UC San Diego

RESEARCH COMPLIANCE AND INTEGRITY

- Conflict of Interest (COI)
- Dual Use Research of Concern (DURC)
- Export Control and Facility Security
- Institutional Animal Care and Use Committee (IACUC)
- Research Ethics and Integrity (Research Misconduct)
- ClinicalTrials.Gov, NIH Good Clinical Practices (GCP) and Responsible Conduct of Research (RCR) Compliance

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Study Coordinator 101

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Brief Into / Background

Michaela Doering, BS

- 25 years in private clinics and pharmaceutical industry: Agouron, Pfizer, Ligand, and Eisai
- Clinical Trials (site level), Clinical Informatics, Medical Writing, and Regulatory
  - Oncology Focused
- 2010 - 2012 - Regulatory Associate, GI Oncology Disease Team at UCSD Moores Cancer Center Clinical Trials Office
- 2012 - present - UCSD MCC Clinical Trials Office, Regulatory Manager
- Piloted use of electronic regulatory binder, Veeva SiteVault, DocuSign Part 11 for research, reliance IRB programs, and central IRBs
- Works with HRPP, PRMC, IBC, and HERC on clinical research policy and practices

Sarah Lazar, MPH

- 2008 - Started at UCSD, Moore’s Cancer Center
- 2009-2018 - SRA, then Clinical Research Program Manager, Dept of Surgery
- 2018 - present - Clinical Research Manager, Division of Neonatology, Dept of Pediatrics
- Piloted many UCSD research programs, such as Velos
- Interested in improving UCSD-RCHSD research affiliation, and access to resources
Why do we need study coordinators?

- Study Coordinators, or Clinical Research Coordinators (CRCs), help bridge the gap between science and innovation and clinical practice.
- CRCs are responsible for managing clinical research activities and ensuring compliance with federal and local guidelines.
Types of Clinical Research

- Questionnaires/Surveys
- Retrospective chart review
- Biospecimen collection
- Prospective database
- Registry
- PI-Initiated Clinical Trial
  - PI wrote protocol
- Industry Sponsored/Industry Funded Clinical Trial
  - Sponsor wrote protocol
- Government Funded Clinical Trial
  - NCI Cooperative Groups
  - NIH
CRC - Typical Duties

- Regulatory and IRB & Other Committee Submissions
  - May be regulatory analyst
- Study File Maintenance
- Ensure adherence to protocol
- Study start-up
  - Site qualification, investigator meetings, SIV, training
- Recruitment
- Screening and enrollment
- Informed Consent
  - May involve clinical team
- Determining and documenting eligibility
- Conducting study visits
CRC - Typical Duties (continued!)

- Collecting and processing samples
- Biohazard shipping
- Completion of Case Report Forms (paper or electronic)
- Documentation/reporting of adverse events
- Development and participation in QI/QA measures
- Sponsor communication
- ClinicalTrials.gov registration
- Ensure appropriate study-related charges
  - Coverage Analysis, Velos, Verification of charges in EPIC
- Audit/Inspection preparation
  - Internal (compliance) and external (sponsor, FDA or other)
Clinical Trials - High Level Overview
Training Requirements

- All UCSD faculty, staff, and students listed as a PI or key personnel must complete appropriate CITI training
  - Biomedical Research and/or Social and Behavioral Research
  - IRB-Mandated course
  - Training refresher every 3 years

- If involved in NIH-funded research or pharmaceutical industry funded research, you must also complete CITI Good Clinical Practice training
  - Training refresher every 3 years

www.citiprogram.org
Study Start Up

- Site Qualification
  - Feasibility, Questionnaire, Survey, Visit, PI Credentials/Qualifications to conduct research

- Internal Review Processes
  - Does your division/department have a review committee?

- Budget Negotiations
  - Who will negotiate? Is budget feasible to continue with submission?

- Contract Submission
  - OCGA vs. OCTA

- Coverage Analysis?
  - Velos
Study Start Up (continued)

- IRB Submission
  - Local or Central IRB
  - sIRB or Reliance pathway
- Ancillary Committees
  - Protocol Review and Monitoring Committee (PRMC)
  - Institutional Biosafety Committee (IBC)
  - Radiation Safety Committee (RSC)
  - COVID-19 Clinical Trials Review Committee
  - Embryonic Stem Cell Research Oversight (ESCRO)
  - Human Exposure Review Committee (HERC)
Important Note on Signatory Authority

- Per Research Compliance and University of California - Policy BFB-BUS-43:
  
  "Individual faculty members and Medical Center personnel are not authorized to sign agreements on behalf of the University and assume personal liability by doing so."
Research at Rady’s

- If you are conducting research at RCHSD, you must also submit a Project Initiation Form to Rady’s Research Administration (research@rchsd.org)
- Rady’s will issue Ready to Accrue and specific Rady’s #
  - Final approval may require approval from medical directors, unit nursing, etc.
Regulatory Documents

- IRB Federal Wide Assurance Letter
- IRB Application and Communications
  - Protocol
  - Investigator Brochure or Product/Device Information
  - Informed Consent/Assent/Parent Permission
  - California Experimental Subject’s Bill of Rights
  - UCSD or RCHSD HIPAA Authorization Form
  - Patient-Facing Study Materials (Questionnaires, Guides, Emergency Cards)
  - Recruitment Materials
  - FDA May Proceed Letter
- Blank CRFs
- Study Manuals
Regulatory Documents (continued)

- Logs
  - Monitoring Visit Log
  - Screening & Enrollment Log
  - Delegation of Authority Log
  - Temperature Logs
  - Protocol Deviation Log
  - Adverse Event Log
  - Concomitant Medication Log

- Essential Docs
  - FDA 1572 (Drug) or Investigator Statement (Device)
  - Protocol and Investigator Brochure Signature Pages
  - CVs and Medical Licenses
  - Conflict of Interest & Financial Disclosure Forms
  - Lab Certifications and Reference Ranges
  - Training Documents
Regulatory Documents (continued)

- Safety
  - Serious Adverse Events or UPRs
  - IND Safety Reports
  - Summary Safety Reports (6-month SUSAR line listings, Development Safety Update Reports)
- Equipment Calibration Records
- Subject Visit Tracking
- Sponsor Correspondence and Site Correspondence
- Monitor Reports
- Other
Pharmacy Documents

- IP / Pharmacy Manual
- Drug/Device Accountability and Dispensation Log(s)
- Drug/Device Receipt, Shipping, Inventory Documents
Delegation of Authority/Tasks Log

- A delegation log (COA/DTL) is a cumulative and comprehensive list of research personnel and their research tasks as delegated to them by the PI of the study.
- It is one of the first documents requested by an auditor or FDA inspector before they initiate their review.
- Delegated tasks should be appropriate to the position, licensure, and training of the delegated individual.
- Delegations should be kept up over the course of the study, adding/removing tasks and personnel and listing start and stop dates. Note - training should be on or before the start date of the delegated task.
- Rotational or hospital staff performing standard procedures that are part of their everyday duties and not being performed solely for research do not need to be listed (e.g. phlebotomists, medical assistants, infusion nurses, etc.)
Protocol Adherence

- HRPP SOPP 3.14 - “Federal regulations require that any modification to an approved protocol must be reviewed and approved by the IRB prior to implementing the change except when necessary to eliminate apparent immediate hazards/risks to subjects.”

- All protocol deviations should be documented
  - Major - deviations that negatively affect the rights, wellbeing, and/or safety of the subject and/or undermine the data integrity of the research.
  - Minor - check with the policies of the IRB of record

- Examples of Major Deviations
  - Lack of legally effective informed consent
  - Breaches of confidentiality
  - Violation of eligibility criteria
  - Missed safety assessments
  - Overdose or under dosing
Protocol Adherence (continued)

- Major violations must be reported to the IRB within 10 working days of awareness of the violation.
  - The clock starts when anyone from the study team becomes aware of the event.
  - Failure to report major deviations are also reportable as deviations to IRB SOP.

- Serious Non-Compliance
  - Deviations that
    - a) that results in substantive harm or damage to the safety, rights, or welfare of human subjects, research staff, or others; or
    - b) substantively compromises the integrity or effectiveness of the research.
Protocol Adherence (continued)

- **COVID-19 Reporting**
  - Actions taken to mitigate or reduce risk due to COVID-19 are allowed without prior IRB approval.
    - Examples: Remote consent, TeleHealth Visits, labs at local facility instead UCSD lab, of missed or delayed appointments
  - By HRPP definition, they are minor protocol deviations.
    - Submit IRB notification with annual renewal.
    - Some study sponsors have their own COVID-19 deviation reporting database (e.g. NCI Alliance)
Scenario 1

- A study sponsor issues a memo requiring an additional tube of blood be collected for research purposes at the study visit. They do not issue a protocol amendment and do not mention that IRB approval is required. You have a patient coming in the following Monday and will need the additional tube of blood drawn then. What do you do next?
  - Draw the additional tube of blood. Sponsor said it’s required and you don’t want a deviation.
  - Discuss the level of risk with the investigator. If she says it’s fine, go ahead and draw the additional blood.
  - Ignore the memo until the sponsor issues a protocol amendment.
  - Submit the sponsor’s memo with updated plan of research and revised consent with the investigator’s risk/benefit assessment to the IRB for approval prior to drawing the additional blood.
  - There’s not enough time before the subject comes in next. Draw the additional blood and tell the IRB about it afterwards.
Scenario 1 - Answer

- Submit the sponsor’s memo with updated plan of research and revised consent with the investigator’s risk/benefit assessment to the IRB for approval prior to drawing the additional blood.
  - All changes in the planned research must be IRB approved prior to implementation. The additional blood drawn is not removing any harm, so it requires IRB approval before implementing.
  - The principal investigator is responsible for assessing all changes to remain compliant with the principals of ethical research: respect for persons, beneficence and justice.
  - Additionally, the additional blood collection is an increase in the risk to the subject and the subject must be informed prior to undergoing the additional collection. The subject has the right to withdrawal consent if they don’t agree with the additional research risk or no longer wishes to participate.
Recruitment

- Recruitment is the first step in the consent process.
- Methods vary, but all must be IRB approved.
  - Internal referral
  - Community outreach
  - Advertisements
  - Flyers, brochures, social media
- Patient-facing recruitment materials require IRB submission.

Don’t overstate benefit and avoid coercive language!
Screening and Enrollment

- Partial HIPAA waiver for recruitment and screening purposes
- Member of clinical team may introduce research and/or member of clinical research team
- Clinical staff not listed as key personnel and trained on study protocol should limit discussions with participants re. research
- Screening may be done via EPIC (inpatient and outpatient lists), OR scheduling lists, etc
- Initial information accessed should be limited
  - What is necessary to determine potential eligibility?
- **BREAK THE GLASS** - must state why accessing, list IRB # (at Rady’s, list RCHSD specific #)
Informed Consent

- Basic Elements (see IRB templates):
  - A statement that the study involves research
  - An explanation of the **purposes** of the research
  - The **expected duration** of the subject's participation
  - A **description of the procedures** to be followed
  - Identification of any procedures which are experimental
  - A description of any reasonably foreseeable **risks** or discomforts to the subject
  - A description of any **benefits** to the subject or to others which may reasonably be expected from the research
  - A disclosure of appropriate **alternative procedures or courses of treatment**, if any, that might be advantageous to the subject
Informed Consent (continued)

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained

- For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained (Indemnification/Injury Clause)

- Research, Rights or Injury: An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject

- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled
HIPAA

- HIPAA Authorization is required for all subjects enrolled in research studies where Protected Health Information (PHI) is being accessed, obtained, or/or added to the EMR

  OR

- Waiver of HIPAA Authorization must be approved by the IRB

- HIPAA template available on HRPP website
  - Language may not be altered - revise/complete: header, sections A, B, and D
  - Sections C, G, and J completed by research subject
  - Section C- may be left blank or N/A
  - Section G- if blank = automatic opt out

- **Note** there is a Rady specific version
Subject Eligibility

- Inclusion/Exclusion Criteria
- Vulnerable populations
- Who is consenting?
  - Adult Consent vs. Parent Permission vs. Adolescent Assent (13-17) vs. Child Assent (7-12)
Eligibility Exceptions

- Protocol Exception to Enroll requests should be rare and clearly determined to be in the best interest of the patient.
- The subject may not be enrolled or continue screening procedures until approval has been granted from a full board IRB.
- Check with sponsor. Do they allow eligibility waivers?
- IRB questions for exception request:
  - Why it is appropriate to enroll this subject is this protocol? Include justification of potential risk to the subject.
  - What specific study criteria are not satisfied by the subject?
  - Will data collected on this subject will be provided to the study sponsor?
  - Will the sponsor amend to the protocol’s inclusion/exclusion criteria?
Study Visits

- Mapping out ahead of time can be useful tool
  - Consider Excel (password protected!) to outline Schedule of Events for each subject
- Complete/link in Velos, as needed, as soon as possible
- Telehealth options via MyChart
- Coordinate research procedures with SOC as much as possible
  - Discuss blood draws, etc with clinical team to coordinate efforts and minimize risks (added “pokes,” additional radiation exposure, etc)
Collecting and Processing Samples

- Coordinate with clinical team whenever possible
- Prepare kits ahead of time and ensure not expired
- Wear appropriate clothing, PPE while processing (lab coat, gloves, goggles)
- Follow Lab Manual or Manual of Procedures (MOP) if sponsor has one
- If transporting/shipping samples, must have appropriate training!
Biohazard Shipping

- Training and Certification are required to ship diagnostic specimens, biological substances, and dry ice
- IATA certification is required - good for two years
- UC Learning Center: “Shipping Biological Substance and Dry Ice”

- Material Transfer Agreements
  - A MTA is required for transfer of “tangible research material” between owner and recipient
  - May be incoming or outgoing
  - Initiated via the eMTA system (emta.ucsd.edu)
Source Documents & Case Report Forms

- **Source Documents**: May be anything you are writing in for the first time
  - EPIC notes, paper sources, EKG printouts, logs, etc.
- **CRFs**: May be sponsor provided or PI/study team created
- **ALCOA-C**
  - Attributable
    - Traceable to person, date, visit
  - Legible
  - Contemporaneous
    - Documented in real time?
  - Original
    - Hard copy, or if electronic, is there an audit trail?
  - Accurate
  - Complete
Press Release

Department of Justice
Office of Public Affairs

FOR IMMEDIATE RELEASE

Tuesday, May 11, 2021

Study Coordinator Charged in Scheme to Falsify Clinical Trial Data
Study coordinator at Unlimited Medical Research in Miami, FL has been indicted by a federal grand jury on charges to include **conspiracy to commit wire fraud and making a false statement**

UMR was hired to conduct a clinical trial designed to investigate the safety and efficacy of an asthma med in children

Study coordinator is alleged to have participated in a scheme to falsify medical records
  - Made it appear as though pediatric subjects scheduled visits to UMR, received physical exams from a clinical investigator, and took drugs as required, when these things had not occurred.

Also alleged to have made a false statement to an FDA regulatory investigator when confronted about her conduct

“Falsifying clinical trial data risks the health and safety of those who might later rely upon the drugs being tested,” said Deputy Assistant Attorney General Arun G. Rao of the Justice Department’s Civil Division. “The Department of Justice will continue to work with its partners at the Food and Drug Administration to investigate and prosecute anyone who endangers the public for financial gain.”
Regulatory Correspondence

- Initial application(s)
- Amendment or revision to the application
  - IRB
  - PRMC (if scientific validity, patient population or statistical plan changes)
  - HERC (if radiation exposure changes)
  - IBC (if exposure risks changes, changes in facilities, or investigational agent handling)
  - RSC (if use of radioisotope changes)
- Safety
  - Major Deviation
  - UPR
  - DSMB review, Feasibility analysis, Safety summary reports
Regulatory Correspondence (continued)

- Continuing Review or renewal application(s)
  - IRB (annually with few exceptions)
  - PRMC (6-, 9-, and 12-month renewal)
  - IBC (annually)
  - UCSD Data Safety Monitoring Board
    - Annual Safety Report
    - Annual audit
    - Interim analyses per protocol

- Study Closure or Termination

- Best practice to be upfront, transparent and honest with the committees. They are there to assist you!
Reporting Adverse Events

- Maintain an AE log that reports the event, dates of occurrence, response, and assessment of relatedness, causality and seriousness (grade).
  - Note - the individual tasked with assessing relatedness, causality, and seriousness should be medically qualified for that task.
- Some AEs may be Serious Adverse Events (SAEs).
  - An event that results in death, hospitalization or prolongation of hospitalization, disability, or congenital abnormalities/birth defects.
  - An event that is life-threatening or requires intervention to prevent permanent damage/disability.
  - Other - refer to the protocol for study specific definitions or exclusions.
- Report the SAE to the sponsor within 24 hours of knowledge of the event.
Reporting Adverse Events (continued)

- An AE or SAE maybe classified as a Unexpected Problem Involving Risks (UPR). A problem or event, which in the opinion of the Principal Investigator was:
  - unanticipated,
  - serious, AND
  - at least possibly related to the research procedures.

An event MUST meet all 3 criteria to be classified as a UPR.

- UPRs are reportable to the IRB within 10 working days of the event.
  - The clock starts when anyone from the study team becomes aware of the event.
  - Failure to report major deviations are also reportable as deviations to IRB SOP.
Scenario 2

A subject is receiving investigational drug on a clinical trial. Following drug administration, he is seen in the Emergency Room with 3rd degree burns on his exposed skin from the fluorescent lighting in his office. He is admitted to the hospital for treatment. The Investigator assesses the injuries as unexpected, definitely related, and serious. What you do next?

A. Treat the burns and send him home with a reminder of his next study visit.
B. Complete an SAE report for the sponsor within 24 hours and UPR for IRB submission within 10 working days.
C. Call the FDA immediately.
D. Complete an SAE report for the sponsor within 24 hours.
E. All of the above.
Scenario 2 - Answer

Complete an SAE report for the sponsor within 24 hours and UPR for IRB submission within 10 working days.

- The subject is hospitalized as a result of an adverse reaction qualifying the event as an SAE reportable to the sponsor within 24 hours of the staff’s knowledge of the event.

- The investigator assessed the event as unexpected, definitely related, and serious. It met all 3 criteria of a UPR qualifying it as a UPR and as an event reportable to the IRB within 10 working days of the event.

- Additional actions as follow-up: Sponsor revised the consent to include the risk of light sensitivity and burns.

- Additional reporting: Report of research-related injury was made to Clinical Research Billing (CRB) for potential injury compensation. Applies to events definitely related to research only.
QA/QI/QC

- **Quality Assurance**: the maintenance of a desired level of quality in a service or product

- **Quality Improvement**: a systematic, formal approach to the analysis of practice performance and efforts to *improve* performance
  - Projects often done internally
  - Many RN/unit-based projects are QI
  - May obtain QA/QI waiver from IRB - particularly important when planning to publish

- **Quality Control**: a process by which entities review the quality of all factors involved in production
  - This is the “inspection” aspect
Sponsors

- Industry Sponsored / Funded
  - CDA/NDA (via OCTA form)
    - Must be signed by university designated official
  - Contract through OCTA

- Grant Sponsored / Funded
  - NIH, NSF, etc.
  - CDA/NDA (via Kuali)
  - Contract through OCGA
  - Funding may be limited or non-negotiable
Monitoring

- May be conducted remote or in-person
- Typically will review regulatory binder/documents, source documentation, and verify CRF data
- Access to electronic health records:
  - “Over the Shoulder”
  - Hard copy (redact PHI if taken off-site)
  - Cloud Based (Health Science OneDrive = HIPAA compliant - redact what is not needed)
  - Secure email (redact what is not needed)
  - “Read Only” Access - application must be submitted through UCSD research unit
  - Temporary: Zoom Conferencing - sharing of screen/EPIC view
Research Billing

- If study involves “billable event(s)” (UCSD technical or professional fee services), a research study account must be established.
- Coverage Analysis will provide “map” of billing.
- Once approved, CA entered into Velos.
- Velos links to EPIC to ensure billing is routed appropriately.
  - This is why it is so important to complete Velos entries in a timely manner!

- Clinical Research Billing (Technical Fees): crb@ucsd.edu
- UCSDH Physicians (Professional Fees): crb@ucsd.edu
- Laboratory Administration: lishelpdesk@health.ucsd.edu
- Imaging Services: Kim Vanleeuwen, kvanleeuwen@ucsd.edu, (619) 543-6760
Research Billing - How to Verify Charges

- In EPIC, Select Account Maintenance
- Under “Patient,” type IRB # followed by *, and “Accept” in lower right corner
- Find “Guar Summary” on the navigation bar and select this to open
- Scroll to bottom of page and locate “Statement Enterprise”
- Select the month you wish to review
- Review statements monthly
- Corrections? Email CRB@ucsd.edu
Audits

- Conduct your study as if an audit or inspection could happen at any time!
- Audits/Inspections may be internal or external
  - Internal: Research Compliance, Clinical Research Billing
  - External: sponsor, 3rd party auditors, FDA
- For Cause vs. Not for Cause/Routine
- Prepare an audit checklist
  - Check out the Research Compliance Pulse page for examples!
Record Retention

- Determine which regulations apply to your specific research
- Keep data for **longest required amount of time**
- If sponsored, must comply with record retention detailed in the award
- **Investigator records, IRB records** - minimum 2 years
- **Federal Research** - **minimum 3 years**
- General Counsel recommends longer retention periods for IRB and academic research records pertaining to **children as subjects**, (seven years after the children reach the age of majority [18 in California]) and for records pertaining to in vitro studies or pregnant women (25 years).
Record Retention (continued)

- **REMEMBER**: Records should not be destroyed without written authorization from the sponsor or granting agency.
- If records moved to long term storage, document where and when, and keep sponsor or granting agency informed.
RESOURCES:
Research Compliance and Integrity:
Phone: (858) 822-4939
Email: rci@ucsd.edu
Website: rci.ucsd.edu
Executive Director: Angela Fornataro McMahill

IACUC:
Phone: (858) 534-6069
Email: iacuc@ucsd.edu
Website: blink.ucsd.edu/sponsor/iacuc
Director: Kristen Anderson-Vicino

Conflict of Interest:
Phone: (858) 534-6465
Email: info-coi@ucsd.edu
Website: blink.ucsd.edu/sponsor/coi
Director: Jennifer J. Ford

Export Control, DURC and Facility Security:
Phone: (858) 246-3300
Email: export@ucsd.edu
Website: blink.ucsd.edu/sponsor/exportcontrol
Director: Michael Miller
COMMUNICATIONS

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- Export Control Helpline: (858) 246-3300, export@ucsd.edu
- IACUC Helpline: (858) 534-6069, iacuc@ucsd.edu
- Hot Topics and Newsletters:
  - Website: http://blink.ucsd.edu/sponsor/rci/news.html
  - Research Compliance and Hot Topics Training Program
  - To be added to the RCI list serv, please email rci@ucsd.edu