Clinical Development Design Framework

Title: Clinical Development Design (CDD) Framework

Type: White Paper

Authors: TBD

OUTLINE NOTES

1. EXECUTIVE SUMMARY:

2. INTRODUCTION:

This work is defined by our need to determine the components, vocabulary, and components of Clinical Development Design Framework. Some might call them the tags, keywords, concepts, or bubbles of Clinical Development Design Framework—mapping the Clinical Development Design Framework. We have protocol components. We have database structures, but we are talking about more than data. We are talking about information. We know what is required for regulatory filings, but how do we elucidate the decision making processes and capture the components that formed a part of our process.

In “Thinking: Fast and Slow” Kahneman explores decision making and discusses ways to abstract the essentials from our design processes.

"...Organizations can institute and enforce the application of useful checklists, as well as more elaborate exercises, such as reference-class forecasting and the premortem. At least in part by providing a distinctive vocabulary, organizations can also encourage a culture in which people watch out for one another as they approach minefields. Whatever else it produces, an organization is a factory that manufactures judgments and decisions. Every factory must have ways to insure the quality of its products in the initial design, in fabrication, and in final inspections. The corresponding stages in the production of decisions are the framing of the problem that is to be solved, the collection of relevant information leading to a decision, and reflection and review. An organization that seeks to improve its decision product should routinely look for efficiency improvements at each of these stages.” (p. 430).

3. PROCESS IN CLINICAL DEVELOPMENT DESIGN FRAMEWORK: In this paper we are working on a roadmap for the process. Just as Kahneman noted we are manufacturing judgments and decision. We need to insure the quality of our products in design, in fabrication, and in final inspection. Each stage demands decisions in how to frame the problem to be solved, collecting the relevant information leading to the decisions, and reflecting and reviewing our decisions. Steven Hirschfeld’s proposes the major components that need to be mapped in the design process. We will discuss how to frame the problems that need to be solved and how to collect relevant the
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information for the decisions that need to be made. [[Ian Fisher will add to this discussion.]]

4. **SEMANTIC TECHNOLOGY**: Once we outline the Design Process, we will start looking at ways to use Semantic Technology to assist us and how other companies have successfully incorporated Semantic Technology. Mitra Rocca will give us a foundation in Semantic Technology and will look at a few of the important structural elements in using semantic technology. Tarek Elbeik will introduce us to the use of Semantic Technology in other industries. He will show us how Raytheon was able to incorporate Semantic Technology in the defense industry. Tarek and Mitra will provide us with additional examples of Semantic Technology and show us tools from other industries that we may be able to use for our design work.

5. **FRAMEWORK**: Now we want to look at those tags that we talked about in the beginning. We need to put together a vocabulary that we can use to tag our work. Asiyah Yu Lin’s will show us the steps in building an ontology. Maria Benjegard and Kerstin Forsberg will then share their work on visualizing the design process. Maria details how the framework is operationalized integrating work the Clinical Trial Transformation Initiative on Quality by Design. We will also look at the Target Product Profile and how this initiative plays an important role in understanding decisions in producing a quality product. We cannot forget risk assessment for any clinical program. Johann Proeve will present his thoughts on how we determine risk assessment in a clinical program. This section will provide us the foundation or framework for CLINICAL DEVELOPMENT DESIGN FRAMEWORK.

6. **REGULATORY REQUIREMENTS**: All of our work in the pharmaceutical industry is bound by regulatory requirements. Hon Son Ko provides us with details about regulatory requirements and helps us think about these requirements influence our decision process. Rashedul Hasan will show us how the ability to map regulations to RDF will support us in achieving a quality product.

7. **EXPERIENCE WITH DESIGN IN PHARMA**: In order to put all of the above suggestions, thoughts, ideas together, we need to see what has already been tried in the pharmaceutical industry. Laszlo Vasko will review the Smart Design Project for Epfia – what worked and did not work. Matt Austin will tell us about their current tool and how change management needs to be part of the endeavor.

8. **CONCLUSION**: Considerations for future work.

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Title: Clinical Development Program Design (CDPD) Framework

Type: White Paper

Authors: TBD

The White Paper

1. EXECUTIVE SUMMARY:

2. INTRODUCTION:

What is a clinical plan (can’t find program)? "A document describing the clinical studies that must be performed during the development of a particular active substance, device, procedure or treatment strategy, typically with the intention of submitting the study data as part of an application to the FDA for marketing authorisation. The plan should indicate appropriate decision points and allow for trial modifications as knowledge accumulates". http://medical-dictionary.thefreedictionary.com/clinical+development+plan

Three broad topics are considered in the development of a clinical development program and include:

1. Establishing a Framework: What are the characteristics of the components that can provide the data and experience to make decisions
2. Operationalizing the activity: Considerations of the activities that need to be addressed and integrated in each component
3. Analyzing the outcomes and making decisions: Several interim decisions may arise before deciding on the end result

The proposed CDPD Framework addresses all components needed for a clinical development program, and includes:

1. Regulatory: Requirements required by regulatory agents, as well as key contacts to facilitate information exchange and the spirit of cooperation.
2. Research and Development: Historical and legacy data, as well as current research in the field of endeavor.
3. Practical Application: The process of collecting all sub-components of information required to implement a program, including cohorts, investigators, third parties, issues, data entry
4. Decision Making and Justifications: The collection all historic information that influenced decision making, as well as individuals making the decisions.
Ultimately, as shown in Figure 3 the clinical trial component of the Design framework will address an intervention, a population and a condition.

As shown in Figure 4, the CDD Framework will:
1. Set goals
2. Characterize Intervention
3. Demonstrate benefit & risk
While the components provide a framework CDPD can be attained, clinical studies must also be considered to further CDPD. They include:

- Designed in order to minimize bias and uncertainty
- Contrived to model circumstances that are generally complex
- Generalized to people similar to those that participated in the study and perhaps extended to other circumstances
- Designed by intent so that the outcome can be replicated

3. PROCESS IN CLINICAL DEVELOPMENT DESIGN FRAMEWORK:

To be consistent, all components need to be addressed from this point forward. The term sub component will be used to define “sub components” of components. We will do away with the term “elements”. This section needs to expand on the components and sub components. A list of Sub components for each component would be necessary to guide the reader and avoid confusion.
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**Paragraph: Ian Fisher**

**Regulatory:**

**Research and Development:**

**Practical Application: Cohort Subcomponent**

![Diagram]

**Favorable benefit with acceptable and manageable risk**

**Characterized target population**

**Calibrated Intervention**

**Figure 2. Practical Application. Cohort Subcomponent - Hirschfeld**

**Decision Making and Justifications:**

Commented [TE8]: Ian Fisher: Add paragraph based on his work. About what?

Deleted: The following figures were presented by Steven Hirschfeld at the 2016 PhUSE CSS Conference.

Commented [TE9]: Hon Sum Ko to develop this section

Commented [TE10]: Who will address this section? Maria?

Commented [TE11]: Steven to develop this section (Practical Application. Cohort Subcomponent)

Commented [TE14]: Steven and OTHERS to develop this section (Decision Making and Justification)

Deleted: Framework

[[Steven Hirschfeld adding a paragraph discussing the difference between component and element.]]
While the components provide a framework of CDPD can be attained, clinical studies must also be considered to further CDPD. They include:

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- Designed by intent so that the outcome can be replicated

### Risk/Benefit

4. **SEMANTIC TECHNOLOGY:**
The conventional approach to store and access information is by categorizing and indexing information into databases. However, the source and type of information used to build databases may not have the same structure, content or fidelity. The collection and incorporation of such information may result in disparate output.
Semantic technologies represent a family of technologies. These include:

- Natural Language Processing (NLP)
- Artificial Intelligence (AI) and expert systems/Knowledge-based systems,
- Data mining
- Classification
- Semantic search.

All these technologies aim at making sense of large and complex sets of data.

Semantic web technologies are World Wide Web Consortium (W3C) standards, which are designed to describe and relate data on the Web and inside enterprises. These standards include:

- Resource Description Framework (RDF), a flexible data model
- Schema and ontology languages for describing concepts and relationships (RDFS and OWL)
- A query language (SPARQL)
- A rules language (RIF),
- And others.

Semantic web technologies are well-suited for implementing algorithms and solutions for semantic technology.

For semantic technology well defined rules are established that convey meaning to specific words. In doing so, an assortment of words that have the same meaning (as defined by semantic rules) allows for an overarching search with far greater returns than relying on a search of each word. Moreover, with linked WEB data, the user can search for information on the WEB and circumvent the need to rely entirely on customized databases. However, some of the linked data sources can be:

- Unstable
- Outdated / not maintained
- Difficult to discover, explore
- Largely undocumented
- Time consuming to create

In other words, the user needs to be aware that not all information listed in the WEB is valid.

[[Add examples from the pharmaceutical industry – perhaps Yosemite Project.]]

While rules are created to establish meaning to specific words, the relationship of words is established through ontology, which defines concepts and their relations, classes, hierarchies. For example, a search for “Batman” on the Walmart website during Halloween will direct the customer to Batman costumes, then to movies. Any other time during the year the search will first come up with movies. This is a simple example of how ontology is used to relate words and meanings in order to provide a valid output. Ontology is more formal than vocabulary, and relies on specific rules as well as a comprehensive
understanding of the field. It would be counterproductive for an electric engineer to develop ontology for biomedical research as it would be for a biomedical researcher to develop ontology for electrical engineering. Consequently, vocabulary and ontologies become their own language, and therefore establishing consistent rules by internationally recognized “ontology” groups becomes a necessity to avoid redundancies and incompatible languages.

As reported in The 2013 Cochrane Technical Report: The role of linked data in meeting our strategic goals, “The choice for all major content providers is not whether to adopt a linked data approach but when. Asking ‘do we need linked data?’ today may be analogous to asking ‘do we really need a website?’ 13 years ago.”

How then, can the pharmaceutical industry use semantic technology in developing a clinical design program? Obtaining intelligence for input into the program design, as well as the intended protocols, appropriate data analyses, clinical study reports and regulatory submission. These components, attainable through semantic technology, are incorporated in the Clinical Design Framework in a comprehensive yet temporal arrangement as described in the section “The design framework, issues and proposed solutions”, below.

Current Use of Semantic Technology

Implementation of semantic technology has been described in the work by Breindel, using Raytheon Integrated Defense Systems as a model to identify industry issues and solutions. In this model, displayed in Figure 5, five issues relating to the implementation of semantic technology were identified and included:

- Incorporation of legacy information
- Ease of adoption
- Robustness of file type support
- Security
- Addressing the end user
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Figure 5. Breindel’s Steps and Tools for Raytheon

In terms of incorporation of legacy information, pre-existing information maintained by the organization must be assimilated and saved, and associated with newly collected information. The goal is to ensure the association of all information to justify prior and ongoing programs, and provide justification for new programs. Ease of adoption addresses what challenges are in place to make the transition, what new software is needed, and what software customization is required to fulfill the organization’s objectives. The robustness of file type support takes into account the backing of several file types incorporated in a single database. These file types reflect how data was previously collected and stored, as well as file types that are currently in use and those that are anticipated. Security options regulate who can access data, and moreover, the means to protect data from unwanted access or manipulation. And finally, addressing the end user provides the ease at which staff can transition to a new system, with a priority to keep the new technology as intuitive and simple as feasible. In short, to implement Semantic Technology requires transitioning from outdated data collecting and sharing within the existing IT infrastructure to a new model that addresses anticipated needs.

Several industry sectors have addressed the challenges described, generating new opportunities to reduce costs, compete and grow. These include, for example, financial services, entertainment, travel, aeronautics, aerospace, avionics, weapons, healthcare and clinical research. Each industry had its specific challenges, but the underlying principal is to rapidly obtain useful information interpretable by the necessary departments to rapidly adapt to a dynamic environment and develop new products, all the while complying with regulations. Where does the pharmaceutical industry fit in this, and what shared tools can be used to benefit the industry as a whole, the individual companies, and the consumers?

5. FRAMEWORK

We have looked at the structure of the Clinical Design Process and the advantages afforded by using Semantic Technology. Next we need to look at the vocabulary for our framework or as we liked to describe as tagging. Asiyah Yu Lin will detail the steps in building an ontology.

[[Asiyah’s outline: Summary and introduction of ontologies, especially Reg2RDF, and its application for Clinical Development Design Framework]]

Figure 6 discusses why we need an ontology.

Ontology
Why do we need an ontology?

Ontologies are content theories about the sorts of objects, properties of objects, and relations between objects that are possible in a specified domain of knowledge. Ontology provides potential terms for describing our knowledge about the domain.

- provide a robust and coherent organization of knowledge
- integrate prior knowledge
- help manage complexity of the domain knowledge
- discover new knowledge
- To share common understanding of the structure of information among people or software agents
- To enable reuse of domain knowledge
- To make domain assumptions explicit
- To separate domain knowledge from the operational knowledge
- To analyze domain knowledge

Figure 6. Why Do Need an Ontology?

Visualizing Clinical Development Design Framework
As shown in Figure 7, Maria Benjegard looks at scientific, operational, and regulatory perspectives for the vocabulary for a clinical design program.

[[work with Maria Benjegard on harmonizing terms throughout the paper.]]
The development of a clinical design program requires the input of three key components, including:

1. Justification from research findings (internal documents and peer review publications) - Scientific
2. Target study subjects (all profiles) - Operational
3. Regulatory information (law and guidance) - Regulatory

While some information is apparent or derived from other clinical design programs, other information, such as research findings, specific patient demographics, or recent changes in regulatory information, is considered crucial for resolution from discussion or input by key opinion leaders.

Input of required information for each component will be influenced by the following variables:

- Remit for consideration
- Perceived and discounted risks
- Perceived and discounted assumption
- Perceived and discounted constraints

Figure 7. Information Needed for a Clinical Design Program

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The framework represents both baseline and temporal input of facts and decisions to facilitate a precise and orderly development of a clinical design program. For example, how will the endpoint be determined, and what type of data is needed? How will the data be captured and measured, and how does it influence decision making and regulatory requirements? How do all of these components uncover missing information? This real-time, high-level association of information compels rapid decision making, thereby avoiding unwanted consequences including deviation from regulatory requirements, risk to study subjects, negative publicity, legal issues, and protracted financial loss.

Consequently, as most clinical design components can be defined by specific topics and subtopics, a standard design for a clinical design program framework with a required knowledge base can be developed. The model can be used to either:

- Obtain information driving the design
- Validate some or all parts of the design
- Combine both information to drive, and validate, some or all parts of the design

The clinical design program framework with the required informational knowledge base can be visualized in Figure 8. This presents a comprehensive temporal model driven by time constraints, sequential input and both dependent and independent variables. The top arrow represents linear time with each traversed circle representing a decision.

![Figure 8: Visualization of activities in design.](image)

Each “decision” is linked to an activity and requires information that provides feedback to the “decision”. It details activities that were influenced by a previous “decision” (i.e.,
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change in study subject age) and those that will influence a subsequent “decision” (i.e., require additional evaluation of a study site).

Consequently, each activity will be defined by different parameters, including:
- What should be considered
- What it will influence
- What it was influenced by
- If additional information is needed
- When to execute
- When to commit and lock in place aspects of the framework

While the clinical design program framework will list the required components (decision and activities), it does not mean it will contain the correct information needed for the protocol, or to initiate the study. As all components (decision and activities) are directly or indirectly linked, this network of checks and balances will either confirm or dispute the type of informational input.

Different steps are taken to validate a clinical design program framework. These may include:
- A framework checklist
- An outcome checklist

A framework checklist will assess the connectivity within the framework, and include:
- Endpoints clearly connected to objectives and measures
- Aspects of design, population, trial design, comparator, drug and geographic location; supporting collected measure
- Assessments linked to the time perspective and connected to the measures.

Once these three aspects are confirmed, an outcome checklist can be followed through representing the patient, site and sponsor as defined in Table 1.

Table 1: Outcome checklist to validate a clinical design program framework prior to protocol development

<table>
<thead>
<tr>
<th>Patient</th>
<th>Site</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Will the patients join the trial?</td>
<td>- Are objectives and endpoints connected?</td>
<td>- Are endpoints supporting design questions?</td>
</tr>
<tr>
<td>- Are all measure collected used?</td>
<td>- Are the objectives describing current procedures and clinical practice?</td>
<td>- Are endpoints supported by the right information from population, trial design, comparator, drug and geographic location?</td>
</tr>
</tbody>
</table>

| Are the measure collected support endpoints? |

The same approach can be used to validate a protocol developed from the clinical design

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program framework. By baselining the output of the design, a change in the protocol can be used to modify the clinical design program framework. Ultimately, this harks back to the clinical design program framework input, and if the scientific, regulatory and operational aspects were appropriately reviewed, documented and decided on to achieve the label.

The same question used as validation of design could be used in validating the protocol. The change management will document changes to design and what changes will impact results and future interpretation.

An example of Tools for the validation can be the perspective of Risk Based monitoring and Quality by Design. This can be used both in the purpose of validation but also as the input to the development of the protocol and to the conduct of the trial to ensure the focus is on what is most critical.

Risk Assessment
As discussed earlier, there is a continuous need for risk assessment. Johan Proeve guides us through this process.

[[Johan or other author: Hon Sum would like to know: Regarding your comment for more examples on "Applying regulatory requirements to the Design Framework is an essential component in controlling risk", it is not clear what "risk" we are trying to address – is it about risk to study subjects, or risk of failure of the Clinical Program,] or risk to the organization itself? These are very different risks and so the statement requires some clarification.]]
Risk Management: Clinical Trials

Risk Management: Systematic process for the assessment, control, communication, and review of risks associated with the planning and conduct of clinical trials and clinical development programs.
- Quality in clinical trials = Quality Risk Management
- Risk: System, Project-Trial

EMA reflection paper on risk based quality management in clinical trials
November, 2013

Figure 9. Risk Management

Figure 10. Components of Risk Management

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6. **REGULATORY REQUIREMENTS**

As we have seen in the framework section, risk assessment and management requires an understanding of regulatory parameters. The design framework can help us with simplifying our understanding and assist us in adherence to the FDA or other regulatory bodies’ administrative practices and procedures. Mapping to regulations and using the Target Product Profile (TPP) to assure that we have captured the essential sub-components in the Design process are important components in adhering to regulatory requirements.

“The FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.”

First it helps us to know the difference between “Guidance” and “Law”, which can best be summarized by 21 CFR Part 10: Food and Drug Administration regulations, recommendations, and agreements.

[[Hon Sum will clarify.]]

These three terms: regulations, recommendations and agreements are differentiated based on the level of legal enforcement. Sometimes, the corresponding documents will contain exceptions that may appear contradictory to the stakeholder. There are a variety of reasons why documents may include exceptions, and are incorporated during advancement from draft to a final version. A close working relation between the stakeholder(s) and the FDA officer helps facilitate a clear understanding.

- **Regulation.** A directive that may contain legally enforceable requirements, as well as guidance and recommendations, which are not legally enforced.

- **Recommendation.** A proposal for the guidance and is based on a law established by a commissioner of a model State or local ordinance that cannot be regulated by the Federal Government.

- **Agreement.** A document stating a negotiated arrangement or memorandum of understanding between the FDA and stakeholder(s), and made accessible to the public.

For Design purposes it is important for us to know when guidance becomes law, we are notified through the Federal Register. A Federal Register notice or regulation is the means by which the Federal Government announces changes in policy. In terms of the FDA, a Federal Register notice or regulation will present a new or change in policy related to, for example, a pharmaceutical product. While the FDA will initiate the draft process, it is highly recommended that the stakeholder(s) contact a representative of the FDA to propose ideas for developing a draft notice or regulation. In doing so, the stakeholder(s)
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and FDA establish a working relation early in the process. Once prepared by the FDA, the draft document is open for discussion and amendments to produce a final document.

Good Guidance Practices is an FDA defined protocol, and used by the FDA to develop, issue and apply a guidance document. A guidance document is a recommendation based on expert opinion (from within the FDA, stakeholders and recognized experts). Applying regulatory requirements to the Design Framework is an essential component in controlling risk.

[[Rashedul – can you tell us why this map is helpful in Designing a product?]]

Figure 11 is provided by Rashedul Hasan. We would like to link Rashedul’s figure to both the regulations and the framework to help us in mapping the regulatory process in Design.

Figure 11. 21 CFR Part 201

Throughout this paper we have been struggling to define a unique and acceptable vocabulary and mapping for our Design work, which meets regulatory requirements. The FDA provides guidance with a list of labelling concepts in The Target Product Profile (TPP) and suggestions for what should be addressed in the label. Sponsors often want more information on adequately addressing these concepts. Another resource can be found in checklists from the FDA, which are provided for sponsors to review their submissions. The 41 item “Selected Requirements of Prescribing Information” checklist details required and optional. Our framework can offer us a link between the Target Product Profile (TPP) and these checklists. We can also link the TPP with Quality by Design and Risk Assessment.

Using the TPP the CDD Framework needs to include details about these labeling concepts:

- **Indications and Usage**
- **Dosage and Administration**

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- Dosage Forms and Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations
- Drug Abuse and Dependence
- Overdosage
- Description
- Clinical Pharmacology
- Nonclinical Toxicology
- Clinical Studies
- References
- How Supplied/Storage and Handling
- Patient Counseling Information

With each of the above sections, the FDA offers some cogent advice. For example, for Indications and Usage, the FDA is looking for a statement with supporting studies that show that the drug is indicated for treatment of a disease or relief of symptoms or in conjunction with a primary therapy. These same type of guidance is found with each of the concepts.

We can link guidance and recommendation in the following way. First, we have the TPP information: For Patient Counseling Information, the FDA requests that information for prescribers to convey to patients be given that discusses side effects, concomitant use, adverse reactions, lab tests for monitoring; and whether a Patient Package Insert will be included.

The TPP section on Patient Counseling can then be linked to the checklist.

**PATIENT COUNSELING INFORMATION Section in the FPI**

40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).

7. EXPERIENCE WITH DESIGN IN PHARMA

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[[Laszlo will review the Smart Design work from Epfia – the successes and failures.19,27 Ian will look at the Quintiles project. Matt will talk about the tool that is presently being used – again discuss successes and failures. They will also look at Change Management and how this plays a role in the use of new CDD Framework tools, 20,28,29]]

[[Notes Ian, Laszlo, Matt Discussion: The work of this group is on macro principles in design thinking. With the framework and TPP there is a real need – for the design thinking. We need to know how this information model can help them. We need testing to make sure it works.
In terms of the work we need the data and IT solutions. Calculations, design thinking, and engaging all the people through a clearly defined and stated goal.]]

8. **CONCLUSION:**

**REFERENCES**


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