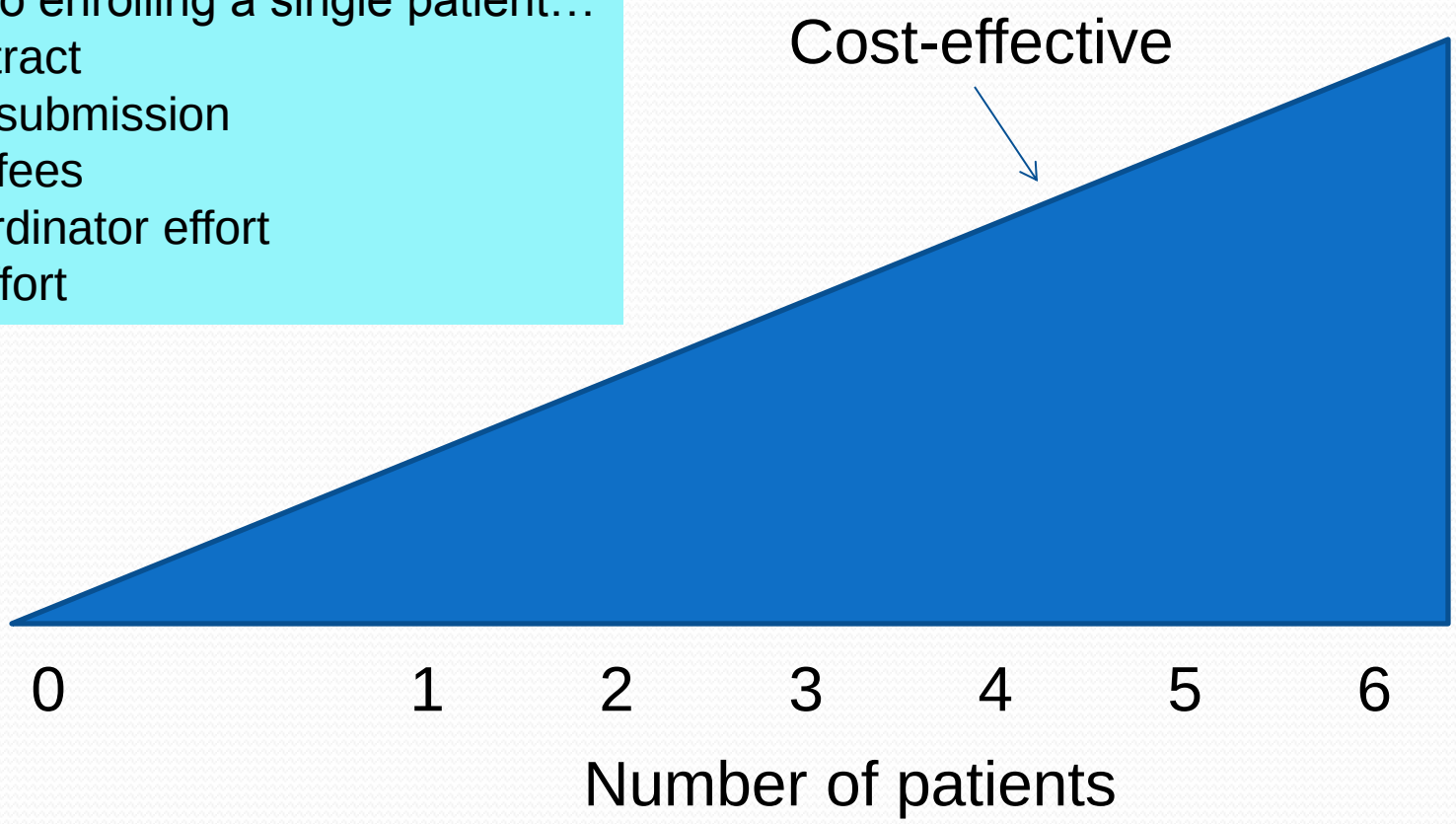
- Protocol Review
  - Schedule of assessments
  - What procedures are done and who can do each procedure
  - Process for labs
  - Special equipment (stadiometer, centrifuge, freezer, etc.)
- Personnel
- Budget Review
  - Start-up costs
  - Budget
  - Enrollment
  - Payment Schedule

Personnel

- Principal Investigator (PI)
  - Oversight of study (recruitment, training, management etc.)
  - Regulatory
  - Physician role
- Sub-Investigator (Physician)
  - Physical exams, perform rating scales at screening and follow-up visits
  - Online training and investigator meeting
  - Assess relationship of adverse events to study drug
- Study Coordinator
  - Recruitment, screening
  - Follow-up (randomization, drug accountability, adverse events, scheduling visits, crisis management)
  - Data management (data entry, study files)
  - Training
  - Regulatory
  - Monitoring visits, resolving queries

Start-up Costs

Prior to enrolling a single patient…
- Contract
- IRB submission
- IRB fees
- Coordinator effort
- PI effort



Budget

- Fees (IRB, administrative, institution, hospital, pharmacy)
- Screen failures (may be limited)
- Payment schedule
- Overhead (indirect costs are generally institution dependent)

3 Types of Budgets:

1) Flat amount per patient
2) Payment per visit**
3) Payment per activity**

Trial Budget Example

Visit/Week	Description	Amount
1 / -1	Screening	$2,470
2 / 0	Follow-Up	$1,070
3 / 1	Follow-Up	$1,150
4 / 2	Follow-Up	$1,150
5 / 3	Follow-Up (with labs, ECG)	$1,600
6 / 4	Follow-Up	$1,150
7 / 6	Follow-Up	$1,460
8 / 8	Visit 8 / ET	$1,800
9 / 9	Down-Taper	$840
	TOTAL	**$12,600**

	Number of Visits	Study Duration	Direct costs per completed subject
Acute double-blind	9	9 weeks	$9,692
Acute double-blind	10	3 months	$7,935
Acute open label	11	3 months	$8,816
Continuation	16	6 months	$6,009
Continuation	16	6 months	$11,187
Continuation	17	10 months	$11,483
Long-term safety	8	3 years	$2,307

**Sponsors typically plan for 10-15 enrolled subjects per site, with competitive enrollment.*

Enrollment

- Sufficient n
  - To become proficient with the protocol (≥3)
  - To cover costs (typically ≥5)
- Time allotted for recruitment
  - Often 1-2 years for multi-site studies
  - SPRITES: 2 years for 900 patients (38 patients per month)
- Competitive enrollment
- Recruitment methods
  - Clinical referrals
  - Media advertising

Payment Schedule

- Depends on type of budget
- Initial start-up costs
  - IRB or other regulatory fees
  - Often provide payment advance (e.g., 10% of total budget)
- Subsequent payments are triggered by CRF completion
  - Monitored patients or patients submitted to data management
  - Queries resolved
- Payment may be made after a certain number of patients are enrolled (e.g. after every 5 patients) or at set intervals (monthly or quarterly)
- Payments may be made 10-15% withheld by sponsor until study completion, upon query resolution and database lock

Regulatory Aspects

- Training
  - Good Clinical Practices (GCP), Human Subjects Protection (HSP), HIPAA
  - Rater training (qualifications)
- Central vs. local IRB
- Contract negotiations
- Conflict of interest, financial disclosures

Study

Ongoing Recruitment and Patient Management

- Ongoing Recruitment
  - Initial and ongoing education of the physician, residents and fellows
  - Central Advertising (radio, television, print)
- Patient Management
  - Study visits (frequency, missed visits)
  - Study coordinator role
  - Adverse events assessment

Source Documentation and Drug Accountability

- Source Documentation
  - Symptom change
  - CC medications
  - SAE and AE documentation
- Drug Accountability
  - Pharmacy role
  - Compliance (pill count)
  - Dispensing medication
  - Returning medications
  - Documentation

Monitor Visits

- Typically, sponsors require that first monitoring visit be conducted within 1-2 weeks of enrollment of the first subject
- Frequency of monitoring visits is determined by sponsor
- Ongoing monitoring visits (e.g., every 6-8 weeks)
- Study coordinator should be available to the monitor throughout the visit, PI should be available for check-in.

Ongoing Regulatory Aspects

- Continuing reviews
- Protocol changes
- MedWatch reports

Post-Study

- Queries
- Final payment
- Final regulatory aspects
- Publication policy
- Audits
- Record Retention

Conclusions

- Highly structured protocols and procedures, with frequent monitoring and regulatory oversight
- Require detailed source documentation
- Provide opportunity for junior investigators and staff to receive excellent training