

Knight Cancer Institute and IRB Updates for Cancer-Related Studies

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Agenda

Topic	Presenter
Centralized Management of INDs and IDEs	Sarah Ward, MS Knight Cancer Institute
Investigator Initiated Trials Involving Drugs or Devices: IRB Review Process	Andrea Johnson, JD Research Integrity Office
New Submission Requirements for Cancer-Related Studies	Susan Aust, MSPH, CRRP Knight Cancer Institute
Knight Data and Safety Monitoring Plan Revision 4 New Requirements	Denise Mathes, BSN, RN, MPH Knight Cancer Institute

Centralized Management of INDs and IDEs

Sarah Ward, MS



KNIGHT
CANCER INSTITUTE
Oregon Health & Science University

Knight & IRB:



Centralize management

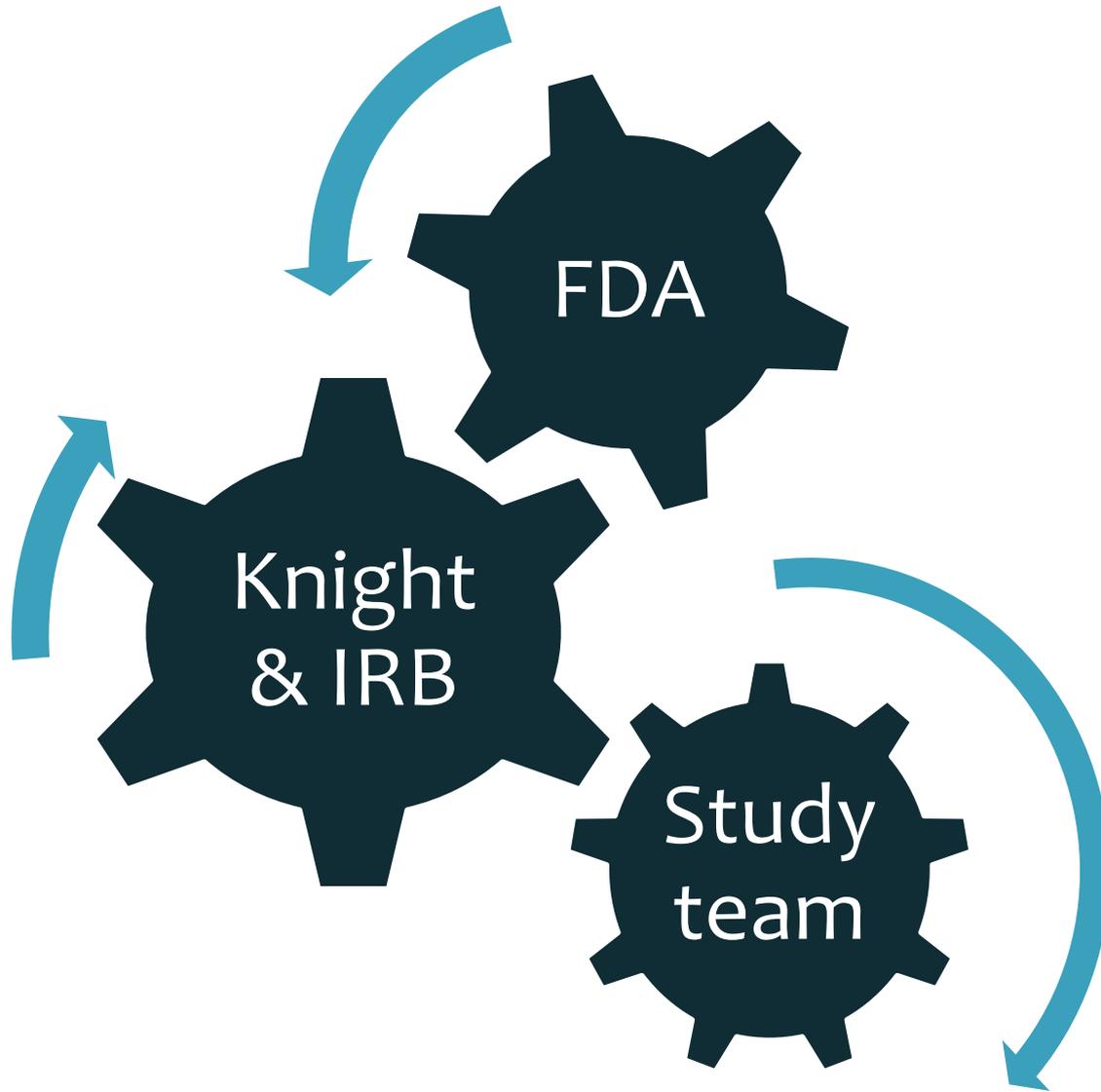
- Applications, reports
- Institutional contact
- Documentation

Reduce Risks

- Sponsor-Investigator
- Reminders

Provide Services

- Holder responsibilities
- Applications, reports
- Templates



Sponsor-Investigator Trials & Risk

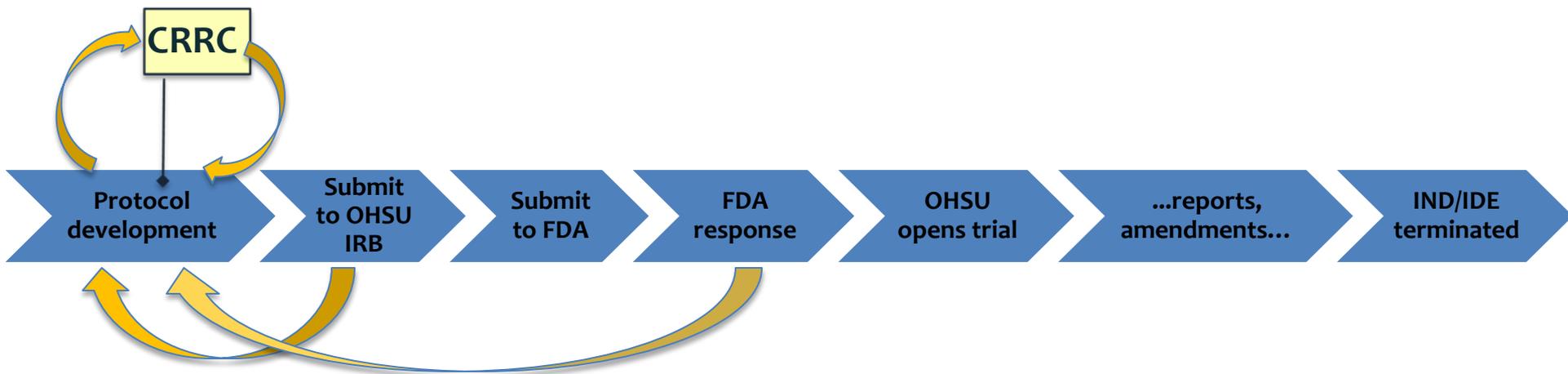
*“Where **problems** have come in recent years, the majority have come in studies where the **investigator was also the sponsor.**”*

David A. Lepak, M.D., Ph.D.

FDA Senior Advisor for Clinical Science

Guide to Good Clinical Practice January 2005

CRRC review: Scientific and Pharmacy Reviews for IND/IDE Need



IND

• Investigational New Drug

CRRC

• Is an application for IND indicated? *per CRRC Reviewer*

• Is application for IND exemption indicated? *per CRRC Reviewer*

IRB

• CRRC determination to IRB; IRB Analyst verifies agreement → joint memo to IRB

FDA

• Submit to FDA

• Final determination

IDE

• Investigational Device Exemption

CRRC

• Is an application for IDE indicated? Risk? *per CRRC Reviewer*

• Is application for IDE exemption indicated? *per CRRC Reviewer*

IRB

• CRRC determination to IRB; IRB Analyst verifies agreement → joint memo to IRB

FDA

• Submit to FDA

• Final determination

FDA Guidance: Special Consideration of Risk/Benefit in Oncology Studies

Risk/benefit is protocol-specific.

Modifications and off-label therapy are common in oncologists' clinical practice.

Bottom line: Does study involve a change in any factor that *significantly increases the risks* or *decreases the acceptability of the risks* associated with use of the drug product? (IND)

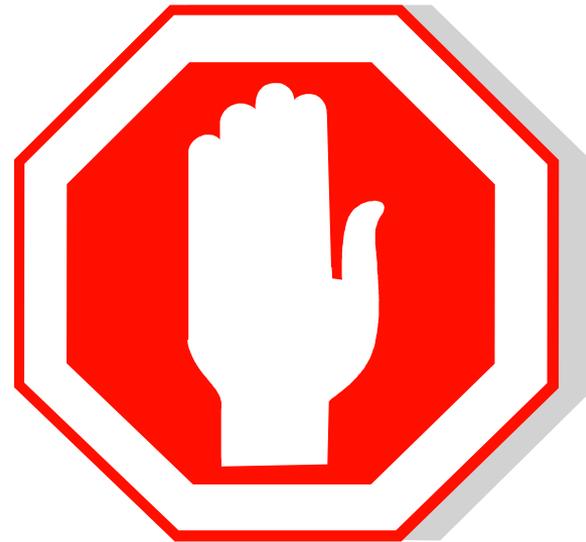
Best Practice:

better to file an application and
let FDA determine its status
(exempt or not exempt) than to
not file

IRB holds key to OHSU start

Whether or not an IND or IDE is required, all clinical research must have IRB approval before study may open to enrollment.

IRB can hold its approval until FDA grants IND or IDE or exemption



Holder Responsibilities: centralized management will help

FDA Report Requirement	Reporting Timeframe
Protocol Amendment	
New Protocol	after IRB approval but before implementation
Change in Protocol	After IRB approval but before implementation
New Investigator	Within 30 days of being added
Information Amendments	At time of occurrence
IND Safety Report	
serious & unexpected	Within 15 calendar days of notice
fatal or life threatening	Within 7 calendar days of notice
Annual Report	Within 60 days of anniversary
Discontinuation of investigation	Within 5 working days of decision
Withdrawal of IND	At time of occurrence

IDE Reporting Requirements		
Type of Experience	Report to OHSU IRB	Report to FDA
Unexpected, related, or possibly related - Death - Potentially life-threatening events	7 days	10 working days (If also meets the definition of an UADE)
Any event that is Unexpected in nature, severity or frequency Related or possibly related OR Expected experience(s) that increases risk of physical or psychological harm	15 days 10 days if meets the definition of UADE	<u>Results</u> of UADE Evaluation 10 working days if UADE OR Annual (if device related)
Expected, not related, and does not increase risk of physical or psychological harm. Serious but not related	Annual	Not required to report events unrelated to investigational device
Failure to obtain informed consent prior to using an investigation device	5 working days	5 working days to sponsor Sponsor has 5 working days to report to FDA
Deviation from the investigational plan to protect the life or physical well-being of the subject in an emergency	5 working days	5 working days
Withdrawal of IRB approval	All IRBs within 5 working days of notification	5 working days
Withdrawal of FDA approval	All IRBs within 5 days of notification	N/A
Current Investigator List	IRB approval required prior to participation	Comprehensive list of investigators every 6 mos
Progress Report	Annually at time of OHSU Continuing review	Annually within 60 days of the anniversary of the IDE
Significant Risk Determination	N/A	5 working days after Sponsor learns of IRB determination
Recall and Device Disposition	Promptly no later than 30 working days	30 working days after the request is made
Termination of study	Notify IRB that study is closed to enrollment and that study visits are done within 3 months of last study visit	Within 30 working days of the completion or termination of the investigation
Final Report	Submit with Modification to terminate protocol at the OHSU IRB	6 months after study completion or termination of IDE

Special Cases: no change to procedure yet

- **Humanitarian Use Device (HUD)**
- **Emergency use IND**
- **Intermediate Use IND**

Investigator Initiated Trials (IITs) Involving Drugs or Devices: IRB Review Process



Andrea Johnson, JD
Regulatory Specialist
OHSU Research Integrity Office

IRB Review Process for IITs

eIRB Submission. Administrative review by Knight staff.



CRRC Review. IRB Regulatory Specialist receives CRRC's assessment regarding IND/IDE regulatory issues and verifies agreement and/or identifies areas for further consideration.



IRB Review. In addition to all standard aspects of review, IRB makes the final determination on:

- Whether **IND exemption** criteria is satisfied
- Whether a non-exempt investigational device is **SR or NSR**, if FDA has not already determined this
- IRB may require investigators to consult the FDA if questions remain.

Drugs: What is the IRB's role?

- IRB determines whether IND exemption criteria are satisfied for unapproved use of an approved drug. **No IND is required if exempt.**
- Unapproved drugs **ALWAYS** require an IND.

IND Exemption Criteria:

- Study is not intended to support FDA approval of a **new indication** or significant change in **labeling**
- Study is not intended to support a significant change in **advertising**
- Investigational use does not **significantly increase the risks** or **decrease the acceptability of the risks** compared to the approved use
- Study is conducted in compliance with **IRB and informed consent** regulations
- Study will not be used to promote **unapproved indications**
- No exception from informed consent for **emergency research**

Devices: What is the IRB's role?

- **Investigators/study staff** determine whether a device is Exempt or Non-Exempt from IDE regulations when completing the IRQ.
- **IRB** verifies this determination.
- **Exempt devices do not require an IDE.**

Exempt devices include:

- **Approved devices for approved use**
- Certain non-invasive diagnostics that are *not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure*
- Devices that are not studied for safety/effectiveness and do not put subjects at risk, and the focus is on:
 - Consumer preference testing
 - Testing a modification to an approved device
 - Testing a combination of two or more approved devices
- Custom devices

Devices: What is the IRB's role?

For **Non-Exempt** devices, if FDA has not made a determination already, IRB determines whether an investigational device is **Significant Risk (SR)** or **Non-Significant Risk (NSR)**.

- SR: Apply for IDE with FDA.
- NSR: No IDE application required.

An SR Device:

- Presents a potential for serious risk to the health, safety, or welfare of a subject and is:
 - Intended as an implant;
 - Used in supporting or sustaining human life; or
 - For a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health.
- **OR**, otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

IRB Submission Requirements

- The IRB will verify that the IRQ drug and/or medical device pages are complete and correct.
- IND/IDE information must be provided in the IRQ when one is required.
- **Required Docs for Drug or Device Studies:**
 - Investigator's Brochure or Device Info
 - If IND/IDE is required, communications from FDA
 - Noting receipt of IND/IDE application (IND/IDE goes into effect 30 days after receipt unless FDA indicates otherwise);
 - Approving IND/IDE application; **OR**
 - Stating that IND/IDE is not required.
 - Documentation of SR/NSR status for devices (FDA and/or sponsor)
- IRB approval is contingent on FDA approval of IND/IDE.

A Quick Word on IVDs

- *In Vitro Diagnostics (IVDs) are **medical devices!***
- Regulation of IVDs is currently the topic of much discussion by the FDA.
- An OHSU policy on IVDs is currently in development. Stay tuned for more details!

An IVD used in a study is generally considered **exempt** if it is **non-invasive** and is **not used as a diagnostic procedure without confirmation** by another medically established diagnostic procedure.

Unapproved IVDs used to **determine subject eligibility for a study, determine placement on a treatment arm, or otherwise make treatment decisions** within the context of a clinical trial are generally **non-exempt devices that may require an IDE.**

New Submission Requirements for Cancer-Related Studies

Susan Aust, MSPH, CRRP

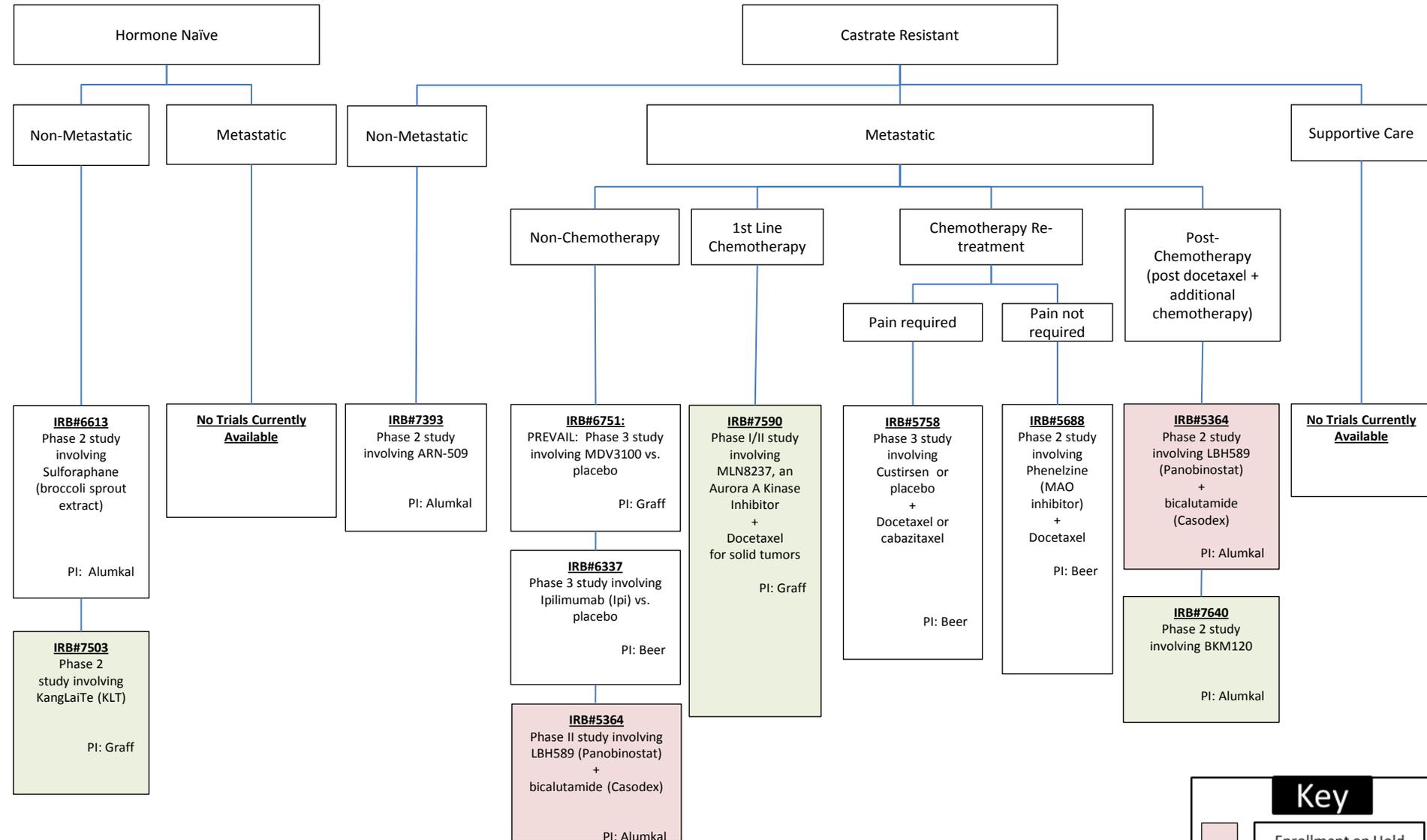


New CRRC Requirements as of 1 Jan 2012

- Disease-specific flowsheets must accompany each new interventional, therapeutic study submission
- Cover letter describing fit of study in portfolio, any significant OHSU contribution to the study and disease site leader sign-off for each new interventional, therapeutic study
- Biostatistics sign-off for all IITs

Disease-Specific Flowsheets

- A disease specific flowsheet must accompany all new cancer-related, interventional, therapeutic study submissions
- Requirement applies to cooperative group studies, industry sponsored studies and investigator initiated studies
- Flowsheets should show the fit of submitted study in current disease site portfolio of studies that are open to enrollment or pending approval
- Disease specific flowsheets can be found at the following link:
<https://bridge.ohsu.edu/research/knight/projects/clintrialflows/SitePages/Flowsheets-Home.aspx>
- PI's will contact Disease Site Leader to approve/add study to flowsheet
- Knight Disease Site Leader can be found on the Knight Intranet at:
<http://ozone.ohsu.edu/cancer/sharedres/kctoresdocs.cfm>



Key	
	Enrollment on Hold
	Open for Enrollment
	In Development

Example of the Prostate flowsheet using the standard format

Cover Letter to CRRC

- PI must include a cover letter with submission, describing appropriateness of the interventional therapeutic study, particularly if there is already study or studies available for targeted population
- Letter should speak to any significant contribution that OHSU has made to development or conduct of study, if applicable
 - PI is national PI or member of steering committee directing development of compound
 - OHSU was involved in development of compound/device under study
 - OHSU conducting ancillary or correlative laboratory work
- Letter must include sign off of Disease Site Leader
<http://ozone.ohsu.edu/cancer/sharedres/kctoresdocs.cfm>

Local Investigator- Initiated Protocol Biostatistics Sign-Off

- Applies to all interventional and non-interventional OHSU Knight investigator-initiated trials (IIT)
- Assures biostatistician has provided consultation on the study design and statistical considerations for each Knight IIT protocol
- OHSU Knight Local Investigator Initiated Trial Biostatistics Approval Form can be found at: <http://ozone.ohsu.edu/cancer/sharedres/kctoresdocs.cfm>
- To request assistance from the Biostatistics Shared Resource go to their Knight home page located at:
<http://www.ohsu.edu/xd/health/services/cancer/research-training/shared-resources/biostatistics.cfm>

Knight Data and Safety Monitoring Plan Revision 4 New Requirements

Denise Mathes, BSN, RN, MPH

Data Safety and Monitoring

Study Type	Monitoring Frequency	Auditing
Pilot/Phase I	Quarterly reports to the Knight DSMC	At least yearly
Phase II/III	Half-yearly reports to the Knight DSMC	At least yearly

Data safety and monitoring activities continue from the time the protocol is OHSU IRB approved and active, to the time when all subjects have completed their treatment and all are beyond the time point at which clinical trial-related adverse events would likely be encountered.

The DSMC does not monitor non-interventional clinical research.

Data Safety and Monitoring – IIT Data Reports

- Expected and actual numbers of patients enrolled to date (local and national if multi-center clinical trial)
- Number of patients treated
- Description of any changes to the clinical trial design since the last DSMC review
- Exceptions in eligibility or treatment
- Dose tier for each patient, for Phase I clinical trials
- Treatment arm and best response to treatment (dependent on endpoint) for each patient, for Phase II and III clinical trials
- Cumulative summary of AEs with type and grade for each patient (Grades 3-5).
 - Grade 1 or 2 AEs may be requested depending on the clinical trial

Data Safety and Monitoring – IIT Data Reports

- List of DLTs
- List of AEs of interest as defined by the protocol
- List of all UPs reported to the OHSU IRB (cumulative)
- List of all protocol deviations reported to the OHSU IRB (cumulative)
- Significant literature reporting developments that may affect the safety of participants or the ethics of the clinical trial
- Results of any interim analyses required by the protocol
- Copies of abstracts or papers written using clinical trial data

Data Safety and Monitoring – IIT Data Reports

Phase-in of reporting requirement:

- New studies: all new studies submitted into eIRB on or after 1 Jan 12
- Ongoing studies: DSMC report required at time of 2012 CRQ; reporting frequency per study phase after CRQ

Report template will be available

Multi-Center IITs

Knight as a participating site

- Knight auditing team will not provide oversight or monitoring for clinical trials conducted outside of the OHSU Knight Cancer Institute.
- The portion of the clinical trial conducted at OHSU will be reviewed for safety and audited according to Knight Cancer Institute standard audit and review procedures.
- Protocols where the Knight Cancer Institute is listed as a participating site must include a detailed clinical trial-specific DSMP specifying the responsibilities and oversight provided by the clinical trial coordinating center.

Knight Cancer Institute as a clinical trial coordinating center

- All participating sites must identify their IRB of record
- Knight coordinating group will identify a protocol manager who is responsible for ensuring the Knight Cancer Institute Coordinating Center Policies and Procedures are followed.
- Protocol specific data and safety monitoring for the entire clinical trial will be conducted by the Knight DSMC according to the phase and risk level of the clinical trial.

Quality Assurance Audits

Sponsor: Local, Investigator Initiated Clinical Trials

- Annual audits or more frequent with clinical trials with potentially higher risks, vulnerable populations or high accruals as specified in the study DSMP
- If a clinical trial is audited by NCI or any other monitoring entity, the investigator should provide the audit findings to the Knight DSMC and IRB.
- External sites participating in a multi-center clinical trial sponsored by an OHSU investigator
 - Have their own DSMP which must be adhered to by monitoring and auditing the clinical trial at their site
 - Audit reports should be sent to Knight DSMC
 - KCTO may conduct audits or may arrange to attend and observe any monitoring or audit of the clinical trial performed by the local site

Ongoing studies:

When to upload revised DSMP into eIRB

IITs: may upload in a modification but must upload by the 2012 CRQ

Quality Assurance Audits

DSMC assessments:

Acceptable	<ul style="list-style-type: none">• Few minor deficiencies• Major deficiencies addressed/corrected prior to the audit
Acceptable, needs follow up	<ul style="list-style-type: none">• Multiple minor deficiencies• Major deficiencies <u>not</u> corrected prior to the audit
Unacceptable	<ul style="list-style-type: none">• Multiple major deficiencies• Single flagrant discrepancy• Multiple, recurrent minor deficiencies

Reporting audit findings to IRB:

- Unacceptable audit: PI submit report upon receipt
- PD or UP as outcome of audit: PI submit report with PD/UP
- No PD/UP and not unacceptable: PI submit report with CRQ

Knight Clinical Trials Office Intranet

<http://ozone.ohsu.edu/cancer/sharedres/kcto.cfm>

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