Adaptive Platform Trials: Scalable from Breast Cancer to COVID"

Investigation of Serial studies to Predict Your Therapeutic Response with biomarker Imaging, integration and Adaptive Learning

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Alfred A. de Lorimier Chair in General Surgery
Professor of Surgery and Radiology
Director, UCSF Carol Franc Buck Breast Care Center
Founder Quantum Leap Healthcare Collaborative
Concepts for Improving the Way We Evaluate New Treatments

• Accelerate Knowledge turns: drive urgency and innovation
• Design trials that incorporating disease heterogeneity
• Metastatic/end stage disease may not be the ideal place for drug development: Move drug development into the earlier stage setting
  • “ethical” dilemma because safety trade offs
  • No chance for cure eliminates concern over lethal harm
• Identify early endpoints that can be captured in the course of care
• Demand- willingness of patients to try a new approach
• Look for big signals (screening phase 2) with seamless confirmation
• Breast cancer was a great place to start
I-SPY 2 VISION

“Make new, better and more personalized treatments, available faster, at a time when patient’s need them most”

• Better: Higher Distant Disease Free Survival AND less toxic
• Personalized: Matching patient’s biology
• Faster: Use early endpoints; Continuous learning
I-SPY 2: Saving Lives by Accelerating Learning

- Focus: Women with Stage 2/3 Breast Cancer at High Risk for Early Recurrence
  - Moving treatment earlier when a great response means CURE

- Maximize the ability to learn about response early in course of care
  - Early endpoint: complete pathologic response (pCR) and MRI tumor volume change
  - Net monetary benefit for achieving pCR: $160,000 (ICER -$45,000)

- Create an adaptive platform:
  - **Efficient:** One trial, 22 agents over 9 years
  - **Flexible:** Standard treatments have evolved
  - **Learning System:** Care and outcomes have improved at all sites
  - **Collaborative:** FDA, Advocates, Pharma, Clinicians/Researcher, imagers, IT scientists
  - **Engine for Discovery:** biomarker rich, qualifying biomarkers can be validated (RCB, ct DNA etc)
Greater Personalization: Driving toward optimal early endpoints

Measure outcomes by subtype
- Standardize imaging, pathology, biomarkers, data collection
GOAL: create collaborative framework

Adapt therapy within trial
- pCR regulatory endpoint (accelerated approval)
- Test multiple novel agents adaptively
- Operational efficiencies, platform trial, culture of innovation
GOAL: Increase pCR in each biomarker signature

Absence of tumor after neoadjuvant chemo (pCR) is optimal early endpoint
- for molecularly high risk disease
- Better by subtype

pCR predicts DRFS HR 0.18 regardless of subtype, therapy
- RCB stratifies outcome
- MRI and biopsy predict pCR
- Many agents identified that improve subtype specific pCR
- Molecular markers better classifiers than receptors

Optimize pCR for each patient
- Stop at pCR, continue if not
- Accelerated approve for agents that generate optimal pCR rates
- Confirm DRFS at 3 years ≥92% for full approval
I-SPY 2 TRIAL Current Study Schema

Notes:
T1a: MRI – optional, physician discretion
T3: MRI – only for patients with FTV<80%

Biomarker-rich protocol
I-SPY2: Early endpoint predicts Event Free Survival for Patients

Original Investigation
February 13, 2020

Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer
An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial

Rita Nanda, MD; Minetta C. Liu, MD; Christina Yau, PhD; et al


Yee et al 2020

Correlation of Event-Free and Distant Recurrence-Free Survival With Individual-Level Pathologic Complete Response in Neoadjuvant Treatment of Stages 2 and 3 Breast Cancer
The I-SPY2 Adaptively Randomized Clinical Trial
Save Lives, Save Time, Save Resources

Metastatic Setting
- Phase 2
- Phase 3

Adjuvant Setting
- SURGERY
- CHEMO
- ACCRUAL
- FOLLOW-UP

Neoadjuvant Setting
- SAFETY
- SAFETY
- SAFETY
- FOLLOW-UP

Standard approach
1 drug 1 trial

I-SPY approach
1 trial, many drugs
Accelerating Knowledge Turns

Time from first introduction in the metastatic (late stage) setting until an effective new drug is available in the high-risk early stage setting where it can save lives

<table>
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<th>Number of patients</th>
<th>Neoadjuvant Approval</th>
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<td>&gt;13,000*</td>
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<td>Perjeta: 9 years</td>
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<td>Pembroluzimab: 6 years</td>
<td>1,200</td>
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<tr>
<td>XX: 3 years</td>
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*pCR as accelerated endpoint enabled access 4 years ahead of the adjuvant APHINITY results
I SPY 2.2: Getting Less Toxic New Therapies to Patients

- A. Untested regimens
- B. Subtype specific rescue
- C. Eventually we will randomize here as well

No Randomization here for now
Benefits of this approach

• Allows non-chemo regimens to start – there are plenty of exciting drugs in development
  • Why not start in the people who would benefit most?

• Moves toward goal of getting away from standard chemo: taxol and AC
  • We can predict whose tumor has gone away by 12 and 24 weeks, and continuously refine capability

• If first combination doesn’t work
  • “rescue” is something patients can feel confident is highly likely to work - SOC option that fits the receptor subtype/biomarker signature for the individual patient’s tumor

• Rank sequences (metrics) to favor least toxic, greatest healthcare value
  • Based on when the pCR is achieved, use PROs (Benefit Index: QALYs)
  • Less duration of therapy and avoiding additional blocks, esp AC has higher value
    • E.g. (%pCR Block A) * 100% + (%pCR Block B) * 80% + (%pCR Block C) * 60%

• Single trial that integrates regulatory confirmation

I-SPY | The right drug. The right patient. The right time. Now.™
I SPY will enable a Sea Change

- Goal: 90% of Patients to pCR without Standard Chemotherapy
- Targeted de-escalation and escalation of therapy based on response
- Improve survival AND decrease toxicity
- Approach in trials should mirror care
# I-SPY 2 TRIAL Study Team

## Working Group Chairs

<table>
<thead>
<tr>
<th>PI</th>
<th>Operations</th>
<th>Biomarkers</th>
<th>Pathology</th>
<th>Advocates</th>
<th>PRO/QOL</th>
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<tr>
<td>I-SPY</td>
<td>Laura Esserman</td>
<td>Angie DeMichele</td>
<td>Laura van ’t Veer</td>
<td>Jane Perlmutter</td>
<td>Michelle Melisko</td>
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## Site PIs

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<th>Columbia</th>
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<td>UCSD: Anne Wallace</td>
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<td>Loyola</td>
<td>UCSF: Jo Chien</td>
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<td>Mayo</td>
<td>UMinn: Doug Yee</td>
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<td>Moffitt</td>
<td>UPenn: Amy Clark</td>
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<td>OHSU</td>
<td>USC: Julie Lang</td>
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<tr>
<td>Swedish</td>
<td>Yale: Tara Sanft</td>
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## Program Management Office

- **Executive Director:** Smita Asare
- **Program Administration:** Kat Steeg, Lorena Kanu, Julie LeDuc, Jill Parker, Melanie Hanson
- **Safety:** Sausan Abouharb, Linda Doody, Monina Angeles, CCSA
- **Data Analysis & IT:** Christina Yau, Adam Asare, Garry Peterson, Amy Wilson, Tim Fu
- **Operations Manager:** Ruby Singhrao
- **Program Oversight:** Anna Barker/ASU, Gary Kellogg/NCI, Janet Woodcock/FDA, Richard Pazdur/FDA, Robert Becker/FDA, ShaAvhree Buckman/FDA, CDER, Steve Gutman, David Wholley/FNIH

- **I-SPY 2 Biomarkers/Specimens:** Lamorna Brown-Swigart, Gillian Hirst, Denise Wolf, Chip Petricoin, Julie Wulfkuhle
- **I-SPY Imaging Lab:** Jessica Gibbs, Melanie Regan
- **Business Development:** Julie Sudduth-Klinger, Dan Dornbusch
- **Grants:** Jeff Matthews

## Sponsor

- **Quantum Leap Healthcare Collaborative**
  - Dave Mandelkern, Nancy Lisser, Mike Bankert, Adam Asare, Smita Asare, Julie Sudduth-Klinger, Dan Dornbusch

## Thank you to the remarkable patients and families, and all of the investigators, staff, our DSMB and advocates for supporting the trial

Many pharma, biotech, and diagnostic companies
A Personalized Approach for Breast Cancer

Do more for the people with higher risk:
De-escalate when treatments are effective: LESS TOXIC
And escalate when treatments are not effective: SAVE LIVES

This can be accomplished if we have the tools and the framework to know the difference.
With COVID, there is an Even Greater Urgency

- The COVID 19 pandemic is a crisis primarily because of the pulmonary toxicity and high associated mortality
  - for a minority of those infected
  - Like cancer, everyone does not have a lethal case
- Solving this problem is critical for SARS-COV2 and other future viruses
- We must prioritize finding high impact treatments to reduce mortality and time on ventilators
  - Independent of vaccine efforts
- The Economy will not recover until we solve this problem
- Every one of us could wind up in the ICU . . .
What is the fastest way forward for those critically ill?

- A pragmatic, real world evidence based adaptive platform trial/learning system
  - Find agents with a big impact: speed time to recovery, drop mortality
  - Find FAST what does not have an impact

- Harness the infrastructure built for the I-SPY 2 TRIAL: Human/Intellectual Capital
  - Best and brightest in ICU medicine, drug development: Cancer and COVID
  - Culture of innovation and collaboration
  - Process efficiencies
  - Partnership with FDA
  - Precompetitive collaboration with industry (pharma/biotech/diagnostics/information technology)

- Engage investigators to build a learning engine that serves patients, *science, learning*, *biologic/omics, clinical, management, and regulatory*
The I-SPY COVID TRIAL
Investigation of Serial studies to Predict Your Therapeutic Response with biomarker Integration and Adaptive Learning
Time to Decision for Graduation or Futility Drop, Accrual = 50 per week

How Does the Trial Work?
Probability distribution for time to decision for effective candidates

This shows that even with 4 agents running simultaneously, a highly effective agent would be recognized and graduate within about 5 weeks. Likewise, most agents would drop for futility in 5 weeks.

In months, not years
Working together, 15-20 sites could test 10 agents in 4 months
FIND 3-4 agents, that dramatically reduce death/time on ventilators

Targeted Immune modulators and antivirals

I-SPY COVID19 = Pre-Competitive Clinical Trial
Precision Medicine for Emerger COVID19 ICU Patients

I-SPY | The right drug. The right patient. The right time. Now.
Working groups

Separate but Aligned

• Operations
• Agents
• Biomarkers: critical opportunity to learn
• Safety
• Stats
• Project Management
• (DMC)
(I SPY 2: Imaging, Pathology)

Shared

• Information Technology
  • clinical and research data. Including Institute for Systems Biology
• IRB
  • Central IRB is Wake Forrest
• Advocates
Strategy for Agent prioritization

1. Scientific validity:
   scientific rationale for efficacy in the setting of pulmonary distress from COVID.
   Endothelial cell repair, immune modulation, complement pathway, anti-virals

2. Ability to scale immediately or within 3-4 months (for global distribution)
   example of remdesivir scarcity is a lesson- and we should prioritize testing of agents that can be deployed now- if none work, obviously we will move to less available agents)

3. Willingness of the manufacturer to partner, be nimble, and ship drug

4. Ease of administration of the drug
Compound Prioritization Process Overview

• A standing committee, the Agents Working Group, of the I-SPY COVID Trial evaluate the safety & potential efficacy of numerous agents – both repurposed and novel drugs.

• No open portal submission but have received significant interest

• 6 sources of compounds:
  • Initial agents were proposed by the COVID R&D Alliance
  • Recently, other large pharma and major biotech companies have submitted compounds for evaluation
  • KOLs, investigators and academia
  • Venture capitalists and investors
  • Disease advocacy organizations but not directly from patients
  • Small biotechs including from Australia and Greece
  • Defense Threat Reduction Agency (DTRA), Department of Defense
  • Operation Warp Speed
COVID R&D was established in mid March to accelerate the development of therapies for COVID-19

Three of first 6 agents have come from this consortium

Context
Industry R&D leaders believe that everything should be done to tackle the COVID-19 humanitarian challenge

Principles of consortium
Accelerate new Covid-19 therapies and vaccines and remain agnostic to consideration for market potential

Group relinquishes rights to intellectual property or contractual alignment for support it provides to independent companies

Approach in agile manner with focus on eliminating all bureaucratic and technical barriers

Focus on filling gaps not adequately filled by other initiatives and where we are uniquely suited to address

Participants
Key Steps in Compound Screening

For companies we decided to deprioritize in the compound screening process, we offer the following:

- Advice on clinical trial design, endpoints, and execution
- Make intro to other trials
- Recommendation on targets for partnering
- Recommendation on potential source of capital
**I-SPY COVID Agents**

- Cenicriviroc, CCR2/5 Inhibitor (Allergan/Abbvie)
- Firazyr (Icatibant), Bradykinin B2 Agonist (Takeda)
- Otezla (Apremilast), PDE4 inhibitor (Amgen)
- Razoprotafib, Tie2 activation (Aerpio Pharmaceuticals)
- Pulmozyme, inhaled DNAse (Roche/Genentech)

Appendices in preparation for several others
Check List as a standard: Integrates with tools that integrate in HER CMS could pay for completion of a daily check list

- **COVID WHO Scale (FDA standard)**
  - If level 6/7 (intubation), standard ventilator settings:
    - paO2/Fio2 OR spO2
    - use of proning
    - Tidal volume
    - Volume control (plateau pressure)
  - If level 7
    - Vasopressors
    - ECMO
    - Dialysis (Kidney Replacement Therapy)

- **Major Adverse Event over previous 24 hours**
  - MI
  - Pneumothorax
  - PE
  - Stroke
  - Dialysis (if not ventilated)

- **Daily**
  - Off Study drug (reason)
  - Continue study drug
  - Dose modification (reason)
  - Dose Hold (reason)

- **Labs/ site reference range**
  - Creatinine, AST, ALT, Bilirubin, CBC/ Differential, PT, PTT, D-Dimer, CRP, BNP, troponin
  - directly pulled from EMR and
  - programmed with Reference Ranges for automated adverse event grading

- **Short list of concomitant medications**
  - Steroids
  - Convalescent plasma
  - Inhaled NO (nitric oxide)
  - Flolan
  - Vasopressors (1-3)
  - Antibiotics (1-3)
### Adverse Event Analysis

#### Adverse Event Type

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8/21/2020 DRAFT I-SPY | The right drug. The right patient. The right time. Now™
Why do we need better systems?

“There are so many people working so hard and achieving so little”

– Andy Grove

The health science/health care industry and the microchip industry are similar in some important ways: both are populated by extremely dedicated and well-trained individuals, both are based on science, and both are striving to put to use the result of this science. But there is a major difference between them, with a wide disparity in the efficiency with which results are developed and then turned into widely available products and services.
Source Data Capture from EHRs to Improve Quality and Efficiency

CRFs ask for data that is not in or easy to find in the notes

ePRO: Electronic Patient Reported Outcomes
EDC: Electronic Data Capture
EHR: Electronic Health Record

PRO: Patient Reported Outcomes
EDC: Electronic Data Capture
EHR: Electronic Health Record

Source Data Capture from EHRs: Using Standardized Clinical Research Data

UDS & FDAD

2019

Source Data Capture from EHRs: Using Standardized Clinical Research Data

Mitra Reccia, Adam Aizman, Laura Escamal, Sue Dubman, Gideon Gordon

1Center for Drug Evaluation and Research, Food and Drug Administration
2University of California - San Francisco (UCSF)
*Quantum Leap Healthcare Collaborative

This project was funded by the Office of the Secretary Patient-Centered Outcomes Research Trust Fund (PCORTF) under the IntrA/Departmental Delegation of Authority Request #075-X-0145-000 with the FDA.
Structured data as “source”

Enable improvements in technology with changes to clinical workflows

PATIENT-REPORTED DATA
- Health History
- Social History
- Health Habits
- Family History
- Symptoms
- Quality of life

CLINICAL
- Diagnostic Findings
  - Clinical Exam
  - Imaging
  - Biopsy Pathology
  - Staging
- Clinical Trial Matching
- Treatment
  - Surgery
  - Systemic
  - Radiation
- Adverse Events

FINANCE/BILLING
- Billing Pre-Authorization
- Billing (Institution)
- Payers (Insurance)

RESEARCH
- Less cleaning required
- Reduced Staffing

ADMINISTRATION

DATA ACCESS
- Single-source of truth
- Consistency among secondary users

Point of Care Data Collection
Evidence Generation Landscape (Interventional Studies)

- Evidence generation for COVID
  - 1,200 trials initiated
  - Limited results to inform standard of care – positive (remdesivir, dexamethasone) and negative (hydroxychloroquine, lopinavir-ritonavir)
  - Over 99% of the 4.5 million Americans infected unable to participate in trials

- Efforts to address outstanding clinical questions
  - NIH ACTIV Partnership
  - Other networks
  - Practical master protocol trials

See Last Slide for References
Practical Trial Network Goals

What | Expansion of existing COVID-19 practical trial networks to develop meaningful evidence faster, by engaging sites that would otherwise not participate in trials

When | Fall 2020
Duke-Margolis Work on Practical COVID-19 RCTs

• Convening series with Master Protocol investigators, Regulators, Health Systems, and Tech Vendors

• Takeaways—
  • Transparent compound selection
  • Multiple Tx and Adaptable Trials
  • Randomization at scale
  • Streamlined data collection and alignment on endpoints
Opportunity to enable trial participation: 20-30% across US

• Standardize data collection tools (foundation for learning healthcare system with wide dissemination)
  • Check list facilitates/standardizes clinical assessment and management, is also trial data
  • Compensation can be for completion of checklist, checklist automates a note
  • Use of QI overlay system that is nimble accelerates learning across pandemic, serious disease
  • Lab data/lab chain of custody/ reference range standards

• Set up a central coordinator hub, not to monitor, but to facilitate care and trials
  • Central pharmacy function could enable non academic sites to participate
  • Bring GCP compliance capability to smaller facilities
    • Site training, site set up

• Central coordinators (that are part of the hub) work to
  • Consent patients (docusign CFR part 11 compliant/FDA tokens)
  • Making sure orders are in and correct
  • Facilitating lab collections
  • Coordinating with local pharmacies for training
  • Coordinating with central pharmacy to make sure the right drug is delivered (12 hrs?)
Strategy for Agent prioritization

1. Scientific validity:
   scientific rationale for efficacy in the setting of pulmonary distress from COVID. The order we put agents in will depend on the answers below.

2. Ability to scale immediately or within 3-4 months (for global distribution)
   example of remdesivir scarcity is a lesson- and we should prioritize testing of agents that can be deployed now- if none work, obviously we will move to less available agents)

3. Willingness of the manufacturer to partner, be nimble, and ship drug

4. Ease of administration of the drug
**What do these agents do?**

- **Immunomodulators** - turning down the immune response (opposite of cancer), anti-inflammatory
  - Otezla (apremilast), Icatibant, celebrex

- **Repairing the cells that are attacked**: Endothelial cell, clotting system
  - Razoprotofib, Pulmozyme, Complement drugs, BTK inhibitors

- **Antivirals**
  - Neutralizing antibodies
  - Hyperimmune serum: passive immunotherapy from recovered patients
I SPY COVID is OPEN!!!!!

- First site/first patient in Thursday July 30 2020
- 6 sites with IRB approval – 4 more next week
- 10 patients enrolled, 20+ in observational cohort
- New sites identified
- Many collaborators
  - PIs: Carolyn Calfee, Kathleen Liu
  - Investigators: Nuala Meyer, Derek Russels, Sheetal Gandotra, Michelle Gong, Mark Moss, Jeremy Beitler, Ellen Burnham, Rada Savic, Paul Volberding, Paul Henderson, Michael Matthay, Clark Files, Karl Thomas and many others

Thanks to Quantum Leap Healthcare Collaborative
Approach to Solving Clinical Problems with Serious Morbidity, Mortality

• Pre-competitive consortium with common purpose
  • FDA, Academics, Community Hospitals, Industry, Advocates, Investigators

• Efficient: Screening many NEW promising agents

• Look for big impact
  • Fail fast
  • Find winners FAST TO SAVE PEOPLES’ LIVES!!!!!

• Replication of the process from Breast Cancer to COVID shows scalability
  • Entire trial process replicated in 8 weeks
    • Consortium/ master protocol/ trial specific data checklists with embedded structure and analytics/ agent selection, ratification, trial “arm”/approval/engagement of investigators and clinicians
    • Entire community across many disciplines working with energy, urgency and purpose
  • 6 agents already approved ready to test, many more in the pipeline