Cost-Effective Data Standardization: How to Integrate CDISC standards into Your Product Development Strategy

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Agenda

- Background
- What is CDISC
- CDISC Models
- Implementing CDISC
- Starting with the End – “Tables First”
- Standards Implementation Strategy
- Standards from End to End
- Implementation Example
- The Future

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Introduction

Wrong Question:

How can we implement CDISC standards to meet FDA submission requirements?

Right Question:

How can we use CDISC standards as part of a cost-effective product development strategy?

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Current Status of Data Standards

- CDISC de facto standard
- Recent FDA draft guidance
- PDUFA V/FDASIA
- Communications with FDA
- FDA investment in CDISC
- Increased number of CDISC submissions

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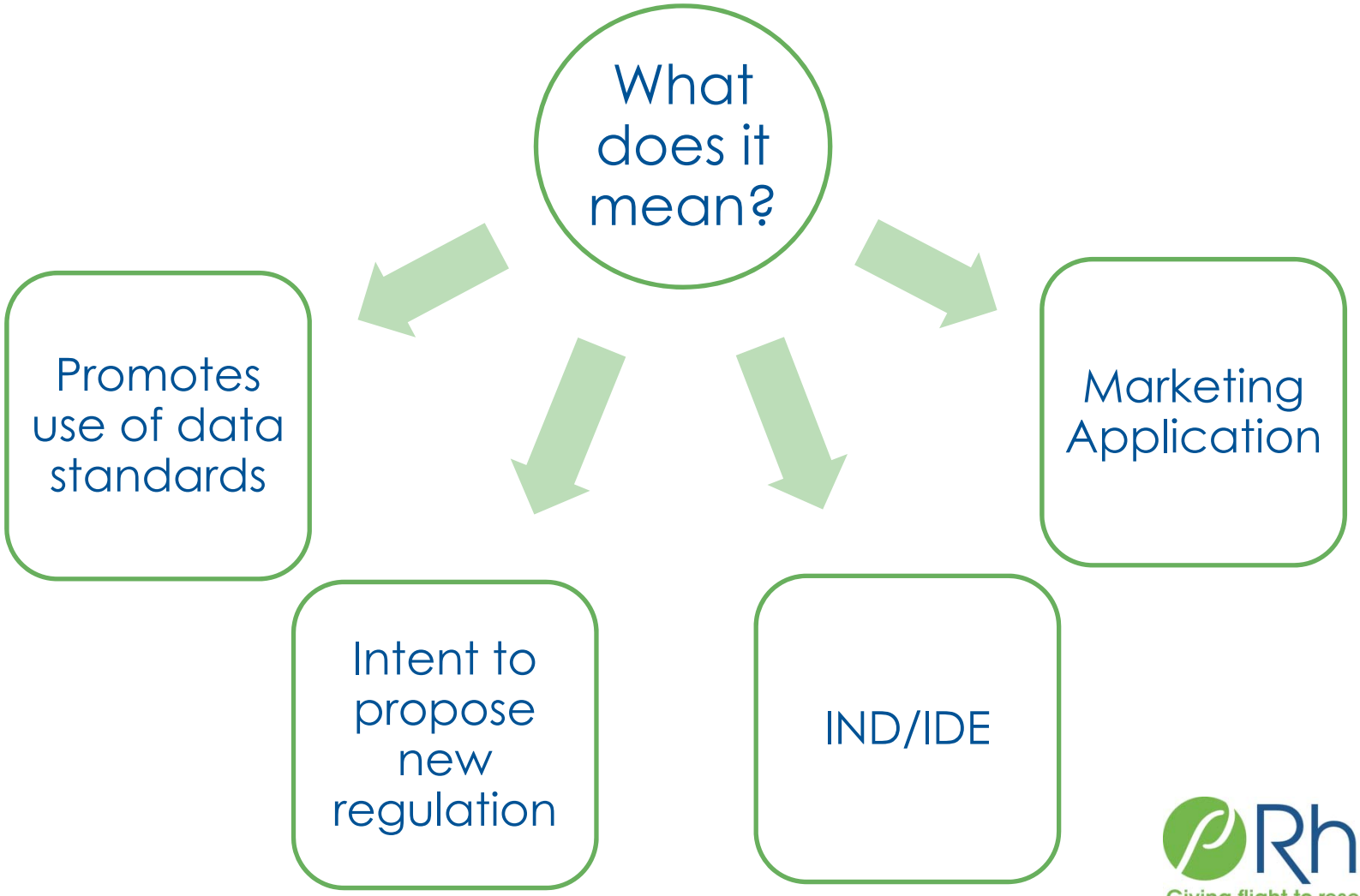
Data Standards: New Guidance



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What is CDISC?

Clinical Data Interchange Standards Consortium

Formed in 1997 as a volunteer group

Open, multidisciplinary, non-profit organization

>150 member companies

Established worldwide industry standards

Extracted from the Clinical Data Interchange Standards Consortium (CDISC) website [http://www.cdisc.org/about/index.htm].

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Polling Question #1

What is your personal experience level working with CDISC?

1. None
2. Not very familiar
3. Somewhat familiar
4. Very familiar

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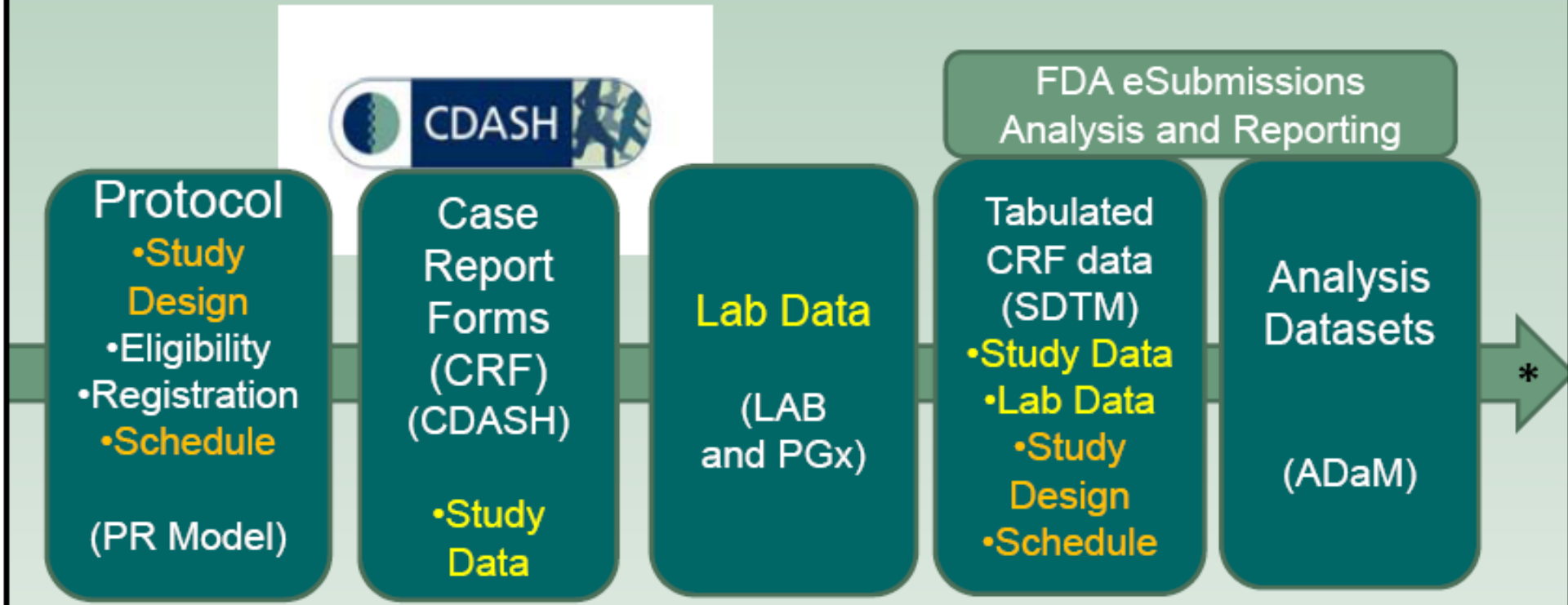
Clinical Research Standards (Content)
(Protocol-driven Research; Protocol →Reporting)



*Transport: CDISC and/or HL7

CDISC Models

- Study Data Tabulation Model (SDTM)
- Analysis Dataset Models (ADaM)
- Clinical Data Acquisition Standards Harmonization (CDASH)
- Operational Data Model (ODM)
- Protocol Representation Model
- Laboratory Data Model (LAB)
- Standards for the Exchange of Non-clinical Data (SEND)

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CDISC Standards & Models

Need to Know Now:	Nice to Know Now:
Clinical Data Acquisitions Standards Harmonization (CDASH)	Operational Data Model (ODM)
Study Data Tabulation Model (SDTM)	Laboratory Data Model (LAB)
Analysis Dataset Model (ADaM)	Standards for the Exchange of Non-clinical Data (SEND)
	Protocol Representation Model

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CDASH

CDASH=Clinical Data Acquisitions Standards Harmonization

Identifies a basic set of data collection fields present on most CRFs	Additional data collection fields to capture specific data points specified in the protocol or to satisfy regulatory requirements	16 domains common across therapeutic areas	Facilitates mapping data to SDTM

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Study Data Tabulation Model (SDTM)

Standard way to represent clinical (raw) data

Standard to submit clinical data to FDA

Standard for exchange, submission, warehousing

Data are grouped into standardized domains (e.g., AE, EG, DM)

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Analysis Dataset Model(ADaM)

General guidelines for analysis datasets

Describes the general structure, metadata, and content for analysis datasets

Design driven by the study's scientific and medical objective

Less structured than SDTM

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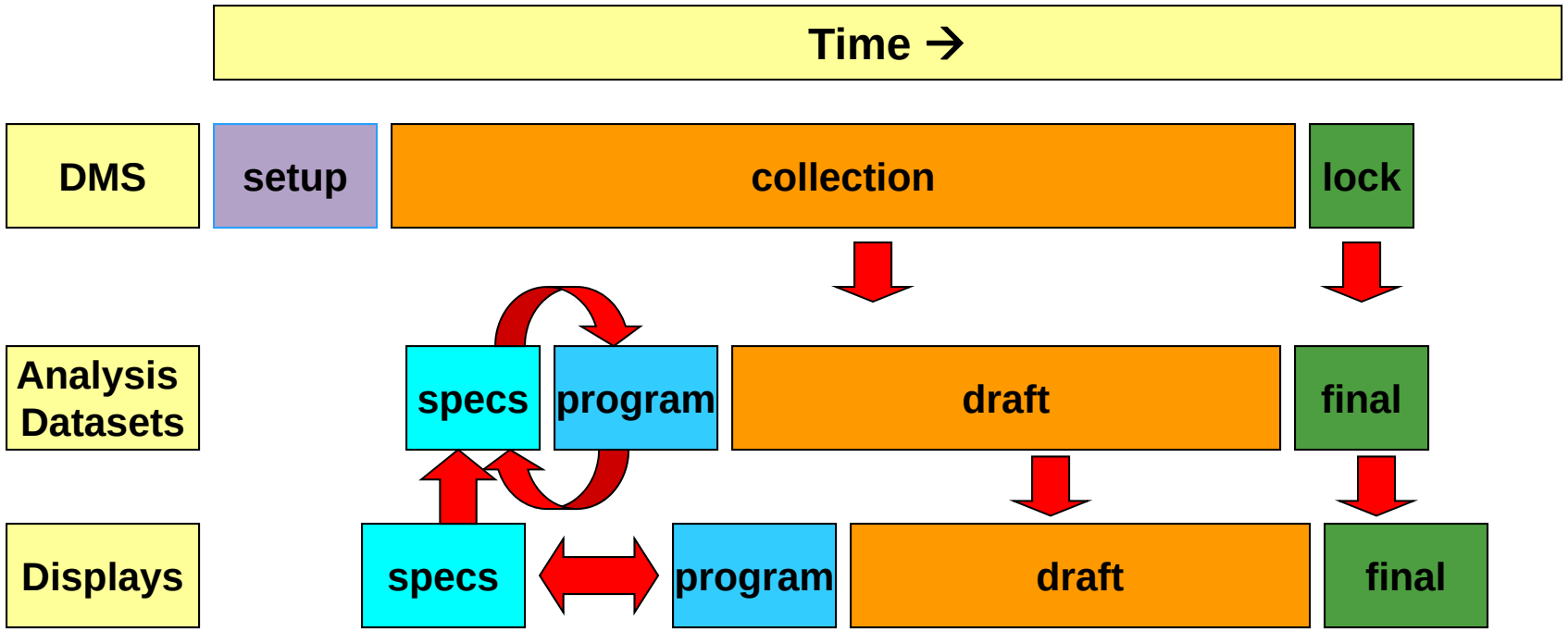
Pre-CDISC Clinical Trial Workflow



DMS = Data Management System

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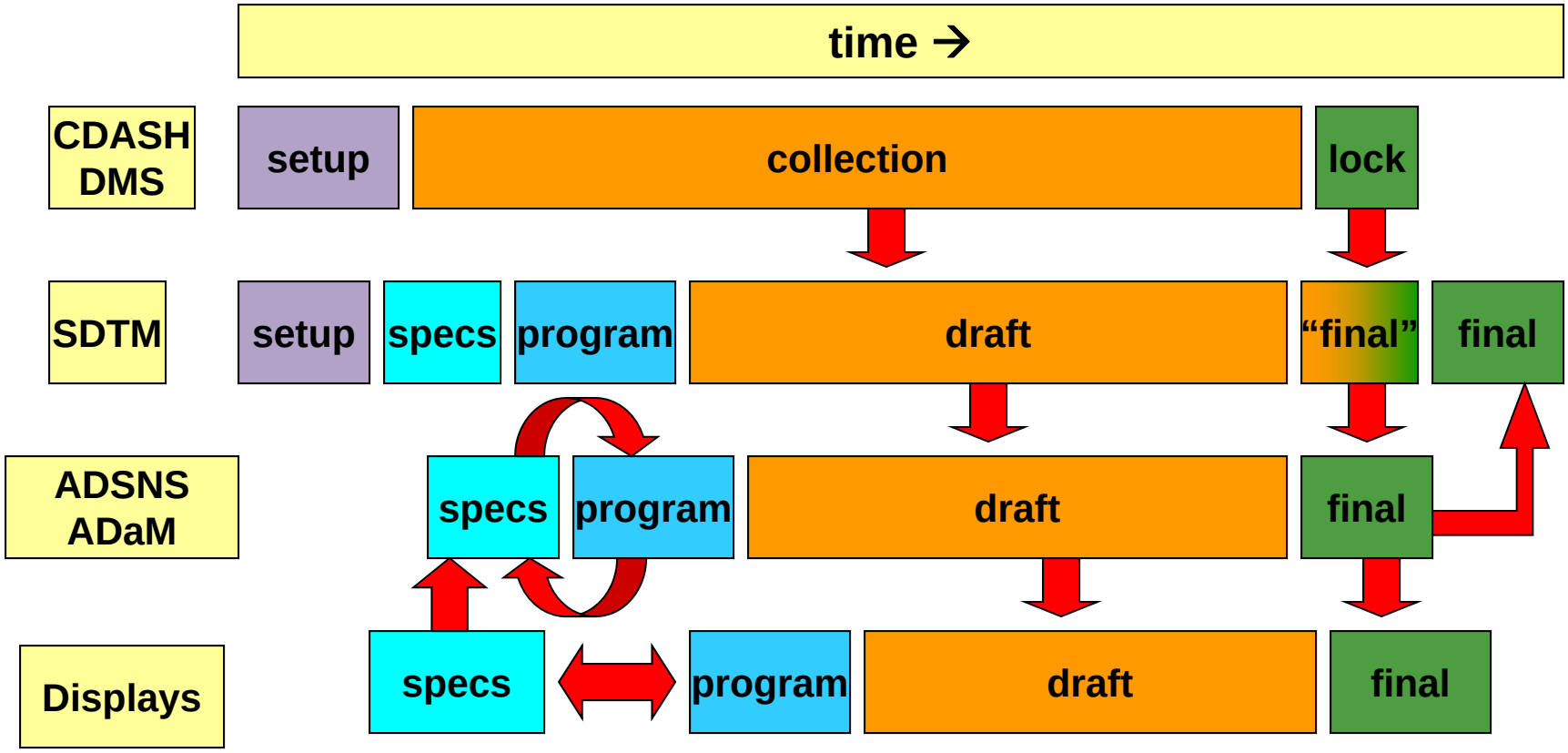
Workflow for CDISC Project



ADSNS = Analysis Datasets

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CDISC Offers More Flexibility

Non-CDISC Project Deliverables:	CDISC Project Deliverables:
• Data Management data • CRT data • Analysis datasets • Dataset specifications • Annotated CRF •Define.pdf for clinical and analysis databases • TLFs	• Data Management data • SDTM datasets • ADaM datasets • Results-level metadata • 2 Annotated CRFs (DM, SDTM) • Define.xml and Define.pdf for SDTM • Define.pdf for ADaM • Additional validation/documentation •TLFs

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Sponsor Impact: Short Term

Need to assimilate standards into processes	More project parts to consider in the timeline	Need to build new tools
Lots of training	More coordination needed	Legacy conversions

Abolafia, J, and F. DiIorio. Brave New World: How to Adapt to the CDISC Statistical Computing Environment. Invited Paper at PharmaSUG, Nashville, TN. 2011.

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Sponsor Impact: Long Term

Development standards and tools established	Standardized datasets across studies and therapeutic areas	Facilitates data exchange with multiple partners
More efficient work flow	Facilitates data integration	Faster and higher quality review

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Polling Question #2

What is your company's current CDISC implementation status?

1. None
2. SDTM and ADaM legacy conversions for adequate and well-controlled studies
3. SDTM and ADaM for all studies
4. SDTM/ADaM and CDASH for all studies
5. End to end CDISC Implementation

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Some Ugly Facts about Drug Development

Patent life of a new compound or treatment:
20 years

Typically:

- Time from patent to approval: **> 12** years and **growing**
- Time available to recoup investment, make profit: **< 8** years and **decreasing**
- Cost of developing a new product: estimates range from **$0.6 billion - $1.2 billion**. **$1.0 billion** is a typical number cited

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Sponsor Impact: Poor Implementation

More work

Delays in timelines, assembling NDA, approval

Lower quality submission

Increased costs

Less remaining time on patent

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Sponsor Impact: Successful Implementation

Faster, more efficient study set up

No delays in current timeline

Lower overall costs of development

Submission easier to assemble, review

Facilitates communication during review

Warehousing and retrieval of information

More remaining time on patent

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CDISC FDA Implementation Progress Report

CDER

- 2010: Received an average of 650+ datasets/week
- 2010: 23% of active NDAs contain CDISC/SDTM data
- 2011: increased to 34%

CBER

- BLA: ~20% of Original and Efficacy Submissions in SDTM
- IND: ~15% of the Phase 3 / 4 Submissions with SAS.xpt files were SDTM

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CDISC FDA Implementation Progress Report

- SDTM and ADaM most frequently used models
- ODM used as format for define file
- CDASH use not widespread, other models not frequently used
- Predominant use: Meet FDA requests for CDISC compliant databases
- Standards not part of an integrated product development strategy

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How Do We Get There? Implementation Strategies

Tables first philosophy	"start with the end in mind"
Data standards implementation plan	**NO LEGACY CONVERSIONS!!**
Extend standards to the beginning and to the end	"from protocol to display"
Take advantage of standards- "Make routine things routine"	Metadata libraries

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Keys to Implementation

- Start with the end in mind
- Extend the Use of Standards end to end
- Data Standards Implementation Plan

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Start With the End in Mind

Key Concepts	• Use of data standards throughout the life cycle • Use of adaptive study designs
ISE/ISS mock displays first	• Based on target product profile or draft label
What displays/analyses are needed to show safety and efficacy	• Determines what studies are needed • Each study contributes to evidence needed for approval

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Start With the End in Mind

For a given study:

- What displays are needed to meet goals of the study?
- Generate mock displays , which …
- Identify required data

Mock displays are driving force

- Dictate data to collect
- Identify what data streams are needed

After mock displays:

- Protocol
- CRFs
- DMS
- Analysis / displays

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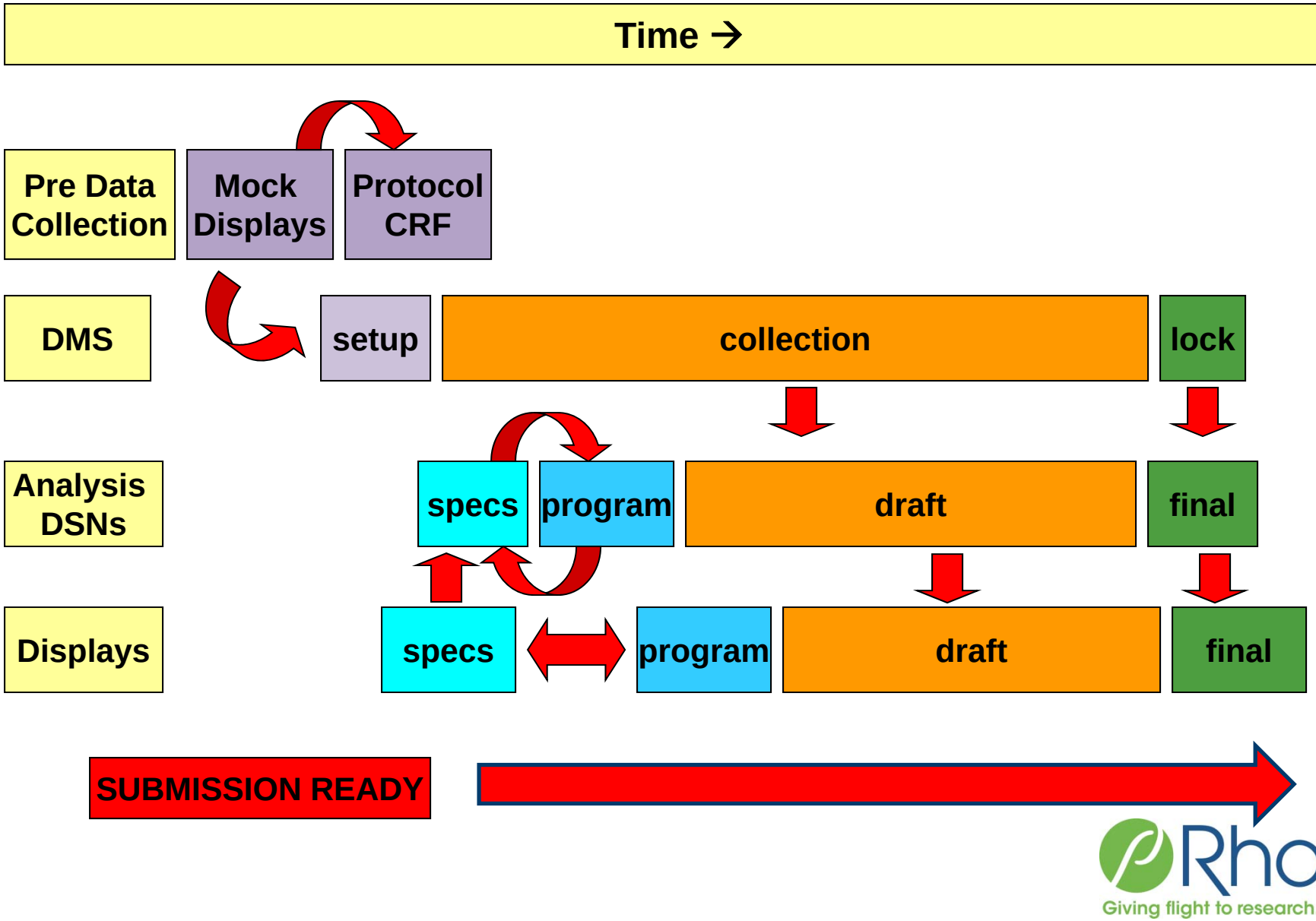
Tables-First Data Flow



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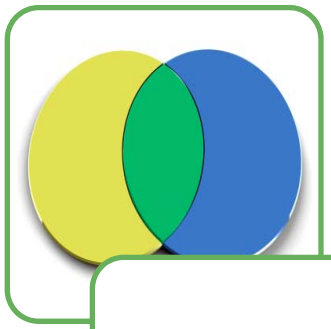
Benefits of This Approach



Overlap studies/ phases

Focused data collection

Early start on analysis

Earlier start on ISS/ISE

Work flow is more focused and efficient!

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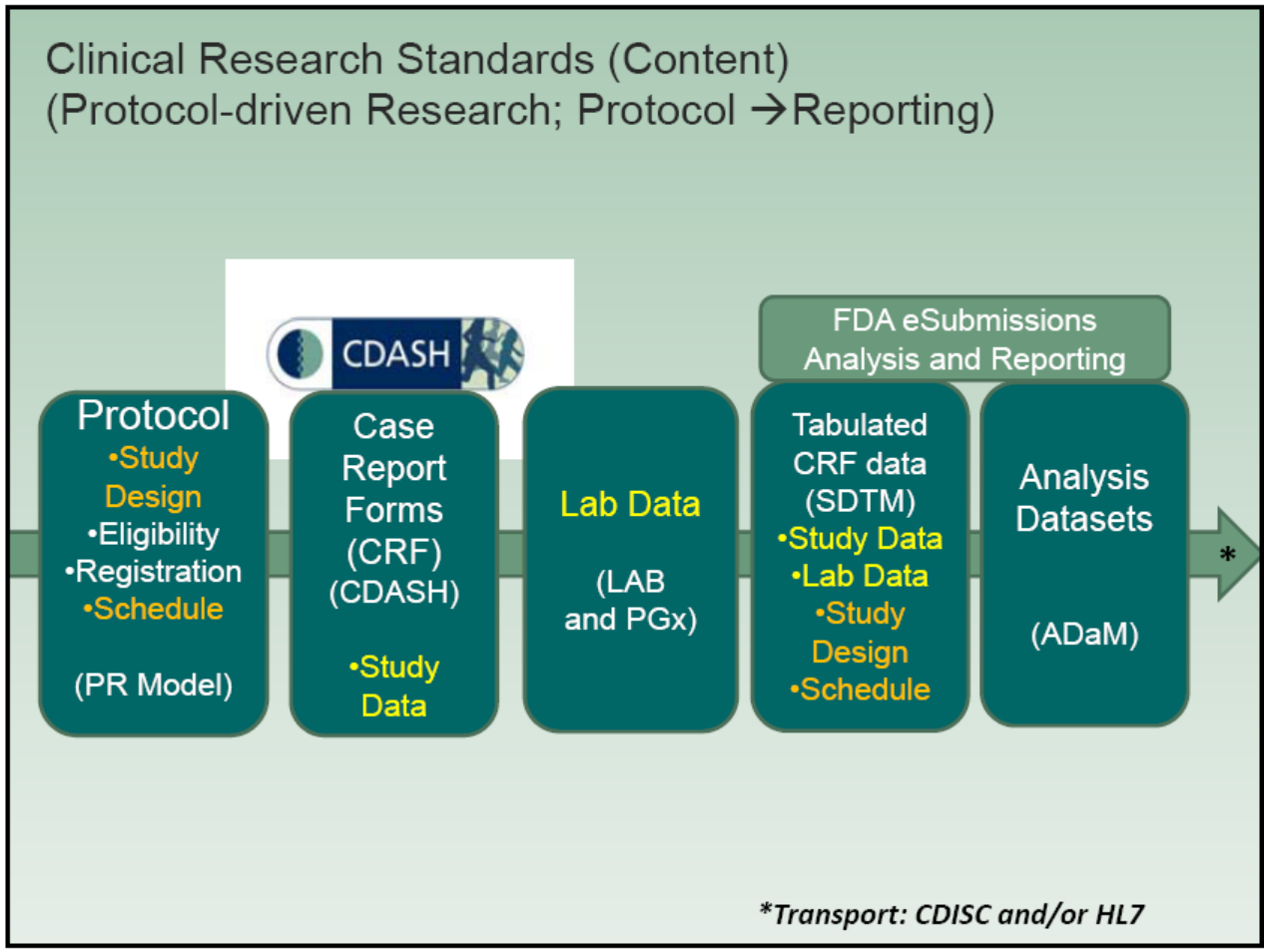
Extend Standards End-to-End: Part1



Underutilizing anything?

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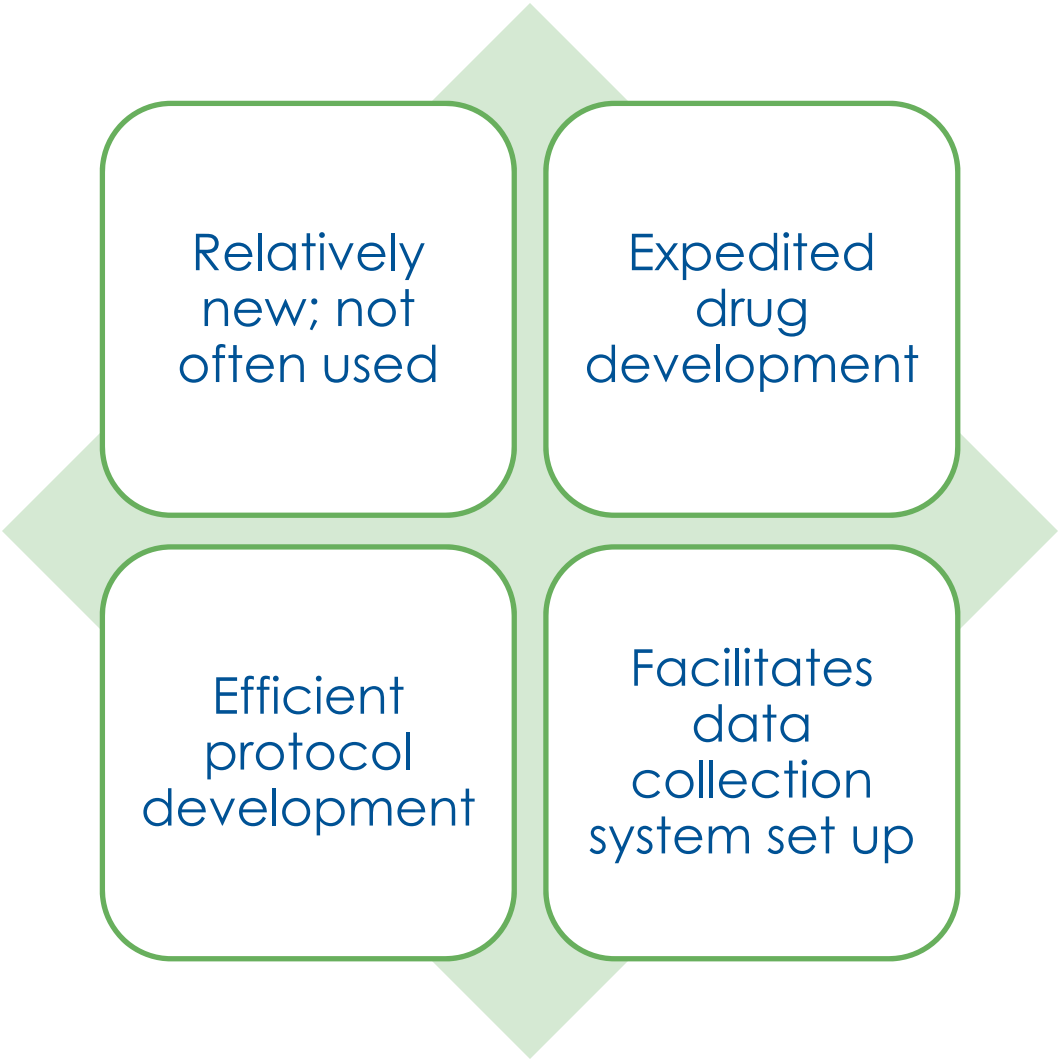
Protocol Representation Model (PRM)



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PRM: Benefits & Efficiencies

Regulatory Submission Preparation

- PIND/PIDE meeting package
- INDs and CTAs
- Annual Reports/DSURs/PSURs
- EOP2 meeting package
- Pre-NDA/BLA meeting package
- NDA/BLA/Marketing Authorisation Application
- 120-Day Safety Updates

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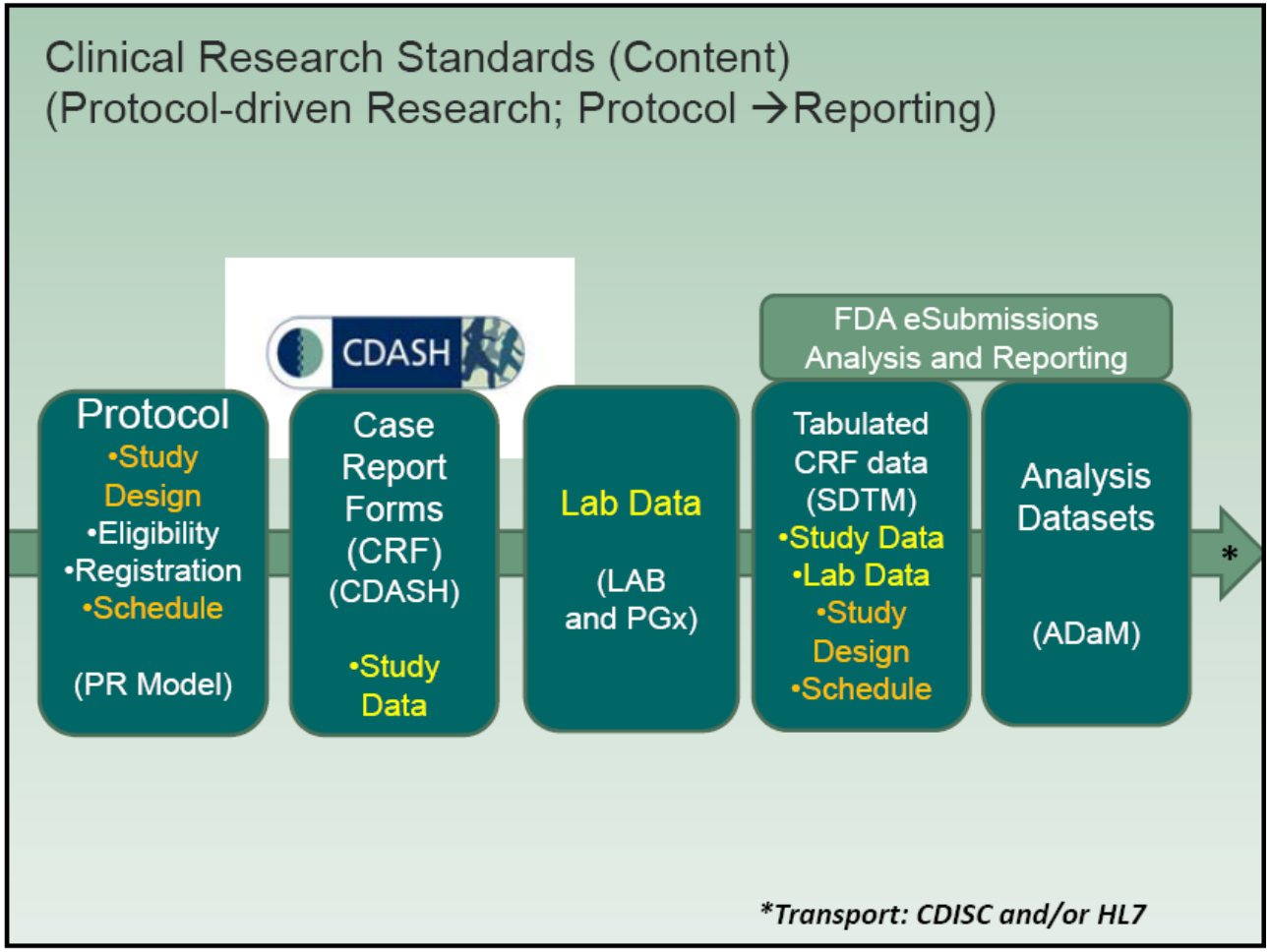
Extend Standards End-to-End: Part 2



***Missing* anything?**

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Extend Standards: Displays/Reporting

- Standards not extended to reporting
- Fewer papers/presentations using standards effectively
- Many displays are common across numerous studies
- Focus of FDA Working Group 5

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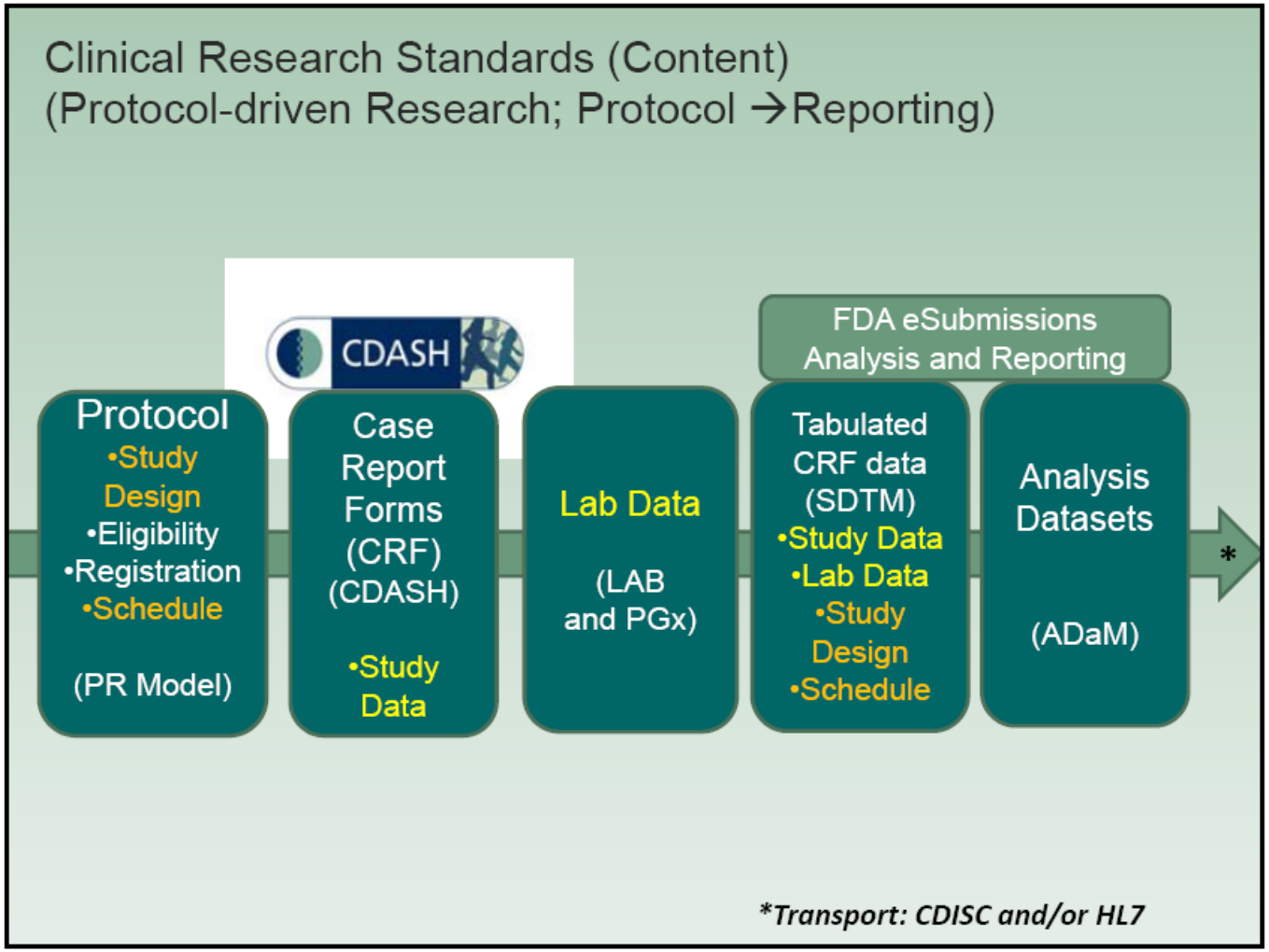
Standards Now Truly End-to-End



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Polling Question #3

What is your disciplinary role in your current company?

1. Statistics
2. Data Management/CRF Development
3. Regulatory
4. Clinical
5. Program Management
6. Executive

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Implementation Plan

Company Size Matters!

- Size and diversity of skill sets
- Resources available

Business Model

- Taking current product to approval?
- Taking current product to proof of concept?
- Partnering as soon as possible?
- Selling as soon as possible?

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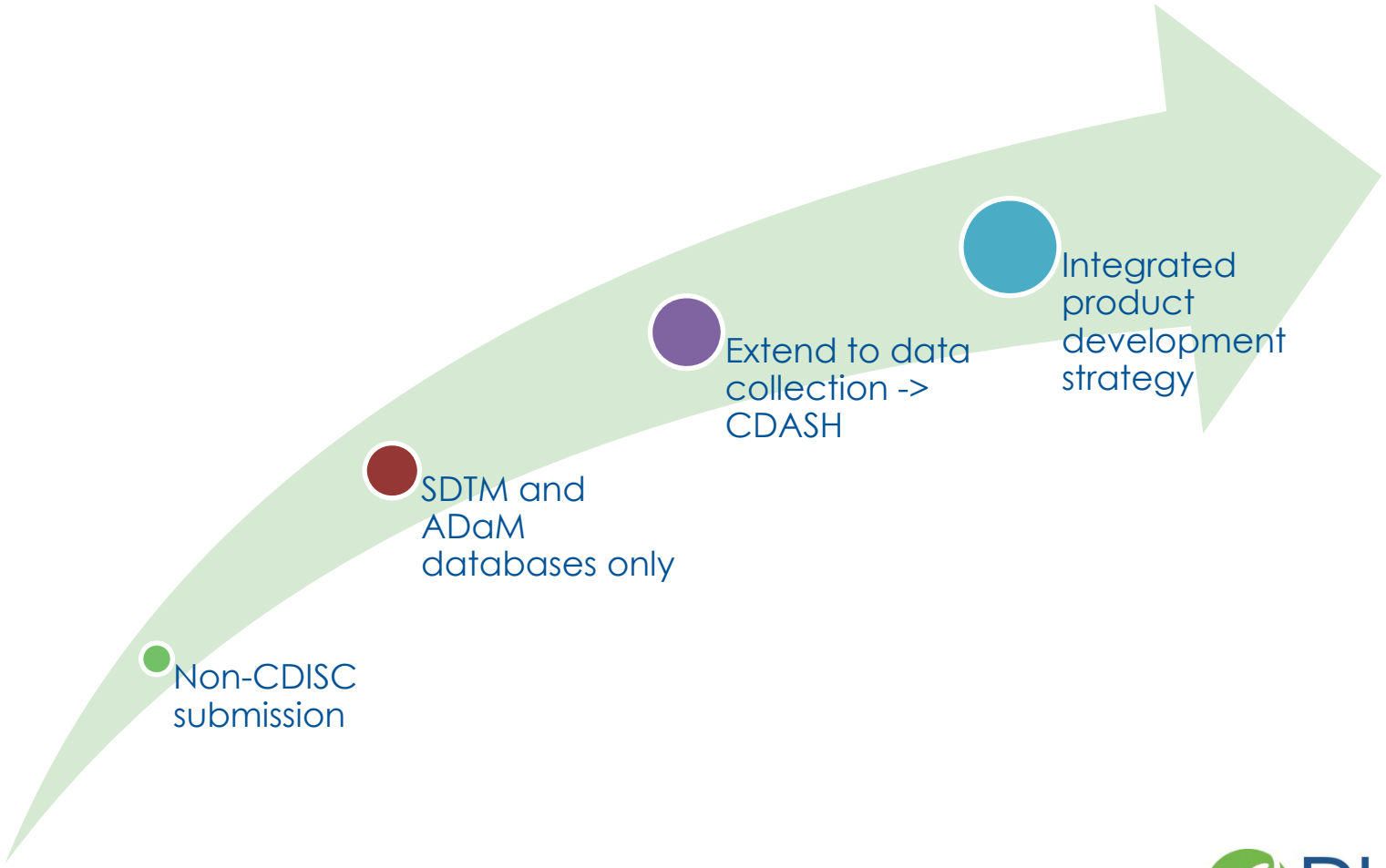
Implementation Strategy



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When to Implement

- Non-CDISC submission
- Legacy conversions for all studies
- SDTM and ADaM only for Phase III
- SDTM and ADaM for all studies
- End to End plan

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Legacy Conversion

Pros

- Most organizations start here
- Gets the FDA what they want
- Responsibility of biostatisticians/programmers
- No investment in CDISC until success of drug likely
- Continued use of existing tools and processes

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Legacy Conversion

Cons

- Lots of work in a short time
- EXPENSIVE!!!
- Must reproduce clinical and analysis db, displays, CSR
- Lower quality
- Diverts resources from ISS/ISE
- Possible submission delay

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Legacy Conversion Post Phase III

Not a good strategy if:

- Working with multiple partners
- Long term goal is to take product to market or partner

Good strategy if:

- Goal is to sell ASAP
- Sell after proof of concept
- Staff does not have skill set to implement
- No $$$ to implement CDISC early in development

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SDTM/ADaM: Implement for Ongoing Studies

- Gets the FDA what they want
- Responsibility of biostatisticians/ programmers
- Long term efficiency and effectiveness
- ↓ cost of analysis/reporting up to 50%
- Common format
- Industry wide standard

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SDTM/ADaM: Implement for Ongoing Studies

Short term considerations:

- More work and less time to do it
- Could affect timelines
- Existing standards and processes
- Most drugs (90%) fail during phase I ->more work with risk of little in return
- Significant changes in internal processes and workflow
- Investment in training and software
- CDISC still not required

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SDTM/ADaM: Implement for Ongoing Studies

Long term considerations:

- Good strategy if plan to take product to market or partner
- Requires staff with diverse skill set to implement CDISC
- Requires $$$ to implement CDISC
- FDA has invested heavily in CDISC
- Proposed regulation to require CDISC

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SDTM/ADaM: Hybrid Strategy

Use CDISC standards only for adequate and well-controlled Phase 3 studies

Advantages

- Much higher probability at this stage that the drug will succeed
- Good chance you can negotiate with FDA to submit only pivotal studies in CDISC format

Disadvantages

- All studies will not be in a uniform format-annoy reviewers, increase difficulty of review
- Integration will be more difficult, especially for safety data
- The FDA may prefer non-pivotal studies in CDISC format

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SDTM and ADaM + CDASH

Same advantages as SDTM/ADaM Strategy

Extends standards to data collection

Global library of data collection elements

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SDTM and ADaM + CDASH

Advantages

- Facilitates SDTM database creation
- Streamlines conversion of DM data to SDTM
- Faster and cheaper SDTM
- Package DM->SDTM
- Cost effective DM-> SDTM for Phase I/II studies
- Extends standards to Clinical Data Management (CDM)
- Improves communication between CDM and biostatistics
- Important for cost effectiveness in products being taken to market

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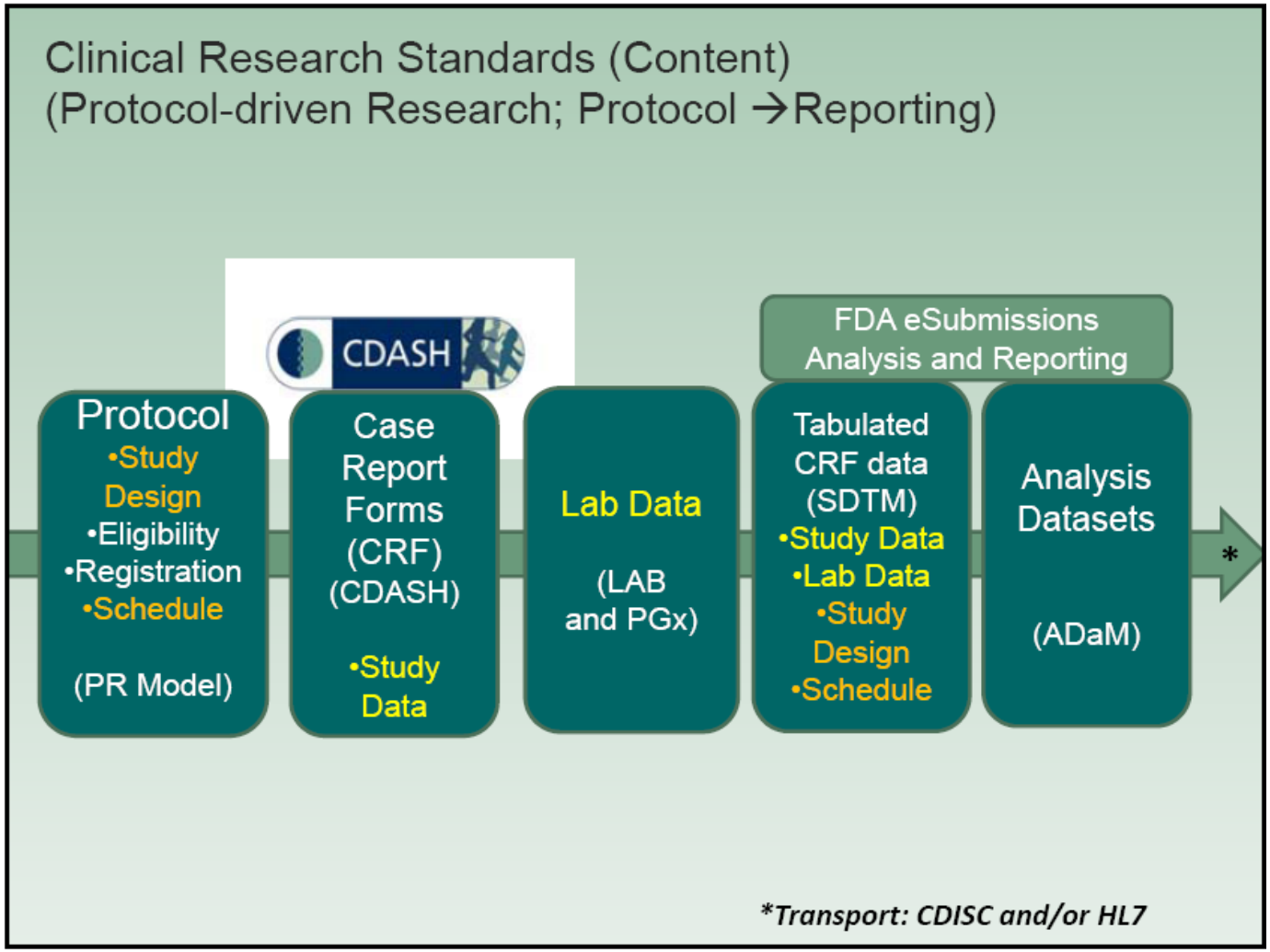
End-to-End Standards Implementation



Displays / Reporting

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End-to-End Standards Implementation

Extend standards implementation all the way upstream

Standards plan required at time of IND/IDE

Create a plan for entire product development life cycle

Start at protocol and end at display production

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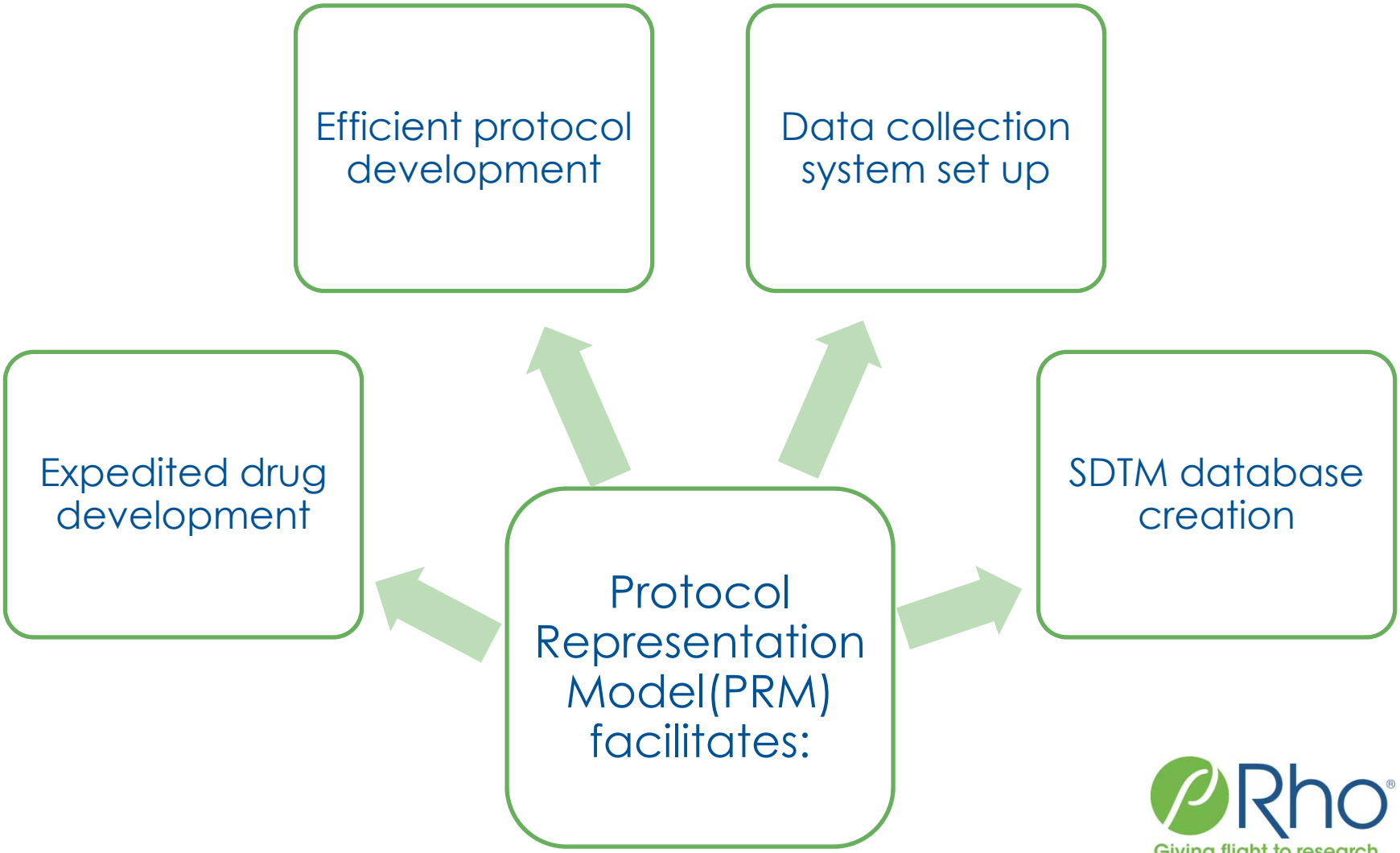
End-to-End Standards Implementation



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End-to-End Standards Implementation

Advantages:

- Includes regulatory and clinical personnel
- Promotes cross-functional communication
- Facilitates regulatory review

Most cost effective when goal is:

- Bring product to market
- Partner (adds significant value)

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End-to-End Standards Implementation

Standards implemented from the beginning

- Can save up to 60% of non-subject participation time and cost
- About half of the value is in the start up stages

Savings depends on several factors

- Existing use of proprietary standards
- Stage of implementation
- Training
- Type and size of study

Business Case for CDISC Standards: Summary, CDISC 2009.

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Polling Question #4

What are your company's future plans for CDISC implementation?

1. Not sure
2. No plans currently
3. SDTM/AdAM for adequate and well-controlled studies
4. SDTM/AdAM for current studies
5. SDTM/AdAM/CDASH for current studies
6. End to End CDISC implementation

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Summary

Data Standards Plan expected at time of IND/IDE

Plan dependent on business strategy, company size, and resources

Successful implementation strategy can

- reduce time and cost
- facilitate regulatory review
- increase time remaining on patent
- increase communication
- increase quality
- "make routine things routine"

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Summary

Change in mindset required

- Tables first
- Expedited Product Development
- Standards beyond biostatistics
- Standards from end-end

"If you are in the drug development business, you now are also in the CDISC Data Standards Business."

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Q&A

Send questions or comments to:

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