



Re-inventing drug development: A case study of the I-SPY 2 breast cancer clinical trials program



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ABSTRACT

Background: In this case study, we profile the I-SPY 2 TRIAL (Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And molecular anaLysis 2), a unique breast cancer clinical trial led by researchers at 20 leading cancer centers across the US, and examine its potential to serve as a model of drug development for other disease areas. This multicenter collaboration launched in 2010 to reengineer the drug development process to be more efficient and patient-centered.

Methods: We conduct several interviews with the I-SPY leadership as well as a literature review of relevant publications to assess the I-SPY 2 initiative.

Results: To date, six drugs have graduated from I-SPY 2, identified as excellent candidates for phase 3 trials in their corresponding tumor subtype, and several others have been or are still being evaluated. These trials are also more efficient, typically involving fewer subjects and reaching conclusions more quickly, and candidates have more than twice the predicted likelihood of success in a smaller phase 3 setting compared to traditional trials.

Conclusions: We observe that I-SPY 2 possesses several novel features that could be used as a template for more efficient and cost effective drug development, namely its adaptive trial design; precompetitive network of stakeholders; and flexible infrastructure to accommodate innovation.

1. Introduction

The “Valley of Death” is the grim phrase that has come to describe the current research landscape of the biotechnology industry in the United States. Drug companies are increasingly challenged to secure adequate funding to advance their candidates from the early stages of research and development to clinical trials. At the same time, investors are hesitant to enter this market due to its low average returns and numerous financial risks.

Drug development investments have a painfully long time horizon—Food and Drug Administration (FDA) approval for a single drug is estimated to take 10 to 15 years from start to finish, and to cost upwards of \$2.8 billion [1]. One reason for such high costs is the significant risk of failure. The risks attribute to the unattractive 0.8% return on capital investment in drug development [2]. These dismal figures illustrate why few investment vehicles other than government funding bodies and charitable institutions are willing to invest in early-stage drug development [3].

The development of new oncology drugs is no exception to this fundraising barrier. Oncology drug development has the lowest phase 3 success rate compared to development in other disease classes, a painful 36.7% compared to 60.1% for all other diseases [4]. Because many cancers are heterogeneous, a one-size-fits-all approach to drug testing is inadequate, and is especially problematic given the enormous size and costs of standard phase 3 trials [5]. Due to the fragmented and competitive nature of the pharmaceutical industry, which can lead to inefficient duplication of effort, the rate of clinical development has lagged too far behind the rate of medical discovery. A clinical trial design that determines a drug's efficacy in phase 1 or 2 could save the industry billions in R & D expenditures due to phase 3 failures, making oncology drug development a much more appealing investment [4,6].

A potential solution to this problem lies in the I-SPY 2 TRIAL (Investigation of Serial studies to Predict Your Therapeutic Response with Imaging And molecular anaLysis 2). I-SPY is a multicenter consortium designed to make drug development a more efficient and collaborative process. I-SPY 2 launched in 2010 as the second iteration of

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the I-SPY initiative and was created by a team of researchers from academic centers across the country, with the active participation of the FDA, patient advocates, and partners in the pharmaceutical industry. Devised to accelerate the clinical trial process for promising new breast cancer therapies, I-SPY 2 is a phase 2 model that utilizes an adaptive design and a patient-centered structure. This unique approach is riddled with many scientific, regulatory, and operational innovations. In this case study, we profile I-SPY 2, and consider its potential to serve as a new template for drug development.

2. Background

The initial spark behind the I-SPY program began in 1998 at the University of California San Francisco (UCSF). Breast cancer surgeon Dr. Laura Esserman and breast magnetic resonance imaging (MRI) expert Dr. Nola Hylton saw a pressing need for a patient-centered trial structure, one that would get the right drug to the right patient as quickly as possible. The two researchers began to seek out like-minded collaborators across government and academia to flesh out the early stages of I-SPY. The team of investigators observed an opportunity for disruption in breast cancer through four key inefficiencies.

The first fault of many breast cancer drug studies was the use of the metastatic setting, after the cancer has spread to other areas in the body, when the disease is treatable but not curable. The use of the metastatic setting in these studies contributes to their near 60% phase 3 failure rates [6]. On the other hand, women with early-stage aggressive localized tumors are rarely the subjects for phase 2 efficacy studies, despite their known high risk. Entrance into a trial is typically considered a last-resort option for these patients. They are left to wait years for a drug to reach approval, often instead treated with hyper-aggressive surgical procedures [7], wasting precious time that could have been used for a less invasive treatment.

Second was the common practice of treating early-stage breast cancer patients with localized tumors post surgery, or adjuvantly. The majority of conventional oncology drug clinical trials only evaluate patients who have undergone adjuvant therapy for their long-term response. Patients were observed until they reached a clinical endpoint, typically recurrence-free survival (RFS). However, five to seven years of follow-up is required to accurately determine RFS, as well as the participation of many thousands of patients and several years to accrue them [8]. When combined with the time to get a drug through the approval process, the total duration may be upwards of 10 to 15 years of time from the start of the first phase 2 trial to full knowledge of the drug's effectiveness in the adjuvant setting [9].

The third fault was the lack of biomarkers studied. The different biochemical characteristics of tumors are generically called biomarkers, and permit cancers to be characterized with a high degree of specificity. However, most breast cancer trials do not address the wide range of potential biomarkers in patients beyond the standard few already in practice (hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2)), leaving many women of less common subtypes with fewer treatment options [10]. Traditionally, only 3–5% of the breast cancer population is recruited to participate in clinical trials, creating an additional bias in testing [11].

Fourth was the structure of standard breast cancer clinical trials. After 70 years, the randomized controlled trial (RCT) is still considered the gold standard in clinical testing. The random assignment of trial subjects to experimental and control groups reduces unconscious bias and mistaken attributions of cause and effect, providing reliable medical evidence for therapeutic performance. Traditional phase 2 RCTs, however, are time-consuming; they typically test a single question at a time, and require tracking RFS of a large number of subjects to be statistically valid. Unfortunately, this is an equally long process for effective and ineffective drug candidates alike, as the randomization process is independent of the ongoing results of the trial. Ignoring trial results until the end is especially inefficient in the presence of multiple

patient subtypes who each respond differently to a given therapy. In an ecosystem where breast cancer can be categorized by a multitude of biomarkers, a standard RCT is simply not feasible to address all possible subtypes found in patients.

A potential solution to address these four inefficiencies, as well as the fragmentation of clinicians, pharma, and regulatory bodies, is I-SPY 2, an ongoing phase 2 trial created as a model of continuous learning in clinical drug development. The objective is to act as a *precompetitive* screening trial, uniting possible future competitors in oncology drug development. The trial is designed to identify effective investigational drugs and share the information across academic, pharmaceutical, biomarker, and other participant groups [12]. I-SPY 2 stands on three legs: its innovative trial design, its collaborative organization, and its operational conduct. In the next three sections, each will be discussed in turn.

3. Trial structure of I-SPY 2

I-SPY 2 is an adaptive phase 2 clinical trial process designed to reduce the time required to learn which different drug candidates are most effective within different tumor subtypes. By using the predictive analytics developed in I-SPY 1, the first iteration of the I-SPY trials, I-SPY 2 can determine more efficiently whether a treatment is likely to be effective for a specific subtype of breast cancer, while addressing the four inefficiencies discussed above. (See Supplemental materials for further discussion on I-SPY 1.)

First, I-SPY 2 treats early stage patients before surgery, or neoadjuvantly. By using a pathologic complete response (pCR), the complete disappearance of a tumor before surgery, as a surrogate for RFS as a clinical endpoint, I-SPY 2 is able to be much more time efficient than standard protocols [13]. This implies that researchers need not wait the 5–7 years to confirm RFS for patients enrolled in the trial. There have been many recent debates over the utility of pCR due to its varying ability to predict RFS by subtype. For example, pCR has been found to be most effective as a predictor for highly aggressive tumor types, such as triple negative, HR-negative, and HER2-positive; while it is generally a poor predictor for HR-positive cancers [14]. However, since I-SPY 2 strives to optimize the clinical trial process for high-risk patients, pCR has appeared to be an appropriate endpoint for their purposes. By using unorthodox imaging methodologies of the time, as well as common platforms for tumor profiling, I-SPY 1 was able to confirm pCR as a key predictor of RFS and that pCR was a better predictor for each individual subtype than for the breast cancer population as a whole [15]. The decision to use pCR was further validated by the FDA in 2013, upon their support of it as an endpoint to gain accelerated approval [16].

Second, I-SPY 2 stratifies their patient populations into more specific groups by evaluating the MammaPrint high and low markers, as developed by Dr. Laura van't Veer of UCSF. These biomarkers add another dimension to the widely studied HER2 and HR biomarkers, allowing the trial to be inclusive to a more diverse array of patients [17]. Taking into account the tumor subtype as determined by biomarker sharpened predictions of long-term patient outcome even more than before [18]. I-SPY researchers still continue to attempt to identify potentially feasible biomarkers to further enhance the trial and subclassify patients. As an example, the team investigated the predictive ability of the BRCAness signature in PARP inhibitor trials [19]. The signature has a possibility of being incorporated in I-SPY 2 following validation in a larger subsequent trial.

Third, to address the immense diversity of breast cancer patients, I-SPY 2 is a variation of a basket trial combined with a platform trial, where it examines up to 12 therapies from different companies in conjunction with each other against 10 different patient groups with specific biomarker signatures [20]. This portfolio-like structure is designed to help high-risk patients by testing many biomarker signature groups simultaneously rather than sequentially, enabling I-SPY 2 to be inclusive to almost all breast cancer patients.

An RCT could not realistically accommodate all of the drugs and patient groups of I-SPY 2; the trial possesses an adaptive design powered by sophisticated statistical analysis, enabling it to test the various drugs against shared control groups for each biomarker signature in a reasonable amount of time. Drugs are assigned to patients using Bayesian methods of adaptive randomization in order to achieve a higher probability of efficacy [21]. In this way, drugs that perform well within a specific patient subtype will be increasingly assigned within that subtype to graduate for that subtype in less time. Conversely, drugs that perform poorly within a specific subtype will be less frequently assigned within that subtype. Once enough subjects have demonstrated statistically the effectiveness of the drug, it will graduate into the confirmatory 300 patient phase 3 trial for the subtypes in which it has an 85% or higher predicted probability of success in a phase 3 setting, or in some cases, where performance is significantly better than the control arm due to factors such as toxicity and side effects. In the same way, if a drug appears statistically futile (less than 10% predicted probability of success in phase 3) against a given biomarker subtype, it can quickly be set aside [22]. Once graduated or dropped, the next drug in the pipeline will replace the current drug, so that the trial remains open and enrolling (Fig. 1).

The 85% graduation threshold sets the bar intentionally high to ensure that only the most promising therapies have phase 3 trials. It also leaves room for error in the event of a significant backlog of patient data. For example, in the case of neratinib, which graduated from I-SPY 2 in HER2 +/HR – indication with a 79% predicted probability of success. The 85% threshold was reached before all patients had completed the treatment regimen and surgery. After all data points were collected, the predictive probability had reduced to 79%. Paired with neratinib's 95% probability of superiority over the trastuzumab plus paclitaxel control, investigators determined the drug effective enough to succeed in a phase 3 setting [34].

Drugs can be dropped or added at any time, ensuring efficient turnover over a target graduation period of eighteen months with patient accrual. Due to its unique adaptive design, I-SPY 2 can accrue less patients to secure detailed information on a drug's performance (Table 1). This feature is particularly beneficial for rare tumor types where accrual is a challenge. This continuously learning model strives to achieve the goal of getting the right drug to the right patient more

quickly.

While they appear a simple and intuitive solution, adaptive trial designs receive a fair amount of criticism among clinicians and biostatisticians alike. The largest concern is the potential creation of unnecessary bias due to modifying the trial based on prior evidence. Experimental arms with marginally better results than other arms could become significantly more favored as more patients are assigned to it. This could increase the likelihood of Type I error, or false positives [23,24]. Another potential source of bias can be created during patient accrual. It is no secret that patients are more likely to be randomized to better treatment arms the later they enter the trial. The entrance of sicker patients into the trial earlier due to necessity followed by healthier patients who can afford to wait later on could create highly biased results [25].

A related issue is how Type I errors are controlled in an adaptive trial. In fact, the very definition of Type I error in this context is not obvious. This subtlety is explained best by Dr. Donald Berry, the biostatistician who helped design the I-SPY 2 protocol and one of the founding fathers of Bayesian adaptive clinical trial design [46]:

Due to the investigation of many therapies on multiple patient subtypes concurrently, I-SPY 2 generates various possibilities of Type I error types. There is no natural analog of Type I error in a trial that determines which subsets of patients benefit from which therapies. The trial could find a therapy's true signature. It also could determine an indication that is larger than the therapy's true signature, one that is a subset of the true signature, or a combination of the two. Thus, there are several types of possible errors in I-SPY 2. All are affected by the design's continuous monitoring aspect, and, because of adaptive randomization, by the presence of other therapies and the effectiveness of those other therapies. They are also affected by the longitudinal modeling used in the trial. The rates of all the error types are found by simulation assuming many different possible scenarios. The error types are specific to the therapy considered and are not modified because many therapies are being considered in the same trial.

Naturally, the Type I error rate control and sample size calculations of I-SPY 2 are quite complex in order to account for these risks. The ongoing adjustments to the trial are made in a manner that attempts to

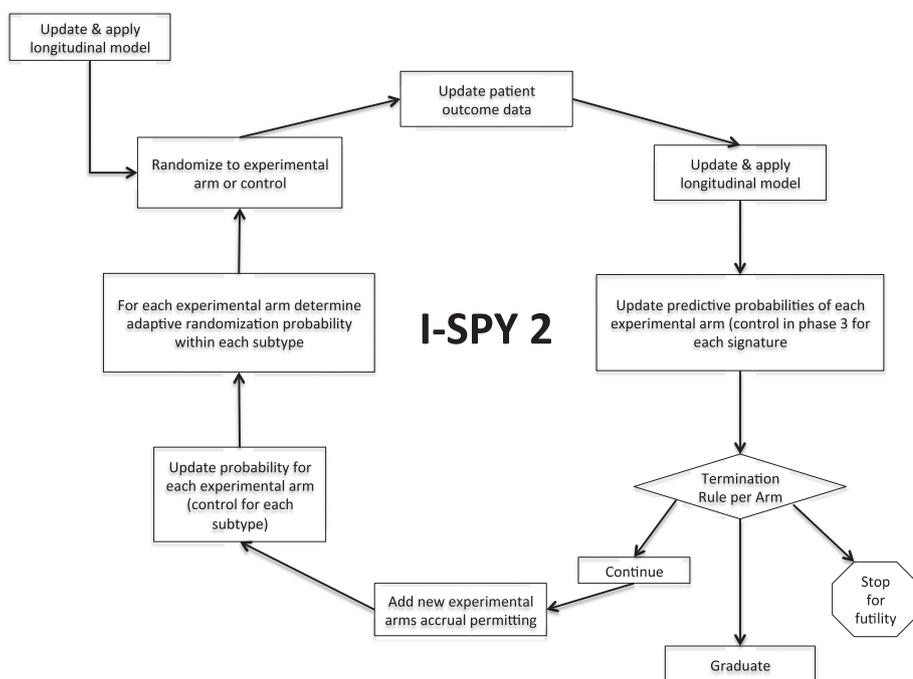


Fig. 1. Flow chart illustrating the steps of the I-SPY 2 trial. (Donald Berry 2016.)

Table 1
The I-SPY 2 graduates [33–38,47].

Drug	Company	Mechanism of action	Predictive probability of success in phase 3	Biomarker signature graduated	No. patients accrued	Date graduated
Veliparib-carboplatin (ABT-888)	Abbvie	poly-ADP ribose polymerase inhibitor	88%	HER2 – /HR – /MP –	72	December 2013
Neratinib	Puma Biotech	tyrosine kinase inhibitor	79%	HER2 + /HR –	115	December 2013
MK-2206	Merck	AKT inhibitor	87%	HER2 + /HR –	93	May 2015
Trastuzumab emtansine (TDM-1; Kadcyla) & pertuzumab (Perjeta)	Genentech	HER2 dimerization inhibitor	94%	HER2 +	52	April 2016
Pertuzumab (Perjeta) & paclitaxel & herceptin	Genentech	HER2/neu receptor antagonist	90%	HER2 +	44	April 2016
Pembrolizumab (Keytruda) & paclitaxel & doxorubicin & cyclophosphamide	Merck	PD-1 Inhibitor	99%	HER2 –	69	November 2016

optimize the statistical validity of the resulting data [26,27]. Because the predictive probability benchmarks for graduating and dropping from the trial are so high and low respectively, it is quite difficult for mediocre drugs to be inaccurately classified. All therapies are tested in a minimum of 20 and maximum of 120 patients before a decision to leave the trial is made, ensuring that no rash decisions are made based on too small a sample size [13]. Furthermore, since I-SPY 2 treats solely in the early-stage, high-risk, neoadjuvant setting, there is a smaller window for patients to consider entering the trial, likely avoiding some of the bias caused by patients waiting to enter. However, it would be interesting to see further investigation from the I-SPY team into the creation and management of bias created by the trial's adaptive design.

A notable innovation within I-SPY 2's trial design is the flexibility to transition to a more effective control arm as new treatments receive FDA-approval. A control treatment in a clinical trial uses a standard therapy, generally the FDA-approved treatment with the best response rate. However, the standard taxane-anthracycline arm has a response rate that varies (by tumor subtype) from 12% to 30% [28]. Because of this, there is a constant desire to improve the standard treatment and ensure that patients have the best probability of response, regardless of their assignment in the trial. For example, in fall 2013, Genentech's investigational drug pertuzumab (Perjeta) was the first drug to receive accelerated FDA approval in the neoadjuvant setting for HER2-positive patients with pCR as an endpoint. The approval redefined the standard of treatment in the neoadjuvant setting for HER2-positive tumors, since Perjeta possessed a higher response rate than the taxane-anthracycline regimen [29]. The I-SPY team was able to seamlessly adopt this change, and modified the randomization probability of the taxane-anthracycline regimen for HER2-positive patients to zero. Furthermore, combination paclitaxel, Perjeta, and Herceptin was already an investigational arm in the trial. After the graduation of this arm, I-SPY 2 transitioned this treatment to a control for HER2-positive patients. This example highlights the adaptive capabilities of I-SPY 2 as medical and technological innovations occur in the industry.

4. Organizational structure of I-SPY 2

I-SPY 2 is conducted by a consortium of individuals and organizations representing a variety of stakeholders in the drug development ecosystem. Its current structure is an umbrella of organizations, committees, and working groups (Fig. 2). All committees are mentioned in this section, and are discussed in greater detail in the supplemental materials.

Nine working groups govern the different branches of I-SPY, and are alphabetically as follows: Advocates, Agents, Biomarkers, Clinical Trial Operations, Imaging, Informatics, Pathology, Project Management, and Statistical Core. Executive Operations (EO) collectively manages the working groups within I-SPY 2 and is chaired by Dr. Esserman and Dr. Donald Berry of MD Anderson. EO reports to the Project Oversight team, chaired by Dr. Anna Barker of ASU and Dr. Janet Woodcock of the FDA, which manages communication with QuantumLeap Healthcare Collaborative (QLHC), the trial sponsor.

An interesting feature of the organizational structure is the deliberate assignment of different principle investigators (PIs) to each of the drugs in the study. This keeps researchers engaged by ensuring that the experts behind the trial continue to have what Dr. Esserman likes to call 'skin in the game'.

While this umbrella structure may appear complex, its goals are simple: to pursue research objectives and ensure oversight in a timely manner by putting experts in charge of the aspects of the trial that fit their expertise.

5. Operational conduct of I-SPY 2

I-SPY 2 is operationally ambitious and complex. However, the modular structure described above ensures efficient operational

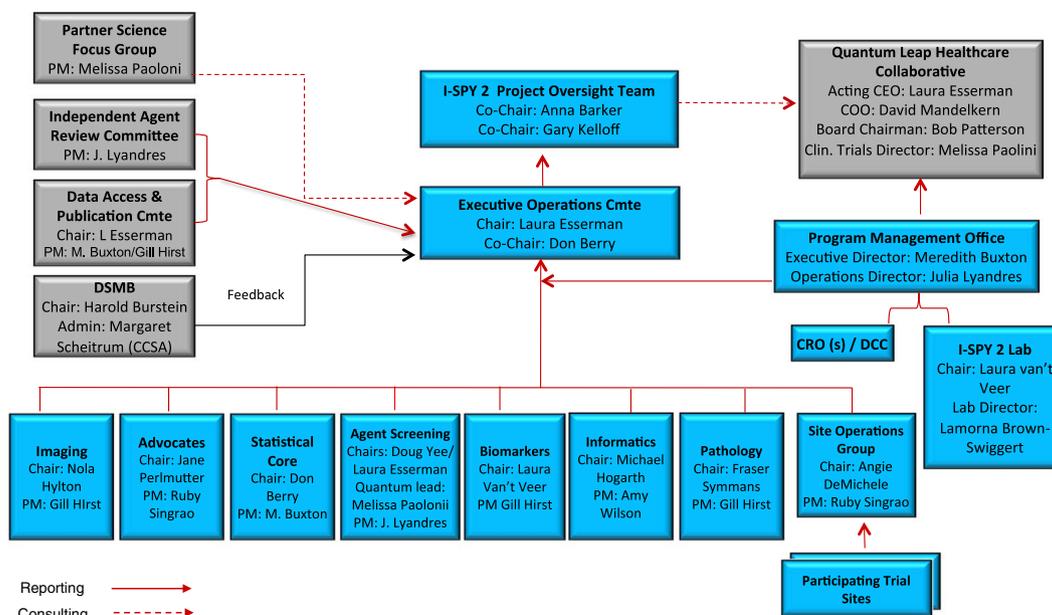


Fig. 2. I-SPY 2 organizational structure as of June 2016. (Meredith Buxton 2016.)

execution. Among the most innovative operational features are the master protocol, patient accrual, and data monitoring.

I-SPY 2's master protocol and the master investigational new drug (IND) application developed by Drs. Esserman, Barker, Berry, and Woodcock are two of the most notable regulatory innovations of the trial. As director of the FDA's Center for Drug Evaluation and Research, Dr. Woodcock's role has been critical in helping to create a system that can operate within the confines of the current regulatory environment. As new drugs are entered into the trial, rather than composing a new protocol for each drug and waiting for its FDA approval, the I-SPY 2 master protocol itself can be modified, avoiding the time-consuming and repetitive process of composition [30]. The body of the protocol describes the details and methods of the trial, omitting the details of the specific therapies. Only the appendices to the protocol are updated to discuss the therapies. The master IND application, which is submitted for FDA approval to ship therapies across state lines to other clinical trial sites, follows this same structure, allowing investigational agents to be added to the protocol without waiting for the thirty-day FDA review period. The master protocol and IND have enabled the seamless transition of investigational agents in I-SPY 2 without disrupting patient enrollment. Since I-SPY's inception, the master protocol and IND have become more prevalent in similar clinical trial structures.

Like any trial, patient accrual is a key component of I-SPY 2's operations. A challenge of testing in an early-stage neoadjuvant setting is that the majority of patients to accrue have been recently diagnosed. The design of the trial, however, makes it easy for patients to consider enrolling. Patient advocates, led by Dr. Jane Perlmutter, train site coordinators on how best to have conversations with recently diagnosed patients about their potential options in a clinical trial. Paired with the trial's unique two-step consent process, patients are provided information in an approachable manner. The advocates' ability to connect with patients and stay close to them throughout the trial process gives them an invaluable perspective that is used to help decide the next drugs to enter the pipeline and dictate the course of innovation within the trial, enabling I-SPY 2 to truly center on the patient's experience.

Data monitoring and quality assurance are crucial to ensuring accurate results and statistically valid randomization assignments. Monitoring and cleaning take place in real time, and the data are sent immediately to the Data Coordinating Committee (DCC) from the trial site. The CTO and the Project Management groups deal with the fluctuations of day-to-day data monitoring. A unique feature of the data-

monitoring plan is its risk-based approach. By cleaning and verifying only the elements that contribute to the primary or secondary endpoints and collecting the most relevant details, data monitors are able to filter through the adverse events in a patient's history—defined as any fluctuation in a patient's baseline levels—and observe the data that matters to the trial, patient safety and indications of response to treatment. This approach adds to the operational efficiency of I-SPY 2, and eliminates the misplaced precision seen in many other clinical trials due to over-processing of irrelevant data, making real-time adaptations infeasible.

A feature that demonstrates the operational flexibility of I-SPY 2 is the ability to accommodate sub-studies into the trial. The I-SPY 2 network is composed of investigators who have a strong desire to make the most of its data-robust trial structure. For example, ACRIN 6698, is a sub-study within I-SPY 2 (now complete) that examined the ability of diffusion-weighted MRI to predict pCR [31]. American College of Radiology Imaging Network (ACRIN) assists the Imaging working group in identifying viable new imaging methodologies, but it also has specific scientific questions that it would like to answer. I-SPY 2 provides a structure to answer these questions. Other ongoing sub-studies within I-SPY 2 are investigating quality of life issues among patients, circulating tumor cells (a possible indication of metastasis), and the low-risk registry (i.e., the patients ineligible for I-SPY 2 due to molecular features that indicate a low early risk for recurrence and a lack of efficacy for chemotherapy). Investigators and collaborators with specific research interests in the trial initiate these studies, while I-SPY 2 provides assistance with reimbursements and data sharing to avoid the collection of redundant data.

6. Results and looking ahead

As of April 2017, I-SPY 2 has graduated six investigational treatments from the study to move on to phase 3 trials, and six additional drugs have either been dropped or are in the process of being evaluated. The graduated drugs have been matched to their most effective biomarker signatures, so that their phase 3 trials will require far fewer subjects to enroll than in standard phase 3 testing (Table 1). The benchmark 85% predicted probability of phase 3 success for their respective signature dwarfs the average 36.7% probability of success observed in traditional oncology drug clinical trials [5]. Furthermore, all of these drugs entered I-SPY 2 and graduated in nearly eighteen months, a considerable feat compared to the median phase 2 trial

duration of over 40 months [32]. These results showcase the promise of adaptive trials in the drug development space.

Over seven years after its inception, I-SPY 2 investigators are still finding ways to improve the clinical trial structure even further. I-SPY 1 helped to establish that patients with different biomarker signatures possessed very different probabilities of achieving pCR with chemotherapy. The Agents working group is looking into expanding the capability of I-SPY 2 to accommodate other treatment types. For example, the space defined by the HR biomarker is complex and evolving, making its drug development particularly challenging. Patients with HR-positive breast cancers are less likely to respond to chemotherapy, but do respond to endocrine (hormone) therapy [39]. By incorporating and comparing different non-chemotherapy treatment types like endocrine therapy, it is plausible that I-SPY 2 could identify the best possible therapies for each tumor subtype.

Investigators are also examining the use of multiple therapies for a single patient in trials with path-dependent protocols, coined the I-SPY 2 Plus project. At this stage of I-SPY 2, if a patient is not responding or progressing with their assigned treatment, it is common for them to leave the trial, and frequently receive a different adjuvant treatment prescribed by their clinician. Unfortunately, there is currently no capability for these patients to be re-randomized in the trial. A change to accommodate these patients will require significant regulatory and statistical modification to the current trial design. However, the I-SPY team has submitted a grant for a program project to turn this idea into an operational plan for modifying the trial, and is speaking with pharmaceutical partners and seeking additional infrastructure and funding for this possibility. The purpose of these extensions to the I-SPY program is to treat all breast cancer patients, while simultaneously decreasing the time required for therapies to get through the three trial phases.

As of now, the I-SPY team is reconfiguring their funding efforts. After 2010, I-SPY 2 received most funding from cancer non-profits, philanthropic organizations, grants, and private individuals, allowing companies to enter their drugs into the trial for little to no cost. However, following the FDA guidance and accelerated approval of Perjeta in the neoadjuvant setting, I-SPY 2 gained the proof of concept it needed to demonstrate its value for using pCR as an endpoint [40]. Consequently, I-SPY 2 began to receive more interest from industry and implemented a “pay-to-play” model, where companies covered the full cost of advancing their drug through the trial. Because the trial provides valuable data on a company’s drug and reduces its time to market, the cost-benefit ratio of I-SPY 2 for the private sector proved to be superior to the traditional trial format for these drugs. For this reason, philanthropic organizations have been less inclined to provide support for I-SPY 2. The team is in the process of seeking a sustainable funding solution via partners who possess a vested interest in making better investments in drug development.

I-SPY 2 has been a successful proof of concept for this team’s vision, demonstrating that a precompetitive ecosystem is possible and can spur innovation in drug development. Already, similar collaborative trial structures have arisen in other disease areas. For example, MICAT (Melanoma International Collaboration for Adaptive Trials) is a multi-drug study inspired by I-SPY 2 that launched in 2014 [22]. The trial was designed by Berry Consultants to address metastatic melanoma phase 2 and 3 trials. GBM AGILE, an adaptive trial to address the malignant brain cancer glioblastoma multiforme, began patient accrual in fall 2016 and was developed by Dr. Barker, Dr. Berry, and a large international group of clinicians, basic scientists, and advocates who hope to demonstrate the power of the adaptive trial model in a rare disease setting [41]. Other examples include efforts in Alzheimers (IMI EPAD), community acquired pneumonia (REMAP-CAP), Ebola, and pancreatic cancer (Precision Promise) [42–45]. These trials are few of many that show the beginnings of change in the culture of drug development.

The I-SPY 2 model has already made waves in oncology drug development. Its potential to significantly reduce time to market and to

provide detailed data is critical to improving the knowledge turnaround of disease treatment. By ensuring a high likelihood of success in the phase 3 setting, the risk of drug development could be considerably reduced. With the I-SPY model as a standard of clinical trial design, investment in drug development could become less risky with a shorter time horizon, and a smarter investment rather than a gamble.

Competing interests

SD declares no competing interests. AWL has personal investments in several biotechnology companies and venture capital funds; is an advisor to BridgeBio Capital, and a director for the MIT Whitehead Institute for Biomedical Research and Roivant Sciences, Ltd.; has received funding support from Natixis Global Asset Management, Alfred P. Sloan Foundation, National Science Foundation, MIT Laboratory for Financial Engineering, BBVA, The Clearing House, Citigroup, and Macro Financial Modeling Group; has received personal fees from AlphaSimplex Group, outside the submitted work; and is on the Board of Overseers at Beth Israel Deaconess Medical Center. AWL is engaged in research, educational, and outreach activities to facilitate the use of financial engineering methods for supporting biomedical innovation, interacting regularly with biotechnology and pharmaceutical companies, life sciences investors, patient advocacy groups and foundations, government agencies and policymakers, and biomedical scientists and clinicians.

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