Data-driven Decision-making Through a Clinical Development Design (CDD) Framework

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Disclaimer/Disclosure

This presentation reflects the views of the presenter and does not represent views or policies of FDA or other organizations.

Presenter has no conflicts to disclose.

Outline of Presentation

- Regulatory standards for clinical development
- Design thinking for clinical development
- Need for clinical development design (CDD) Framework
- CDD Framework description
- Decision-making and data
- Potential use of CDD Framework for decisions and examples
- CDD Framework future prospects

Regulatory Standards for Clinical Development

In the U.S., clinical development of a drug product is regulated by statutes, regulations and guidances.

- Statutes are laws passed in Congress and signed into effect by the President, e.g., Food, Drug and Cosmetic Act .
- Regulations are promulgated by FDA and come into effect upon codification by Final Rule in the Federal Register, e.g., labeling regulations on prescription drugs.
- Guidances provide FDA's current thinking of and its recommendations on a specific topic, e.g., ICH guidances.

Design Thinking for Clinical Development

A PhUSE cross-industry initiative including participants from industry, FDA, and academia to work on an information model to underpin clinical development program design.

- Design as a process of creation, development and optimization of scientifically robust, operationally feasible and commercially relevant research program to generate compelling evidence for internal decision making and public confidence in the efficacy, safety and cost-effectiveness of new medical products.

Need for Clinical Development Design (CDD) Framework

Four key challenges were identified in achieving consistent high-quality development program designs*:

- Design information captured ad hoc.
- Inability to learn from past programs, within organizations and externally.
- Current industry information standards not covering program level or the rationale behind designs.
- Limited opportunities for progress in improving clinical development programs due to lack of new and collaborative tools.

*Vasko *et al*. Therapeutic Innovation & Regulatory Science 2015;49:116-25.

CDD Framework Description:
The Framework in a Nutshell

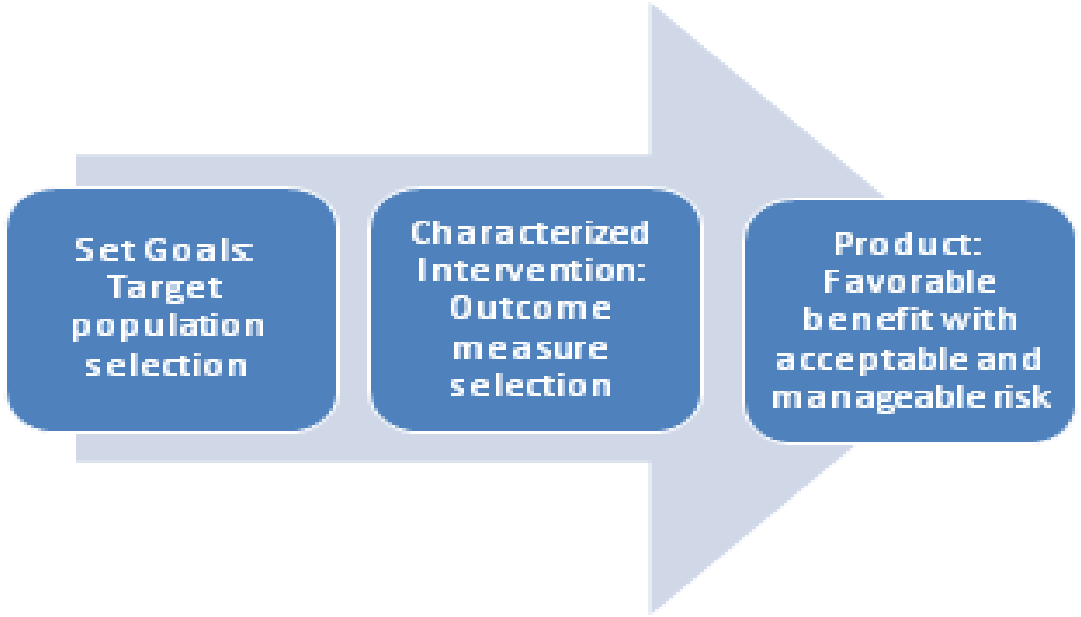
CDD Framework as an information model for capturing design decisions during clinical development of medical products and evidentiary basis for decisions, from inception to post-marketing surveillance.

- Development with considerations of the ontology and rationale behind clinical development program efforts.
- Exploration of the basics of design decisions and their value in achievement of high product quality: need for appropriate decision-making, interactions with regulatory agencies and management of risks associated with the program.
- Plans for mapping and tool-building to foster quality, which are dedicated to align with the Target Product Profile (TPP) of medical products and Kahneman's notion of reducing noise and improving decision-making.

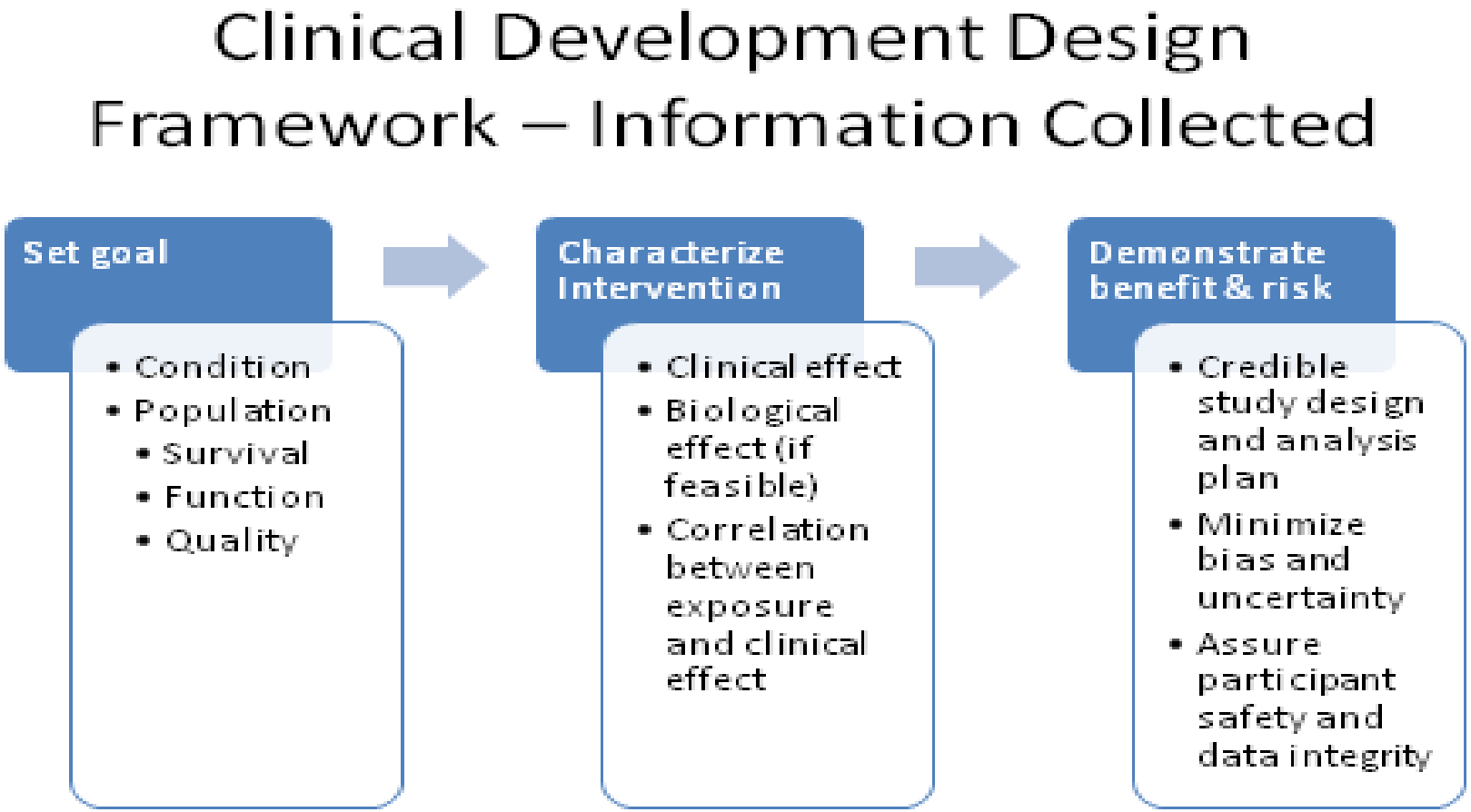
CDD Framework Description: *Elements (1)*

Clinical Development Design (CDD) Framework

- A suggested approach to CDD Framework is:

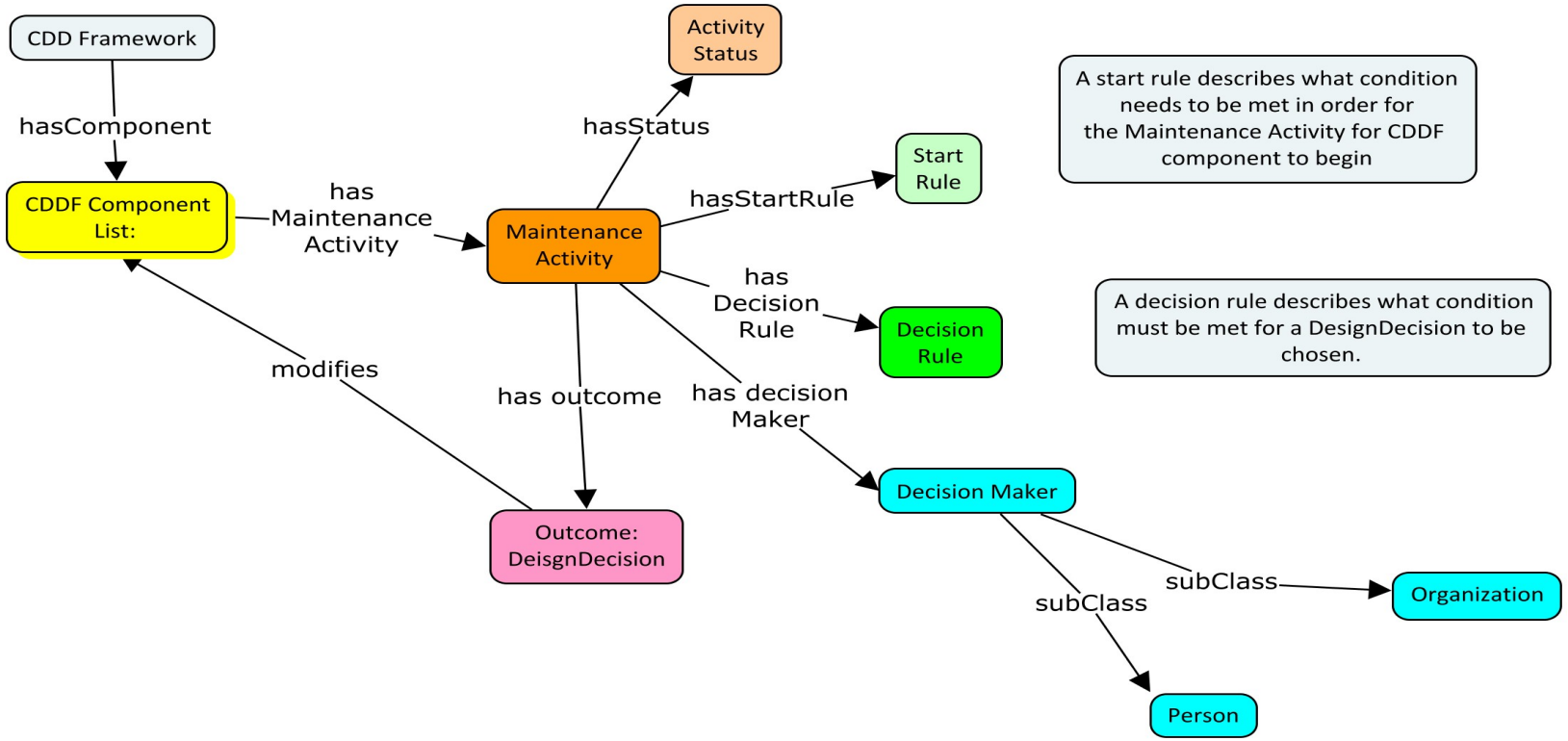


CDD Framework Description: *Elements (2)*

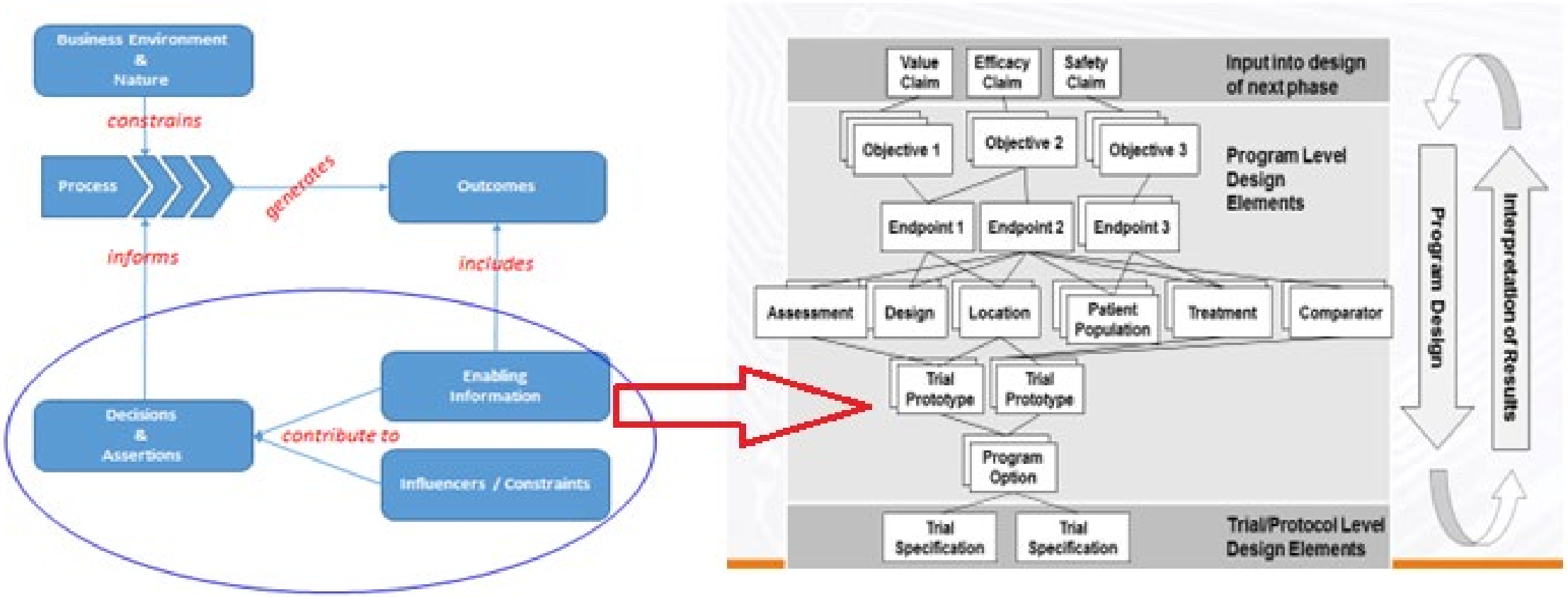


CDD Framework Description:
Concept Map (1) – Generic CDD Framework Map

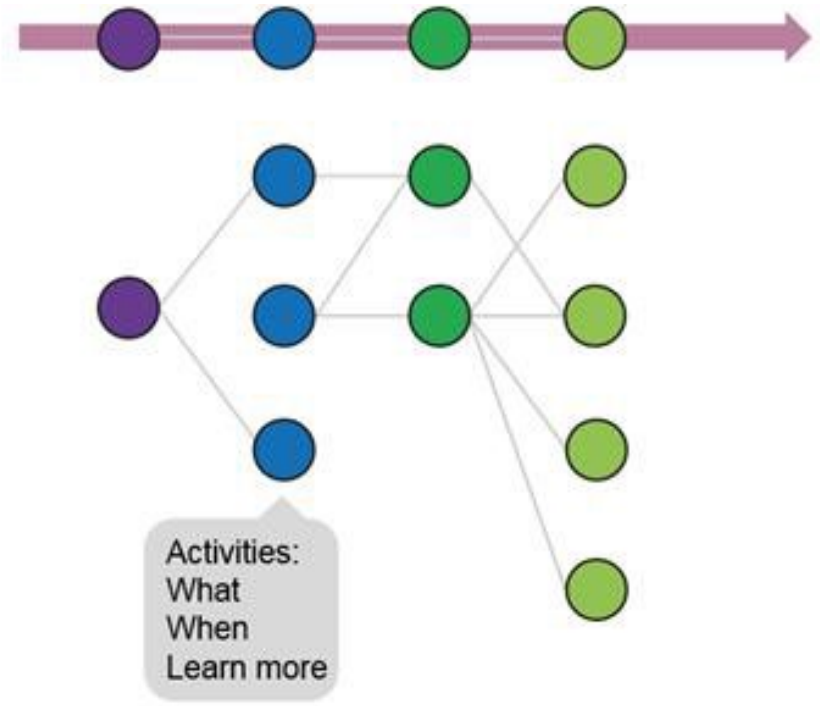
Figure 2. Generic Clinical Development Design Framework



CDD Framework Description:
Concept Map (2) - Supporting Claims



CDD Framework Description:
Concept Map (3) - CDD Activities in Its Simplest



- There is linear progression from first-in-human studies to postmarketing data collection.
- Each activity involves data-driven decision-making based on previous activity/activities.
- Data accumulation provides information model for knowledge management.

Decision-making and Data:
What Drives Decision-Making? (1)

Clinical development decision-making is different from clinical decision-making. Considerations include:

- Intervention versus target population
- Societal benefit
- Quality versus practicality
- Time-lines of the organization
- Anticipated success of development program
- Regulatory environment
- Investment return

Decision-making and Data:
What Drives Decision-Making? (2)

What do the patients really want?

- Do the study outcomes pertain to appropriate benefits desired by patients with the condition or a subset of such patients?
- Are the risks considered acceptable by patients with the condition?
- Because of patient heterogeneity, there will be variability in the answers to the above questions: clinical development decision-making needs data support to accommodate such variability.

Decision-making and Data:
What are Data?

Data are a set of values of subjects with respect to qualitative or quantitative variables (Wikipedia).

- Data are not monolithic. There are various types of data and may depend on how one classifies them.
- Data from clinical research may be raw data (from the case report forms) organized into tabulations or summary data after analysis presented as tables, listings or figures.
- Data from clinical research are also considered for analytic purposes as continuous and discrete.

Decision-making and Data: *What is Evidence?*

Evidence is information in support of an assertion (Wikipedia).

- Clinical study data provides evidence in support of safety and efficacy of a medical product.
- For drug products, substantial evidence of effectiveness from adequate and well-controlled investigations is required to support marketing.
- Evidence-based decision-making for clinical development is ultimately a data-driven process.

Decision-making and Data:
How do Data relate to Evidence?

Via ANALYTICS -

- Raw data from case report forms *per se* require organization and formatting into standard databases for analysis.
- Most decision-making processes are based on summary (analyzed) data, which provide the evidentiary support for the decision.
- Good quality data are necessary for good decision making.

Decision-making and Data:
Traditional versus Real World Data

Real World Data (RWD) – FDA defines RWD as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, e.g.:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices

Decision-making and Data: *Real World Evidence*

Real World Evidence (RWE) – FDA defines RWE as clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

- RWE can be generated by different study designs or analyses, including but not limited to:
  - randomized trials, including large simple trials,
  - pragmatic trials, and
  - observational studies (prospective and/or retrospective).
- RWE needs to be "fit-for-purpose" to be considered useful.

Decision-making and Data: *Artificial Intelligence*

Artificial intelligence will impact clinical development decision-making by:

- Accelerating the pace of clinical trials with facilitation of patient matching and hence enrollment, leading to earlier information to aid in decision-making
- Improving data collection and medication adherence, leading to higher quality data for decision-making.
- Ability for continuous monitoring of physiological and behavioral changes in patients, facilitating check-ups to provide real-time data to help decision-making.

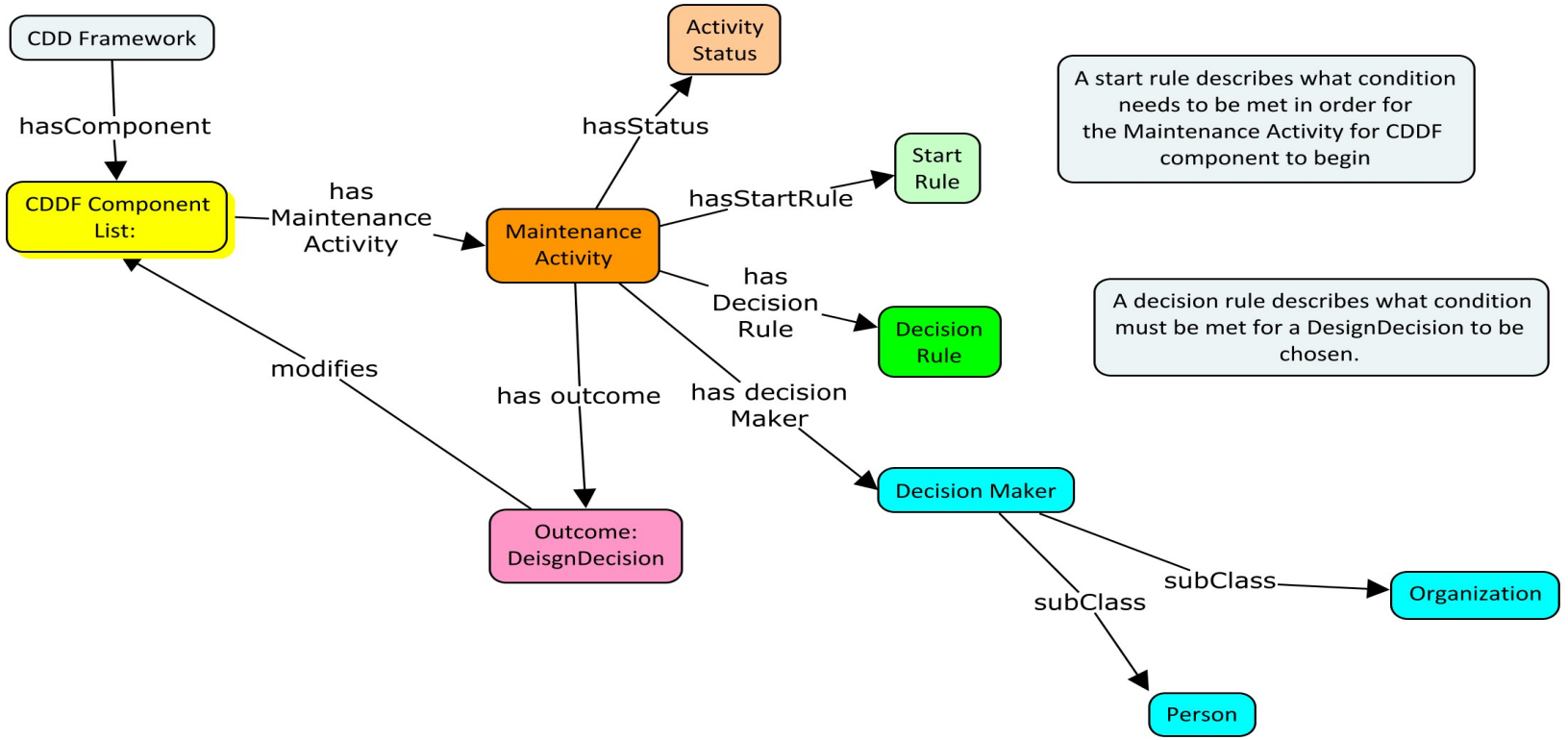
Decision-making and Data:
Challenges to Decision-making with Breakthrough Technology

Newer developments in data collection such as real world data, artificial intelligence and machine learning pose challenges in clinical development decision-making because:

- There are potential uncertainties of data quality.
- Validation or qualification of the methodologies to support decision-making may not have been conducted.
- Sponsors may be reluctant to use without recognition by regulators.
- Machine learning algorithm updates will require data and pose uncertainties in the interim.

Decision-making and Data:
CDD Framework - Decision-making

Figure 2. Generic Clinical Development Design Framework



Potential Use of CDD Framework for Decisions

Possible Rules:

- No Go as priority decision: Go is default - projects not to continue when data indicate success likelihood below threshold
- Go as priority decision: No Go is default - projects only to initiate or continue when data indicate success likelihood above threshold
- Go and No Go concurrently evaluated independently: success likelihood to failure likelihood compared to establish a hierarchy within the portfolio of all projects, with supporting data on the prospect of success.

Example of Potential Use of CDD Framework for Decisions (1): *Regulator*

- No Go as priority decision: Go is default – investigational new drug applications going into effect 30 days after submission unless put on clinical hold
- Go as priority decision: No Go is default – marketing applications for prior approval or clearance before marketing
- Go and No Go concurrently evaluated independently – unapproved bulk drug substances being considered for a list for compounding based on data submitted by nominators to meet specific criteria

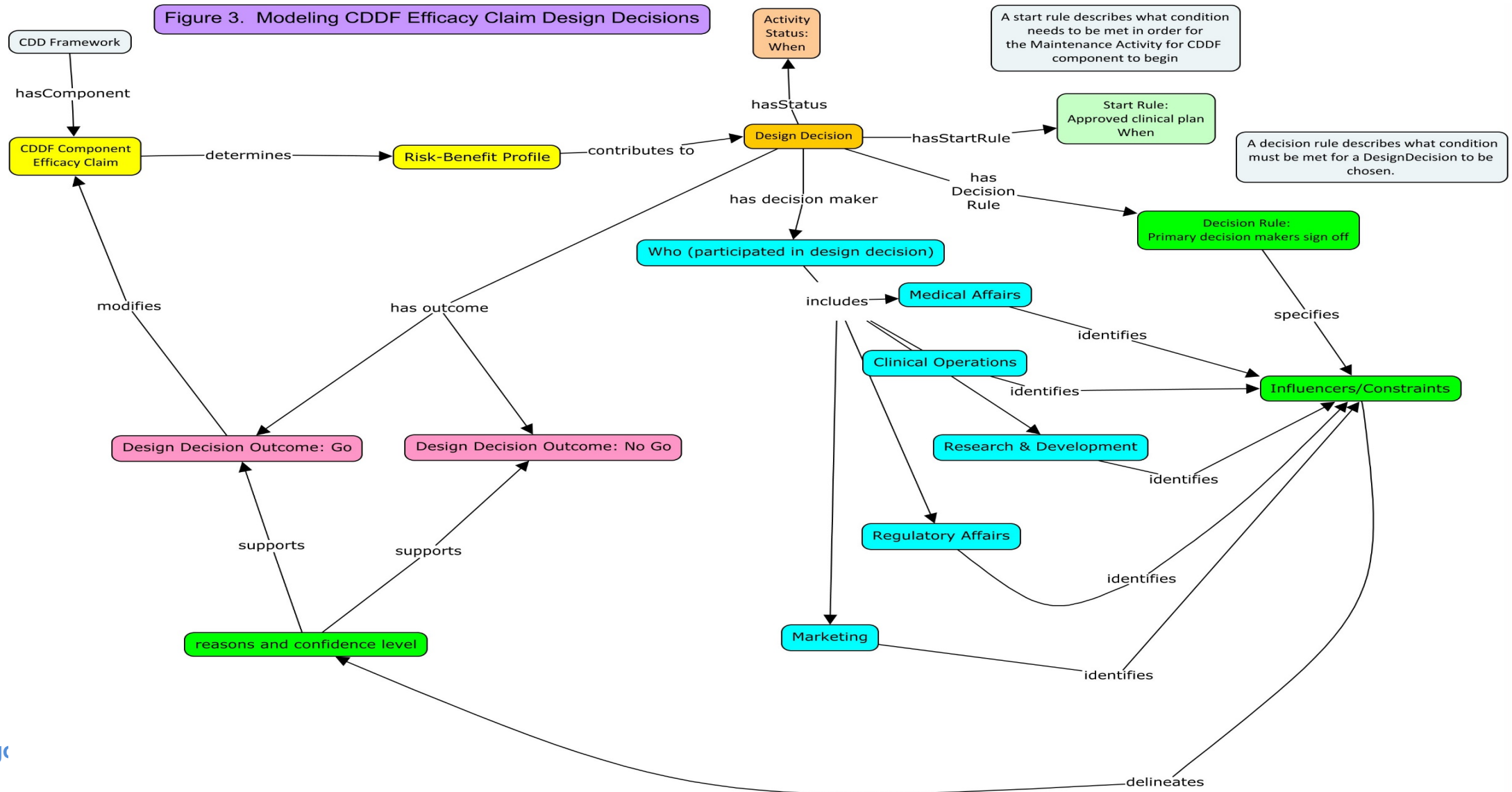
Example of Potential Use of CDD Framework for Decisions (2): *Academia*

- No Go as priority decision: Go is default – investigator to obtain informed consent of subjects participating in clinical research
- Go as priority decision: No Go is default – competitive funding to support clinical research with grants and contracts
- Go and No Go concurrently evaluated independently – investigator to make decision whether to apply for funding for a clinical research based on preliminary promising efficacy data of a drug with serious potential toxicity

Example of Potential Use of CDD Framework for Decisions (3): *Industry*

- No Go as priority decision: Go is default – submission of NDA upon obtaining data from successful clinical trials
- Go as priority decision: No Go is default – first-in-human study dose escalation depending on safety of initial dose
- Go and No Go concurrently evaluated independently – clinical site selection based on investigator qualifications, geography, IRB approval, etc.

Example of Potential Use of CDD Framework for Decisions (3a): *Industry*



CDD Framework Future Prospects

We have presented a CDD Framework as an information model to facilitate decision making based on data.

- Technological developments in data collection and management will change the research landscape and aid in the development of a more mature model for modern decision-making.
- There is need for tools such as CDD ontology to map out the design process and potential creation of a semantic web of RDF data cubes.
- The framework can serve as an instrument for data sharing to facilitate clinical research.

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Questions*?

*For additional questions after this event, you may contact Mary Banach at: marybanachphdmph.gmail.com
Publications and other References are available in PhUSE Wiki Archive:

- https://www.phusewiki.org/wiki/index.php?title=Introduction_to_Clinical_Development_Design_(CDD)_Framework