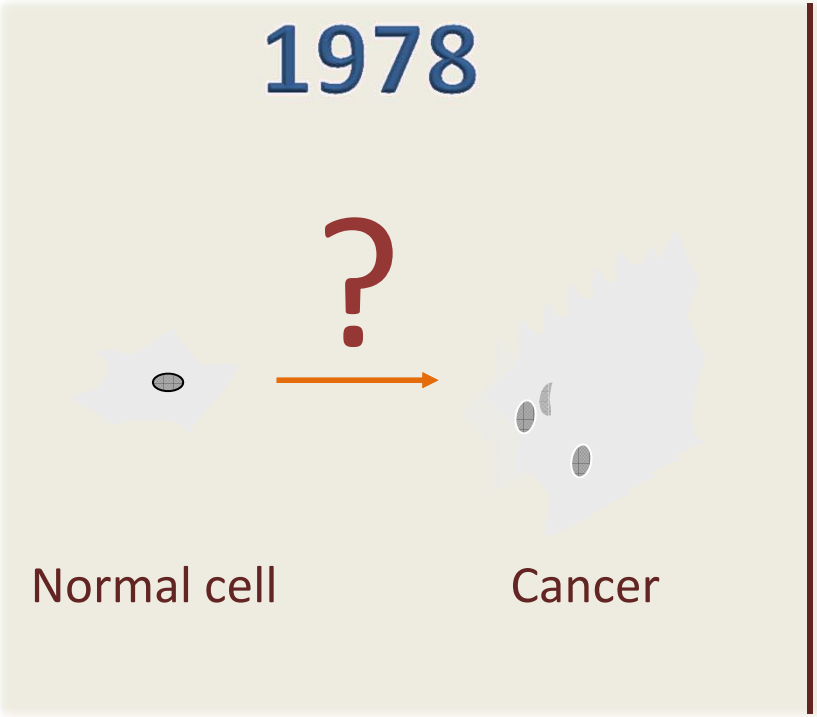
I-SPY 2 TRIAL

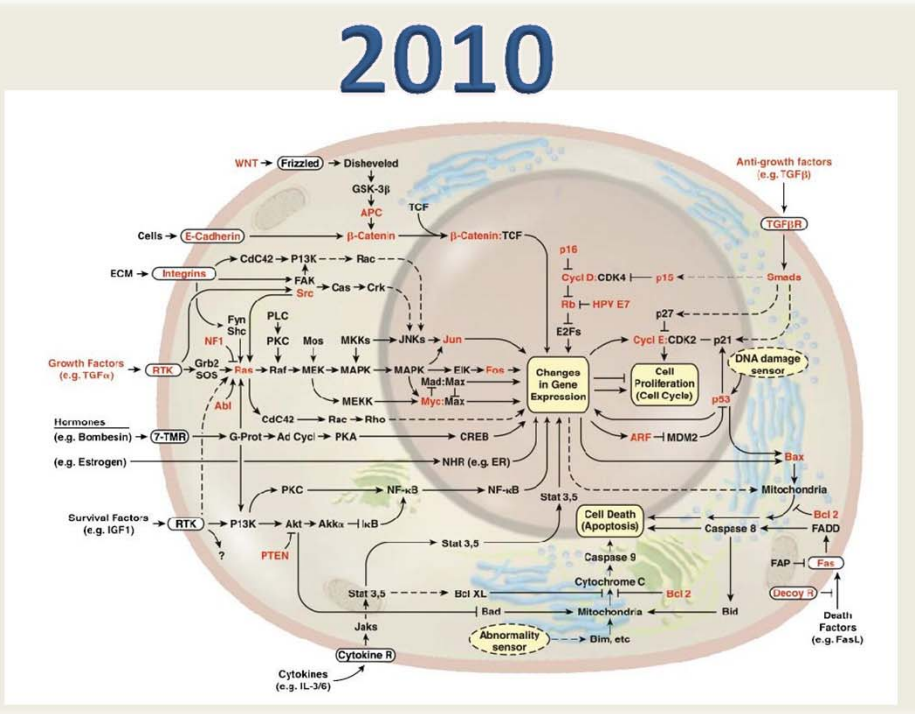
How it Works

April 9, 2013

The Challenge in Breast Cancer

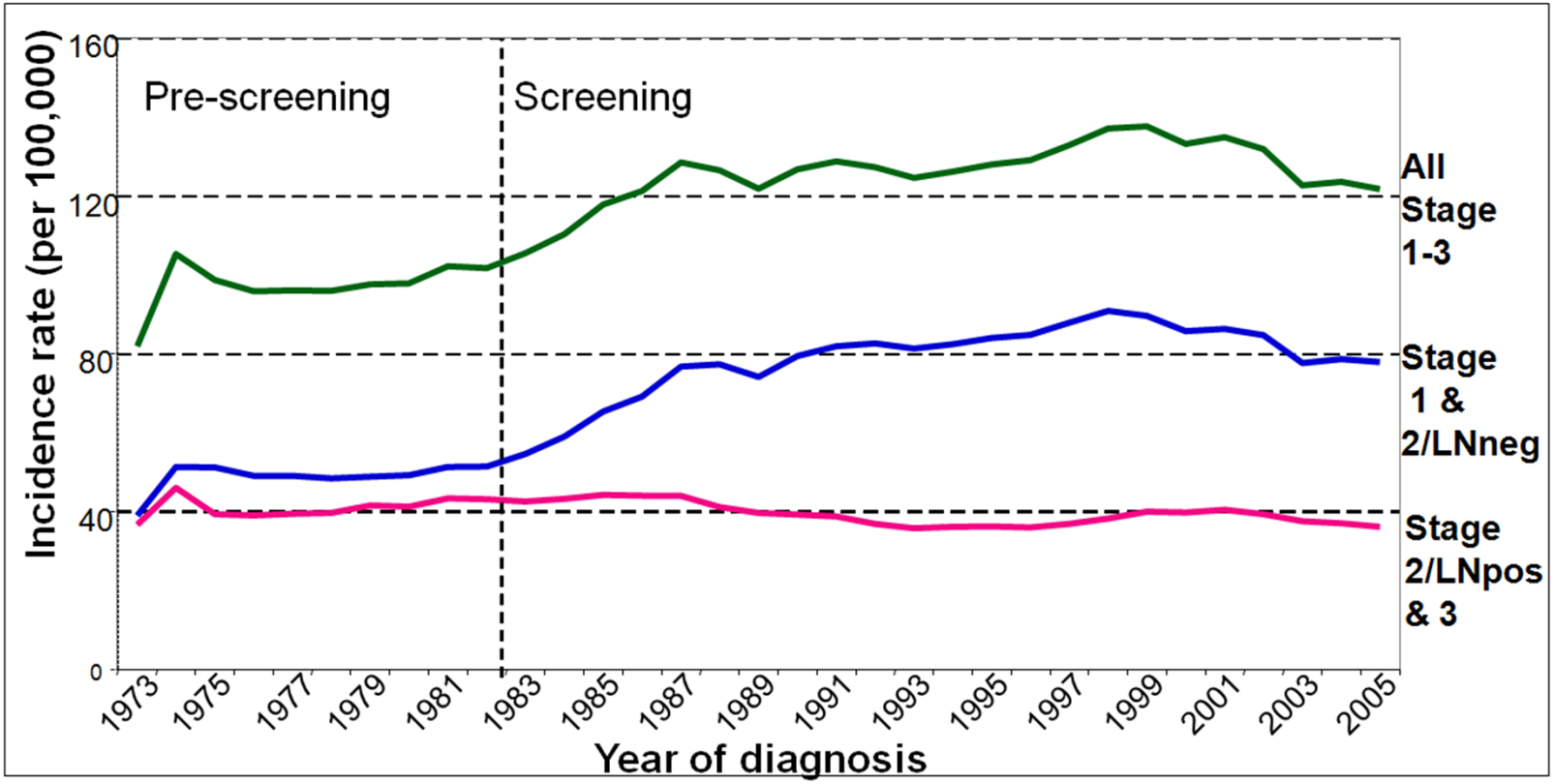
- Breast Cancer is a common and serious disease
  - Over 200,000 new cases of invasive breast cancer each year
  - Over 40,000 women will die each year because of breast cancer
  - Added complication is the heterogeneity of the disease





The Challenge in Breast Cancer

- Screening is prevalent
  - Has increased the fraction of low risk tumors but only minimally decreased the fraction of high risk tumors
  - Denominator of many adjuvant trials includes lower risk tumors



The Challenge in Breast Cancer

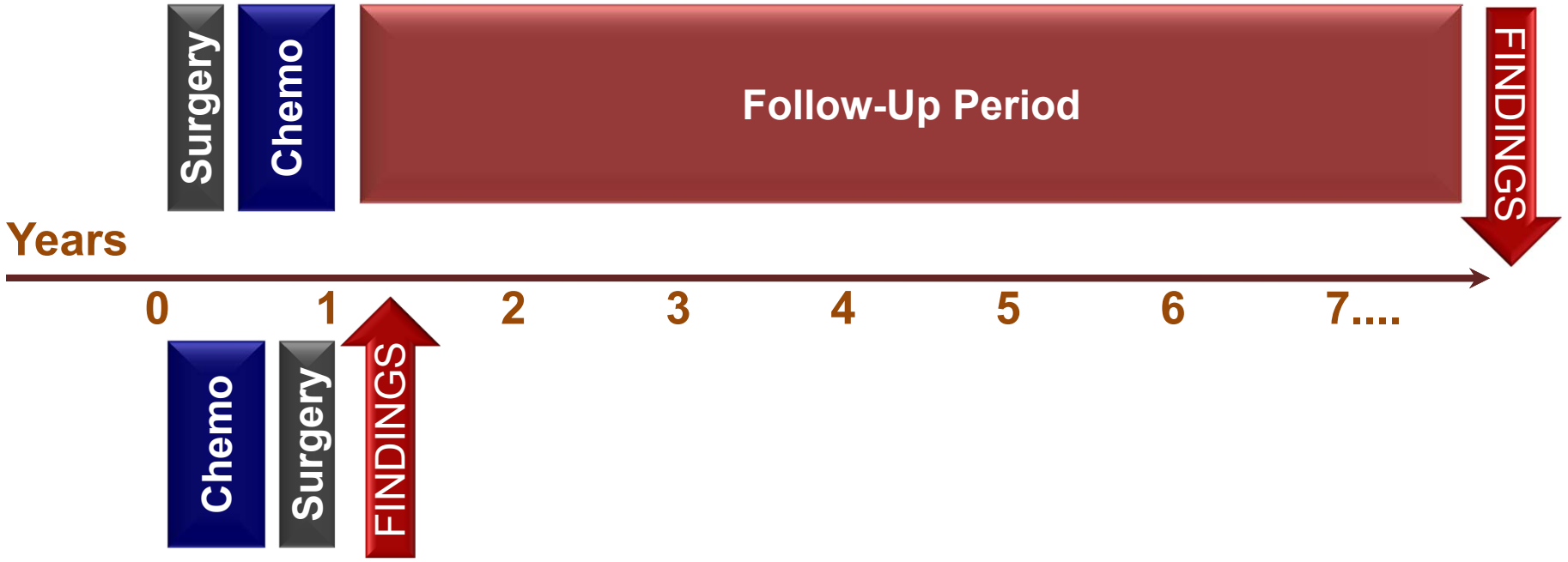
- Many treatments have been successful in improving outcomes
  - But for women with aggressive cancers that do not respond well to current treatments, their prospect for survival is grim

I-SPY 2 TRIAL

Neoadjuvant Approach Dramatically Accelerates Knowledge Turns

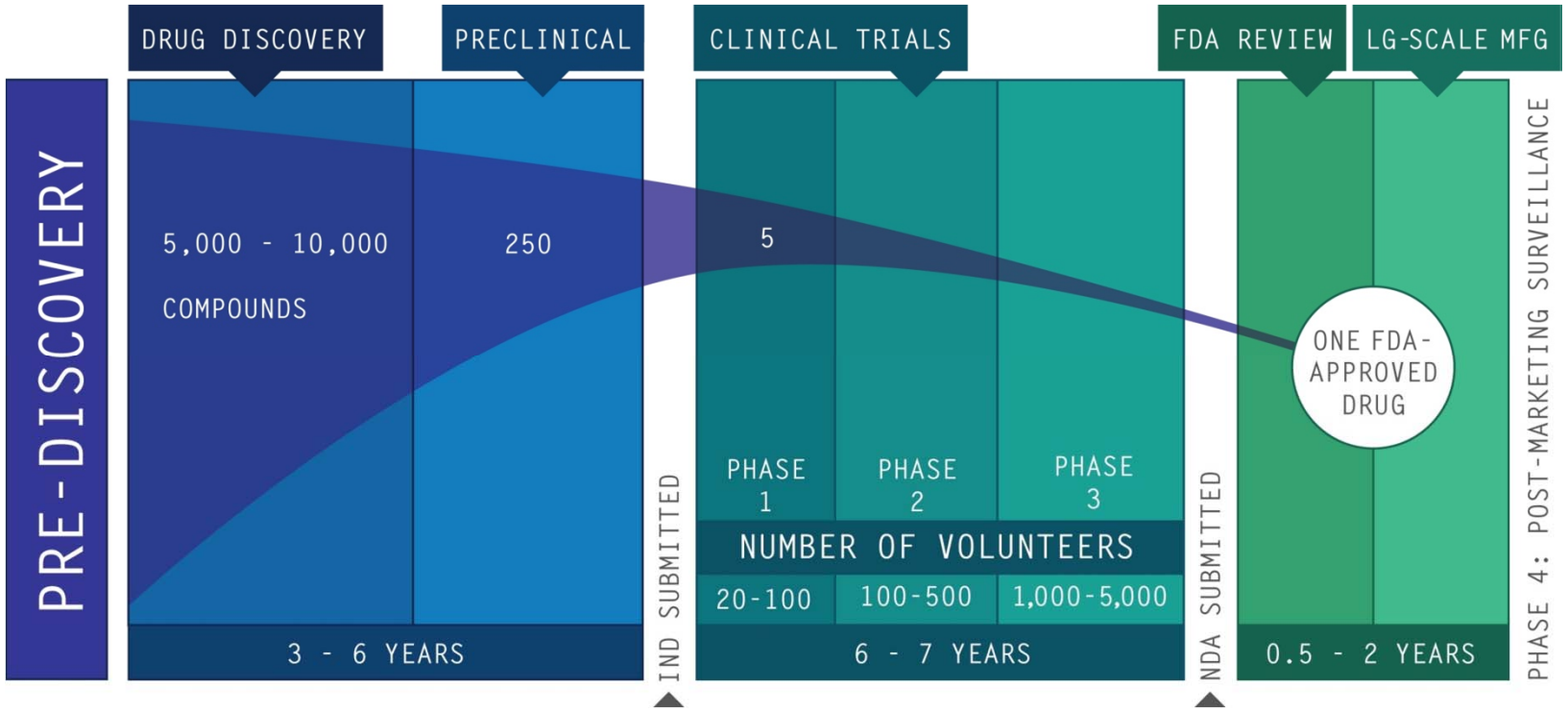
Metastatic Approach → 2 to 4 year knowledge turns

Adjuvant Approach → 6 to 9 year knowledge turns



Neoadjuvant Approach → 1 year knowledge turns

Current Model Drug Discovery



One FDA-Approved Drug - Start to Finish

- 10-15 Years
- 1,000 – 6,000 Volunteers
- $1 Billion

I-SPY 2 TRIAL

CALGB INTERSPORE ACRIN NCICB

CALGB 150012/150007 and ACRIN 6657

Investigation of

Serial studies to

Predict

Your

Therapeutic

Response with

Imaging

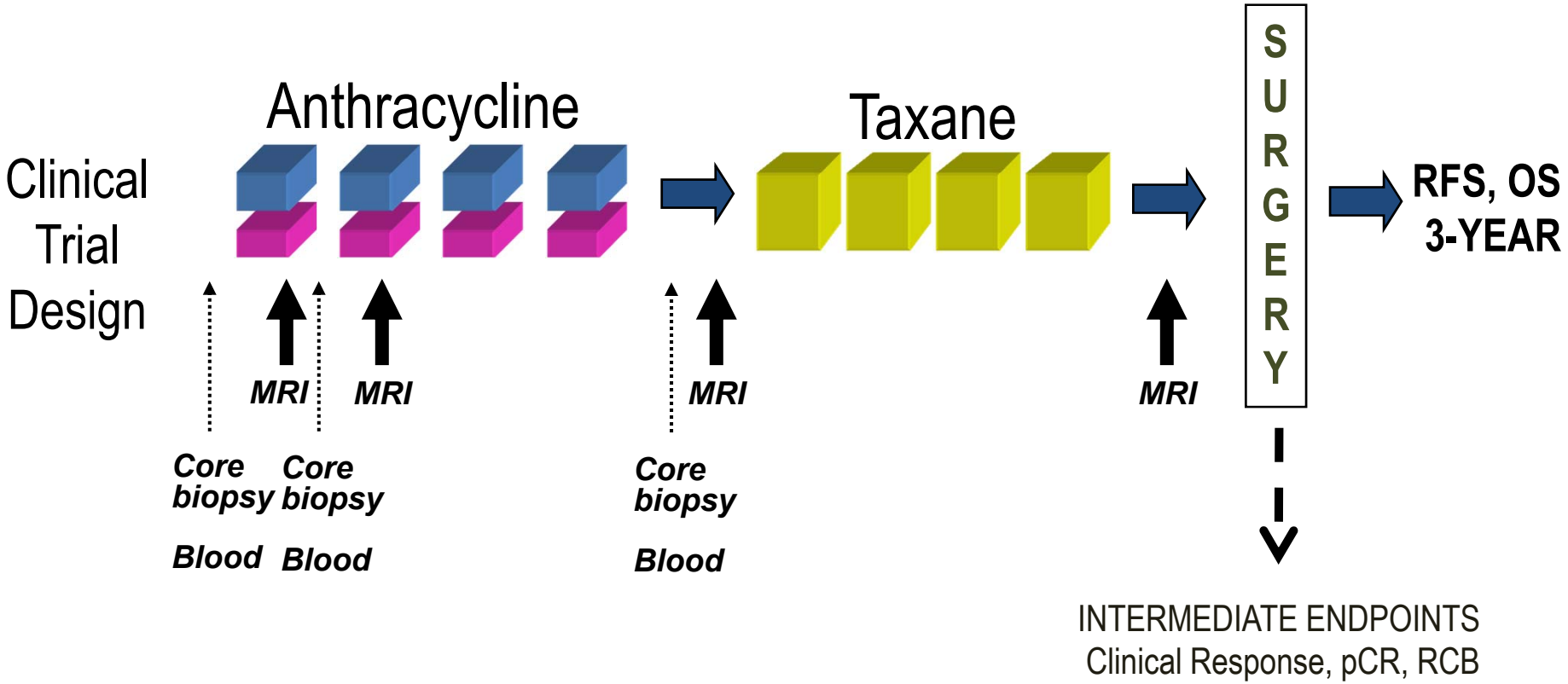
And

Mo**L**ecular Analysis

I SPY WITH MY LITTLE EYE

A BIO-MARKER BEGINNING WITH X

I-SPY 1 / ACRIN 6657 (Open 2002-2006)



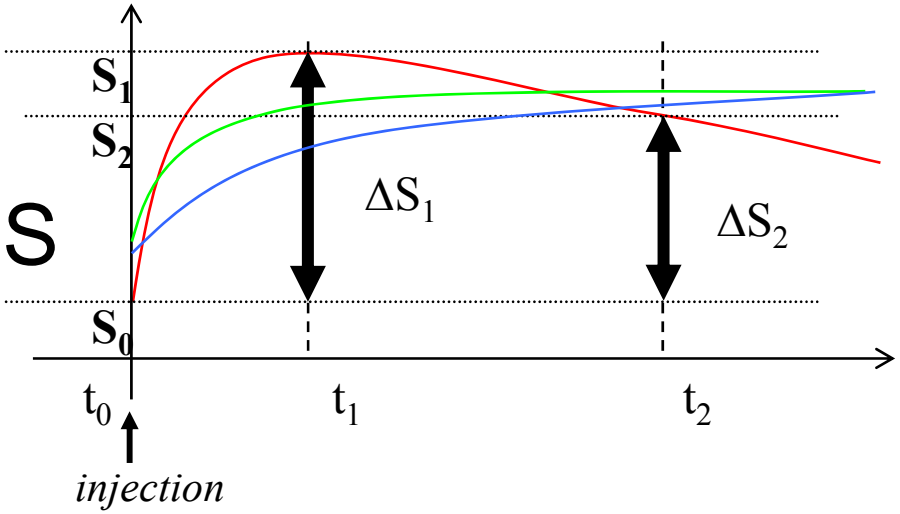
- Tumors ≥ 3cm eligible
- Enrolled 237 patients, 221 completed the study

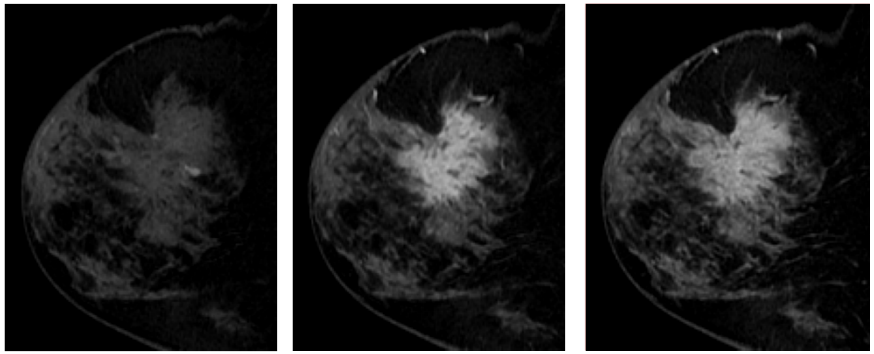
Primary Imaging Measurement in I-SPY 1

Longest Diameter, Volume, Signal Enhancement Ratio

Tumor volume based on the Signal Enhancement Ratio (SER)

ENHANCEMENT KINETICS:

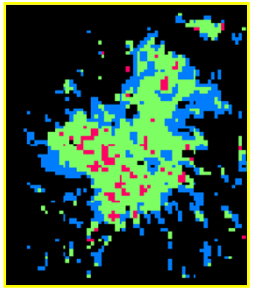




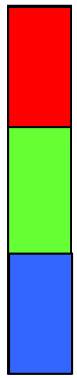
S0 S1 S2

$$PE = \frac{\Delta S_1}{S_0}$$

$$SER = \frac{\Delta S_1}{\Delta S_2}$$



SER map



Washout
SER>1.1

Plateau
0.9≤SER≤1.1

Gradual
SER<0.9

I-SPY 2 TRIAL

Rates of pCR Differ Based on Biomarker Profile, I-SPY 1

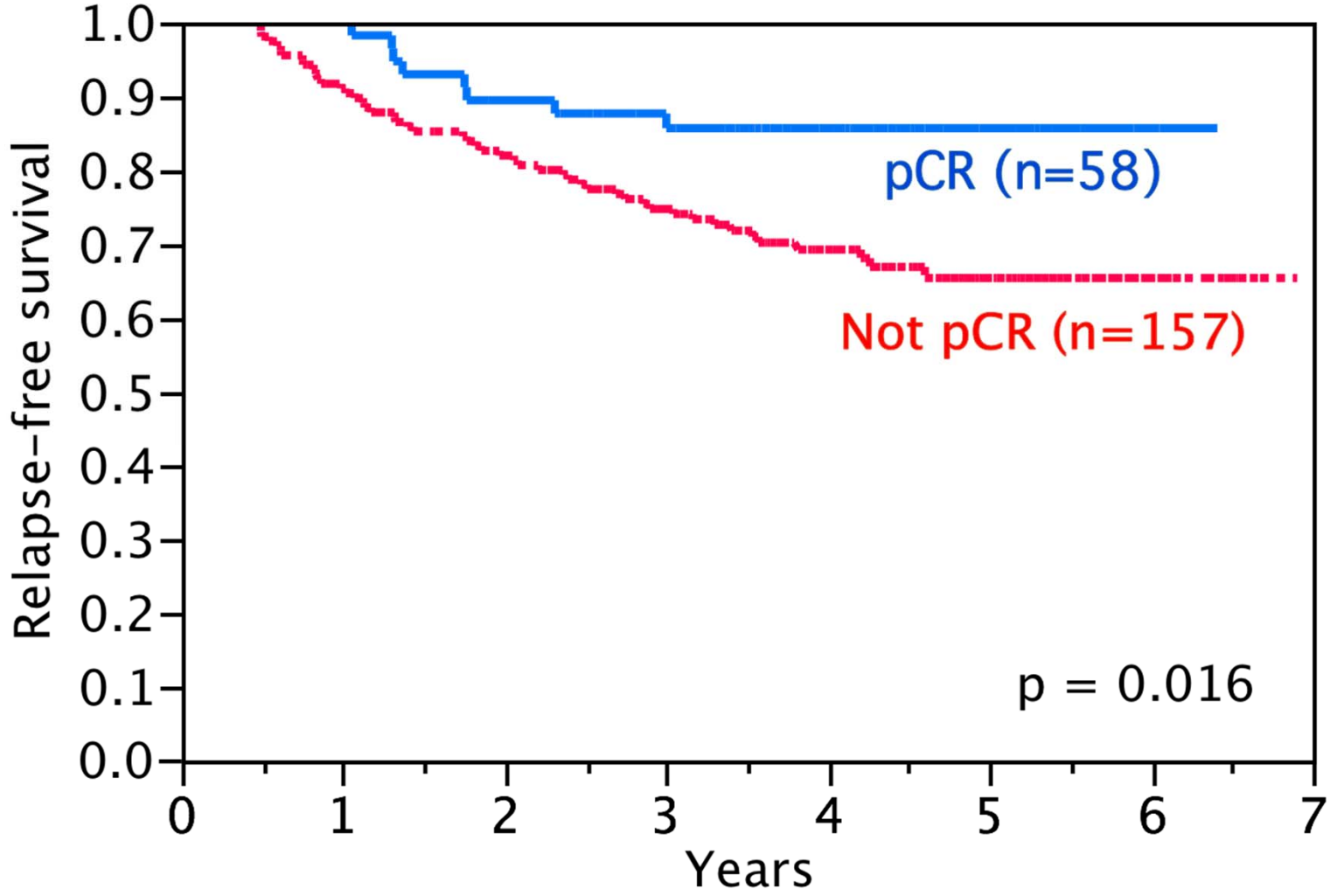
Pathologic Complete Response (pCR)

	HR+	HR-	
HER2+	**33%**	**45%**	*39%*
HER2-	**9%**	**33%**	*18%*
	14%	*38%*	*27%*

**Excludes patients who received trastuzumab (n=20)*

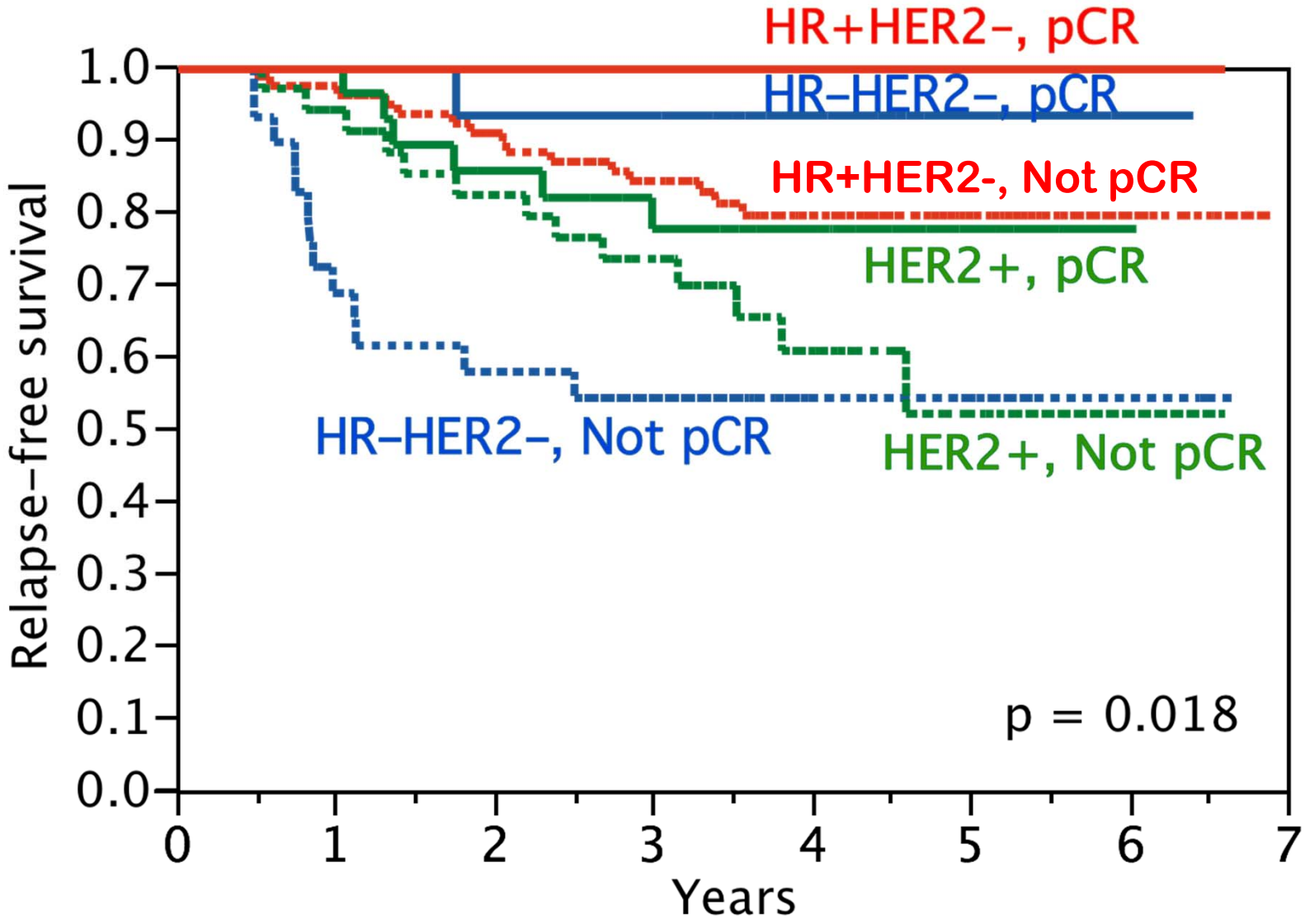
I-SPY 2 TRIAL

Response to Therapy is Associated with Better Relapse Free Survival, I-SPY 1



I-SPY 2 TRIAL

pCR Performs better by Subtype, Simpson's Paradox

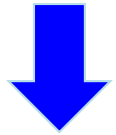
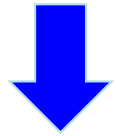


Overall Findings from I-SPY 1

- Patients in I-SPY 1 are most at risk of relapse, death
  - 91% of I-SPY patients had poor risk biology (tumors ≥ 3cm)
- pCR is highly predictive of outcome
  - Stronger predictor when analyzed by subgroup (Simpson's Paradox)
  - Can be used as trial endpoint for evaluation of novel agents
- MRI Volume change is a non-invasive way to predict pCR
  - Standard developed for MRI volume change

Why I-SPY 2?

Inefficient clinical trials account for a majority for the time and cost associated with the failures of the current system

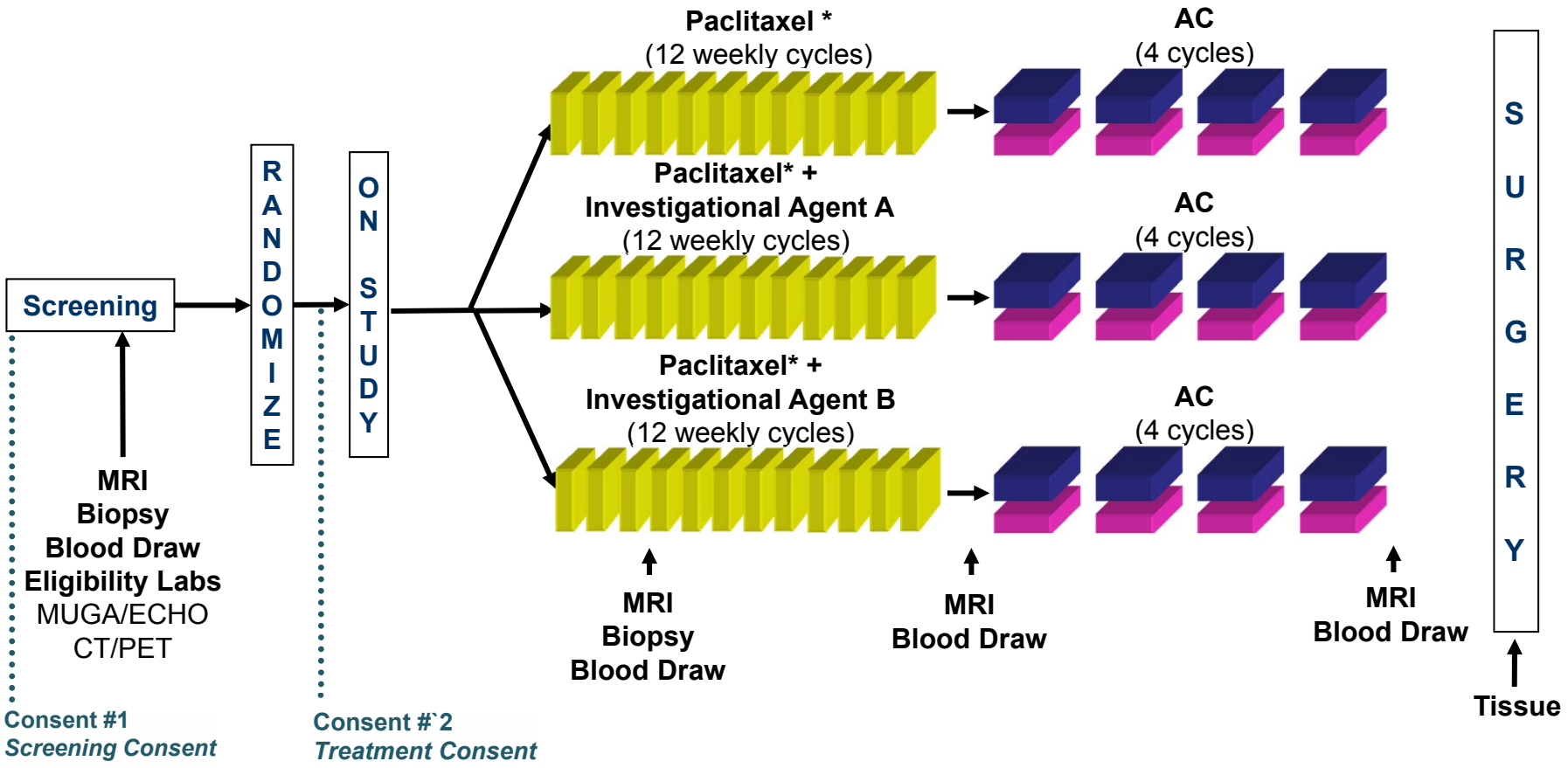
- Increase the number of agents and targets tested within 1 clinical trial 
- Reduce time to conclusive results with neoadjuvant treatment 
- Concurrent development of predictive biomarkers for each agent tested 
- Reduce number of patients/volunteers required with adaptive randomization 

I-SPY 2 TRIAL Design Summary

- Neoadjuvant standard control (taxane-based)
- Balance randomization to investigational agents initially
- Build predictive index for each therapy/biomarker combination
- Adaptively randomize incoming participants
- Evaluate many drugs & combinations
  - Successes graduate to phase 3
  - Underperformers dropped for futility

I-SPY 2 TRIAL

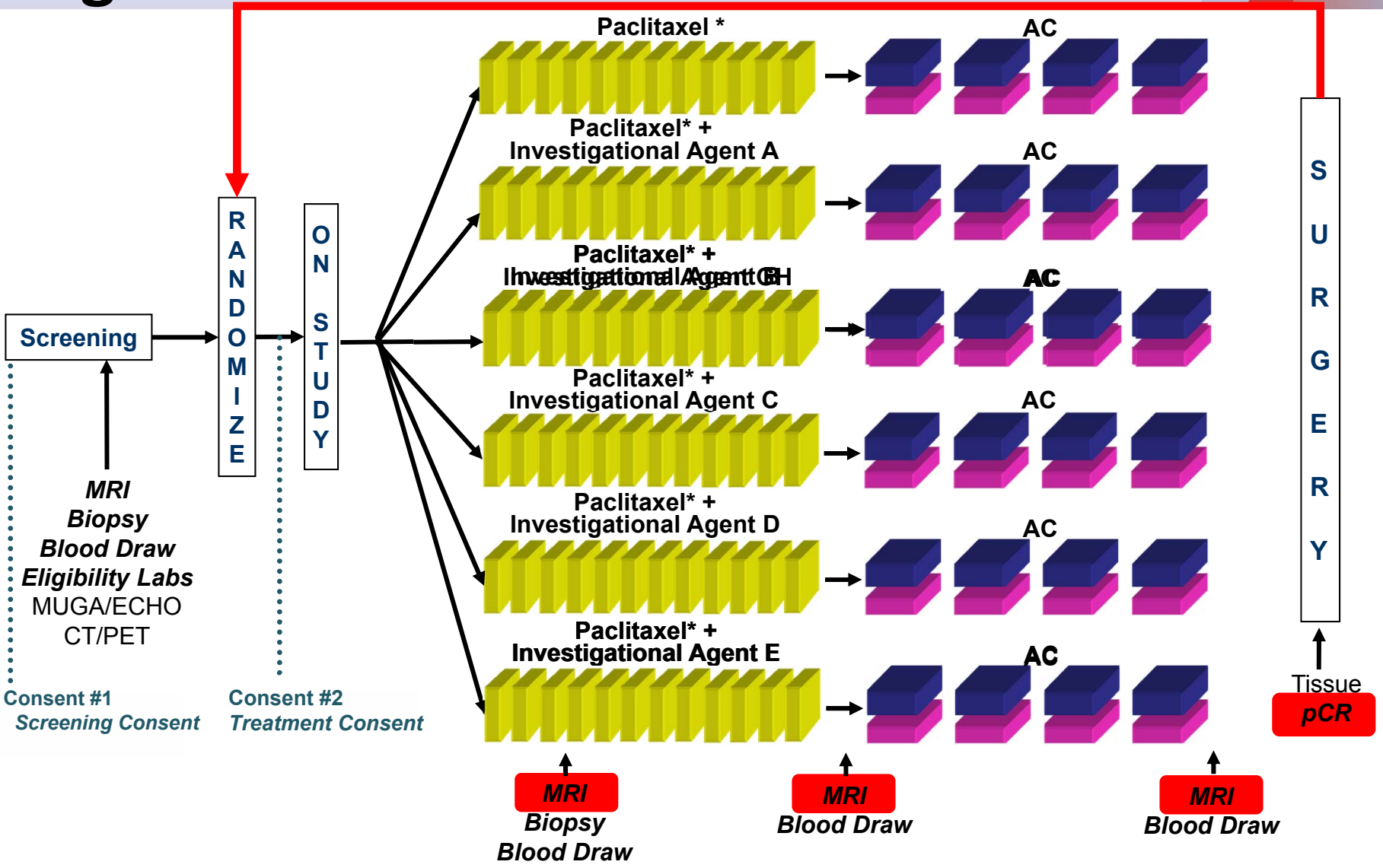
Summary of Study Plan



* HER2 positive participants also receive Trastuzumab.
An investigational agent may be used instead of Trastuzumab.

I-SPY 2 TRIAL

Learn, Drop, Graduate, and Replace Agents Over Time



* HER2 positive participants also receive Trastuzumab.

I-SPY 2 TRIAL: Protocol & Master IND Structure

- The protocol and the Master IND* are structured to enable seamless addition and release of investigational agents over the course of the trial
  - Enrollment does NOT stop during agent transition
- When an investigational agent is added to or released from the trial only appendices require updating

I-SPY 2 PROTOCOL STRUCTURE

* *The Master IND structure allows new investigational agents to be added to the protocol without the 30-day FDA review period.*

Two Part Consent Process

Screening Consent

- Allows *Surgeons*, *Oncologist*, or *Radiologists* to consent a patient
  - Consent covers screening phase procedures, overview of treatment phase procedures, and randomization but <u>not</u> specific treatment information
    - Part of Screening is to determine biomarker profile for which treatment patient is eligible for

Treatment Consent

- Details treatment patient is actually randomized to along with re-reviewing treatment phase study procedures
- Treatment Consent is 2 parts: Main treatment consent + Investigational agent supplemental consent
  - Treatment Consent is obtained after randomization, and only for agent(s) patient is randomized to

I-SPY 2 TRIAL

Two Part Consent Process

Screening Consent

Assess Eligibility

Treatment Consent, Patient On Study

Patient is Eligible & Randomized

Eligibility Determined by:

- ER, PR, HER2
  - By standard community methods
- MammaPrint & HER2 TargetPrint
  - By Agilent 44K microarray from Agendia
- MRI Volume
  - Auto-calculated from Sentinelle workstation
- Labs & ECHO/MUGA
  - Standard blood labs, extra exclusionary labs for investigational agents (will vary during the trial)

I-SPY 2 TRIAL

Two Part Consent Process

Screening Consent

Assess Eligibility

Patient is Eligible & Randomized

Treatment Consent, Patient On Study

Is Patient Eligible?

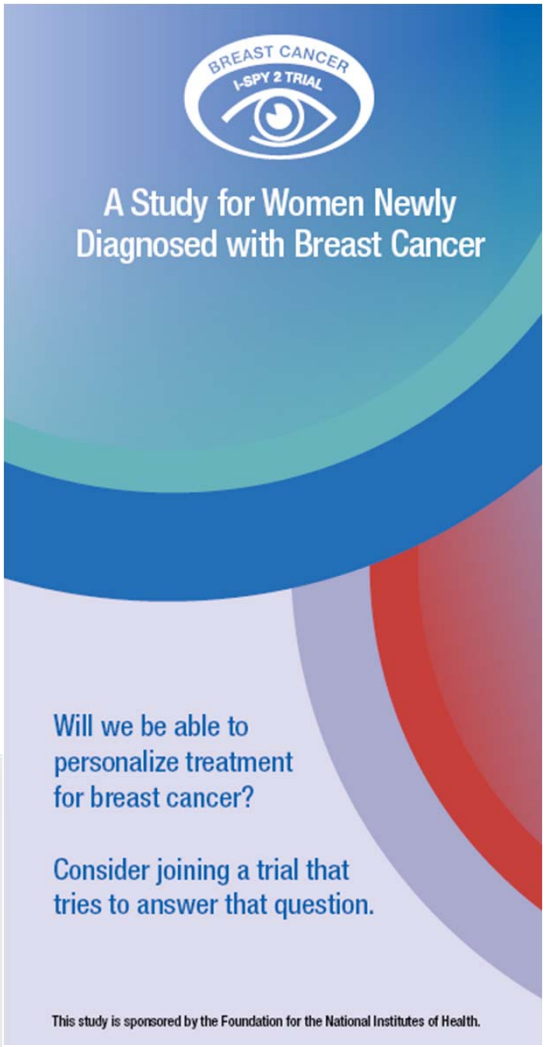
(based on stratifying biomarkers)

	MammaPrint Low		MammaPrint High	
	ER+	ER–	ER+	ER–
HER2+	Eligible	Eligible	Eligible	Eligible
HER2–	*Not Eligible**	Eligible	Eligible	Eligible

*May be eligible to participate in Low-Risk Registry Trial

Tools for Discussing Trial to Patients

- Patient Brochure
  - General introduction to I-SPY 2
- Video/DVD
  - General introduction to I-SPY 2
- Website www.ispy2.org
  - Detailed information about I-SPY 2



Informatics System for Trial Data

Data collection is real-time, web based

- Trial depends on rapid
  - Eligibility assessment & assignment of therapeutic intervention
  - Outcome data (MRI volume & surgical pathology)
  - Safety data
- Verification of data by DCC

Simultaneous evaluation of treatment efficacy and response by biomarkers

- MRI Volume, pCR, RCB
- ER, PR, HER2, MammaPrint
- Qualification & Exploratory Biomarkers

Researchers have access to data early and in an integrated fashion

Randomization as a web service

- Updated daily based upon previous patient's response data

I-SPY 2 TRIAL

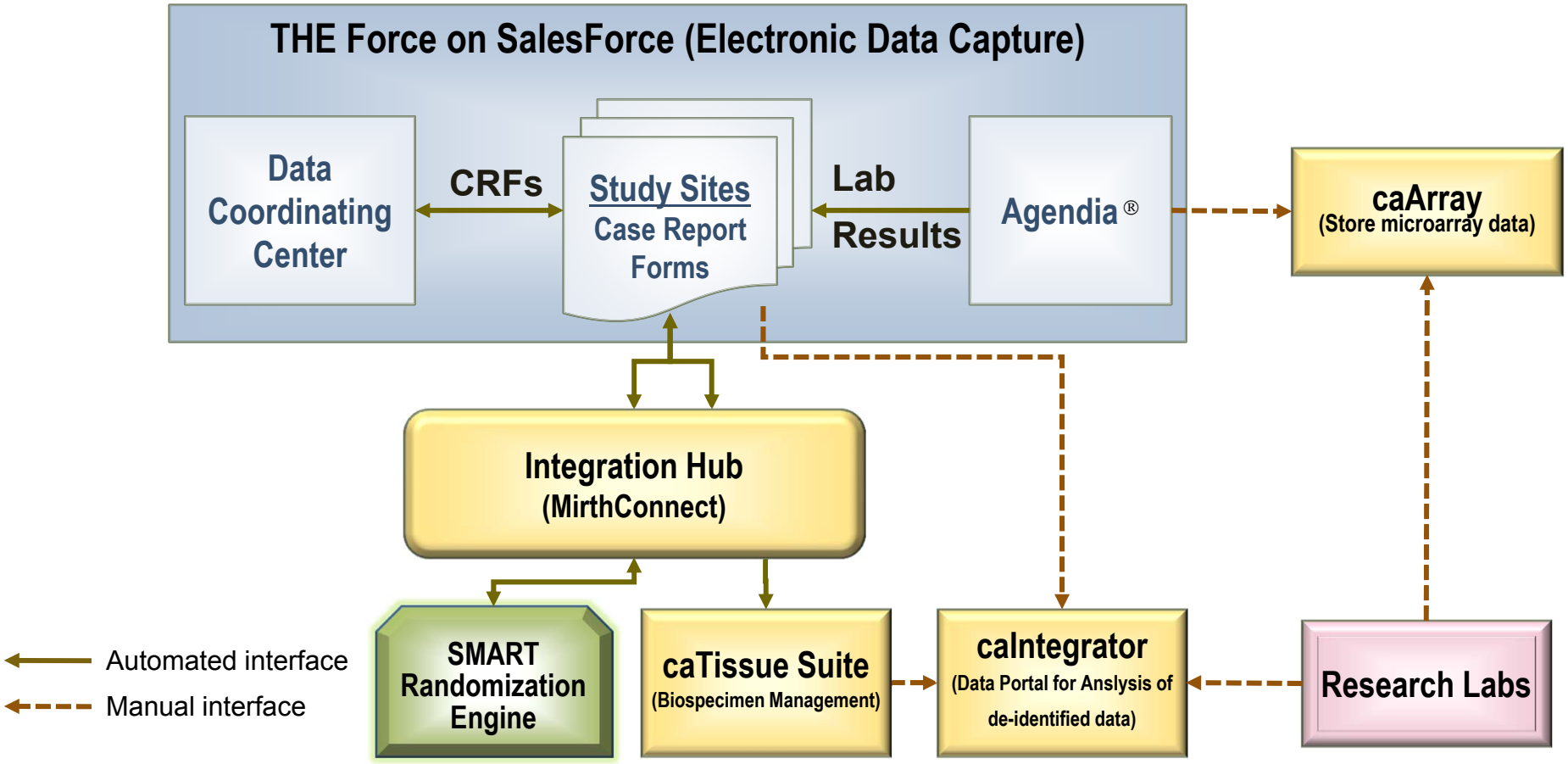
TRANSCEND Overall Objectives

- Develop an information management platform to support adaptive clinical trials like I-SPY 2
  - Manage trial data across multiple sites with 1 central data coordinating
  - Provide real-time data verification for more efficient analysis of trial data
  - Randomization as an automated web service
  - Combining evaluation of drugs and biomarkers together
    - Biomarker data of various types (microarray, imaging, sequencing, etc..)
  - Scientists need access to data early and in an integrated fashion (one stop shopping)
- Provide a demonstration of caBIG infrastructure in use in a large multi-center trial

I-SPY 2 TRIAL

TRANSCEND v1.5 – with THE Force

(Trial 2 Health Expedited on SalesForce)

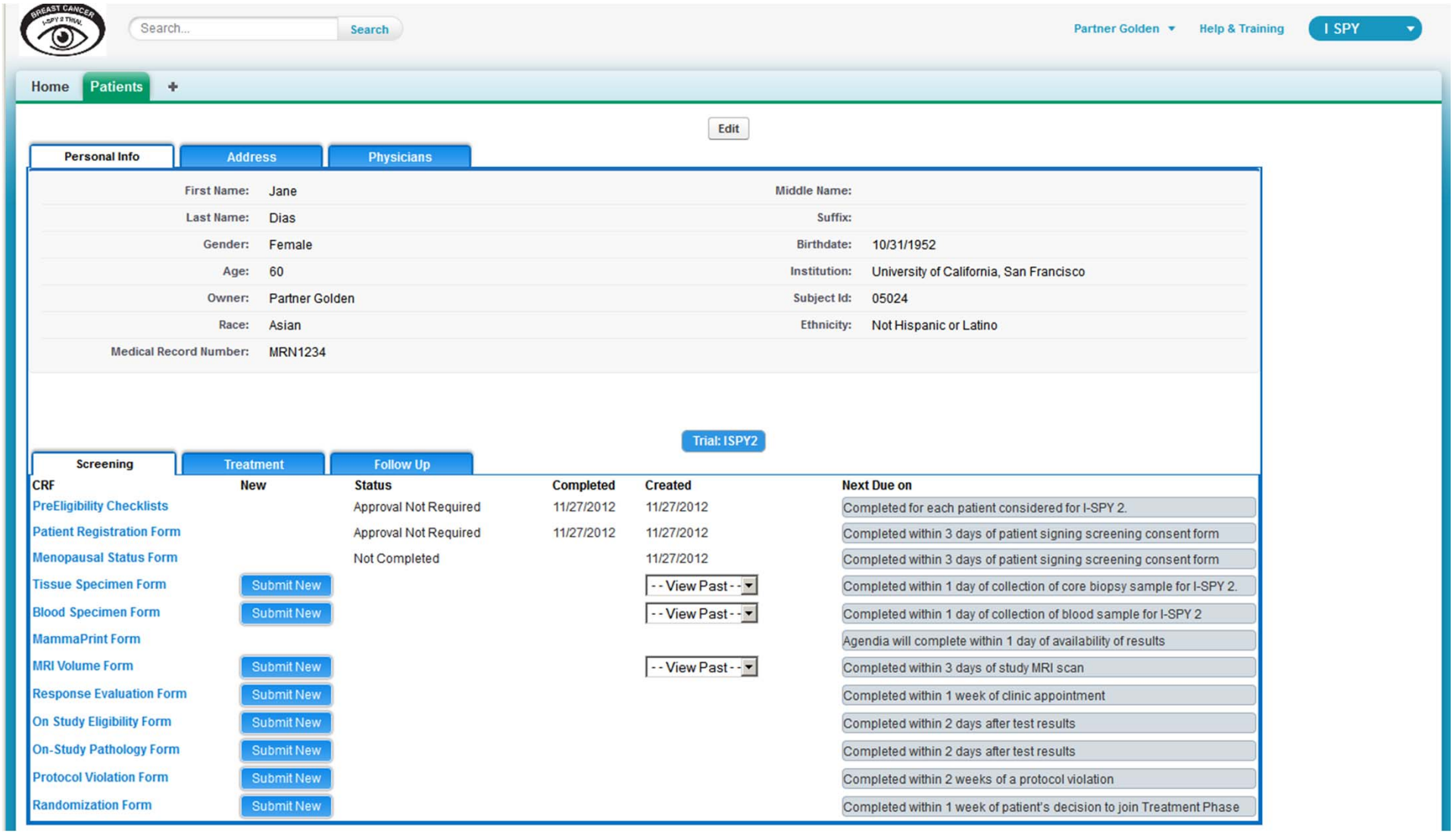


Data Capture and Integration with THE Force:

- Data is captured on CRFs, verified and approved for accuracy by DCC. Data is share with other applications to support the conduct of clinical research, including randomization as a web service

I-SPY 2 TRIAL

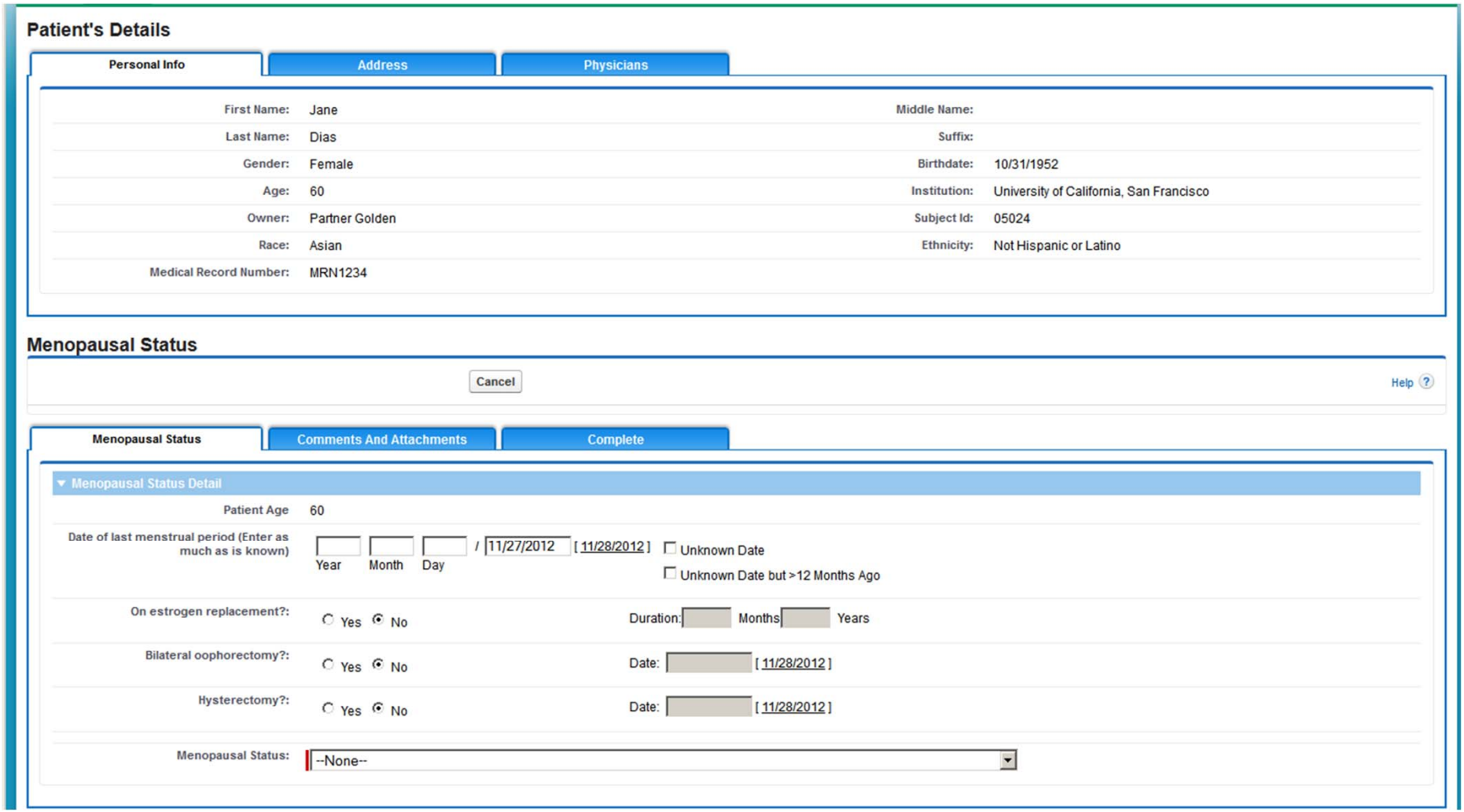
THE Force Functionality – Case Report Forms



I-SPY 2 TRIAL

THE Force Functionality – Case Report Forms

- Data elements are coded at point of data entry



Patient's Details

Personal Info | Address | Physicians

First Name:	Jane	Middle Name:	
Last Name:	Dias	Suffix:	
Gender:	Female	Birthdate:	10/31/1952
Age:	60	Institution:	University of California, San Francisco
Owner:	Partner Golden	Subject Id:	05024
Race:	Asian	Ethnicity:	Not Hispanic or Latino
Medical Record Number:	MRN1234		

Menopausal Status

Cancel Help

Menopausal Status | Comments And Attachments | Complete

Menopausal Status Detail

Patient Age: 60

Date of last menstrual period (Enter as much as is known): Year / Month / Day / 11/27/2012 [11/28/2012] ☐ Unknown Date ☐ Unknown Date but >12 Months Ago

On estrogen replacement?: ○ Yes ◉ No Duration: Months Years

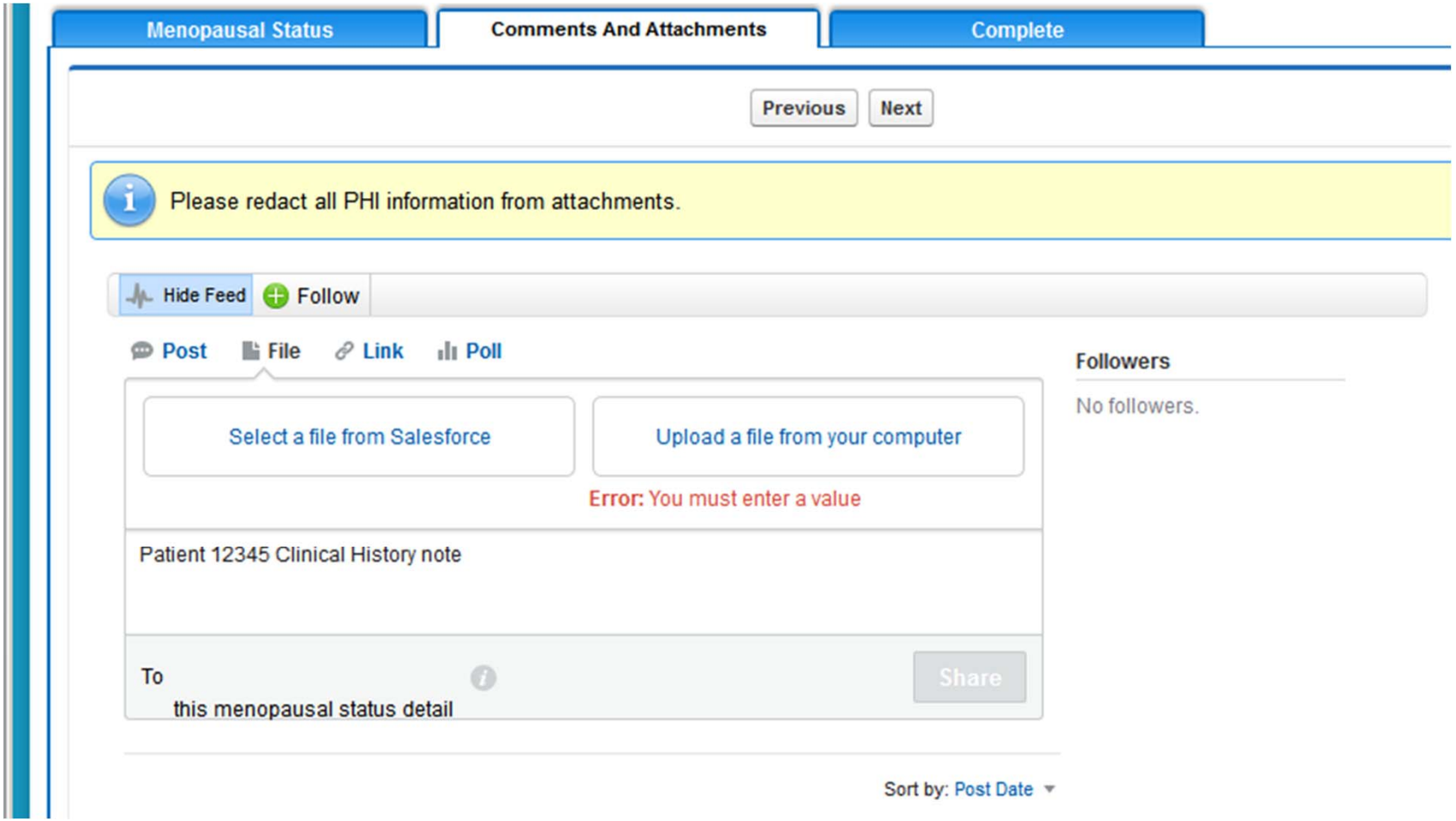
Bilateral oophorectomy?: ○ Yes ◉ No Date: [11/28/2012]

Hysterectomy?: ○ Yes ◉ No Date: [11/28/2012]

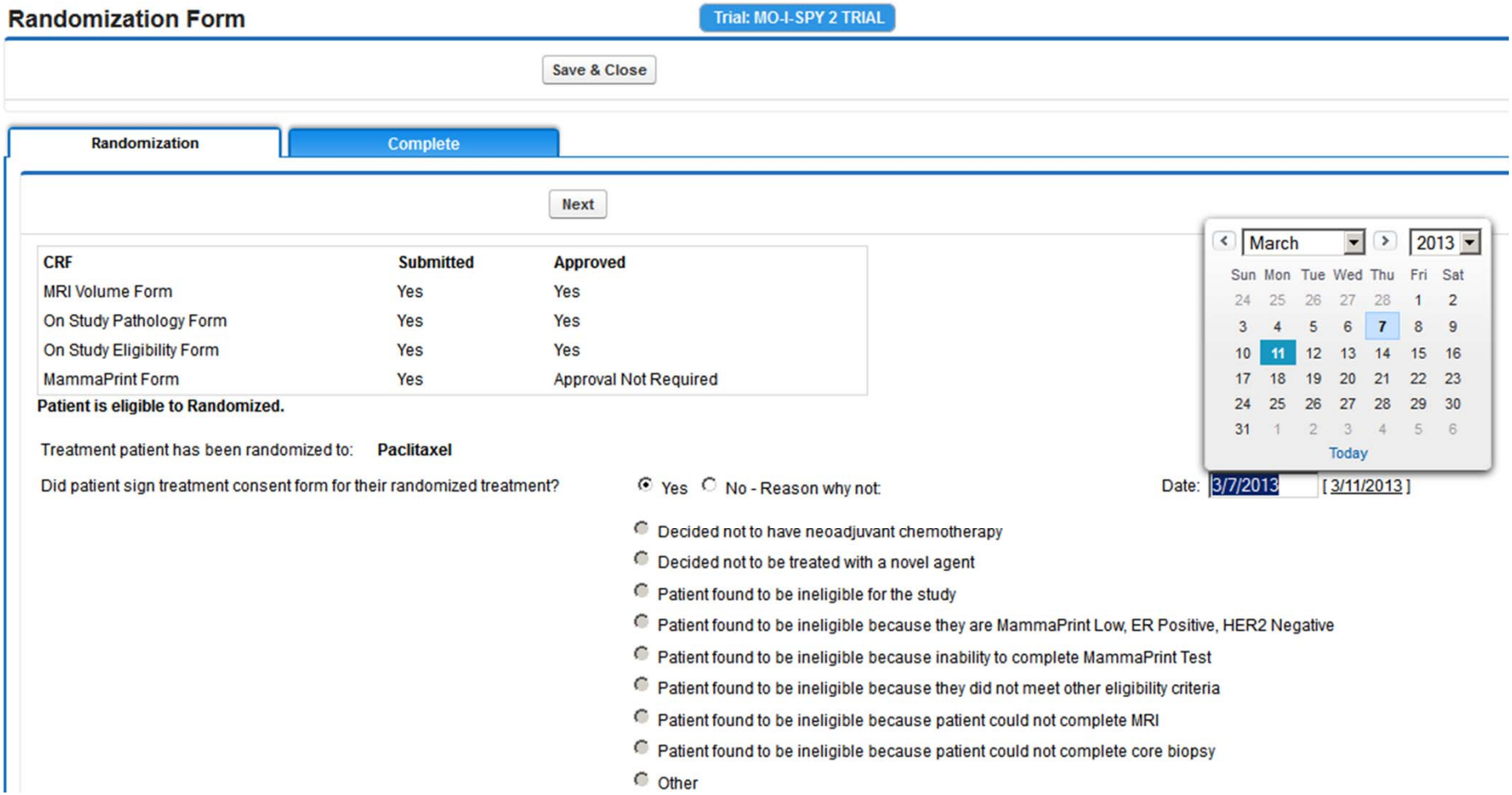
Menopausal Status: --None--

TRANSCEND – CRF & Source Documents

- Electronic copy of source documentation with each CRF
- DCC can verify CRF in real-time, approved data is locked



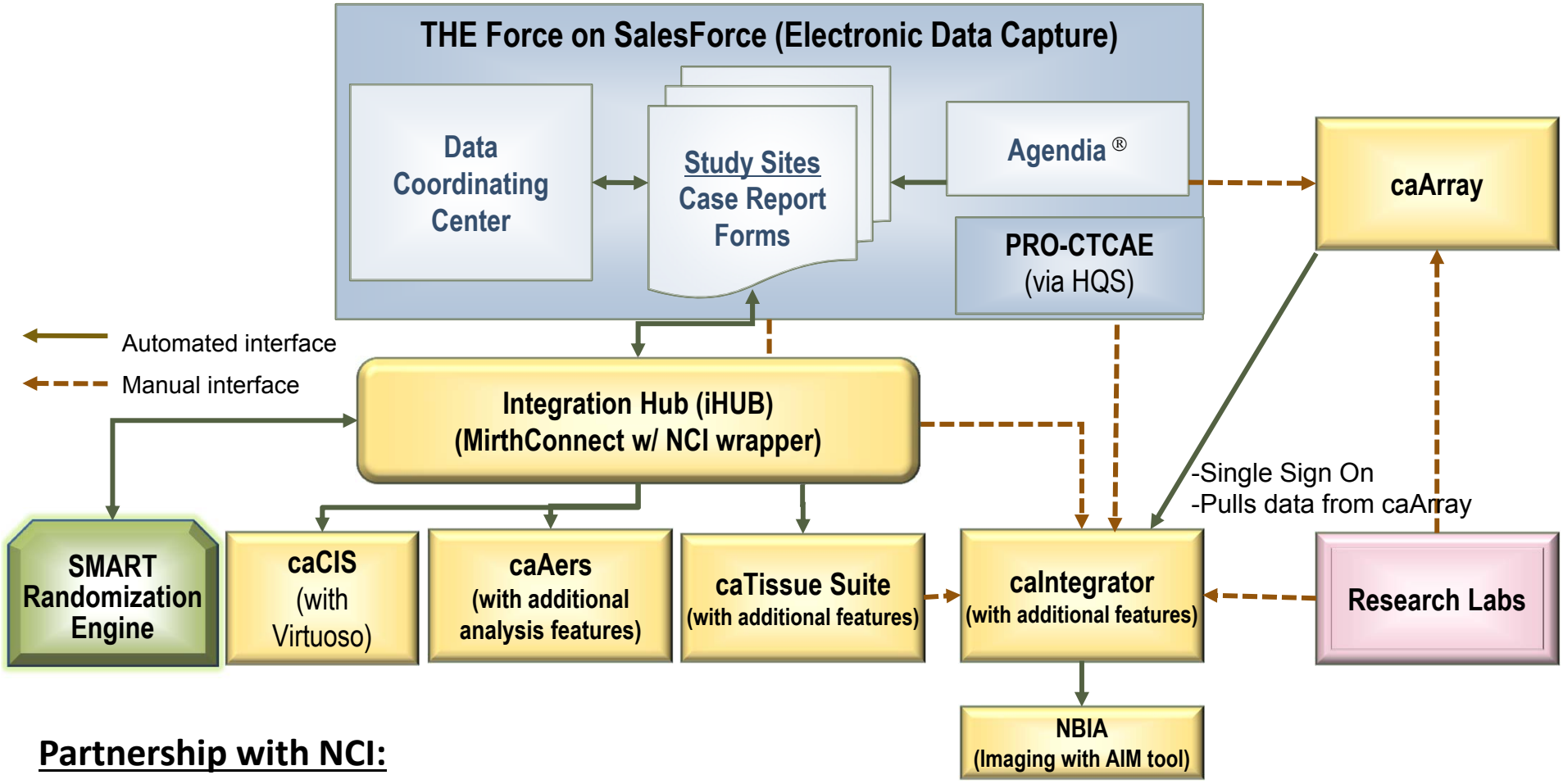
THE Force Functionality – Randomization



- Only when completed and approved CRFs are done will patient be randomized. Randomization happens when user selects this Form (< 1 sec)

I-SPY 2 TRIAL

2TRANSCEND – Deploying June 2013



Partnership with NCI:

- Patient Portal in THE Force, including patient study calendaring
- Additional Integration with Applications (e.g. caAers, caCIS data warehouse, PRO-CTCAE, updated versions of caTissue, caIntegrator, caArray