Physician vs. The Physician-Investigator

Presented by Paul Martin, MD

9:30am-10:30am

UW Husky Union Building

Physician vs. the Physician Investigator:

Is There A Difference?

Paul Martin, MD
Member, Fred Hutch

FRED HUTCH
UNIVERSITY OF WASHINGTON
CANCER CONSORTIUM

ITHS | Institute of Translational Health Sciences
ACCELERATING RESEARCH. IMPROVING HEALTH.

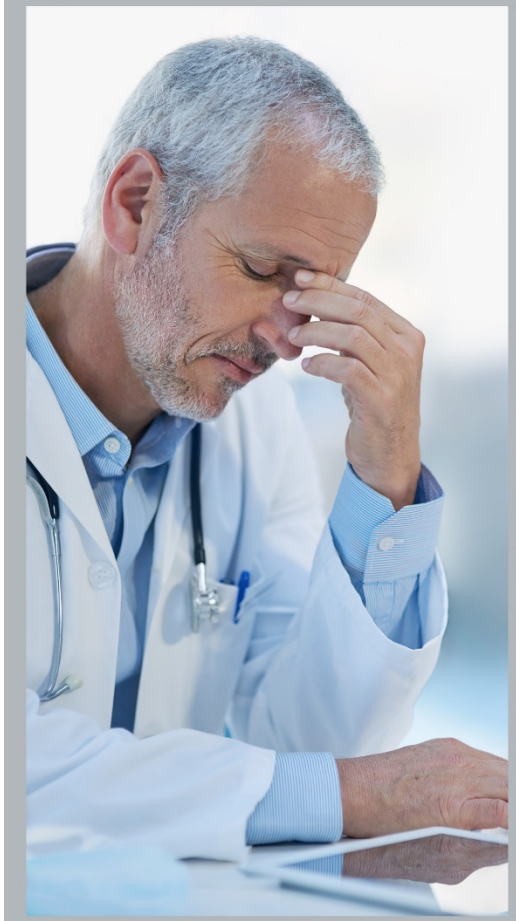
Learning Objectives

By the end of the session, you will be able to:

- Describe how participation as an investigator in a clinical trial differs from usual clinical care
- Assess whether your temperament is well suited for a career with a major focus on clinical trial research

EXPERIMENT

FAIL



LEARN

REPEAT

Dimension	Physician	Physician-Investigator
Patient care decisions		
Interventions, procedures		
Accountability		
Documentation		
Team		
Management		

Dimension	Physician	Physician-Investigator
Patient care decisions	Clinical practice guidelines, experience, scientific literature, patient beliefs/values	

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re·search

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re·search

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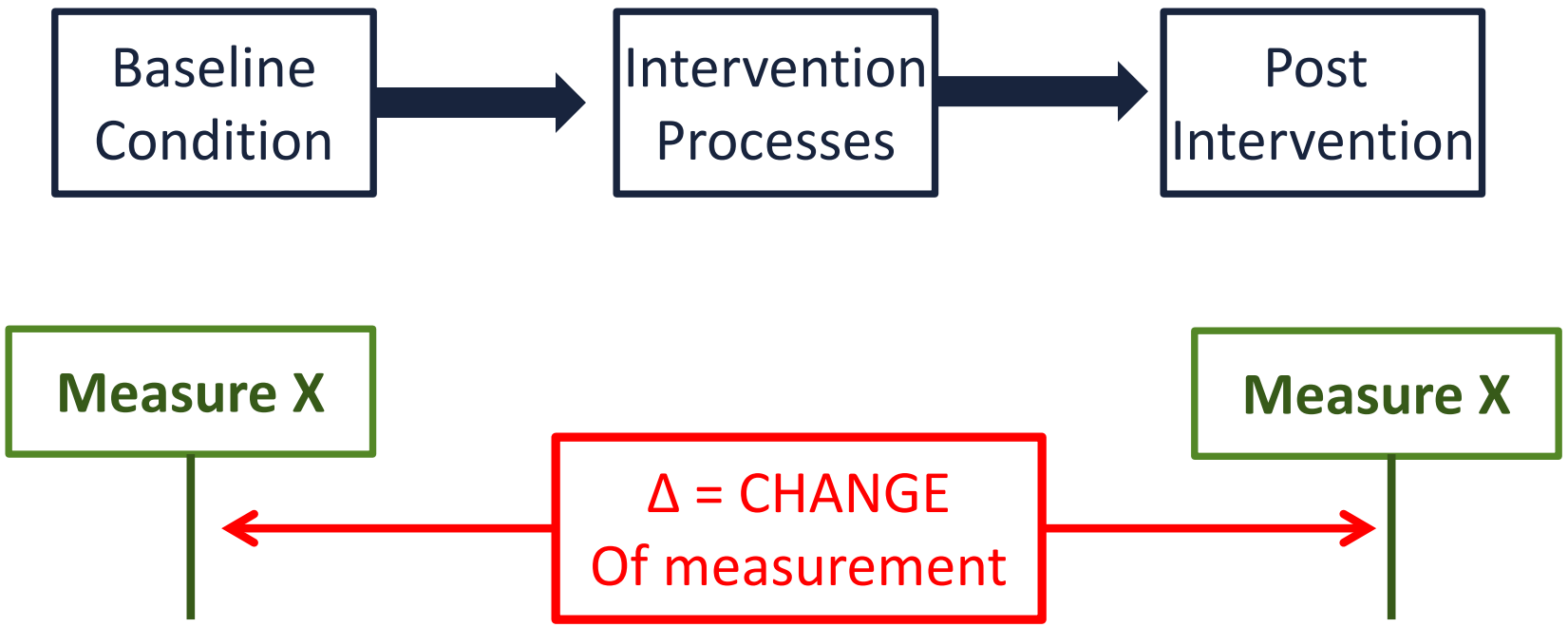
Noun

1. **<u>Diligent</u> and <u>systematic</u> inquiry or investigation into a subject in order to discover or revise facts, theories, applications, etc.**

Dimension	Physician	Physician-Investigator
Patient care decisions	Clinical practice guidelines, experience, scientific literature, patient beliefs/values	**Care necessary for quality study data as dictated by study protocol**, patient safety

Clinical Research – basic plan



Dimension	Physician	Physician-Investigator
Patient care decisions	Clinical practice guidelines, experience, scientific literature, patient beliefs/values	**Care necessary for quality study data as dictated by study protocol**, patient safety

- Study protocol
  - Objectives
  - Eligibility criteria
  - Required procedures and assessments
  - Contraindicated medications
  - AE review reporting requirements
  - Stopping rules
  - Outcome criteria

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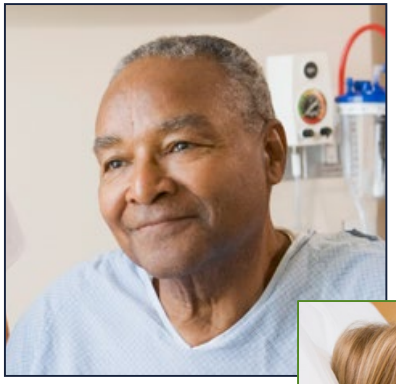
Human volunteers

- Protect rights, safety and welfare



Dimension	Physician	Physician-Investigator
Interventions, tests, procedures	Standard of care	

Dimension	Physician	Physician-Investigator
Interventions, tests, procedures	Standard of care	Additional interventions and/or testing at specific time points

Example Time and Events Schedule

	Screen Day –28 to –1	CRU Admission (Baseline)	Day 1			Day X to X	Prior to Discharge (Day X)	Follow-up ≥3 days and ≤5 days after Discharge
			Pre-dose	Dosing	Post-dose	Post-dose		
Informed Consent Form Signed	X							
Eligibility Review and Confirmation	X	X	X					
Medical History	X							
Physical Examination	X	X					X	X
Height Assessment	X							
Weight Assessment	X	X	X				X	
Urine Drug Test	X	X						
HIV & Viral Hepatitis Screen	X							
Vital Signs	X	X	X		X	X	X	X
12-lead ECG	X	X	X		X	X	X	
Clinical Laboratory (Blood) and Urinalysis	X	X	X		X	X	X	
Prior Medication Assessment	X	X	X					
Serum Pregnancy Test	X							X
Urine Pregnancy Test		X						
CRU Admission		X						
Randomization			X					
Administer Study Drug				X				
Pharmacokinetic Sampling (Blood)			X		X	X	X	
Pharmacokinetic Sampling (Urine)			X		X	X	X	
Treatment-Emergent Adverse Events				X	X	X	X	X
Concomitant Medication Assessment				X	X	X	X	X
CRU Discharge							X	X

Dimension	Physician	Physician-Investigator
Accountability	Patient and family, Institutional policies, state laws and licensing board, Medicare guidelines	

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Accountability	**Institutional policies, state laws and licensing board, Medicare guidelines**	**Cancer Consortium entities, Study Sponsor, IRB, ICH GCP, state and federal regulations (FDA, HHS, etc.)**

- Rules and Standards Governing Clinical Research
  - Study Protocol
  - Cancer Consortium/Institutional policies
  - IRB requirements
  - ICH Guidelines for Good Clinical Practice (GCP)
  - FDA – Title 21 CFR Parts 11, 50, 54, 56, 312, 314, and 812
  - HHS – Title 45 CFR Part 46

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Accountability	Institutional policies, state laws and licensing board, Medicare guidelines	Cancer Consortium entities, Study Sponsor, IRB, ICH GCP, state and federal regulations (FDA, HHS, etc.)

Text from an actual FDA Warning Letter:

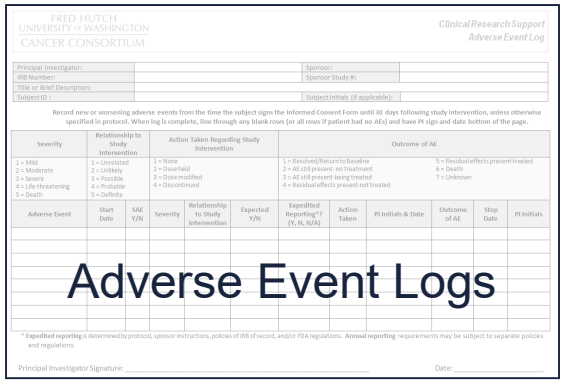
3. Failure to ensure that the investigation was conducted according to the signed agreement, investigational plan, and applicable FDA regulations…

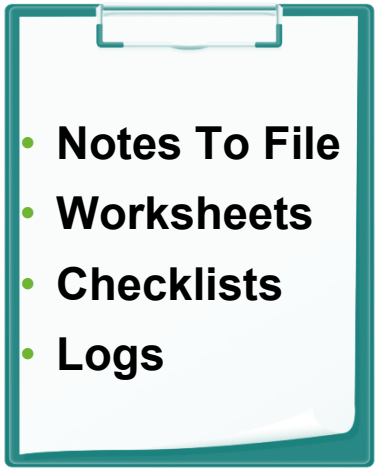
As a clinical investigator, you are responsible for ensuring that an investigation is conducted in accordance with the investigational plan, the signed agreement, and applicable FDA regulations…

You failed to follow the Clinical Investigation Plan, Protocol RAL 1. In addition, the study changes were not reported to the IRB, nor was prior approval obtained from the IRB. Examples of your failure include, but are not limited to, the following:

Dimension	Physician	Physician-Investigator
Documentation	EMR / patient charting, consents for care	

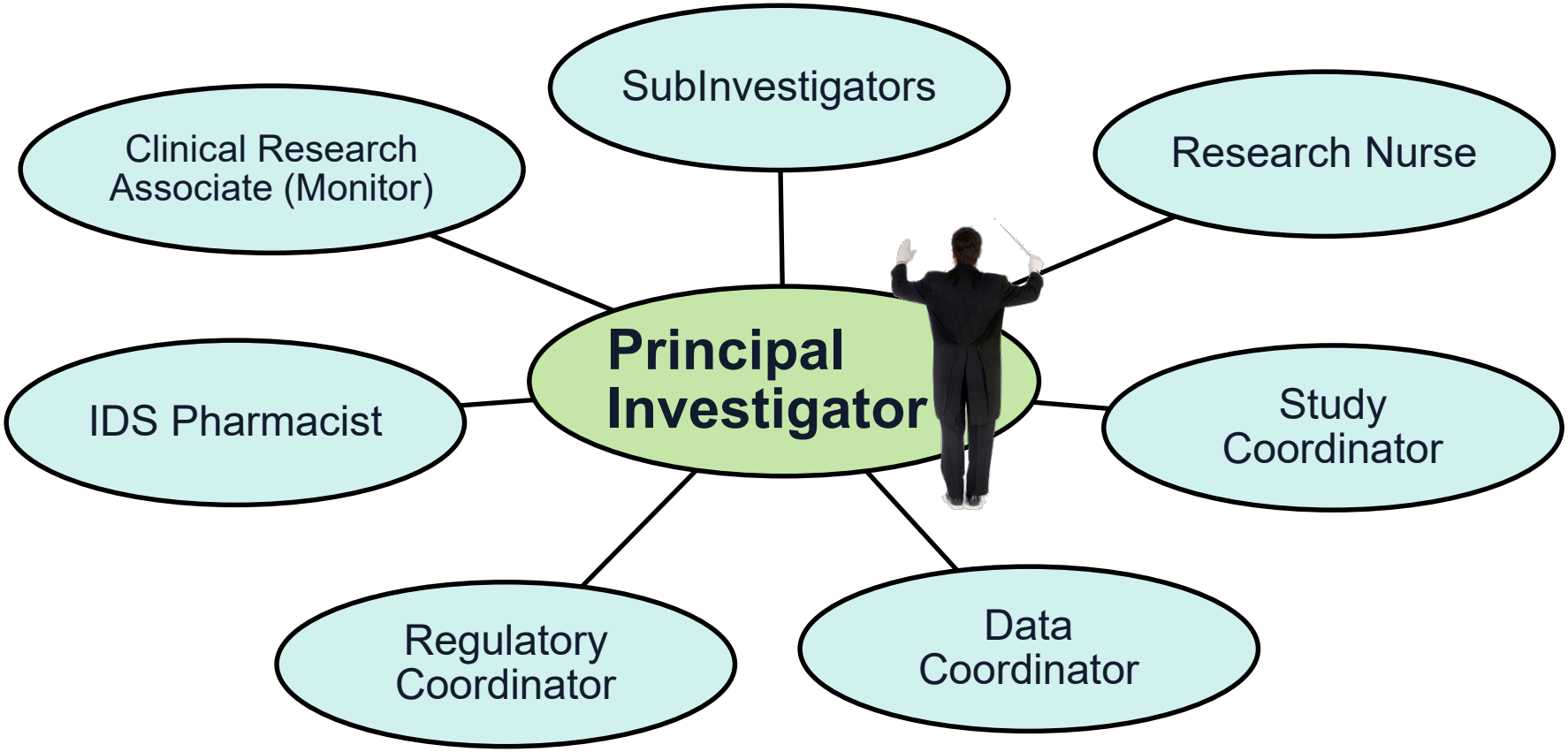
Dimension	Physician	Physician-Investigator
Documentation	EMR / patient charting, consents for care	Research chart, informed consent documents, CRFs/database, tracking tools, other reg docs





Dimension	Physician	Physician-Investigator
Team	PAs, ARNPs, RNs, MAs, ancillary services	

Dimension	Physician	Physician-Investigator
Team	PAs, ARNPs, RNs, MAs, Dental, ancillary services	Clinical Research Team



Dimension	Physician	Physician-Investigator
Management	Orders, patient visits, chart and lab review, medical rounds, continuing education	

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Management	Orders, patient visits, chart and lab review, medical rounds, continuing education	Study operations, compliance, recruitment, budget and contracts, patient billing, personnel training

- Organized
- Detail-oriented
- Flexible
- Collaborative
- Manage time wisely
- Passionate
- DRIVE in continuing research education

Knowledge Base

Clinical Research Regulations

Human Subjects Protection

Protocol Design & Development

Protocol Review & Approval Process

Informed Consent Elements / Process

Clinical Research Documentation

Budget Development

Patient Billing Procedures

Medical Background

Trial Monitoring & Auditing Procedures

Learning Objectives

- Describe how participation as an investigator in a clinical trial differs from usual clinical care
- Assess whether your temperament is well suited for a career with a major focus on clinical trial research

Credits

Kersten Brinkworth
Stacey Long Genovese

“What is the Difference between 14 Days and 15 Days?”

Case No. 1: Carl Steubing

- 1985—diagnosed with colon cancer, successfully treated
- Jan 2001—diagnosed with stomach cancer
- Feb 2001—offered participation in clinical trial

Study Design

- Randomized prospective trial
- Experimental arm: Docetaxel plus Cis-platinum or Docetaxel plus 5-fluorouracil
- Standard treatment: Cis-platinum plus 5-fluorouracil

Steubing Evaluation

- Feb 13—lab tests done
- Feb 15—date of lab tests in CRF
- Feb 22—started study treatment
- Protocol requirement $\leq$ 8 days from lab test to start of treatment
- Exclusion criteria
  - Previous malignancy
  - Creatinine clearance < 60 mL/min
- Steubing creatinine clearance 49.5 mL/min

Steubing Outcome

- July, 2001—completed 6 cycles of treatment per protocol
- March, 2002—died after further treatment with Docetaxal and Xeloda

Medical Considerations

- All three agents approved by FDA
- 5-FU—not given if WBC is low or if bilirubin > 5.0
- Cis-platinum—dose reduced by 50% if creatinine clearance is 30 – 60 mL/min
- Docetaxel—not given if bilirubin is $\geq$ 1.5

Medical Assessment

- Any of the agents could have been used “off study”
- Possible harm if cis-platinum was given at 100% dose with creatinine clearance < 60 mL/min
- Protocol treatment did not cure the cancer

Regulatory Assessment

- Patient not eligible for at least two reasons
  - Prior cancer
  - Renal impairment
- Patient not eligible because lab tests not done within required time-frame
- Intentional misrepresentation of test dates in CRF

Case No. 2: James DiGeorgio

- Gastric cancer
- Phase II study of
  - α-difluoromethylornithine (DFMO) plus
  - Cis-platinum and
  - 5-fluorouracil
- DFMO is an investigational irreversible inhibitor of ornithine decarboxylase, which is needed for synthesis of polyamines

Eligibility Assessment

Test	Protocol Exclusion	5/25/01 Results	CRF
Creatinine	> 1.75	1.9	1.3
Cr Clearance	< 60	41	60.3
AST	> 85	99	39
Bilirubin	> 1.0	1.9	0.9
Alk. Phos.	> 340	378	208

DiGeorgio Outcome

- Completed treatment on June 6, 2001
- Died on June, 11, 2001
- Death reported to sponsor on June 14, 2001

Medical Assessment

- Nephrotoxic study drug likely contributed to death
- Neither DFMO or 5-FU is known to cause renal toxicity
- Death was most likely caused by administration of cis-platinum at an inappropriately high dose, relative to the baseline level of renal function

Regulatory Assessment

- Subject not eligible for at least 5 reasons
- Intentional misrepresentation of test results in CRF
- Delayed reporting of death

Albany Stratton VA Hospital

- 1993—complaints by hospital pharmacist and pharmacy manager
- Mid 90's—internal investigation, no significant changes implemented
- Dec, 2001—routine monitoring visit by drug company. Findings led to formal audit.
- 2002—Drug company audit led to notification of FDA about problems. FDA was aware of problems from a prior notification.

FDA Investigation and Consequences

- Nov, 2002 to Jan, 2003—51-day investigation by FDA
- Report of FDA Inspectional Observations
- Protocol investigator and research assistant dismissed
- Mrs. DiGeorgio filed $20 million law suit for wrongful death against US Department of Veterans Affairs
- Mrs. Steubing also sued Veterans Administration

Paul Kornak

- Attended medical school in Grenada
- 1990—New Jersey medical license application denied because of falsified documents
- 1991—Iowa medical license revoked because of false information on application
- 1993—convicted for mail fraud in Pennsylvania after falsifying information on an application for a medical license, resulting in 3 years of probation and $2500 fine

Career at Albany Stratton VA Hospital

- 1999—Hired as research assistant, later promoted to Chief Research Assistant
- VA business card identified as M.D.
- Passed exam covering informed consent and clinical fraud
- “Inherited” by Dr. James Holland, who was medical investigator for protocols and was later appointed Chief of Oncology
- Jan, 2001—fired by VA after FDA inspection

Legal Actions Against Kornak

- March, 2003—Mrs. Steubing filed class action law suit
- Oct, 2004—indicted on 48 felony counts, including fraud, manslaughter and criminally negligent homicide of James DiGeorgio
- Jan, 2005—pled guilty to 3 counts, including fraud, making false statements, and criminally negligent homicide
- May, 2005—will go to jail, possibly 4 to 20 years

Dr. Holland
Inspectional Observations by FDA

- Failed to personally conduct or supervise the clinical investigations
- Failed to protect the rights, safety and welfare of subjects
- Repeatedly or deliberately submitted false information to the sponsor
- Failed to conduct studies or ensure they were conducted according to the protocol
- Failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual

False Information

- In most cases, misrepresentation was designed to make subjects eligible for studies
- One protocol required EKG within 14 days of enrollment
  - 3 subjects had EKG > 14 days before enrollment (dates falsified in CRF)
  - 4 subjects had no study-related EKG before enrollment (EKG after enrollment or long before enrollment with dates falsified in CRF; in one case, EKG was from a different subject)
  - 2 of the above subjects had EKG abnormalities deleted from the CRF

Dr. James Holland—Epilog

- Jan, 2003—fired by Albany Stratton VA after FDA inspection
- March, 2003—Mrs. Steubing filed class action law suit
- Hired by an oncology center in Georgia
- Investigation by Georgia Medical Board found no evidence of misconduct
- Sept, 2004—FDA issued NIDPOE
- Possibly facing federal criminal indictment

FDA Notice of Initiation of Disqualification Proceeding and Opportunity to Explain

"FDA asserts that you have failed to protect the rights, safety and welfare of subjects under your care, repeatedly or deliberately submitted false information to the sponsor and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data, and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator in a written response or at an informal conference in my office."

“What is the Difference Between 14 Days and 15 Days?”

- Depends on the “hat” you’re wearing
- If a “medical” hat—no difference
- If an “investigator” hat—Protocol Violation