

Introduction to Clinical Research (at MSK)

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

Paul Sabbatini, MD

SVP Clinical Research

Oct 15, 2025



Memorial Sloan Kettering
Cancer Center

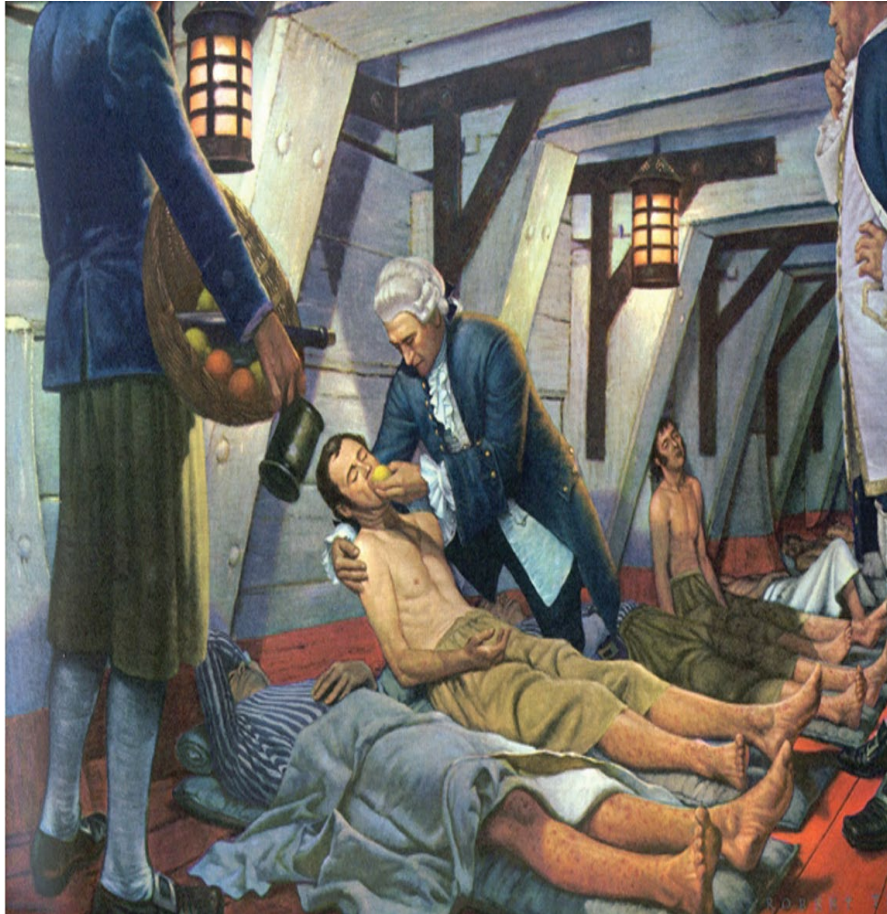
Objectives

- 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.

“Father of Clinical Trials”: James Lind



Treatise on Scurvy 1753

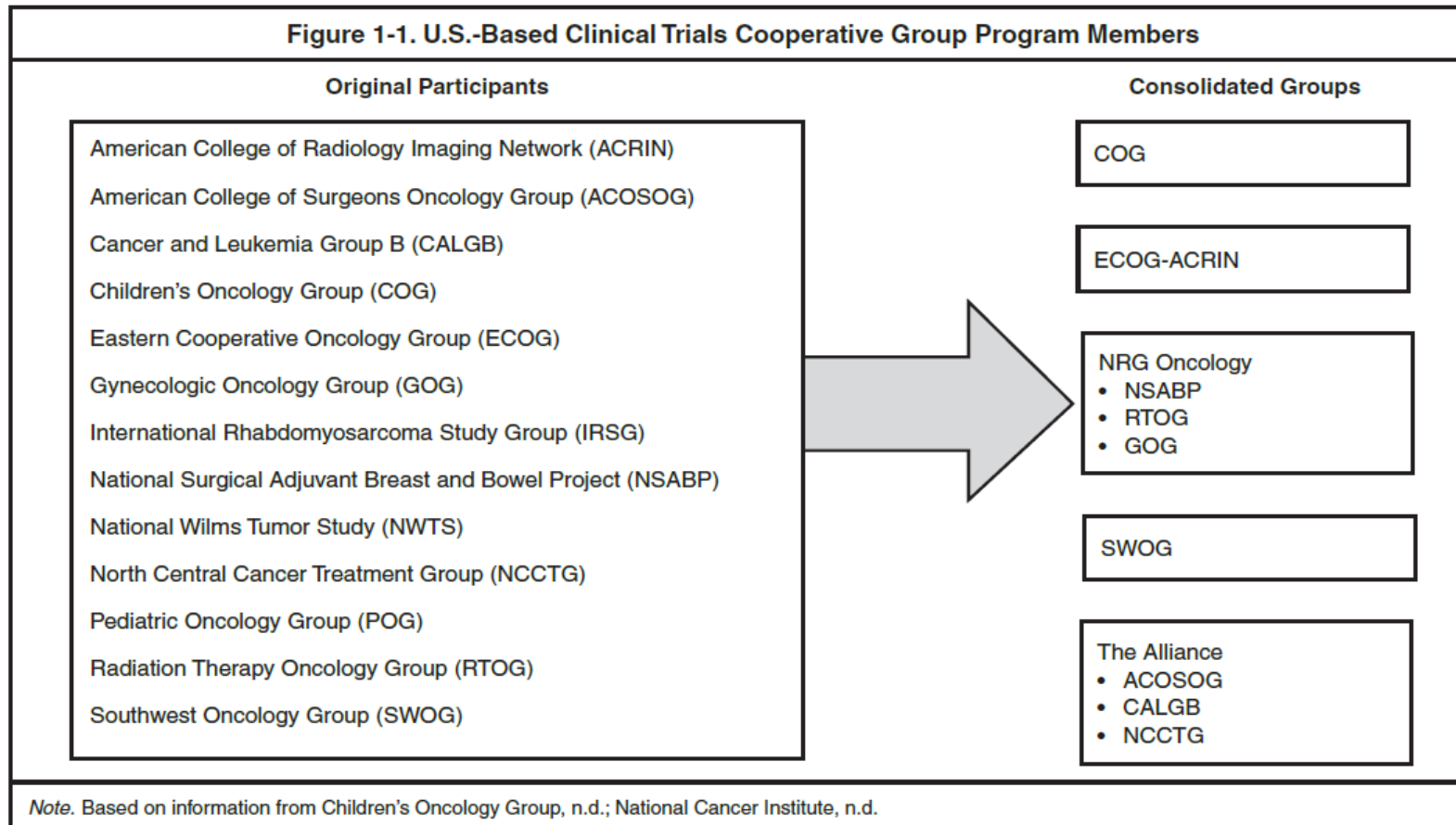
“They all in general had putrid gums, lassitude and weakness of the knees”

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

Cooperative Groups and Clinical Trials

1950's

2010 +



Events in Human Subjects Protection

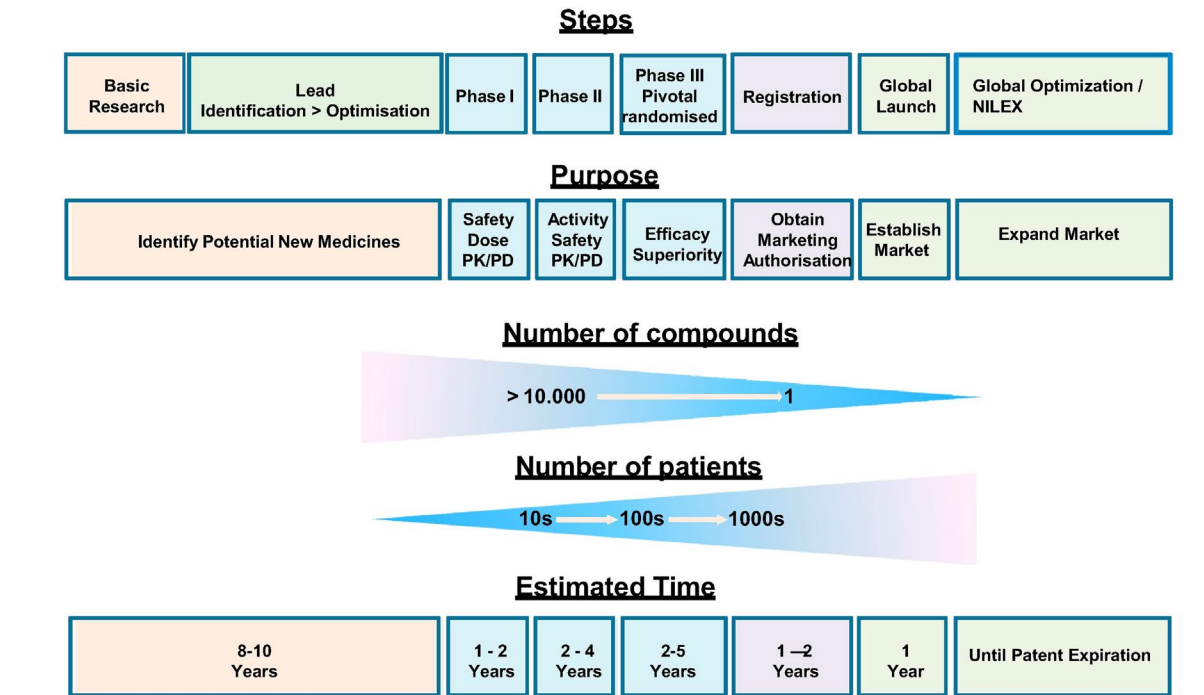
- Nuremberg Doctors Trial
 - Nuremberg Code (1947)
 - Voluntary consent essential
 - Declaration of Helsinki (1964)
 - Risks not exceed benefits
 - Tuskegee Syphilis Study (1932-1974)
 - National Research Act 1974
 - Belmont Report (1979)
 - Respect for persons, justice, beneficence
 - DHHS regulations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

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Historical Drug Development

Oncology Drug Development: The Traditional Model



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

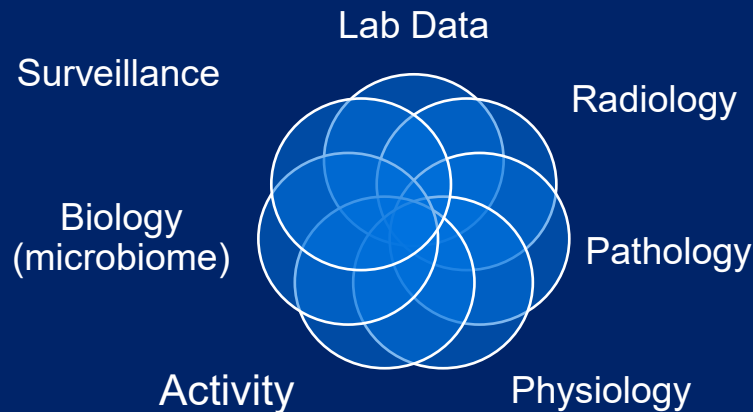
More Drugs

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

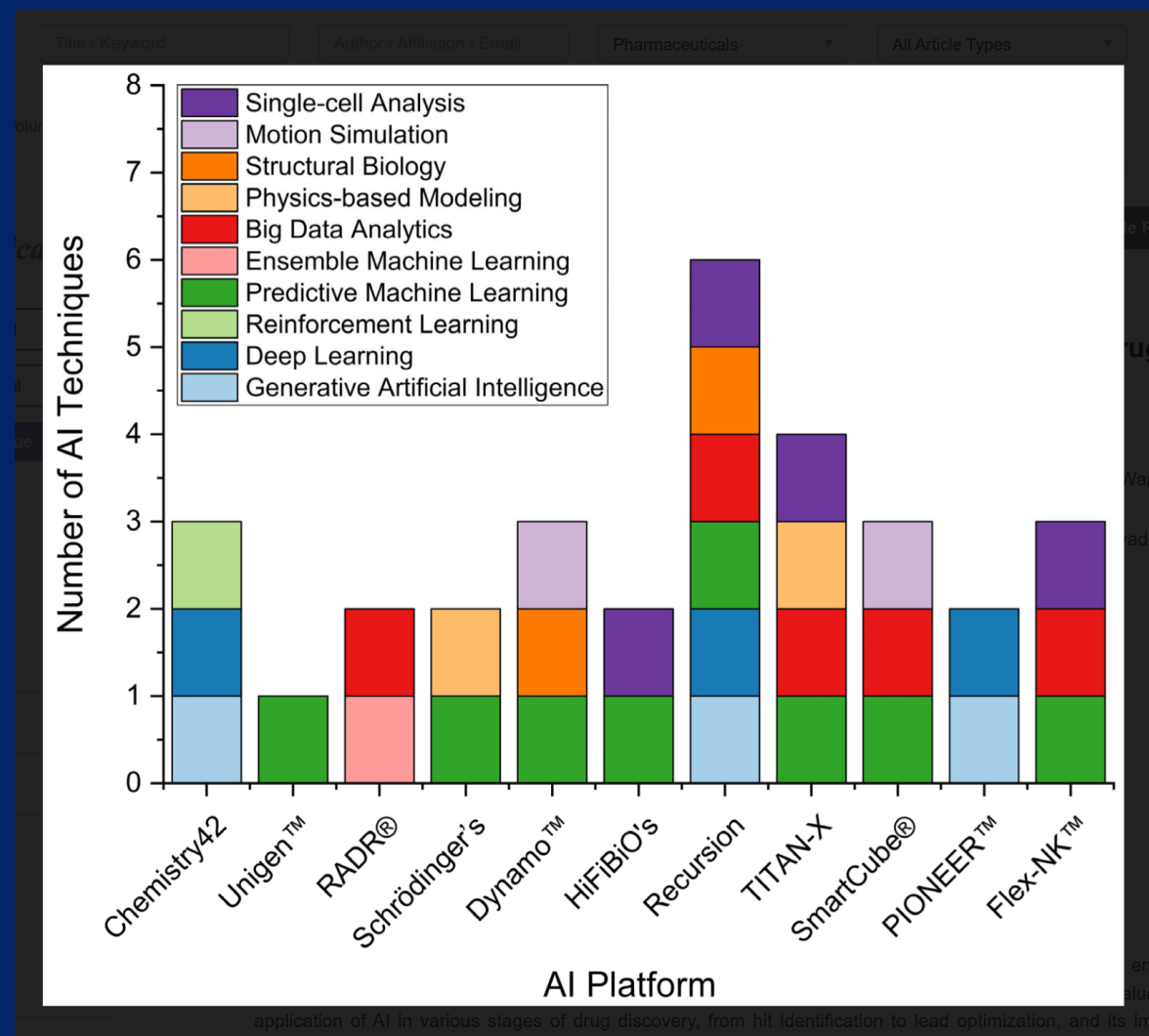
100K+ patients, > 96K
tumors, 30+ % clinically
relevant alteration

Mutations differ in
metastasis from same
tumor

More Technology

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

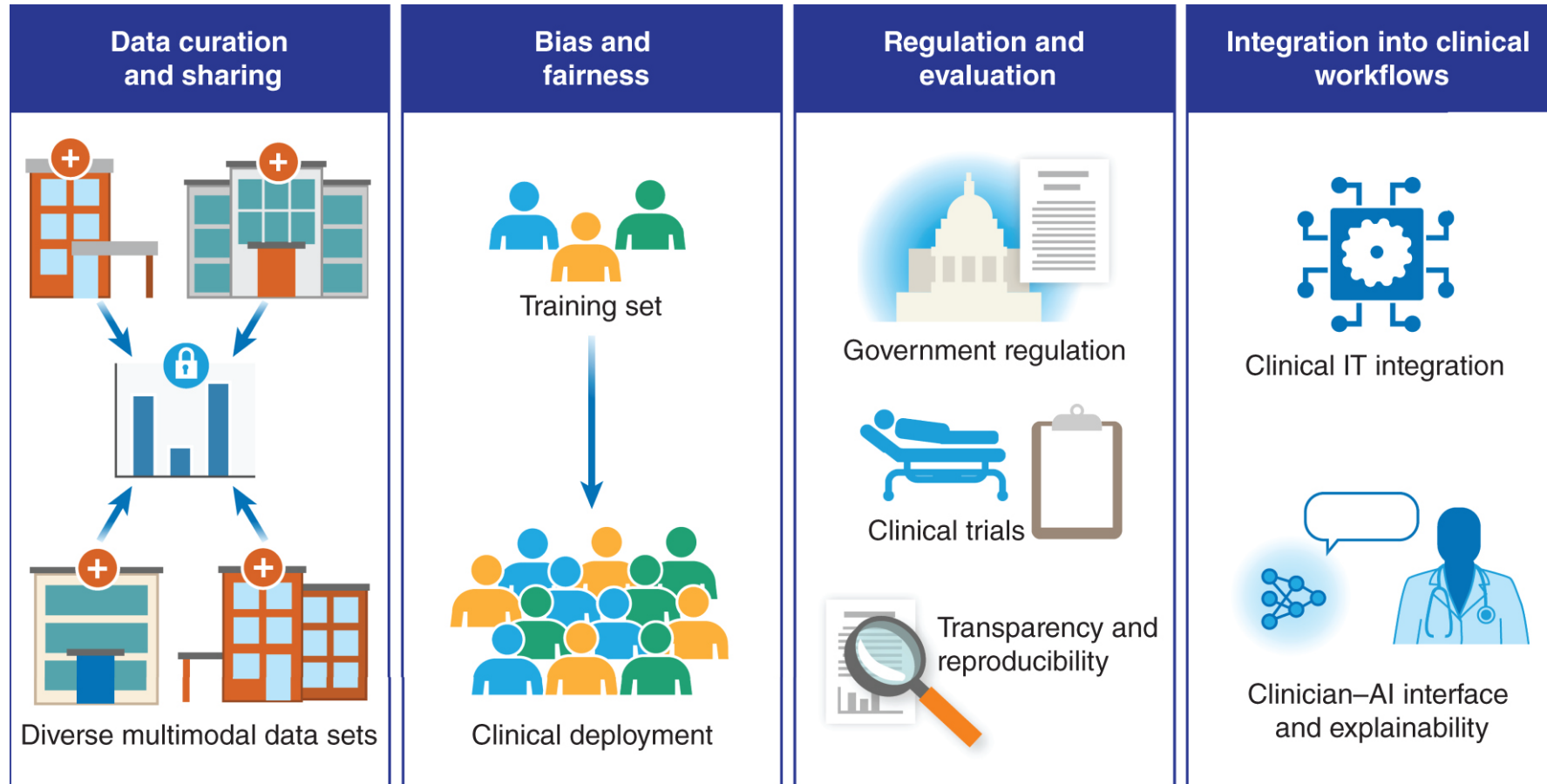
Dermawan et al. Pharmaceuticals. 2025.



AI: Challenges / Opportunities for Clinic

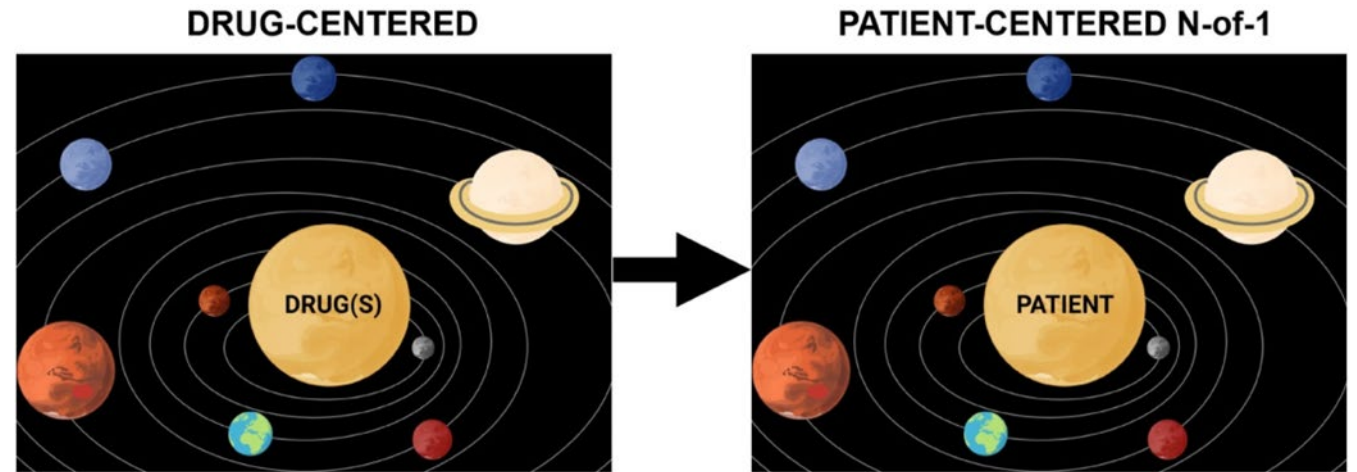
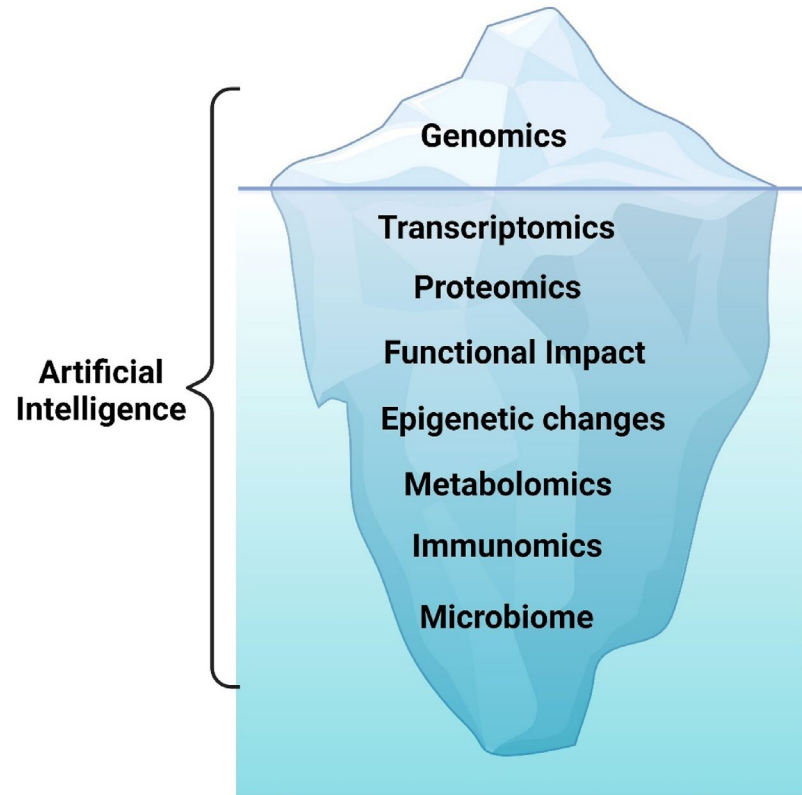
From: **Artificial Intelligence in Oncology: Current Landscape, Challenges, and Future Directions**

AACR American Association
for Cancer Research[®]



Cancer Discov. 2024;14(5):711-726. doi:10.1158/2159-8290.CD-23-1199

Multi-modal and Patient Centered Trials



Challenges: Design versus Speed

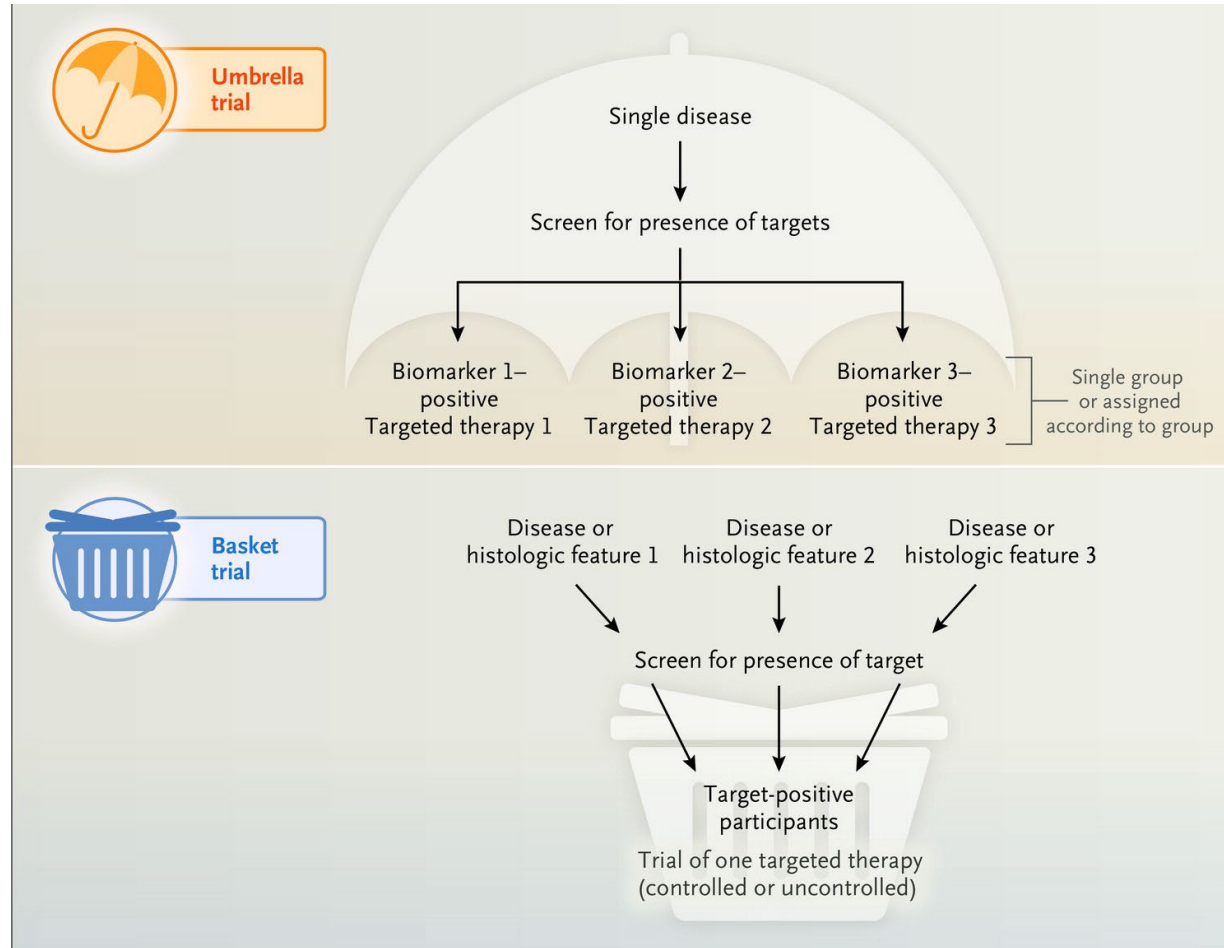
Traditional

- 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



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.

Innovation Requires Distributed Access

Decentralized Clinical Trials

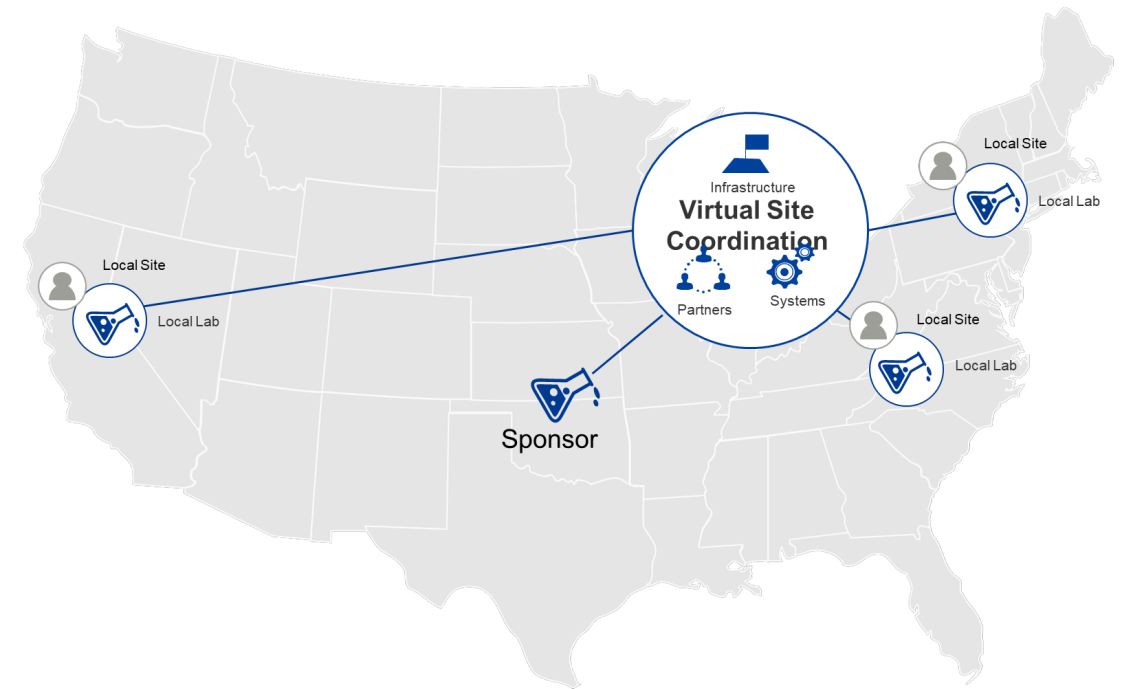


Innovation Requires Distributed Access

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

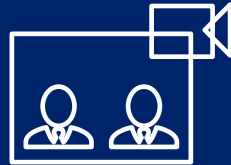
Decreased overhead costs, less operational burden, more throughput

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

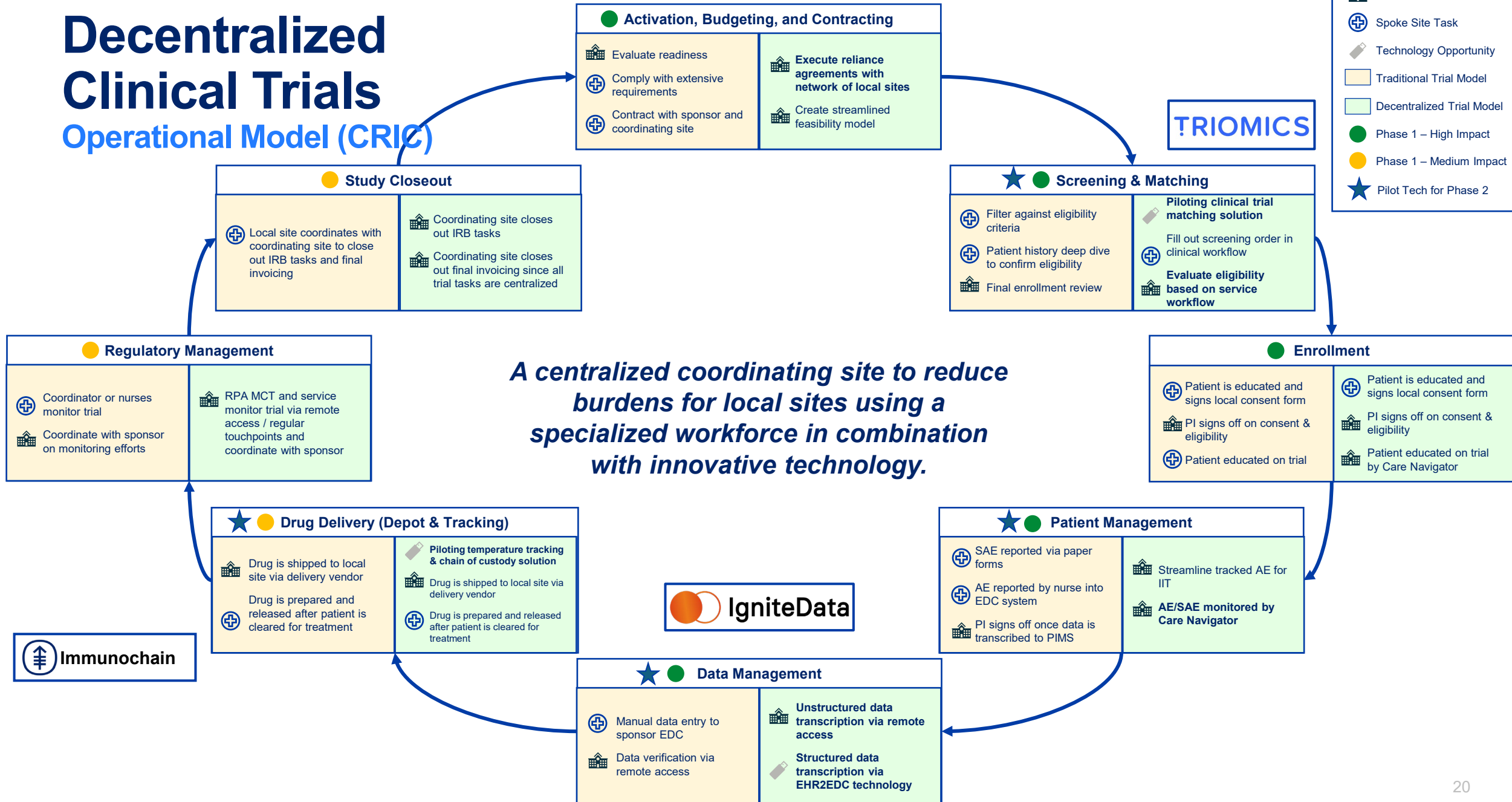


EPIC EHR
Transition

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

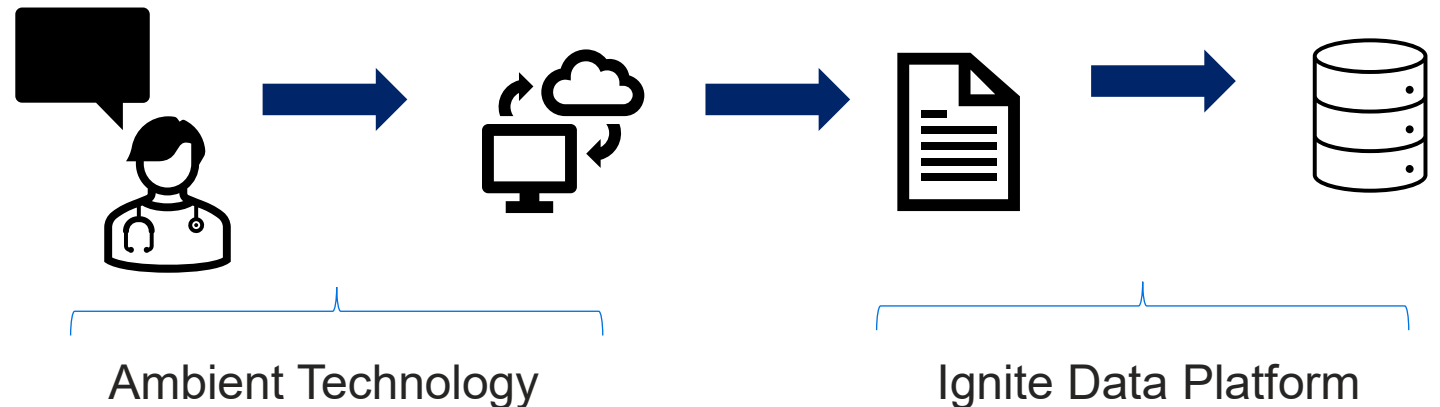
10 vendors / MSK mentors

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

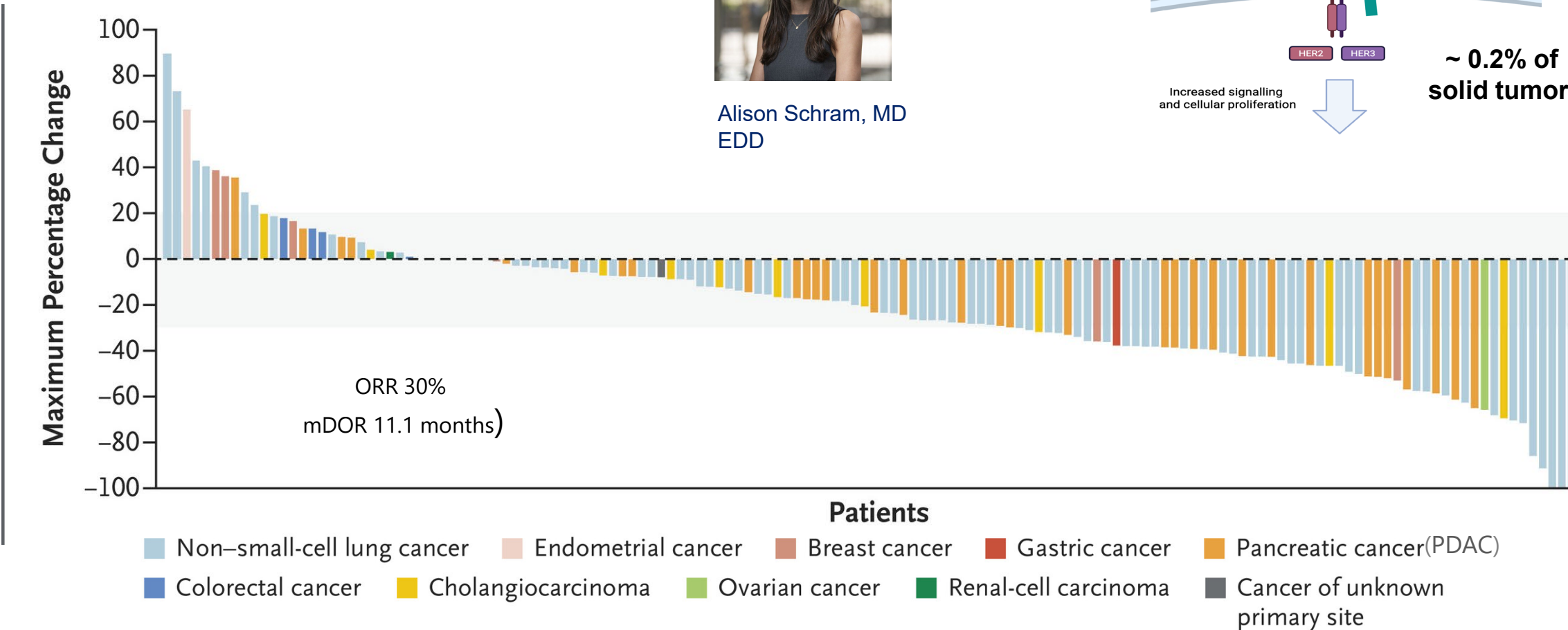
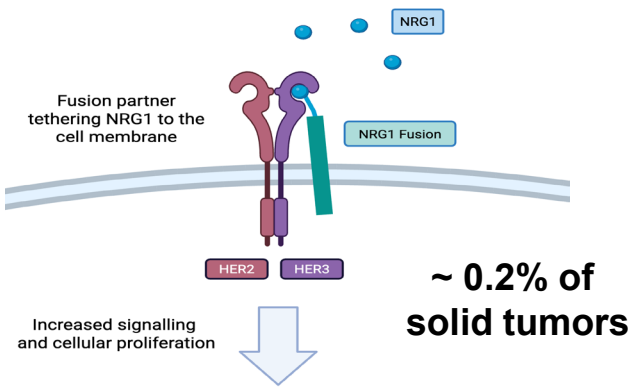


High Impact Example: Zenocutuzumab in NRG1 Fusion+ Solid Tumors FDA Approval

Screening, Access and Logistics



Alison Schram, MD
EDD



Objectives

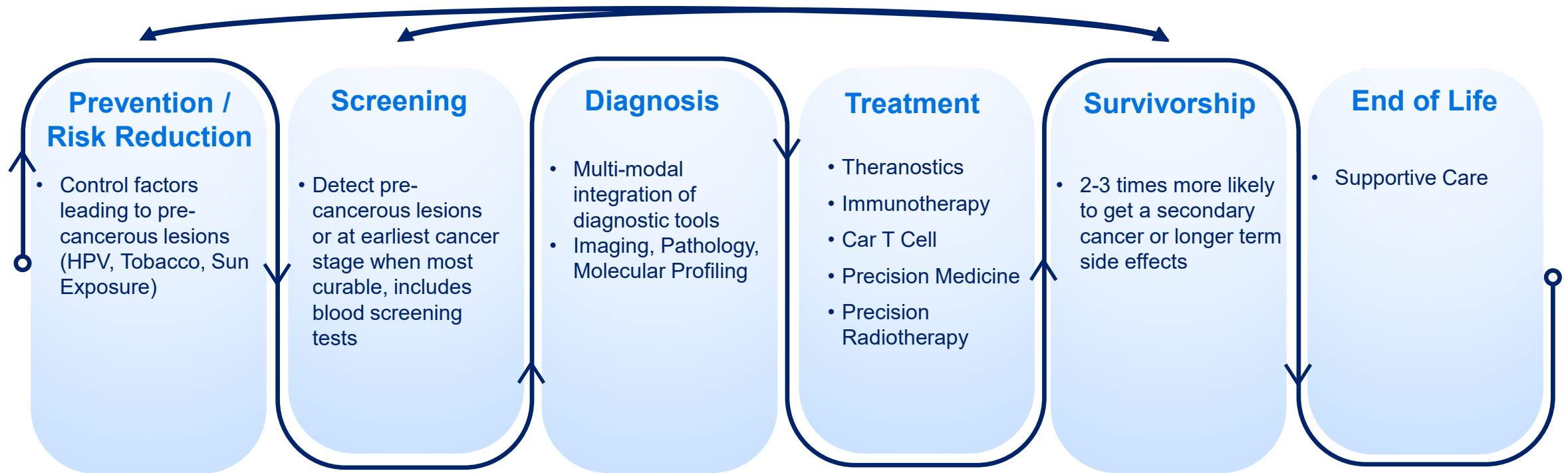
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Scientific Discovery at MSK: Clinical Context



- Exceptional strength across research landscape from fundamental discovery to clinical investigation- talent, institutional resources, and freedom to discover
- Maximized impact by seeing scientific discoveries all the way to clinical use

MSK Programs Address Biologic Continuum of Cancer



TRANSLATIONAL SCIENCE

PATIENT CENTERED DISCOVERY (CLINICAL RESEARCH PROGRAM)

Requires Strategic Investment

Clinical Research and Patient Care is Bidirectional.



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

2016

Protocol 16:1406
Lete-cel (NYESO-1) TCR in
myxoid round cell liposarcoma

ORR 20-40%
DOR 5-7m

2019

Protocol 19:316
Afami-cel (MAGE-A4 TCR) in
synovial sarcoma + MRCLS

ORR 39% (SS), 25% (MRCLS)
DOR 12m (SS), 4m MRCLS)

2020

Protocol 20:055
Lete-cel (NYESO-1) TCR in
synovial sarcoma + MRCLS

ORR 43%
DOR 12.2m

- **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

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

Ref: D'Angelo SP, JCO in press

- 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

- 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)

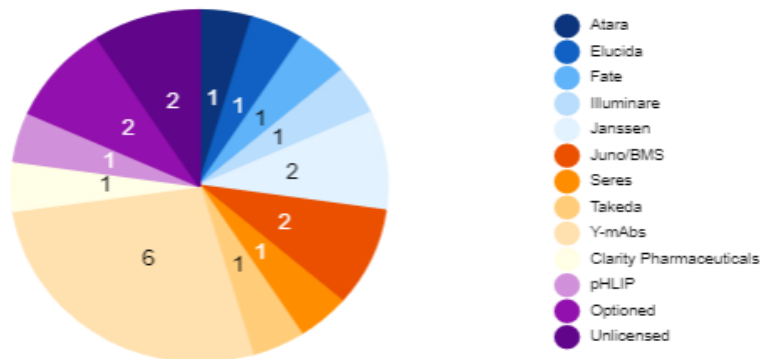
Translational Research
(HOPP)

Clinical Research
(Effector Arm)

OTD

Office of Technology
Development

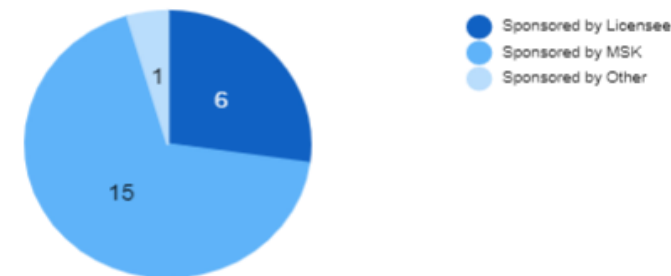
Trials OTA at MSK by Licensee



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



Innovation Requires Core Services: MSK Biobank



Hikmat Al-Ahmadie, MD



Ross Levine, MD

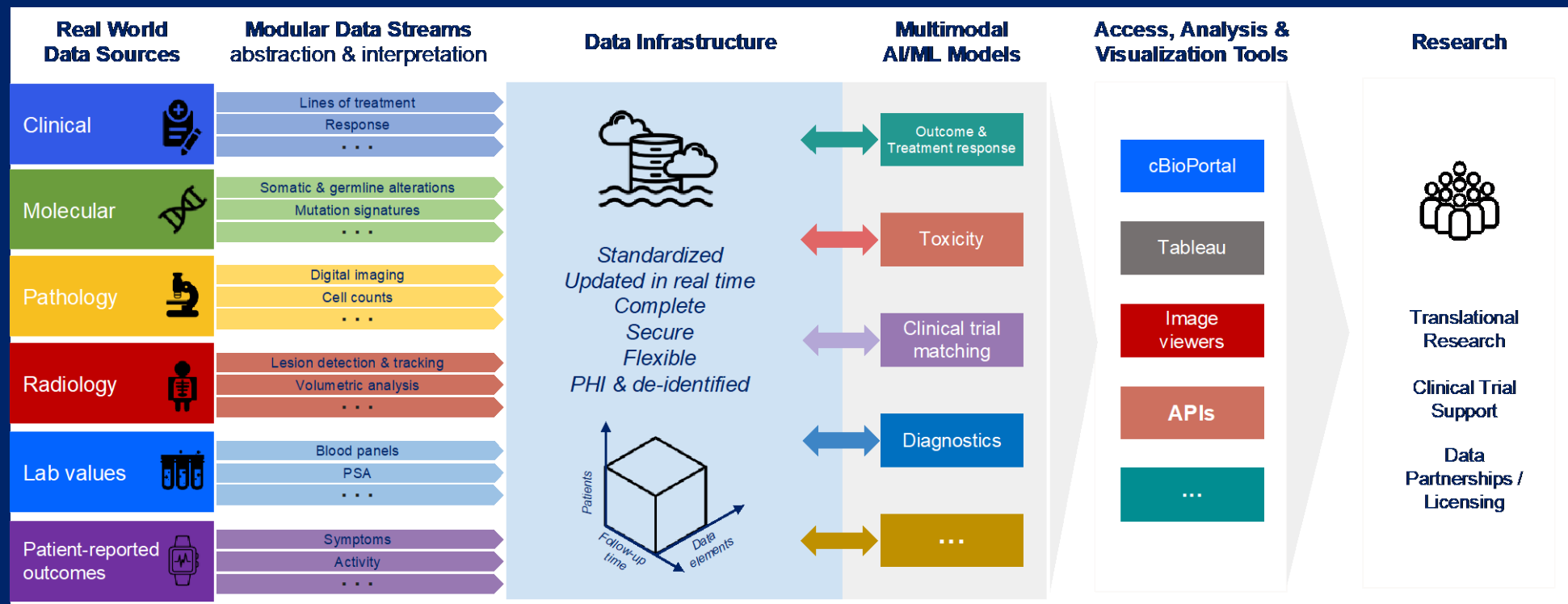
- Nearly 1 million specimens
- Work is underway to optimize:
 - increase collections in networks
 - samples needed for key discovery/translational research (organoids and single cell studies)
 - collaborations with academic and industry partners
- Key facilitator of next steps – understanding response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

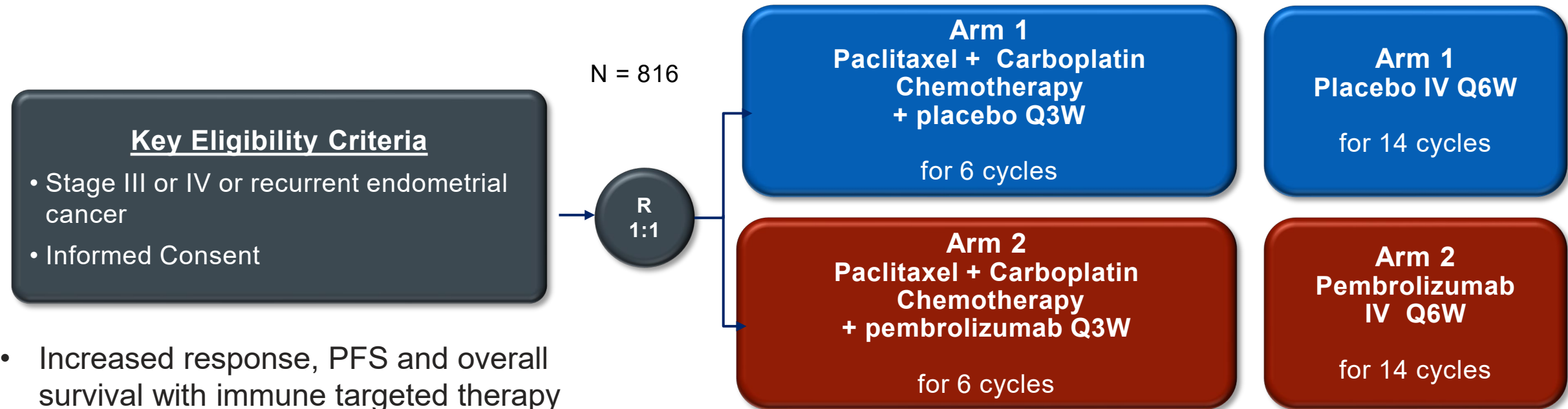
Additional Support: Computational Oncology/ Shah et al.

CDSI Director: Niki Schultz PhD

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

High Impact Example: Using MSK Biobank and CDSI



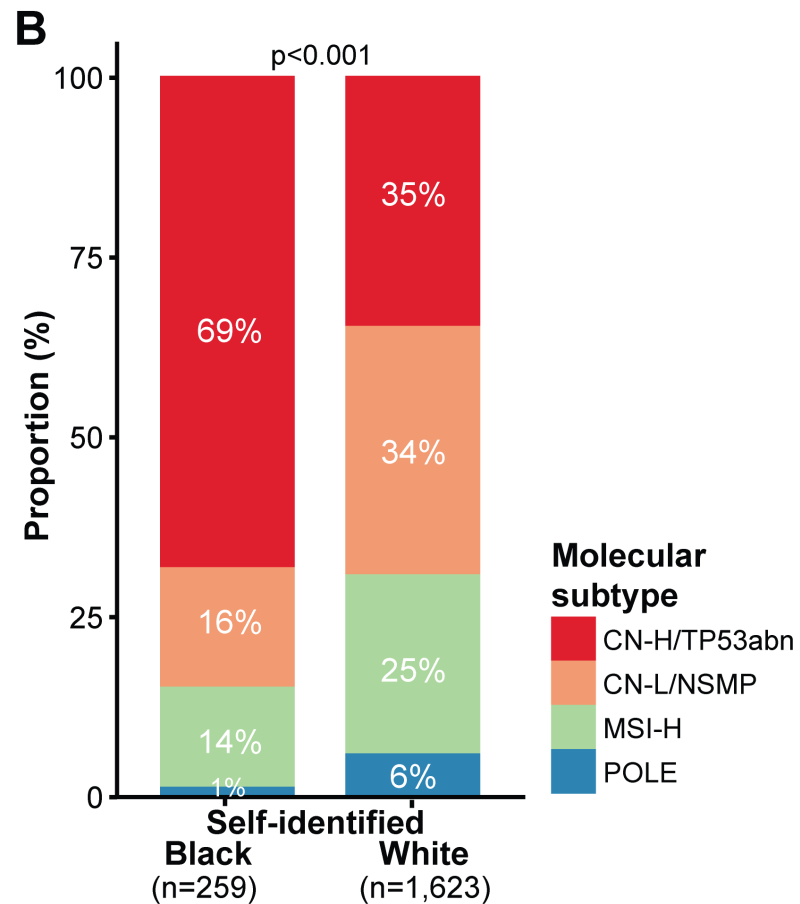
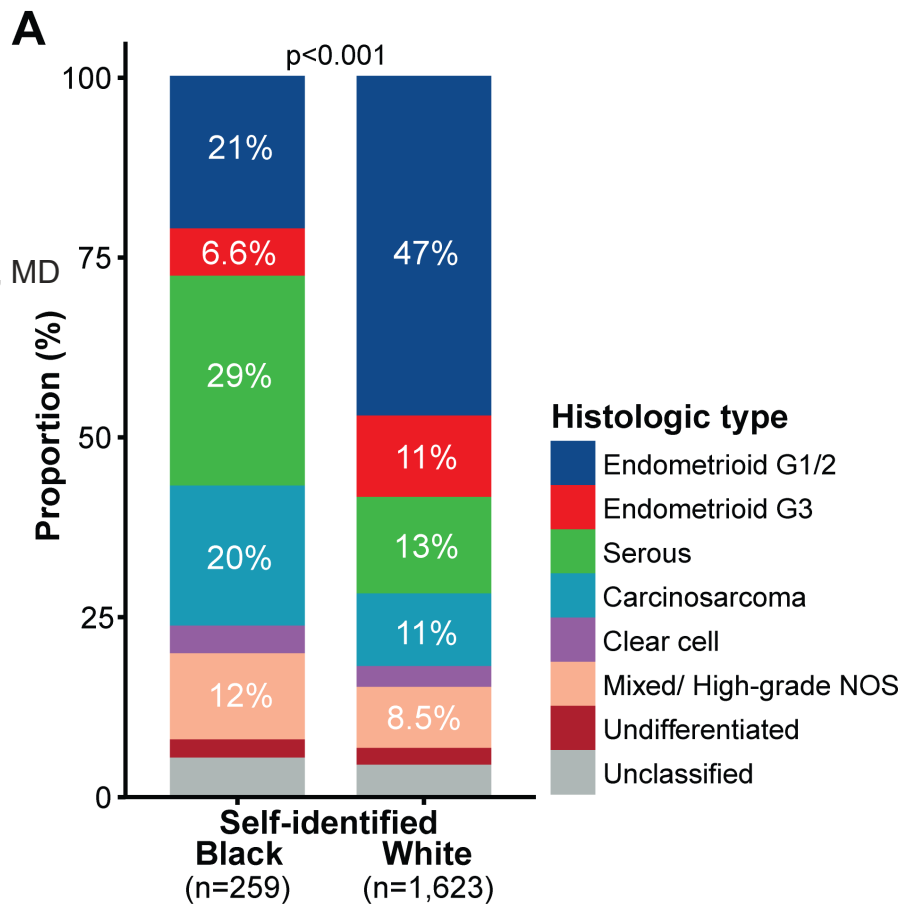
Carol Brown, MD

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)

Clinical Research: Value to Patients

FDA DRUG APPROVALS

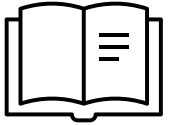
40+

**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

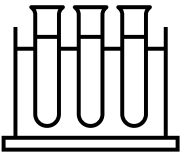


- Clinical Trials are recommended as preferred options in multi-disciplinary Cancer Treatment Guidelines (NCCN, ASCO, others) – integral part of care

30% of patients participate across life cycle at MSK



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



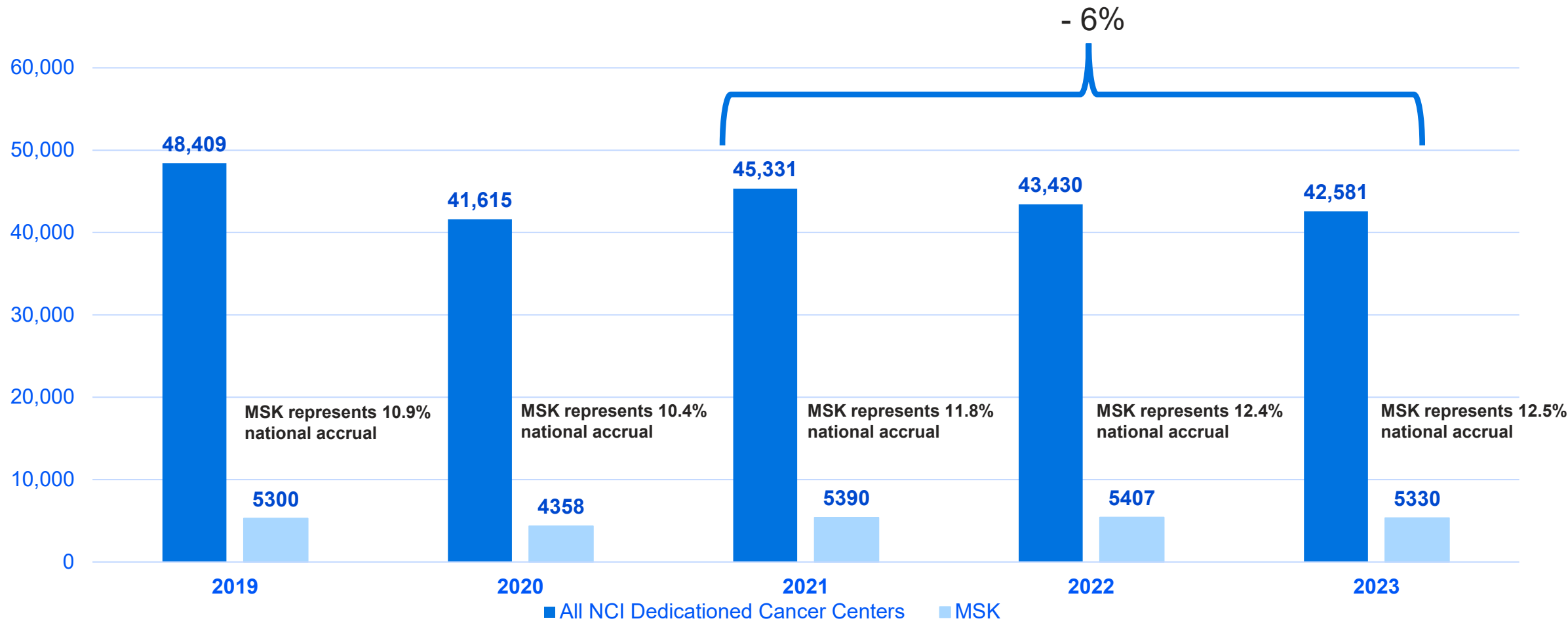
- Mechanism to move MSK developed projects from bench to bedside



- Generates clinical revenue

Interventional Treatment Trial Enrollment

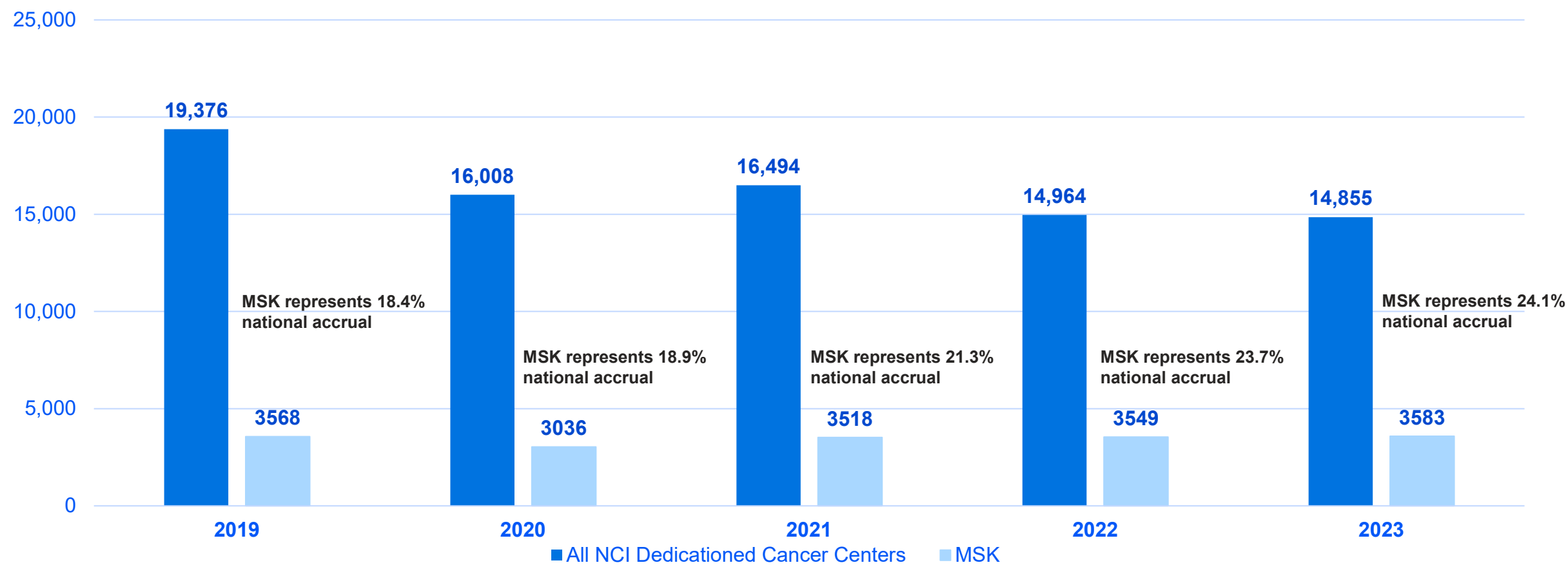
(72) NCI-Designated Cancer Centers* compared to MSK Enrollment



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

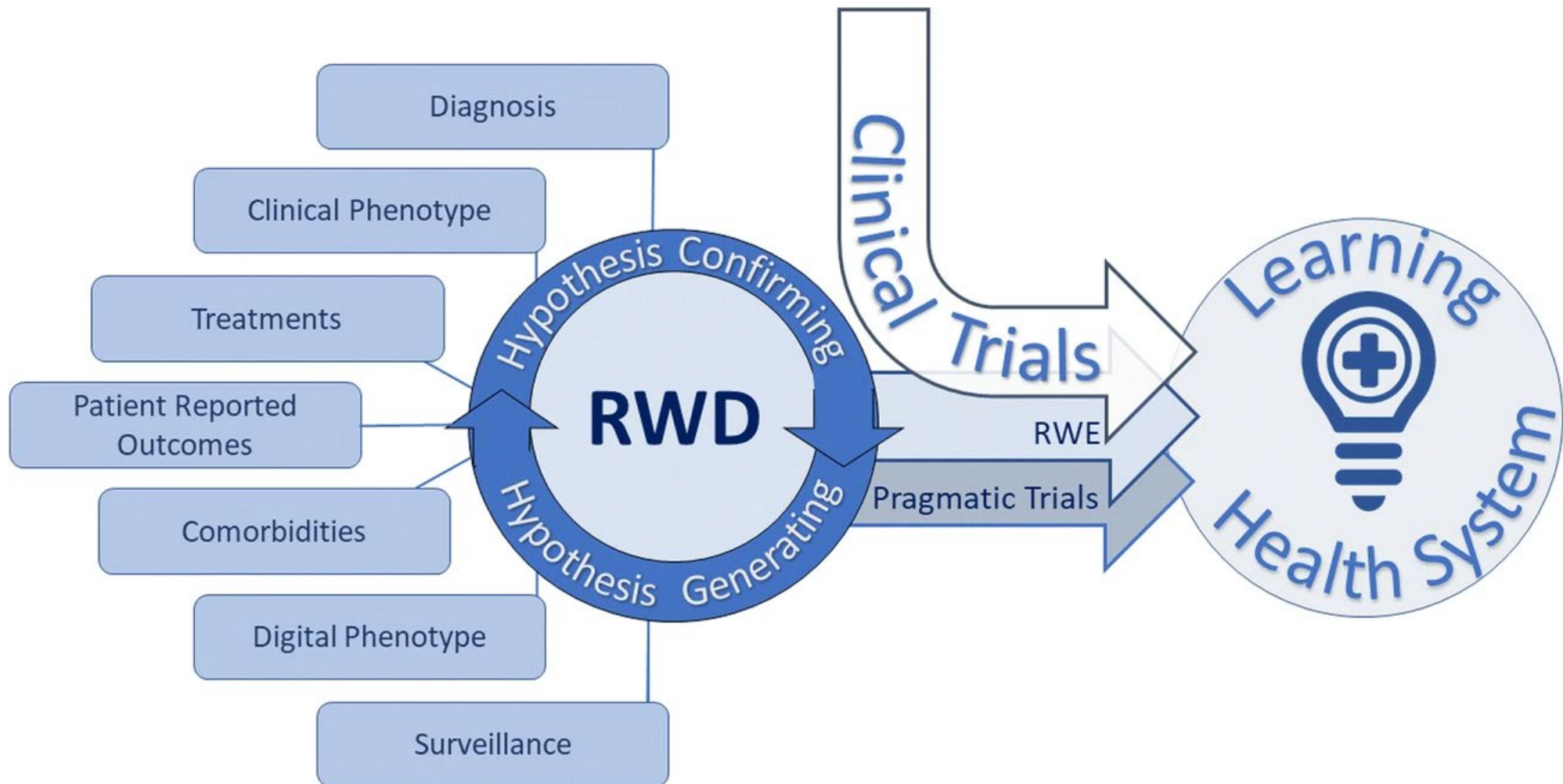
Memorial Sloan Kettering Cancer Center Investigator Initiated (MSK Sponsored) Interventional Accruals

(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

Pragmatic Clinical Trials

Defining the role of pragmatic clinical trials in cancer clinical research: outcomes of a collaborative workshop hosted by the European Organization for Research and Treatment of Cancer

Borges et al. Lancet Oncology (26): 2025

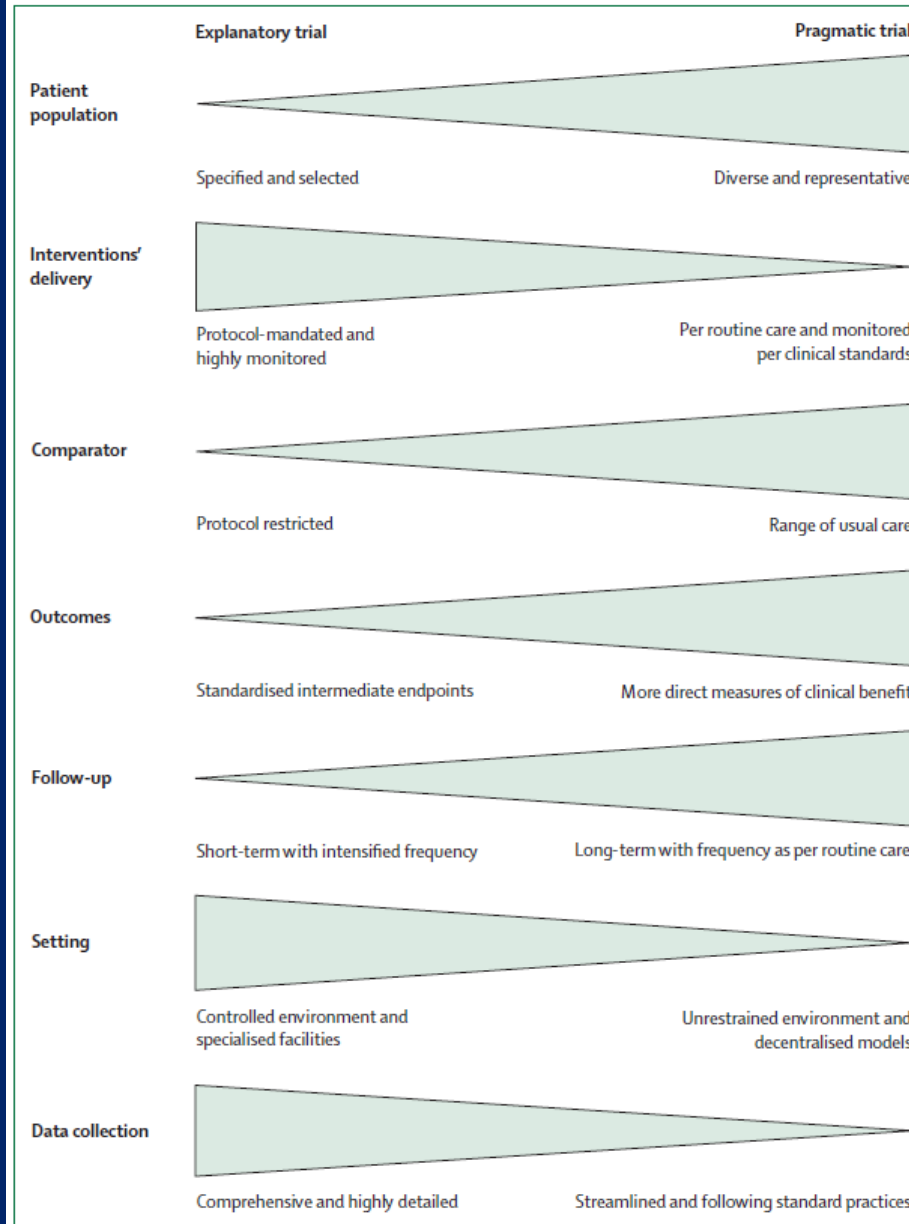


Figure: Overview of explanatory-pragmatic continuum
Wedge width indicates increased focus on each study characteristic.

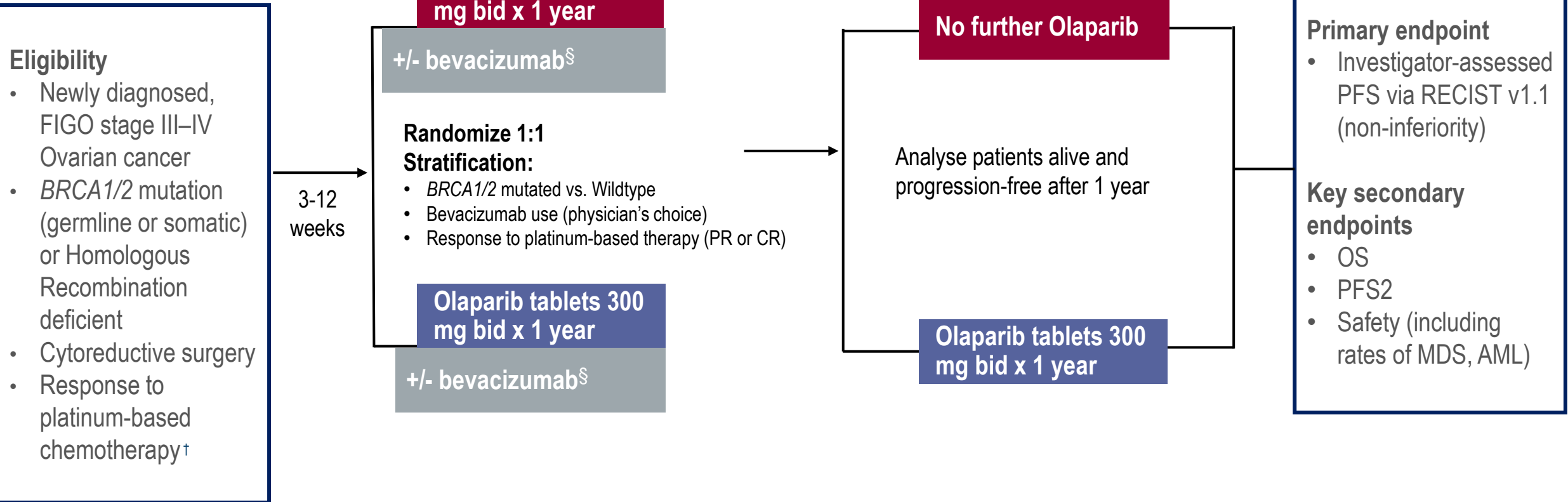
High Impact Example: Reducing Toxicity



Ying Liu, MD
GYN and Clinical Genetics

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

Maintenance therapy

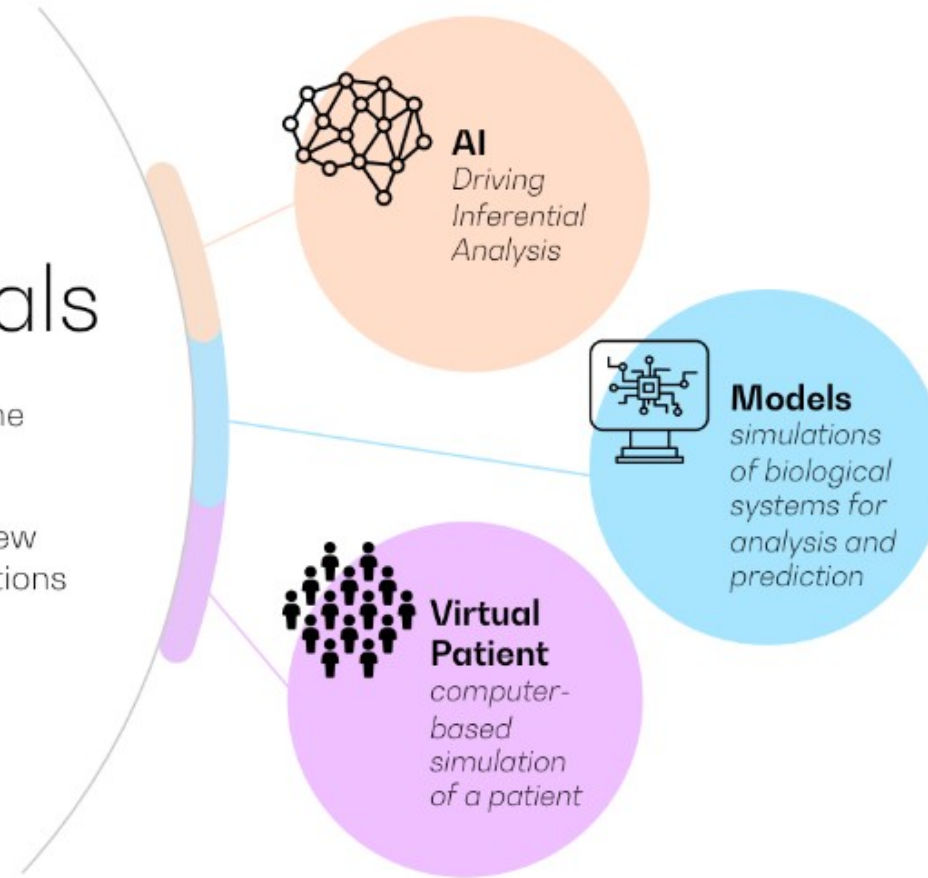


What is an *in silico* trial?

Mainstream definition by scientists and regulators

in silico trials

the use of individualized computer simulations in the design, development or nonclinical, clinical and regulatory evaluation of new drugs, devices or interventions



Main advantages of conducting *in silico* trials:

- Cost Reduction
- Time Efficiency
- Reduced Ethical Concerns
- Exploration of Complex Systems
- Prediction and Optimization

MSK CHORD: A Clinicogenomic, Harmonized, Oncologic Real-World Database

Article

Automated real-world data integration improves cancer outcome prediction

<https://doi.org/10.1038/s41586-024-08167-5>

Received: 9 January 2024

Accepted: 8 October 2024

Published online: 6 November 2024

Open access

 Check for updates

Jee et al. Nature: 2024

Justin Jee^{1,5}, Christopher Fong^{1,5}, Karl Pichotta^{1,5}, Thinh Ngoc Tran^{1,5}, Anisha Luthra^{1,5}, Michele Waters¹, Chenlian Fu¹, Mirella Altos¹, Si-Yang Liu¹, Steven B. Maron^{1,2}, Mehnaj Ahmed¹, Susie Kim¹, Mono Pirun¹, Walid K. Chatila¹, Ino de Bruijn¹, Arfath Pasha¹, Ritika Kundra¹, Benjamin Gross¹, Brooke Mastrogiacono¹, Tyler J. Aprati², David Liu², JianJiong Gao³, Marzia Capelletti², Kelly Pekala¹, Lisa Loudon¹, Maria Perry¹, Chaitanya Bandlamudi¹, Mark Donoghue¹, Baby Anusha Satravada¹, Axel Martin¹, Ronglai Shen¹, Yuan Chen¹, A. Rose Brannon¹, Jason Chang¹, Lior Braunstein^{1,2}, Anyi Li¹, Anton Safonov¹, Aaron Stonestrom¹, Pablo Sanchez-Vela¹, Clare Wilhelm¹, Mark Robson^{1,2}, Howard Scher^{1,2}, Marc Ladanyi¹, Jorge S. Reis-Filho¹, David B. Solit¹, David R. Jones¹, Daniel Gomez¹, Helena Yu¹, Debyani Chakravarty¹, Rona Yaeger^{1,4}, Wassim Abida^{1,4}, Wungki Park^{1,4}, Eileen M. O'Reilly^{1,4}, Julio Garcia-Aguilar^{1,4}, Nicholas Socci¹, Francisco Sanchez-Vega¹, Jian Carrot-Zhang¹, Peter D. Stetson¹, Ross Levine^{1,4}, Charles M. Rudin^{1,4}, Michael F. Berger¹, Sohrab P. Shah¹, Deborah Schrag^{1,4}, Pedram Razavi^{1,4}, Kenneth L. Kehl^{1,2}, Bob T. Li^{1,4}, Gregory J. Riely^{1,4}, Nikolaus Schultz^{1,2,5} & MSK Cancer Data Science Initiative Group*

Deeply annotated clinical and genomic data for >100,000 patients with cancer

Updated daily. Available to all with MSK email

Demonstrates feasibility of automated annotation from unstructured notes

Shows those that include features extracted with natural language processing (such as sites of disease) outperform predictive models solely based on stage or genomic characteristics

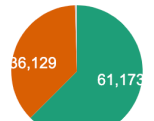
Supports in silico trial development

cbioportal.mskcc.org/study/summary?id=mskimpack



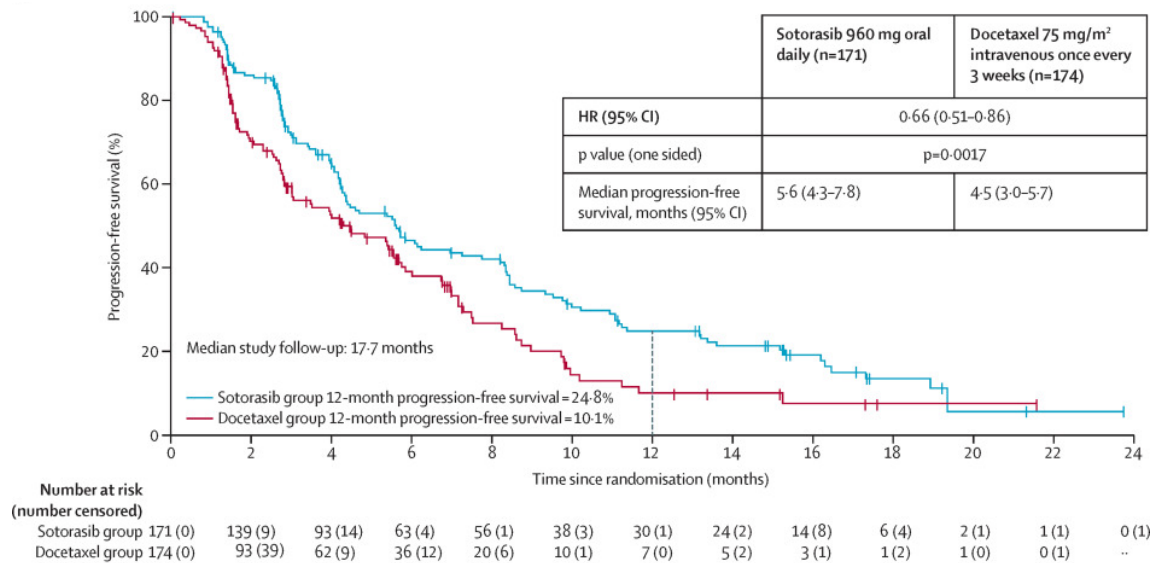
Data Sets Web API R/MATLAB Tutorials/Webinars FAQ News Visualize Your D

103,154 patients | 151,131 samples

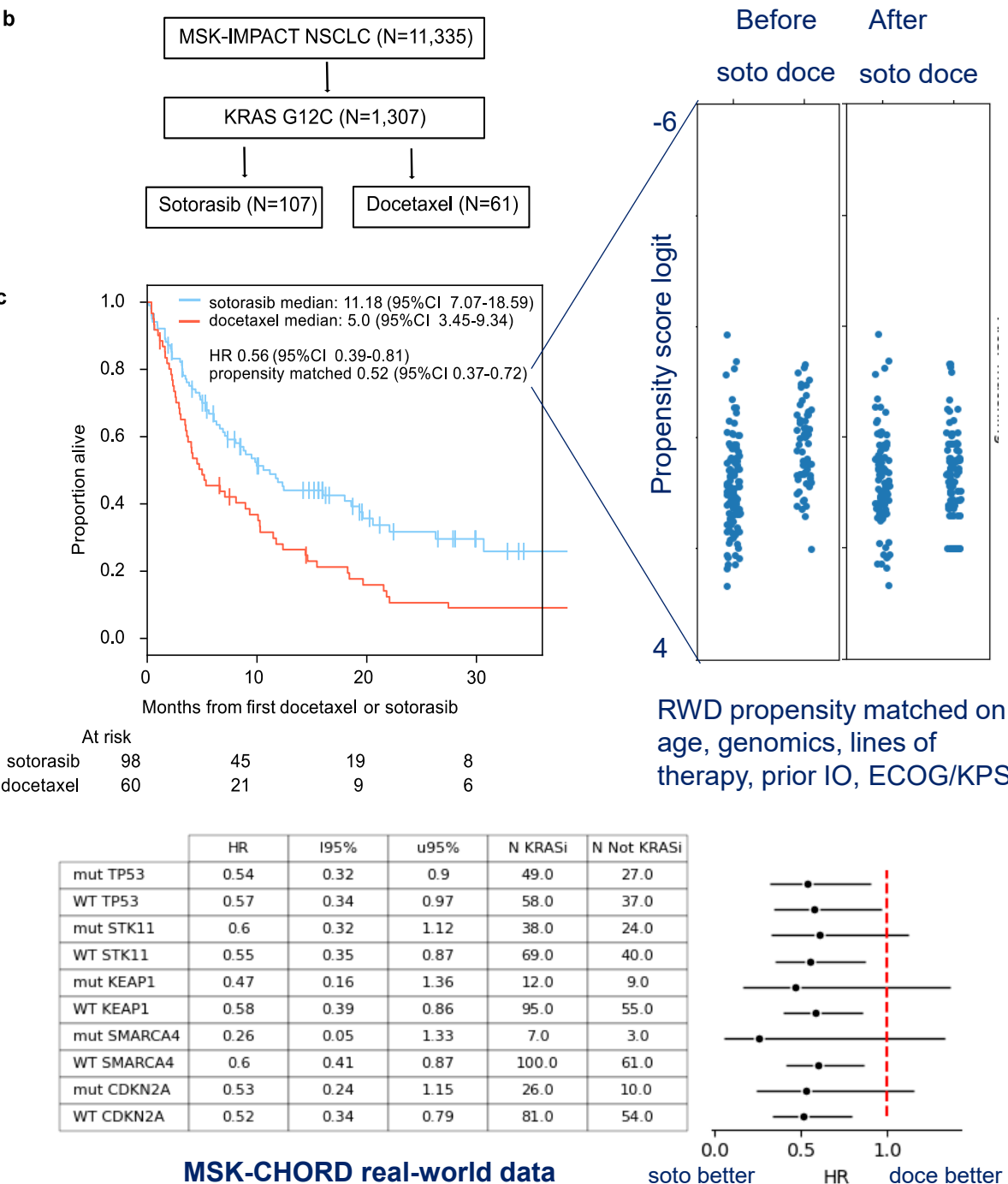
Cancer Type			Cancer Type Detailed			Overall Survival Status	
	#	Freq		#	Freq		
Non-Small Cell Lung Cancer	19,761	13.9%	Lung Adenocarcinoma	15,512	10.9%		
Breast Cancer	11,012	7.7%	Pancreatic Adenocarcinoma	6,234	4.4%		
Mature B-Cell Neoplasms	10,381	7.3%	Breast Invasive Ductal Carcinoma	6,125	4.3%		

Example at MSK: Replicating CODEBREAK 200 trial with real-world data (RWD) from MSK CHORD

Allows for OS and genomic subgroup analysis not possible in original trial



CodeBreak 200 Trial. De Langen et al Lancet 2023



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

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Collette Houston†
VP, Clinical Research Compliance

Stephanie Terzulli, PhD‡
VP, Clinical Research Operations

Lauren Evans
Nurse Leader

Theresa Elko
Clinical Trials APP
Manager

Marlon Lasa-Blandon
Nurse Leader

Yelena Shames
Nurse Leader

Cheryl Fischer
Nurse Leader

Karima Yataghene, MD
Sr. Director, Clinical
Research Quality
Assurance

Ann Rodavitch
Sr. Director, Protocol
Activation & Review
and HRPP

Mary Warren
Sr. Director,
Multi-Site Compliance

Rich Ellis
Sr. Director, Regulatory
Oversight & Product
Development

Joe Lengfellner
Sr. Director,
Clinical Research
Information Technology

Nicholas Cimaglia**
Director, Protocol Core
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Chanda Delgado§
Sr. Director,
Protocol
Operations

Mayra Nicola
Director,
Education and Outreach

Jaclyn Nunner¶
Sr. Director,
Protocol
Operations

Amanda Mayer**
Associate General Counsel
Clinical Research Contracts

Barry Zakrzewski**
Sr. Director, CR Finance

Lawrence Lupkin§§
Director, Operations and Finance

*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”?

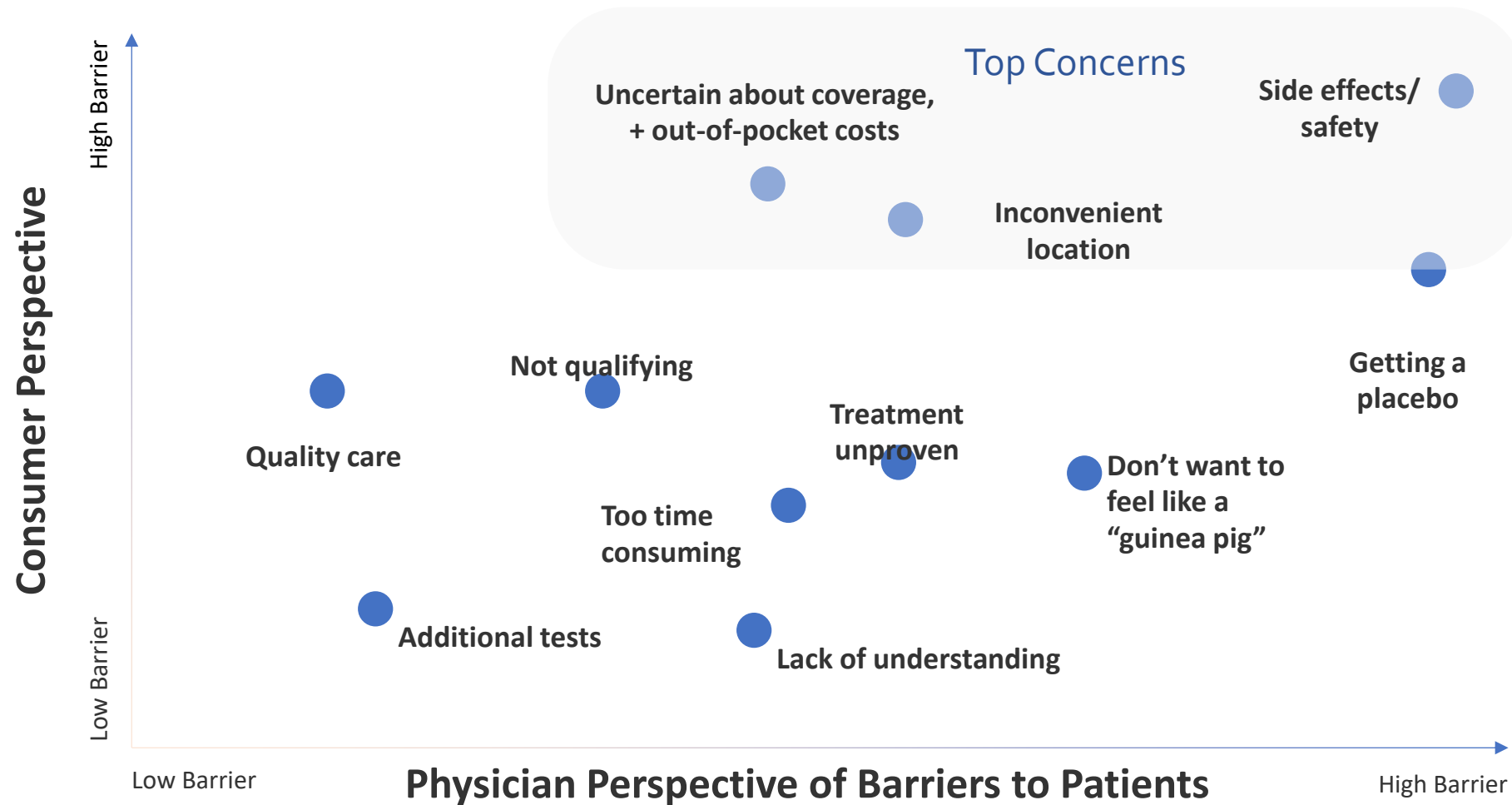
- Integrated into planning from screening to diagnosis to treatment to survivorship
- Care decision (s)

Standard treatment

Vs.

Investigational Treatment

Barriers to Enrollment



Objectives

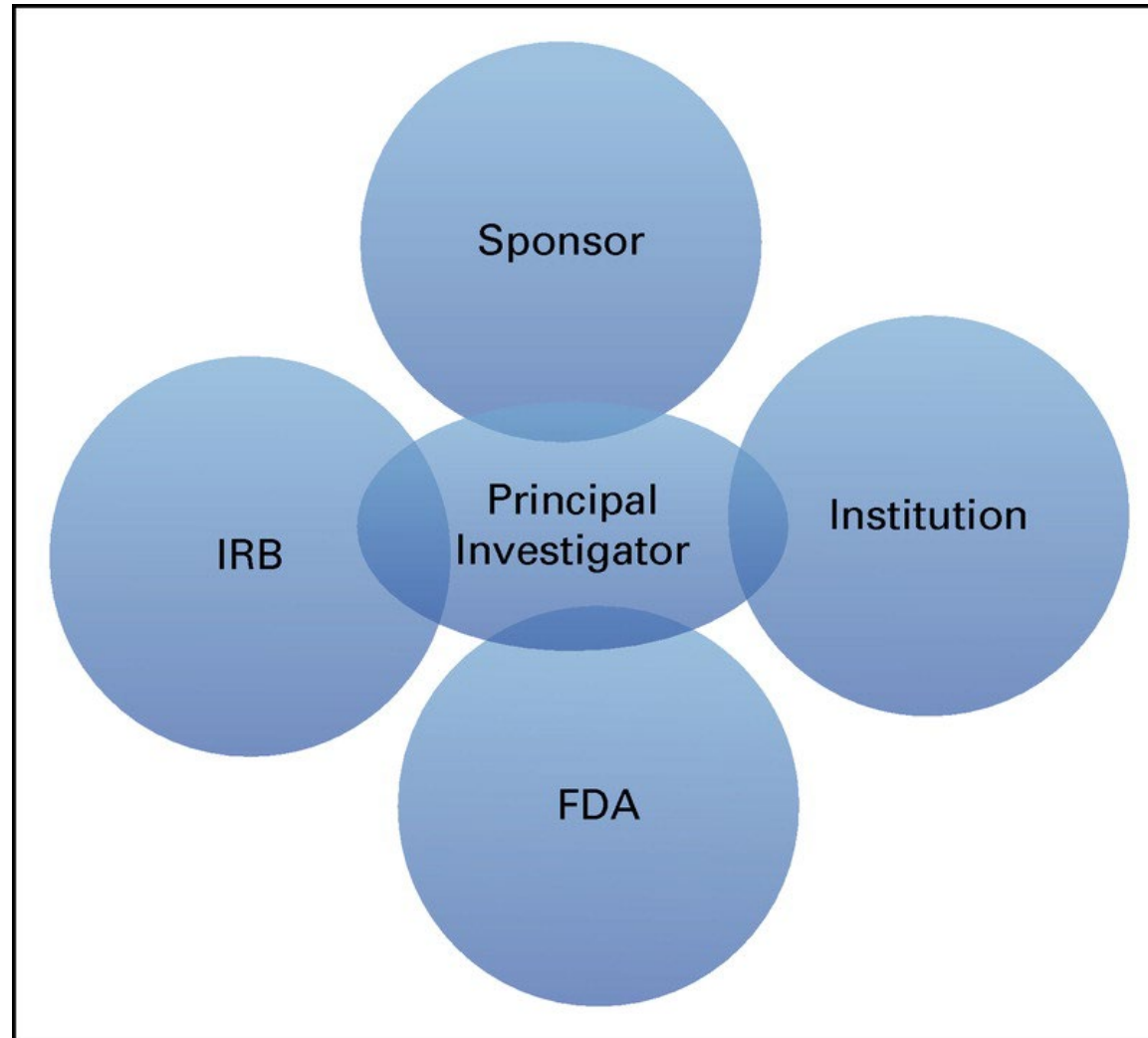
- Brief history of clinical research
- Challenges and opportunities in modern trials
- MSK Clinical Research Program
- The Principal Investigator and oversight

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



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



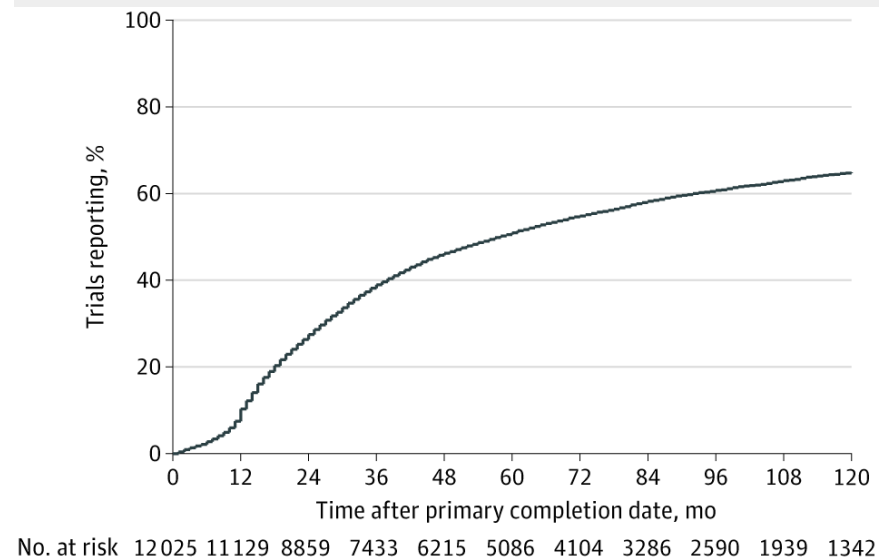
Oversight and Federal Agencies

- 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".

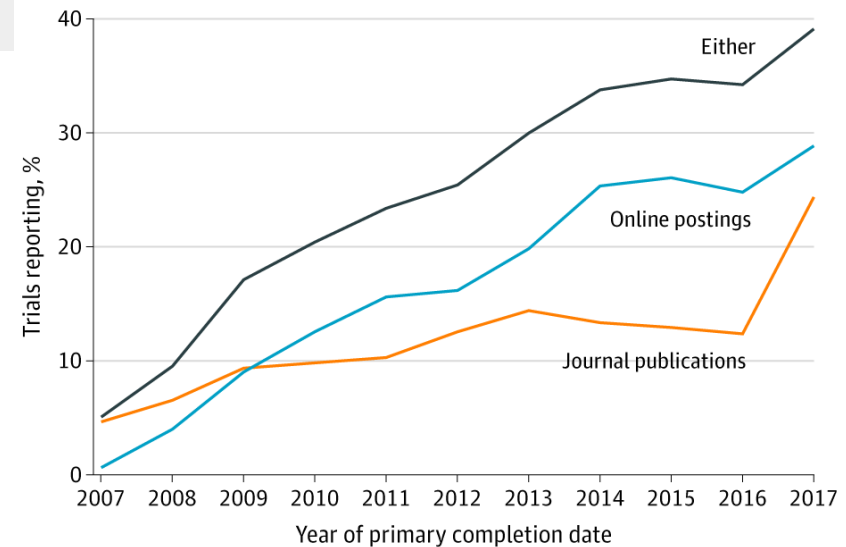
Oversight and Reporting

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**

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
- $\pm$ 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)