Adaptive Design of Clinical Trials: Understanding the Barriers to Adoption

by

Ayesha N. Khalid, MD

Bachelor of Science, Physiology, McGill University, 1997
M.D., Doctorate of Medicine, The Pennsylvania State University of Medicine, 2003

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Signature of Author: Signature redacted
MIT Sloan School of Management
May 8, 2014

Certified by: Signature redacted
Andrew Lo, PhD, Thesis Advisor
Charles E. and Susan T. Harris Professor of Finance, MIT Sloan School of Management

Reviewed by: Signature redacted
John Van Maanen, PhD, Reader Review
Professor of Organization Studies, MIT Sloan School of Management

Accepted by: Signature redacted
Stephen J. Sacca, Director
MIT Sloan Fellows Program in Innovation and Global Leadership

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Abstract

There is great competition for clinical research funding. This is in part due to the National Institute of Health's reduced budget to support such initiatives. It has resulted in a growing trend for clinical research to use adaptive design models to accelerate clinical trials and at the same time reduce overall cost.

Although such models have existed for several years, the pace of adoption remains slow, especially for early-stage clinical research. Through a review of relevant literature and interviews with industry experts, this thesis explores the barriers that inhibit the adoption of adaptive design of clinical trials. Reasons uncovered include: a lack of novel funding mechanisms, regulatory uncertainty, logistical difficulties, overly technical communications, a lack of collaboration among stakeholders, and an inability to recruit and retain patients. Then follows a series of possible solutions – some already functioning, others possible – for each of the barriers.

This research found that unless efforts are devoted to addressing these underlying barriers, the widespread adoption of adaptive designs for clinical trials will not occur. The thesis concludes with recommendations and suggestions for future research.

Thesis Advisor: Andrew W. Lo
Title: Charles E. and Susan T. Harris Professor of Finance

Thesis Reader: John Van Maanen
Title: Erwin H. Schell Professor of Management

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Ayesha N. Khalid
Cambridge, Massachusetts
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CHAPTER 1. Introduction

"It is not the strongest of the species that survive,
nor the most intelligent,
but the one most responsive to change." [1]

In the United States, traditional clinical trials have a long history of involving industry, academia, and government institutions (such as the National Institutes of Health (NIH)) to address relevant medical questions and develop novel therapeutics. For a variety of reasons, clinical trials have become extremely expensive, have encountered difficulty enrolling patients, and utilize inefficient implementation methods. Nevertheless, patient advocacy groups clamor for better, less costly treatment alternatives. Recently, some groups have pressured the Food and Drug Administration (FDA) to provide faster, more streamlined protocols to accelerate the pace of therapeutic drug development.

In response, the FDA drafted guidelines to promote adaptive designs for clinical trials. These guidelines give researchers some flexibility to redesign their trials at interim stages and thereby reduce inefficiencies. With such guidelines in place, this study explores reasons why the adaptive design methodology is not more widely adopted.[2]

1.1 Thesis Aims

This thesis identifies major barriers that hinder the adoption of adaptive design models of clinical trials. It is not my intention to ascertain the best type of adaptive

[1] Charles Darwin, Taken from: On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life. Dated:1859.

[2] To facilitate a targeted discussion, this thesis focuses on clinical trials related to drug development.

design or advocate the best mechanism for funding. Rather, my aim is to explore why, given the steps taken by the FDA, the needed paradigm shift has failed to occur. Key conditions obstructing adoption may serve as leverage points to aid in the implementation of adaptive design and accelerate the pace of drug discovery.

1.2 Methodology

I conducted a review of relevant literature that focused on "adaptive design" and "clinical trial" published between 1990 and February 2014. Articles were limited to those written in the English language, and were sorted using the keywords "challenge(s)" and "hurdle(s)" to target articles of interest. Searches indices included Pubmed and NCBI. I identified more than 150 articles.

In addition, interviews were conducted with leaders in industry, academia, and hospital management in Cambridge, New York City, and San Francisco. Subjects were identified based on their expertise in clinical trials, as funded clinical researchers, those holding senior positions in pharmaceutical or biotech firms, or heads of a patient advocacy organization. Appendix A provides a list of types of interviewees.

Thirty interviews were conducted, and results were collated into a series of barriers rather than as itemized individualized responses. In instances where an interviewee felt comfortable being identified as the source for a particular quote or figure, that person is identified by their initials in parentheses following the quote. Otherwise, anonymity is preserved.

I conducted all interviews in 45-minute sessions with no questions provided in advance. Answers were recorded by hand in annotated fashion. All interviewees were

asked five standard questions (see Appendix B), followed by an open-ended conversation that allowed them to expand on their thoughts about adaptive design. The final ten minutes of each interview sought their recommendations for the future direction of clinical trial research. Common barriers emerged from these interviews, which are synthesized in a systems dynamics model.

Chapter 1 provides an introduction to the topic, including an overview of clinical trial design, followed by the aims of the thesis and an outline. Chapter 2 defines the term "adaptive design of clinical trials" and discusses its utility. Chapter 3 frames the dilemma of why adaptive trials are not being adopted. Chapter 4 discusses barriers that may be preventing such adoption, and Chapter 5 provides some solutions that were suggested or have been tried. Chapter 6 provides a summary, including a systems dynamics model that synthesizes the barriers and solutions for acclerating the pace of adoption. The chapter concludes with recommendations.

CHAPTER 2. Defining Adaptive Design

U.S. regulations mandate that healthcare products undergo rigorous analysis to meet public safety standards. Initially, the FDA was concerned with public safety and minimizing risk. In recent years, however, given the amount of money invested in the U.S. pharmaceutical industry, the FDA has become increasingly concerned with the declining number of curative medications that are manufactured and brought to the U.S. market.[3] Consequently, several patient groups in the U.S. are clamoring for change in drug development models.[4] Historically, drug development involved utilizing randomized controlled groups to assess a particular dosage of a medication. This is a lengthy and expensive process. Recently, the FDA began to allow the trial of adaptive designs as a method of accelerating the pace of discovery.

The origins of *adaptive design of clinical trials* can be traced back to the 1970s when the FDA began to explore randomized design. At that time the FDA also introduced the concept of design of adaptive trials.[5] Among the categories of adaptive

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[3] Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski. "The price of innovation: new estimates of drug development costs." *Journal of Health Economics,* 22(2):151–185, 2003.

[4] M.A. Proschan, K.K.G Lan, and J. Wittes. *Statistical Monitoring of Clinical Trials: A Unified Approach* (New York: Springer, 2006). See also: FDA, *Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics* Available from: <http://www.fda.gov/downloads/Drugs/.../ Guidances/ucm201790.pdf>. Also, S.M. Paul, D.S. Mytelka, C.T. Dunwiddie, et al. "How to improve R&D productivity: The pharmaceutical industry's grand challenge." *Nature Reviews Drug Discovery*, No. 9, 2010: 203-214.

[5] FDA, http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf>. Also: W. Brannath, P. Bauer, W. Maurer, M. Posch. "Sequential tests for noninferiority and superiority." *Biometrics* 59, 2003: 106-114. Also: S. Chow, M. Chang. *Adaptive Design Methods in Clinical Trials*. Boca Raton, FL: Chapman & Hall/CRC, 2007. Also: M. Krams, K.R. Lees, D.A. Berry. "The past is the future: innovative designs in acute stroke therapy trials," *Stroke* 36; 2005: 1341-47.

trials, two types are routinely cited: group sequential designs, and sample size re-estimation.[6]

The FDA defines an adaptive design of a clinical trial as "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study."[7]As noted in Exhibit 2.1 below, modifications of adaptive designs are *planned,* and are performed only at pre-determined time points. For example, the design can be adapted to modify the number of patients enrolled in the study, referred to as "sample size re-estimation." Possible allowed modifications include:

- eligibility criteria
- study dose
- treatment duration
- study endpoints
- laboratory testing procedures
- diagnostic procedures
- criteria for evaluation and assessment of clinical responses.

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[6] S. Coburger, G. Wassmer. "Sample size reassessment in adaptive clinical trials using a bias corrected estimate," *Biometrical Journal* 7; 2003: 812-825. See also: J.S. Denne. "Sample size recalculation using conditional power." *Statistics in Medicine* 2; 2001: 2645-2660. Also: H. Müller, H. Schäfer. "Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and of classical group sequential approaches," *Biometrics* 57; 2001: 886-891. Also: C. Jennison, B.W. Turnbull. *Group Sequential Methods with Applications to Clinical Trials*. Boca, Raton, FL: Chapman & Hall/CRC, 2000.

[7] FDA. Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics. 2010. See: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf>.

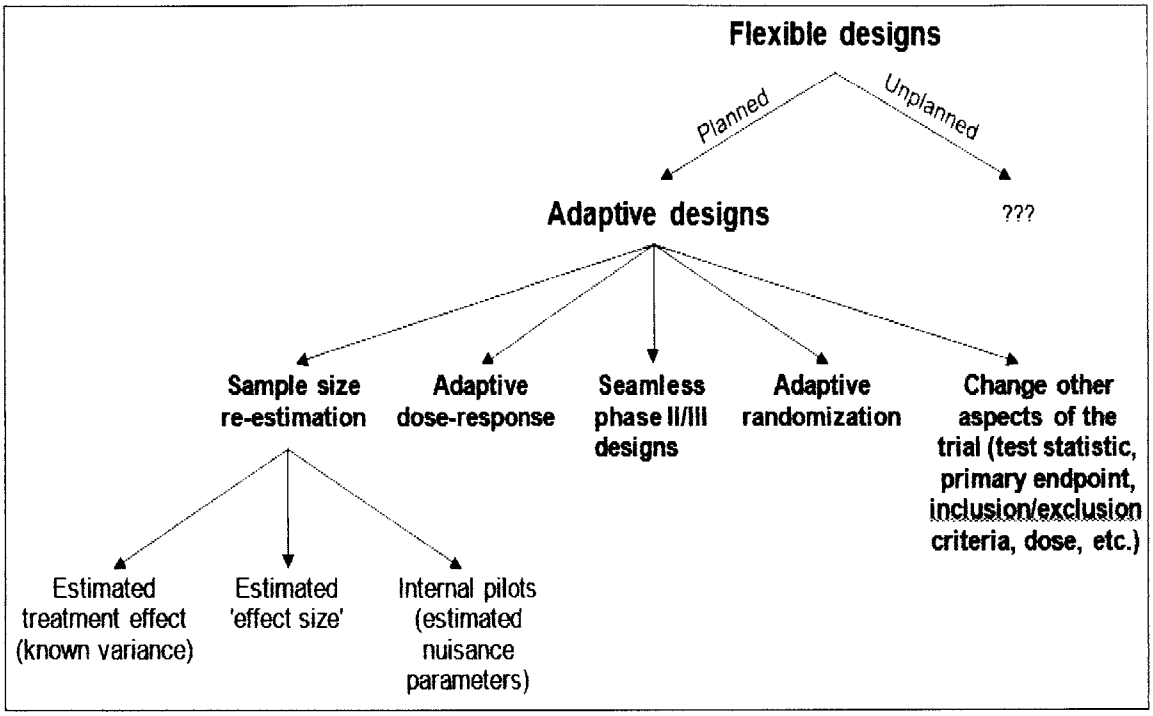

Exhibit 2.1 Adaptive Design Modifications

Source: Coffey and Kairalla, p.2.

The statistical design of an adaptive clinical design involves performing a Bayesian analysis upfront and then conducting one of the following modifications as an accepted adaptive approach:

- randomization
- study design
- study hypotheses
- sample size
- data monitoring
- interim analysis
- statistical analysis plan
- methods for data analysis

This list illustrates the complex nature of the statistical design of an adaptive clinical trial (ACT).[8]

The FDA recently expanded its recommendations to include an accelerated path to approval for drugs that address "unmet needs for serious or life-threatening illnesses."[9] However, recent studies have shown a low adoption rate, with a relatively small percentage of clinical trials making use of the accelerated pathway. For example, a 2005 investigation by the Pharmaceutical Researchers and Manufacturers of America (PhRMA) looked at the implementation of adaptive designs in clinical drug development.[10] PhRMA found that while many companies realize the potential advantages of using an adaptive design, there are significant operational barriers to implementation. As a result, the industry adoption rate is only 20%.[11] Further, the ACTs that are used take a simple approach. At a meeting of early-stage-pharmaceuticals chief medical officers, most companies touting their success of adaptive designs actually made relatively small adoptions, such as re-estimating the number of patients enrolled. These companies did not try to develop a wholly different clinical trial design based on the

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[8] J.A. Quinlan, M. Krams. "Implementing adaptive designs: logistical and operational considerations." *Drug Inf J* 2006; 40 (6): 437-44. See also: J. Quinlan, B. Gaydos, J. Maca, et al. "Barriers and opportunities for implementation of adaptive designs in pharmaceutical product development." *Clin Trials*. 2010;7:167-173. Also: V. Dragalin, B. Bornkamp, F. Bretz, et al. "A simulation study to compare new adaptive dose ranging designs," *Statistics in Biopharmaceutical Research* 2010; 2(4): 487-512.

[9] FDA. "Challenge and opportunity on the critical path to new medical products." March 2004. Available at: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf>. Accessed September 14, 2011. See also: FDA. "Critical path opportunities report." March 2006. Available at: <http://www.fda.gov/downloads/>.

[10] C. Chuang-Stein, M. Beltangady. "FDA draft guidance on adaptive design clinical trials: Pfizer's perspective." *J Biopharm Stat*. 2010; 20 (6):1143-9. See also: T. Cook D.L. DeMets, "Review of draft FDA adaptive design guidance," *J Biopharm Stat*. 2010; 20 (6):1132-42.

[11] J-M. Fernandez, R. Stein, and A. Lo. "Commercializing biomedical research through securitization techniques." *Nature Biotechnology*, 2012; 30: 964–975. In a panel discussion at the CMO Summit in Boston in May 2014, Merck was cited as having up to 40% of its clinical studies having some *adaptive* component.

factors outlined above. Dr. Kenneth Getz, moderator of the panel, questioned if a lack of understanding of how to implement statistical models was the primary barrier to implementing ACT design.

2.1 Why Should Researchers Employ Adaptive Design?

Given the complexity of establishing an ACT, it is valid to discuss *why* researchers should employ these methods. One compelling justification is that ACTs are more cost-effective, shorten the development cycle, and reduce overall costs. Unlike standard clinical trials, adaptive design incorporates "futility analysis," which permits companies to stop trials early when a possible treatment does not demonstrate benefit. This results in greater cost savings, as shown in Exhibit 2.2.

	Mid-Size Company	Large Company
Direct Cost	$5 - $10MM	$20 - $50 MM
Indirect Cost	$15 - $35 MM	$50-$100MM

Exhibit 2.2 Savings from Early Terminations of Clinical Trials

Note: According to Tufts Center for the Study of Drug Development (CSDD) modeling, savings from early terminations may be tremendous.

Source: Copyright, used with permission from Tufts CSDD.

Another source of cost savings comes from minimizing protocol amendments. Protocols must be developed for clinical trials in order to establish rules for consistent administration of a drug (the time of day, with or without food, etc.) Changing protocols in the context of an ongoing trial is expensive, as it involves preparation of FDA filings,

coordination with hospitals and doctors, and the involvement of lawyers. However, utilizing an adaptive design means protocol amendments are minimized. As shown in Exhibit 2.3, this can produce significant cost savings.

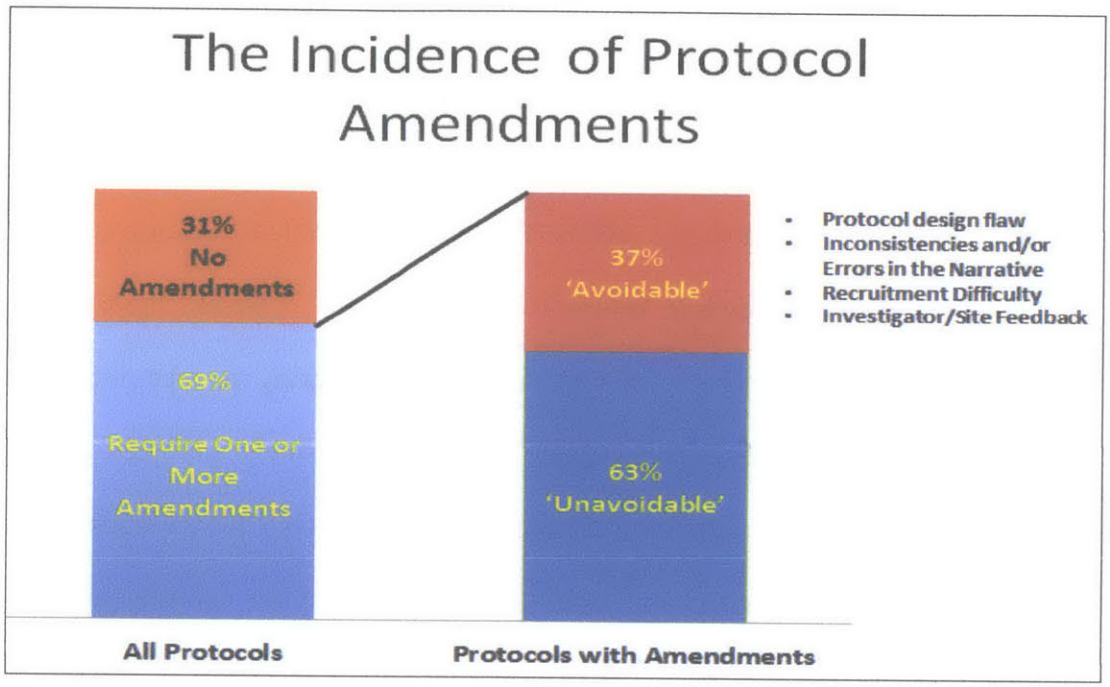

Exhibit 2.3. Incidence of Protocol Amendments

Note: According to Tufts CSDD 2010 analysis of 3,596 amendments and 19,345 changes. Source: Copyright, with permission from Kenneth Getz, Director of Sponsored Research Programs & Research Associate Professor, Tufts Center for Study of Drug Development.[12]

Ethical considerations also provide another justification for adaptive design. When using an adaptive design, pharmaceutical companies can minimize the number of patients undergoing the trial. Given the risks of such trials (when safety and efficacy have not yet been established), this design exposes the fewest number of patients to possible risk.

[12] Protocol amendments discussed in: Getz, KA and Zuckerman R, et al. Measuring the Incidence, Causes, and Repercussions of Protocol Amendments. *Drug Information Journal*, Vol. 45, pp. 265–275, 2011.

CHAPTER 3. The Current Dilemma

"We are now in a major inflection point in health care and whereas single product innovation is commonly seen in healthcare, system-driven innovation is harder to achieve"[13]

Both the pharmaceutical and biotechnology industries are facing significant challenges to their business models, including the so-called "patent cliff" (the phenomenon that occurs when a drug patent expires and soon after there is an abrupt drop in sales)[14]. The industry claims that patent expirations are expected to result in $209 billion of lost revenue between 2010 and 2014.[15] Overall, there is a decreased tolerance of risk among investors, with 2008 marking a precipitous decline in shareholder value of over US$850 billion. Increasingly complex processes for "translating" scientific discoveries into clinically relevant therapeutics have made it difficult for pharmaceutical and biotech companies to replace expiring patents with new molecular therapies.[16] The cost of drug development and new molecular entities (NMEs) has skyrocketed to approximately US$1.2 billion per drug (see Exhibit 3.1).

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[13] Gigi Hirsch, Executive Director, Center for Biomedical Innovation and Program Director, NEWDIGS.

[14] DGC. Pharmaceutical Sector Inquiry Preliminar Report. Technical report, European Commission, Brussel, Belgium, 2008. <http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/preliminary_report.pdf>.

[15] A.W. Lo, and S.V. Naraharisetti. "New Financing Methods in the Biopharma Industry: A Case Study of Royalty Pharma, Inc." December 15, 2013. Available at: <http://ssrn.com/abstract=2330089 or http://dx.doi.org/10.2139/ssrn.2330089>. See also: S.M. Paul, D.S. Mytelka, C.T. Dunwiddie, et al. "How to improve R&D productivity: The pharmaceutical industry's grand challenge." *Nature Reviews Drug Discovery* 2010; 9: 203-214.

[16] F.R. Lichtenberg. "The impact of new drug launches on longevity: Evidence from longitudinal, disease-level data from 52 countries, 1982–2001," *International Journal of Health Care Finance and Economics* 2005; 5 (1): 47-73.

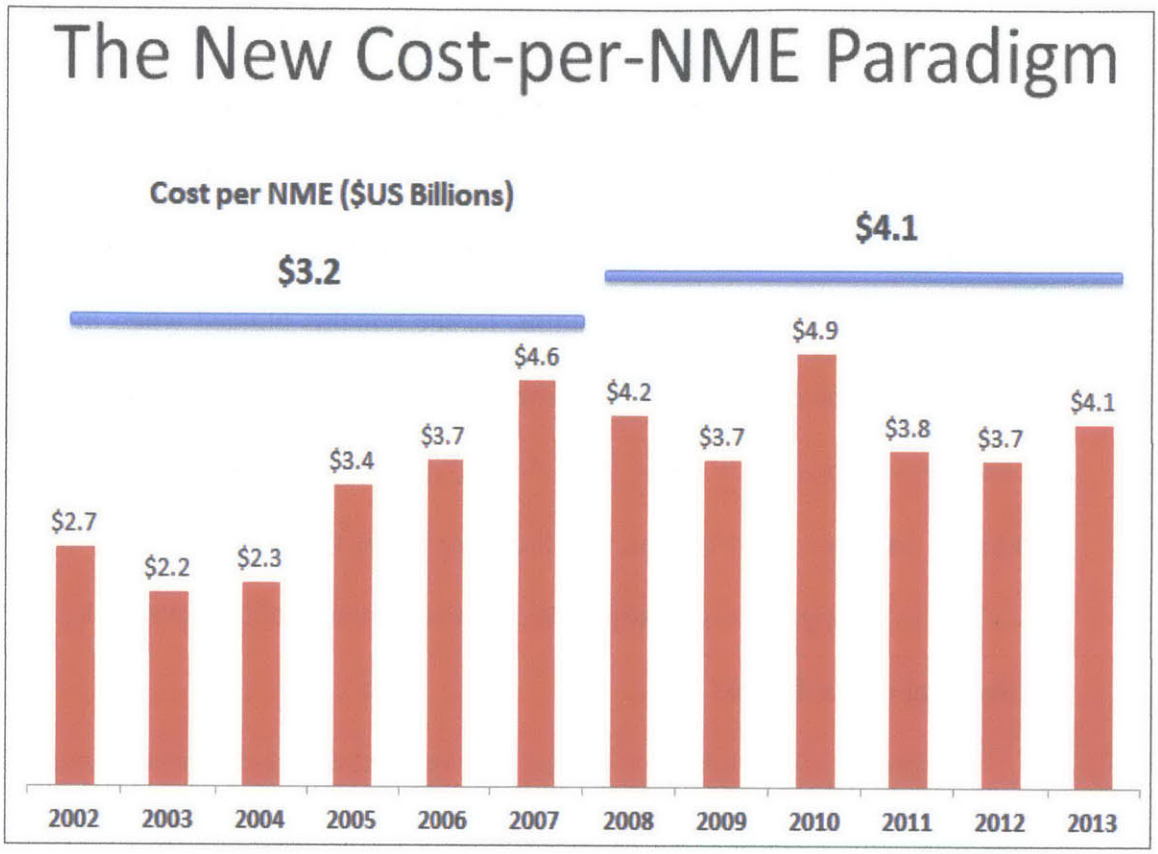

Exhibit 3.1 The New Cost-per-NME Paradigm
Expenses presently associated with each new molecular entity (NME).
Source: Copyright, with permission from Kenneth Getz, Director of Sponsored Research Programs & Research Associate Professor, Tufts Center for Study of Drug Development

Decreased productivity in drug development, combined with rising costs, is leading to questions about whether novel financing mechanisms are needed.[17] The FDA has tried to stimulate innovation by encouraging new models of development. However, companies view this as a "risky proposition" in terms of assuring that their drug will be approved (Anonymous). As set forth above, adoption rates of adaptive design hover at or below 20%.

[17] J-P. Garnier. "Rebuilding the R&D engine in big pharma," *Harvard Business Review*, 2008; 86 (5): 68–76. The model summarizes the most common themes identified in interviews as a causative factor that inhibits greater adoption of adaptive designs of clinical trials.

CHAPTER 4. Interview Findings: Barriers

To assess the responses provided by interviewees, it is important to understand the traditional method of clinical trial design. In Phase I, the researcher typically reviews unblinded data observed during the clinical trial. At the end of Phase I, he/she stops, reviews, and plans. When Phase II begins, he/she remains blinded when interim results are available. At the end of Phase II he/she again stops, reviews data, and plans for Phase III. The cycle repeats for Phase III. These phases are referred to by researchers as "windows" and they exist to maintain the integrity of the research and to protect from bias. There is no opportunity to adjust dosing, make minor adjustments to design, or stop the treatment if it is deemed futile.

In contrast, with adaptive design, the researcher pre-determines specific times when he/she will "look into" the window to assess the next best option.

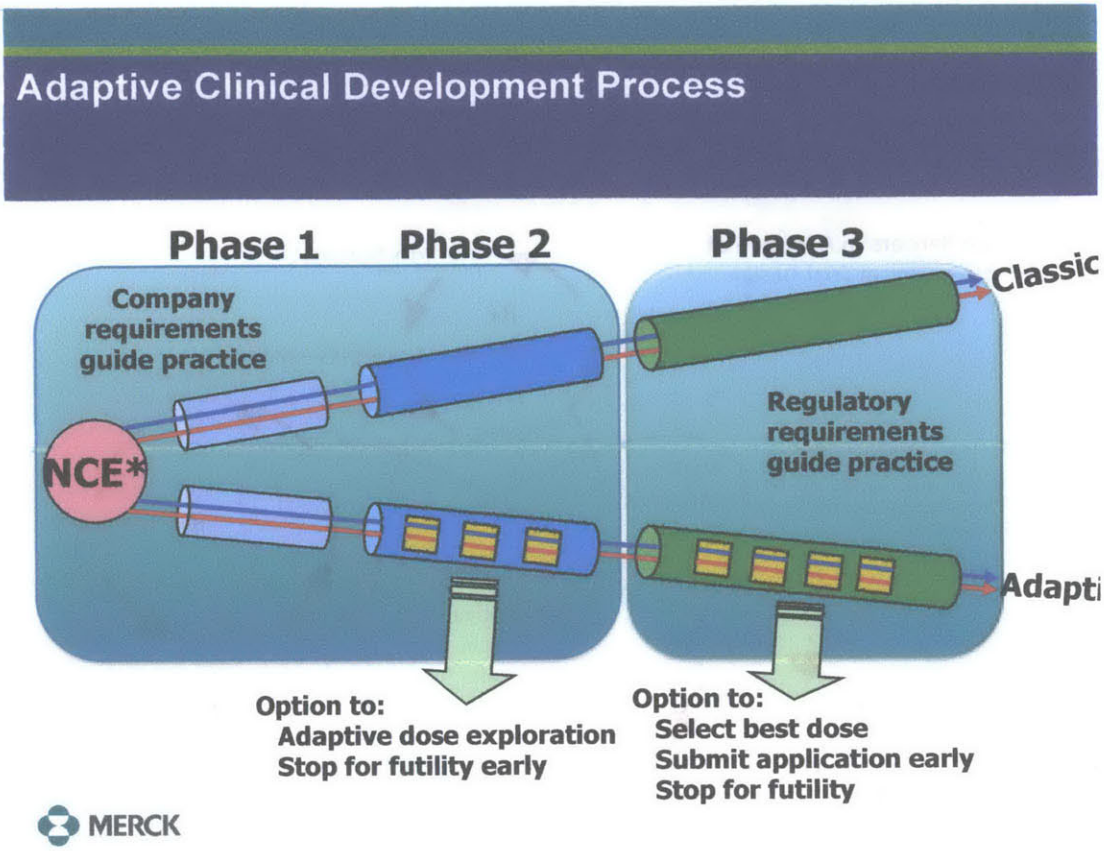

Exhibit 4.1: Window into the trial while it's in progress

Source: Merck™. Presented at "Patients as Partners" conference, The Conference Forum, NewYork City, February 2, 2014.

The interview findings coalesced around six identified barriers that obstruct the adoption of adaptive designs of clinical trials:

1. Funding
2. Logistics
3. Regulation
4. Communication
5. Collaboration/Partnerships
6. Patients

Exhibit 4.2 illustrates the dynamics surrounding each barrier and how they interact to delay the adoption of adaptive designs. Each barrier is discussed in the following sections.

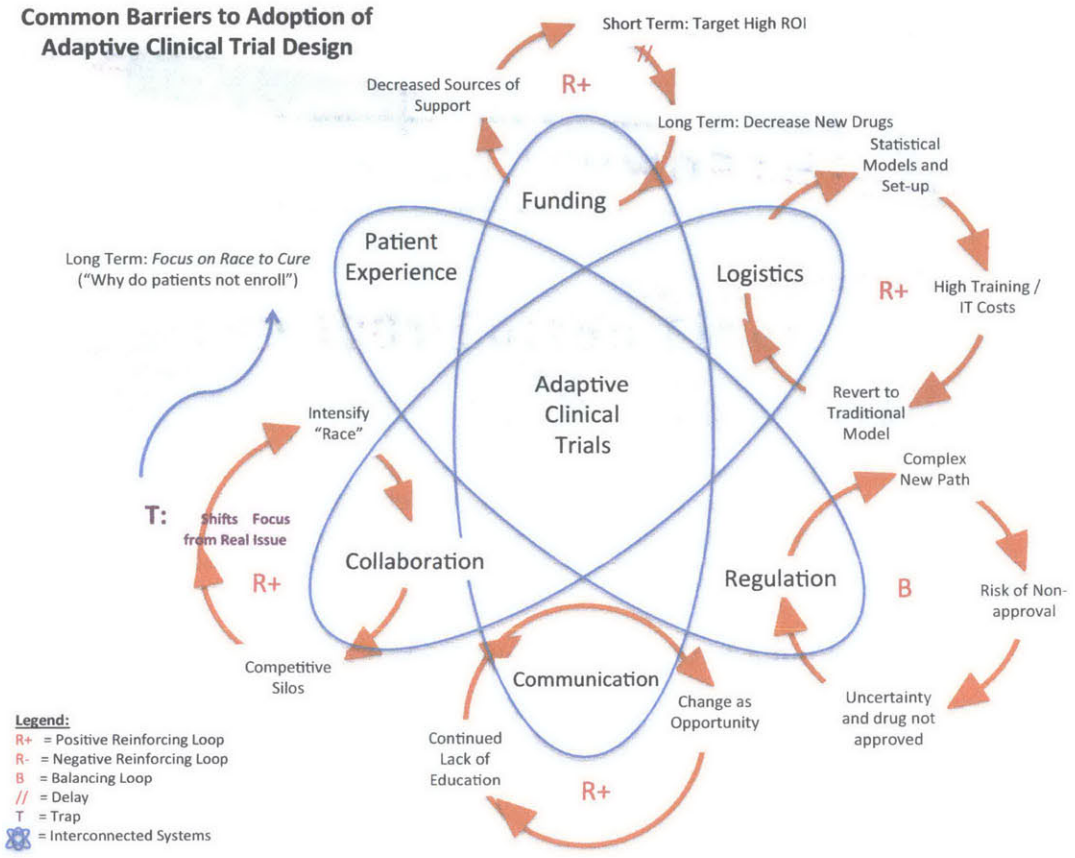

Exhibit 4.2 The Adaptability Network

Source: Created by thesis author.

4.1 Funding

Competition for dwindling government grants is a key factor that limits collaboration among researchers (including adoption of adaptive design of clinical trials). One interviewee noted that academia is notoriously "dysfunctional in its lack of collaboration" (Anonymous). With increasingly fierce competition for NIH grant funding and the U.S. government sequestration that led to an additional reduction of 700 competitive grants, academic researchers must compete to obtain grants for salary support and academic positions.

Over 85% of pre-clinical research is conducted by academics. For professors, being the first to discover and publish is the key to success for promotion and tenure within academic institutions. Young academicians must demonstrate research productivity, typically defined in terms of quantity of publications. The quality of submissions is important, but secondary to the *number* of publications. The competition to publish and be promoted is fierce. Hence, there is little incentive to share data or collaborate in larger multi-institutional trials. Instead, to procure grants, academics tend to select short-term projects with high ROIs that guarantee eventual publication. This has a profound effect on the training young academics receive and the types of skills they develop.

NIH grants require a specified format, and as one interviewee stated, a generation of scientists is being trained to "write an ROI grant and to replace imagination with desire to get funded . . . breeding a generation of scientists who are formulaic in their approach." The specified methodology of grants may "squelch the spark of innovation and creativity" required for groundbreaking research" (Anonymous).

Several academicians stated that the NIH is "risk averse in its approach to funding" (JWK, SAQ, CC), and that the majority of NIH funding goes to established researchers with an solid track record (TLS, SAQ, CC, JWK). Smith, a physician and senior academic investigator, said that funding for "small- to medium-scale pilot projects is the challenge." Many young researchers fall over the "academic research cliff" and leave research altogether. Adding to this is the prohibitive cost of conducting research in academic institutions that maintain a high overhead, some as high as 40% (CC, KN).

In financial markets and using financial engineering tools, asymmetric information often provides opportunity for profit and in the case of clinical trials, the asymmetry lies between stakeholders who are running the trials (i.e., big pharma and large academic medical centers) and the consumers within the system (patients, clinical providers who are enrolling the patients). The funding loop shown in Exhibit 4.2 above shows why funding limitations lead to decreased development of new drugs. If this tide is not stemmed, over the long term this will lead to fewer novel therapeutics.

It is essential to frame the question of funding mechanisms within a larger ecosystem of adaptive design innovation. The interviews revealed that decreased sources of revenue cause companies to target high ROI. However, limited targets that overlap will lead to fewer new drugs in the long term.

4.2 Logistics

"I have sat on the executive board of a CRO for twenty years and never once has a conversation about adaptive design come up . . . not once."(Anonymous)

The logistics of implementing an adaptive trial were a frequently mentioned difficulty. The key is knowing when to adapt. Determining this requires consultation with a strong operations team that works closely with the statisticans to design the adaptive trial so that the analysis follows a logical flow. Most clinical scientists have little training in statistics and, as both Dr. Camargo and Dr. Gigi Hirsch stated, most clinician scientists are "poorly equipped" to handle a question about how to set up the trial's adaptation. In fact, several interviewees stated that many researchers "lack education about proper statistical design" in general (CC, TLS, RJG). Intimidation stemming from the need to do computer modeling of adaptive designs precludes many researchers from taking part. Another operational challenge is the time constraints facing academic investigators (JWK, CC, SAQ, TLS, GM).

Another operational challenge is the time constraints facing academic investigators (JWK, CC, SAQ, TLS, GM). As Wiley ("Chip") Souba[18] eloquently stated, an academic surgeon has to divide his/her time between seeing patients, the operating theatre, and conducting meaningful research. With such stringent constraints, "the wheels have to be greased ahead of this individual so that all the ... bureaucratic hurdles ... such as hiring a research nurse and submitting an IRB application are all taken care of" (CC). For physician researchers, conducting adaptive clinical research increases the complexity

[18] Dean, Geisel School of Medicine, Dartmouth College.

of their work by orders of magnitude. Logistics are the "most difficult hurdle to overcome once you have funding" (CC).

In order to handle this, flow of the work is very important, and the following pieces are a necessity when setting up any clinical trial:

- relevant data on progress
- processes in place for conducting the interim analyses
- decision points and knowing how to implement them
- access to timely information

Hirsch discussed workflow in adaptive trials in terms of the *sequence* followed. She argued that traditional trials are carried out in a linear fashion; the challenge with an adaptive trial is implementing steps with built-in feedback loops to help make decisions at key points. The feedback may be in the form of a computer simulation as a planning scenario. For example, each time a Phase II or III "seamless integration method is employed, it involves group sequencing and generates a multi-drug portfolio that monitors the drug's progress in real time" (GH). The drug development process is often depicted as a funnel, as shown in Exhibit 4.3.

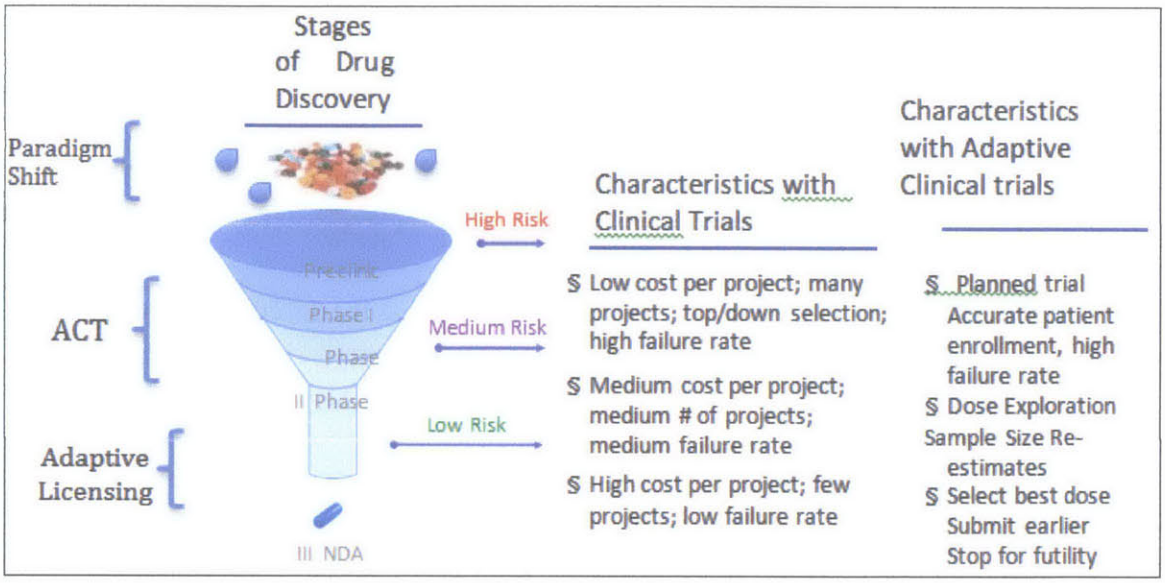

Exhibit 4.3 Paradigm Shift Model

Source: Lo & Naharesetti, 2014: 15. Adapted by the thesis author, with permission from authors.

Clinical trials usually affect Phases II and III (at bottom of funnel). The trials require significant set-up and scenario planning, and the inflow into Phase II is still limited (depicted as water droplets) as it moves into the funnel. Similarly, the output of clinical trials involves getting through Phase III and the New Drug Approval (NDA), which results in the narrowing depicted as a bottleneck. Note the contrast between traditional clinical trial design and the ACT design. On the left, parentheses indicate that ACTs affect Phases II and III most frequently, while adaptive licensing[19] affects late-Phase III/NDA. My interviews focused on assessing the pre-clinical phase and how to allow for more inflow.

Adaptive licensing addresses regulators' concerns that there be minimal risk to patients. This makes it possible to widen the outflow of the funnel. It alters the process to allow a new target drug to be tried in a specific patient population. Adaptive licensing may help regulatory agencies feel comfortable about slightly relaxing their tight control

[19] *Adaptive licensing* is defined as a prospectively planned approach to drug licensing, ideally done in concert with prescriber and coverage decisions.

on market release. The caveat is that the FDA receives feedback on all patient data to assess safety and side effects within that population. The real question is how to get more inflow by aligning financial incentives with the ability to continuously pilot.

In Phase II, an adaptive design helps to elucidate dose- response relationships, whereas in Phase III, adaptive design helps to adjust the sample size or stop a trial early that is deemed "futile."

4.3 Regulation

"In order for adaptive designs to succeed, the FDA has to be able to trust that the pharmaceutical companies maintained the integrity of the trial...We broach this topic by doing a good job and hiring an outside consulting company to analyze the interim results on our behalf. This separates the sponsor of the trial from any knowledge of the interim results. This then helps convince the FDA that the results from the entire trial will be valid."[20]

Regulatory uncertainty emerged as a common theme from interviews. Sean Herron, a White House Innovation Fellow currently at the FDA, mentioned that coming in as an outsider, it was apparent that the primary goal is the safety of the public. To produce effective regulations, regulators must understand the basic processes of a particular drug, its marketing, its toxicology and biopharmaceutical issues, as well as clinical urgency that may impact its development. Herron mentioned that the last few decades have seen a marked shift as regulatory agencies become open to ACTs, and innovation is openly discussed with him at the FDA. Following its Draft Guidance on adaptive design clinical trials, the FDA now encourages extensive interaction to ensure appropriate feedback.

Another, less positive, view is that a great deal of confusion surrounds ACTs, and a general perception that the FDA sends "mixed messages" (Anonymous). One interviewee stated that the FDA creates "hoops to jump through it is and difficult to believe that the guidelines will not change partway through the study" (Anonymous). Thus his company feels more comfortable with traditional clinical trials, despite the fact that it is an innovative Boston-based biotech firm.

[20] Dr. Jerald Schindler, Senior Executive, Merck.

In assessing the regulatory barriers to the adoption of adaptive trials, the challenge is to understand exactly where the FDA is positioned on the subject of acceptance of clinical trials. Why is the FDA so hesitant in some settings? Critics of adaptive trials say that in earlier pivotal trials (for example, ECMO) the adaptation was too early and proper randomization was not carried out.[21]

The exploratory stage of drug development is attractive given that futility analysis can be easily performed as well as planned flexibility in dose-finding protocols. However, when adaptive trials can be implemented according to FDA standards remains unclear. Recently, the Tufts University's Center for Clinical Trials reported that regulatory agencies are open to innovation and planned ACTs. In contrast, interviews with industry leaders revealed that "regulatory functions are risk-averse to adopting sophisticated adaptive design approaches" and for that reason firms are awaiting greater clarity from the regulatory agencies.

In the interviews, senior academicians and industry leaders agreed that the prime FDA directive is to remove risk from drug development and keep the public safe. Yet, there is a question as to whether the FDA handles requests for adaptation effectively. One question to Herron was whether there is awareness among the FDA leadership that the complexity of regulatory language makes it difficult for industry or academics to understand. This relates to another theme of conversational domains, but it also emphasizes the difficulty the FDA faces when it is *trying* to be helpful, yet the public's

[21] ECMO (extra-corporeal membrane oxygen) has been critiqued as an example of a trial that utilized game theory in its randomization design. ECMO is a way to filter a human being's blood in order to re-supply oxygen. It was assessed in infant, and the first infant who received conventional treatment died. The next one was randomized to the ECMO arm and survived. Subsequent infants were randomized to the ECMO arm, and it was declared to be better treatment. Critics of the study design are critical that the adaptation was far too early and improperly done.

understanding of FDA-proided information is limited due to its inherently complex language. In its defence, the FDA recently made additional efforts to open source its knowledge, but its complexity remains.

Another area of interest from the interviews was the seamless design[22] of clinical research relating to Phase II and III integration with adaptive design. Critics warned that using seamless design can be costly given that large sample sizes may be required that may still generate less confidence in the answer.[23]

Overall, it appears from the interviews that the FDA itself, as well as data monitoring boards and other regulatory bodies, are struggling with their role in the new era of clinical trial design.

4.4 Communication

"It takes several years to simply master communication; only then can the meaningful work begin." (Souba)

Many articles in the literature discuss the "patent cliff" and its financial implications. However, there is also an "academic researcher cliff." Many young clinicians enter academia with the intention of carrying out funded research. Souba points out that it takes years to master the systematic language in funded academic research. This includes the realization that conducting a Randomized Control Trial (RCT) funded by the NIH involves the language of scientists; or that writing a grant proposal requires

[22] "Seamless Design" means there is no long pause after the interim analysis (e.g., between two independent studies, or between stages of a single study), and data collected both before and after the interim analysis are used in the final analysis. It describes the process of combining data in the final analysis, and is an element of all adaptive designs.

[23] J. Maca, S. Bhattacharya, V. Dragalin, et al. "Adaptive seamless phase II/III designs: background, operational aspects, and examples." *Drug Inf J* 2006; 40: 463-73.

the applicant to follow a specific, technocratic format. The academic research cliff implies that while many academics hope to fund a research career, few are able to do so. This is a great loss to the wider clinical research engine, and has continued largely unchanged. When pressed as to *why* this occurs, Souba explained that in the first several years, a researcher has to learn to speak and write in a language that statisticians and basic scientists understand. Given the complexity of statistical analysis and technical formatting, it soon leaves behind those who cannot master it quickly.

Applying this analogy to the adoption of adaptive design reveals a similar situation: statistical conversations around trial setup, and the subsequent Bayesian analysis proceed in such technical verbiage that most clinicians and scientists find it difficult to understand. Recent articles citing the need for not one but three statisticians on each study suggest, I believe, an unrealistic approach to dealing with this issue. To increase adoption of adaptive design, more personnel must be trained, and the best way for this to become widespread is for the methodology be simplified to basic statistical language and taught to multiple stakeholders, not by introducing more statisticians.

Interviewees suggest that educating personnel on the importance of adaptive design and how to put simple models in place will enable a reinforcing cycle of trial completion. As adaptive trials becomes more mainstream, the education of clinical researchers will allow scalable solutions and lead to a clinical trials "dashboard." However, in order to have such a system work, the IT stakeholders need to speak a language that other stakeholders understand.

The interviews helped me uncover the fact that scientists are inherently "adaptive" in their thinking. This may mean clinician scientists can be re-engaged by

creating a new funding model (SAQ). The process of scientific inquiry requires asking questions and—based on the data—modifying assumptions and retesting hypotheses. Scientists often enter research for the "pure joy and creativity associated with scientific discovery" (SAQ) and as one interviewee pointed, scientists would prefer above all to doing good science.

One interviewee (SAQ) proposed a model that outlines steps for guiding exploratory research:

1. Begin with the epidemiologic analysis of the clinical disease.
2. Use observational cohort analysis and set up multiple small-scale pilots to generate queries that direct the next series of studies.
3. Set up clinical trials that specifically answer questions of interest in concert with a good statistical evaluation.
4. Use the pilot data generated to apply for large-scale NIH funding. Both Dr. Langer and Dr. Souba noted that many young academics are not given the resources to fund such pilots.

Another interviewee said that an equitable system should be built with win-wins for multiple stakeholders, which removes unhealthy competition. Top priorities for research are identified. A call to action requests that any consortium create a drug that is superior to what is available for this disease right now, and accomplish it first, allowing partnerships between pharma, industry, and academia. Should any group succeed, they have exclusive rights to sell in this drug class, and the incentives of these exclusive rights should be huge. In order to get these rights, the drug companies should be encouraged to pool resources together with other stakeholders.

4.5 Collaboration

"Few individuals are comfortable shining in reflected light." (Souba)

A major barrier to adaptive design is the lack of incentives that encourage major stakeholders to work together rather than compete. A common theme that emerged in the interviews is the need for more collaboration and fewer siloes in research. Hirsch, a physician and academic at MIT, and Una, an angel investor in healthcare, were asked: "How is innovation dffused into a system when the system is dysfunctional and communication is limited?" Hirsch is convinced that the traditional model of linear, sequential, siloed innovation must change. It is critically important that the innovation process allow key stakeholders (e.g., industry, regulators, payers, clinicians, patients, etc.) to interact around a new product earlier and more frequently throughout the product lifecycle. Una believes that if we take a systemic approach to innovation and view the macro level, two hurdles must be overcome: (1) current policies regulating clinical trials, and (2) current standard processes of execution. In terms of policy, regulatory agencies have to provide clear incentives for industry and academia in order to make use of the adaptive design of clinical trials.

From a scientific standpoint, key levers at each step should be discussed. Hirsch elaborated by saying that if the system is dysfunctional in utilizing resources and its approach, then increased funding may be premature until the process is carefully analyzed. She noted that results stemming from recent work would recommend extending this concept to encourage stakeholders to coordinate prospectives iteratively throughout

the product lifecycle for better coordinated and adaptive approaches to development, approval, reimbursement, and product use. She notes: "If stakeholders interacted earlier and more frequently with executives, our work suggests that this can help reduce time, cost, and risk, and increase predictability throughout the lifecycle." Many interviewees echoed the view that while funding is of paramount importance, the system is in flux and must first be re-configured to allow adaptive trial design (JWK, RG, CC, TLS).

In thinking about the current process of traditional clinical trials, a linear flow through a stage-gate process allows silos to exist, and as Hirsch notes, "increasing the funding while maintaining such a framework may not solve the overall issue of building trust and encouraging collaboration." She elaborated: "The current process is linear and stage-gated for drug design. It proceeds from left to right with scientific inquiry → molecular investigation and findings → clinical trials with phases (I, II, III)→ new drug approved as NME → market release with little feedback." She continues: "The major problem with left-to-right innovation is that it proceeds without a deep understanding of what the market/customer needs. That need is often not a monotherapy but actually a product or service solution." Hirsch and others recommend beginning with end-stage therapeutic targets to define goals and tailor the process, thereby aligning all shareholders around a shared vision of the desired outcome.

4.5.1 Academic/Industry Partnerships

Several academic institutions have created financial arrangements to develop therapeutics in partnership with pharmaceutical companies. For example, Yale University and Gilead Pharmaceuticals are collaborating to provide cancer researchers with US$40

million over four years (2010–2014). In return, Gilead retains the right to license the technologies first. However, while this is a good deal design, simply allowing the company to have right to technologies may not be enough to encourage *true collaboration* in terms of the scientific research. Similarly, Johnson & Johnson's Innovation Center seeks collaborations with academia. J&J's investment capital and the academic demand for funding represents a ripe financial opportunity. However, as several interviewees stated, J&J's scouts target successful researchers and investigators who are already well-funded (TLS, KN, SAQ, CC). Instead, academia needs ways to "ensure that academicians do not run out of funds just as they are gaining momentum, especially if their research is promising." (SAQ)

At present, in academia, as clinical investigators complete studies and procure funding, they are promoted based on number and quality of publications. This leads to fierce competition for tenure. Instead, an incentivized system that rewards collaboration on clinical trials as one pillar of promotion would be the first step.

Like NIH, J&J is also "risk averse," so it is not interested in becoming involved in ACTs. Instead, the J&J Innovation Center is seeking technologies that can be absorbed rapidly into J&J's already-existing product lines. This further reinforces the feedback loop in the systemic map where novel therapeutics are not encouraged through early-stage research.

4.6 Patient Experience

In the view of the many participants in the healthcare environment, the impetus for change may have to come from the end consumer, i.e., the patient. Scientific analysis

of the patient experience reveals that more than one-third of patients have little to no understanding of what it means to be in a clinical trial, and half of patients asked felt they had no moral obligation to participate in clinical trials.[24] Because the lack of patient engagement is pervasive in the clinical trials community, it is not surprising that one of the major barriers to adoption of adaptive design is fear that not enough patients will be enrolled—a concern cited by several interviewees (RJG, WW, NB).

In fact, patient recruitment and compliance remain one of the largest logistic hurdles. To overcome this, it is important to consider database management and privacy considerations. The point was raised: Who owns that data? Hospitals? Pharmaceutical companies? The government? Many would argue that the patient owns the data. All stakeholders need to have this discussion, and to involve patient groups, thus allowing a user-centered design approach to clinical trials – something that is so far missing. A patient-designed process for clinical trials that (1) uses adaptive design to focus on getting the right numbers of patients instead of as many as possible, and that (2) designs a patient experience that understands the financial and emotional toll on those involved in a trial, and (3) one that provides a forum for discussion that does not violate the trial design. With the advent of social media, as one interviewee discussed at length, today it is much easier for patients to find each other, and especially if they have a rare disease, chances are they are in the same clinical trial.

[24] C.S. Coffey, and J.A. Kairalla. "Adaptive clinical trials: progress and challenges." *Drugs R&D.* 2008; 9 (4): 229–42.

CHAPTER 5. Proposed Solutions for Identified Barriers

Chapter 4 identified six barriers that obstruct the adoption of adaptive designs for clinical trials:

1. Funding
2. Logistics
3. Regulation
4. Communication
5. Collaboration/Partnerships
6. Patients

This chapter proposes one or more solutions for each barrier. Many of these solutions were identified by the interviewees through their own personal and professional experiences.

5.1 Funding

5.1.1 The Megafund Model

Given that the process of drug development is expensive and risky, the lack of enthusiasm among equity/venture capital investors is understandable. From 2007 to 2012, venture capital investment in biotech declined by 35%, and as large-scale investments into a broad array of pre-clinical studies are not occurring, academia is looking for other innovative options.

Recently, a so-called "megafund model" was introduced, which recommends increasing the scale of investment and pooling a large number of drug development

efforts into a single financial entity.[25] Combining multiple projects into a single investment portfolio takes advantage of diversification and a higher risk-adjusted return. The investments are called research-backed obligations (RBOs) and are structured as financial tools resembling bonds, providing investment opportunities for fixed-income investors. RBOs therefore provide a much larger capital pool than to traditional venture capitalists or equity investors.

While earlier studies of the megafund model focused on large-scale investments, a recent study by Fagnan et al. (2013) used simulations to demonstrate that a megafund model for so-called "orphan diseases,"[26] having an investment of approximately US$575 million, is expected to yield double-digit returns, with as few as 10 to 20 orphan disease projects in the portfolio. In this case, the risks are less with a smaller portfolio, especially because the rate of return on orphan diseases is high and remains consistent throughout the drug's lifecycle. This megafund model depends on targeting effective clinical trials, which fits well with the ACT model where trials are vetted using futility analysis to ensure that non-promising trials end quickly.

In summary, the need for early-stage research requires an infusion of capital that is outside current funding streams from pharma and the NIH. When the megafund model was mentioned to interviewees as an adaptive financing option, most senior academicians were curious. Camargo noted: " I have heard a lot about adaptive design of clinical trials

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[25] Fernandez, Stein, and Lo. "Commercializing biomedical research," 2012: 964–975. See also: D. Fagnan, J-M. Fernandez, A.W. Lo, and R.M. Stein. "Can financial engineering cure cancer?" *American Economic Review Papers and Proceedings*, 2013; 103:406–411.

[26] An orphan disease is any disease (usually rare) that affects a small percentage of the population. By definition, an orphan disease is one that affects fewer than 200,000 individuals in the U.S.

but I've not heard about adapting the financing around such efforts.... it's an interesting idea" (CC).

5.2 Logistics

5.2.1 Merck Solutions

Some companies have successfully overcome the logistics barrier. Merck is an industry leader in terms of the number of trials it undertakes using adaptive trial design. Since 2008, 20-25% of its clinical trials have been adaptive, and in the last year, the number of ACTs has been as high as 40%, according to interviews with Jerald Schindler and other senior executives who consult for the company (Anonymous).

Schindler noted that Merck also realized savings of millions of dollars per year by using futility analysis in adaptive trial design. The company concluded that ACTs have to be incorporated across an entire drug portfolio and not one trial at a time if it hopes to leverage the cost savings more rapidly. And despite savings millions of dollars, the reality is that each drug currently costs more than US$2 billion to develop, so the smaller savings are not sufficient to justify the larger development cost.

Given that Merck conducts trials using ACT for an appropriate number of patients, this addresses many's fundamental concerns of recruitment. Many companies are on the leading edge of clinical trial innovation and can help foster the process of innovation.

5.2.2 Oregon Sinus Center ACT

In an interview with Dr. Timothy Smith, a senior NIH-funded investigator in Portland, Oregon, he said that hiring a statistician 15 years ago provided him with a mentor to help him write his first NIH grant. When asked *why* he believes so many young academicians fall off the academic research cliff, he said that working in concert with a statistician who is an integrated part of his healthcare delivery team is essential. Most young faculty do not have access to such a resource. In Smith's clinical enterprise, his statistician provides invaluable guidance on statistical design to young and mid-career faculty. Smith said another key was providing support for his statistician to help other sites vet their statistical analyses. Many senior investigators at prominent institutions may not have this statistical support.(TLS, SAQ, JM)

When I interviewed Smith's statistician, he said that a major hurdle was the lack of an IT platform that could communicate seamlessly with remote investigators.(JM) He had to manually upload data and train all personnel, which required considerable time. Following the study, he performed meticulous checks to ensure all the data were complete, and he noted that it was quite a task logistically to ensure that all sites were moving forward simultaneously when appropriate enrollment was reached.

5.2.3 Integrated Software Platforms

During the interviews, it became clear that clinical research is not equipped to handle adaptive design. IT support and software platforms are required, and they have to be sufficiently flexible to handle multiple inputs. Several companies provide scalable

solutions, including Tessella, Cytel, and Aptiv Solutions, and all promote their ability to provide services in the clinical trials domain.

As Valerie Bowling noted, they provide some IT structure in a rapidly changing industry. She mentioned that clinical trials in Asia now comprise 15% of clinical subjects enrolled. One company announced a full-services hub with cloud-based management to work with investigators on simple adaptive models.[27]

5.2.4 Multi-Institutional Sites

The logistics of clinical trial execution, especially in hospitals, is a complex and fluid process that involves knowing that any given time one-third of the centers enrolled will have problems with patient enrollment and retention and will require trouble-shooting on a daily basis. Dr. Carmargo successfully runs trial across 50 sites, and he states that each clinical trial, whether adaptive or not, is its own "separate animal—always costing more than you think and taking longer than predicted, so in a sense we are already adapting in clinical research but often in a haphazard, unplanned way."

5.3 Regulation

5.3.1 Leaders as Champions

Executives within the organization, whether senior physicians in academia or senior executives in the pharmaceutical industry, must demonstrate strong support for this

[27] Adaptive clinical solution <http://www.adaptive-clinical.sg> professes to offer low-cost solutions for collecting, capturing, and managing clinical trial data. It is well-suited for Phase I and II short-duration pilot trials with an easy pre-launch process of no more than two weeks for analytical set-up. They also claim that given their "robust architecture," they have Phase III, IV, and multi-site capability that allows multiple sophisticated add-ons to perform more complex adaptive designs.

new methodology and function as the ACT "champions" within their organizations. To achieve this, a strong educational and training focus is needed throughout the organization.

5.3.2 Data Monitoring Committees

The complexity of adaptive trial design has led to the growth of Data Monitoring Committees (DMCs), another regulatory body that has access to seamless design information and can monitor the phases to determine whether adaptations are appropriate. Their role may include decision making for interim analyses, including safety issues related to the trial. Recently, external DMCs have increased in number, especially given their oversight of Phase III pivotal trials, and the trend has shifted away from a sponsor carrying out interim analyses and interpreting results itself. In particular, Phase III pivotal trials are important because they are the basis of regulatory approval. External monitoring bodies and DMBs can be especially helpful in the adoption of adaptive design because they can help the pharmaceutical sponsor to focus on safe and effective new products, as well as encourage abandoning products that will not come to market.

Interviewees identified that the key challenges facing DMCs and external review boards include standardization of personnel training, and ensuring that the DMCs understand both the sponsor and the regulatory perspectives. One proposal at a large pharmaceutical company includes sponsors setting up a steering committee to oversee multiple trials and to communicate with the DMCs to relay current news and information about studies being conducted. In return, the DMCs remain well-informed about the protocols and decision guidelines in the charter, and provide an unbiased review of the

data and future guidance. In theory, this should meet the high standards required of regulatory agencies.

One way to improve the functioning of these DMCs is to face the following issues and resolve them:

- Currently there is no formal training for DMC members.
- The training and experience of DMC members is not consistent.
- All members need to understand the process and the science involved in interim data monitoring.
- There should be a mechanism for keeping DMC members up to date as the field evolves.
- They should understand their inherent expectations and responsibilities.
- A central group could provide training.
- Discuss with pharma the binding secrecy of the information; i.e., is the DMC allowed to release results to the public or only to the drug company itself?[28]

In summary, novel methods for establishing trust in DMCs are an essential part of the paradigm for the clinical trials engine.

Certainly, regulators come under great scrutiny, and senior managers need to take limited and controlled risks that are inherently opposed to the role they were hired for. Similarly DMCs are asked "to monitor but not interfere" (Anonymous), and the role of each stakeholder is not well-delineated.

Interviewees regularly mentioned that the uncertainty of a trial is one of the least-discussed points of view, and that researchers should wait "to see what the data shows," a common saying in academic research. In fact, most believed that the elements of greatest

[28] Adapted from a Merck initiative being conducted at present: *Recommendations for Data Monitoring Boards,* with permission from Dr. Jerald Schindler, Merck. Adapted by thesis author.

uncertainty should be addressed first in a pre-study simulation scenario as well as from an optimization standpoint. Regulatory agencies must note that the *adaptive* is an inherent part of the design, and is not a substitute for inadequate planning.

Finally, some specific principles were offered at a recent lecture by a representative of Biogen IDEC™, including a matrix for approaching regulatory agencies:

- Pre-specify all decision rules
- Explore the impact of decisions using simulations
- Early and frequent interactions with regulators
- Simulate, simulate, simulate
- Feed back and iterate based on data collected to learn from nuances of the site, the disease, the patient category

5.3.3 Predictive Data Modeling for FDA Approval.

There are new approaches in terms of data modeling for regulatory approval Professor Robert Langer, in a recent lecture, talked about the creative approach taken by Momenta. This company submitted a robust data package in collaboration with Sandoz™ to obtain approval from the FDA for the generic version of a complex drug molecule ***without*** clinical studies to establish safety and efficacy.[29] At one point, the company was asked to submit additional data to confirm that it had the same immunogenicity profile as Lovenox™. Using their extensive knowledge of the biology of low molecular weight heparins, Momenta's scientists assembled a compelling and convincing data package and

[29] Since 2005, Momenta, in partnership with Sandoz, worked meticulously to submit a robust data package (as well as additional data when requested) in order to get a complex drug approved without clinical studies so as to establish the safety and efficacy of a drug equivalent in activity to the widely used medication Lovenox™.

met the FDA's multiple-point criteria for approval. While this represents a very different approach, it is adaptive design in a new sense, and signals that the FDA is open to innovative approaches.

It is essential, therefore, to frame the question of funding mechanisms within a larger ecosystem of *adaptive design* innovation. The interviewees signal that decreased sources of revenue have caused companies to target drugs that have the potential for high ROI, including orphan diseases. Limited targets, however, that all overlap, will lead to fewer new drugs in the long term.

In looking at the model, a linear flow through a stage-gated, three-phase process allows silos to exist, and increasing the funding while maintaining such a framework may not solve the overall issue of building trust and encouraging collaboration. Certainly, adaptive design for clinical trials will begin to shift the paradigm in terms of flexibility of the process. It also demonstrates an awareness by the FDA that changes in the process are needed.

5.4 Communications

All interviewees converged on the common theme of communication. It was generally agreed that open communication is lacking among stakeholders. The Conference Forum is an organization focused solely on bringing key stakeholders together to discuss the challenges. Bowling noted that while external communication among stakeholders is essential, internal organizational resistance to change is also high, because ACTs represent a changed way of doing things. Internal champions who train and educate clinical teams are essential, according to Bowling. Senior management

support of the effort is equally essential for launching an internal educational campaign and supporting adaptive trial design.

5.4.1 Mentors

What differentiates those who succeed in the clinical research realm? Good mentorship is the answer echoed by many interviewees, especially physician researchers. Souba advises that having a cohort of mentors to guide a researcher through the process of grant-writing, the clinical trial process, statistical analysis, and patient recruitment goes a long way to assuring successful funding. Souba stated: "Few people are comfortable shining in reflected light," and his advice for mentors is to train their mentees as part of succession planning. When he moved from a purely research career to pursue administrative leadership, Souba made sure his successor would be more published and accomplished than he had been. He did this by teaching him the "conversational lingo" critical to success. The value of good mentorship within the clinical research community cannot be understated, and investigators have to learn to speak the language of the FDA and the NIH.

5.5 Collaboration

5.5.1 Informal Networks

Despite the industry's tight-knit relationships between academic heads of departments and industry leaders, informal channels and networks should also be leveraged to persuade decisions makers of the reliability of FDA and NIH commitment to adaptive design.

5.5.2 Cluster Randomized Design

One positive example of encouraging collaboration within institutions is cluster randomized design. This enables each academic site to function as one arm of a trial while also being adaptive because it is simpler from a logistics standpoint. Richard, a physician well-versed in clinical trial design, stated that this way one hospital does not have to randomize with each patient, which creates an easier workflow.

Another interviewee noted that individual clinical research sites are *willing* to *adapt* in order to fulfill the needs of a study as long as the operational burden to their staff is minimized (CC). He manages 50 sites at a time and has to troubleshoot the various arms of the study constantly by setting expectations, including the number of patients needed or the dosages dispensed. His team then ensures that each site stays in the study by managing operational complexities on a daily basis.

Hirsch talks about a "collective paralysis" that is presently found in some clinical researchers. She states: "'Collective paralysis' is a term I use to reflect something much larger than a problem solely with clinical researchers. It is what kept the adaptive licensing paradigm merely an idea, and kept it from moving into action due to the interlocking risks of regulators, payers, and industry sponsors. I'm not sure if such paralysis in found only in the context of clinical researchers."

Camargo differs from most of the interviewees in that he believes the single most important component in the adoption of adaptive trials design is *managing relationships*. When investigators are in the midst of a trial, there is a certain amount of support and tacit knowledge that needs to be conveyed to help troubleshoot the various parts of a clinical trial. His team does this daily, and while Camargo envisions future clinical

research with adaptive design, he reiterates that the present infrastructure of the clinical research engine is ill-prepared for adaptive design.

5.5.3 Incentive Structure

As noted, at present in academia as clinical investigators complete studies and procure funding, they are promoted based on the number and quality of their publications. This leads to fierce competition for tenure. Instead, an incentivized system that rewards collaboration on clinical trials as one pillar of promotion would be the first step.

5.5.4 Shared Workspaces

The product design literature emphasizes how much structure drives behavior. It is also clear that having shared workspaces and open innovation venues where academicians and pharmaceutical companies can openly discuss possible directions at an early stage is necessary. One such example is Johnson & Johnson, which invested in shared lab space in Cambridge, Massachusetts. It became clear that the "cubicle mentality" should be abandoned in favor of adopting open, more collaborative spaces.

Rather than hoping research will translate into clinical relevance, there should be ongoing dialogue and established trust by aligning scientific development with appropriate financial incentives. Trust continues to emerge as a basis for collaboration, and there has to be "transparency in the process" with an acknowledgment that all must cooperate.

The key impetus is that groups that do not succeed should move to another disease or category to prevent duplication of efforts in the same arena. This creates a "microcosm of competitive innovation" within each disease research state, and similar design challenges that lead to agile development of the type found in many software companies.

5.6 Patient Experience

5.6.1 Patient Advocacy Support Groups

Recently, patient advocacy organizations have emerged as leading proponents for change in the drug development process and improvements in patients' experiences. Specifically, interviewees who are advocates in the rare diseases space emphasized that "rare diseases are not rare," and that even though "rare diseases impact more people than AIDS and cancer combined, 95% of rare diseases do not have a single FDA-approved treatment" (NB). From the perspective of the rare disease community, the fact that 40% of the FDA pipeline is for orphan drugs supports the notion that these diseases will find some treatment soon. Despite the desire to innovate, however, Boice said that "according to estimates from the NIH, it will take 10,000 years at the current rate of FDA drug approvals to find therapies for all the people suffering from rare and genetic diseases."[30] 10,000 years! This is sobering and has led to discussions in patient advocacy groups to provide links to encourage adaptive trial design and to bring together pharmaceutical companies, scientists, and the regulatory community in a way no other stakeholder has been able to do. Given that patient groups are not accountable to shareholders for profit

[30] See <http://www.globalgenes.org>.

as pharmaceutical companies are, the groups are able to demand conversations around measuring key metrics and accountability for the NIH dollars being spent. Smaller companies such as Biogen, IDEC, and Shire are seizing the opportunity to create a new type of pharmaceutical company that is smaller, more nimble, and able to adapt to the types of clinical trials that are being demanded.

One interviewee cited the example of a previous GlaxoSmithKline study that had problems with social media interactions among patients enrolled in a clinical trial (Anonymous). The patients' families started a closed Facebook group and began to compare symptomatology with each other. Through discussions of specific symptoms, the families identified which participants were being given the placebo and then many threatened to quit the trial *en masse* if those members were not offered the therapy (Anonymous). At the time, this posed a dilemma for GlaxoSmithKline; today it raises ethical questions about how to tie financial incentives to the metrics of a clinical trial that involves patient advocacy groups.

CHAPTER 6. Summary

6.1 A Model for Adaptive Clinical Trials (ACTs)

Exhibit 6.1 is a system dynamics model that shows how to increase the rate of adoption of adaptive design of clinical trials. The model is designed so that adding real-time data will model the increase in the rate of adoption of ACT design.

The initial starting point is **potential clinical trials** from which *adoption rate* determines the *flow* toward **adaptive clinical trials. Initial adopters (A_0)** denotes early adopters who pioneer the simple adaptive design. The adopters of adaptive design then have to increase the number of trained personnel staff, and the loop on the extreme right denotes the reinforcing effect of trained personnel meeting other successful adaptive design personnel.

The **"word of mouth"** *reinforcing loop* forms an informal network by which adoption grows, and represents the growth of a concept in any industry.

In the middle of the model, **contact with successful adopters** allows shared best practices and promotes collaboration, leading to a direct increase in **adoption from word of mouth**. However, this interaction is held in check by the lack of communication in industry and academia and these silos represent a *balancing loop*.

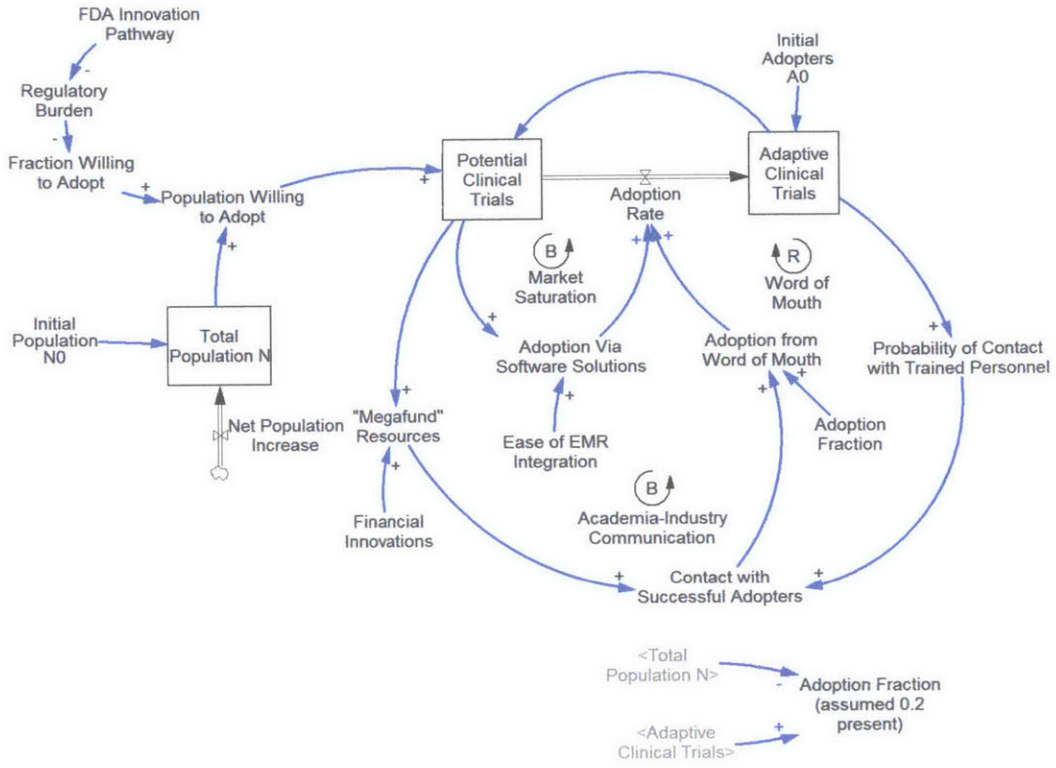

Exhibit 6.1 Model of Adoption of Adaptive Design of Clinical Trials

Terms:

N = Total Population of Clinical Trials
P = Potential Adopters
PWA = Population of Clinical Trials Willing to Adopt
N_o = Initial Population of Clinical Trials (# initial total)
A_o = Initial Adopters of Adaptive Design of Clinical Trials

Adoption Fraction: Adopters of Adaptive Design (# Trials) / Total Population (# Clinical trials); cited as 20% in the literature at present. *Hence:*

N = INTEGRAL(Net Population Increase, N0)
Adopters = INTEGRAL(Adoption Rate, Initial Adopters)
Potential Adopters = MAX(0, Population Willing to Adopt)
// = Delay effect
R = Reinforcing Effect
B = Balancing Effect

Adoption Rate = Rate at which traditional clinical trials are converted to adaptive design

Source: Adapted from Bass-Diffusion Model of VCR Adoption. System Dynamics Course Assignment in course taught by Professor John Sterman, MIT Sloan School of Management, 2014.

Moving to the middle-left, recent literature focuses on the need for increased financial resources to overcome the "valley of death" in early-stage clinical research. A **"megafund resources"** model is proposed, reinforced by the creation of **financial innovations**. In order for this to succeed, the financial community should ascertain the success factors of early adopters through direct interaction and have mutually understandable "conversations," as outlined in the interviews, thereby leading to a *reinforcing loop* of available funding supporting increased adoption rate.

On the left side, the **initial population of clinical trials**, depicted as $\mathbf{N_0}$, feeds into Total Population (of clinical trials), an increasing number as the clinical research engine continues to grow. Of **Total Population N,** there is a percentage willing to adopt; in order to increase this fraction, the regulatory burden has to decrease in both complexity and uncertainty. As shown in the top left, the FDA' s announcement of an innovative open pathway articulates its intent to ease regulatory uncertainty and aid in increasing the *adoption rate* toward adaptive design.

Finally, the overall accelerated adoption of adaptive design is denoted as a percentage in the bottom right, which serves as a final output of this model. It is noted that this percentage is currently 20% given current citations in the literature.

6.2 Recommendations

Given the quantity of research and interview findings presented here, where does it all lead? PriceWaterhouseCoopers' Global Advisory Group, among others, predicts some $155 billion in lost revenues from prescription drug sales over the next decade (Arlington).

In view of the challenges discussed throughout this thesis, it is clear that the pharmaceutical industry needs to move away from its sometimes serendipitous efforts to create the next "blockbuster drug"[31], and instead utilize a service-based business model that delivers tailored, specified outcomes at the right price for the market. Within this new paradigm of "innovation by design," the pharmaceutical companies that re-engineer their clinical trials to reflect current patient diseases will create a competitive advantage for their company over others.

My interview research, and the extensive literature published on adoption of ACTs, shows clearly that this topic is intensely debated. By synthesizing my findings from the interviews, I can make several recommendations:

1. Cost savings from adaptive designs can be substantiated by incorporating simple changes, such as futility analysis and sample size re-adjustments. One global company reportedly saved US$70 million over the last year from adoption of adaptive design in its Phase II dose finding studies.
2. Despite the industry's tight-knit relationships between academic heads of departments and industry leaders, informal channels and networks should also be leveraged better in order to persuade decisions makers of the reliability of FDA and NIH commitment to adaptive design.
3. As one researcher astutely pointed out, landmark studies using adaptive design are published in reputable journals, but until such publications become an established

[31] "Blockbuster Drug" in the pharmaceutical industry is a drug that generates more than $1billion in annual revenues.

norm and are well understood by the lay scientific community, the studies will continue to be misunderstood.

4. Making funding more available, and untying its linear relationship to promotions and tenure, will enable healthy competition and increased collaboration in academia.
5. Operational aspects of adaptive design, including education and personnel training as well as a good IT platform for full scenario planning and database support, are essential elements of any system before embarking on adaptively designed protocols. High training costs and lack of internal organizational buy-in often cause reversion back to traditional models.
6. Regulatory uncertainty should be addressed, and complex adaptive designs should be well vetted with the FDA so that risk of non-approval is minimized. Eliminating risk in medications is as essential as de-risking portfolio investment by ensuring success if delineated metrics are met. Momenta™ is an excellent example of using mathematical predictive modeling, which led to the first FDA generic version of a complex drug molecule ***without*** the normal extensive clinical studies to establish safety and efficacy.
7. Executives and entire clinical research teams should view the change toward adaptive design as a competitive opportunity. More education on the language of clinical trials (statistics, set-up, execution) should be part of the push toward increasing effective, multi-lateral communication. For example, statisticians should become integrated partners in the healthcare delivery system by vetting clinical research at the outset and continuing throughout the study.

8. In order to demystify adaptive design for clinical trials, industry-wide adoption must be spearheaded by proponents who are medical experts and clinical operations experts. This will prevent the perception that statisticians are the only ones clamoring for adoption of ACTs. Adaptive financing will follow suit as the metrics and goals of each step is well demarcated and predictively modeled.
9. Executives within the organization, whether senior physicians in academia or senior executives in pharma, must demonstrate strong support for this new methodology and function as the ACT "champions" within their organizations. To achieve this, a strong educational and training focus is needed throughout the organization.
10. A multi-disciplinary team comprised of clinicians in academia, pharmaceutical or biotech firms, and regulatory agencies, along with epidemiologists, is needed in order to work collaboratively. These relationships between industry and academia need to be re-defined with the appropriate alignment of financial and rewards-based incentives. One way to begin is to reward collaborative multi-institutional research both in terms of funding as well as promotions and tenure.
11. Removing competitive silos and sharing best practices will shift focus to the long-term goal: cures for patient disease. As patient advocacy groups rightfully argue, patient enrollment and retention in clinical trials is dependent on greater transparency of goals and objectives, and a partnership of industry-academia with patient advocacy organizations is needed to maximize study populations that are part of the studies.
12. The need is intensified as clinical trials become global in nature. Globalization raises questions about genetics and epigenetics, all of which will require careful database

management and seamless integration with electronic medical records to keep track of every patient and document/monitor which trial they are enrolled in.

13. Measurement and data monitoring are essential for tracking the study design and adapting at the right pre-determined interval. Data systems should be leveraged to continuously learn and iterate to improve the process. This will also allow a careful analysis of cost of the study and validate internal organizational cost-savings for the organization.

Biomedical research is an extremely complex, expensive, and uncertain ecosystem. Organizations that are agile recognize when their interventions are working or not working. These firms then make decisions about whether to stay the course or change directions. In the case of drug development, making these decisions *early* can limit the time spent getting through an clinical trial process and can often curb the cost of completion.

Appendix A

Interviewees

- Dean of an Ivy League medical school
- Senior executives (CIO, CMO, CEO) of nearby Boston-region hospitals
- Senior executives in pharmaceutical companies in Boston
- Senior executives in biotechnology companies
- Academic faculty at Harvard Medical School
- Academic faculty at Massachusetts Institute of Technology with a focus in healthcare related innovation
- CEOs of patient advocacy organizations
- CEOs of medical organizations
- CEOs of innovative firms in the health-care space involved in clinical trial design
- Director, Innovation Center at Cambridge (MA)-based firm

List of Key Interviewees:
Valerie Bowling
Executive Director,
The Conference Forum

Carlos A. Camargo, Jr, MD, DrPH
Professor of Medicine, Harvard Medical School
Professor of Epidemiology, Harvard School of Public Health
Staff Emergency Medicine Physician, Massachusetts General Hospital
Director, EMNet Coordination Center

Marsh N. Carter BS
Previous Chairman, NYSE Group, Inc

Eliot Chaikof, MD, PhD
Chairman,
Roberta and Stephen R. Weiner Department of Surgery
Beth Isreal Deaconness Medical Center

Zen Chu, MBA
Accelerated Medical Ventures, LLC
Faculty, MIT Health Care Ventures Course

Kenneth Getz, MBA
Director of Sponsored Research Programs & Research Associate Professor
Tufts Center for the Study of Drug Development

Richard Gliklich, MD
Director, Clinical Outcomes Research Unit
Massachusetts Eye and Ear Infirmary

David Goldenberg, MD, FACS
Chief
Division of Otolaryngology- Head and Neck Surgery
Pennsylvania State University College of Medicine

John D. Halamka, MD, MS
Chief Information Officer
Beth Isreal Deaconness Medical Center

Gigi Hirsch, MD
Executive Director, Center for Biomedical Innovation
Massachusetts Institute of Technology

Adam B. Landman, MD, MIS, MS, MHA
Chief Information Officer
Brigham and Women's Hospital

Christian Lim
MBA Candidate, MIT Sloan School of Management

Gregory Martin, MD
Chief Medical Officer
Emerson Health System

Kuldeep Neote, Ph.D.
Senior Director-New Ventures/Scout
Johnson & Johnson™ Innovation Center-Boston

Sean Herron BS
FDA Project
White House Innovation Fellows Program

Jess Mace, MPH
Research Associate
Treatment Outcomes Research Program Coordinator,
Oregon Sinus Center

Sadeq A. Quraishi, MD, MHA, MMSc
Assistant Professor of Anaesthesia, Harvard Medical School
Director, Vitamin D in Stress Laboratory

Una Ryan, PhD
Bay Bio

Jerald Schindler, Ph.D.
Vice President, Late Development Statistics
Merck™

Wiley "Chip" Souba, MD, ScD, MBA
Vice-President for Health Affairs
Dean, Geisel School of Medicine

Robert Urban, Ph.D.
Head,
Johnson & Johnson™ Innovation Center-Boston

D. Bradley Welling, MD, PhD, FACS
Chair, Harvard Medical School Otology and Laryngology
Chief, Massachusetts Eye and Ear Infirmary

Jeanine P. Wiener-Kronish, MD
Chief, Anesthesia and Critical Care,
Massachusetts General Hospital

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APPENDIX B

Standard Interview Questions

1. How do you define *adaptive design* of clinical trials?

2. Have you conducted an adaptive clinical trial at your institution?
   If so, how was that experience?

3. What do you see as the major challenges to adaptive trial design?

4. What do you see as the key leverage points that can be altered in order to move clinical trials forward more rapidly?

5. How might you design innovation in the clinical trials space?

Appendix C

Glossary of Terms

ACO	Accountable Care Organization
ACT	Adaptive Clinical Trial
CRC	Clinical Research Center
CRO	Clinical Research Organization
DMB	Data Monitoring Board
FDA	Federal Drug Administration
NCI	National Cancer Institute
NDA	New Drug Approval
NIH	National Institutes of Health
NME	New Molecular Entity
Patent Cliff	When a drug patent expires, and the medication becomes generic, causing the originating company to lose substantial revenue
Phase I	First Phase of a Clinical Trial
Phase II	Second Phase of a Clinical Trial
Phase III	Third Phase of a Clinical Trial
PhRMA	Pharmaceutical Researchers and Manufacturers of America
RBO	Research Backed Obligations
RCT	Randomized Control Trial
Seamless Design	The process of combining data in the final drug analysis. An element of all adaptive designs. There is no long pause after the interim analysis, and data collected before and after the interim analysis are used in the final analysis.

Bibliography

Adams, C.P., and V.V. Brantner. "Spending on new drug development." *Health Economics*, 2010; 19(2):130–141.

"Advancing Regulatory Science through Novel Research and Science-Based Technologies" (U01). Available at: <http:// grants.nih.gov/grants/guide/rfa-files/RFA-RM-10-006.html>. Accessed September 14, 2011.

Bauer, P., and K. Köhne. "Evaluations of experiments with adaptive interim analyses." *Biometrics* 1994; 50: 1029-1041.

Biometrical Journal. "Adaptive designs in clinical trials." Special Issue. August 2006.

Bornkamp, B., J.C. Pinheiro, and F. Bretz. "MCPMod – An R package for the design and analysis of dose-finding studies." *Journal of Statistical Software* 2009; 29 (7): 1-23.

Brannath, W., P. Bauer, W. Maurer, and M. Posch. "Sequential tests for noninferiority and superiority." *Biometrics* 2003; 59, 106-114.

Bretz, F., H. Dette, and J.C. Pinheiro. "Practical considerations for optimal designs in clinical dose finding studies." *Statistics in Medicine* 2010; 29, 731-742.

Bretz, F., J.C. Pinheiro, and M. Branson. "Combining multiple comparisons and modeling techniques in dose-response studies." *Biometrics* 2005; 61(3), 738-748.

Bretz, F., H. Schmidli, F. Koenig, et al. "Confirmatory Phase II/III clinical trials with hypothesis selection at interim: General concepts." *Biom J* 2006; 48 (4): 623-34.

Burman, C.F., and C. Sonesson. Are flexible designs sound? *Biometrics* 2006; 62: 664-83.

Cearnal, L. "The birth of the NETT: NIH-funded network will launch emergency neurological trials." *Ann Emerg Med.* 2006; 48: 726-728.

Chow, S., and M. Chang. *Adaptive Design Methods in Clinical Trials*. Boca Raton, FL: Chapman & Hall/CRC, 2007.

Chuang-Stein, C., and M. Beltangady. "FDA Draft Guidance on adaptive design clinical trials: Pfizer's perspective." *J Biopharm Stat.* 2010; 20 (6):1143-49.

Coburger, S., and G. Wassmer. "Sample size reassessment in adaptive clinical trials using a bias corrected estimate." *Biometrical Journal* 2003; 7: 812-825.

Coffey, C.S., and J.A. Kairalla. "Adaptive clinical trials: progress and challenges." *Drugs R& D* 2008; 9 (4): 229-42.

Cook, T., and D.L. DeMets. "Review of draft FDA adaptive design guidance." *J Biopharm Stat.* 2010; 20 (6):1132-42.

Denne, J.S. "Sample size recalculation using conditional power." *Statistics in Medicine* 2001; 2: 2645-60.

DiMasi, J.A., R.W. Hansen, and H.G. Grabowski. "The price of innovation: new estimates of drug development costs." *Journal of Health Economics* 2003; 22 (2): 151 –185.

Dragalin, V., B. Bornkamp, F. Bretz, et al. "A simulation study to compare new adaptive dose-ranging designs." *Statistics in Biopharmaceutical Research* 2010; 2 (4): 487-512.

Fagnan, D., J-M. Fernandez, A.W. Lo, and R.M. Stein. "Can financial engineering cure cancer?" *American Economic Review Papers and Proceedings* 2013; 103: 406–411.

Fernandez, J-M, R. Stein, and A. Lo. "Commercializing biomedical research through securitization techniques." *Nature Biotechnology* 2012; 30: 964–975.

Food and Drug Administration (FDA). "Challenge and opportunity on the critical path to new medical products." March 2004. Available at: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf>. Accessed September 14, 2011.

Food and Drug Administration (FDA). "Critical path opportunities report." March 2006. Available at: <http://www.fda.gov/downloads/>.

Food and Drug Administration (FDA). "Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics: DRAFT GUIDANCE." 2010. Available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf>.

Gallo P., C. Chuang-Stein, V. Dragalin, et al. "Adaptive designs clinical drug development: An executive summary of the PhRMA Working Group." *J Biopharm Stat* 2006; 16: 275-83.

Garnier, J-P. "Rebuilding the R&D engine in big pharma." *Harvard Business Review* 2008; 86 (5): 68–76.

Gaydos, B., M. Krams, I. Perevozskaya, et al. "Adaptive dose response studies." *Drug Inf J* 2006; 40: 451-61.

Jennison, C., and B.W. Turnbull. *Group Sequential Methods With Applications to Clinical Trials*. Boca Raton, FL: Chapman & Hall/CRC, 2000.

Jennison, C., and B.W. Turnbull. "Meta-analysis and adaptive group sequential designs in the clinical development process." *Journal of Biopharmaceutical Statistics* 2005; 15: 537-58.

Kling, J. "Biotechs follow big pharma lead back into academia." *Nat Biotech* 2011; 29 (7): 555–56.

Krams, M., K. R. Lees, and D.A. Berry. "The past is the future: innovative designs in acute stroke therapy trials." *Stroke* 2005; 36: 1341–47.

Lichtenberg, F.R. "The impact of new drug launches on longevity: Evidence from longitudinal, disease-level data from 52 countries, 1982–2001."*International journal of Healthcare, Finance, and Economics* 2005; 5 (1): 47–73.

Light, D.W., and R.N. Warburton. "Extraordinary claims require extraordinary evidence." *J Health Econ* 2005; 24: 1030–33.

Lo, A.W., and S.V. Naraharisetti. "New financing methods in the biopharma industry: A case study of Royalty Pharma, Inc." December 15, 2013. Available at: <http://ssrn.com/abstract=2330089 or http://dx.doi.org/10.2139/ssrn.2330089>.

Maca, J., S. Bhattacharya, V. Dragalin, et al. "Adaptive seamless Phase II/III designs: background, operational aspects, and examples." *Drug Inf J* 2006; 40: 463–73.

Müller, H., and H. Schäfer. "Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and of classical group sequential approaches." *Biometrics* 2001; 57: 886–91.

Nass, S.J., and H.L. Moses. *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*. Washington, DC: National Academy Press, 2010.

Paul, S.M., D.S. Mytelka, C.T. Dunwiddie, et al. "How to improve R&D productivity: The pharmaceutical industry's grand challenge." *Nature Reviews Drug Discovery* 2010; 9: 203–14.

Proschan, M.A., K.K.G. Lan, and J. Wittes. *Statistical Monitoring of Clinical Trials: A Unified Approach*. New York: Springer, 2006.

Quinlan, J., B. Gaydos, J. Maca, et al. "Barriers and opportunities for implementation of adaptive designs in pharmaceutical product development." *Clin Trials* 2010; 7: 167–73.

Quinlan, J.A., and M. Krams. "Implementing adaptive designs: logistical and operational considerations." *Drug Inf J* 2006; 40 (6): 437-44.

Rosenberger, W.F., and J. Lachin. *Randomization in Clinical Trials*. New York: Wiley & Sons, 2002.

ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ UCM077254.pdf. Accessed April 25, 2010.

Steven, M.P., D.S. Mytelka, C.T. Dunwiddie, et al. "How to improve R&D productivity: the pharmaceutical industry's grand challenge." *Nat Rev Drug Discov* 2010; 9 (3): 203–14.

Tralau-Stewart, C.J., C.A. Wyatt, D.E. Kleyn, and A. Ayad. "Drug discovery: new models for industry–academic partnerships." *Drug Discovery Today* 2009; 14(1–2): 95–101.

Whitehead, J., Y. Zhou, S. Patterson, et al. "Easy-to-implement Bayesian methods for dose-escalation studies in healthy volunteers." *Biostatistics* 2001; 2: 47–61.