Investigator Initiated Trials

Administrative Considerations for Successful Study Start-Up

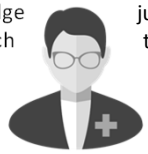
Presented by Liz Christianson & David Russell

Session Highlights

- Protocol Development - Effect on Billing Strategy and Budget
- Applying for Industry Sponsorship
- Sponsorship Regulatory Requirements
- IIT Timeline

Preliminary Considerations

Large number of new PIs/resident MDs with minimal knowledge of clinical research administration

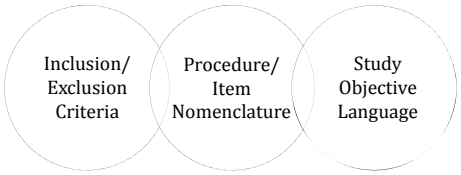


85% of investigators have participated in just 1 clinical trial throughout their career[1]

1. Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. Washington (DC): National Academies Press (US); 2010. 2, The State of Clinical Research in the United States: An Overview.

Interventional vs. Observational Intent Strongly Affects Billing

Focus Areas of the Protocol:



Key Terms

- **Observational studies:** The investigator makes no intervention and patients are allocated treatment based on ***clinical decisions***[1]
- **Interventional studies:** Participants are ***assigned*** to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes[2]

1. Thadhani R. Formal trials versus observational studies. In: Mehta A, Beck M, Sunder-Plassmann G, editors. Fabry Disease: Perspectives from 5 Years of FOS. Oxford: Oxford PharmaGenesis; 2006. Chapter 14. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11597/
2. "Glossary of Common Site Terms." *Glossary of Common Site Terms - ClinicalTrials.gov*. N.p., n.d. Web. 26 Mar. 2017.

Key Terms

- **Coverage Analysis:**
  - A breakdown of the study calendar
  - Shows each protocol required visit and activities at each visit
  - Includes analysis for why the patient should or should not be billed for each protocol required item or service
  - Can/should be used to develop and access study budget and finances

Inclusion / Exclusion Criteria

Observational	Interventional
…have been scheduled to undergo femoral stent placement procedure using SuperStent • Patient specific med notes used for billing justification	…have stenotic, restenotic, or occluded lesion(s) located in the native superficial femoral artery and a Rutherford Clinical Category Score of 3-5 • More detailed inclusion/exclusion criteria will make applying all billing rules easier • Inclusion/exclusion criteria can serve as a med note for all

Procedure / Item Nomenclature

Observational	Interventional
Angiographic data from stent placement	Angiography

Study Objective Language

What is the PI's true intent?

Observational	Interventional
Treat with routine care, then collect patient data	Assign patients to specific treatment groups
Standard billing = billing based on normal, non-research care and policies	Research billing = billing determined before the patient enrolls in the study

Case Scenario 1: Objective Language Modification

- Dr. Payne and Dr. Hurtz both perform stent placement procedures
- Dr. Payne typically prescribes Plavix post-surgery management, but Dr. Hurtz suggests Effient post-surgery
- They intend to collaborate on a study in order to figure out whose standard of care achieves better results and poses minimal risk

Case Scenario 1: Objective Language Implying Intervention

"To assess the efficacy of Plavix versus Effient in reducing thrombolytic events in patients following stent placement"

Case Scenario 1: Assuming Interventional Intent

- The protocol requires coagulation testing (PTT and PT/INR) at screening, discharge, 30 day follow-up, 60 day follow-up and 90 day follow-up

Case Scenario 1: Analysis

Item and Services	Protocol Location	CPT /HCPCS Codes	QI/QII Modifiers	Screening	Stent Placement Procedure	Discharge	30 Day Follow Up	60 Day Follow Up	90 Day Follow Up	Comments
PT/INR	Prot. P. 6	85610	Q1 or No	SOC		SOC	R	R	R	According to NCD 190.17, "PT may be used to assess the risk of developing or thrombosis in patients who are going to have a medical intervention which could be associated with increased risk of bleeding or thrombosis" (NCD 190.17). PT at screening and discharge are reasonable and necessary/routine clinical management of the patient. Coverage is governed by NCD 190.17. According to NCD 190.17, "when testing is performed to evaluate a patient with signs or symptoms of abnormal bleeding or thrombosis and the initial result is normal, it is ordinarily not necessary to repeat testing unless there is a change in the patient's medical status." Following discharge, this assumption cannot be made for all patients so PT/INR at follow-up visits after discharge are not reasonable. Coverage limited by NCD 190.17.
PTT	Prot. P. 6	85730	Q1 or No	SOC		SOC	R	R	R	According to NCD 190.16, "[PTT test may be used to] assess the risk of developing a thrombosis in patients who are going to have a medical intervention which could be associated with increased risk of bleeding or thrombosis" (NCD 190.17). PTT at screening and discharge are reasonable and necessary/routine clinical management of the patient. Coverage is governed by NCD 190.16. According to NCD 190.16, "when testing is performed to evaluate a patient with signs or symptoms of abnormal bleeding or thrombosis and the initial result is normal, it is ordinarily not necessary to repeat testing unless there is a change in the patient's medical status." Following discharge, this assumption cannot be made for all patients so PTT at follow-up visits after discharge are not reasonable. Coverage limited by NCD 190.16.

Case Scenario 1: Assuming Interventional Intent

- The site intends to enroll 20 patients over the course of this study
- PT/INR =$17
- PTT=$25
- Venipuncture =$10
- Budgetary impact due to interventional status= ($17+$25+$10)/visit x 3 visits/patient x 20 patients/study **= - $3,120**

Case Scenario 1: Objective Language Implying Observation

"To compare the frequency of thrombolytic events in patients prescribed Plavix to patients prescribed Effient following stent placement."

Suggestions for Success

- Administrators:
  - Required PI education prior to any research endeavors
    - Sessions put on by CTO or workshops from outside experts
  - Tailor protocol submission form
    - Include more examples, links to video explanations and helpline phone

Suggestions for Success

- PIs:
  1. Understand ramifications of inaccuracy
  2. Learn enough to recognize when you need help
  3. Seek help (offer a service to the PIs- this will help build the relationship with the PI for other studies down the road and in turn help build the department)

Part 2

INDUSTRY FUNDING

Applying for Industry Funding

- Large pharmaceutical companies offer funding through IIT sponsorship programs
- To be considered, study objectives should align with the sponsor's areas of interest

IIT Sponsorship Program Links

- Sanofi
  - http://www.sanofi.us/l/us/en/layout.jsp?scat=0E0D4D31-992C-46B3-A65B-7FFD4CDFFC8F
- Pfizer
  - http://www.pfizer.com/research/rd_partnering/investigator_initiated_research
- Merck
  - http://merckresearch.net/misp.html
- Bristol-Myers Squibb
  - http://www.bms.com/clinical_trials/investigator_sponsored_research/Pages/default.aspx

Case Scenario 2: Industry Funding

- PI sees many patients with PD-L1 expressing tumors
- Pembrolizumab is approved for many kinds of PD-L1 expressing cancers but not all
- The PI thinks pembrolizumab could be effective in a certain patient class for which the drug is not yet FDA approved
- The PI applied for an IND and was approved, making pembrolizumab the investigational item for the IIT
- Under these circumstances, pembrolizumab cannot be billed to the patient

Case Scenario 2: Industry Funding

- A typical regimen of pembrolizumab consists of ~150mg every 3 week cycle for about 24 cycles
- The PI plans to enroll 10 patients
- $ 6,474/dose x 24 doses/patient x 10 patients/study = **$1,553,760 DEFICIT**

Case Scenario 2: Industry Funding

- The investigator was on the ball and recognized that Merck could benefit greatly by expanding pembrolizumab's appropriate patient class and also by exposure with non-biased data.
- This PI applied for drug provision through Merck's Investigator Studies Program and saved the site and patients… **= $1,553,760**

Anti-Kickback Statute

- Always look at payment to assure there is no violation with the Anti-Kickback Statute

Any remuneration from a manufacturer provided to a purchaser that is expressly or impliedly related to a sale potentially implicates the anti-kickback statute and should be carefully reviewed. To reduce risk, manufacturers should insulate research grant making from sales and marketing influences.

Source: OIG Pharma Compliance Guidance – 68 Fed. Reg. 23736

Part 3

FINAL RULE

Final Rule Effective Dates

Final Rule effective date: January 18, 2017

Final Rule compliance date: April 18, 2017 (90 days after Effective Date)

- Responsible party has until April 18, 2017 to come into compliance with Final Rule requirements

Do I use the Final Rule or Original Statute?

- **Registration information** determined by Study Start Date
  - Study Start Date on or after January 18, 2017: **FINAL RULE**
  - Study Start Date before January 18, 2017: **STATUTE**
- **Results information** determined by Primary Completion Date
  - Primary Completion Date on or after January 18, 2017: **FINAL RULE**
  - Primary Completion Date before January 18, 2017: **STATUTE**

Final Rule, Section IV.F. Table on Applicability of Requirements in 42 CFR 11
Final Rule Webinar Series – ClinicalTrials.gov

Key Definitions

- "Study Start Date" Definition (42 CFR 11.10(b)(16))
  - **Estimated date** on which the clinical trial will be open for recruitment of human subjects, **or**
  - **Actual date** on which the first human **subject was enrolled**
- "Enroll or Enrolled" Definition (42 CFR 11.10(a))
  - A human subject's, or their legally authorized representative's, **agreement to participate** in a clinical trial following **completion of the informed consent process**, as required in 21 CFR Part 50 and/or 45 CFR Part 46, as applicable.
  - Potential subjects who are **screened for the purpose of determining eligibility** for a trial, but **do not participate in the trial**, are **not considered enrolled**, unless otherwise specified by the protocol.

Final Rule, Section IV.A.5. What definitions apply to this part? - § 11.10
Final Rule Webinar Series – ClinicalTrials.gov

Key Definitions

- "Primary Completion Date" (PCD) (42 CFR 11.10(a) and (b)(17))
  - Date the **final subject was examined or received an intervention** for the purposes of final collection of data for the primary outcome
  - If multiple primary outcome measures, the date on which **data collection is completed for all of the primary outcomes**
  - Estimated date updated to **actual primary completion date**

Final Rule, Section IV.A.5. What definitions apply to this part? - § 11.10
Final Rule Webinar Series – ClinicalTrials.gov

Applicable Clinical Trial

- "Defined in 42 CFR 11.10
- "Applicable drug clinical trial" and "applicable device clinical trial", for example:
  - "a **controlled clinical investigation**, other than a phase 1 clinical investigation, of a **drug product**… or a **biological product** subject to Food and Drug Administration (FDA) regulation"

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

General NCT Number Requirements

- All Applicable Clinical Trials must be registered on clinicaltrials.gov to receive a unique NCT #
- NCT # is required on the claim to CMS when billing routine costs of a clinical trial
- The use of NCT999999 is no longer allowed

Selected Changes Made by Final Rule

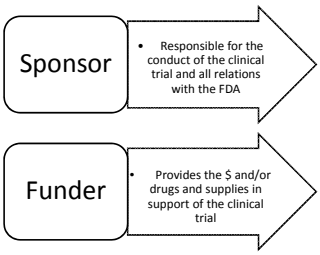
1. Additional data elements are required for **registration and results information** submission
2. Results information is required for **ALL applicable clinical trials** that are required to register
3. An expanded access record is required if an investigational drug product studied in an applicable drug clinical trial is **available through an expanded access program**
4. Some data elements must be updated **more frequently** than the standard 12 months
5. Responsible parties can evaluate whether a clinical trial is an applicable clinical trial (ACT) based on **required registration data elements**
6. Corrections to submitted information will be required within **15 days** (for registration information) and **25 days** (for results information)

For complete list and further definitions: https://prsinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf

WHO?

"Sponsor" ≠ "Funder"

- It's essential to make the distinction between the study's financial funder and the study's true sponsor
- With industry studies, sponsor and funder are often the same party. In IIT studies they often are not



Every Applicable Trial Needs a Sponsor

- Determining who is the sponsor:
  - For clinical trials conducted under an investigational new drug application (IND), or an investigational device exemption (IDE), the holder of the IND or IDE holder is considered the sponsor.
  - For clinical trials that are not conducted under an IND or IDE, whomever is the person or entity that initiates the trial by preparing and/or planning the trial, and who has authority and control over the trial, is considered the sponsor.

Source: 42 CFR 11.4(c)(1)

Responsible Party

- Each applicable clinical trial or other clinical trial must have one (and only one) responsible party
- The sponsor of the clinical trial will be considered the responsible party unless and until a principal investigator has been designated the responsible party

Designating PI as the Responsible Party

The sponsor *may* designate a principal investigator as the responsible party if such principal investigator meets all of the following requirements:

(A) Is responsible for conducting the trial;
(B) Has access to and control over the data from the trial;
(C) Has the right to publish the results of the trial; and
(D) Has the ability to meet all of the requirements for submitting and updating clinical trial information as specified in this part.

Source: 42 CFR 11.4(c)(2)

New Responsible Party Requirements

- Per 42 CFR Part 11, the responsible party for an applicable clinical trial (ACT) must:
  - Register the ACT on ClinicalTrials.gov no later than 21 days after enrollment of the first participant;
  - Update the ACT on ClinicalTrials.gov at least once every 12 months with some items requiring update within 15 or 30 days of a change (e.g., Recruitment Status, Primary Completion Date within 30 days)
  - Submit summary results (including adverse event information) not later than 1 year after the trial's Primary Completion Date, with delays allowed in some circumstances

Some Regulatory Sponsorship Tasks

- For IDE and IND's:
  - Maintain the IDE or IND (if applicable) per requirements
  - Form 1572 Statement of the Investigator
  - Form FDA 3674
  - IND and IDE safety reports if applicable
  - An investigator brochure (IB) if there is not one already available for the same drug or device under a separate IND or IDE
  - Maintain drug or device accountability for all investigational product
  - IND or IDE annual reports to the FDA

Some Regulatory Sponsorship Tasks

- Study monitoring -21 CFR Part 213 Subpart D
  - Delegation of Authority forms
  - AE logs
  - Financial Disclosure forms
  - Records of drug receipts, shipments, disposition and destruction
  - CRF completion and record retention for at least 2 years after marketing approval of the drug
  - SAE reports
  - IRB notifications regarding changes in risk
  - Final Trial Report form to the FDA- Title VIII of the Final Rule

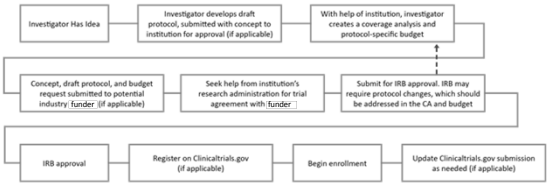
Creating Source Documents

- When creating source documents, use the FDA ALCOA Rule
- ALCOA:
  - **Attributable**: You need to be able to trace back to subject, date and visit
  - **Legible**: It needs to be clear enough to read
  - **Contemporaneous**: Data needs to be recorded as it happens.
  - **Original**: Assure it is not a copy
  - **Accurate**: All of the data is correct

Part 4

PUTTING IT ALL TOGETHER

Model for Attack



Commonly Forgotten Considerations

- Assure a thorough statistical analysis is done on the FRONT END. Know what the power (sample size) needs to be in order to achieve your trial goals.
- Create a detailed oversight plan for the trial. This should include assuring validity of your data, the conduct of the study, and patient safety.

Takeaway Checklist for IIT Studies

- Clearly define study status in the written protocol
  - Objective statement
  - Inclusion/Exclusion criteria
  - Procedure nomenclature
- Complete coverage analysis using proper billing strategy
- Build study budget
- Apply for outside funding if needed and appropriate

Takeaway Checklist for IIT Studies

- Do plenty of up-front protocol development and assure proper statistical analysis can be done
- Expect IRB requested changes
- Work closely with your institution's research administration throughout the entire process
- Register on clinicaltrials.gov if applicable

Why Participate in IITs?

- Stimulate lucrative partnerships with Industry Sponsors → Create industry trial opportunities
  - Industry sponsors looking for IITs to provide additional transparent data for their products
- Support your PI's initiatives and interests
- Support the transition of novel therapies to standard practice

Questions? Contact Us

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