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Evolution of a Robust Design Framework for Clinical Development

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Abstract

Numerous attempts have been made to increase the efficiency of clinical studies, but the productivity of clinical development remains low. This article describes an organization's journey to enhance clinical program design, with a focus on decision-making so the right questions are asked and answered to support key decisions during development. AstraZeneca Pharmaceuticals developed and implemented a structured approach to the design of clinical development programs, in which dedicated design teams linked the target product claims transparently to study objectives, endpoints and scheduled assessments. A software suite (the "Workbench") and a competence development program further backed the clinical trial design framework. Adoption of the key principles among design teams was good and some improvement in the logical flow of clinical design decisions was observed. While better design quality, less complexity of trial design, and fewer amendments were observed two years after implementation in 2011, the organization also recognized additional improvement needs, such as nimble, transparent decision-making, clear decision rights, and a flexible approach to design across high-level product strategy and clinical study protocols.

1. Introduction

Clinical trials are slow, expensive and often ask the wrong questions. Improving the process of designing clinical development programs can help address these deficiences[1,2].

Numerous customers and stakeholders guide development of new drugs. Key among them are health authorities, who specify the evidence required for regulatory approval. Therefore, a development program focused on fulfilling regulatory requirements ought to result in more timely approval of a medicine. However, authorities on regulatory submissions found that many issues were caused by study designs not generating the required information for approval[3,4]. Furthermore, an assessment of study protocols suggests that 22% of procedures performed in the clinical studies did not support key objectives[5]. So, it seems that clinical research often fails to generate the desired evidence, while at the same time generating superfluous information that does not assist with decision-making. This evidence suggests that there are deficiencies in how the pharmaceutical industry designs clinical development programs and trials.

This article describes the development and implementation of a structured clinical development design framework at AstraZeneca Pharmaceuticals. A key objective of the framework was to generate a development program of study protocols that efficiently supports the product vision and target product claims. Section 2 summarizes the results of a cross-industry analysis of best practices in organizations that design and develop innovative products. Section 3 describes the three dimensions of the resulting design framework. Section 4 describes implementation of the framework. Section 5 presents feedback from drug project teams that implemented the framework. Section 6 summarizes improvements observed in key performance indicators. Section 7 discusses strengths and limitations of the framework. Section 8 sets forth conclusions.

2. Clinical trial design framework: purpose and desired attributes

AstraZeneca commissioned the Hay Group to conduct a study to identify best practices common to organizations involved in the design and development of cutting-edge products. The Hay Group asked the R&D heads and/or portfolio leaders of these organizations the following questions:

- What does a "design focused" organization look like?
- How best to build a design-focused organization?
- How best to manage the transformation to a design-focused organization (change process)?
- What are the tangible (measurable) benefits of this change?
- What do "teams" look like (if there are teams)?
- What does the clinical scientist of the future look like?
- How do we innovate on a sustained and sustainable basis?

Data from the study were combined with responses from internal interviews, as well as with a prior analysis of innovation practices by Fortune Magazine's "Most Admired" companies to identify a set of best practices and desired attributes for design-focused organizations. Table 1 summarizes the attributes found by the Hay group:

Table 1. Best practices in design-focused organizations

- Have a reproducible, systematic, best-practice-based approach grounded in a few key principles that are fully embedded in the organization.
- Have an "open" approach to design that fosters creation of connections and collaborations.
- Have well defined and delineated "design teams" that drive business outcomes. Design teams are lean, flexible, agile and consist of scientific and technical experts relevant to key design decisions on the program.
- Have simple methods for assessing design performance and quality based on a few key metrics for the activities that drive value creation.
- Understand that the way people actually do the work of designing (processes and practices) has the greatest impact on outcomes. Team structures can be flexible depending on the type of program and decision. An evidence-based approach to design that seeks and reconciles different shades of expert opinion into a coherent whole is a key characteristic of successful design teams.
- Have active and built-in knowledge management. The exercise and results of decision-making generate knowledge from which other design teams can benefit.

Survey Source: Hay group

3. Design framework: key dimensions

AstraZeneca's R&D organization developed and introduced a comprehensive new framework as part of a large-scale change program to drive improvements in three domains, recognizing that (a) staff capabilities, (b) organizational structure, and (c) processes are closely interlinked and need to be adjusted simultaneously to ensure a holistic, balanced approach to change (Figure 1).

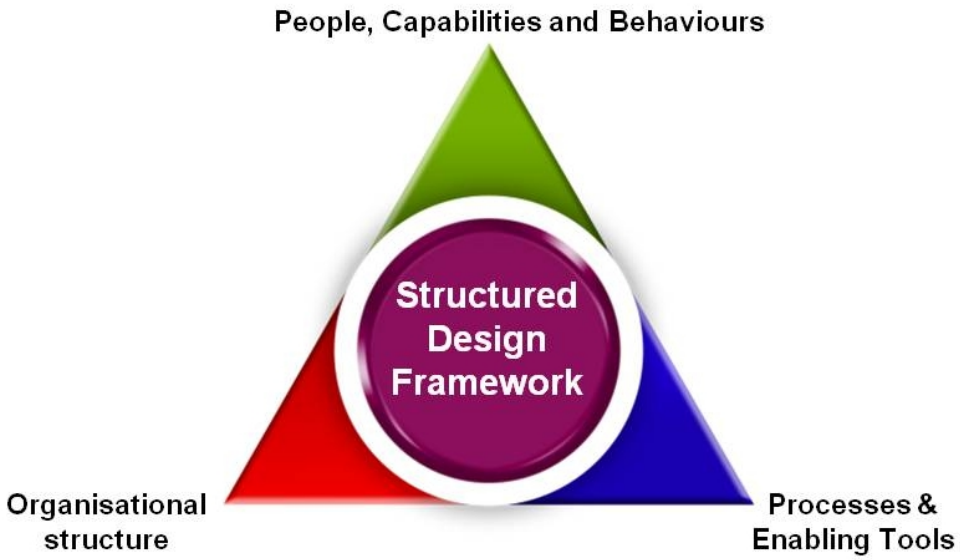

Figure 1. Framework for Clinical Trial Design: Key Improvement Areas

People, capabilities and behaviors

The framework was designed to drive a progressive culture and way of working, where excellence in design is expected and maintained through an environment of learning and continuous improvement.

Over and above processes and organizational structure, scientists' thinking skills are paramount to the success of a design activity. Therefore, a capability development program was introduced to strengthen creative thinking and improve communication among experts.

One core tenet of this change program was a commitment to the principles of Integrative Thinking™. Integrative Thinking is an approach to decision-making, originated by Roger Martin and based on interviews with successful leaders from various fields of business[6]. It is characterized by the following abilities:

- The ability to hold in mind two seemingly opposed mental models and stimulate the brain to come up with alternatives that are better than either option
- The ability to avoid leaping to solutions and, instead, accepting uncertainty during the decision-making process
- The ability to challenge both conscious and previously unconscious assumptions about what is relevant
- The ability to use abductive reasoning (from observation to hypothesis) to embrace novel or surprising data and use it as a springboard to a new theory
- The ability to allow curiosity to lead to creativity in decision-making

AstraZeneca expected an Integrative Thinking mindset to motivate decision-makers to seek alternative options for clinical development programs, identify the strengths of each option, and find a superior solution that integrates these strengths. Integrative Thinking was also intended to motivate design teams to engage internal and external experts who could

contribute information, broaden perspectives, and enrich the thinking process. Targeted training sessions were delivered throughout the R&D organization to embed Integrative Thinking as a core skill for decision-makers involved in clinical program and trial design.

Organizational structure

A new organizational structure was introduced to create small, empowered and dedicated design teams that led the scientific aspects of clinical trial design. Each design team had a physician, a statistician, and an information expert as its core members. The organizational structure provided the flexibility to include other domain experts (Clinical Pharmacology, Patient Safety, Health Technology Assessment, etc.) at the right times during design process. In addition to using Integrative Thinking and drawing upon their own expertise, teams were charged with integrating the views of other experts and wide-ranging information sources into their design work.

Process and enabling tool

To guide the design of clinical trials and programs (the configuration of one or more trials), a design framework was created, as illustrated in Figure 2. The process of program design begins with identification of "customer" needs (e.g., patients, physicians, payers, regulators, key opinion leaders) and an evaluation of the ability to meet those needs based on current and anticipated future knowledge. A clear specification of the information needed to make the next key business decision drives the selection of questions. These questions then form the "design remit" or charter for the design team. During the design process, a team typically moves back and forth between claims, design questions, and other downstream steps in an iterative fashion.

At this stage of the design process, the creative funnel is kept wide open to allow consideration of potential "out of the box" options. Options for how each question could be answered are identified. Special attention is given to key questions, e.g., what methods of analysis are available, what comparators could be used, what treatment doses and formulations could be tested, what study designs might be possible, what study populations could be engaged, and geographically where could the studies be conducted. The design team creates a portfolio of possible trials that can be combined in various configurations to create clinical development programs that optimize for different combinations of speed, cost and robustness, depending on the business situation. With an effective design process, the end result is a clinical development program that is superior in one or all dimensions to the initial alternatives.

A software tool, called the "Workbench," was developed to support the design process. The Workbench is a web-based workflow tool that lends transparency to the design process and also serves as a project memory that enables reuse of design elements in future programs.

4. Implementation of the design framework

Implementation of the design framework started in 2011 and was supported by an intensive change campaign. Approximately 1,600 people in the development organization received targeted training in new ways of working. Of those, 460 people were trained in Integrative Thinking. A support organization, the Design and Interpretation Centre of Excellence, was created to provide methodological hands-on support to design teams. "Integrative Thinking Clinics" were offered to help resolve complex questions. "D&I Champions" were embedded in the organization. All projects with design activities were required to form design teams and to document design activities in the Workbench.

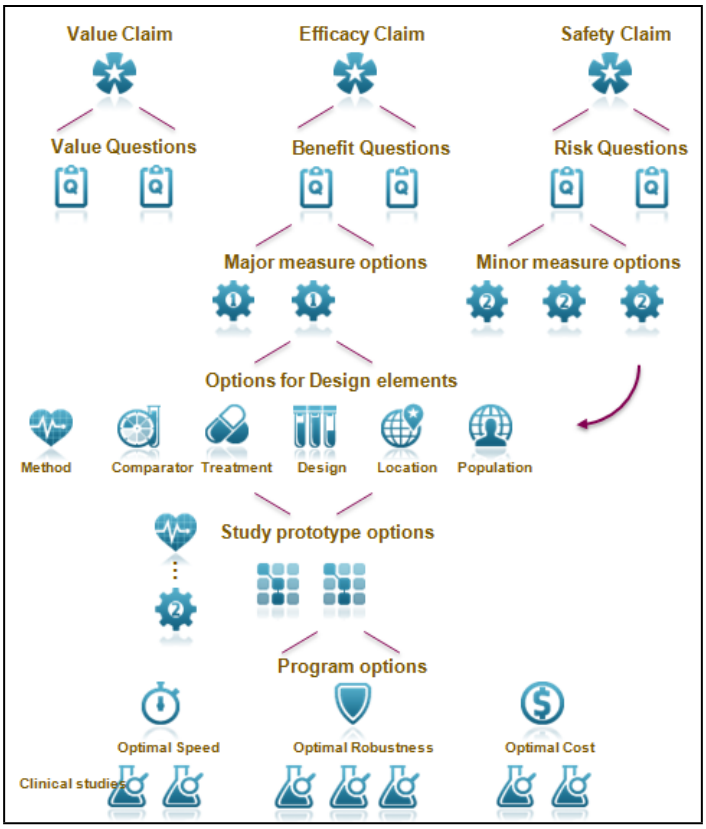

Figure 2. Framework for Design of Clinical Development Programs

A review two years after implementation found that all clinical projects with design activities had formed design teams according to the model. Approximately 70% of development programs were at least partly designed using the Workbench: During the two-year period, about 170 design activities were initiated in the Workbench. Of those, 120 evaluated design elements and 70 of those had completed the entire design process from design remit to program options per the process shown in Figure 2.

5. Feedback from design teams

Feedback on the new way of working was gathered through systematic interviews, as well as spontaneous feedback from design teams. Feedback on the design framework was generally positive because it encouraged in-depth analysis and creativity early in the development process, thereby minimizing wasted time and effort due to poor design decisions.

Executives appreciated the transparency of the approach, which gave them visibility into the design process outside formal reviews. It also enabled frequent, ad hoc interactions with the design teams, in addition to formal reviews.

In many cases, the new design process revealed a lack of clarity in the product vision and the questions the studies were meant to answer. This was a positive and intended result, which led to identifying additional opportunities to evolve the program design.

As the organizational structure provided flexibility to the core team when it came to including other domain experts, the size of design teams varied across projects. Some

design teams successfully implemented the new small-team approach and found it more efficient. However, many teams retained the old approach of calling a large, standing group of people to attend design meetings, which was perceived as being more inclusive. However, inclusivity came at the cost of being ineffective for various reasons, including having to communicate across regions, ensuring availability of a large number of team members, and resource constraints across multiple ongoing projects. Hence, a key challenge appeared to be striking the right balance between a small, empowered team and involvement of the full range of domain experts. The absence of clear guidelines on decision rights[7] and lack of clarity on accountability of various domain expert areas for various design decisions may have contributed to the variable inclusion of domain experts on design teams.

Both design teams and executives generally favored the Integrative Thinking approach. While some individuals said it was just common sense, the majority found it helpful as an explicit framework that encouraged creativity. The process of identifying, analyzing and integrating multiple options was considered effective, but sometimes generated too many, sometimes unrealistic, options. Some teams found it worthwhile to limit free-ranging discussions to only certain, complex situations and use the faster, tried-and-true approach to simpler, more familiar situations.

Both design teams and executives generally found the Workbench tool useful for documenting decisions and sharing information between projects, but too slow and cumbersome to support active collaboration or design activities. That may explain why use of the Workbench peaked one year after implementation and then declined.

Members from 13 design teams among the first to complete the design of an entire program using the design framework were interviewed. The findings from these interviews were as follows:

- All design teams perceived improvements in the quality of their clinical development programs, e.g., responsible scientists believed that the right studies were being performed.
- Eight design teams believed that the framework helped them generate options that reduced cost to a greater extent than the options they had considered before using the framework. Four teams also perceived that they reduced the time it took to design the program.
- Three design teams stated that a thorough approach to design aided in making the decision to terminate development without conducting additional studies.

6. Impact on key performance indicators

The leadership team had agreed upon four leading key performance indicators (KPIs) to assess whether the initiative resulted in an improved outcome across the entire clinical development organization: quality of design, complexity of clinical trials, number of protocol amendments, and time for protocol development.

Quality of design

To assess overall quality of design across multiple proposed program options (typically one option each, optimizing cost, speed and robustness), senior internal reviewers of development programs were asked: "To what extent was the committee satisfied with the overall quality of the design options proposed?" Subject to the limitation that this was an informal and unvalidated survey with no baseline assessment, teams that used the Workbench were more likely to achieve higher design quality scores (Figure 3), but there was no clear trend of change over time.

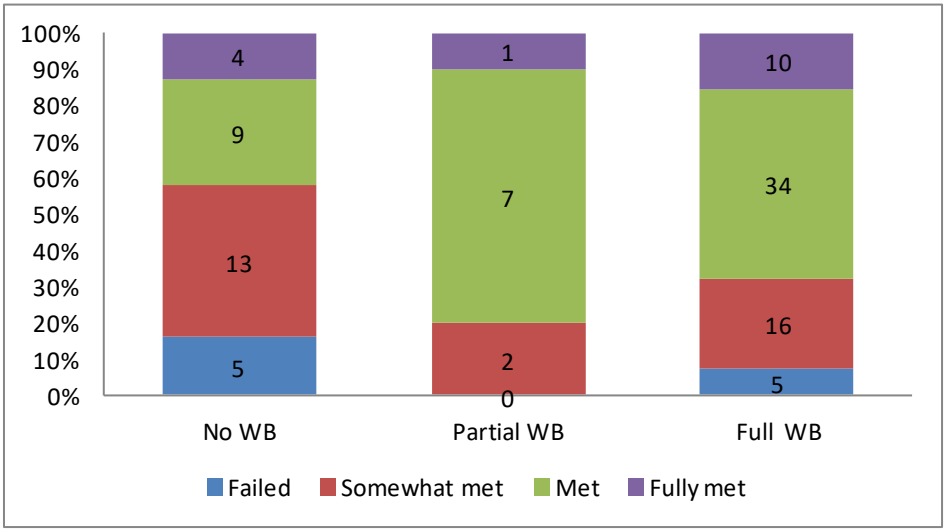

Figure 3. Assessment of Design Quality by Peer Reviewers
(WB stands for D&I Workbench.)

Complexity of clinical trials

Complexity of protocols was assessed using the methodology described by the Tufts Center for the Study of Drug Development[8]. A subset of AstraZeneca studies was benchmarked against an industry average stratified for therapeutic area and phase of development. The results suggest that, prior to the framework implementation, AstraZeneca Phase 1-3 studies were substantially more complex than the industry average, but, since the introduction of the design framework, they are now roughly at the industry average for all phases (Figure 4).

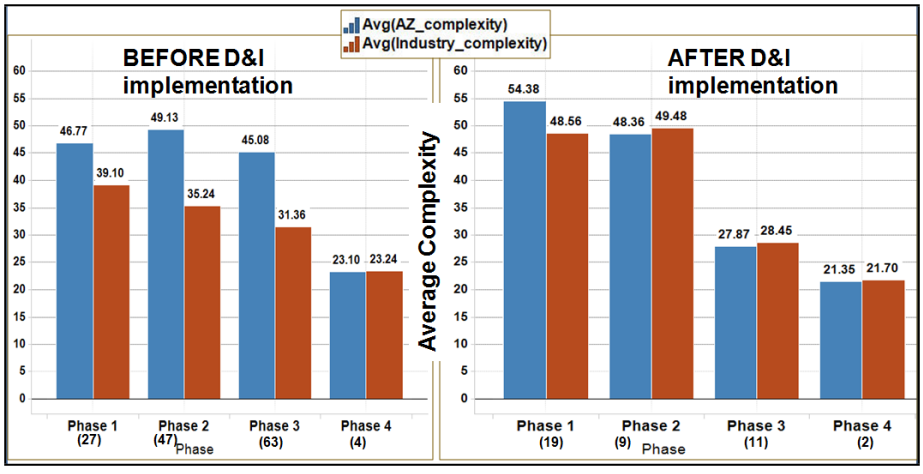

Figure 4. Complexity of Clinical Trials Before and After Introduction of the Design Framework.
(Numbers in parentheses are numbers of AstraZeneca studies assessed.)

Number of protocol amendments

The average number of protocol amendments was measured by counting the number of amendment documents in the regulatory document repository and dividing by the number of ongoing studies. This measurement did not control for the age of the studies or how many different amendments are described in each amendment document.

Across all phases and therapeutic areas, in a sample of 710 studies before introduction of the design framework, there were 1.8 amendments per ongoing study. After introduction there were 1.2 amendments per ongoing study in a sample of 134.

Time for protocol development

It was anticipated that a thorough design effort would result in faster protocol development, as measured from the date the study outline (i.e., the output from design that provides the scientific content for authoring protocols) was approved by senior management until the date the study protocol was finalized, because the new design process would reduce the need for changes downstream during protocol development. However, no effect on time for protocol development was observed, perhaps because vendors produced many protocols with a contracted time for development.

7. Discussion: Evolution of the design framework

Two years after implementation, it appeared that the clinical trial design framework had brought both qualitative and quantitative benefits to drug development. All of the key performance indicators had methodological limitations, but as both the qualitative and quantitative metrics largely pointed in the same direction it was reasonable to conclude that the intervention had a positive effect. Given the extensive change campaign, it is possible that part of the observed effect was due to heightened management focus on the design process.

Since then, the design framework has evolved in response to feedback from design teams during implementation. Some of the more recent refinements are as follows:

1. Since executives appreciated increased transparency in decision-making with the new framework, this aspect was further strengthened with the introduction of new decision tools and techniques, such as multi-criteria decision analysis (MCDA)[11].
2. In many cases, the design process revealed a lack of clarity in the product vision and the questions the studies were meant to answer. In response to this feedback, initiatives aimed at improving the process for developing target product profile and target product claims have been initiated.
3. The process of identifying, analyzing and integrating multiple options was considered effective, but sometimes generated too many, sometimes unrealistic options. Uncertainty quantification for program options was therefore introduced as a way to evaluate options based on their ability to address key program risks and uncertainties.
4. A need for simpler, data-driven, nimble decision-making was recognized. In response to this need, while design teams adopted the basic principles inherent in the new design framework, a prototyping-based, flexible and agile approach to design was incorporated.
5. The principles of Integrative Thinking were recognized as highly valuable for decision-making during clinical trial and program design. It was further strengthened

through greater focus on decision analysis as a set of tools to enhance quantitative evaluation of design options, supported by creative, transparent decision-making.

8. Conclusion

The new framework for clinical trial and program design presented an opportunity to achieve high-quality decision-making in drug development. After two years of deployment, tangible progress along the journey toward consistently high-quality clinical trial design was observed. The principles behind the framework gained acceptance within the clinical development organization and areas of improvement were identified, particularly in terms of simplifying parts of the methodology that were perceived to be demanding and time consuming. The new framework has proved to be a solid foundation for ongoing refinements in the design process.

The quality of decision-making in an R&D organization is expected to be only as strong as its weakest link among several interlinked organizational capabilities. In addition to the use of quantitative techniques for evaluation of benefit-risk during drug development, qualitative and behavioral aspects, such as transparency of rationale and assumptions, clear accountability and decision rights, and an Integrative Thinking stance were found to be crucial to the success of clinical trial design and interpretation.

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