Clinical Research Study Management & Compliance:

Conducting Clinical Research at MSK and other NCI Designated Cancer Centers

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Agenda

Overview: MSK’s Clinical Research Program

MSK’s Research Council

- Performance Monitoring Sub-Committee
- New Protocol Reviews

How to Design Successful Trials

OVERVIEW:
MSK's Clinical Research Program

Dana Rathkopf, MD

NCI P30 Cancer Center Support Grant (CCSG)

1971 National Cancer Act developed the CCSG as a mechanism to assure rigorous internal oversight of scientific aspects of all cancer clinical trials

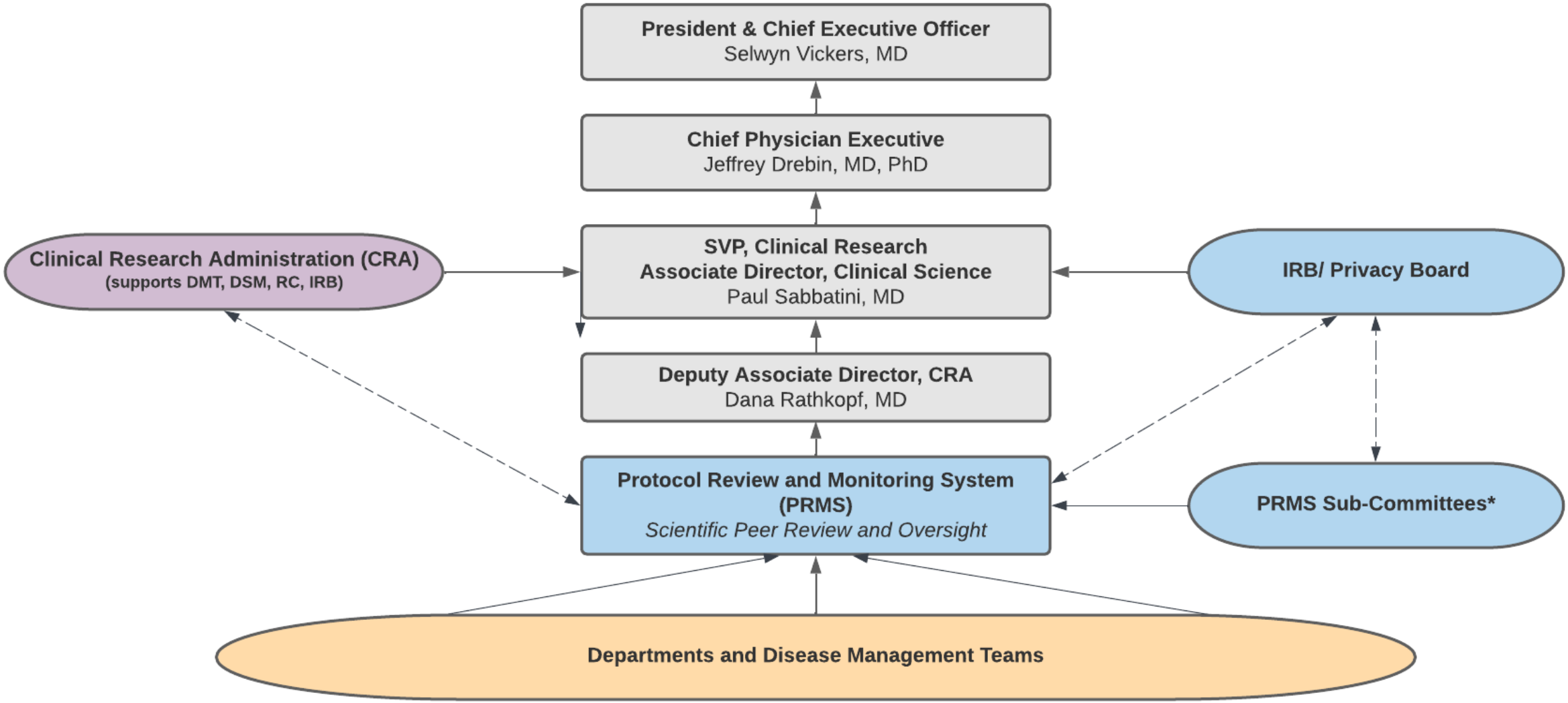
CCSG requires a ***Protocol Review and Monitoring System (PRMS)***

PRMS = two-stage scientific review:

1) Disease/Discipline
2) Scientific Peer-Review of **patient-oriented** research programs

PRMS review should be complementary to IRB and DSMC

MSK's Protocol Review & Monitoring System (PRMS) Reporting Structure



Protocol Activation, Review & Human Research Protection Program Unit

(Ann Rodavitch)

Protocol Activation Core (PAC) (Emily Valentino)

Centralized Study Start Up Experts

Consent Writing

Eligibility Checklists (ECL)

Regulatory Documentation Set Up

Epic Research Ordering Tools (ROT)

Liaison with PI, Study Team, Sponsor, Finance, Contracts

Protocol Review Core (PRC) (Sara Hanley)

Dept Committees (22):

Anesthesiology
Biostatistics
Clinical Trials Nursing/APP
CTS
Computational Oncology
Epidemiology
Health Outcomes
Investigational Drug Service (IDS)
Laboratory Medicine
Medical Physics
Medicine PDC
Medicine Steering
Neurology
Neurosurgery
Nursing
Pathology
Pediatrics
Pharmacy
Psych & Beh Sciences
Radiation Oncology
Radiology

Institutional Committees (9):

DSMC
DSMB
Peds DSMC
Perf Monitoring Committee
Research Council A
Research Council B
Committee on Radiation
Investigational New Drug
Radioactive Drug Research

Feasibility Committees (3):

Correlative Science Program
Multi-Site Compliance
Regional Network

Minimal Submission Requirements

Data Standards

Human Research Protection (HRPP) (Roy Cambria)

Institutional Review Board

Privacy Board

Genomic Advisory Panel

AAHRPP*(Association for the Accreditation of Human Research Protection Programs)* Accreditation Oversight and Management

Exempt/Human Subjects Research (HSR)/Engagement Determinations

Consent Office

Safety/Noncompliance Review

Federal regulatory incident reporting

Department of Defense (DoD) HSR Compliance

Research Council Mission

MSK's Stage 2 PRMS functions are carried out by the Research Council, which provides scientific peer review and oversight of MSK's clinical trial portfolio:

New Protocols

- Scientific validity, feasibility, and institutional priority

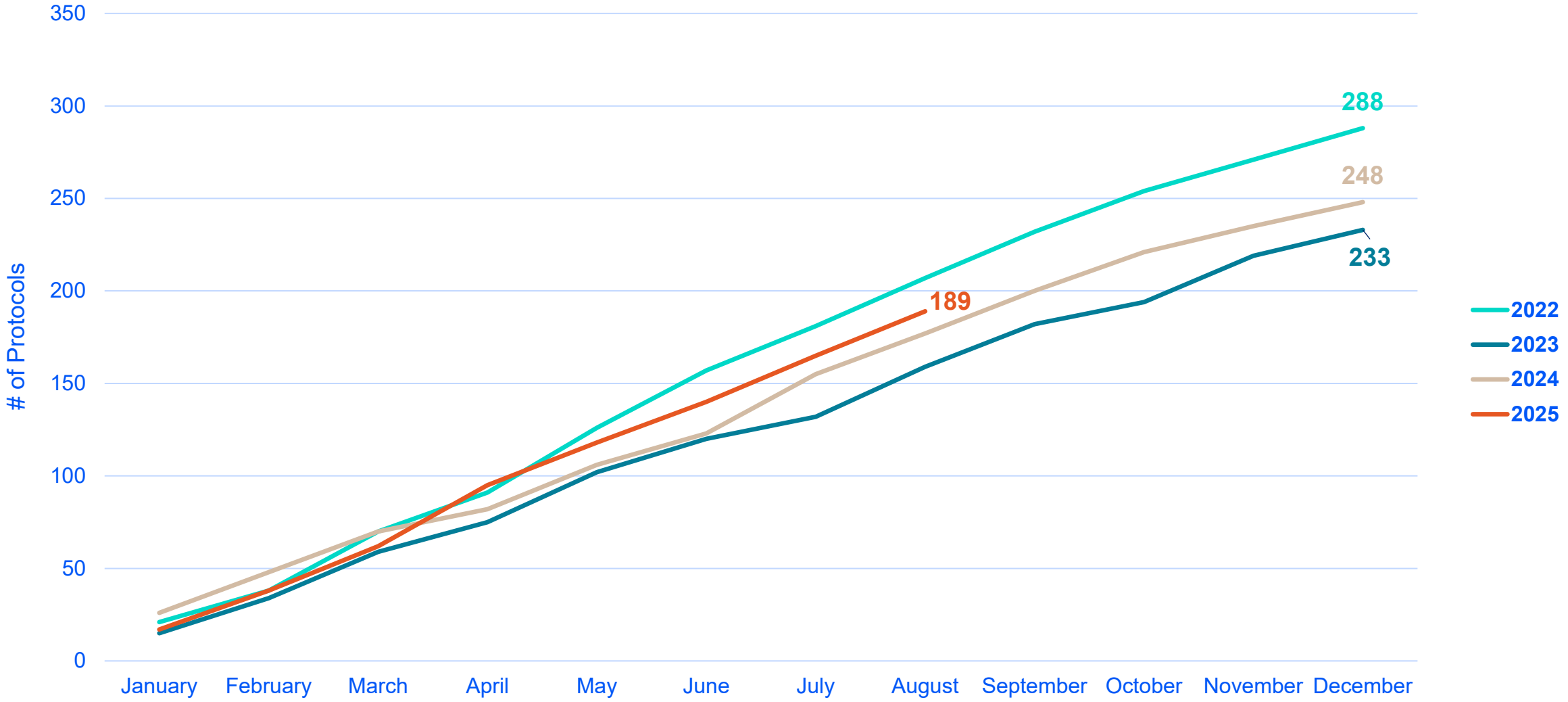
Amendments

- IRB/PB-approved protocols with significant design changes

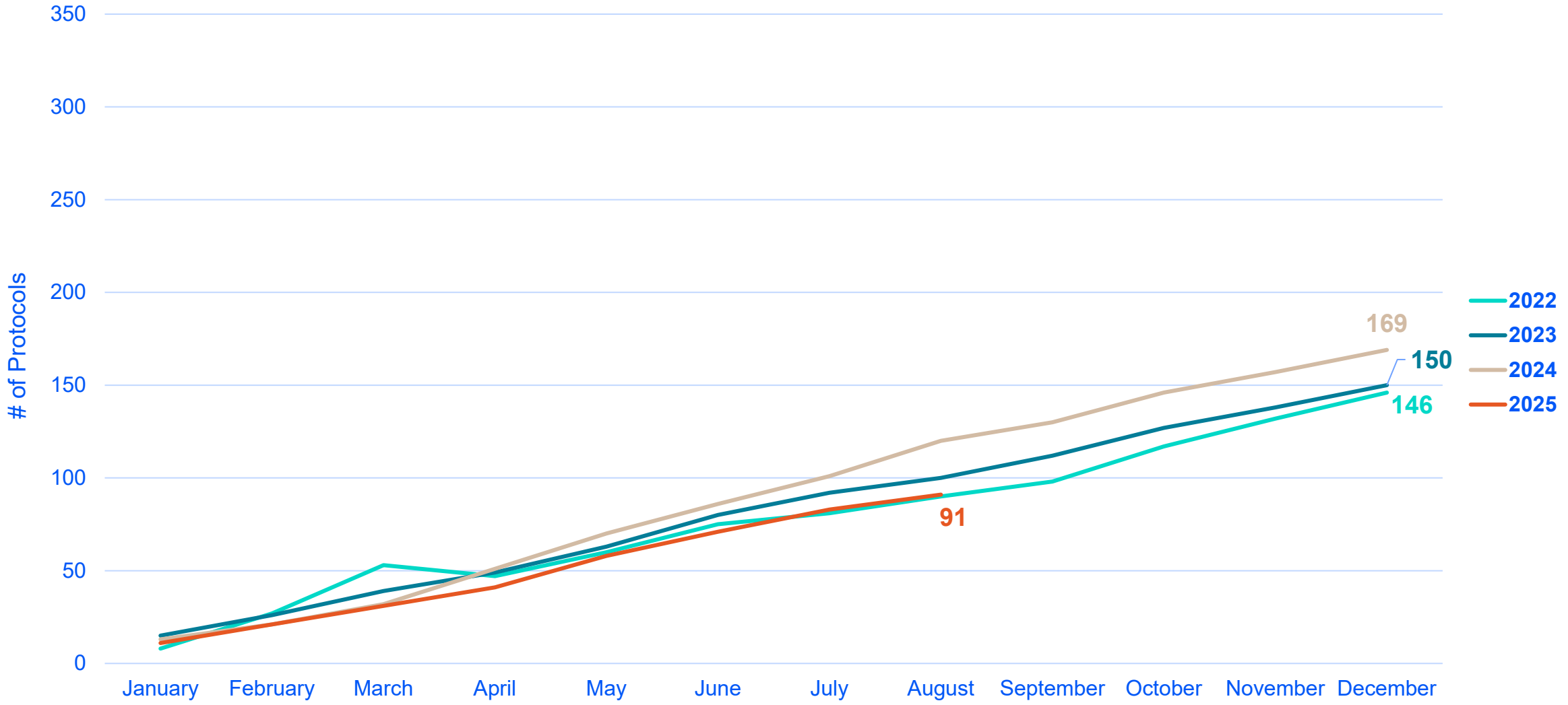
Research Portfolio (continual review)

- Scientific progress

Research Council Cumulative New Protocol Volume



Research Council Cumulative New Amendment Volume



Research Council Performance Monitoring Sub-Committee

Research Council Mission

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Amendments

- IRB/PB-approved protocols with significant design changes

Research Portfolio (continual review)

- Scientific progress

Performance Monitoring Committee (established 2021):
Monitor scientific progress of MSK's clinical research portfolio
and identify/address protocols with low potential for completion.

Performance Monitoring Guidelines

Continual Monitoring

Criteria	• 0 accruals >6 months
Workflow	• 0 accruals >6 months (reminder sent) • 0 accruals >12 months (response required)

Annual Monitoring

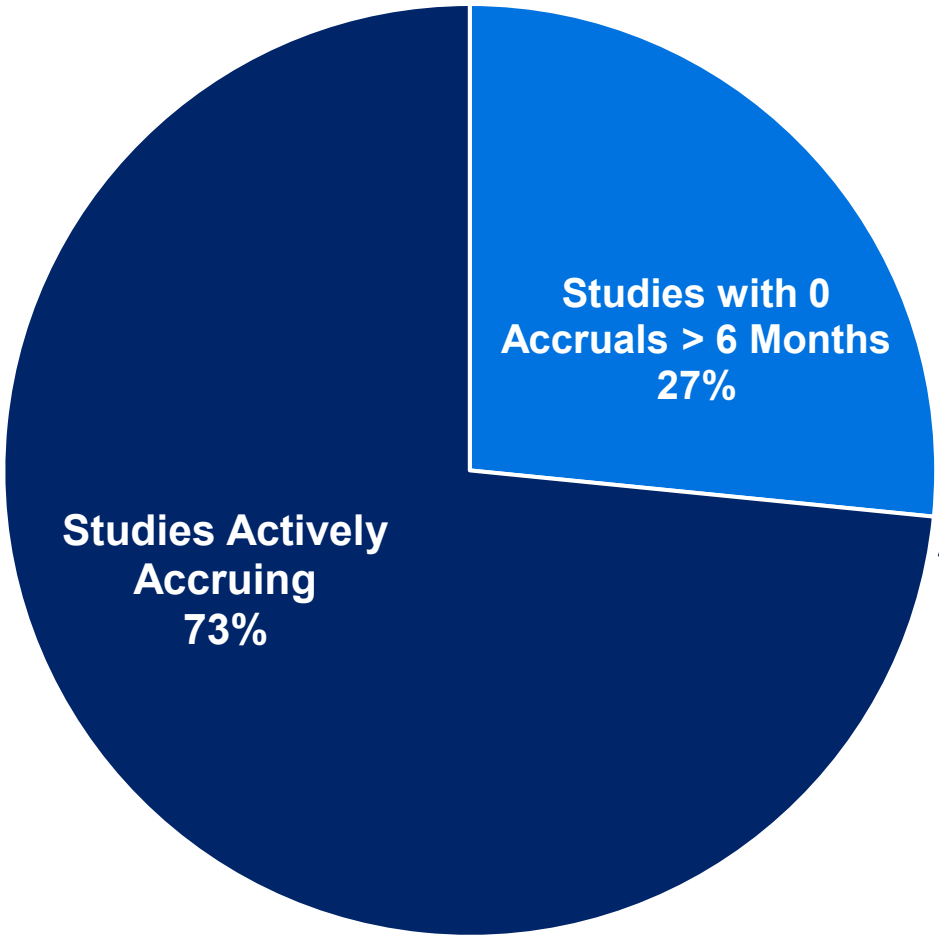
Criteria	• ETC >5 years • OTA >5 years
Workflow	• Response required

Note that there are adjusted guidelines for Pediatrics, NCI Network, and rare disease trials

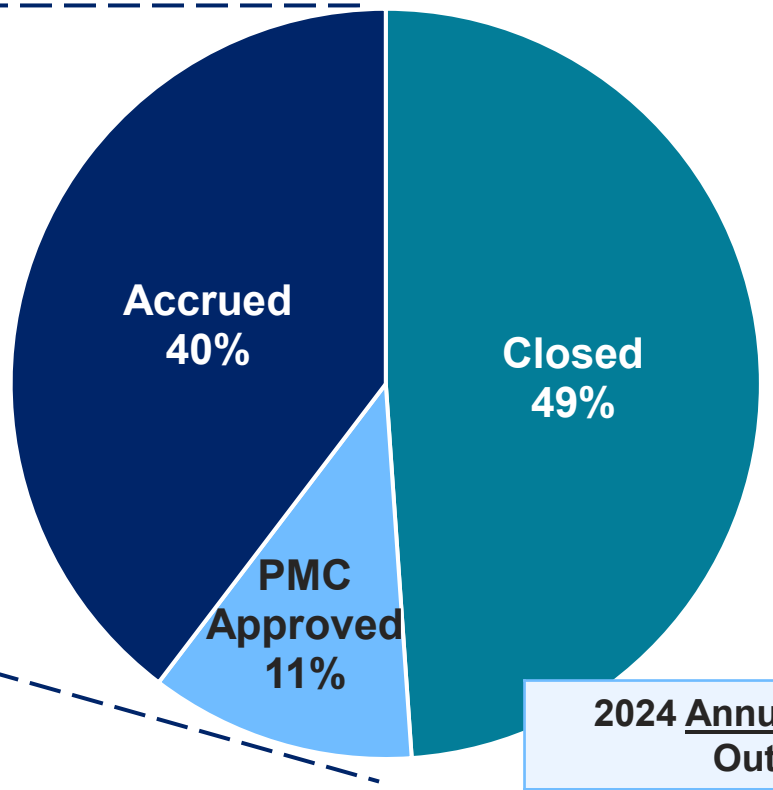
ETC=Estimated Time to Completion
OTA=Open to Accrual (one-time review)

Performance Monitoring Outcomes

2024 Portfolio
(844 open studies)



2024 Continual Monitoring Outcomes
(227 studies)



2024 Annual Monitoring Outcomes	
Accrued	49%
Closed	37%
Open (no progress)	14%

YOUR TURN!

IN THE CHAT, MSK'S RESEARCH COUNCIL IS RESPONSIBLE FOR:

A. Patient safety
B. Scientific merit
C. Data integrity
D. All of the above

B

RC's scope is scientific merit, prioritization, feasibility, and scientific progress

Research Council
New Protocol Review

Mark Dickson, MD

Research Council: Membership

~70 Members across Research Councils A & B

Program Membership:

- Clinical Research
- Population Sciences Research
- Imaging and Radiation Science
- Experimental Therapeutics

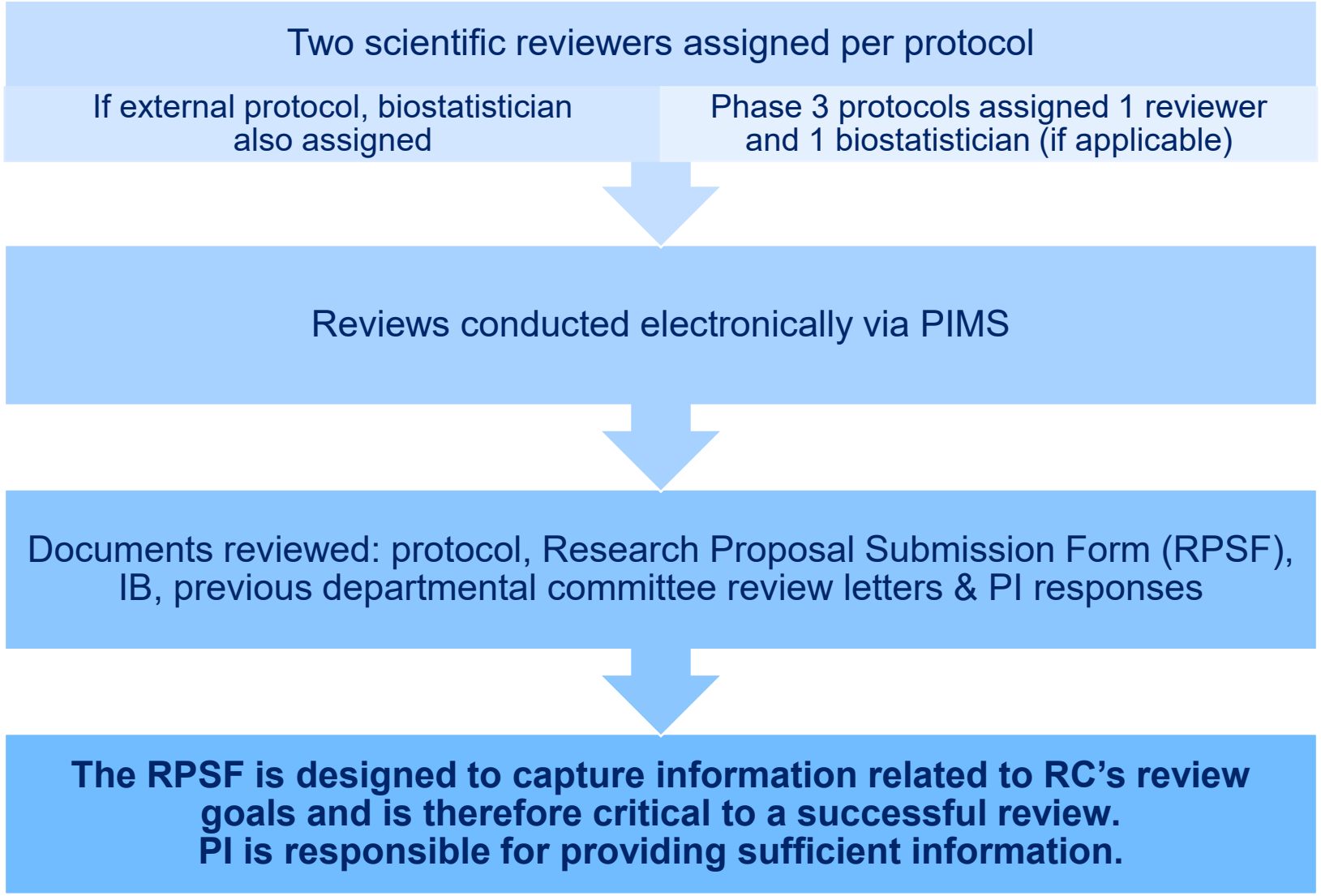
Institutional Committee Membership:

- IRB/Privacy Board
- DSMC/DSMB
- Investigational New Drug/Device Committee

Clinical, Scientific and Operational:

- Oncology (all disciplines)
- Psychosocial/QOL
- Biostatistics
- Genetics
- Epidemiology
- Radiology
- Anesthesiology
- Pathology
- Nursing
- Laboratory Medicine
- Research Operations

Research Council Review Process



RPSF: Background/Scientific Rationale

A.1 In no more than a few sentences and in a language useful to a non-specialist, highlight how the background data supports the scientific rationale for this study:

This section should include information that is not in the protocol document such as:

- **Summary, clarification, or expansion of background section regarding importance of the research question.**
- **Additional or recent background information such as preclinical data, previous phase data, rationale for study drugs/combination.**
- **Referencing specific sections of the protocol document can be helpful to reviewers.**
- **What highlights would you like to identify for reviewers?**

RPSF: Importance to the PI

A.4 How does this protocol support the PI's research interests and/or plans for future studies?

- How is the study important to the PI's career, clinical research portfolio, research interest?
- What is the PI's relationship with the company?
- Will this support the PI's goals/plans for future studies?
- If the PI is temporary and there is a plan to update in the near future, please specify this here.

A.5 Please select all options that apply to MSK's role in this study:

- ☐ Publication/Authorship previously discussed with sponsor
- ☐ Protocol Development
- ☐ Correlative Study Analysis: For all patients Globally/Nationally
- ☐ Correlative Study Analysis: For MSK patients only
- ☐ Product Development: For all patients Globally/Nationally
- ☐ Product Development: For MSK patients only
- ☐ Leadership (Global/National PI, Steering Committee Member, Lead Site, etc.)
- ☑ Other, Specify

If any of the above are selected, please explain:

Provide an explanation for each role chosen.

RPSF: Accrual Plan for Cohorts and Other Sites

A.7	Are multiple phases/cohorts occurring on this protocol?	YES
A.7.a	If Yes, is MSK participating on all phases/cohorts?	NO
A.7.a.1	In which phases and/or cohorts will MSK participate?	

If no, confirm text here includes what phases/cohorts MSK will participate in and rationale (if applicable). Please also note if the sponsor is aware of this choice. This information will focus reviewers on MSK's participation.

A.7.a.2 Indicate which phase/cohort is currently enrolling participants and specify number of participants accrued on each phase/cohort.

Provide response.

A.7.a.3 Provide the timeline for sponsor to activate the cohorts/phases in which MSK will participate.

If MSK will only participate in the phase II or dose expansion cohorts, indicate if the safety profile has been established and a treatment dose has been determined for the expansion cohort/phase.

If the safety profile has not been established, please reach out to zzPDL_RTM_CRA_PAC_Managers@mskcc.org prior to submitting to determine if protocol is ready for activation.

Provide response to include timeline, confirm if safety profile has been established, dose to be used for expansion cohort/phase II portion.

A.8	Is this protocol already open and accruing participants elsewhere?	YES

If Yes, provide information below about the study status. Include number of participants accrued to date, and current phase of the study.

Accrual to date should be provided with a note on what date this was confirmed with the sponsor. If one phase is complete or almost completed (for example, dose escalation), what is the status of the trial and what were the findings (safety data, dosing) etc.? How does this impact MSK's participation?

RPSF: Competing Studies

A.9	Are there existing or planned protocols competing for similar participants?	YES

If Yes, complete this table in order of protocol priority with the IRB# or title of planned study and the PI's name:	
IRB#, PAC# or Title of Planned Protocol	**PI**
IRB# if already open, PAC# if in review pipeline or Title of Planned Protocol	**John Doe, MD,PhD**

A.10 Provide a clear prioritization plan for all competing studies listed above. Specify how accrual will be affected for any studies already opened to accrual.

Prioritization plan should be clear and explicit for each study as it relates to this current study.

- **Clearly state how each study listed in A.9 will be prioritized for protocols competing for similar patient populations.**
- **Information must be consistent with number of eligible patients seen at MSK each year (E.4).**
- **Justification for sufficient patient population should be provided.**
- **Specify how accrual to currently opened studies will be impacted by opening an additional study completing for similar patient population.**

RPSF: Estimated Accrual/Time

E. PROTOCOL PARTICIPANTS		
E.1	Total expected accrual (all sites)	75
E.2	Please indicate protocol phase	I/II
E.3	Total expected accrual with MSK oversight (includes accruals at MSK, Regional Network, Alliance, CHERP, and all participating multicenter sites)	50
E.3.1.a	Total expected accrual at MSK sites (include Manhattan and Regional Networks)	50
E.3.1.b	Total expected accrual at external sites (include Multicenter, Alliance, and CHERP)	0
E.3.2.a	What is the expected accrual with MSK oversight in Phase I?	25
E.3.2.b	What is the expected accrual with MSK oversight in Phase II?	25
E.4	Total estimated number of participants eligible for this protocol annually at MSK	50
E.5	Anticipated protocol accrual time at MSK: (years)	3.5

If the anticipated protocol accrual time is greater than 3 years, please provide a brief justification in the space below.

Institutional expectation is that most protocols will complete accrual within 3 years. Strong justification is needed for trials expected to accrue for longer than 3 years.

Avoiding Common Pitfalls

Scientific Rationale:

- Provide adequate preclinical/clinical data

Design:

- Ensure the study can answer the question proposed

Prioritization and Feasibility:

- Ensure competing studies are prioritized, MSK has the patient population, all tests can be done, respond to previous committee concerns, etc.

Cohort Justification:

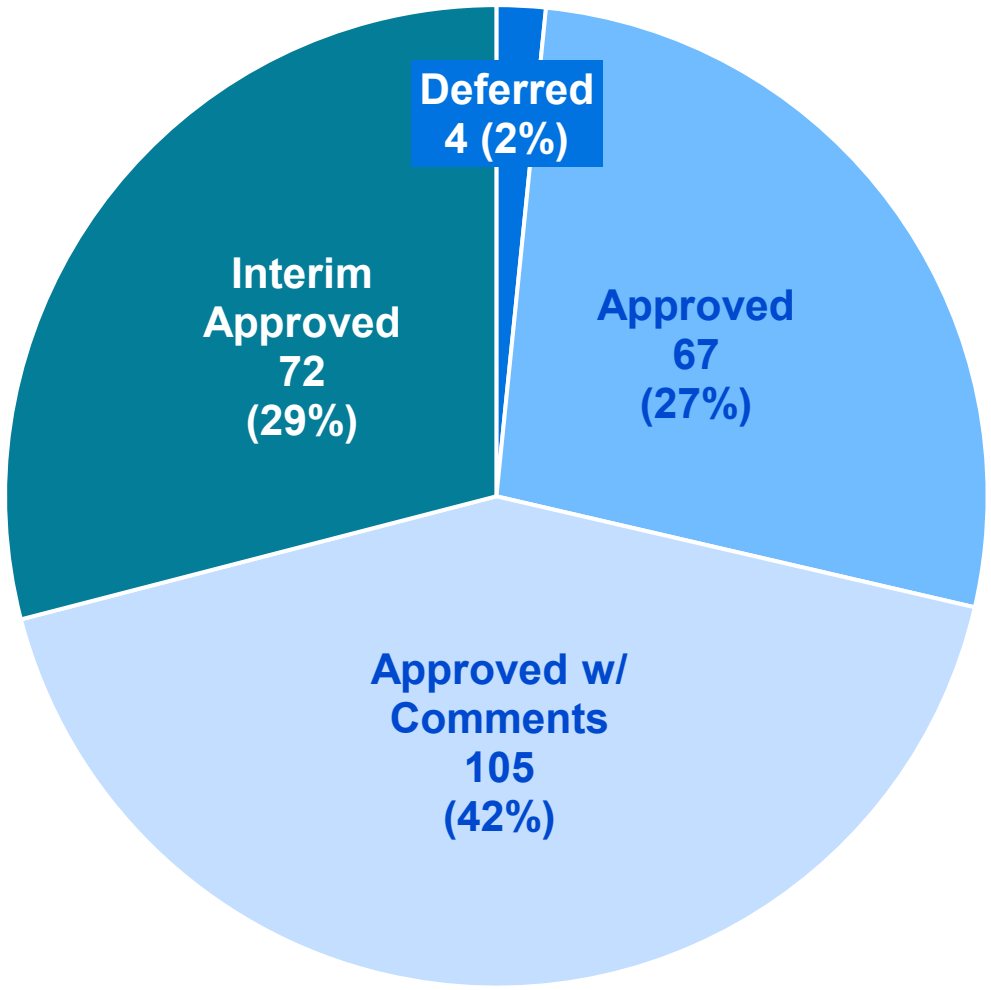
- Expansion and backfill cohorts should be well-justified
- Stopping rules should be provided when indicated
  - Futility and safety rules can be difficult to implement when accruing rapidly elsewhere, so provide as much data as possible from the sponsor on results to date whenever possible

Research Council Actions

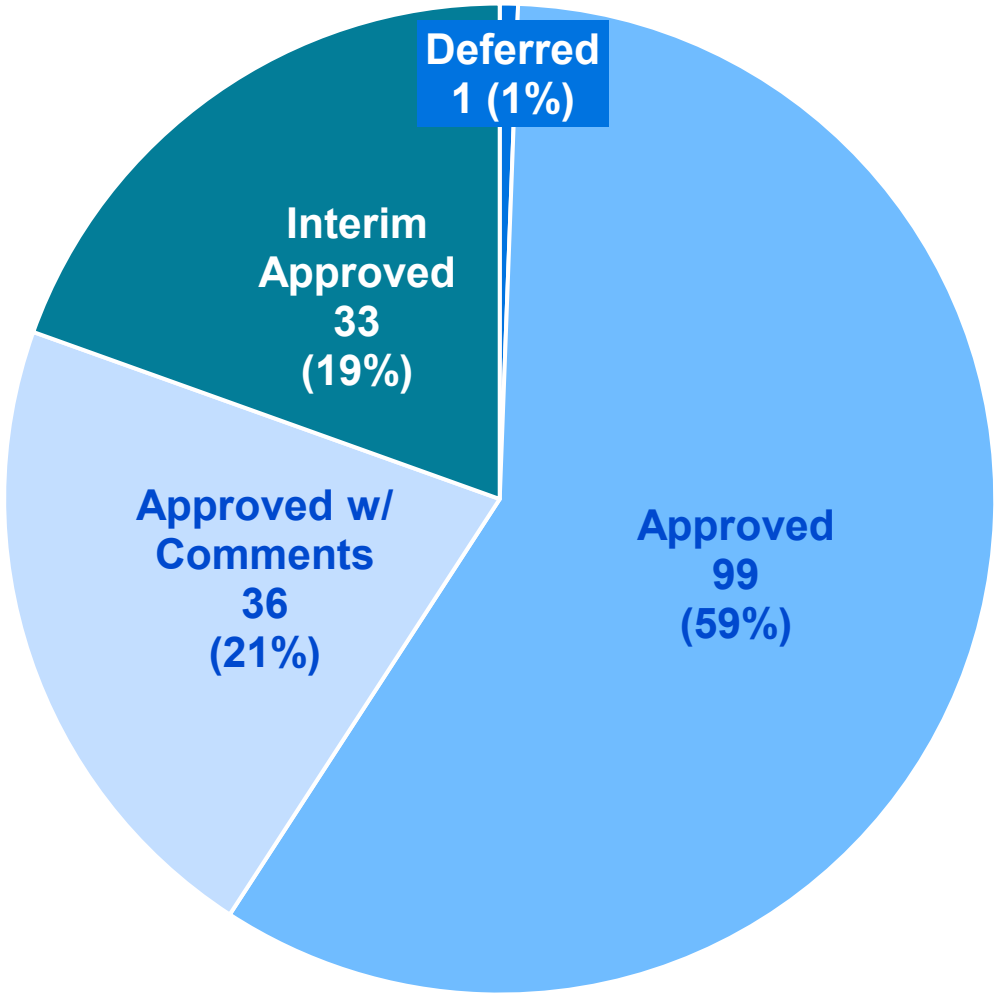
Actions	Definition
Approve/ Approve with comments	Protocol can move forward in review & activation process
Interim Approve	Response is required and will be reviewed outside of meeting
Defer	Response is required and will be reviewed at meeting
Reject	Protocol cannot move forward in review & activation process

Research Council: Review Determinations, 2024

248 New Protocols



169 New Amendments



YOUR TURN!

IN THE CHAT, A PROTOCOL WILL BE DEFERRED BY THE RESEARCH COUNCIL WHEN:

A. Sufficient prioritization of competing studies is not provided
B. The study design does not answer the primary endpoint
C. Stopping rules are unclear

B

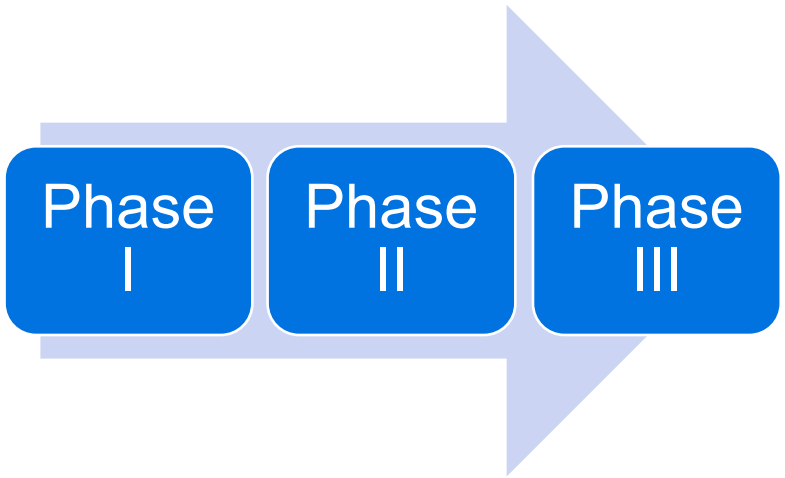
Protocols are interim approved rather than deferred if prioritization or stopping rules require further clarification

How to Design Successful Trials

Alexia Iasonos, PhD

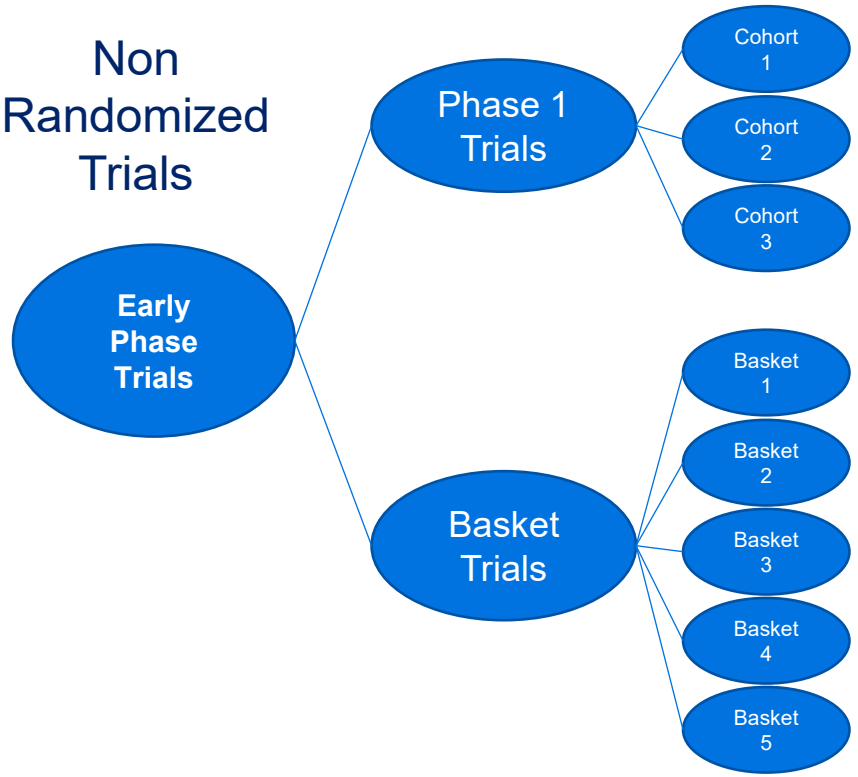
Current Landscape

Old paradigm: single disease



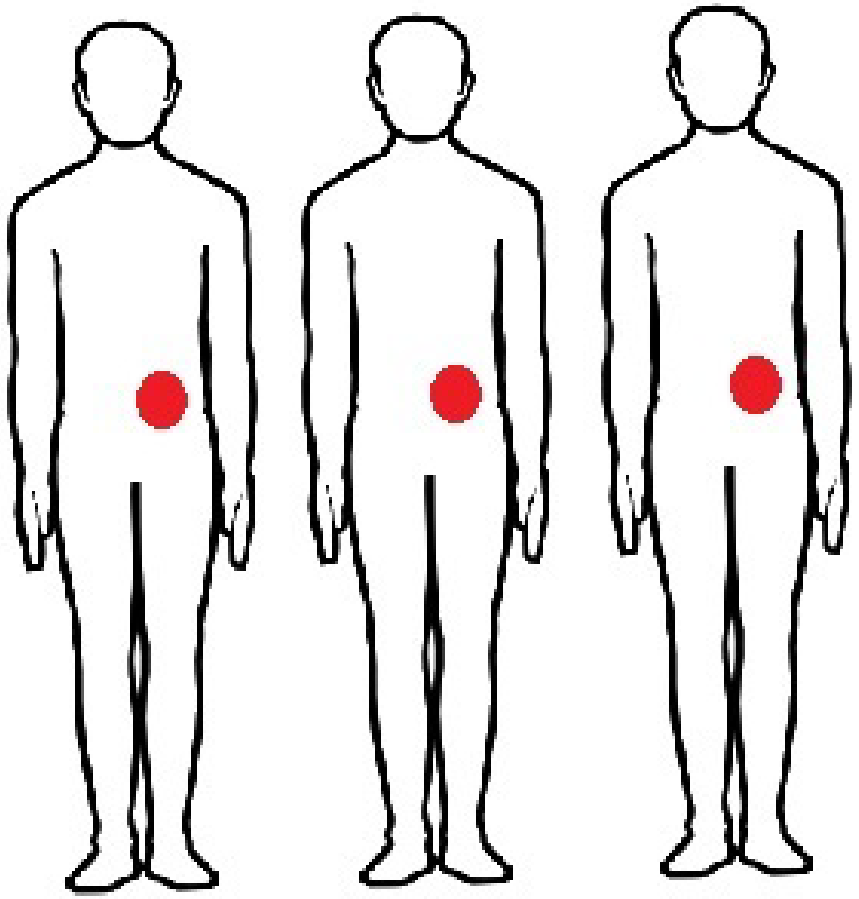
Drug approval

Multiple disease types



Source: Citation

Traditional Single arm Phase II Trial



Does the drug work in this particular cancer?

- Is the response rate with this drug greater than the response rate of standard therapy (historical estimate)?

Basket Trials

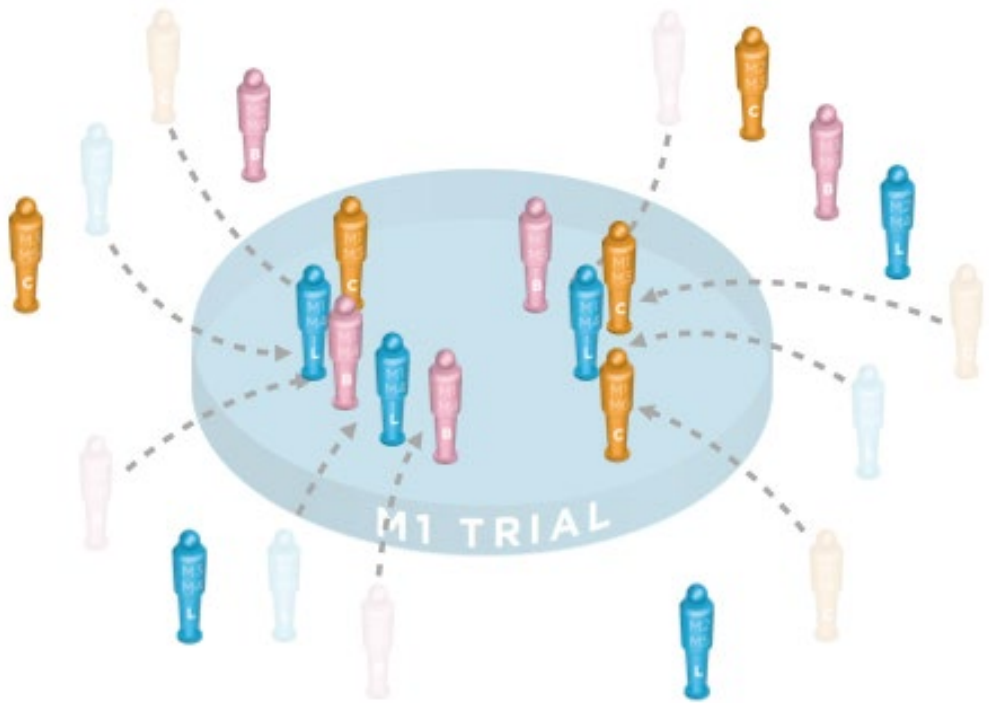
Combining multiple histologies in a single trial

In its most basic form, a basket trial is specific to a molecular target and a targeted regimen, with histologies forming the baskets

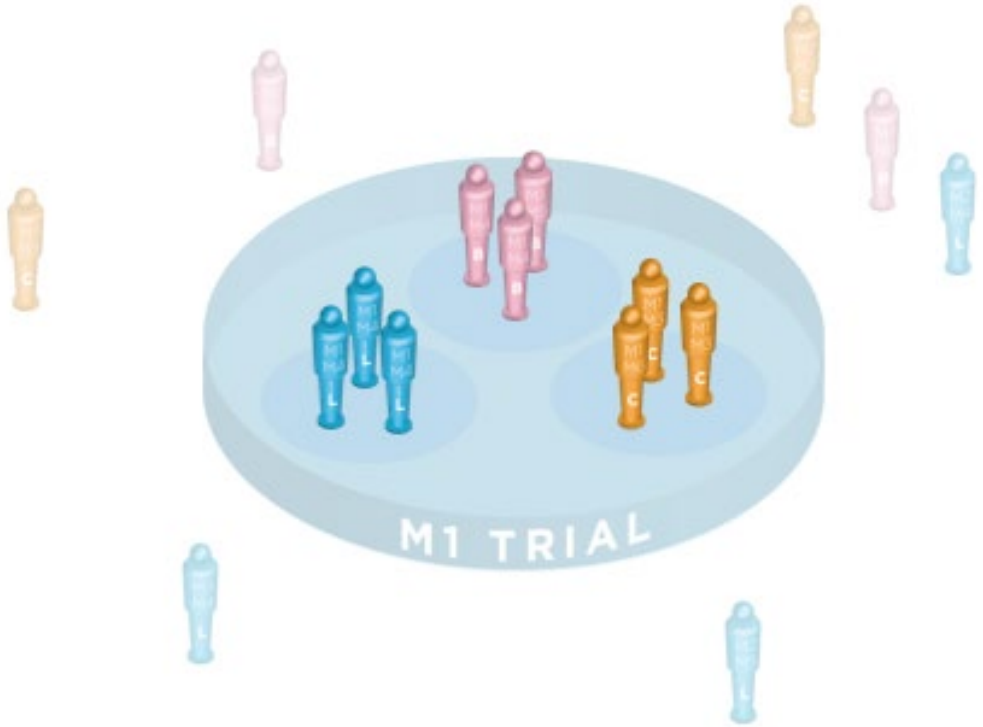
- Single drug/target, multiple disease sites
- Example: Vemurafenib Hyman et al. NEJM 2015

Implications for Clinical Trial Design: non-randomized setting

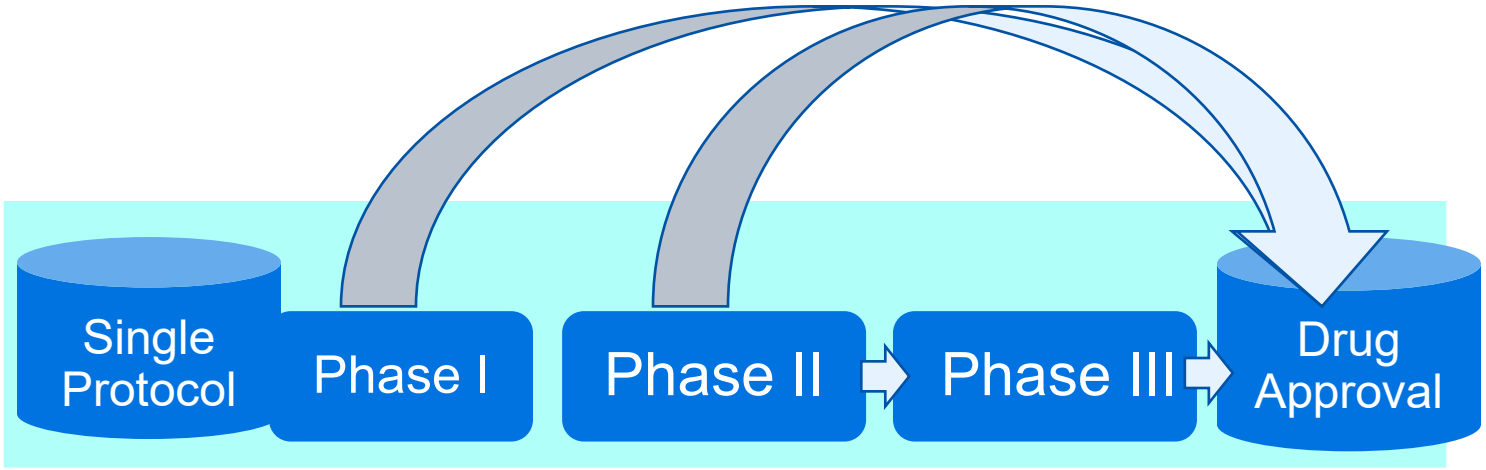
Patient Selection: Molecularly Defined Subgroups



Basket Trials: Definition of Basket



New Landscape of Drug Development



Single Protocol	Objectives
• Early phase trials	Safety and efficacy Identify right population, dose, schedule, combination
• Adaptive protocol	Multiple and prespecified hypotheses
• Amended protocol	Evolve over time

Objective

Can we do many trials with the cost and sample size of a single trial?

Can we answer multiple questions in a single trial?

- It can be done in a rigorous and efficient way
- What is the price to pay?

Challenges

Which agents to prioritize?

Stop an inactive drug as early as possible and take an active drug forward

- Identify active vs not active drug
- Minimize number of patients for inactive agents
- Maximize number of patients for active agents

Optimization with respect to sample size/ trial duration

Define criteria for a successful trial

What is a successful trial vs. what are we going to learn?

Single hypothesis

Met primary endpoint

Phase I	Phase II	Phase III
Safety rate DLT < 30%	Efficacy rate ORR ≥ 30%	OS in Arm A > OS in Arm B HR > 1

Multiple hypotheses

Phase I (DEC)	Phase II (basket)	Phase III
Safety and Efficacy Define population for further study Define dose toxicity profile Define dose efficacy profile	Efficacy overall Efficacy by disease subtype	Two arm trial Umbrella Platform (new trt can be entered/dropped)

Did it answer the Multiple Aims Definitively?

Randomized Phase I Protocols at MSK

694 protocols opened to accrual from 2023 through August 2025 (excludes biospecimen and retrospective protocols)

- 245/694 (35%) are randomized
- 218 excluding NA, pilot, IV

N = 245

Phase I	**29**
Phase I/II	19
Phase II	76
Total Ph I or II	**124/245 (51%)**
Phase II/III	7
Phase III	87

Randomized Phase I Clinical Trials in Oncology

Randomization to Treatment Groups

- Role of randomization in early phase trials
  - Dose levels
  - Schedules
  - Single agent vs combination agents
- Which questions can be addressed by the trial?
- Incorporating a dose-expansion cohort
- Optimising the effort to identify the best dose

Controllable and Uncontrollable Factors

- Groups defined by
  - Dose/ schedule, dose levels, type of treatment
- Genetic markers, prior therapies, comorbidities (fixed)
- Confirmation trials: bridging between completed and current studies (peds, combinations)
- Backfill cohorts (dose level)

Source: Citation

Expansion Cohorts

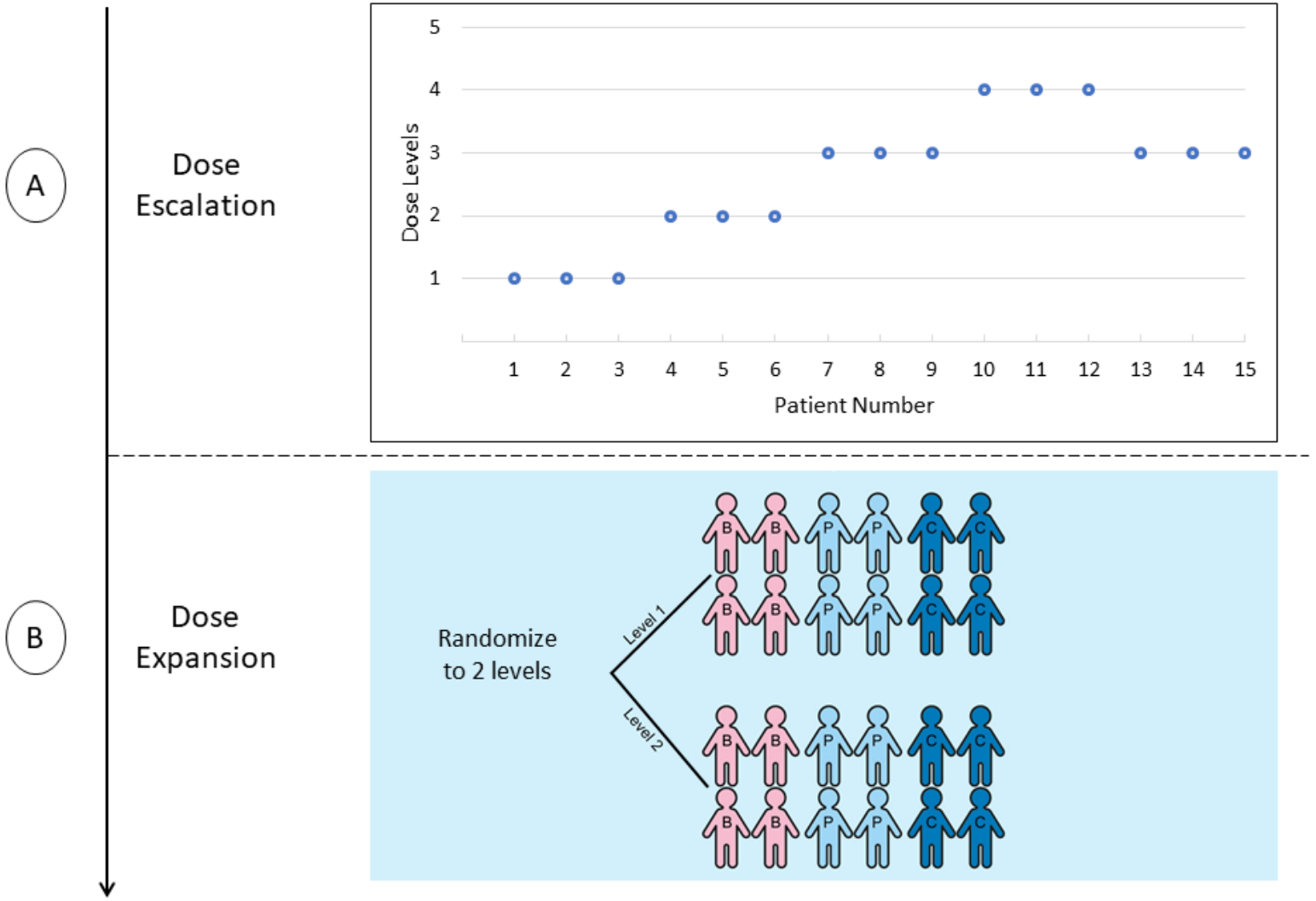


Figure 1. Sequential dose exploration

Expansion Cohorts

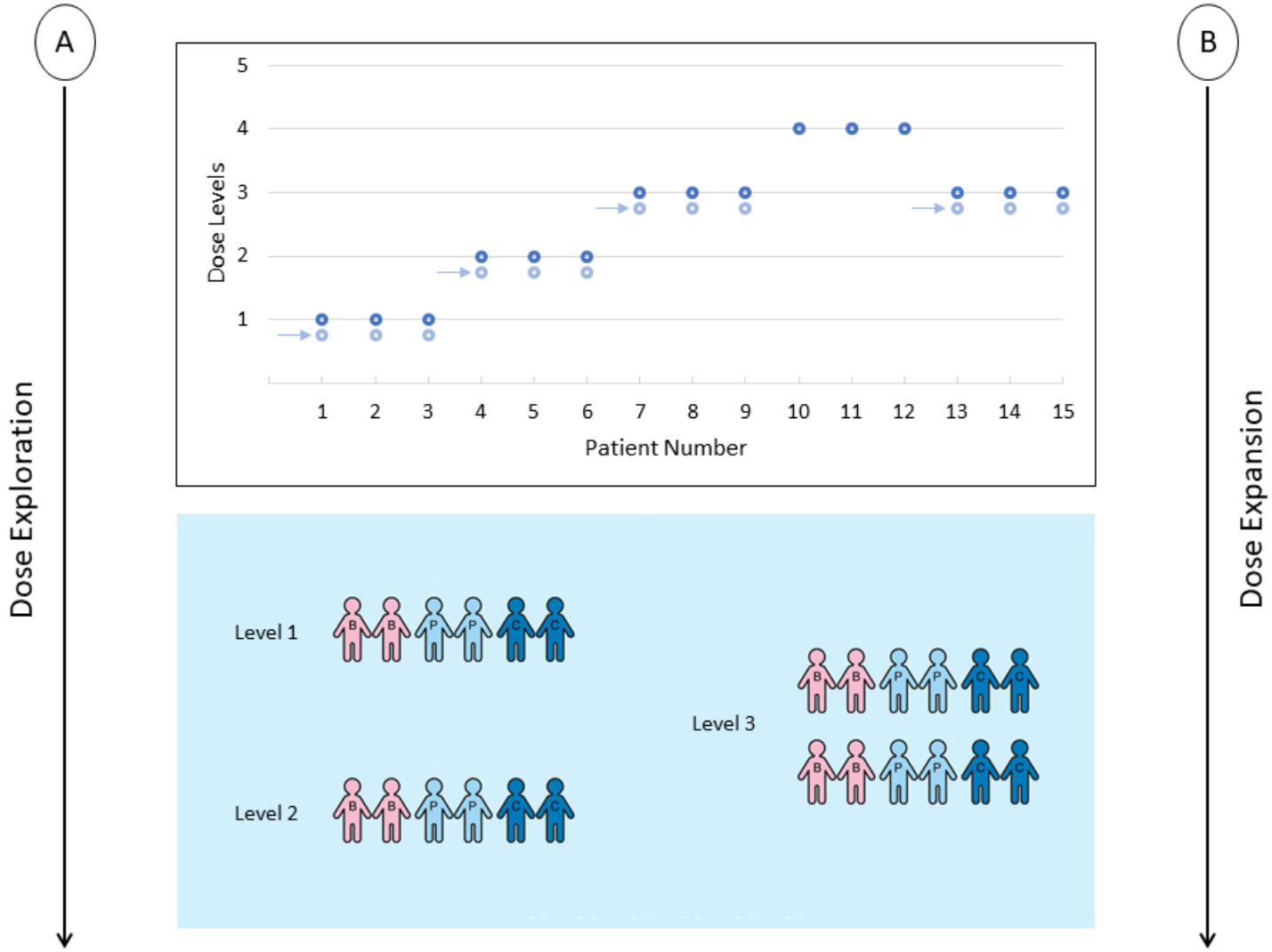


Figure 2. Simultaneous dose exploration

Timing of Dose Expansion

After MTD is established (safety evaluation is completed)

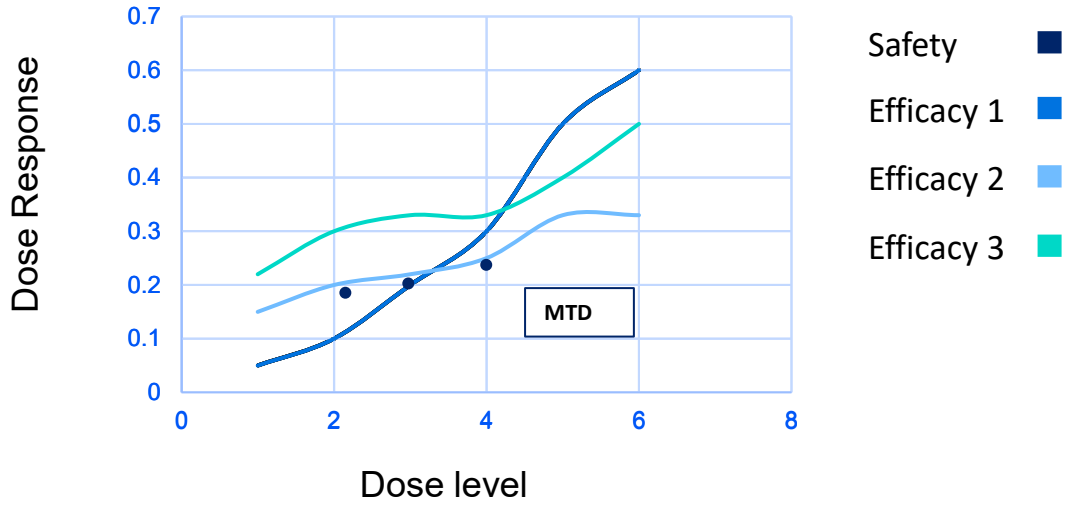
- Dose escalation ➡ safety
- Vicinity of MTD (+/- a level)
- Dose expansion ➡ efficacy (safety)

Before MTD is found

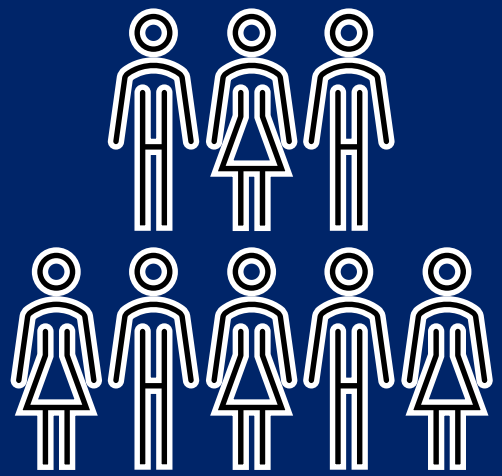
- Dose exploration (start spreading experimentation early)
- What prevents us from spreading experimentation
  - We do not know that the curve is flat – the purpose of the trial is to obtain preliminary evidence that the curve is flat

Backfill Cohorts –

Is the dose toxicity curve flat?



Backfill Guidelines



For backfill cohorts substantially below the MTD or (more commonly) when MTD has not yet been defined, RC reviewers should:

- Ensure the objectives and size of backfill cohorts are clearly stated & study design and analysis plan reflects these objectives
- Consider the scientific rationale for the backfill including the process for selecting the dose levels to backfill
- Ensure the dose selection process includes provisions against selecting clinically ineffective doses based on available data and current practices

Scientific Rationale

How many patients to address the scientific question?	• Regardless of the activity of the drug • Optimal – minimum to address the scientific question or maximum to provide access
How to best interpret the data from large Phase I trials?	• Minimize biases - randomized vs non-randomized setting
How to obtain rigorous data to understand why the drug failed?	• Dose, schedule, patient population, wrong combination • Inform future directions/ investigations

Not all drugs are a success story

What can we learn from a negative trial to inform future trials/ hypotheses?

- Phase I and Phase II, Cannistra JCO 2009, 2010

Do we have enough and reliable data (rigorous) to answer the questions:

- Why did the drug/combination fail?
  - Wrong schedule /dose?
  - Did we choose the wrong patient population?
  - Is there efficacy in some subpopulation?
  - Was our historical control or estimate off?

Summary

Clinical application	Statistical
Combination regimens	Efficiently answering the question: Right dose
Pediatrics	How many patients? How to best treat pts?
Expansions	Treatment allocation – experimentation
Backfill	Randomization
Design/ Analysis/ Interpretation	

YOUR TURN!

IN THE CHAT, Phase 1 clinical trials in oncology are typically assessing safety alone.

- **True**
- **False**

FALSE

YOUR TURN!

IN THE CHAT, A clinical trial design needs to be optimal.

- **True**
- **False**

FALSE

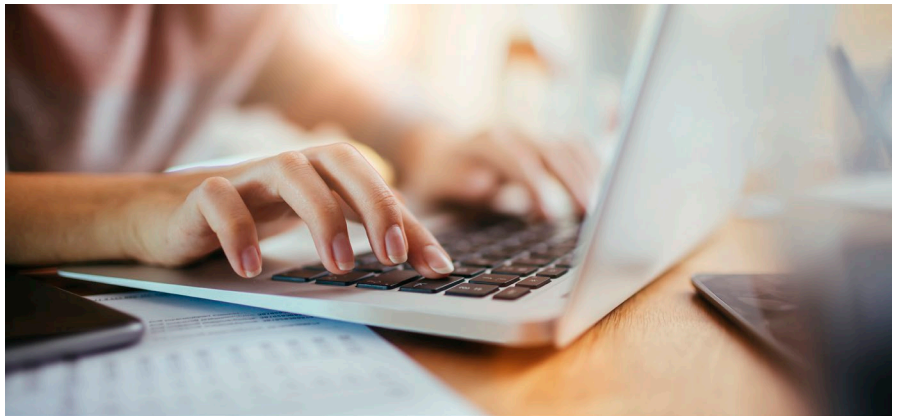
YOUR TURN!

IN THE CHAT, Dose expansion cohorts are defined by disease type and/or molecular defined subgroups.

- **True**
- **False**

TRUE

Research Council Resources



Research Council Portal Page

Performance Monitoring Committee Portal Page

CCSG P30

Expansion Cohorts SOP

Backfill Guidelines

Questions?