Memorial Sloan Kettering Cancer Center

Conduct of the Trial Part I

OBJECTIVES

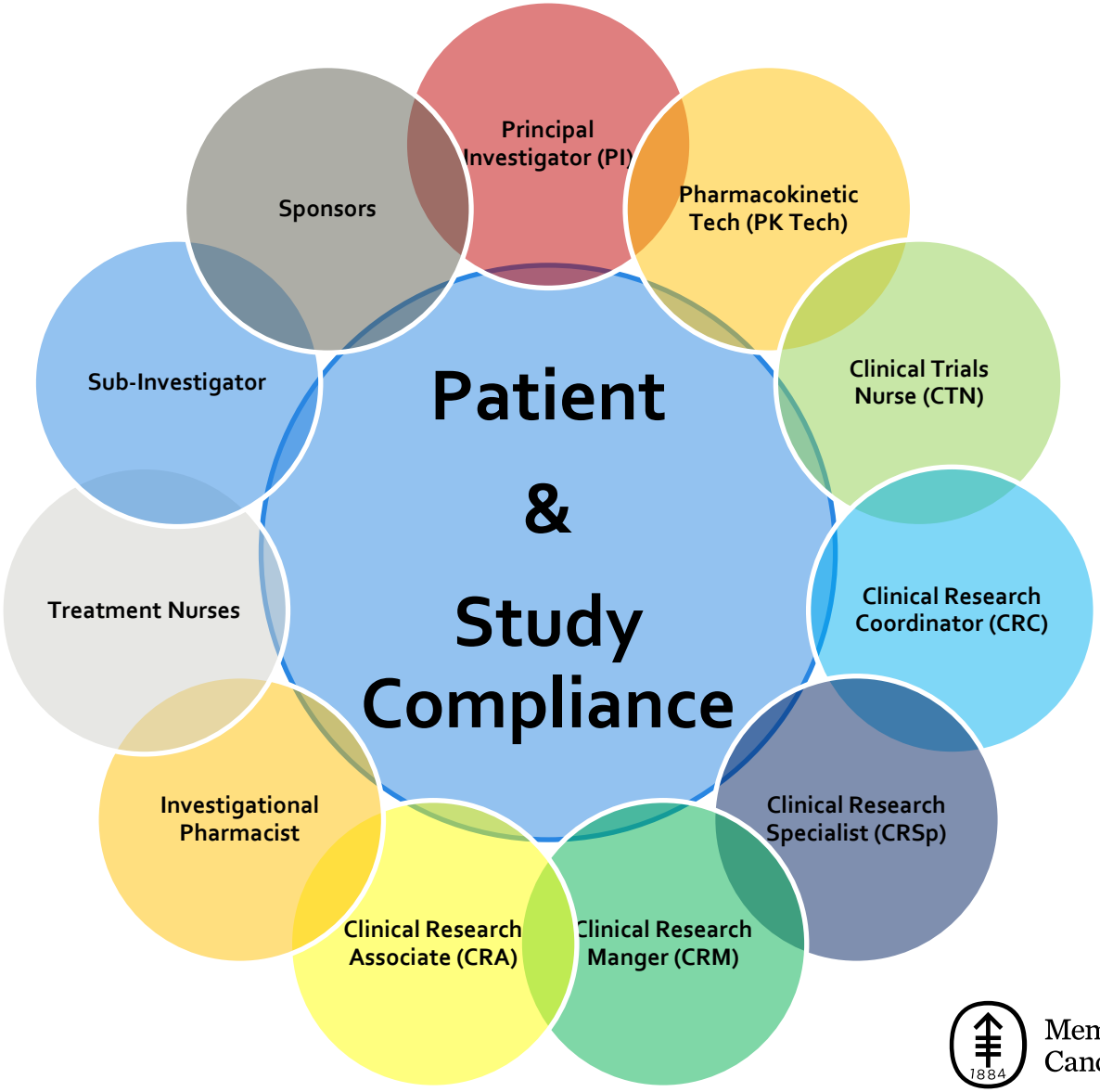
Review the roles and responsibilities of the research team

Describe plans for research rigor and integrity

Review accruing Patients & developing an Eligibility Checklist

Discuss creating attainable and reasonable deliverables when writing the protocol

Let's meet the team!



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Principal Investigator & Sub-Investigators

Principal Investigator(PI)

Primary Responsibility is study integrity

Also responsible for: trial management, safety, study staff, patient accrual, patient care

Sub-Investigator(Sub-I)

Share Responsibilities P.I.

Patient accrual

Patient care

Consenting Professionals

Only study staff authorized to obtain informed consent

Typically all investigators

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Principal Investigator Responsibilities

- **Trial Oversight including:**
  - Recruitment & Consenting of trials participants
  - Medical care of subjects
  - Communication with Internal Review Board(IRB)
  - Compliance with Protocol
  - Investigational Product accountability
  - Safety Reporting

Sponsor Responsibilities

- **Some of the responsibilities of the Sponsor include**:
  - Submit (Investigational New Drug)IND application with FDA.
  - Select Investigators qualified by training and experience.
  - Select Monitors qualified by training and experience.
  - Submit changes to the investigational plan to the FDA throughout the study.
  - Ensure the Investigators are compliant with the agreement, protocol, FDA and IRB.
  - Report Unanticipated adverse effects (UAE) to the FDA.
  - Maintain accurate, complete and current records.
  - Submit reports regularly within the required timeframes to the FDA
- **Sponsor team includes**:
  - Medical Monitor
  - CRA/ Monitor
  - Contract Research Organization (CRO)
  - Data Manager
  - Biostatician

Why do you need a study team?

Principle Investigator Responsibilities

- **Trial Oversight including:**
  - Recruitment & Consenting of trials participants
  - Medical care of subjects
  - Communication with Internal Review Board(IRB)
  - Compliance with Protocol
  - Investigational Product accountability
  - Safety Reporting
  - Ensure accurate/timely data collection and input.

How do you put together a study team?

Generalist vs specialist

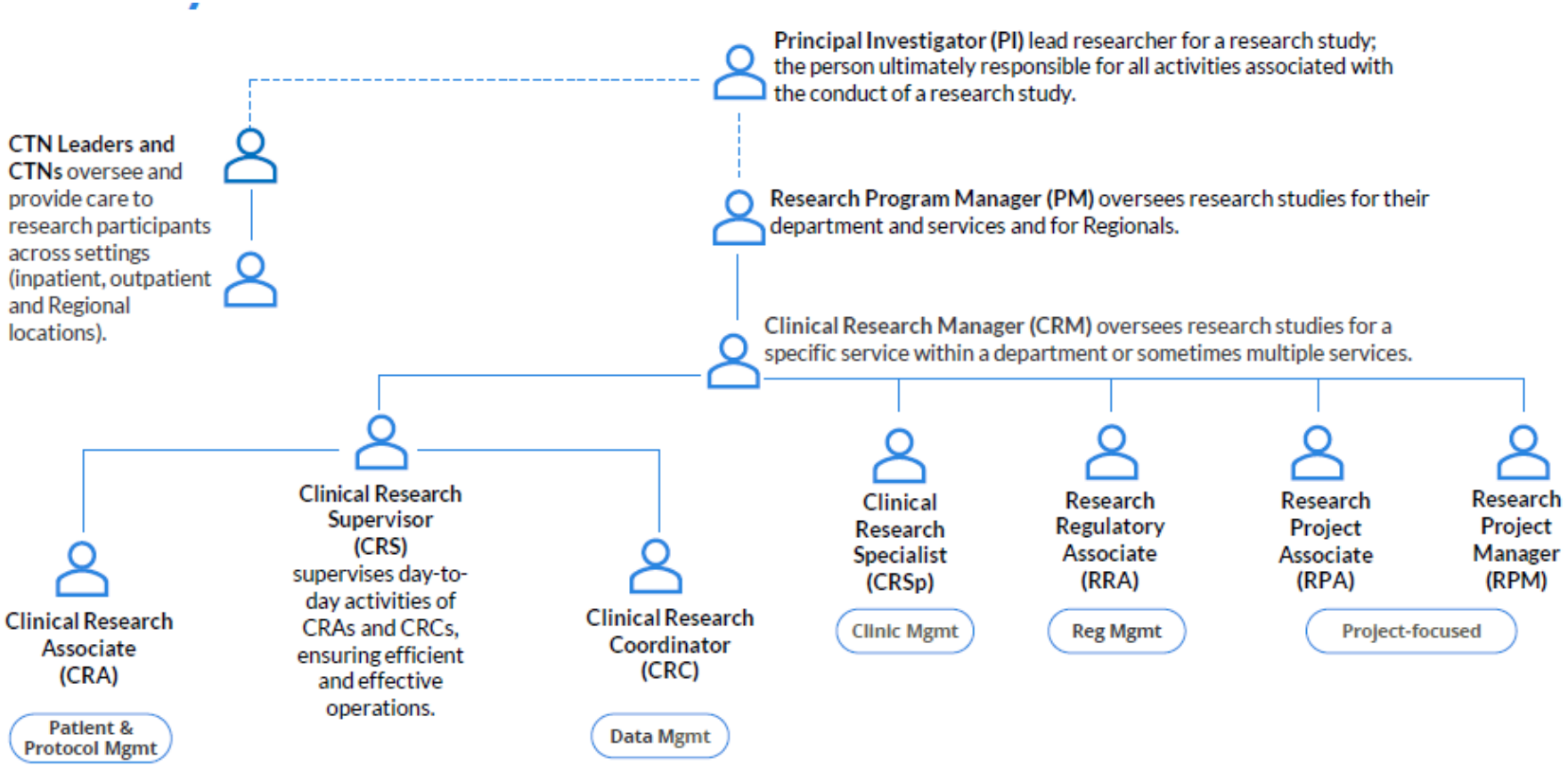
Research Nurse

Research Nurse
+
Administrative
Person

Research Nurse
Data person
Regulatory Person
Patient Management

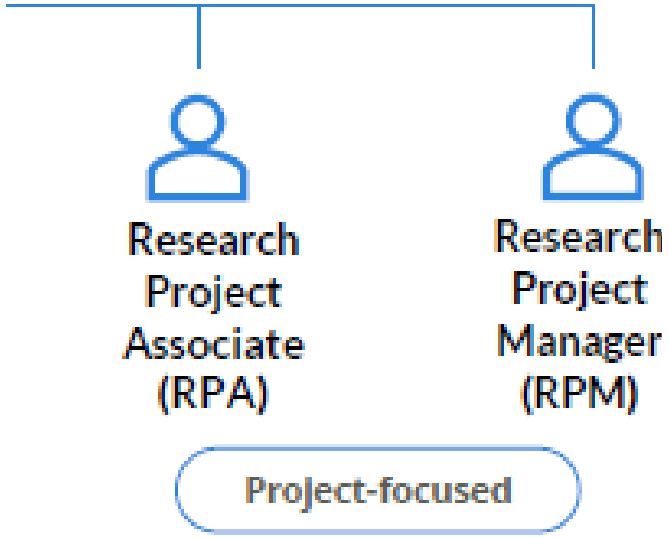
Study Team Roles @MSK

The Big Picture



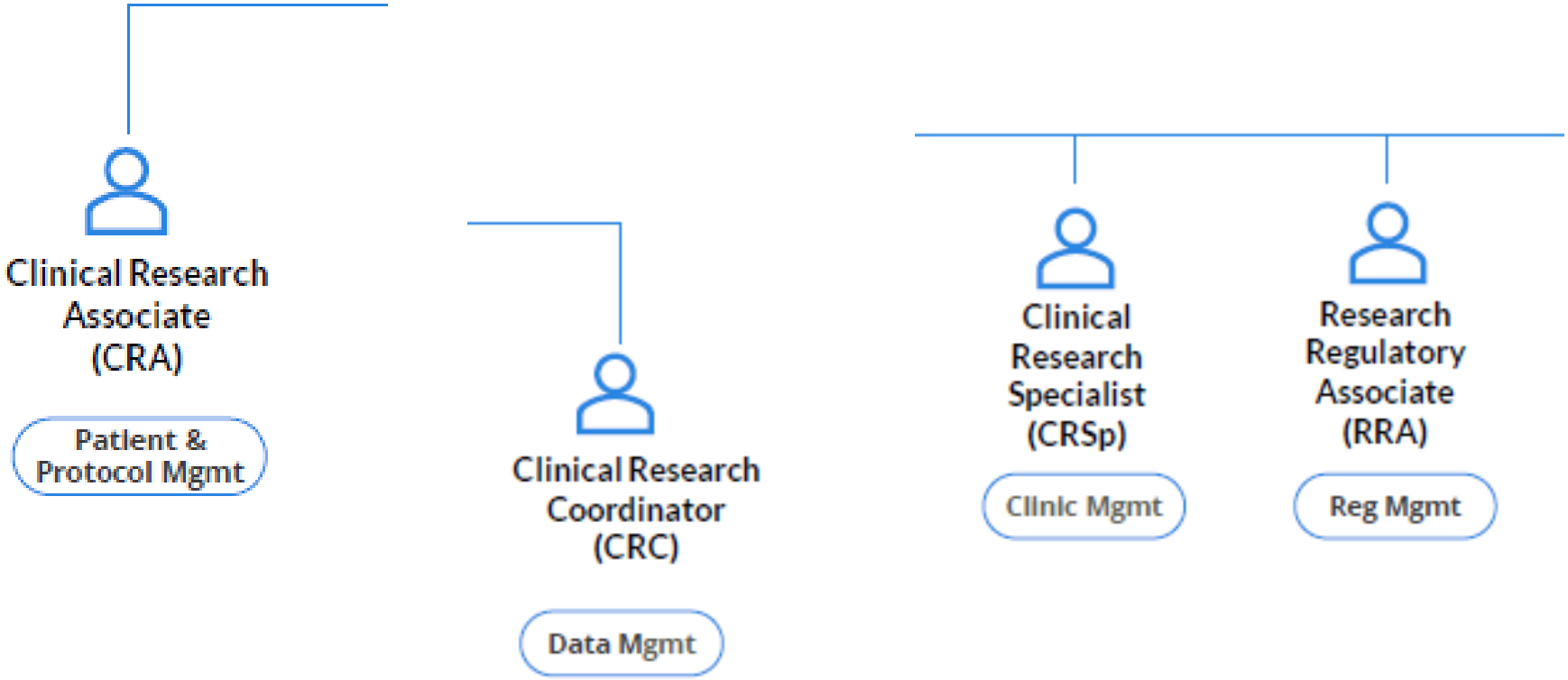
Study Team Roles @MSK

The Team that does data projects
(not what we are talking about today)



Study Team Roles @MSK

The Core non-clinical Study Team



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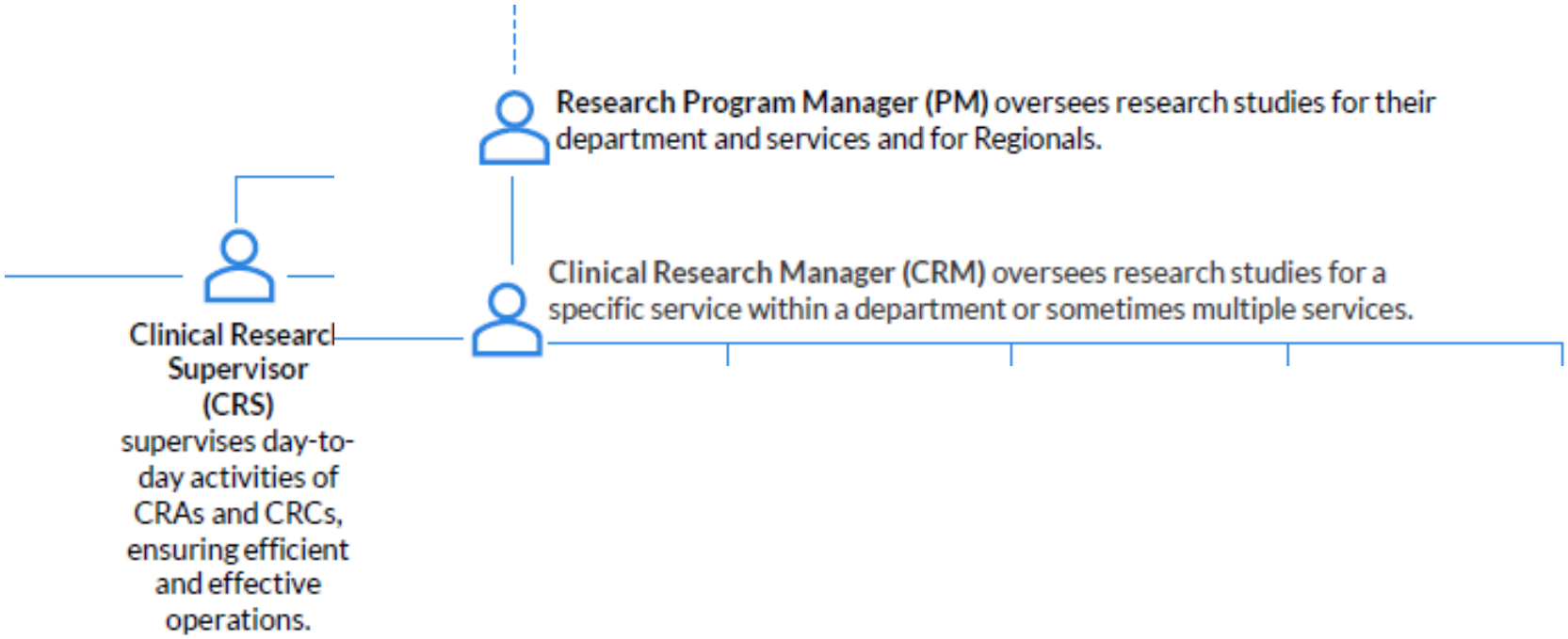
Study Team Roles @MSK

The Managers



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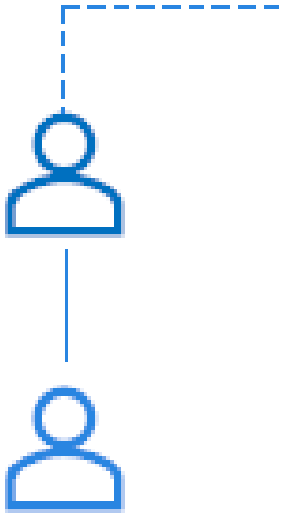
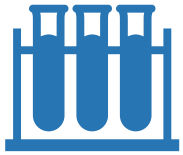
Study Team Roles @MSK

CTN Leaders and CTNs oversee and provide care to research participants across settings (inpatient, outpatient and Regional locations).



Investigational Pharmacist & Pharmacokinetic Technician (PKT)

- **Investigational Pharmacist**
  - Prepares study drug per protocol
  - Maintains accurate drug accountability records
    - Receipts of drug shipment/invoices
    - Drug accountability record forms/database
  - May assist with concomitant med review and home medication reconciliation
- **Treatment Nurse**
  - Administer study drug per protocol
  - Communicate outcomes with research team
  - Reinforce education
- **Pharmacokinetic Technician (PKT)**
  - Collect Research Human Tissue Samples
  - Sample Processing & Shipping
  - Study EKG's



Clinical Trials Nurse(CTN)

Figure 2. Oncology Clinical Trials Nurse Competency Model

ANA—American Nurses Association; ONS—Oncology Nursing Society

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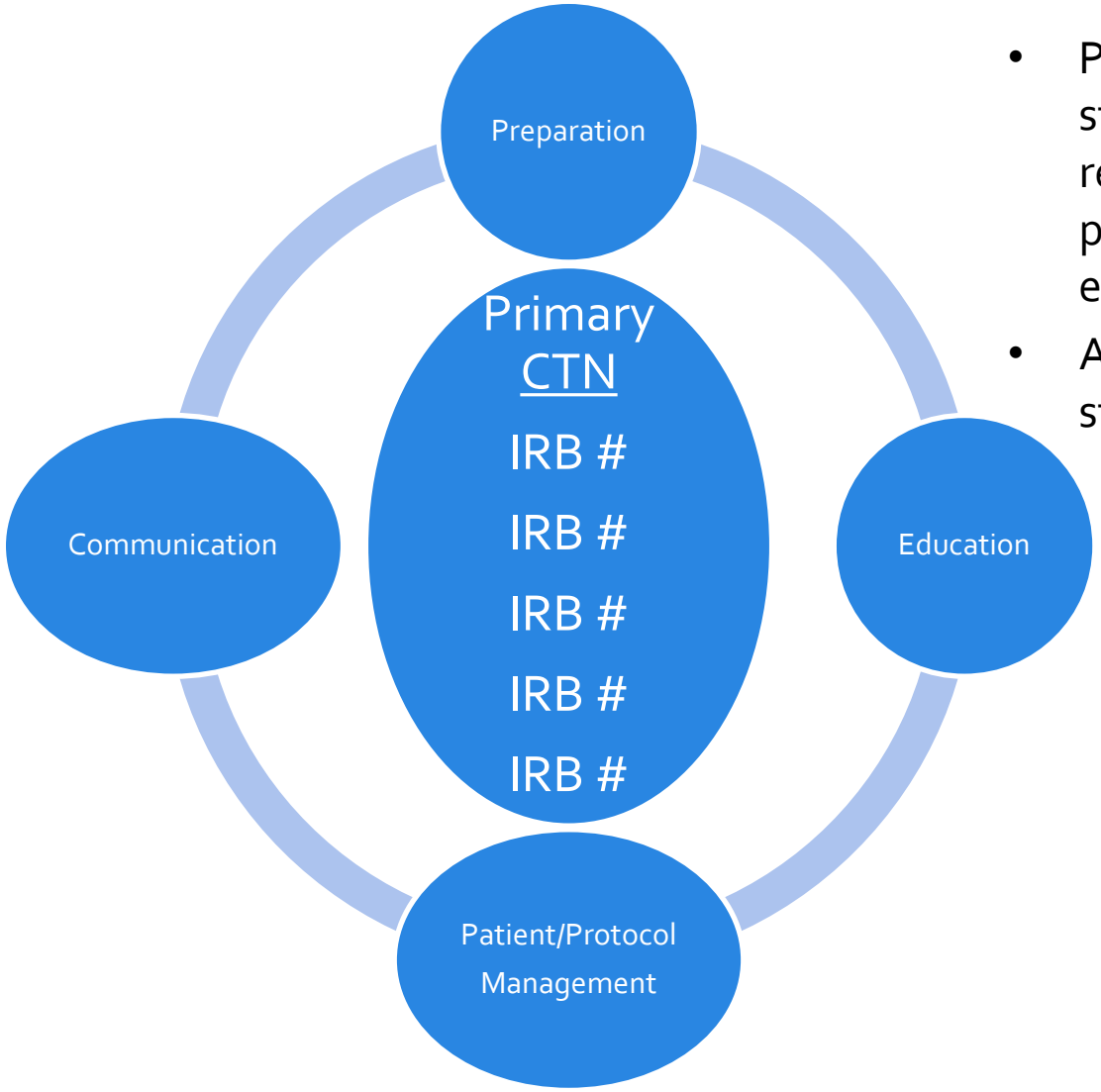
Clinical Trials Nursing @ MSK



- Primary **research** nursing provides a structure for building trusting relationship(PI, CRM, CRC), that provide for a caring and healing environment.
- Aligning Clinical Trials Nurses with studies allows for:
  - Opportunity for CTN to gain expertise in a subset of protocols
  - Improve knowledge, competency, accountability and continuity
  - Improve communication
  - Enhanced preparedness

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Key Responsibilities of Primary CTN

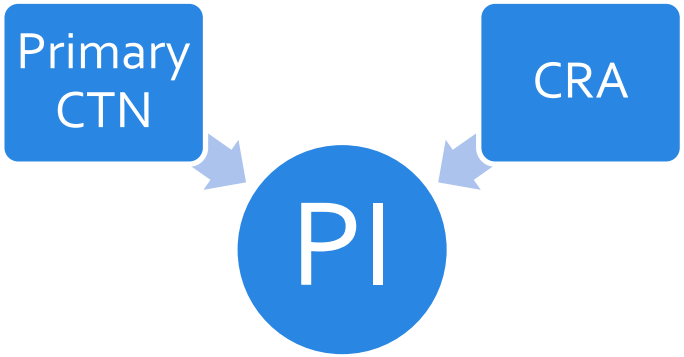
- **Patient Management**
  - Telephone triage
  - Clinic visits
    - Medication reconciliation
    - Patient education
    - Toxicity assessments
    - Coordination of care

- **Protocol Management**
  - PI meeting participation
  - Protocol Start Up
    - Protocol Review Tool
    - Study tools
    - Inservice development

–SAE narrative submission(initial & f/u)

–ECL completion & eligibility confirmation

–Query resolution



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Monitor Responsibilities (highlights)

5.18.4 Monitor's Responsibilities

The monitor(s), in accordance with the sponsor's requirements, should ensure that the tri al is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see sections 4.1, 4.2, 5.6) and these remain adequate throughout the trial period, that facilities including laboratories and equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

(i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

(ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

(iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

(iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

(v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

- The monitor is the main line of communication between the sponsor and the investigator
- Verifying that the investigator has adequate qualifications and resources
- Verifying investigational product
- Verifying that investigator follows the protocol
- Verifying that written informed consent was obtained
- Ensuring/verifying all aspects of study conduct

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) https://www.fda.gov/media/93884/download

Monitoring summary report

Dear Marina and the PRA Health Sciences Team,

Thank you for the monitoring follow up letters dated 24-Aug-2020 and 11-Sep-2020 and thank you for the recent monitoring visits on 04-05-Aug-2020 and 01-02-Sep-2020.

This letter is in response to the interim monitoring visits for the above-mentioned study and addresses outstanding action items noted in prior monitoring visits, to date.

Extracted from the monitoring follow up letters are what we understand to be all open pending items. Our site's response to these items is listed below. Please let us know if you have any questions regarding this list.

Administrative Issues:

Type	Description	Date Identified	Action Required	Site Response
Site Personnel/Facilities	CRA to review ML's, CV's, GCP and protocol v4 training for new Sub-I's: Adam Schoenfeld MD; Andrew Chow MD; Andrew Plodkowski MD; Nathaniel Swinburne MD; Robert Young	02-Sep-2020	2Sep2020 (ML) CRA to review new Sub-I's ML, CV's, GCP and protocol v4 training in sites electronic study files during next remote visit in Oct.	Study team will continue to have all regulatory documents available for RMVs.
Administrative	CRA did not meet with PI to discuss recruitment and visit.	02-Sep-2020	2Sep2020 (ML) CRA to meet with PI to discuss visit and recruitment	To be scheduled for next RMV on 10/26/20 – 10/28/20
Laboratory	Site study laboratory Manuals were not reviewed during remote visit on 1-2Sep2020	02-Sep-2020	2Sep2020 (ML) CRA to review site study laboratory manuals during next monitoring visit in	Study team will continue to have all protocol-related

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11/10/2020

Re: MSK Online Monitoring Visit Feedback Form Results

Dear [redacted],

Your Online Monitoring Feedback Form from [redacted] (IQVIA) for Protocol [redacted] on 10/20/2020 has been received and no substantive issues have been indicated. Thank you for performing high quality work on this study.

The recent monitoring visit was rated as **ACCEPTABLE** by Clinical Research Quality Assurance (CRQA)

If you have any questions or concerns, please do not hesitate to contact me using the details provided.

Regards,

Francine Puma
Manager, Monitoring Program
Clincal Research Quality Assurance
Clinical Research Administration
633 3rd Avenue, 15th Floor
New York, NY 10017
Phone: (646) 227-2159
Email: pumaf@mskcc.org

Accruing Patients & Developing an Eligibility Checklist

Accruing Participants

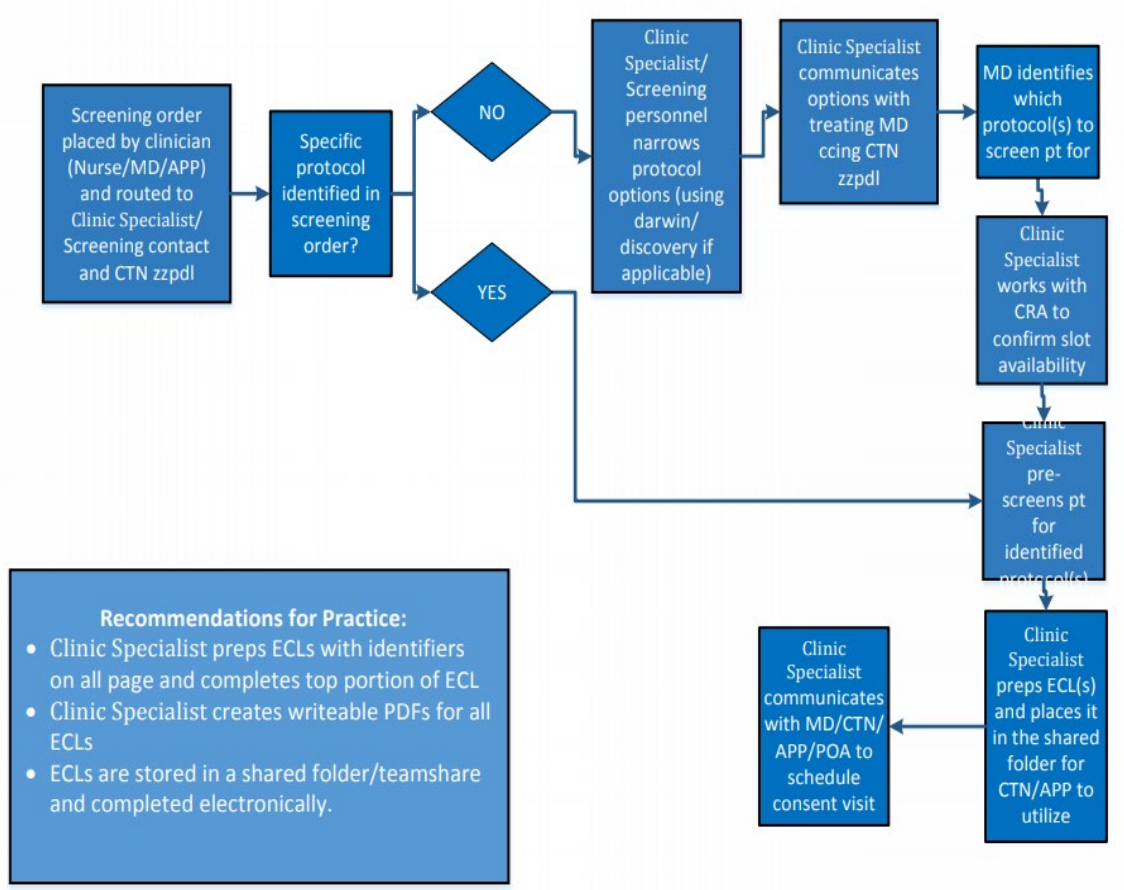
Plan for recruitment:

- Develop a recruitment plan during the protocol planning stage.
- Avoid unnecessarily restrictive inclusion and exclusion criteria; think about the widest net, not the "perfect" participant.
- Develop a profile of prospective study participants with consideration for:
  - What would motivate individuals to join the study?
  - Sources from which the target population is likely to obtain information
- Review recruitment, dropout, and screening success rates from previous studies and implement strategies that build on previous successes and incorporate lessons learned.
- Consider assessments at locations convenient for participants.
- Consider offering participants transportation to and from the study site.
- Choose appropriate staff members to conduct recruitment.

Accruing Participants @MSK

Plan for identifying and screening for participants:

- Develop a recruitment plan during the protocol planning stage.
- Develop a profile of prospective study participants
- Choose appropriate staff members to conduct recruitment.
- Utilize a structured prescreening approach



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An electronic screening tool can notify docs

darwin

Gregory,

The patient(s) below under your care have been identified as having a MET-dependent cancer (MET exon 14 alteration/amplification/expression).

This potentially qualifies them for participation in MSK IRB #20-299, A Phase 1/2 Study of the Biparatropic MET-MET Inhibitor, REGN5093.

Key inclusion / exclusion criteria:
- Advanced disease, must have received prior standard of care therapies
- RECIST 1.1 measurable disease
- Normal organ function (ANC 0.5, Hg 8, Plat 75, Bili <=1.5x ULN, AST/ALT <=2.5x ULN)
- No prior treatment with MET-targeted biologic therapy unless the cancer has a MET exon 14 alteration
- No untreated or active primary brain tumor, CNS mets, leptomeningeal disease or spinal cord compression

The study is open in Manhattan campus & Westchester for all protocol activities, and open at Monmouth with limited activities. The sponsor provides some reimbursement for protocol-related travel and hotel stays.

If you feel that any of these patients might be appropriate I would be happy to discuss with you more or see the patient anytime.

Best,
Alex

Alexander Drilon MD
drilona@mskcc.org

An electronic screening tool can notify docs

[redacted]
[redacted]
Female - 75 yr old
last tx: [redacted]

Primary Solid Oncologist
rielyg@mskcc.org

Event: **Upcoming Scan**
IRB: **21-499** - A Phase 1/2 Study of the Highly Selective ROS1 Inhibitor NVL-520 in Patients with Advanced NSCLC and Other Solid Tumors (ARROS-1)
PI: **Drilon, Alexander ,MD** - Medicine/ Early Drug Development Service

matched: **1389** day(s) ago
based on: **EZR (NM_003379) - ROS1 (NM_002944) fusion: c.1090+285:EZR_c.5557+112:ROS1del**
Lung Adenocarcinoma (LUAD)
cBioPortal

Your patient has a cancer with a ROS1 fusion and may be a candidate for treatment with the next-generation ROS1 TKI NVL-520 in an ongoing phase 1/2 basket study (IRB #21-499).

NVL-520 was designed to (1) be a more potent ROS1 inhibitor compared to prior TKIs, (2) have substantial activity in the CNS, and (3) target ROS1 TKI resistance mutations. Furthermore, it is projected to have a better safety profile compared to older agents due to its selectivity and lack of TRK inhibition.

Please note that if your patient is interested in this trial, a full review will need to be performed to determine eligibility. This includes a review of potential qualifying biomarkers, some of which may require actionability confirmation via a second test.

An eligibility summary is included.

ELIGIBILITY
-any metastatic solid tumor with ROS1 fusion
-no limit on prior ROS1 TKIs for expansion cohorts (1 prior ROS1 TKI is required for escalation)
-no limit on prior cytotoxic/immune therapy
-evaluable disease allowed in escalation; measurable disease required for expansions
-asymptomatic CNS disease allowed

Click here to email the study team

Next Scan
2025-10-31 09:00
KOCH MRI 2

Next Dr Visit
2025-10-31 13:00
RIELY, GREGORY J

How can we facilitate accrual?

- Consider group-wide screening request process
  - How is it staffed (nurses, research admin staff)?
  - Who do they screen (All visits? All new visits? Only selected by providers)?
- Weekly discussions about open protocols
- Active prioritization for given clinical context
  - (e.g. first line metastatic disease)

Eligibility

- Inclusion/Exclusion Criteria
  - List of criteria guiding enrollment of participants into a study
- A subject is eligible if s/he meets all inclusion and exclusion criteria.
- Every criterion MUST have a source document in the EMR.

Eligibility Documentation: Sample Checklist

Instructions:

- *Answer each criterion by responding **'Yes','No'** or **'NA'**. A participant is eligible if s/he meets all inclusion and exclusion criteria.*
- *Every criterion MUST have a source document in the EMR. If a criterion does not have a primary source document in EMR, the eligibility checklist (ECL) will be considered the primary source document per criterion. Follow CR SOP 414 "Source Documentation".*

INCLUSION CRITERIA

#	Inclusion Criterion *Each criterion is to be listed as a statement copied directly from the protocol; do not convert to a question.*	Response (Yes/No/ NA)
1.0	Age ≥ 18 years **(YES)** Date of birth: _____/_____/_____ MM DD YYYY	_____ AGE
2.0	Written informed consent **(YES)**	_____
3.0	Advanced biopsy-proven metastatic or recurrent non-small cell lung cancer **(YES)**	
4.0	Somatic activating mutation in EGFR in a prior tumor biopsy or cfDNA sample **(YES)**	_____
5.0	Patients will have progressed on standard of care therapies **(YES)** *(Check all that apply)* ☐ Patients with EGFR exon 20 insertions will have progressed on platinum-based chemotherapy ☐ Patients with EGFR alterations sensitizing to tyrosine kinase inhibitors (TKIs) will have progressed on osimertinib ☐ Patients will be allowed to have received other systemic therapies since progression on the above, including investigational agents at least 28 days or 5 half lives prior to the first dose of study drug, whichever is shorter	_____
6.0	**For Cohort A:** Subjects must have at least one measurable (at least 10 mm) intracranial disease according to RECIST 1.1. **(YES / NA-if cohort B)**	_____
7.0	**For Cohort A:** Subjects must have new or progressing CNS metastases. **(YES / NA-if cohort B)** **Note:** Extracranial measurable disease is not required.	_____

- Checklist helps to ensure that participants meet eligibility

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Ensuring Source Documentation for Eligibility

Definition: Original documents, data, and records that are used in a clinical trial

Key Purposes of Source Documents:

- Provide original documents, "raw" data and records
- Documentation where protocol-specific data are abstracted from and transferred to case report forms (CRFs)

Examples:

- Informed consent process
- **Concomitant Medications**
- Protocol related visits
- **Results of study required scans/tests (e.g. RECIST)**
- Study drug administration
- PK recording
- Patient correspondence
- Adverse events/Serious adverse events
- Unscheduled visits

YOUR TURN!

- **IN THE CHAT INDICATE WHICH OF THE BELOW COULD BE UTILIZED TO CONFIRM THE FOLLOWING ELIGIBLITY CRITERION:**
  - Participant DOES NOT have persistent toxicities (>CTCAE Grade 2) caused by previous cancer therapy

TODAYS LAB REPORT IN EMR

PATIENT REPORT OF OUTSIDE LABS

Practical considerations

Time: Does the investigator have adequate time to devote to study oversight and the work that he/she must perform? If not, then no new studies should not be started until there is.

Practical considerations

Other Obligations: Are there anticipated personal, financial, or professional obligations for the investigator or the study staff that might interfere with meeting the study commitments? New studies should not jeopardize ongoing research projects, nor should they delay a trainee's progress on their research.

Practical considerations

Funding: Is there adequate funding (budget appropriate), sufficient personnel and space for study procedures available to conduct the study?

Practical considerations

Study Procedures: Does the investigative team have the ability and hospital credentials needed to perform all required study procedures?

Practical considerations

Are facilities and equipment adequate to perform the study?

Practical considerations

Contract Terms: Does the investigator and/or administration agree with the terms of the contract set forth by the sponsor?

Practical considerations

Available Subject Population: Will there be enough prospective participants available and are there reasonable expectations that enough will agree to participate and complete the study during the time frame planned for the study?

To be continued…