Tufts Clinical and Translational Science Institute

Demystifying Cancer Clinical Trials

Clinical Trials
From PI-Initiated to Collaborative Research

February 10, 2017

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Team Science & Engaging with Industry

Andrew Evans, DO, MSc

Director, Tufts Cancer Center
Chief, Division of Hematology/Oncology
Director, Lymphoma Program
Professor, Tufts University School of Medicine

Robert E. Martell, MD, PhD

Medical Oncologist
Tufts Medical Center
Associate Professor
Tufts University School of Medicine

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Team Science (Collaboration): In Academics, Clinical Research, and Grants

Dr. Andy Evens

Team Science/Collaborations: AGENDA

- Cultivating Collaborations/Team Science 101
- Team Science in Clinical Studies
- Team Science in Grants

Why Do I Want a Collaborator?

- I can't do/know everything myself
  - Both clinical medicine and basic science are becoming increasingly complex and separated by an increasing chasm[1]
- More meaningful clinical trials
  - Clinical research is perceived as poorer quality than basic science[2]
  - More efficient use of funding/dollars[3]
- Access to different funding sources
  - E.g., NIH, Foundations

1. Portilla. Sci Transl Med 2010;2
2. Campbell. JAMA 2001; 286(7):800
3. McCammon. Sci Tranl Med 2012;4

Collaborations Pearls

- Very difficult to do it alone
- Utilize different avenues to find/establish collaborations (e.g., ASH/ASCO, Cooperative Groups, Small venues/meetings)
- Try find a scientist and/or pathologist to collaborate with
- Don’t always expect 1st author

Barriers to Collaboration[1]

- Infrastructure
  - Limited access to qualified investigators
  - Limited access to technology
- Resources
  - Increased costs/share revenue
  - Limited funding (not supported by industry)
- Academic culture
  - Authorship
  - Intellectual property (industry partners)
  - Time sink
  - Loss of focus
- Regulatory impediments
  - Within academic institutions
  - From industry (IP issues)

Pober. FASEB 2001;15

Where Can I Find a Collaborator?

- Collaborators within the institution
- Collaborators at other academic institutions
  - Including International
- Collaborators in industry/pharma
- Collaborations with community oncology!

Collaborations within the Institution

- Advantages
  - Proximity
  - Better revenue/resource sharing
- Disadvantages
  - Limited selection of investigators/technologies
  - Hard feelings if things don’t work out or collaborators don’t fulfill commitments

Lessons I learned: Finding a collaborator

- Volume and diversity are important
  - Get used to writing study concepts quickly and frequently.
- Find someone you'd like to work with and then find a shared goal
  - seems a backwards, but it may be the more realistic strategy
- Decide what you want to do and then find a collaborator
  - You might get lucky and find someone doing exactly what you need help with
- Offer your services as a collaborator
  - Translational/lab people are often looking for clinical collaborators but aren't sure where to find them
- Attend other peoples meetings
  - Meet as many people as you can and get to know what they like

Lessons I learned: Maintaining a collaboration

- If something (project/relationship) is working, keep working on it
  - If you don't really like it, stop
- What do you bring to the collaboration?
  - Data? Samples? Clinical perspective?
  - Be a gatekeeper to something
- Don't just be the delivery guy/girl
  - Try to contribute something to the project
- Time
  - Be prepared to carve out a large piece of time; regular, in person meetings are important
- Define roles
  - Agree on action plans

Collaborations with Other Institutions

- Advantages
  - More likely to find someone in your field
  - Increase sample size
  - Increase validity coming from multicenter study
- Disadvantages
  - Less in-person communication
  - Cost/revenue sharing
  - Challenges convincing funding agencies of successful collaboration

Examples of collaborations with other institutions

CLINICAL TRIALS AND OBSERVATIONS

Brief report

A retrospective multicenter analysis of elderly Hodgkin lymphoma: outcomes and prognostic factors in the modern era

Andrew M. Evens,[1] Irene Helenowski,[2] Erika Ramsdale,[3] Chadi Nabhan,[4] Reem Karmali,[5] Britt Hanson,[6] Benjamin Parsons,[4] Scott Smith,[6] Annette Larsen,[1] June M. McKoy,[7] Borko Jovanovic,[2] Stephanie Gregory,[6] Leo I. Gordon,[8] and Sonali M. Smith[3]

[1]Division of Hematology/Oncology, University of Massachusetts Medical School, Worcester, MA; [2]Department of Preventive Medicine, Northwestern University, Chicago, IL; [3]Department of Medicine, Division of Hematology/Oncology, University of Chicago Hospitals, Chicago, IL; [4]Department of Medicine, Division of Hematology/Oncology, Advocate Lutheran General Hospital, Park Ridge, IL; [5]Division of Hematology, Rush University Medical Center, Chicago, IL; [6]Division of Hematology/Oncology, Loyola University Medical Center, Maywood, IL; [7]Division of Geriatric Medicine, Feinberg School of Medicine, Northwestern University, Chicago,

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Multicenter Analysis of 80 Solid Organ Transplantation Recipients With Post-Transplantation Lymphoproliferative Disease: Outcomes and Prognostic Factors in the Modern Era

Andrew M. Evens, Kevin A. David, Irene Helenowski, Beverly Nelson, Dixon Kaufman, Sheetal M. Kircher, Alla Gimelfarb, Elise Hattersley, Lauren A. Mauro, Borko Jovanovic, Amy Chadburn, Patrick Stiff, Jane N. Winter, Jayesh Mehta, Koen Van Besien, Stephanie Gregory, Leo I. Gordon, Jamile M. Shammo, Scott E. Smith, and Sonali M. Smith

Examples of collaborations with other institutions

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Hypoxia-Inducible Factor-1 α Expression Predicts Superior Survival in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP

ndrew M. Evens, Laurie H. Sehn, Pedro Farinha, Beverly P. Nelson, Adekunle Raji, Yi Lu, Adam Brakman, amsi Parimi, Jane N. Winter, Paul T. Schumacker, Randy D. Gascoyne, and Leo I. Gordon

bjh research paper

Analysis of very elderly (≥80 years) non-hodgkin lymphoma: impact of functional status and co-morbidities on outcome

Chadi Nabhan,[1] Sonali M. Smith,[2] Irene Helenowski,[3] Erika Ramsdale,[2] Benjamin Parsons,[4] Reem Karmali,[5] Josephine Feliciano,[6] Britt Hanson,[4] Scott Smith,[4] June McKoy,[7] Annette Larsen,[8] Andrew Hantel,[5] Stephanie Gregory[5] and Andrew M. Evens[8]

[1]*Division of Hematology/Oncology, Department of Medicine, Advocate Lutheran General Hospital, Park Ridge,* [2]*Division of Hematology/Oncology, Department of Medicine, University of Chicago Hospitals,* [3]*Department of Preventive Medicine, Northwestern University, Chicago,* [4]*Division of Hematology/Oncology, Loyola University Medical Center, Maywood,* [5]*Division of Hematology, Rush University Medical Center,* [6]*Division of Hematology/Oncology, Northwestern University, Feinberg School of Medicine,* [7]*Division of Geriatric Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, and* [8]*Division of Hematology/Oncology, University of Massachusetts Medical School, Worcester, MA, USA*

Summary

Data on outcome, prognostic factors, and treatment for very elderly non-Hodgkin lymphomas (NHL) is sparse. We conducted a multicentre retrospective analysis of NHL patients ≥80 years (at diagnosis) treated between 1999 and 2009. Detailed characteristics were obtained including geriatric syndromes, activities of daily living (ADLs), and co-morbidities using the Cumulative Illness Rating Scale-Geriatrics (CIRS-G). We identified 303 patients: 170 aggressive NHL (84% B cell/16% T cell) and 133 indolent NHL (82% B cell/18% T cell). Median age was 84 years (80–95). A geriatric syndrome was present in 26% of patients, 18% had ≥1 grade 4 CIRS-G, and 14% had loss of ADLs. At 49-month median follow-up, 4-year progression-free (PFS) and overall survival (OS) for aggressive NHLs were 31% and 44% respectively (stage I/II: PFS 53% and OS 66%; stage III/IV: PFS 20% and OS 32%; $P < 0{\cdot}0001$ and 0·0002, respectively). Four-year PFS and OS for indolent NHL were 44% and 66% respectively, regardless of stage. Multivariate regression analysis identified two key factors that predicted inferior PFS and OS for both NHL groups: lack of CR and loss of ADLs. Prospective studies for very elderly NHL that incorporate geriatric tools, especially ADLs, are warranted.

Keywords: non-Hodgkin lymphoma, elderly, geriatric syndromes, functional status, co-morbidities.

Examples of collaborations with other institutions

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Lymphoma Occurring During Pregnancy: Antenatal Therapy, Complications, and Maternal Survival in a Multicenter Analysis

Andrew M. Evens, Ranjana Advani, Oliver W. Press, Izidore S. Lossos, Julie M. Vose, Francisco J. Hernandez-Ilizaliturri, Barrett K. Robinson, Stavroula Otis, Liat Nadav Dagan, Ramsey Abdallah, Aimee Kroll-Desrosiers, Jessica L. Yarber, Jose Sandoval, Kelley Foyil, Linda M. Parker, Leo I. Gordon, Kristie A. Blum, Christopher R. Flowers, John P. Leonard, Thomas M. Habermann, and Nancy L. Bartlett

Andrew M. Evens, Tufts University School of Medicine, Boston; Aimee Kroll-Desrosiers, University of Massachusetts Medical School, Worcester, MA; Ranjana Advani and Stavroula Otis, Stanford University Medical Center, Stanford, CA; Oliver W. Press and Linda M. Parker, Fred Hutchinson Cancer Research Center, Seattle, WA; Izidore S. Lossos, Liat Nadav Dagan, and Jose Sandoval, University of Miami School of Medicine, Miami, FL; Julie M. Vose, University of Nebraska Medical Center, Omaha, NE; Francisco J. Hernandez-Ilizaliturri, Roswell Park Cancer Institute, Buffalo; Ramsey Abdallah and John P. Leonard, Weill Cornell Medical College, New York, NY; Barrett K. Robinson, Indiana University School of Medicine, Indianapolis, IN; Jessica L. Yarber and Leo I. Gordon, Northwestern University Feinberg School of Medicine, Chicago, IL; Kristie A. Blum, The Ohio State University, Columbus, OH; Christopher R. Flowers, Emory University, Atlanta, GA; Thomas M. Habermann, Mayo Clinic, Rochester, MN; and Nancy L. Bartlett, Washington University School of Medicine, St. Louis, MO.

Published online ahead of print at www.jco.org on September 16, 2013.

Presented at the 11th International Conference on Malignant Lymphoma, Lugano, Switzerland, June 15-18, 2011, and the 53rd American Society of Hematology Annual Meeting and Exposition, San Francisco, CA, December 11-13, 2011.

A B S T R A C T

Purpose
Lymphoma is the fourth most frequent cancer in pregnancy; however, current clinical practice is based largely on small series and case reports.

Patients and Methods
In a multicenter retrospective analysis, we examined treatment, complications, and outcomes for Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) occurring during pregnancy.

Results
Among 90 patients (NHL, n = 50; HL, n = 40), median age was 30 years (range, 18 to 44 years) and median diagnosis occurred at 24 weeks gestation. Of patients with NHL, 52% had advanced-stage versus 25% of patients with HL ($P = .01$). Pregnancy was terminated in six patients. Among the other 84 patients, 28 (33%) had therapy deferred to postpartum; these patients were diagnosed at a median 30 weeks gestation. This compared with 56 patients (67%) who received antenatal therapy with median lymphoma diagnosis at 21 weeks ($P < .001$); 89% of these patients received combination chemotherapy. The most common preterm complication was induction of labor (33%). Gestation went to full term in 56% of patients with delivery occurring at a median of 37 weeks. There were no differences in maternal complications, perinatal events, or median infant birth weight based on deferred versus antenatal therapy. At 41 months, 3-year progression-free survival (PFS) and overall survival (OS) for NHL were 53% and 82%, respectively, and 85% and 97%, respectively, for HL. On univariate analysis for NHL, radiotherapy predicted inferior PFS, and increased lactate dehydrogenase and poor Eastern Cooperative Oncology Group performance status (ECOG PS) portended worse OS. For HL patients, nulliparous status and "B" symptoms predicted inferior PFS.

Conclusion
Standard (non-antimetabolite) combination chemotherapy administered past the first trimester, as early as 13 weeks gestation, was associated with few complications and expected maternal survival with lymphoma occurring during pregnancy.

J Clin Oncol 31:4132-4139.

Team Science: Clinical Research

Implementing a protocol

- Big picture
  - GCP
  - Project management
- Details
  - Protocol training
  - Data management
  - Ongoing regulatory work (IRB, DSMB, FDA)
- (S)AEs, deviations/waivers, amendments
  - Other sites?
  - Drug accountability
  - CROs/monitors (industry studies)
- Incorporation of translational/laboratory science
  - Lab manual
  - Team work

It takes a village …

- Clinical investigators
- PA/NPs
- Research nurse
- Data manager
- Regulatory manager
- Investigational drug pharmacist

YOU

- Research phlebotomist
- Budget personnel
- Statistician
- Translational scientists
- Referring physicians
- Patients

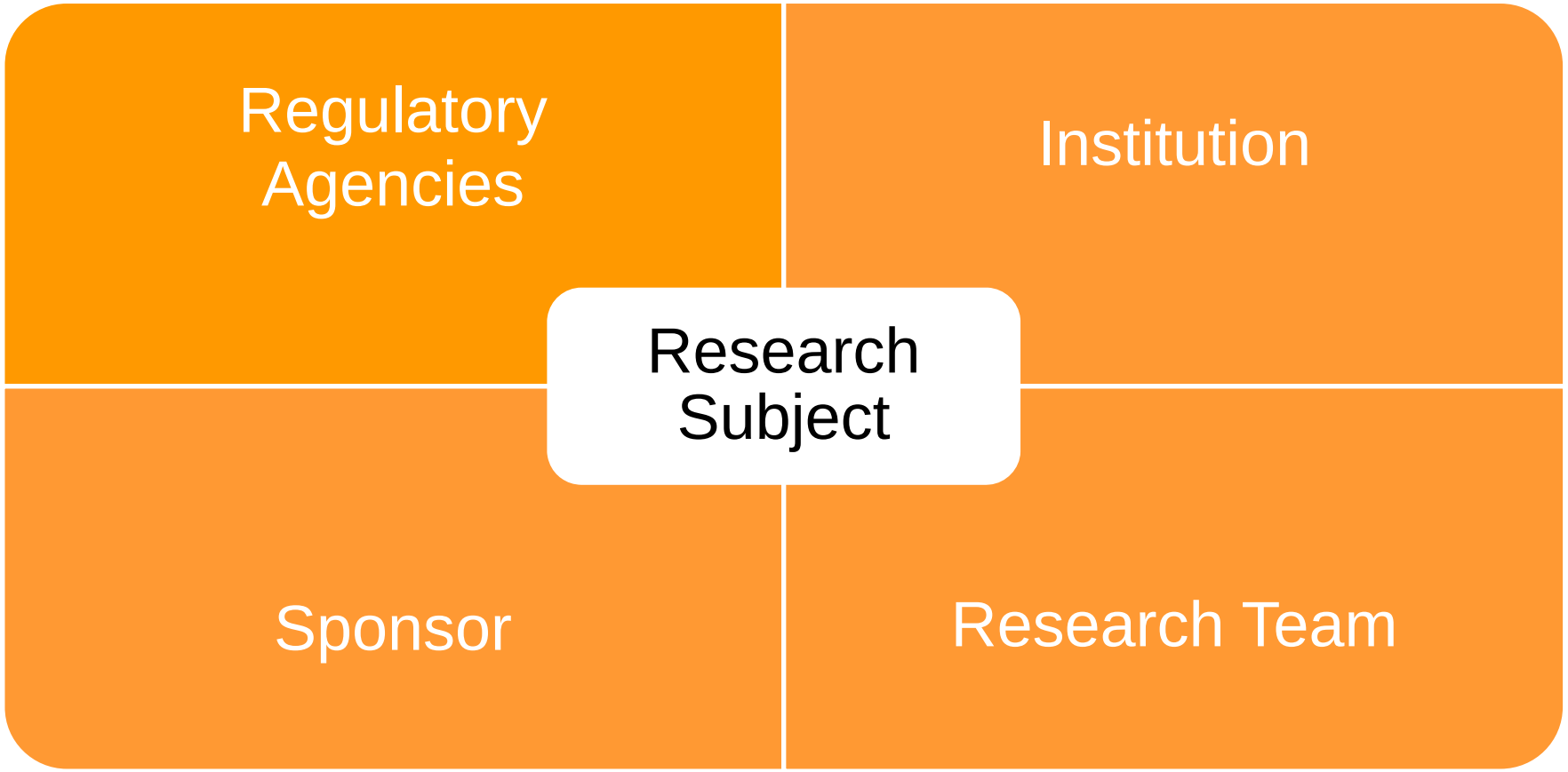
Finding the right people

- If you assemble your own team
  - Concerned about and committed to the project
  - Enthusiastic, proactive
  - Can devote time to the initiative
  - Have the right skills
- If you work with an existing team
  - Consider benchmarks
  - Give feedback often
  - Define all roles, including your own
  - Practice listening
  - Communicate effectively
  - Don’t make decisions without all the information

Teams can and do fail

- Excessive work load
- Team leaders do not control individual team members
- Inadequate resources
- Frequent changes in team makeup (RETENTION)
- Purpose of team is not clear
- Inadequate planning
- Many other reasons!

Investigator Responsibilities



Multi-site IST

- As the study sponsor/PI, you are responsible for the conduct of the study at other sites.
- Consider developing an office policy that includes the following details for all studies (all of which can be done via phone/internet):
  - Site initiation visit, monitoring plan, close out visit
- Consider developing a protocol-specific strategy for communication between sites.
  - Teleconference, group email, etc.

FDA

- The study sponsor (holder of the IND) is responsible for submitting the following to the FDA:
  - Protocol amendments
  - IND safety reports must be provided to FDA and all participating sites.
    - Mandatory reports (serious and unexpected)
    - MedWatch forms (3500A if you hold the IND)
    - Timing depends on severity (7 vs. 15 days)
    - Initial report and follow up report
  - Annual IND report
    - The FDA will not remind you
    - This keeps going as long as the protocol is open
      - E.g., upfront RIT study closed after 5 subjects but we are committed to reporting for 5 years

IRB

- The PI at each site is responsible for submitting the following to the IRB:
  - Continuing reviews – usually annually
    - Cumulative AEs (toxicity log)
    - Violations/deviations
  - Amendments
  - Updates to IB
  - Deviations/planned deviations
  - SAEs
    - Each IRB has a policy regarding SAE reporting

DSMB

- DSMB reports are defined by DSMP
- DSMP should be defined in advance and should include the following:
  - Data to be included
    - E.g., safety, efficacy, enrollment
  - Timing of submissions
  - Stopping rules
  - Which DSMB will be used
- Recommend a DSMB for all investigator-initiated (at least phase II and phase III trials)

CRO/Monitor

- CROs work for the study sponsor to ensure that the study is completed rapidly, that the protocol is followed, and that the data is accurate
- CROs provide some distance between industry and the study
- CROs are paid large sums of money and must justify their existence by doing a good job and sometimes by creating work that may not be relevant
- Despite the largely adversarial relationship, monitors are not the enemy; take time to meet them (but not too much)
- Be ready to intervene if there are issues between the monitor and the regulatory coordinator/data manager

Does all the work pay off??

Cancer Therapy: Clinical

The Novel Expanded Porphyrin, Motexafin Gadolinium, Combined with [^{90}Y]Ibritumomab Tiuxetan for Relapsed/Refractory Non-Hodgkin's Lymphoma: Preclinical Findings and Results of a Phase I Trial

Andrew M. Evens,[1] William G. Spies,[2] Irene B. Helenowski,[3] David Patton,[1] Stewart Spies,[2] Borko D. Jovanovic,[3] Sarah Miyata,[1] Elizabeth Hamilton,[1] Daina Variakojis,[4] Jun Chen,[5] Louie Naumovski,[5] Steven T. Rosen,[1] Jane N. Winter,[1] Richard A. Miller,[5] and Leo I. Gordon[1]

Team Science: Grants

Scientific Grant Opportunities

- **R01 (up to 5 years), R21 (1-2 years), and R03 (1-2 years)**
  - **R01**: Clinical Oncology (C-ONC) section ($250,000 per year in direct costs)
  - **R21**: Exploratory/Developmental Research Grant Award; no “parent” awards; combined budget for direct costs for the two year project period may not exceed $275,000 (no renewals)
  - **R03**: Pilot or feasibility studies; secondary analysis of existing data; small, self-contained research projects; development of research methodology; development of new research technology ($50,000/year)

R01: Specific Aims *(example)*

- **<u>Aim 1</u>: To investigate the lethality and mechanistic importance of suppressing MEK/ERK and downstream substrates (e.g., MCT-1) with a potent 2nd generation MEK inhibitor alone and with rational combinations in B-cell and T-cell NHL cells, *in vivo* xenografts, and tumor graft models.**
- **<u>Aim 2</u>: To determine global alterations in translation (translational profile) within B- and T-cell lymphoma cell lines and primary lymphoma samples following exposure to small molecule MEK inhibitor therapy alone and in combination, compared with shRNA MCT-1 and MEK-2 KO's.**
- **<u>Aim 3</u>: To complete a phase II clinical trial for patients with relapsed/refractory DLBCL using single-agent AZD6244 Hydrogen-Sulfate formulation anti-MEK therapy to determine clinical efficacy and investigate novel biomarkers of resistance and response (*clinicaltrials.gov* NCT01278615).**

Scientific Grant Opportunities (cont)

- **R41/42: Small Business Technology Transfer (STTR) or R43/44: Small Business Innovative Research (SBIR)**
  - **Assists small business and research communities in commercializing innovative technologies**
  - **Three-phase structure:**
    - I - Feasibility study to establish scientific/technical merit of the proposed R/R&D efforts (generally, 1 year; $150,000)
    - II - Full R/R&D efforts initiated in Phase I (generally 2 years; $1,000,000)
    - III- Commercialization stage (cannot use STTR funds)

Scientific Grant Opportunities (cont)

- **DoD**
- **VA Merit (Hematology Section)**
- **National Heart Lung and Blood Institute (NHLBI), AHA, DoE, etc**
- **FDA Orphan Drugs (OOPD)**
  - E.g., Phase 1 Study of Umbilical Cord Blood Derived CD19 Specific T cell Therapy in the Treatment of Advanced B Cell Malignancies—$600,000 over three years (MDACC)

“Team” Grants

- **P01 (Program Projects)**
- **U01 (Consortiums)**
- **SPORE (Specialized Program of Research Excellence)**
- **Specialized Center of Research (SCOR) program (Leukemia and Lymphoma)**

Niche Grant Opportunities

- **Institutional (esp. CTSIs and Cancer Centers)**
- **Patient-Centered Outcomes Research Institute (PCORI)**
- **Industry grants (usually Ad Hoc and more scientific- lab or correlative studies)**

Summary

- Finding and cultivating collaborators/teams takes time and persistence
- Teams take many forms (clinicians, stats, pathologists, lab scientists, industry, etc)
- Leverage team science for: retrospective projects, clinical trials, grants, etc
- Maintaining collaborations takes insight, work, and leadership (esp. clin. Trials)
- All for one and one for all!

QUESTIONS?

Team Science and Engaging with Industry

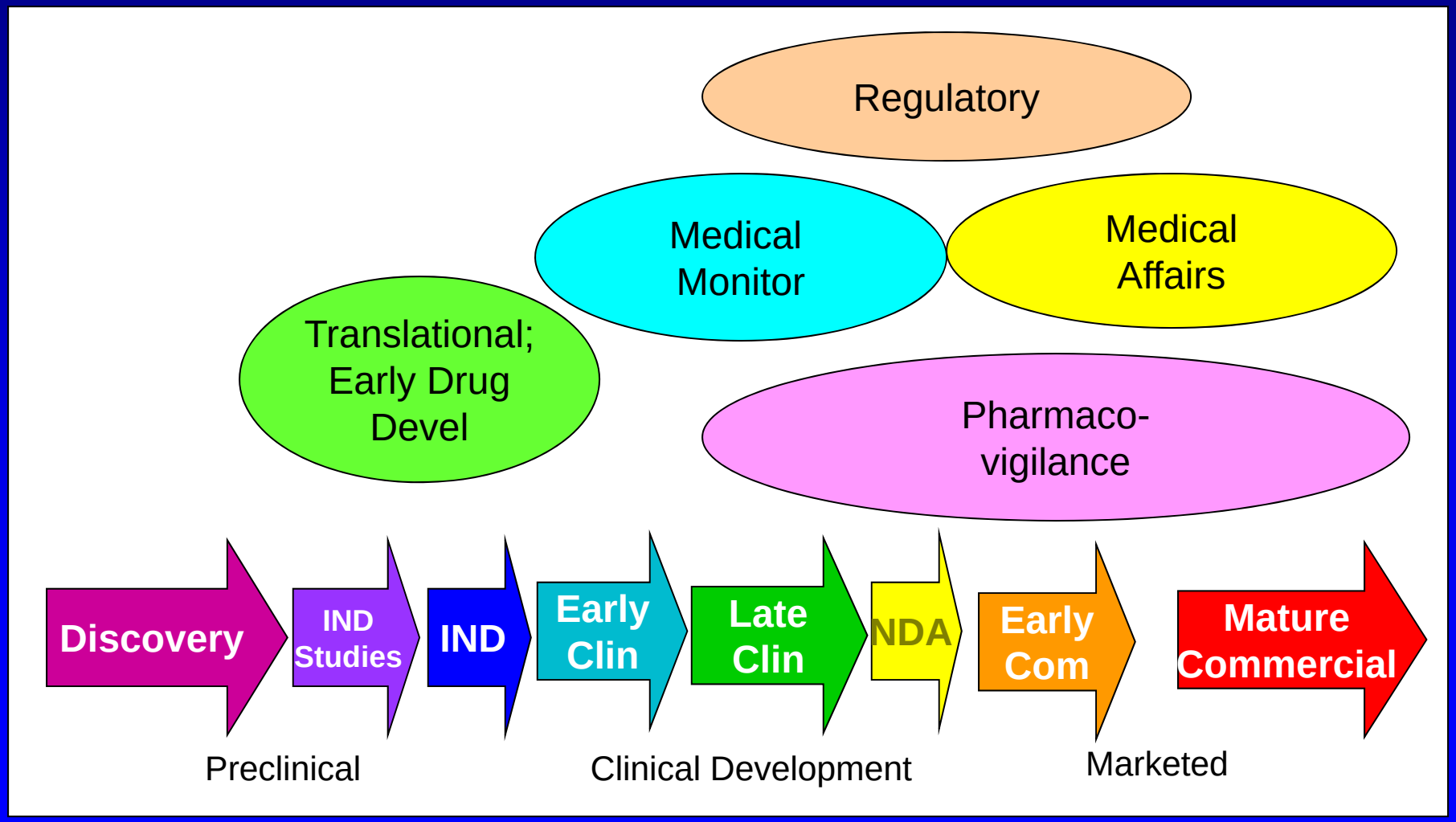
Robert Martell, MD, PhD

Tufts Medical Center

Ecosystem of Company-Run Studies

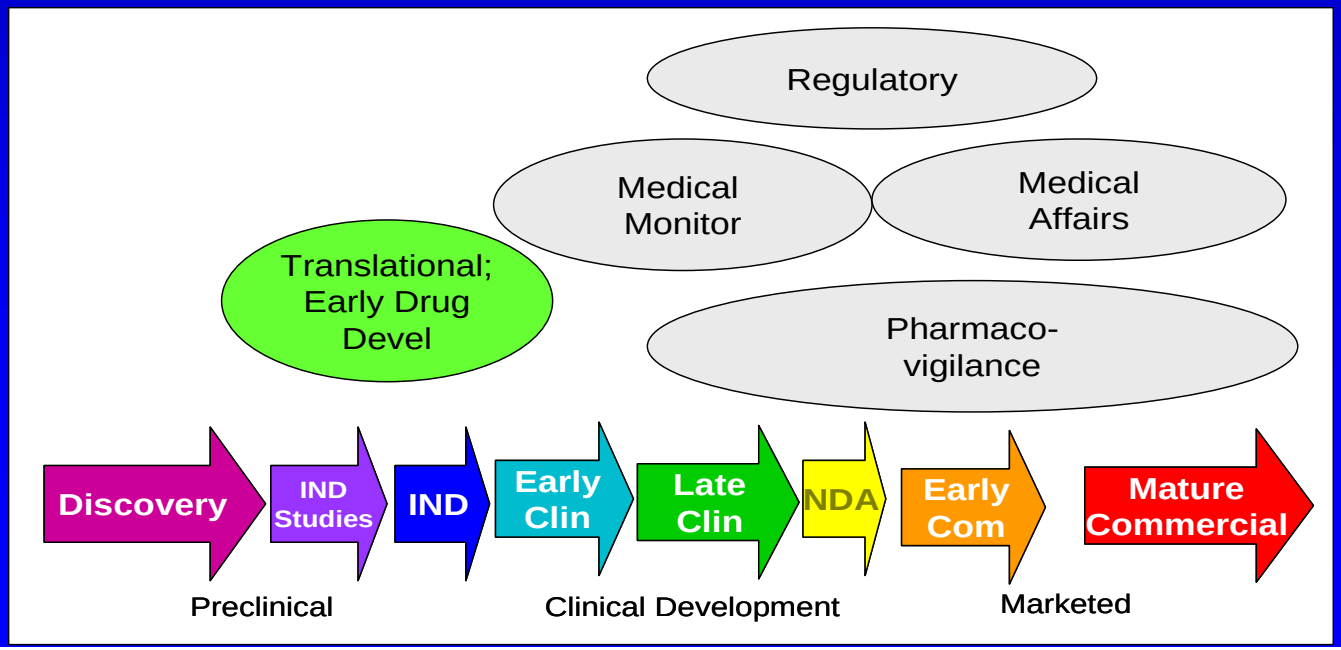
Academic	Company	CRO #1	CRO #2
Lead Investigators	Clinical Strategy	Medical Monitor	Pharmacovigilance
Investigators	Biostatistics	Clinical Operations	Imaging
Scientists	Biology		ECG
	Regulatory		
	Clinical Pharmacology		
	Medical Monitor		
	Clinical Operations		
	Pharmacovigilance		
	Data Management		
	Medical Affairs		
	Commercial		

Physicians in the Pharmaceutical Industry



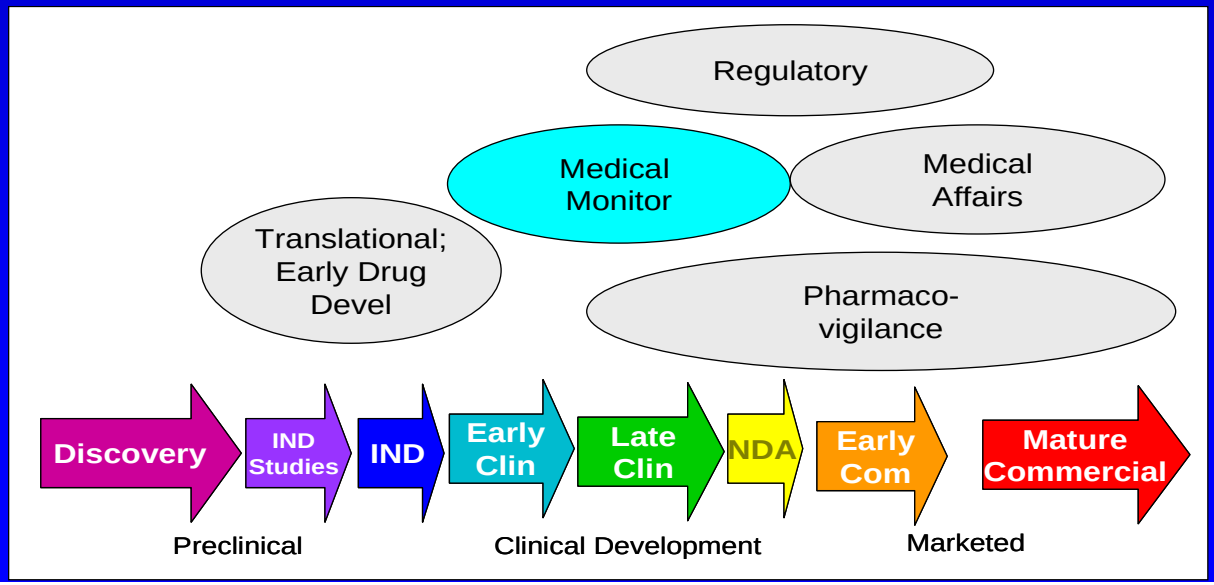
Translational/Early Drug Development Physician

- Identify targets and develop assays
- Develop biomarker assays and strategies
- Design/implement phase 1 studies
- Monitor safety



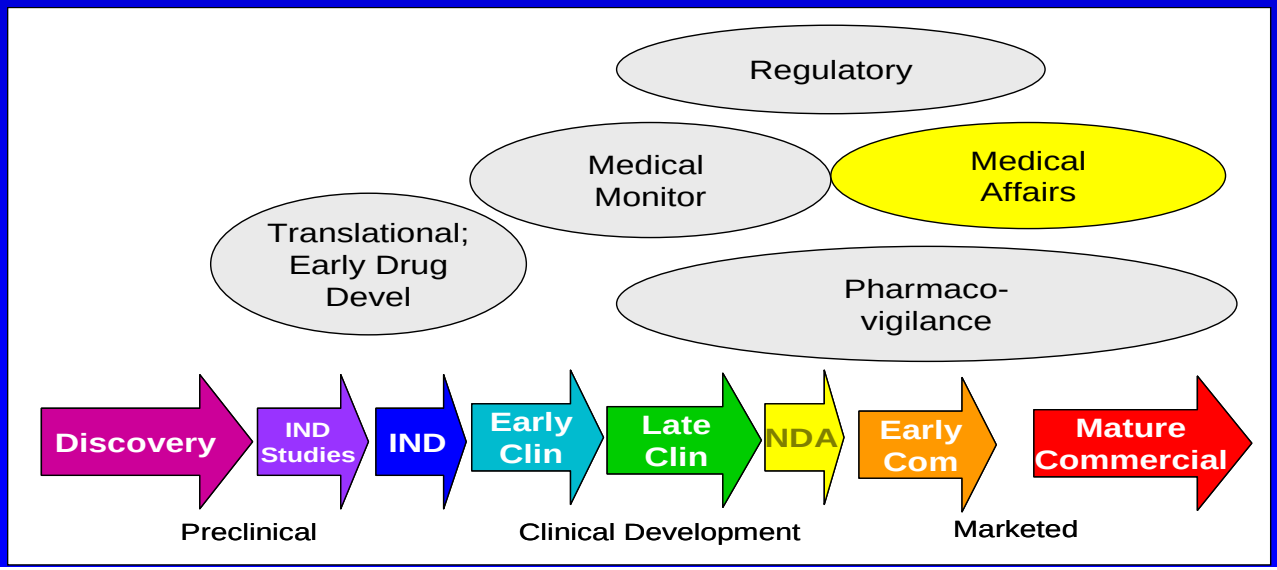
Medical Monitor

- Design & implement phase I-III studies
- Work closely with investigators
- Monitor safety
- Clinical development strategy



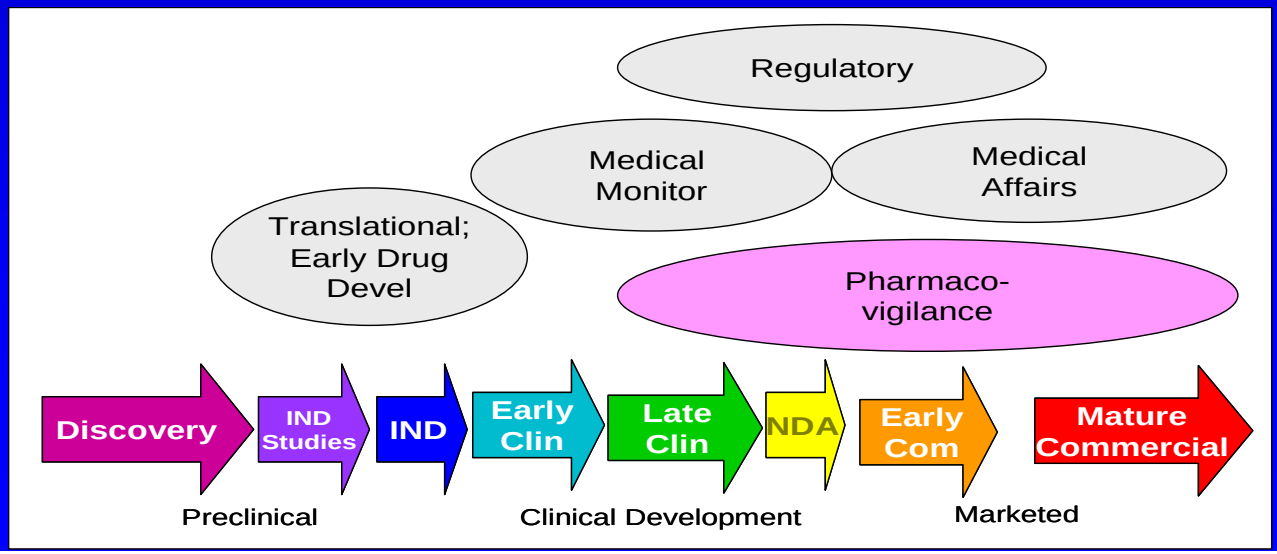
Medical Affairs

- Work with Investigators to design & implement studies to expand label
- Develop physician and investigator relationships geared to better utilization of a drug
- Ensure marketing material is appropriate



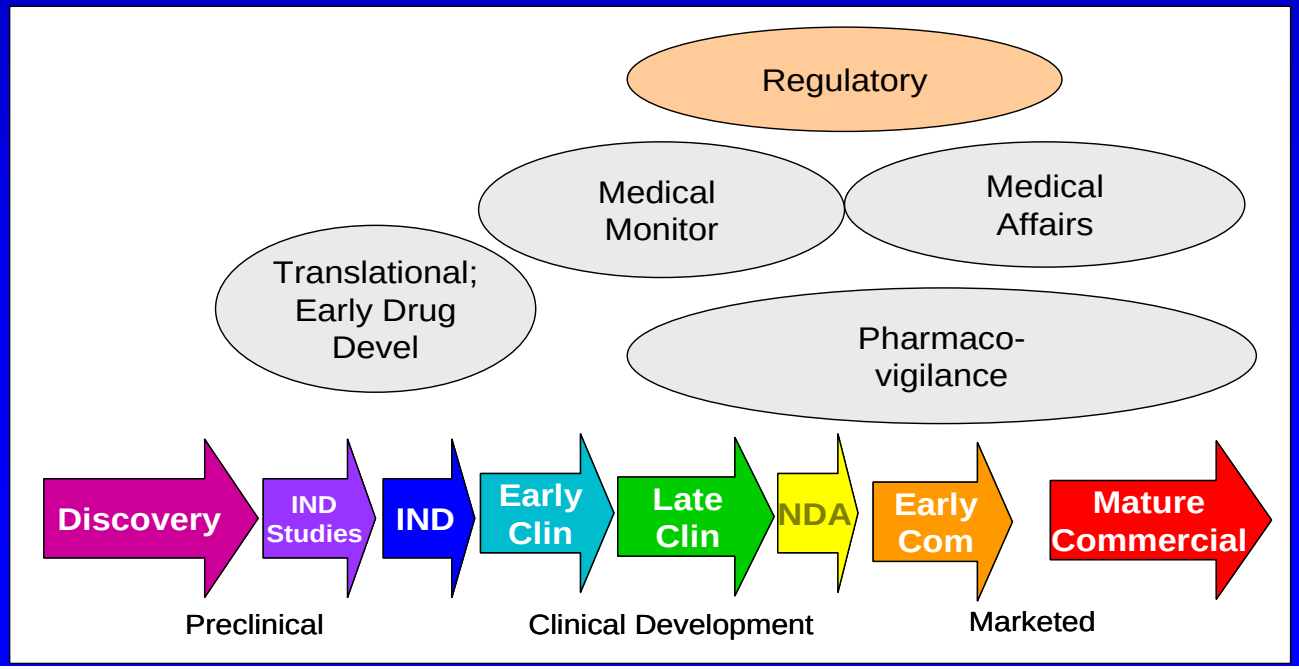
Pharmacovigilance

- Monitor safety events and aggregate safety data
- Ensure appropriate regulatory reporting
- Implement appropriate safety controls
- Assess signals relative to known data



Regulatory Physician

- Prepare regulatory documents
- Advise on FDA/EMA processes and precedents
- Develop registrational strategy
- Interact with regulatory authorities



Navigating Pharma to Gain Access to Novel Molecules

- Before reaching out
  - Develop thorough understanding of the molecule, including MOA, PD, PK
  - Develop concept: creative, compelling, but also **rational** and **practical**
    - » Identify an indication not yet pursued
    - » FDA approvable indication; Map studies required
    - » Include correlative studies (identify collaborator)
  - Organize data you (or others) have with related molecules and relevant assays
  - Consider what needed
    - » Amount of drug needed for clinical study (and/or preclinical studies)
    - » Budget
      - Drug only
      - Drug + <$100k (or $5k/patient)
      - Drug + $30k per patient
    - » Investigator IND (vs Company IND)

Navigating Pharma to Gain Access to Novel Molecules (cont.)

- General Principles
  - Lack of responsiveness from one person doesn't mean lack of interest from company
  - The company can't guide you
- Network within company
  - **Medical Affairs:** Local representative, Physician, Head of Med Affairs
  - **Development:** Clinical Strategy, Head of Medical Development, Medical Director
  - **Non-Clinical:** Biology lead, Scientist
  - **Commercial:** Sales rep
  - **Corporate Leaders:** CEO, CMO, President

Thank You

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Food and Drug Administration (FDA)

Andreas Klein, MD

Director, Hematologic Malignancies Program
Assistant Director, Bone Marrow and Hematopoietic Cell Transplant Program
Chair, Tufts Health Sciences Campus Institutional Review Boards
Associate Professor, Tufts University School of Medicine

Robert E. Martell, MD, PhD

Medical Oncologist
Tufts Medical Center
Associate Professor
Tufts University School of Medicine

Tufts | CTSI
Tufts Clinical and Translational Science Institute

FDA

Robert Martell, MD, PhD
Tufts Medical Center

IND (Investigational New Drug)

- Request for authorization from the FDA to administer an investigational drug or biological product to humans
  - Once IND is open clinical testing can be done
  - All treatment of people prior to FDA approval is done under an IND; after approval, research continues to be done under an IND
  - Single patient or compassionate use IND
- Includes
  - Animal study data and toxicity data
  - Manufacturing information
  - Clinical protocols
  - Data from any prior human research
  - Information about the investigator
- FDA review
  - 30 days to review
    - » Approval to begin clinical trials.
    - » Clinical hold to delay or stop the investigation
      - Participants are exposed to unreasonable or significant risk.
      - Investigators are not qualified.
      - Materials for the volunteer participants are misleading.
      - The IND application does not include enough information about the trial's risks.
  - While IND open, the developer must provide the FDA new protocols, safety updates and real-time information on serious side effects. When trial is complete, study reports must be submitted.

NDA (New Drug Application)
BLA (Biologics Licensign Application)

- The purpose is to demonstrate that a drug is safe and effective for its intended use
- Includes
  - Everything about a drug—from preclinical data to Phase 3 trial data—in an NDA. Developers must include reports on all studies, data, and analyses. Along with clinical results, developers must include:
  - Proposed labeling
  - Safety updates
  - Drug abuse information
  - Patent information
  - Information from studies conducted outside the United States
  - Institutional review board compliance information
  - Directions for use
- **FDA Review**
  - Accept or refuse the application within 60 days (eg if incomplete)
  - Team has 6 to 10 months to make a decision on whether to approve the drug
    - » Full review of each section by specialist (eg medical officer, statistician, pharmacologist
    - » FDA inspectors travel to clinical study sites to conduct a routine inspection. The Agency looks for evidence of fabrication, manipulation, or withholding of data.
    - » The review team issues a recommendation, and a senior FDA official makes a decision.
- **FDA Advisory Committee**
  - If questions arise that require independent expert advice, an Advisory Committee (eg ODAC (Oncology Drug Advisory Committee)) will be convened. This also allows the public to make comments.
- **FDA Approval**
  - If approvable, the FDA works with applicant to develop prescribing information.
  - If issues still need to be resolved, developer requested to address questions based on existing data, or perform additional studies.

Other Terminology

- EMA (European Medicines Agency) – FDA equivalent
- CDER (Center for Drug Evaluation and Research) has responsibility for prescription and nonprescription or over-the-counter (OTC) drugs.
- GCP (Good Clinical Practice) – international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.
- GLP (Good Laboratory Practice) - regulations set the minimum basic requirements for: study conduct, personnel, facilities, equipment, written protocols, operating procedures, study reports, and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated product

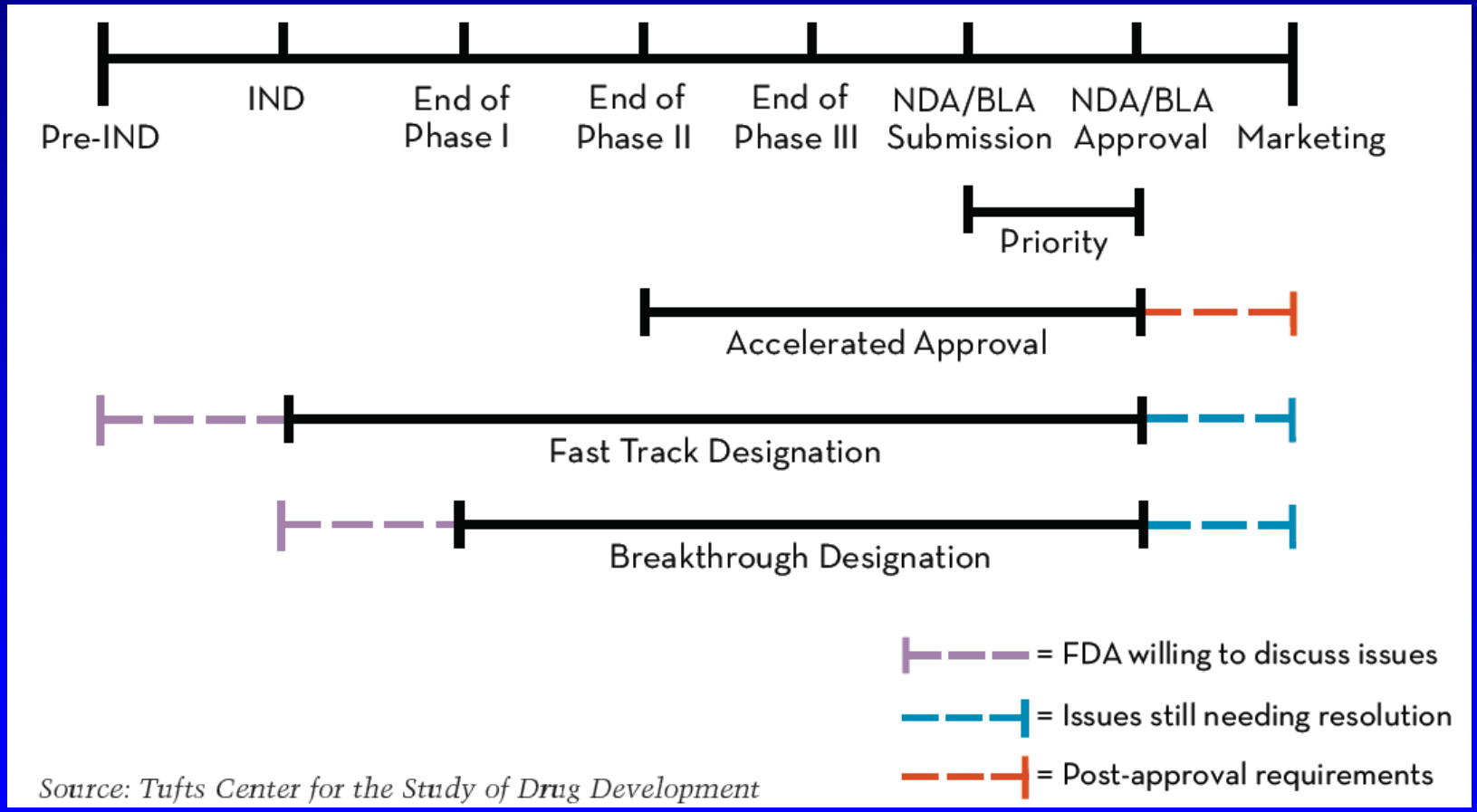
FDA Meetings

- Opportunities to ask for help from FDA :
  - Pre-IND application, to review FDA guidance documents and get answers to questions that may help enhance their research
  - After Phase 2, to obtain guidance on the design of large Phase 3 studies
  - Any time during the process, to obtain an assessment of the IND application, eg Clinical Pharmacology, CMC, Safety
  - Not a requirement to take FDA's suggestions.
    - » As long as trials are thoughtfully designed, safeguard participants, and otherwise meet Federal standards, FDA allows wide latitude in clinical trial design.
- During NDA/BLA review

Special Initiatives To Facilitate Anticancer Drug Development

- Accelerated Approval
  - Allow drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint.
- Fast Track
  - Facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
- Breakthrough Designation
  - A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy
- Priority Review
  - FDA's goal to take action on an application within 6 months
- Facilitating patient access to unapproved anticancer agents
- Advisory committee membership and voting rights to patients and patient representatives
- Reducing the need for IND applications for investigator-initiated studies for marketed agents in non-labeled cancer indications

FDA Programs to Expedite Drug Development & Review



Tufts CSDD 2015

The FDA and You!

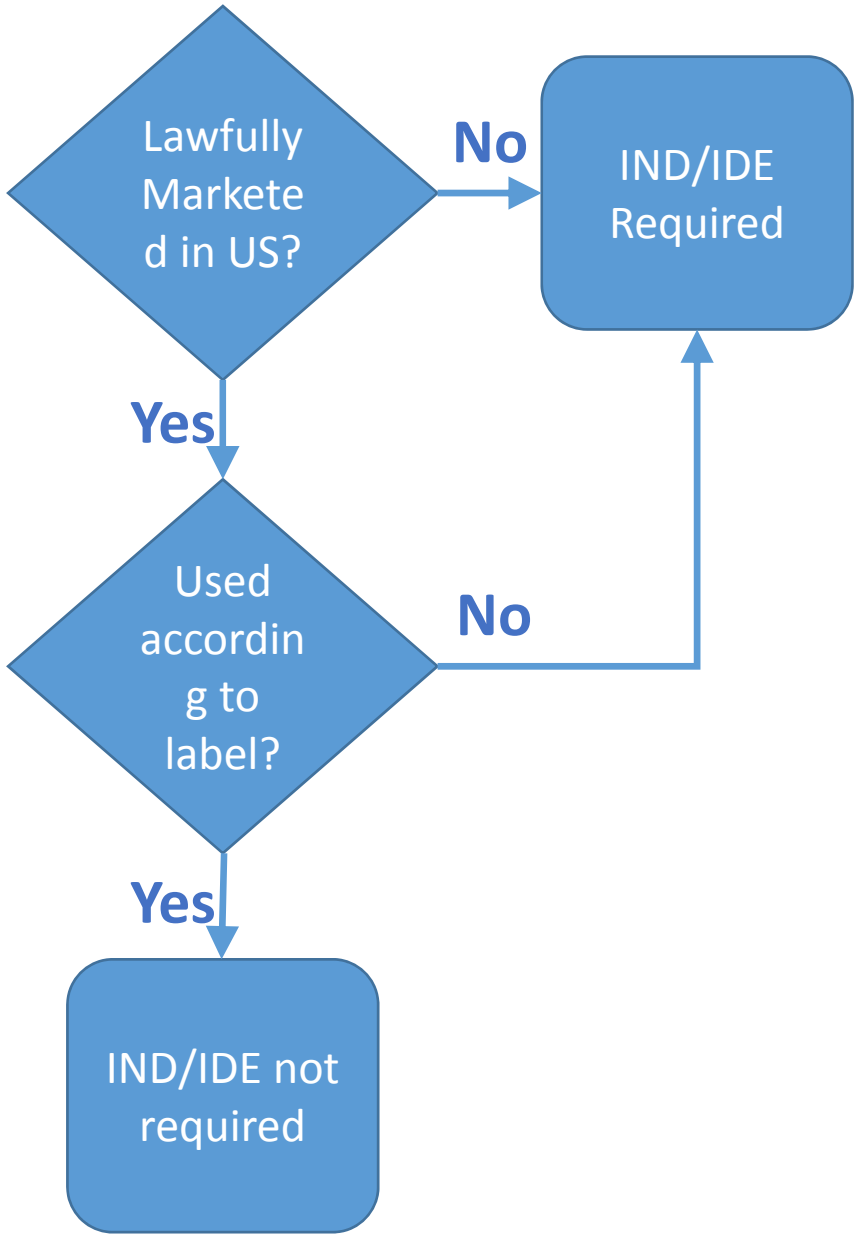
Sponsor and Investigator Responsibilities

Introduction / topics

- IND / IDE
- Form 1572 / Box 9 Commitments
- Adverse event reporting

IND / IDE

- Federal oversight of interstate commerce
- Transport/sale across state lines requires license
- Exemption for drugs / devices in development



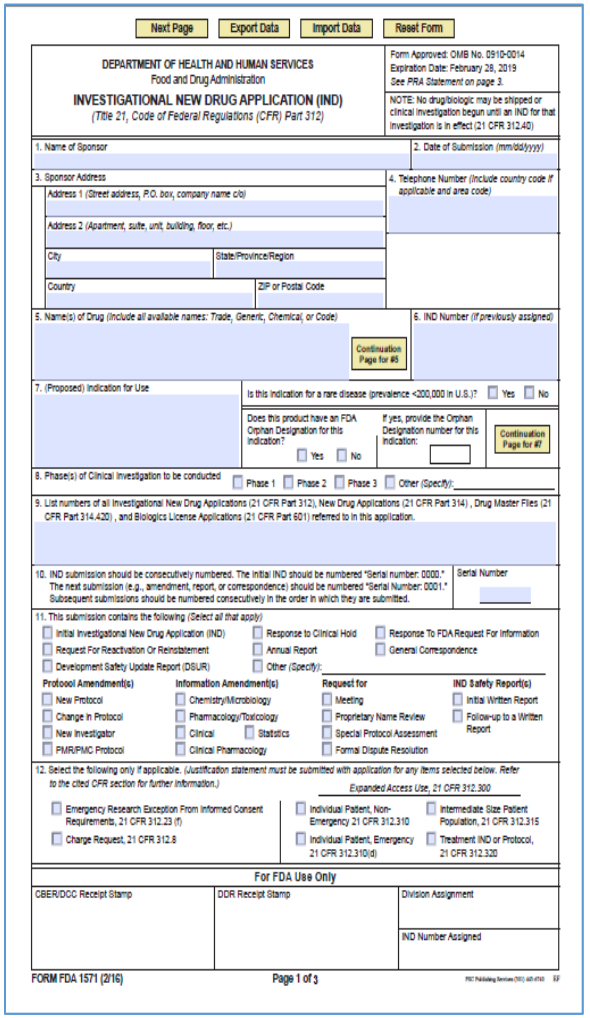
“Drug” as defined by FDA

- Substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and
- Substances (other than food) intended to affect the structure or any function of the body of man or other animals
- Note: vitamins / supplements are subject to regulation if used as a drug (to effect bodily function or health outcome)

Investigational New Drug (Application)

Complete Form 1571

- Protocol
- Product description
  - Investigator brochure / Package insert
  - Manufacturing information
  - All known safety and efficacy data
  - Cross file vs Drug Master File
- FDA has 30 days to respond (“30 day hold”)
  - Approve
  - Clinical Hold – more action needed
- Annual updates required



Next Page | Export Data | Import Data | Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: February 28, 2019
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
2. Date of Submission *(mm/dd/yyyy)*
3. Sponsor Address
Address 1 *(Street address, P.O. box, company name c/o)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
City
State/Province/Region
Country
ZIP or Postal Code
4. Telephone Number *(Include country code if applicable and area code)*
5. Name(s) of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*
Continuation Page for #5
6. IND Number *(If previously assigned)*
7. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes No
Does this product have an FDA Orphan Designation for this indication? Yes No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
8. Phase(s) of Clinical Investigation to be conducted Phase 1 Phase 2 Phase 3 Other (Specify):
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.
Serial Number
11. This submission contains the following *(Select all that apply)*
Initial Investigational New Drug Application (IND)
Response to Clinical Hold
Response To FDA Request For Information
Request For Reactivation Or Reinstatement
Annual Report
General Correspondence
Development Safety Update Report (DSUR)
Other *(Specify)*:
Protocol Amendment(s): New Protocol; Change in Protocol; New Investigator; FMR/PMC Protocol
Information Amendment(s): Chemistry/Microbiology; Pharmacology/Toxicology; Clinical; Statistics; Clinical Pharmacology
Request for: Meeting; Proprietary Name Review; Special Protocol Assessment; Formal Dispute Resolution
IND Safety Report(s): Initial Written Report; Follow-up to a Written Report
12. Select the following only if applicable. *(Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)*
Expanded Access Use, 21 CFR 312.300
Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
Charge Request, 21 CFR 312.8
Individual Patient, Non-Emergency 21 CFR 312.310
Individual Patient, Emergency 21 CFR 312.310(d)
Intermediate Size Patient Population, 21 CFR 312.315
Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only
CBER/DCC Receipt Stamp
DDR Receipt Stamp
Division Assignment
IND Number Assigned

FORM FDA 1571 (2/16) Page 1 of 3

IND Exemptions for marketed drugs

In order to qualify for exemption from the requirement to obtain an IND, the following criteria must be met (21 CFR 312.2(b)):

1. Study not intended to support a new indication or change in labeling
2. Drug is lawfully marketed in the US
3. Does not involve route of administration, dose, patient population or other factor that would substantially increase or decrease acceptability of risk
4. Conducted in compliance with requirements for IRB review
5. Not intended to promote or commercialize the drug

Cancer considered particularly risky, thus #3 may be interpreted rather broadly

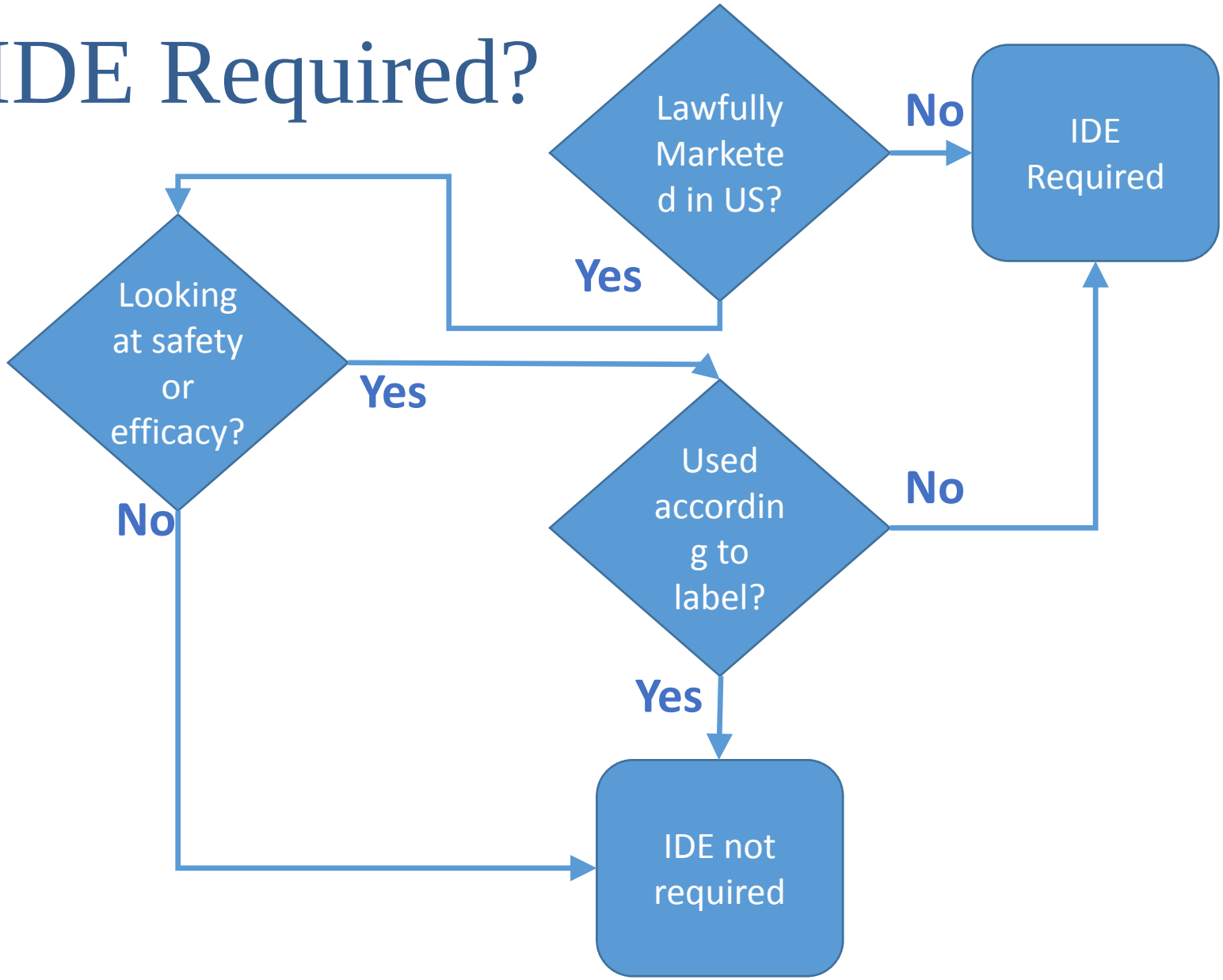
“Device” as defined by FDA

- An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article which is:
  - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - intended to affect the structure or any function of the body of man or other animals, but does not act through chemical action within or on the body and which is not dependent upon being metabolized for its action

Significant vs Non-Significant Risk Device

- Significant Risk device is
  - Intended as an implant, or
  - Is purported to be for a use in supporting or sustaining human life, or
  - Is for a use of substantial importance in diagnosing, curing, mitigatin, or treating disease
  - and presents potential for serious risk to the health, safety, or welfare of a subject
- IDE's for NSR devices may be granted by an IRB
- IDE's for SR devices are issued by the FDA

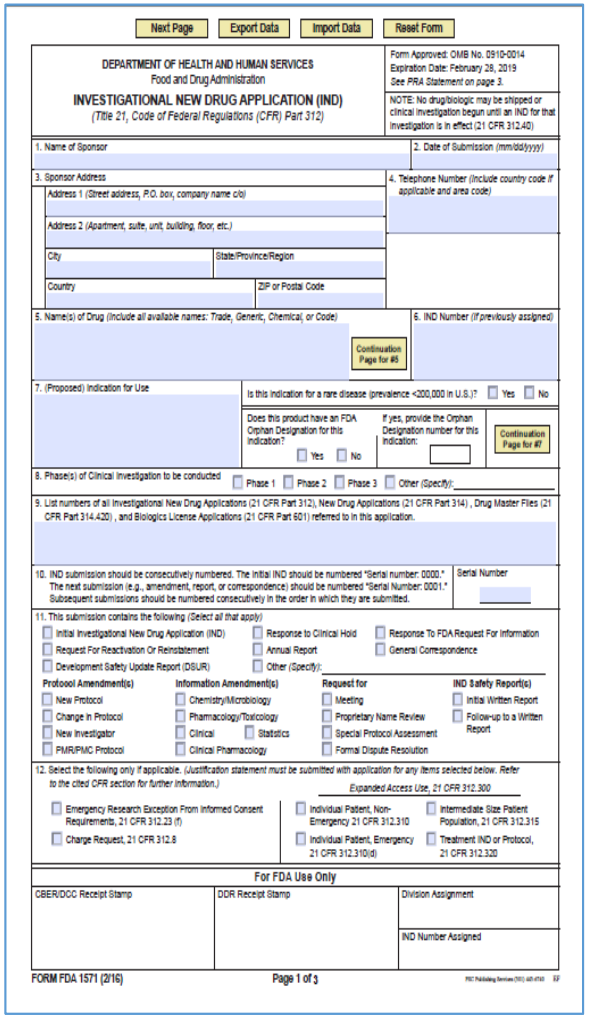
Is IDE Required?



Investigational Device Exemption

Submit form 1571

- Protocol
- Device description
  - Manufacturing information
  - All known safety and efficacy data
  - Cross file
- FDA has 30 days to respond
- Annual updates required



Next Page | Export Data | Import Data | Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: February 28, 2019
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

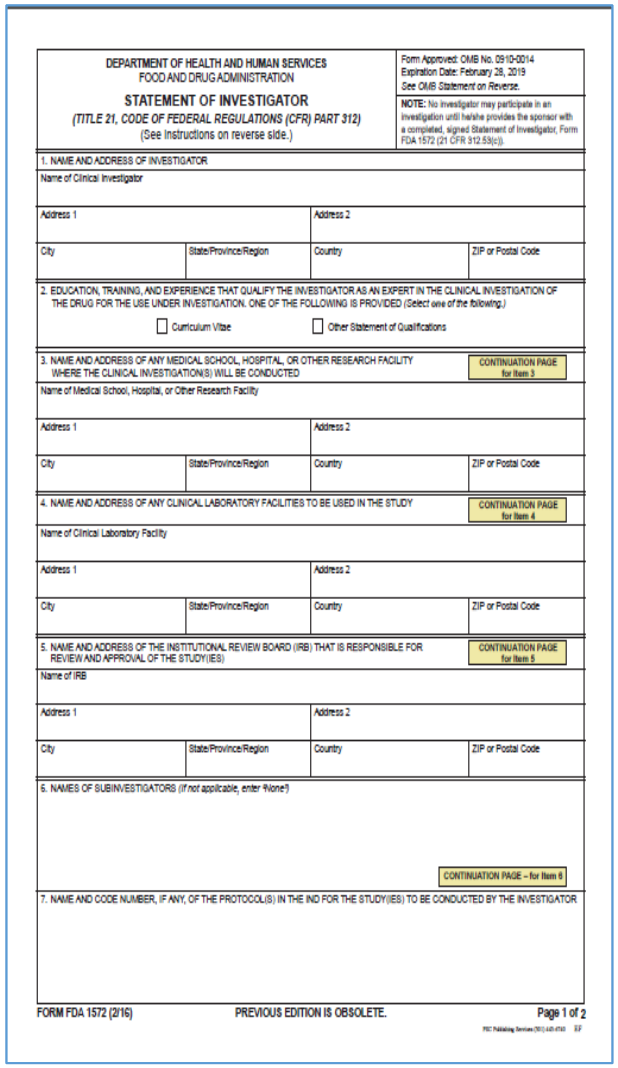
1. Name of Sponsor
2. Date of Submission (mm/dd/yyyy)
3. Sponsor Address
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City
State/Province/Region
Country
ZIP or Postal Code
4. Telephone Number (Include country code if applicable and area code)
5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code)
Continuation Page for #5
6. IND Number (If previously assigned)
7. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes No
Does this product have an FDA Orphan Designation for this indication? Yes No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
8. Phase(s) of Clinical Investigation to be conducted Phase 1 Phase 2 Phase 3 Other (Specify):
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.
Serial Number
11. This submission contains the following *(Select all that apply)*
Initial Investigational New Drug Application (IND)
Request For Reactivation Or Reinstatement
Development Safety Update Report (DSUR)
Response to Clinical Hold
Annual Report
Other (Specify):
Response To FDA Request For Information
General Correspondence
Protocol Amendment(s): New Protocol; Change in Protocol; New Investigator; FMR/PMC Protocol
Information Amendment(s): Chemistry/Microbiology; Pharmacology/Toxicology; Clinical; Statistics; Clinical Pharmacology
Request for: Meeting; Proprietary Name Review; Special Protocol Assessment; Formal Dispute Resolution
IND Safety Report(s): Initial Written Report; Follow-up to a Written Report
12. Select the following only if applicable. *(Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)*
Expanded Access Use, 21 CFR 312.300
Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
Charge Request, 21 CFR 312.8
Individual Patient, Non-Emergency 21 CFR 312.310
Individual Patient, Emergency 21 CFR 312.310(d)
Intermediate Size Patient Population, 21 CFR 312.315
Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only
CBER/DCC Receipt Stamp
DDR Receipt Stamp
Division Assignment
IND Number Assigned

FORM FDA 1571 (2/16) Page 1 of 3

FDA Form1572

- Investigator contract
- Required for all investigators in FDA-regulated research
- Documentation of qualifications
- Contact information for responsible parties
- “Box 9 Commitments”
  - Acknowledgement of Investigator responsibilities



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: February 28, 2019
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Clinical Investigator

Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select one of the following.)*

☐ Curriculum Vitae ☐ Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED — CONTINUATION PAGE for Item 3

Name of Medical School, Hospital, or Other Research Facility

Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY — CONTINUATION PAGE for Item 4

Name of Clinical Laboratory Facility

Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES) — CONTINUATION PAGE for Item 5

Name of IRB

Address 1 | Address 2

City | State/Province/Region | Country | ZIP or Postal Code

6. NAMES OF SUBINVESTIGATORS *(If not applicable, enter "None")* — CONTINUATION PAGE – for Item 6

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR

FORM FDA 1572 (2/16) PREVIOUS EDITION IS OBSOLETE. Page 1 of 2

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

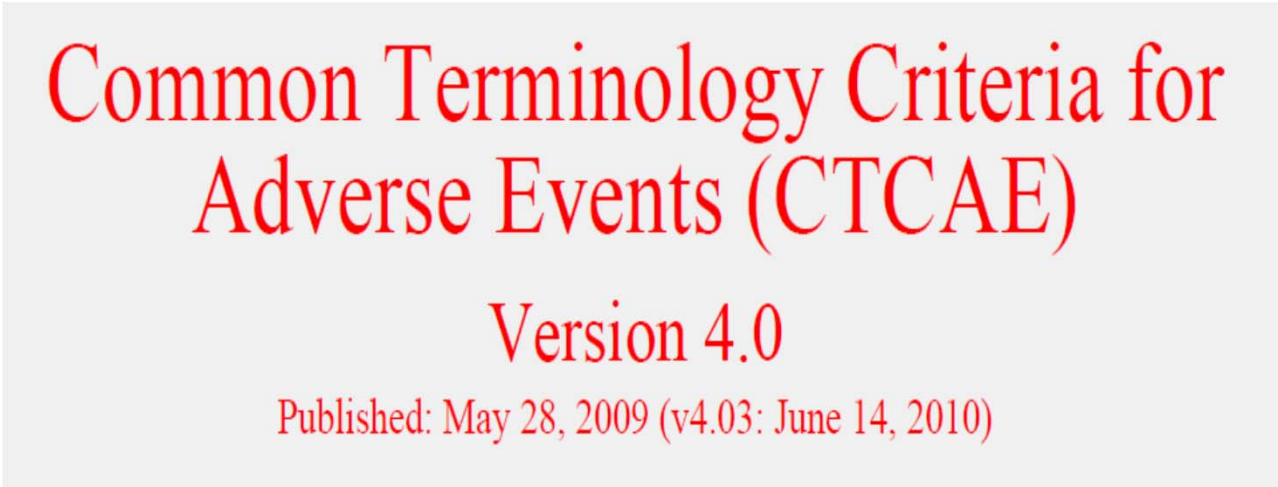
Safety Reporting in Clinical Trials

Adverse Event

- Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32(a))
- AKA *Adverse Experience*
- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of a drug
- Does not imply or require evidence of causality
- *Investigator* identifies and reports the AE to the sponsor

Adverse Event Severity

- AE can be mild, moderate, severe, life threatening, or result in death
- By convention and convenience, cancer study AE's graded according to



Blood and lymphatic system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					

CTCAE v4.03, June 2010

Suspected Adverse Reaction (SUSAR)

- Any AE for which there is a reasonable possibility that the drug caused the event (21 CFR 312.32(a))
- “reasonable possibility” means there is evidence to suggest a causal relationship
- *Sponsor* is responsible for making determination regarding causality

Unexpected Events

- AE or SUSAR is *unexpected* if
  - Not listed in investigators brochure (not previously observed)
  - Occurs with greater frequency or severity than previously identified
  - Does not mean “unanticipated” for patient / disease
- Applies to specific drug, not class

Serious Adverse Events (SAE)

- AE or SUSAR is *serious* (21 CFR 312.32(a)) if it results in:
  - Death
  - Life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization
  - Persistent or significant incapacity or substantial disruption in ability to conduct normal life functions
  - Congenital anomaly / Birth defect
  - Other events may be serious if requires medical or surgical intervention to prevent one of the outcomes listed above.
- Investigator or sponsor may determine event is serious

Investigators vs. Sponsors

- Investigator
  - *Investigator* means an individual who actually conducts a clinical investigation
- Sponsor
  - *Sponsor* means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization
- Sponsor-Investigator
  - Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed

21 CFR 312.3(a)

Sponsor Responsibilities

- Report all potentially serious risks from clinical trials or other sources
  - Report to FDA and all investigators to whom sponsor is supplying the drug
  - Report within 15 calendar days
- Evaluate event in context of other related reports or events known to sponsor
- Conduct ongoing safety evaluations including periodic review and analysis of entire safety database

Sponsor *Reporting* Responsibilities

- Sponsor must report as IND safety report within 15 days:
  - Serious and Unexpected Suspected Adverse Reaction
    - *Serious*
    - *Unexpected*
    - *Suspected Adverse Reaction*
  - Findings from other sources
    - *Other studies*
    - *Findings from animal or In Vitro testing*
  - Increased occurrence of SUSAR

Investigator Responsibilities

- Record all *relevant* Adverse Events
- Report Serious Adverse Events to Sponsor ASAP
- Reports required to IRB
  - Harm experienced by subject which was unexpected and at least possibly related
  - Identified new or increased risk (sponsor report, publication, new IB, etc)

Sponsor-Investigator Responsibilities

- Sponsor-investigators required to comply with responsibilities of ***both*** sponsors and investigators
- Responsible for reporting to
  - FDA
  - Other investigators
  - IRB

Thank You

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Compliance Issues

Doug Reichgott, MS

Director, Financial and Regulatory Operations/Policy

Tufts Medical Center

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Compliance Issues for Clinical Research

- Conflict of Interest
- Insurance Billing

Tufts Medical Center

Goals

- Understand Regulations, Policies, and Procedures Related to Conflict of Interest Disclosure

- Understand Regulations, Policies, and Procedures Related to Insurance Billing for Subjects Enrolled in Clinical Research Projects

Tufts Medical Center

Conflict of Interest

Tufts Medical Center

Conflict of Interest

- Widespread physician interaction with industry
  - Total 94%
  - Consulting 26% (lead authors 34%)
- Very small amounts can be influential
- Unconscious, unintentional bias
- Individuals often unaware of bias

Dana J, Loewenstein G. A Social Science Perspective on Gifts to Physicians from Industry. *JAMA*. 2003;290;252-255.

Campbell E, Blumenthhal, D et al. A National Survey of Physician-Industry Relationships. *NEJM*. 2007;356:1742-50.

Tufts Medical Center

COI Management Issues

- Reporting level
  - Consulting v. Pens
- Institutional v. Personal
- Non Financial
- Management Plans Effectiveness
- Multiple Policies

Tufts Medical Center

“Promoting Objectivity in Research”

42 CFR Part 50 Subpart F

http://www.gpo.gov/fdsys/pkg/FR-2011-08-25/pdf/2011-21633.pdf

Tufts Medical Center

Who?

- **SENIOR/KEY PERSONNEL**
  - PI
  - Senior/Key personnel
    - *Designated by Institution in the grant application or any other report submitted to the PHS*

Tufts Medical Center

What?

- **Significant Financial Interests**
  - Spouse
  - Dependent children
- **Related to Institutional Responsibilities**
  - Research
  - Clinical
  - Education
  - Service on panels

Tufts Medical Center

Significant Financial Interest

- **Publicly traded entity:**
  - Remuneration received in the twelve months preceding disclosure exceeds $5,000.
    - *Salary*
    - *Consulting*
    - *Speaking*
    - *Authorship*
  - Equity exceeds $5,000
    - *stock*
    - *stock options*

Tufts Medical Center

Significant Financial Interest (cont.)

- **Non-Publicly Traded Entity**
  - remuneration received in the twelve months preceding the disclosure exceeds $5,000
  - any equity interest

- **Intellectual property rights**
  - Upon receipt of income.
  - *Not if through hospital*

Tufts Medical Center

Not Significant Financial Interest

- **NOT SFI**
  - Mutual funds and retirement accounts
  - Federal, state or local government agency
  - Institution of higher education
  - Academic teaching hospital
  - Medical Center
  - Research institute that is affiliated with an Institution of higher education

Tufts Medical Center

Not Significant Financial Interest

- **Support provided by your institution**
  - Grant Salary Support
  - Travel reimbursement
  - IP distribution

If the check comes from Tufts Medical Center it is NOT a Significant Financial Interest

Tufts Medical Center

Not Allowed

- **Sponsor Recruitment Bonuses**
  - In-Kind
- **Recruitment Bonuses to physicians**

Tufts Medical Center

When?

- **Annual Disclosure**
- **Update within 30 days of any change**
- **At time of submission of grant or IRB application**

Tufts Medical Center

How?

- **Annual and Grants**
  - eRES

- **IRB**
  - Submitted to IRB/reviewed by institutional COI committee

Tufts Medical Center

Definition of FCOI

- An SFI that could directly and significantly affect the design, conduct, or reporting of research.
- Determined by institutional committee.
- Investigators submit **SFI**, institution determines **COI**.
- All COI must be made available upon written request.

Tufts Medical Center

Research COI committee

- CSO
- Research VP
- Chair of Medicine
- Compliance Representative
- Director of Research Policy

Tufts Medical Center

What if a COI determination is made?

- **Report**
- **Mitigation plan**
  - Disclosure
  - Review by outside party
  - Removal of Conflict
- **May be asked to not serve as PI**

Tufts Medical Center

Sub-Recipients

- Certify they have a Compliant COI policy

  Or

- Provided a policy

Tufts Medical Center

Training

- **Required least every 4 years**
  - Or if policy changes
  - Or if they are found to be out of compliance

- **eRES**

Tufts Medical Center

Summary

- Significant Financial Interest (SFI) disclosure.
- Related to Institutional Responsibilities.
- $5,000
- Report SFI/Institution determines COI
- Training Every 4 years
- eRES

- Hospital Policy v. Research Policy

Tufts Medical Center

Insurance Billing for Clinical Research

Tufts Medical Center

Clinical Research Ancillary Care Billing Compliance

- **Emory University to Pay $1.5 Million To Settle False Claims Act Investigation**
  - August, 2013
  - Emory billed Medicare and Medicaid for activities performed during clinical trial participation despite the fact that the sponsor of the trials had already agreed to pay those costs.

Tufts Medical Center

Rush Medical Center
$1 Million

University of Alabama
$3.4 Million

Tenet HealthCare
$1.9 Million

Tufts Medical Center

GAO reports federal government wasted $125 billion in 2014 alone

Tufts Medical Center

Requirement

- A Medicare Coverage Analysis (MCA) must be completed for every study that includes patient care.
- Includes a Medicare Qualifying Analysis (MQA) and Billing Grid.
  - For industry studies, prior to contract execution
  - For non-industry studies, prior to activity set-up
    - *We recommend prior to submission*
  - Applies to all studies/patients regardless of insurance
    - *All subjects need to treated the same*

Tufts Medical Center

Medicare Coverage Analysis (MCA) Process

Qualifying Study Review
(Is it a qualifying clinical trial)

Create Billing Grid
(What is routine care?)

Communicate

Operationalize

Clinical Trial Policy

National Coverage Decision (NCD) for Routine Costs in Clinical Trials (310.1)

www.cms.hhs.gov/clinicaltrialpolicies/

Two Main Points

1. 10 standards for a study to qualify
2. Billing is allowed for “Routine Services”

(Devices are under a separate law)

Tufts Medical Center

Medicare Coverage Analysis (MCA) Process

Qualifying Study Review
(Does the study meet the 10 standards?)

Tufts Medical Center

The First 7 Standards

1. The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes;
2. The trial is well-supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use;
3. The trial does not unjustifiably duplicate existing studies;
4. The trial design is appropriate to answer the research question being asked in the trial;
5. The trial is sponsored by a credible organization or individual capable of executing the proposed trial successfully;
6. The trial is in compliance with Federal regulations relating to the protection of human subjects; and
7. All aspects of the trial are conducted according to the appropriate standards of scientific integrity.

Tufts Medical Center

“Deemed Studies”

Deemed studies automatically cover these 7
(Must fit **one** of these categories)

- Trials funded by NIH, CDC, AHRQ, CMS, DOD, and VA

or

- Trials supported by centers or cooperative groups that are funded by these groups

or

- Trials conducted under an investigational new drug application (IND)

or

- Drug trials that are exempt from having an IND

Tufts Medical Center

The Other 3 Standards

Must meet **all** of these standards

- Investigate an item or service that falls within a Medicare benefit category

and

- Enroll patients with diagnosed disease

and

- **Be designed with therapeutic intent (primary endpoint of efficacy/effectiveness)**

Tufts Medical Center

What if a Study is NOT Qualifying?

- NOTHING CAN BE BILLED TO INSURANCE

Tufts Medical Center

State Law

- Affordable Care Act says (in principal) that these requirements apply to all insurers, not just Medicare
  - They don't have to pay for investigational treatment, drug or device

Tufts Medical Center

Medicare Coverage Analysis (MCA) Process

Create Billing Grid
(What is routine care?)

Tufts Medical Center

So What is Covered?

- Routine Costs
  - Conventional care
    - *Items or services that are typically provided absent a clinical trial*
  - Detection, prevention and treatment of complications
  - Administration of the investigational item

Just because it can, doesn't mean it has to

MEDICARE GIVETH & MEDICARE TAKETH AWAY

Tufts Medical Center

Who Has This Information?

- Physicians!
- They need to sign off on documents that items are routine.

Tufts Medical Center

Additional Thoughts

- If it is only to assess inclusion/exclusion it CANNOT be billed
- All subjects must be the same
- Medicare *will* pay for subject injury
- REMEMBER
  - If it isn't ROUTINE CARE, **it can't go to insurance**
  - If it is paid for by the sponsor, **it can't go to insurance**
  - If it is listed in the consent form as FREE, **it can't go to insurance**

Tufts Medical Center

Two More Thoughts

- No paying co-pays
- No sponsor payments in the case of insurance denial (payer of last resort)

Tufts Medical Center

Billing Grid

- Clearly shows what can be billed to insurance and what must be paid by the study funds

- Start with the “Chart of Events”

or

- Start with Study Budget and change from $ figures to Insurance or Research

Tufts Medical Center

The Lottery Test

IF YOU WIN A BILLION DOLLARS AND NEVER COME BACK TO WORK WE NEED TO KNOW WHAT CAN BE BILLED WHERE

Tufts Medical Center

Billing Grid

Procedure	V1	V2	V3
Consent	x		
Physical	x	x	x
CBC	x	x	x
Chest X-Ray		x	x
MRI		x	x
Drug Infusion		x	x
LFTs		x	x
PK		x	x

Tufts Medical Center

Billing Grid

Procedure	V1	V2	V3
Consent	Study		
Physical	Study	Study	Study
CBC	Study	Routine	Routine
Chest X-Ray		Study	Routine
MRI		Study	Routine
Drug Infusion		Routine	Routine
LFTs		Routine	Routine
PK		Study	Study

PURE RESEARCH

Tufts Medical Center

Billing Grid

Procedure	V1	V2	V3
Consent	Study		
Physical	Study	Study	Study
CBC	Study	Routine	Routine
Chest X-Ray		Study	Routine
MRI		Study	Routine
Drug Infusion		Routine	Routine
LFTs		Routine	Routine
PK		Study	Study

PAID BY STUDY

Tufts Medical Center

Billing Grid

Inclusion Only

Procedure	V1	V2	V3
Consent	Study		
Physical	Study	Study	Study
CBC	Study	Routine	Routine
Chest X-Ray		Study	Routine
MRI		Study	Routine
Drug Infusion		Routine	Routine
LFTs		Routine	Routine
PK		Study	Study

“Standard of Care”

Tufts Medical Center

Billing Grid

Research Only

Procedure	V1	V2	V3
Consent	Study		
Physical	Study	Study	Study
CBC	Study	Routine	Routine
Chest X-Ray		Study	Routine
MRI		Study	Routine
Drug Infusion		Routine	Routine
LFTs		Routine	Routine
PK		Study	Study

Administration of Investigational Item

Follow up for Known Toxicity

Tufts Medical Center

Billing Grid

Procedure	V1	V2	V3
Consent	Study		
Physical	Study	Study	Study
CBC	Study	Routine	Routine
Chest X-Ray		Study	Routine
MRI		Study	Routine
Drug Infusion		Routine	Routine
LFTs		Routine	Routine
PK		Study	Study

Tufts Medical Center

Medicare Coverage Analysis (MCA) Process

Communicate

Tufts Medical Center

Document Agreement

- Make sure all the documents agree
  - Billing Grid
  - Budget
    - *Watch for items that can be billed to insurance that are paid by sponsor*
  - Consent Form
    - *Watch for "Free", "At No Cost". Make sure it is clear what will be billed to insurance*
  - Contract

Tufts Medical Center

Who Needs to Know?

- Administrator
- PI
- Coordinators
- Schedulers
- Ancillary Departments

Tufts Medical Center

Medicare Coverage Analysis (MCA) Process

Operationalize

Tufts Medical Center

Medical Center Systems

- Complete Pre-registration Forms
- Follow Ancillary Care Provider systems (Radiology/Cardiology)
- Check for Errors
- Follow-up on Amendments

Tufts Medical Center

Questions?

Douglas Reichgott
Director of Financial and Regulatory Operations,
Director of Neely Center for Clinical Cancer Research

Research Administration

617-636-5609
dreichgott@tuftsmedicalcenter.org

Tufts Medical Center

Thank You

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Overview of Next Session

March 10, 2017

8th Floor Conference Room

35 Kneeland Street

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Agenda

Meeting Agenda
Clinical Trial Oversight

Registration	**12:30 – 1:00 PM**
Neely Center for Clinical Cancer Research *Doug Reichgott and Elizabeth Grimm*	**1:00 – 1:30 PM**
Multi-Center Clinical Trials *Karen Freund and Susan Parsons*	**1:30 – 2:15 PM**
Break & Snack	**2:15 – 2:30 PM**
Cooperative Group Studies *Jack Erban & Susan Parsons*	**2:30 – 3:15 PM**
Data Management Tools *Robin Ruthazer*	**3:15 – 3:45 PM**
Panel Discussion *Andy Evens, Bob Martell, Wasif Saif, Susan Parsons, Andreas Klein*	**3:45 – 4:30 PM**
Conclusion *Andy Evens*	**4:30 – 5:00 PM**

Tufts | CTSI

Tufts Clinical and Translational Science Institute

Pre-Work

No Pre-Work!

Tufts | CTSI

Tufts Clinical and Translational Science Institute