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Real-World Application of the Protocol Representation Model

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ABSTRACT
While the adoption of standards is seen as key to driving efficiencies in many areas of the clinical research process, organizations have been slow to recognize the benefits gained from the standardization of protocol through the application of the Clinical Data Interchange Standards Consortium's (CDISC) Protocol Representation Model (PRM). This presentation will begin by exploring the benefits and practical application of the protocol standard. We will discuss examples of how applying structure to the key clinical concepts within a protocol can lead to improved protocol design, earlier feasibility and an ability to use past studies to guide design decisions. We will then build on these benefits by showing how the same structured information, when combined with other CDISC standards, can drive automation of downstream systems and processes. The presentation will conclude with thoughts on how simple changes to the way protocols are designed and authored can enable the adoption of eProtocol and PRM.

INTRODUCTION
The adoption of standards is, in many areas of the clinical research process, seen as key to driving efficiencies. However, organizations have been slow to recognize the benefits gained from the standardization of the protocol through the application of the Protocol Representation Model (PRM).
The reasons for the aversion to standards in protocol authoring and to the adoption of technology to support its implementation can be traced in part to the following root causes:

- Lack of an implementable protocol standard
  - The PRM is a domain analysis model and until recently was not available in a form which could be easily implemented, making many of the discussions around its benefits theoretical.
- Lack of proven value of standardization of the protocol
  - Until very recently, there has been little proven, published information on the value of such standardization.
- Confusion of standardization of content over structure
  - When protocol standardization is discussed, the immediate reaction is that standardization is not possible as every protocol is different. However, if the focus is shifted to structure and not content, then this is not the case.
- The user/resource type involved in the protocol development process
  - Standardization is not a normal part of the clinical science process. Combined with the resources that are typically less technical in nature, this raises barriers to the adoption of technology and process change needed for implementation.
- The criticality of the protocol development process
  - The protocol is central to all activities within a clinical trial and is often developed under extreme time pressure, making it a high-risk area for significant process change.

In this presentation, we will show how the PRM can be used on its own and with other industry standards to drive significant efficiencies and improvements in the protocol design and authoring process, and how simple changes to the process can be applied to leverage these benefits.

MATERIALS AND **METHODS**
The following activities have been conducted to identify real-world application of protocol standardization, and to identify process change and benefit:

- A review of sponsor protocol development strategies was conducted to identify where the concepts of structured protocol are being applied, and to identify the benefits that sponsors are expecting to see. Anecdotal evidence was collected to demonstrate value where detailed metrics could not be provided.
- A review of literature has been completed to quantify the impact of poor protocol design on cost, complexity and amendments to quantify the potential impact of a structure protocol model.
- An analysis of data from recent third party research that applied retrospective structuring to protocols, to demonstrate design issues that could have been identified with a structured approach.
- An analysis of content reuse was conducted to demonstrate the extent of reusability of structured protocol content across clinical documents and systems. A calculation of the economic impact of automated reuse enabled by structure will quantify the potential value to a sponsor for adoption of the standard.

RESULTS
The literature review yielded the following statistics, all of which can be impacted and improved by the application of a structured protocol model:

- Protocol Amendments [1]
  - 69% of protocols have at least one amendment
  - 46% of amendments occur BEFORE first patient first dose
  - 37% of amendments are considered "somewhat" or "completely" avoidable
  - A typical amendment adds 61 days and costs $450,000+ to implement
- Increase in protocol complexity and burden [2]
  - 48% increase in the median number of unique procedure per protocol (2000/2003 – 2008/2011)
  - 57% increase in the median number of total procedures per protocol 2000/2003 – 2008/2011)
  - 64% increase in total investigative site burden (2000/2003 – 2008/2011)
  - 270% increase in case report form (CRF) length (2000/2003 – 2004/2007)
- Downstream impact [3]
  - 15-30% of data collected is never used in a new drug application (NDA)

The review of sponsor strategy and expectations showed the following [4]:

- 30-50% reduction in protocol development process time
- $150k reduction/late phase per patient study costs
- 30-50% reduction in electronic data capture (EDC) study start-up
- 50% reduction in time exporting to ClinicalTrials.gov
- 75% reduction in full-time equivalent (FTE) for set up of visit schedule in clinical systems

In addition, and perhaps most tellingly, the retrospective structuring and analysis of over 115 recently completed Phase II and III protocols—as part of a study led by the Tufts University Center for the Study of Drug Development [5]—identified design flaws consistent with the expectation that a 10-20% reduction in data collection can be achieved.

- Roughly a quarter of all procedures in these protocols were found to be "non-core"—that is, not directly tied to the trial endpoints as agreed upon prior to the study by the U.S. FDA for demonstrating the safety and efficacy of the drug or therapy in question.
- The non-core procedures represent roughly 20% of a clinical trial's budget—an estimated $1 million in non-core procedure costs per clinical study.

CONCLUSION
Recent research has shown that the application of structure to the key clinical concepts within a protocol can lead to improved protocol design, earlier feasibility and an ability to use past studies to guide design decisions, and that a clear business case of the real-world application of PRM can be constructed.

The key to successfully implementing and applying PRM is to make simple changes to the way protocols are designed and reviewed, to draw on structure to allow reuse and to increase interoperability. In addition, PRM's impact can be significantly increased by pairing it with industry data for protocol complexity and procedure cost.

REFERENCES

[1] Getz, Zuckerman, Cropp, Hindle, Krauss. Measuring the Incidence, Causes and Repercussions of Protocol Amendments Drug Information Journal. 2011 45(3); 265 – 275

[2] Assessing the impact of protocol design changes on clinical trial performance, Tufts Center for the Study of Drug Development, Tufts University, Boston, MA

[3] Assessing the downstream impact of protocol design complexity, Tufts Center for the Study of Drug Development, Boston, MA

[4] Medidata Solutions analysis of information gathered from three sponsors

[5] Protocol Data Relevance Working Group Study, Tufts Center for the Study of Drug Development, Boston, MA

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