Introduction to Clinical Research (at MSK)

(*NIH Definition: “Patient Oriented Research” involving human participants requiring direct interaction)

Paul Sabbatini, MD

Sep 4, 2025

Memorial Sloan Kettering
Cancer Center

Objectives

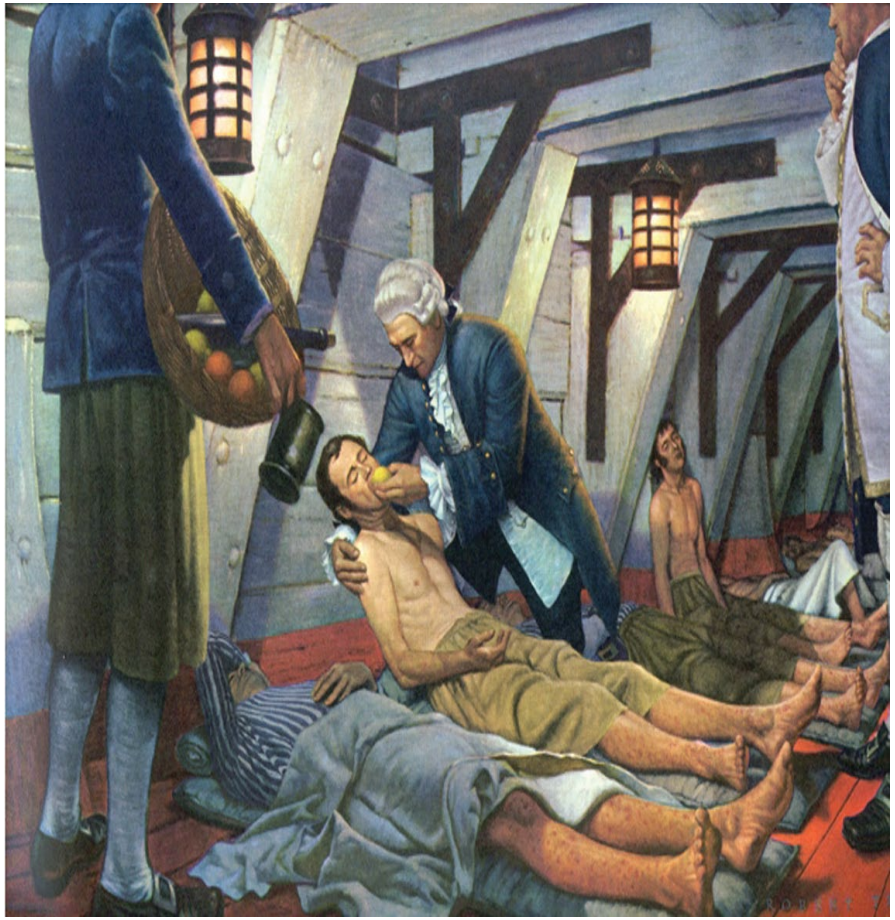
- Brief history of clinical research
- Challenges and opportunities in modern trials
- MSK clinical research program
- The Principal Investigator and oversight

Canon of Medicine: 980 AD

- Seven Principles
  - Drug must be prepared and stored consistently; “pure”
  - Experiment on a “single” not “composite” malady
  - Test on at least 2 contrary conditions
  - Potency sufficient for the disease “minimum effective dose”
  - Timing of observation should rule out “natural healing”
  - Results should be reproducible
  - Animal testing is important, but human testing is required.

Adapted, Ulster Medical Journal 1991; Avicenna

“Father of Clinical Trials”: James Lind



Treatise on Scurvy 1753

“They all in general had putrid gums, lassitude and weakness of the knees”

- Isolation
- Groups of 2
- 6 therapeutic interventions
- documentation

Cooperative Groups and Clinical Trials

1950's

2010 +

Figure 1-1. U.S.-Based Clinical Trials Cooperative Group Program Members

Original Participants	Consolidated Groups
American College of Radiology Imaging Network (ACRIN)	COG
American College of Surgeons Oncology Group (ACOSOG)	ECOG-ACRIN
Cancer and Leukemia Group B (CALGB)	NRG Oncology • NSABP • RTOG • GOG
Children's Oncology Group (COG)	SWOG
Eastern Cooperative Oncology Group (ECOG)	The Alliance • ACOSOG • CALGB • NCCTG
Gynecologic Oncology Group (GOG)	
International Rhabdomyosarcoma Study Group (IRSG)	
National Surgical Adjuvant Breast and Bowel Project (NSABP)	
National Wilms Tumor Study (NWTS)	
North Central Cancer Treatment Group (NCCTG)	
Pediatric Oncology Group (POG)	
Radiation Therapy Oncology Group (RTOG)	
Southwest Oncology Group (SWOG)	

Note. Based on information from Children's Oncology Group, n.d.; National Cancer Institute, n.d.

Events in Human Subjects Protection

- Nuremberg Doctors Trial
  - Nuremberg Code (1947)
    - Voluntary consent essential
  - Declaration of Helsinki (1964)
    - Risks not exceed benefits
- Tuskegee Syphilis Study (1932-1974)
  - National Research Act 1974
  - Belmont Report (1979)
    - Respect for persons, justice, beneficence

- DHHS regulations
  - 45 CFR Part 46 – “the common rule” (1991)
  - Subparts for vulnerable populations
    - Pregnant women, prisoners, children

- Last updates – implementation over 2022)
  - Single IRB review for multi-center studies
  - Informed consents posted

Green JM et al. Implementation of single IRB review for multisite human subjects research J Clin Transl Sci. 2023 Apr 4;7(1)

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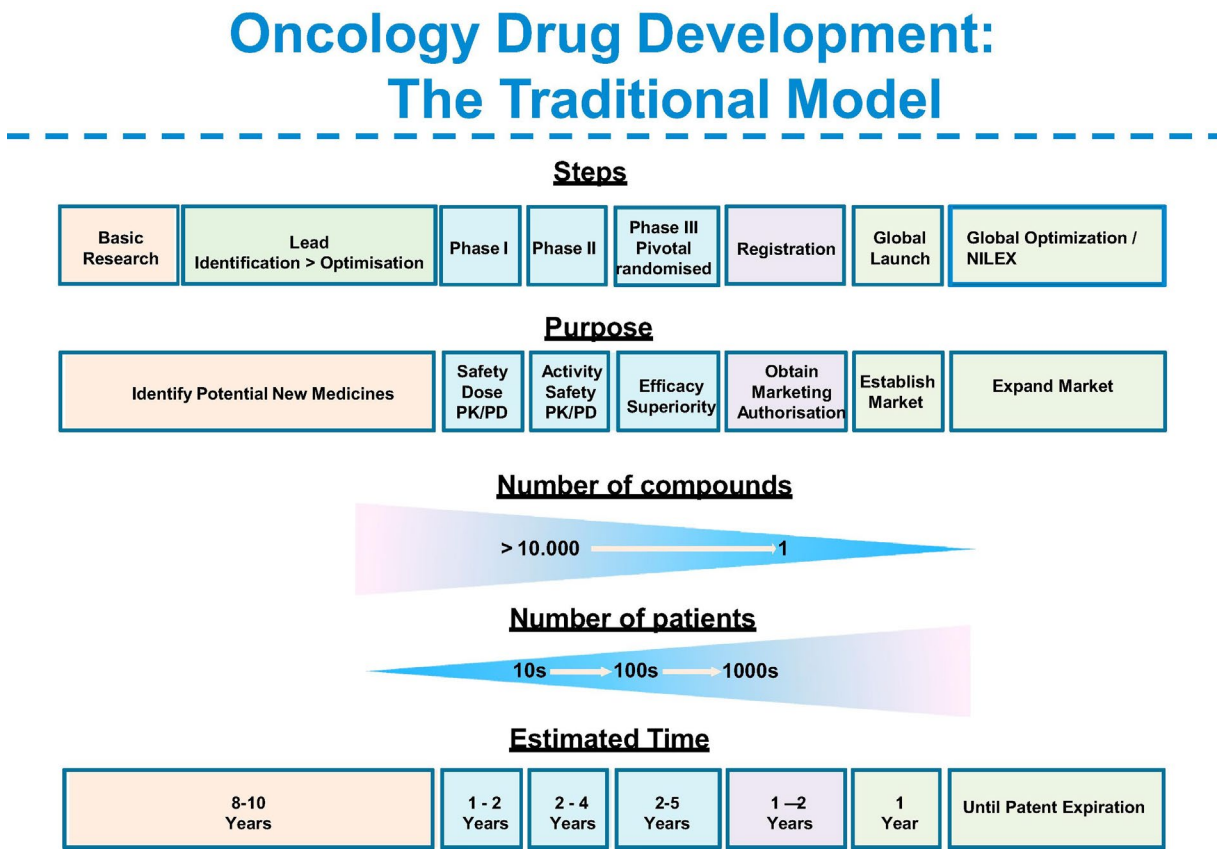
Historical Drug Development



Zhang JY et al. Synthesis and clinical application of new drugs approved by FDA in 2022. Mol Biomed. 2023 Sep 4;4(1):26.

Innovation in Clinical Research Needed

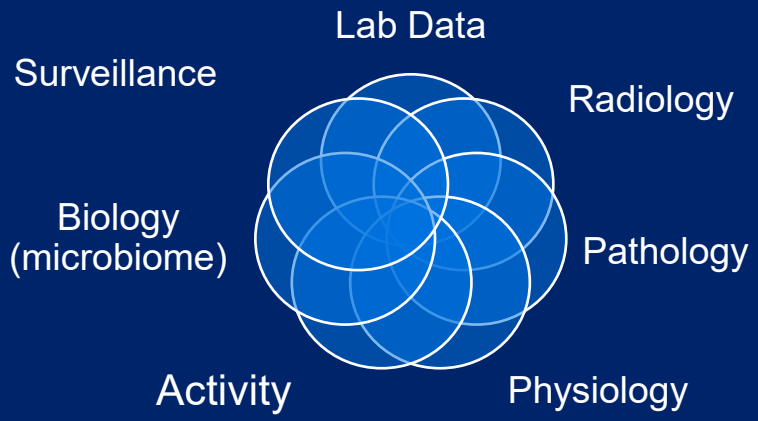
More Drugs

40%*

% of global R and D pipeline is cancer- related

34% 2018

More Patient Cohorts



The “Digital” Patient

More Tumor Cohorts

Kravis Center Molecular Oncology /MSK IMPACT/OncoKB

100K+ patients, > 96K tumors, 30+ % clinically relevant alteration

Mutations differ in metastasis from same tumor

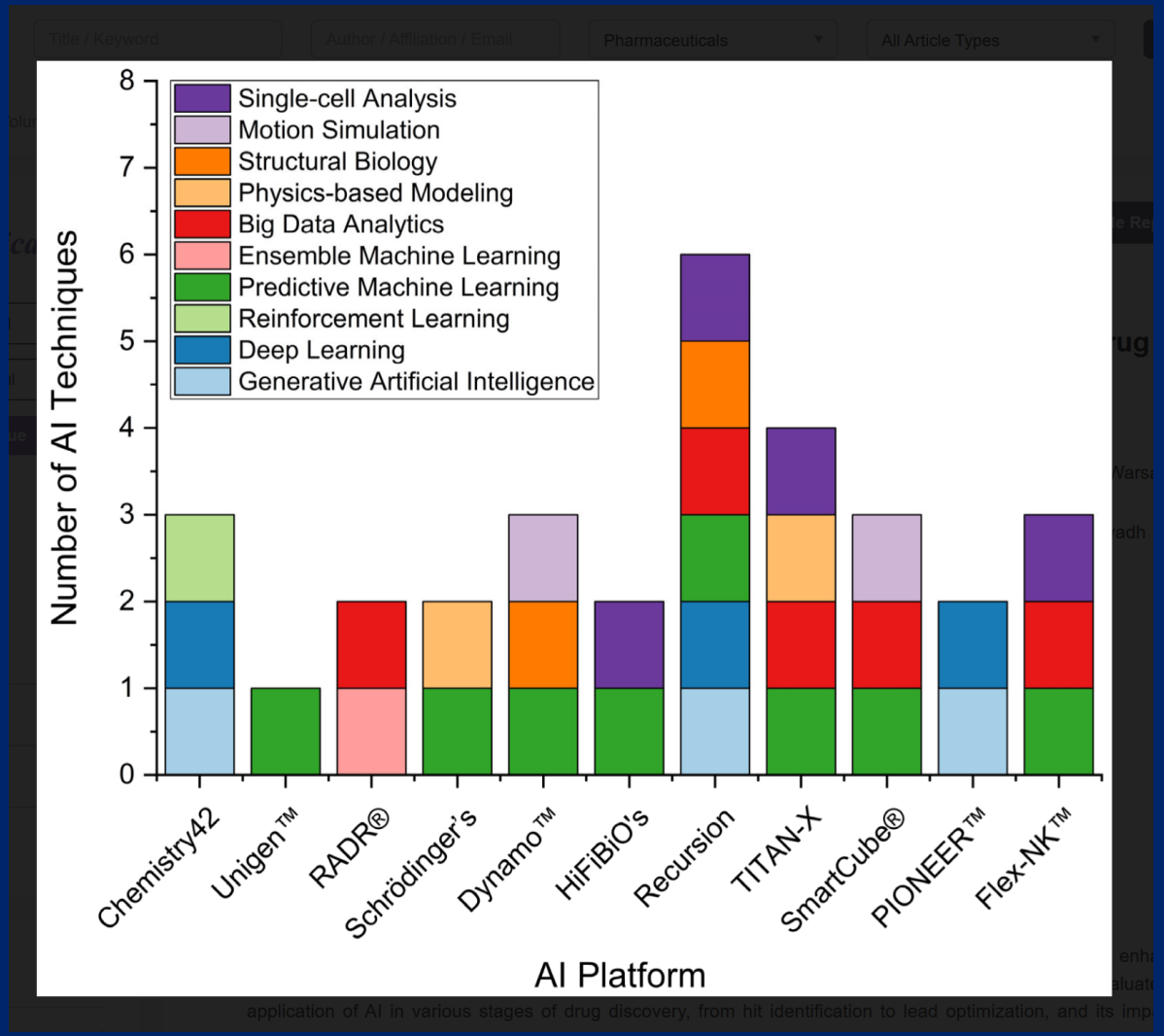
Nguyen et al. Cell 2022

*Source: Informa. R&D Review 2019, McKensie 2022

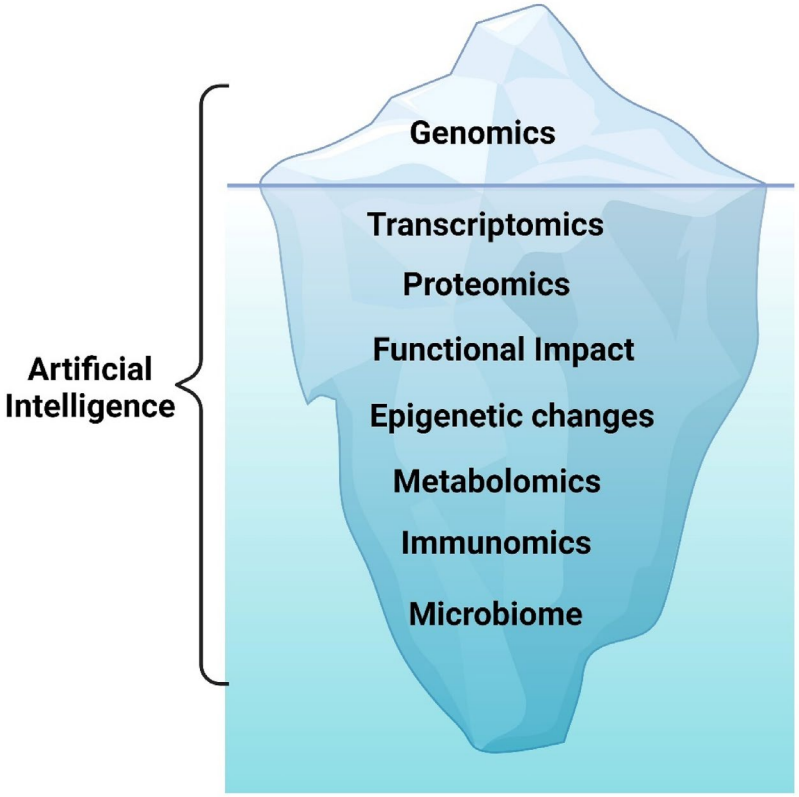
More Technology

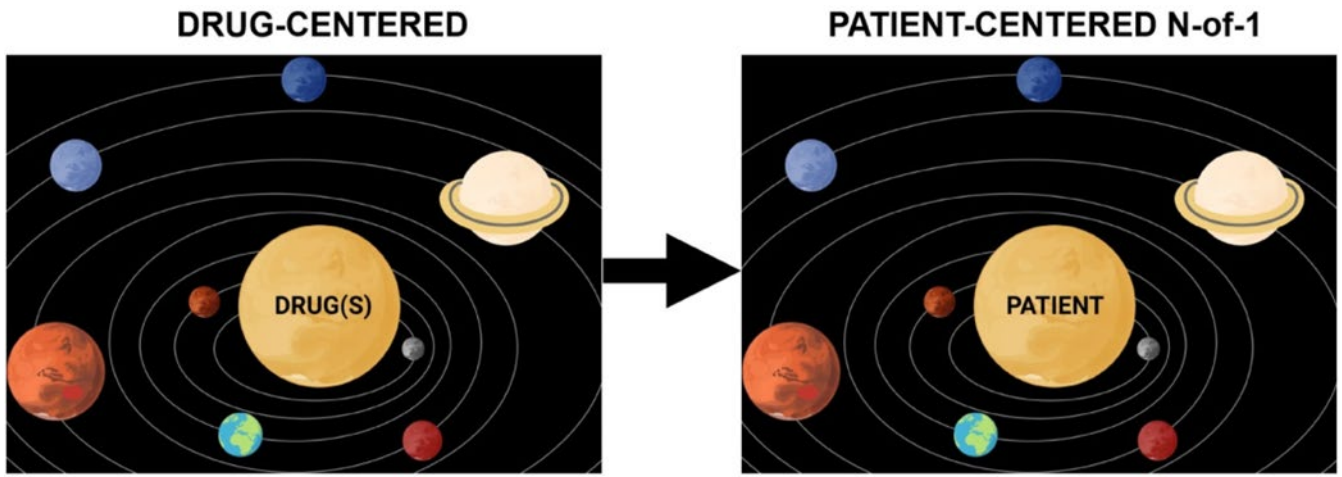
From Lab to Clinic: How AI is Reshaping Drug Discovery Timelines and Industry Outcomes

Dermawan et al. Pharmaceuticals. 2025.



Multi-modal and Patient Centered Trials





CA A Cancer J Clinicians, Volume: 75, Issue: 3, Pages: 243-267, First published: 22 January 2025, DOI: (10.3322/caac.21880)

Challenges in Modern Trials: Standard of Care or Clinical Research?

"……. something is either research or standard care; it cannot be both"
(e.g., Miller and Rosenstein, NEJM 348: 2003)

Versus

"Enrollment on an investigational study is state-of-the-art care for many patients in oncology today" 2025 (ASCO, NCCN, advocacy organizations, etc.)

Much of the treatment-related research we do here is performed in a care-delivery context with characteristics of both care and research.

From a legal, regulatory, and procedural point of view, it is all research.

Challenges: Design versus Speed

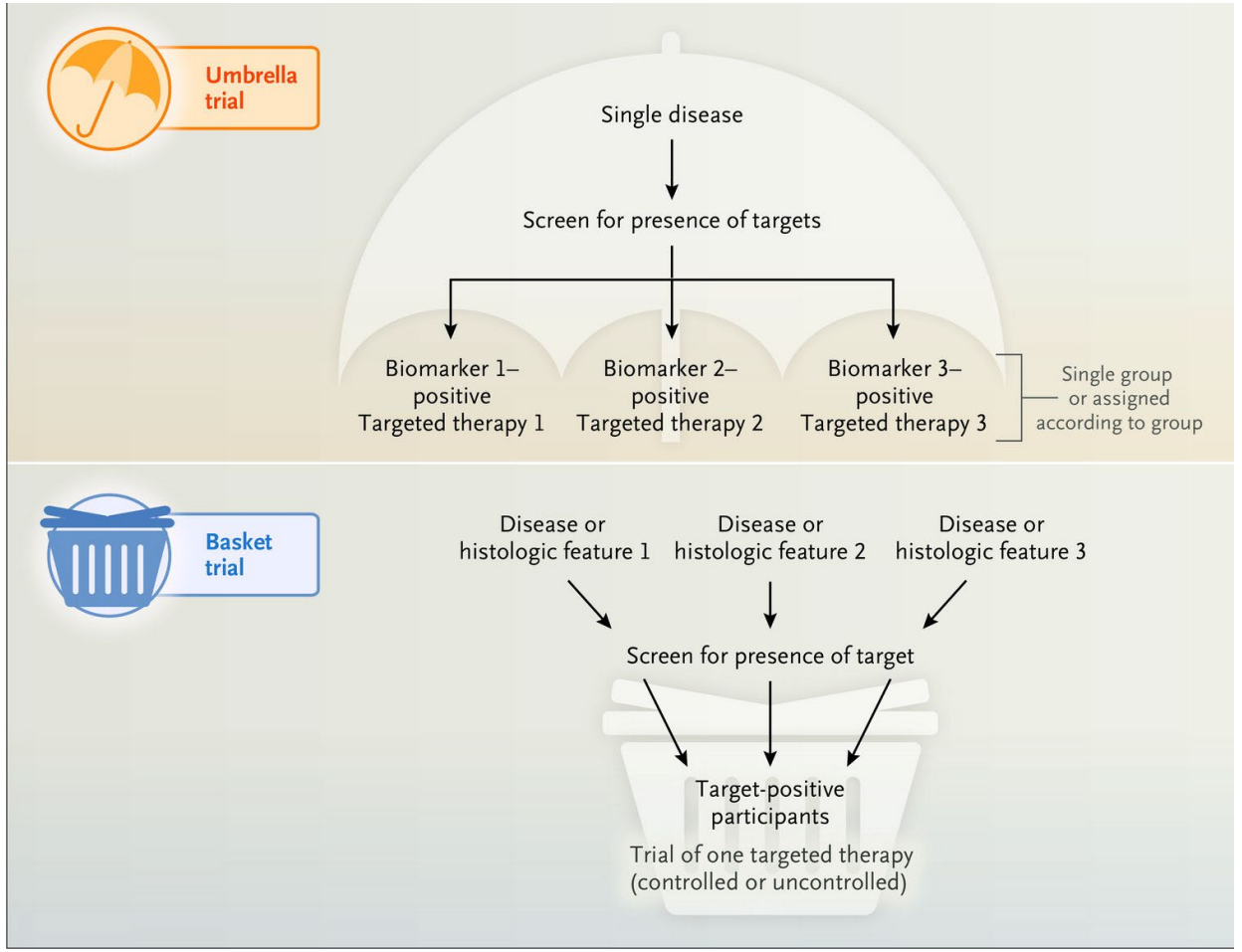
Traditional

- Phase I (3+3 design)
  - Dose
  - Safety
  - Pharmacokinetics
- Phase II (n = 35)
  - Single disease
  - Efficacy
- Phase III
  - Is it more effective than the standard?

Today

- Phase I (3 + 3, adaptive, other)
  - Dose
  - Safety
  - Pharmacokinetics
  - Expansion / efficacy
- Real World Evidence
- Pragmatic
- Umbrella
- Basket

Challenges: Design versus Speed



Drazen et al. NEJM 377:2017

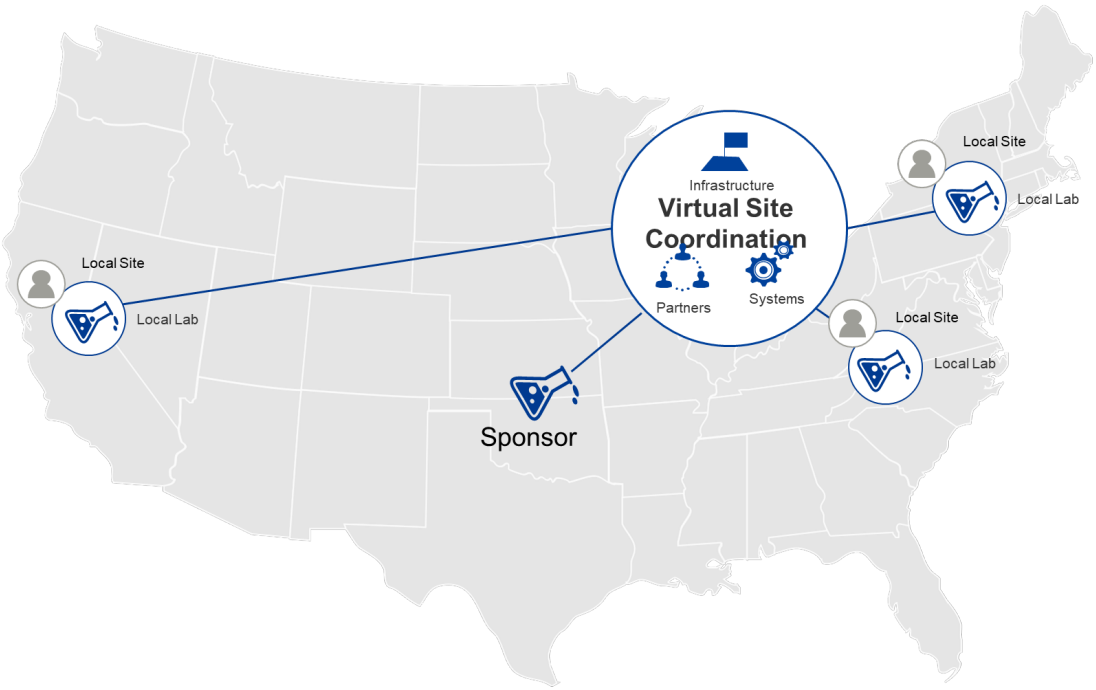
Innovation Requires Distributed Access

Decentralized Clinical Trials

Innovation Requires Distributed Access

Traditional Model

Decentralized Model



Integrating Stakeholders

Tools and Processes

PATIENTS

Trial availability and access

PHARMA

Scalable approach that shortens development time

CLINICAL PROVIDERS

Integrated workflows and clinical decision support

REGULATORS

Partners with experience to streamline

PAYORS

Cost versus benefit

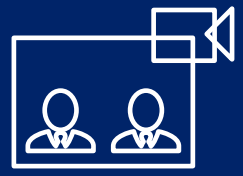
SITES

Decreased overhead costs, less operational burden, more throughput

Optimization for Decentralized Trials

Tools and Processes

COVID (80%)



TELEHEALTH and mHealth applications (eConsent)

WEARABLES for continuous data collection

APPLICATIONS for monitoring adherence

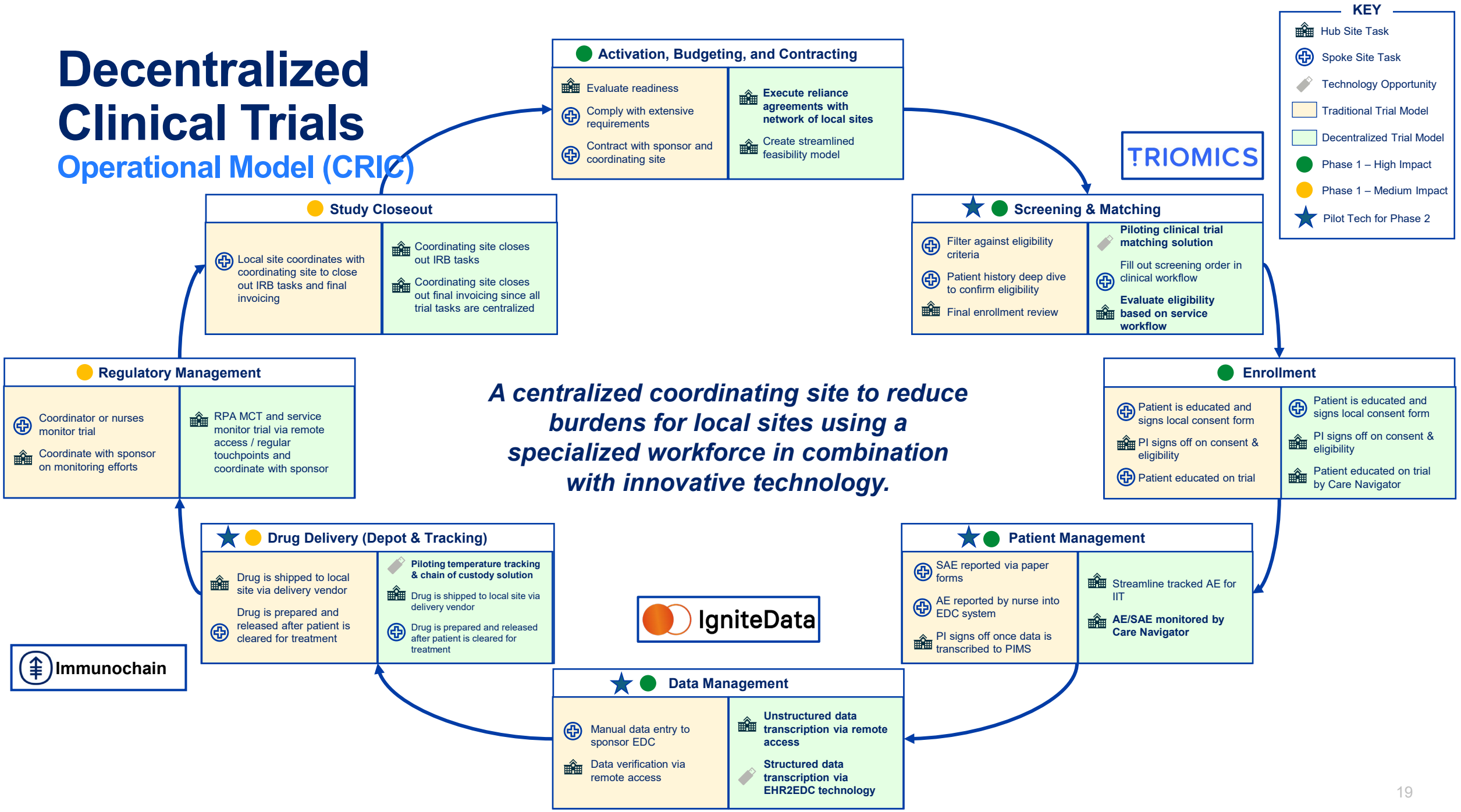
ELECTRONIC patient reported outcomes

EPIC EHR Transition

Technology Partnerships: Clinical Research Innovation Consortium (CRIC)

Decentralized Clinical Trials

Operational Model (CRIC)



Technology Solutions

Clinical Research Innovation Consortium (CRIC)

Ambient Listening Technology

Ignite Data Platform

iHUB/DigITs/OTD

iHub Challenge

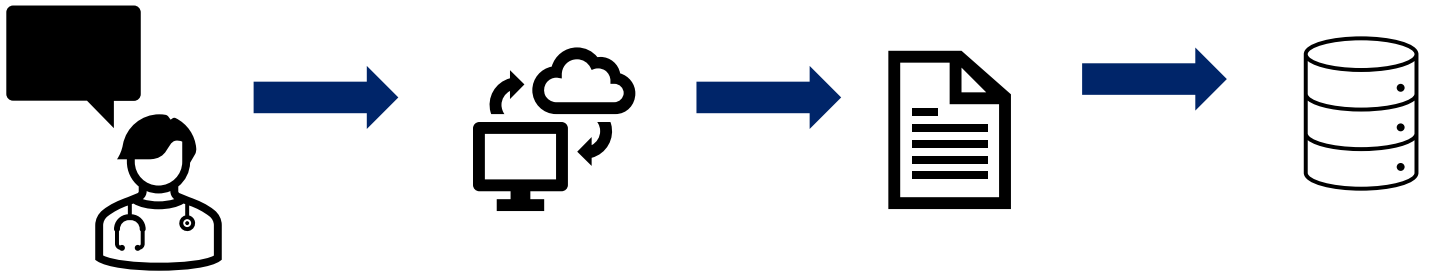
10 vendors / MSK mentors

CRIC

- Working with 2 ambient technology providers
- Evaluating data EHR to EDC platform

Research use-cases include:

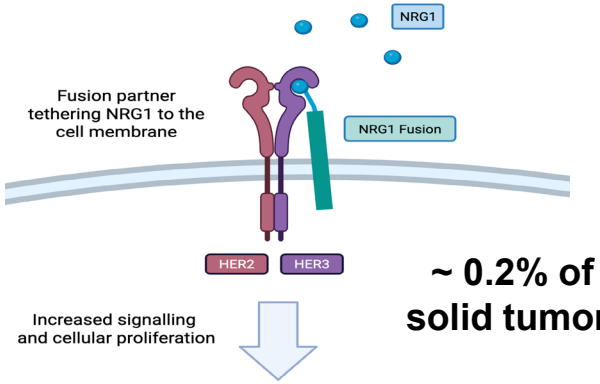
- Capturing adverse events in real time
- Capturing structured, coded data at point of care, reducing research coordinator manual abstraction
- Patient reported outcomes via speech
- Moving data electronically from EHR to EDC



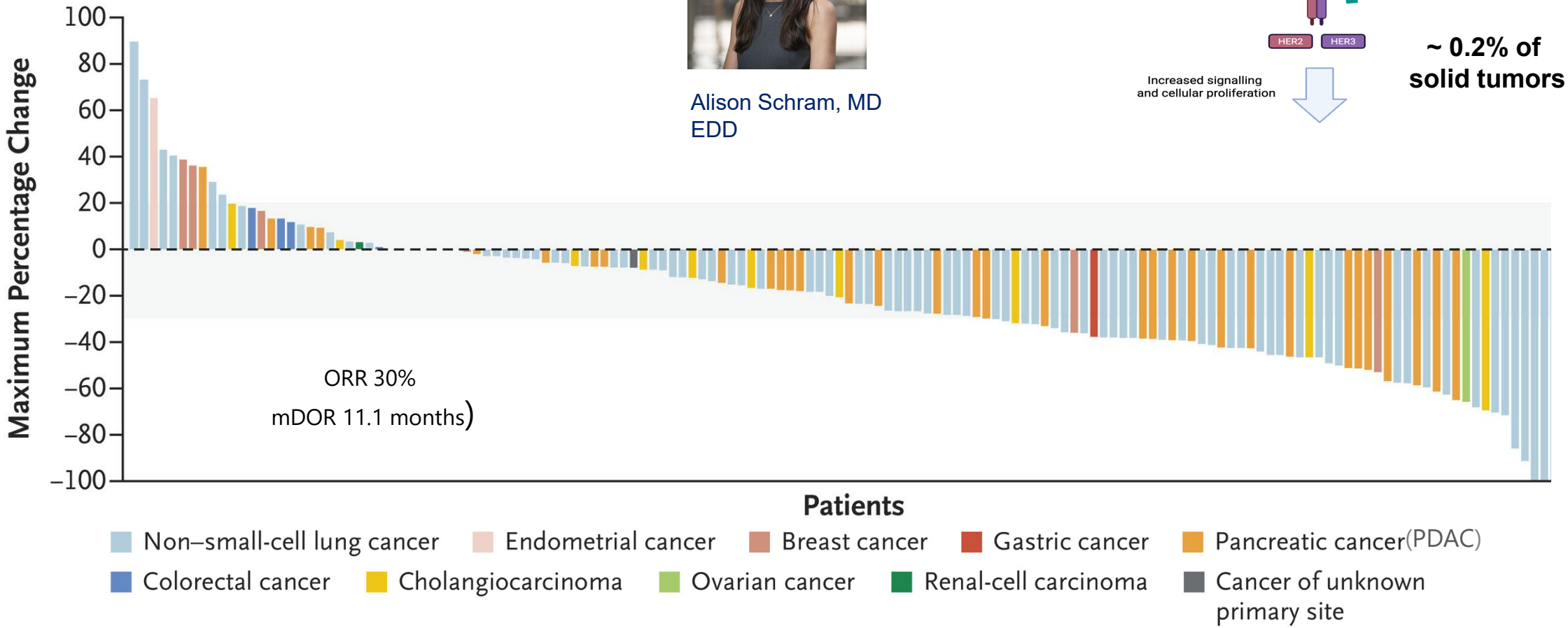
High Impact Example: Zenocutuzumab in NRG1 Fusion+ Solid Tumors FDA Approval

Screening, Access and Logistics

Alison Schram, MD
EDD



~ 0.2% of solid tumors



Schram et al., *NEJM* 2025

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Clinical Research and Patient Care

High Impact Example: Rare Disease Drug Development (DMT)

Evolution of T cell directed Therapies In Sarcoma at MSK

2013

Protocol 13:236

Lete-cel (NYESO-1) TCR in synovial sarcoma

ORR 20-50%

DOR 15-30 weeks

- **Higher LDR impacts efficacy (Flu 120mg/m2 + Cy 2700mg/m2)**
- **Correlates of response**: expansion, persistence, IL15 levels, depletion of lymphocytes
- **Correlates of resistance:** loss of HLA expression & Ag presenting machinery

Ref: D'Angelo SP, Cancer Discovery 2018

2016

Protocol 16:1406

Lete-cel (NYESO-1) TCR in myxoid round cell liposarcoma

ORR 20-40%

DOR 5-7m

- **Correlates of response:** Expansion, persistence, IL15 levels, depletion of lymphocytes
- **Tocilizumab doesn't appear to impact efficacy**

Ref: D'Angelo SP, JCO in press

2019

Protocol 19:316

Afami-cel (MAGE-A4 TCR) in synovial sarcoma + MRCLS

ORR 39% (SS), 25% (MRCLS)

DOR 12m (SS), 4m MRCLS)

- Clinical correlates: Lower disease burden, higher MAGEA4 expression, lack of bridging therapy
- **Higher cell dose may impact efficacy**
- **Integrating cells early is likely better**

FDA approved in 2024

Ref: D'Angelo SP, Lancet 2024

2020

Protocol 20:055

Lete-cel (NYESO-1) TCR in synovial sarcoma + MRCLS

ORR 43%

DOR 12.2m

- Primary endpoint met

BLA planned for 2025

Ref: D'Angelo SP, ASCO 2024 (manuscript in preparation)

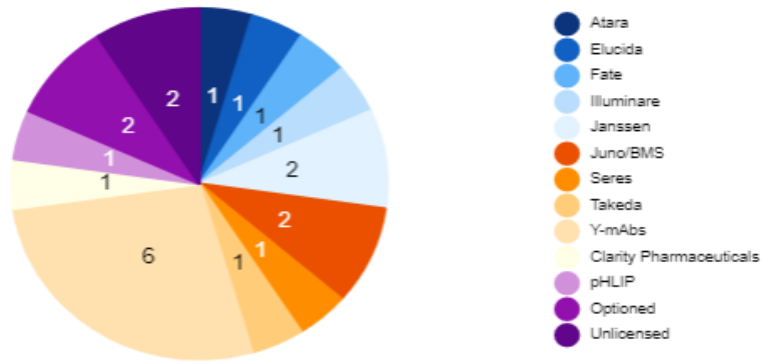
Sandra D'Angelo, MD
Sarcoma Service

A specific objective of the MSK Clinical Research Program is to support research across the continuum.

Pre-Clinical SKI (Fundamental Discovery) → Translational Research (HOPP) → Clinical Research (Effector Arm)

OTD Office of Technology Development

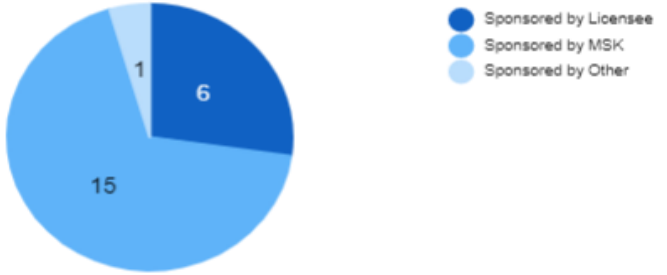
Trials OTA at MSK by Licensee



Clinical Trials at MSK using MSK-developed assets

Trials OTA	22
Trials OTA (licensed assets)	18
Trials OTA (optioned assets)	2
Trials OTA (unlicensed assets)	2

Trials OTA at MSK by Regulatory Sponsor



Yashodhara Dash, MBBS, MBA, PhD

Innovation Requires Core Services: MSK Biobank

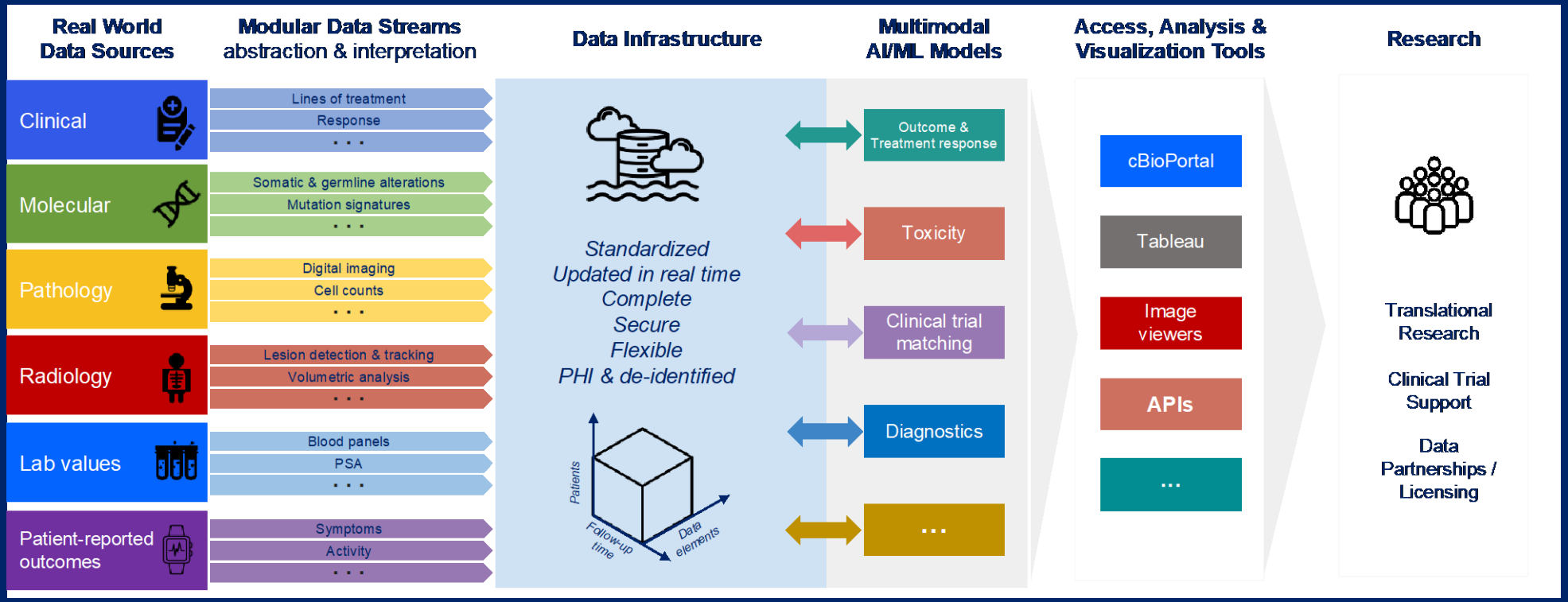
Hikmat Al-Ahmadie, MD

Ross Levine, MD

- Nearly 1 million specimens
- Work is underway to optimize:
  - increase collections in networks
  - samples needed for key discovery/translational research (organoids and single cell studies)
  - collaborations with academic and industry partners
- Key facilitator of next steps – understanding response and resistance and biomarker development

Innovation Requires Core Services: Cancer Data Science Initiative (CDSI)

Niki Schultz PhD



Working to optimize:
- Automated data abstraction
- Access to all relevant investigators

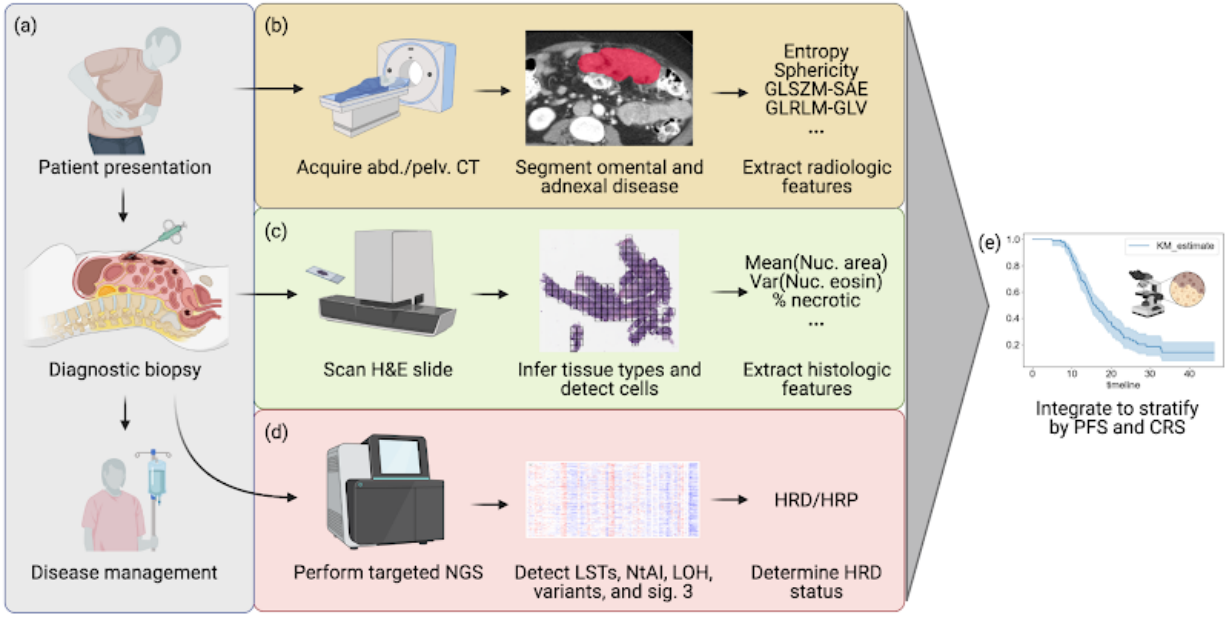
- Providing analysis and visualization tools

Additional Support: Computational Oncology/ Shah et al.

CDSI Director: Niki Schultz PhD

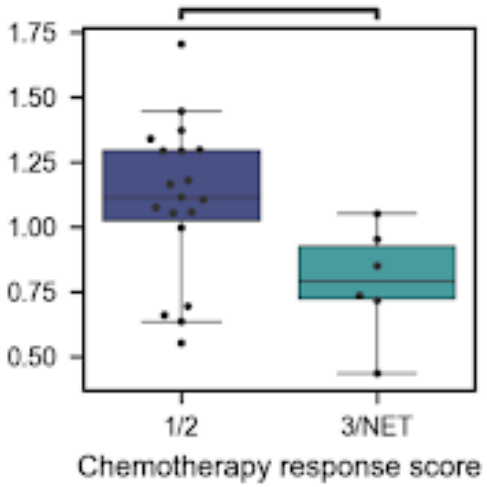
MSK MIND:
Multi Modal Integration of Data

Ovary Cancer Use Case
Which ovarian cancer patients respond to standard chemotherapy?



Single Characteristics (unimodal) **modestly** predict patient **outcomes.**

MSK MIND analysis (multi-modal) **clearly identifies** patients who respond to standard therapy.

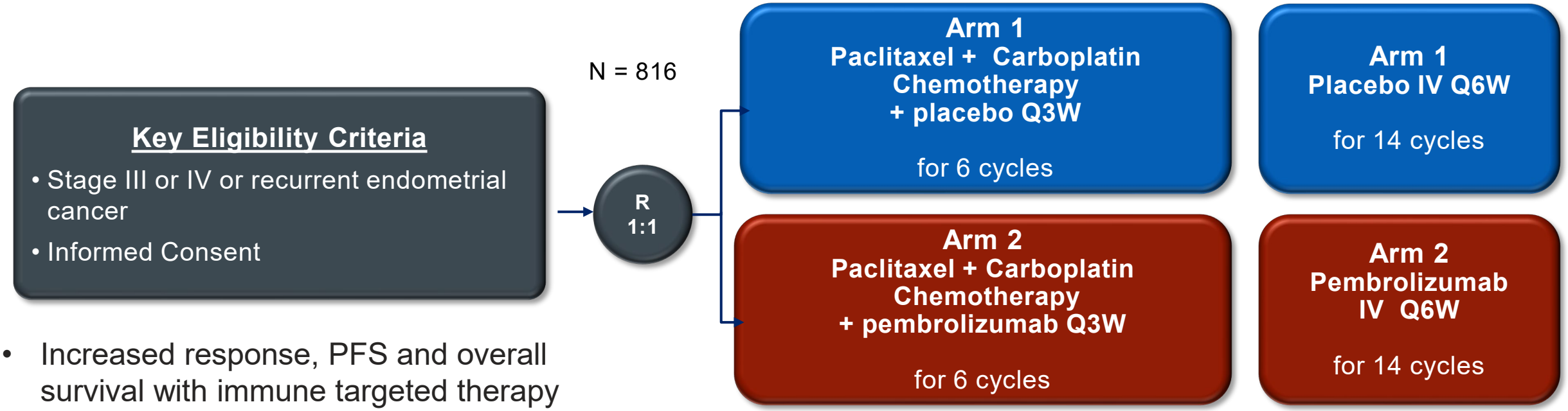


Provided by Boehm, Shah, et al. Computational Onc, MSK, 2021

High Impact Example: Using MSK Biobank and CDSI

Interventional Studies (NCI Cooperative Groups)

Pembrolizumab Plus Chemotherapy in Patients with Advanced Endometrial Cancer



- Increased response, PFS and overall survival with immune targeted therapy
- New standard of care for all patients
- Collaboration with MSK Biobank, Cancer Data Science Initiative and Health Care Disparities Group

Aghajanian et al. New England J Med: 2023

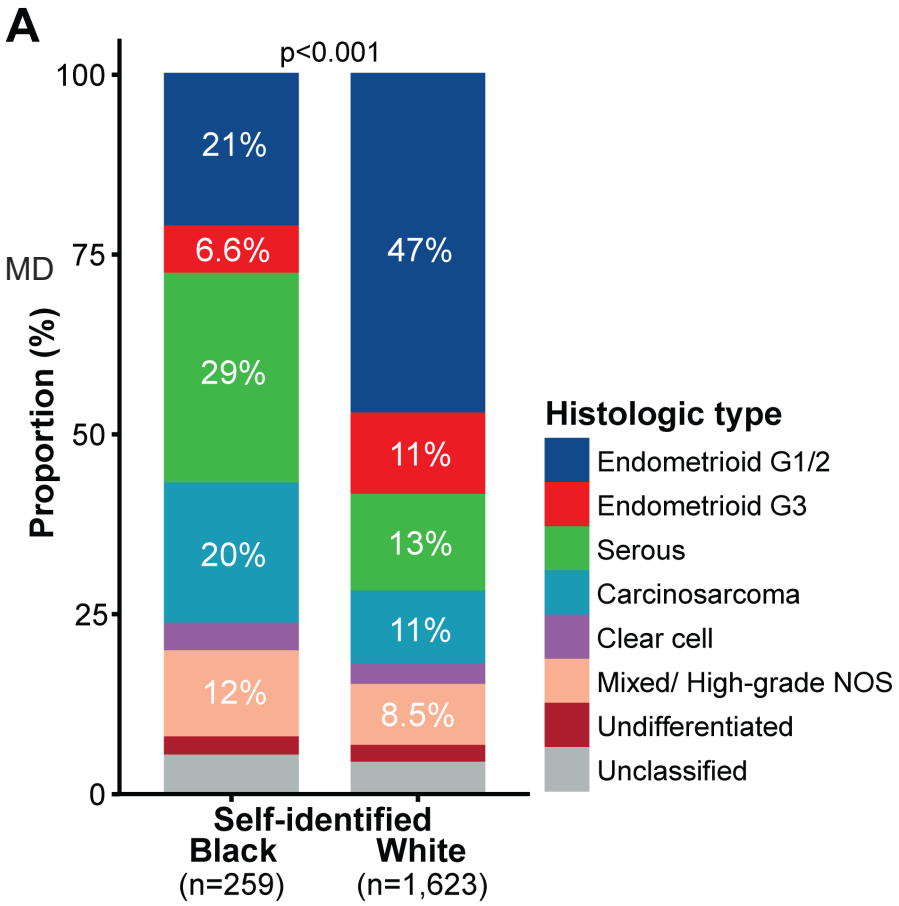
High Impact Example: Using MSK Biobank and CDSI

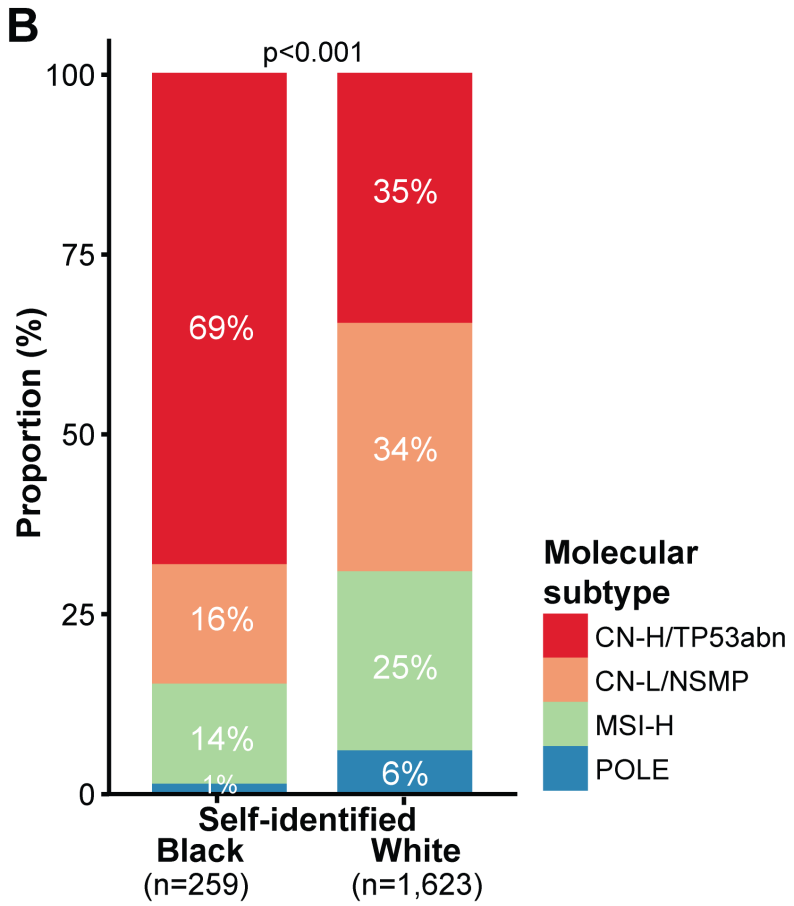
Carol Brown, MD

Carol Aghajanian, MD

Lora Ellinson, MD

Ying Liu, MD





N = 1182. Significantly higher prevalence of high-risk histologic and molecular subtypes
Higher frequency of CCNE1 amplification (WEE1 and ATR inhibitors)

Weigelt et al, Cancer Discovery 2023

Clinical Research: Value to Patients

FDA DRUG APPROVALS

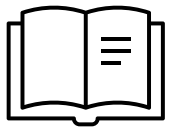
40+

MSK investigator significant* supporting role
2019-current

* = global PI, lead accrual, MSK developed product

Other Metrics: Non-Drug Approval Related (Surgical, Modality based, Non-Interventional, Device) Research

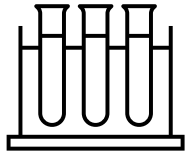
Clinical Research: Value to MSK



- Clinical Trials are recommended as preferred options in multi-disciplinary Cancer Treatment Guidelines (NCCN, ASCO, others) – integral part of care

30% of patients participate across life cycle at MSK

- Clinical research is our most desired asset in partnership and talent discussions

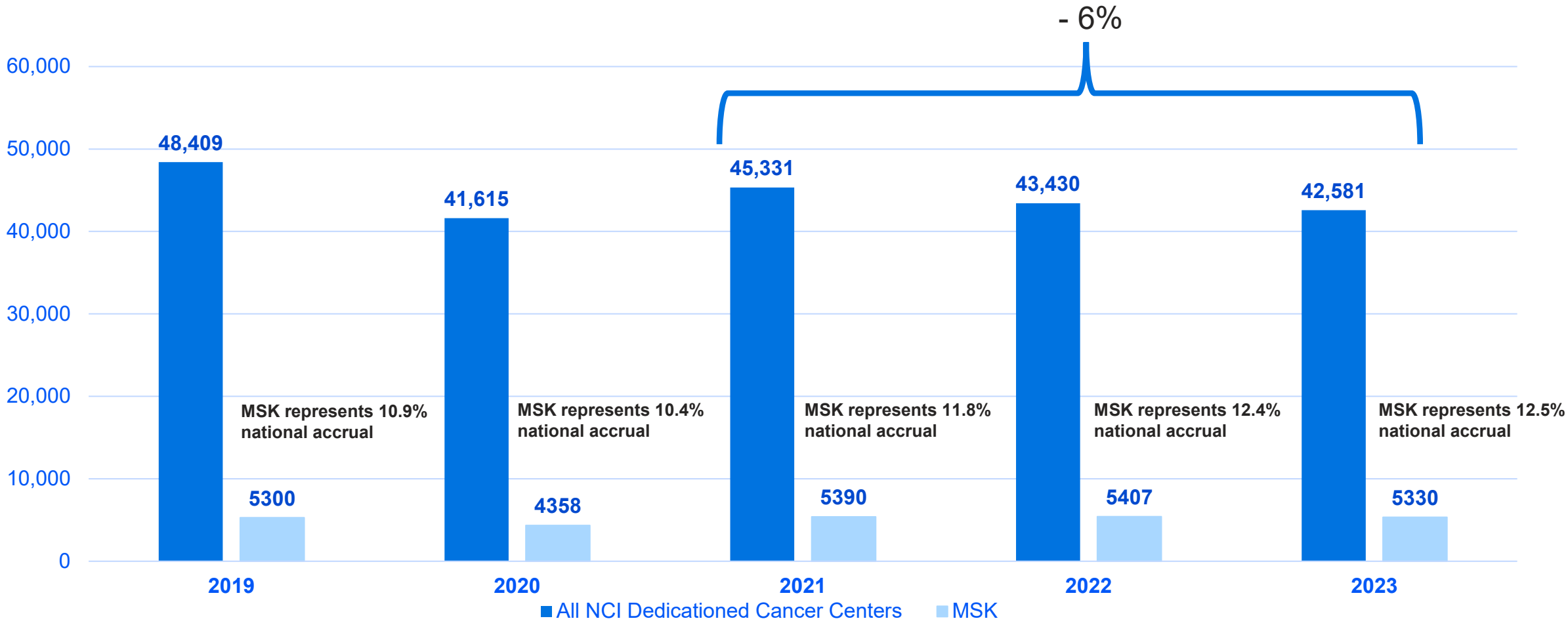


- Mechanism to move MSK developed projects from bench to bedside

- Generates clinical revenue

Interventional Treatment Trial Enrollment

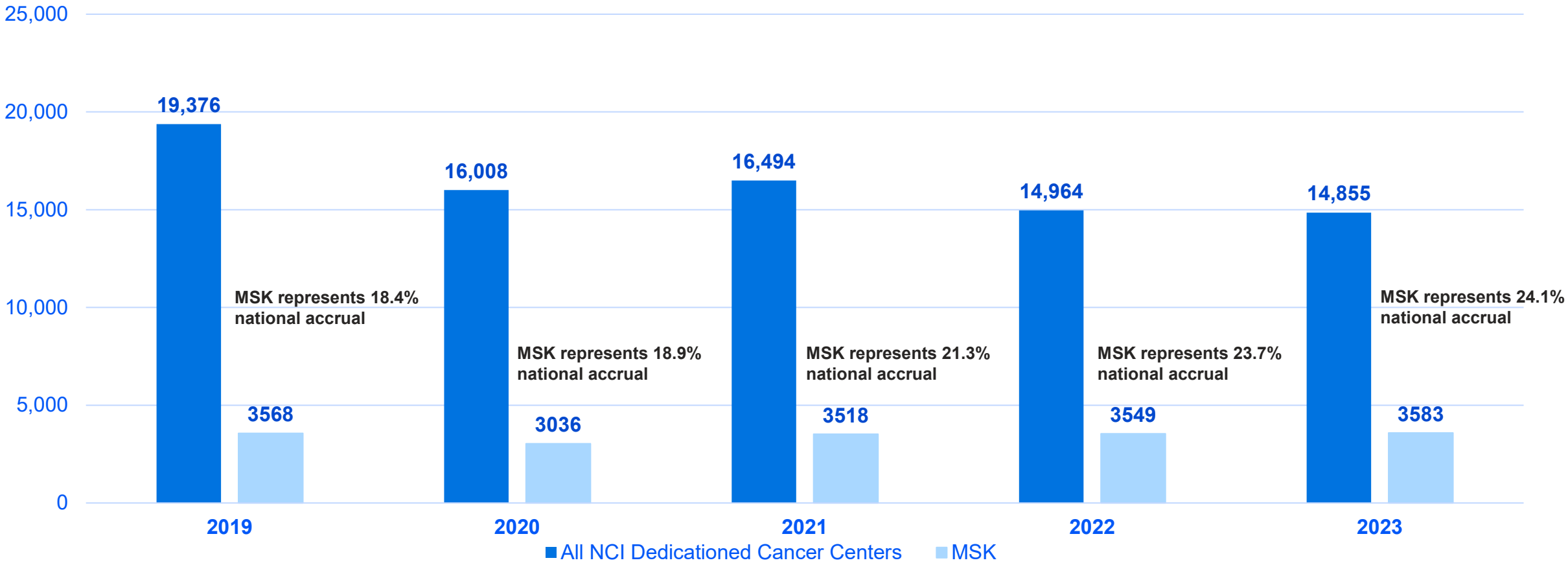
(72) NCI-Designated Cancer Centers* compared to MSK Enrollment



* Interventional Treatment Trial Data from NCI's Clinical Trials Reporting Program (CTRP) as of 4/23/24

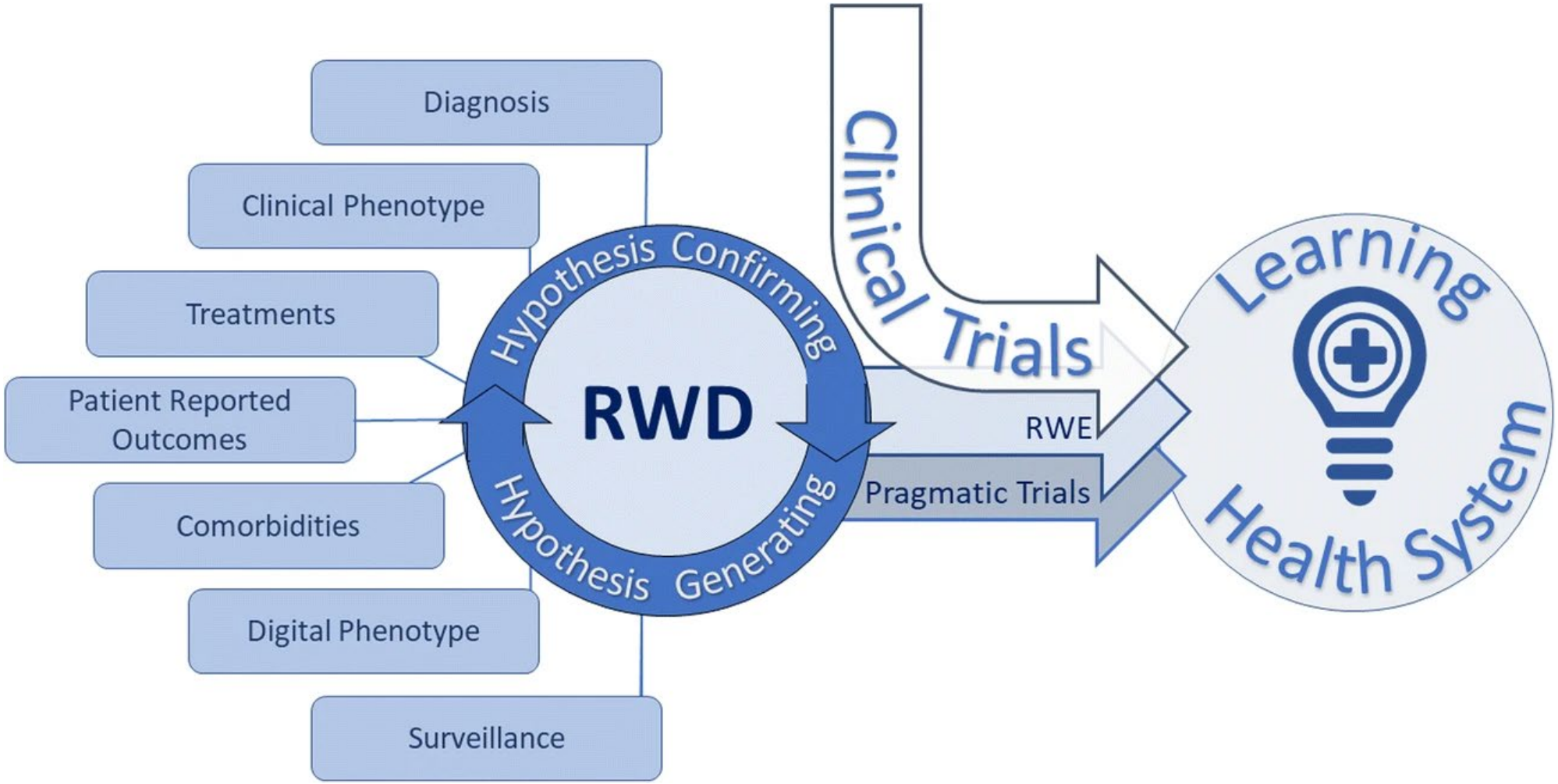
Memorial Sloan Kettering Cancer Center Investigator Initiated (MSK Sponsored) Interventional Accruals

(72) NCI-Designated Cancer Centers* compared to MSK Enrollment



* Interventional Treatment Trial Data from NCI's Clinical Trials Reporting Program (CTRP), last complete year

Next Steps With Data Aggregation: “Real World Evidence”



Streamlining Clinical Trials Working Group (SCTWG): Support for Decentralized Trials

Convened July 2022

November 9, 2022 (interim report)

https://deainfo.nci.nih.gov/advisory/ctac/1122/Meropol-Mandrekar2.pdf

March 13, 2024 (final report)

https://deainfo.nci.nih.gov/advisory/ctac/0324/Mandrekar2.pdf

MSK leads: Carol Aghajanian, Isabel Preeshagul, Roy Cambria, Ann Rodavich, Sara Hanley

High Impact Example: Reducing Toxicity

Leading Cooperative Groups / Pragmatic Trial Design (1/25)

Ying Liu, MD
GYN and Clinical Genetics

Eligibility

- Newly diagnosed, FIGO stage III–IV Ovarian cancer
- *BRCA1/2* mutation (germline or somatic) or Homologous Recombination deficient
- Cytoreductive surgery
- Response to platinum-based chemotherapy†

3-12 weeks

Maintenance therapy

Olaparib tablets 300 mg bid x 1 year
+/- bevacizumab§

Randomize 1:1
Stratification:

- *BRCA1/2* mutated vs. Wildtype
- Bevacizumab use (physician's choice)
- Response to platinum-based therapy (PR or CR)

Olaparib tablets 300 mg bid x 1 year
+/- bevacizumab§

Analyse patients alive and progression-free after 1 year

No further Olaparib

Olaparib tablets 300 mg bid x 1 year

Primary endpoint

- Investigator-assessed PFS via RECIST v1.1 (non-inferiority)

Key secondary endpoints

- OS
- PFS2
- Safety (including rates of MDS, AML)

Infrastructure: Manage Life Cycles of Clinical Research Projects (Protocols)

DEVELOPMENT

- Iterative process with sponsor (MSK, pharma, national cooperative group)
- Protocol development template
- Budgets / contracts

ACTIVATION

- Departmental review (science and plan)
- Institutional review (priority / competing studies)
- IRB (Human Subjects Protection)

ACCRUAL

- Evaluate for performance
- Identify problems and amend

MONITORING/AUDIT

- Compliance with study plan and patient safety
- Informed consent procedures

CLOSEOUT

- Clean / lock data
- Biostatistical analysis
- Manuscript preparation

Time

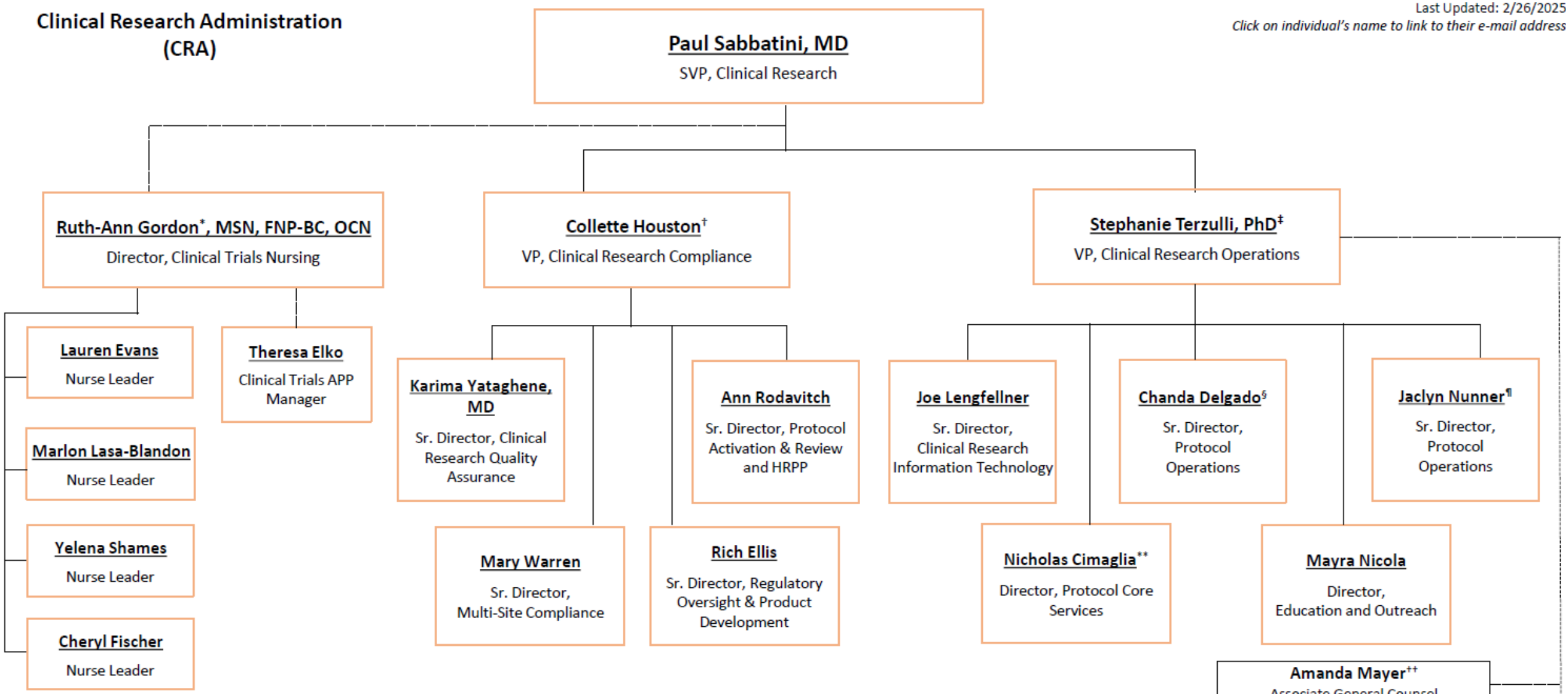
CRA Infrastructure: Supports Highly Regulated Activity

N = 1300+

Clinical Research Administration (CRA)

Last Updated: 2/26/2025

Click on individual's name to link to their e-mail address



*Reports to Chief Nursing Office
† Dual Reporting to Debra Berns, SVP & Chief Risk Officer
‡ Oversees Pediatrics and Medicine/GU
§ Director, Protocol Operations for Radiology, Surgery, Epi/Bio, Med Physics, Psychiatry & Behavioral Sciences, and Rad Onc
¶ Director, Protocol Operations for Medicine and Neurology
** Dual Reporting to Collette Houston
†† Reports to Office of General Counsel
‡‡ Reports to Office of Research and Project Administration (ORPA)
§§ Reports to Office of Technology Development (OTD)

When is a clinical trial “best”?

- Integrated into planning from screening to diagnosis to treatment to survivorship

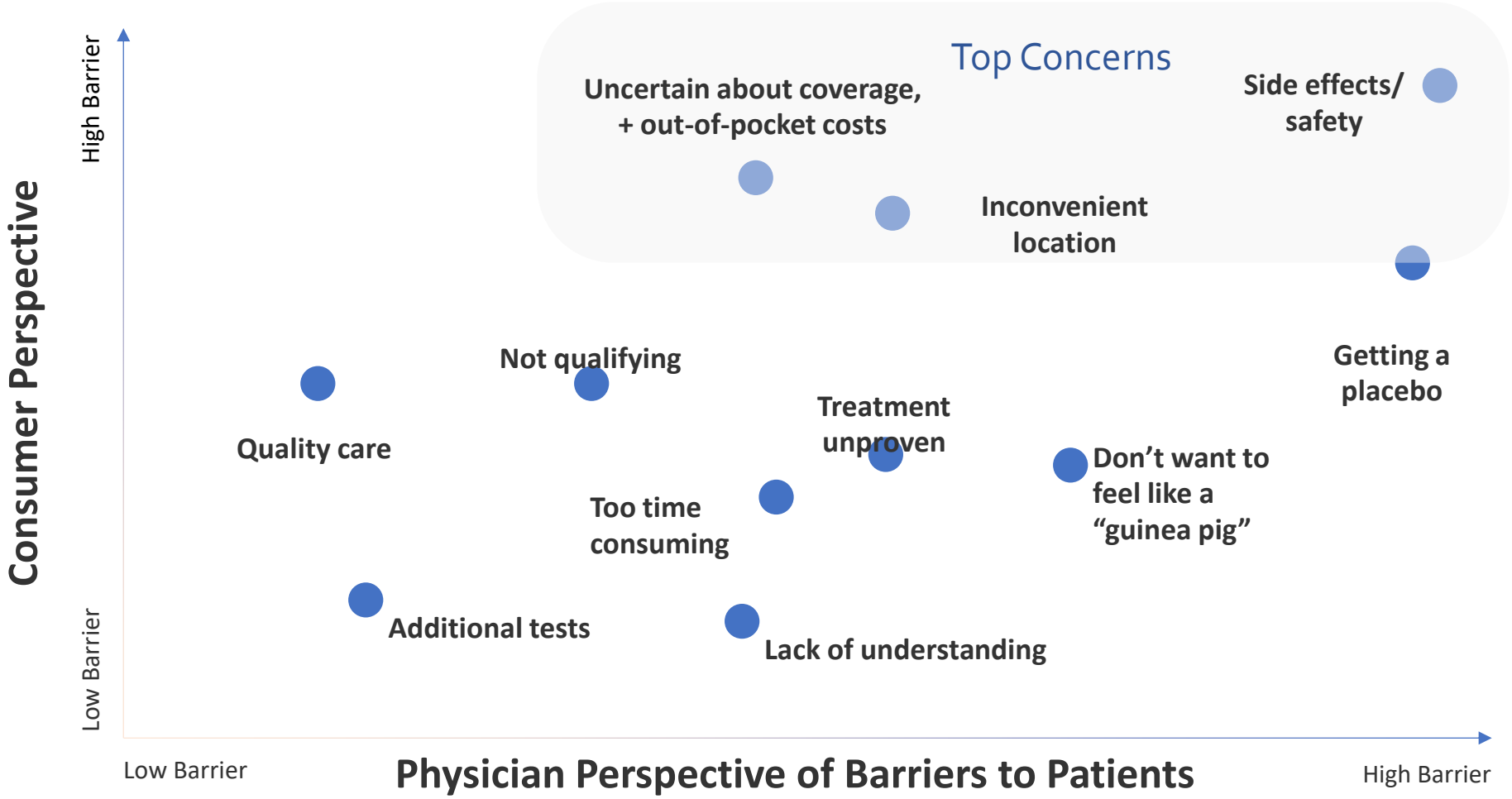
- Care decision (s)

Standard treatment

Vs.

Investigational Treatment

Barriers to Enrollment



Mancini et al. JCSO 2018;16(2):e81-e88

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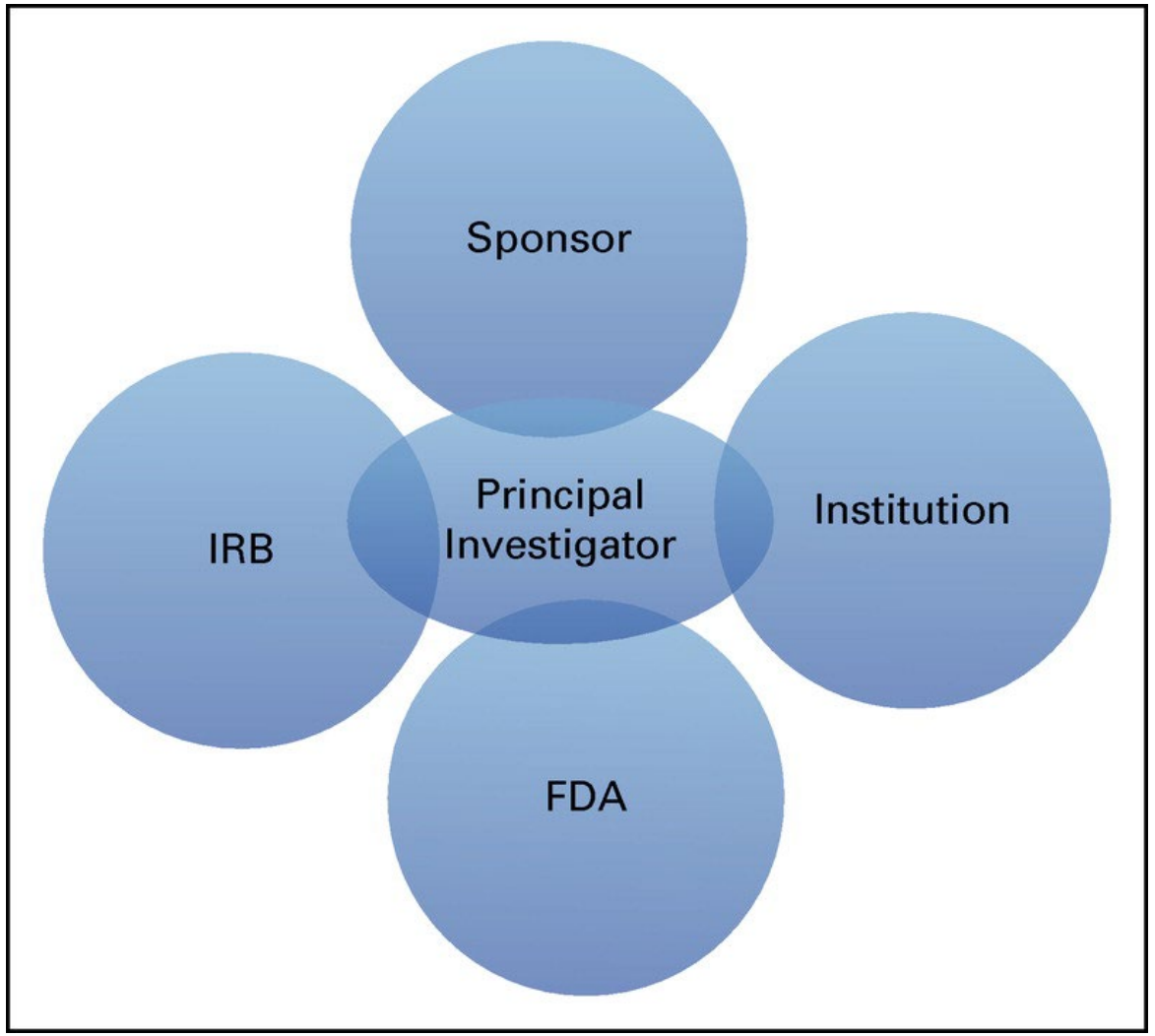
The Principal Investigator (PI)

Abuse Endangered Veterans in Cancer Drug Experiments – New York Times

- **"…were systemic weaknesses in the human research protections program, especially in studies funded by industry…."**
- **"…was a research culture where rules weren't followed, protocols were not strictly applied, and supervision was non-existent…."**
- **The FDA started proceedings to disqualify Dr. X (lead investigator) from conducting further research because he had failed to protect patients under his care in X.**

Responsibilities of the PI



Saleh et al. JOP 14: 2018

Responsibilities of the PI

- Design of study (the intellectual leader)
- Coordinates functioning of the research team
- Oversees data acquisition, analysis, and reporting
- Ensure that all regulatory and reporting requirements are observed

Supported by Institutional Infrastructure

Challenges of the PI

- Time and financial demands of clinic practice
- Increasing complexity of regulations
- Increasing complexity of contracts (“promises”)
- Potential lack of supporting infrastructure
- Inadequate research training
- Data collection issues (world of EHR)
- Globalization

Oversight and Federal Agencies

- Office of Human Research Protection (OHRP)
  - 45CFR46 (the “common rule”) – applies to all research using US federal funding, including indirect or partial support such as funding of infrastructure. Oversees IRB system and investigates allegations of substandard human subjects protection or IRB performance.

- Food and Drug Administration (FDA)
  - 21CFR – regulations are implementations of the Food Drug and Cosmetic Act and apply to research with all investigational substances or devices being tested in humans under an “IND” or an “IDE” whether federally funded or not.

- Office of Research Integrity (ORI)
  - Oversees investigations by institutions of alleged research misconduct involving federal research funds

Oversight and Federal Agencies

- National Institutes of Health (NIH)
  - use of federal funds according to a grant's terms of award
  - minority representation on clinical trials
  - data safety monitoring
  - education and training of clinical researchers
  - data audits
  - animal welfare

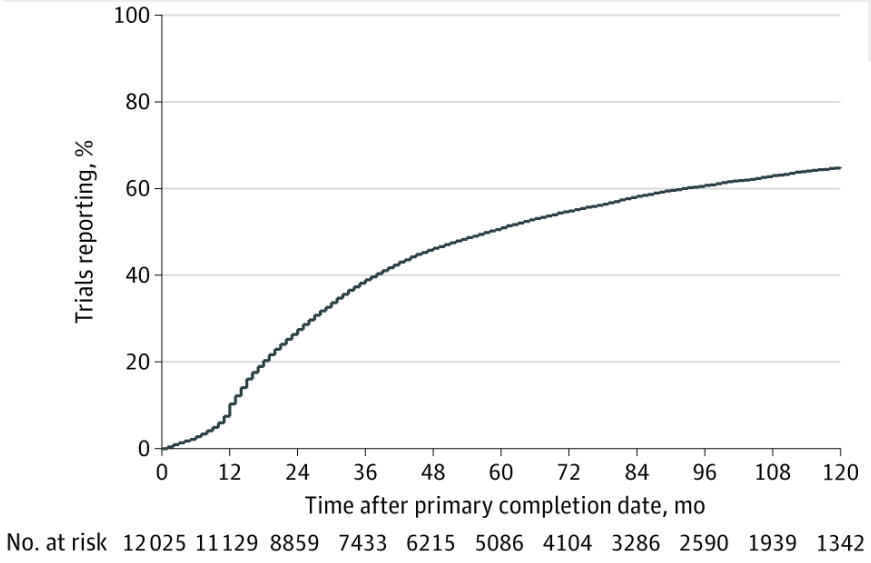
- Office of Civil Rights (OCR)
  - HIPAA and Health Information Privacy

- Center for Medicare and Medicaid Services (CMS)
  - not a research agency
  - monitoring programs to assure that Medicare funds are used only for services that are "reasonable and necessary"
  - routine care costs may be billed if trials are "qualifying".

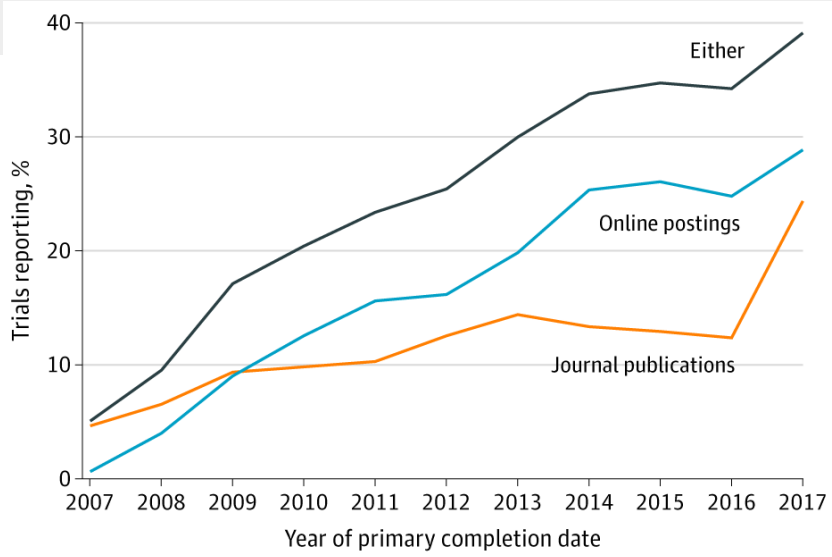
Oversight and Reporting

JAMA Netw Open. 2021;4(5):e2110438. doi:10.1001/jamanetworkopen.2021.10438

From: **Evaluation of Oncology Trial Results Reporting Over a 10-Year Period**



Cumulative % reported on ClinicalTrials.gov or in Journal Articles



Change in % reported within 24 months of primary completion date

Clinicaltrials.gov

Oversight of Commitment and Conflict

Commitment to patients best interest

- Access to most novel therapy
- Optimal Care

Commitment to pursuit of new knowledge

- Professional Recognition
- ± Financial Benefit
- Desire for rapid enrollment

Commitment to MSK vs Outside Organizations

- Drug or device sponsor
- Speaker programs
- Professional Societies

AAMC: https://www.aamc.org/initiatives/research/coi/

MSKCC See “Policy on Conflict of Interest and Conflict of Commitment” at MSK Intranet>TOC>Conflicts of Interest

Support for the Investigator

- Clinical Trials Training Courses (CITI, Gerstner Clinical Research Study Management and Compliance)

- Clinical Research Administration
  - Data
  - Regulatory
  - Compliance
  - Clinic Support Staff
  - Clinical Trials Nursing

- Mentors (Co-PI, other investigators)

Clinical Research at MSK

Identifies MSK as World's Leading Authority on Cancer (Set Care Standards)

Innovation is the primary differentiator which attracts patients

Key to increase the value of MSK IP, strategic asset for partners / faculty talent

New research opportunities expand our reach (Decentralized Trials, Data Services [AI integration], Translational Research [bi directional learning])

Key Issue: Sustainability, Funding and Optimal Size (Resources, Technology, Priority)