

Cost-Effective Standards Implementation: A New Paradigm for the Drug Development Life Cycle

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Warning



- This presentation contains a mixture of
 - Reality
 - Aspirations
 - Authors' vision for how we can greatly increase efficiency for product development

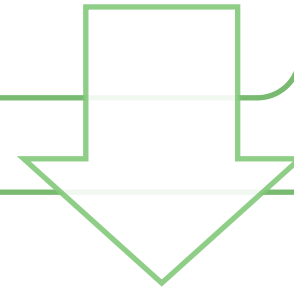
Agenda

- **Background**
- **Implementing Data Standards/CDISC**
- **Starting with the End – “Tables First”**
- **Standards Implementation Strategy**
- **Standards from End to End**
- **Conclusion**

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?

Current Status of Data Standards

CDISC de facto standard

Recent FDA draft guidance

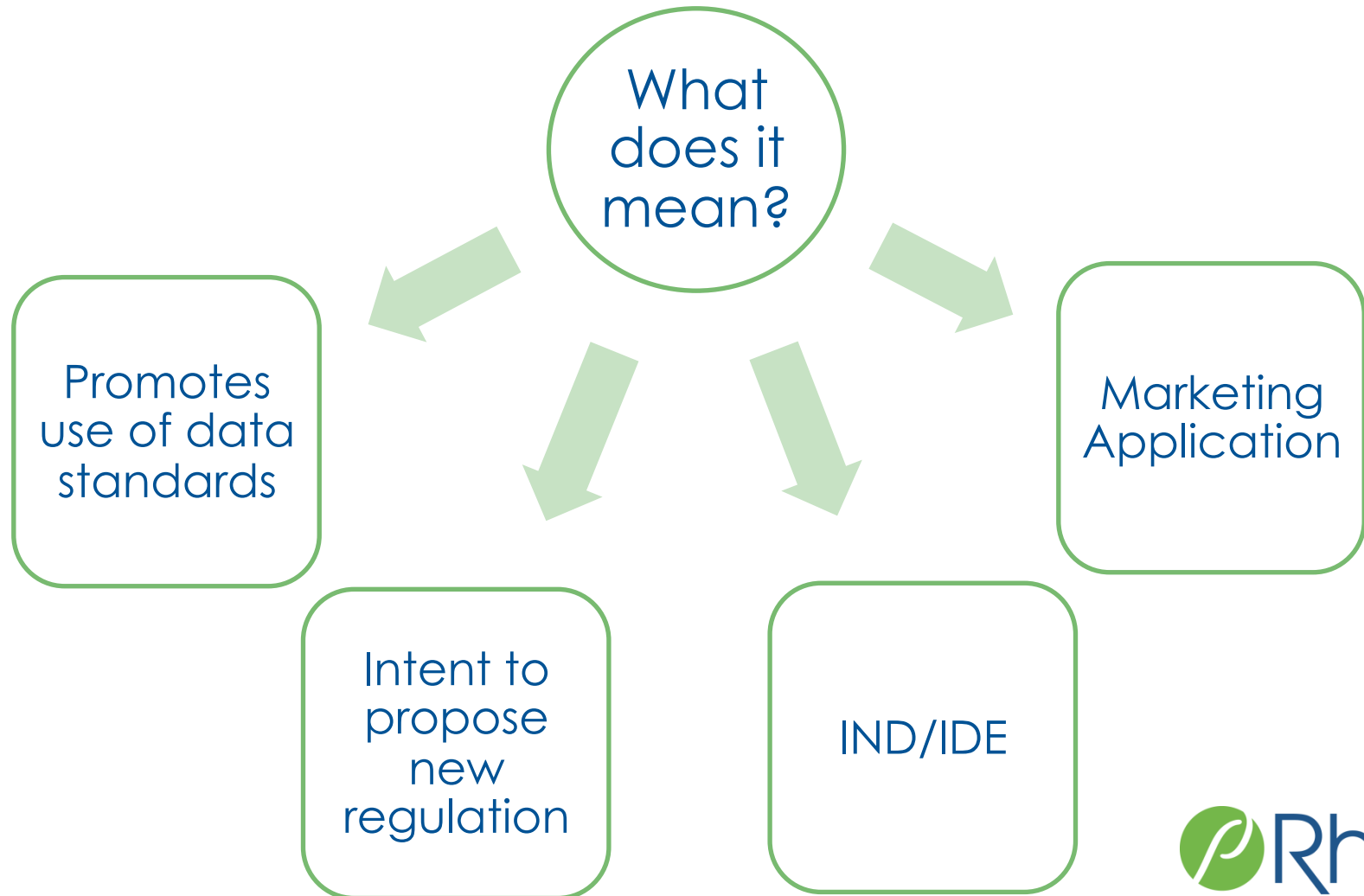
PDUFA V/FDASIA

Communications with FDA

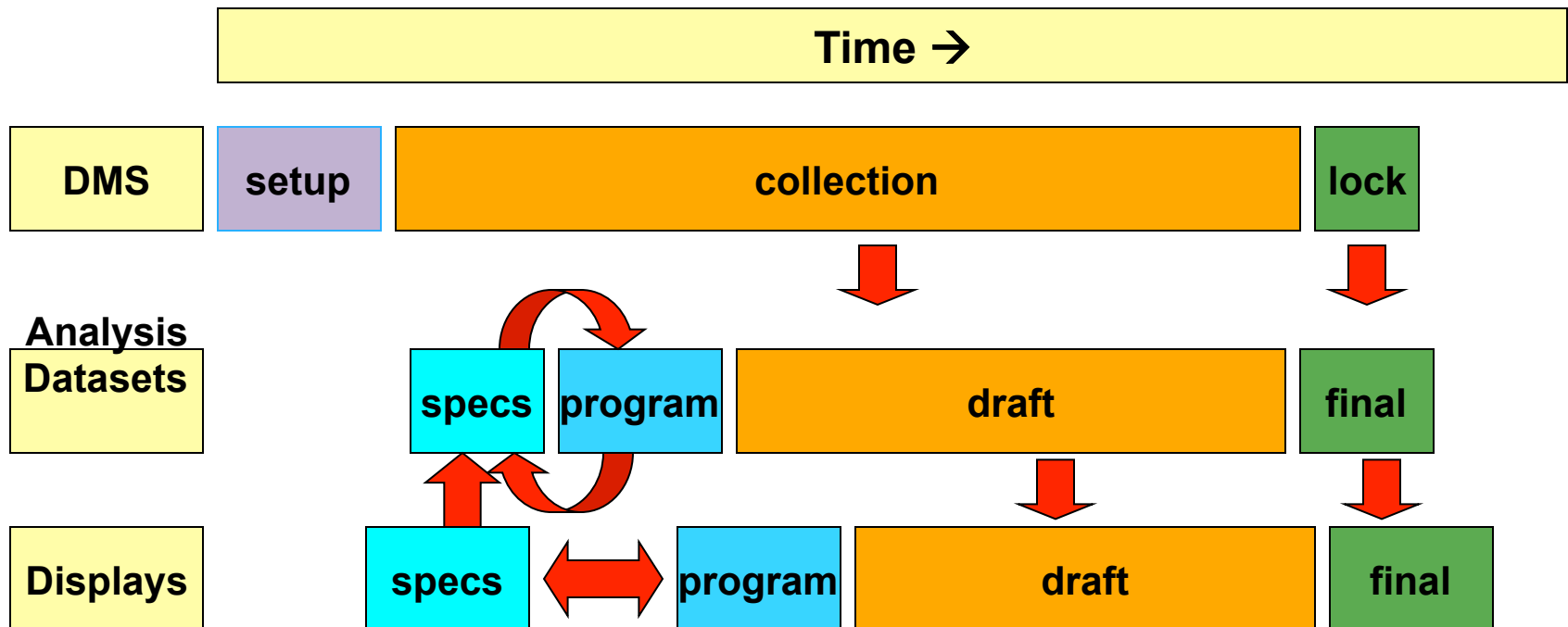
FDA investment in CDISC

Increased number of CDISC submissions

Data Standards: New Guidance

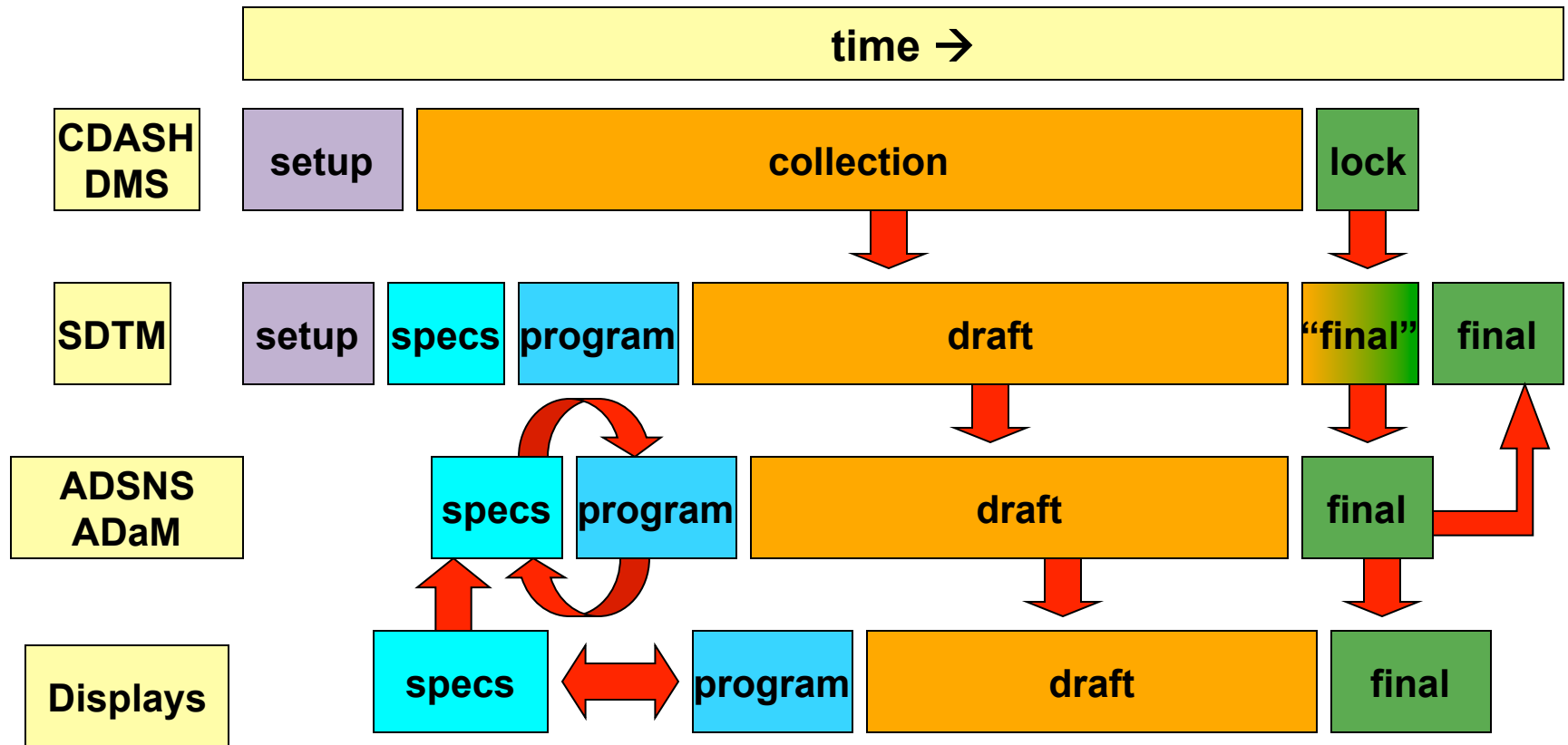


Pre-CDISC Clinical Trial Workflow



DMS = Data Management System

Workflow for CDISC Project



ADSNS = Analysis Datasets

CDISC -> More Deliverables

Non-CDISC Project Deliverables:

- Data Management data
- CRT data
- Analysis datasets
- Dataset specifications
- Annotated CRF
- Define.pdf for clinical and analysis databases
- TLFs

CDISC Project Deliverables:

- 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

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. Dilorio. Brave New World: How to Adapt to the CDISC Statistical Computing Environment. Invited Paper at PharmaSUG, Nashville, TN. 2011.

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

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

Sponsor Impact: Poor Implementation



More work



Delays in timelines, assembling NDA, approval



Lower quality submission



Increased costs



Less remaining time on patent

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

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

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

Keys to Implementation



- Start with the end in mind



- Extend the Use of Standards end to end



- Data Standards Implementation Plan

Start With the End in Mind

Key Concepts

- Use of data standards throughout the life cycle
- Use of adaptive study designs

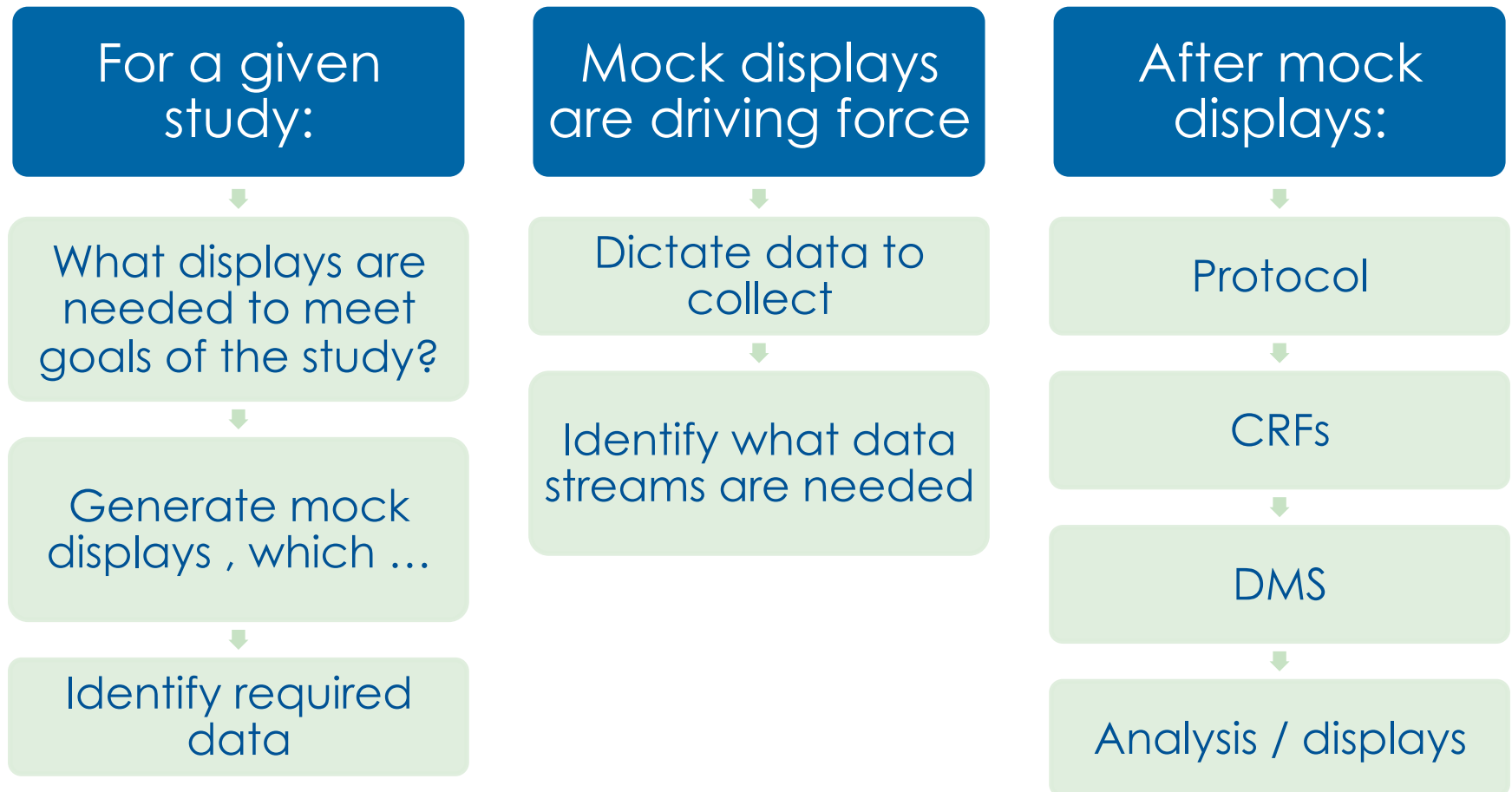
ISE/ISS mock displays first

- Based on target product profile or draft label

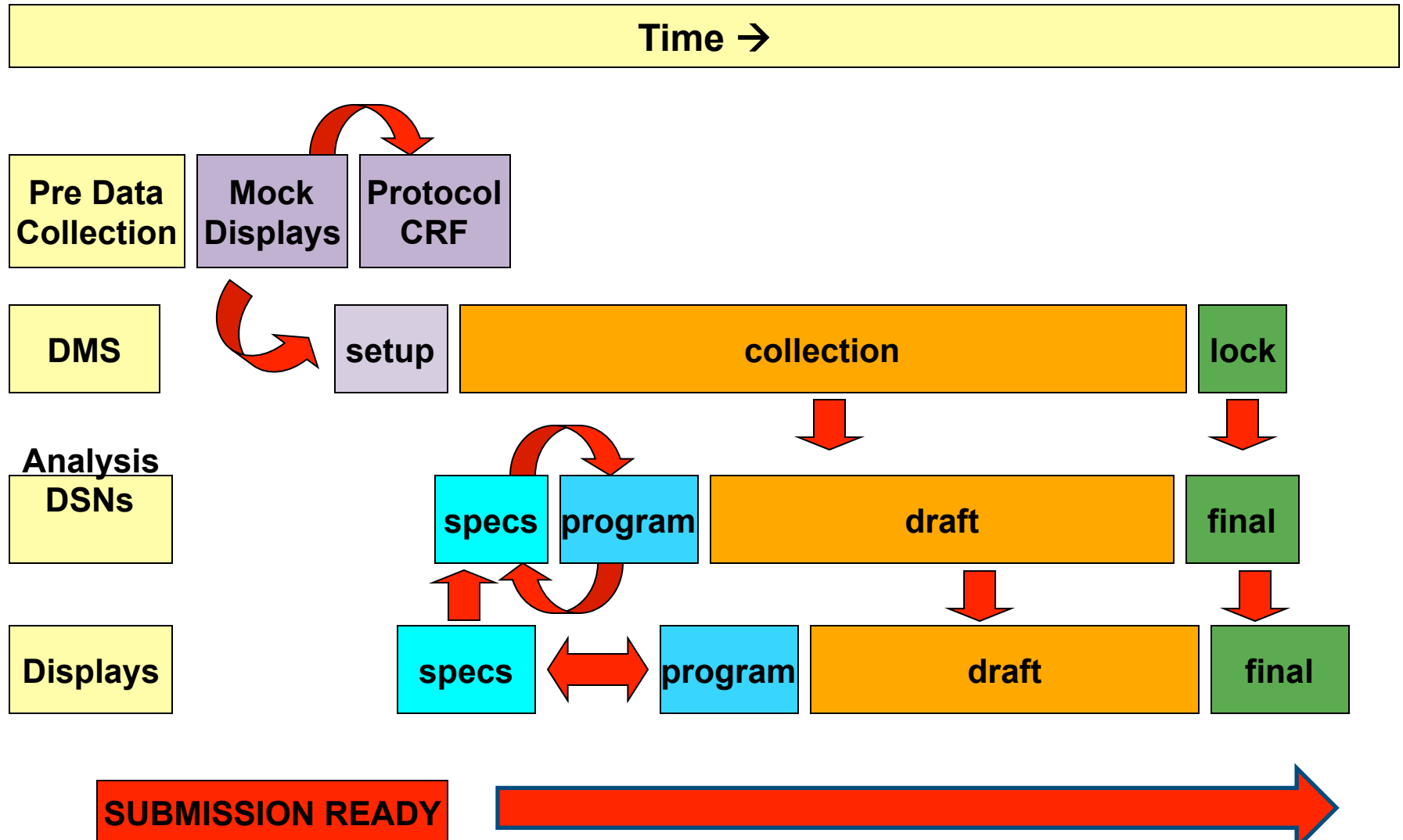
What displays/analyses are needed to show safety and efficacy

- Determines what studies are needed
- Each study contributes to evidence needed for approval

Start With the End in Mind



Tables-First Data Flow

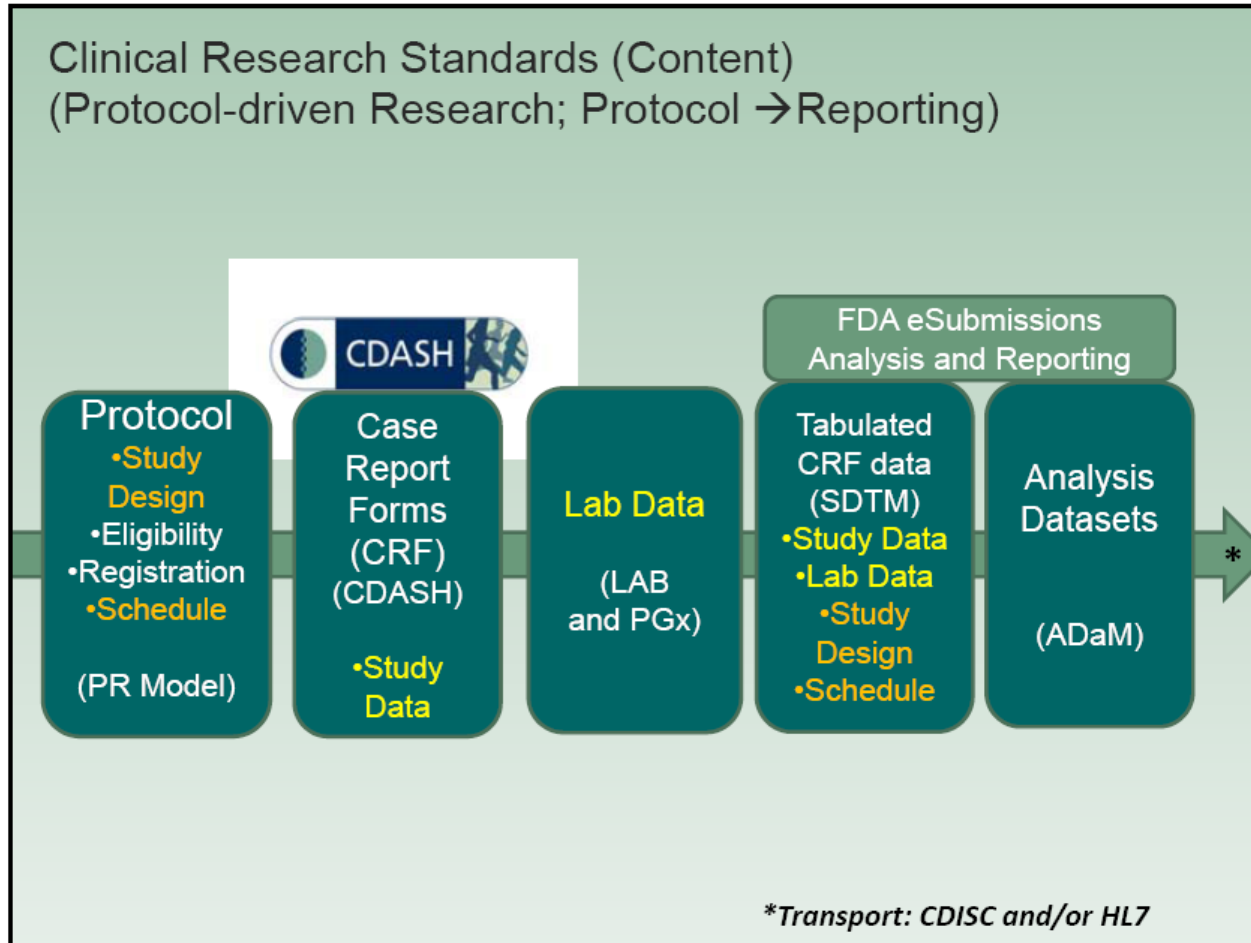


Benefits of This Approach



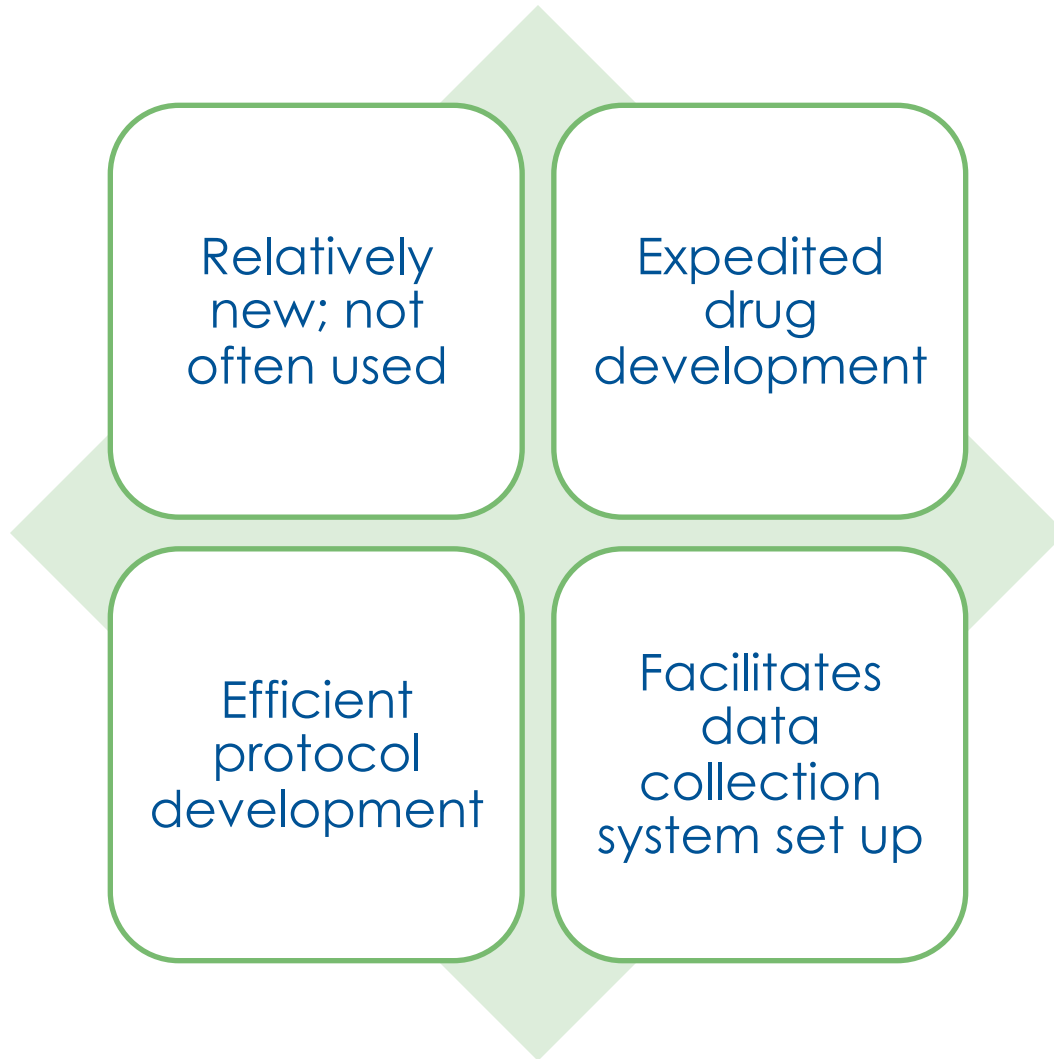
Work flow is more focused and efficient!

Extend Standards End-to-End: Part 1



Underutilizing anything?

Protocol Representation Model (PRM)

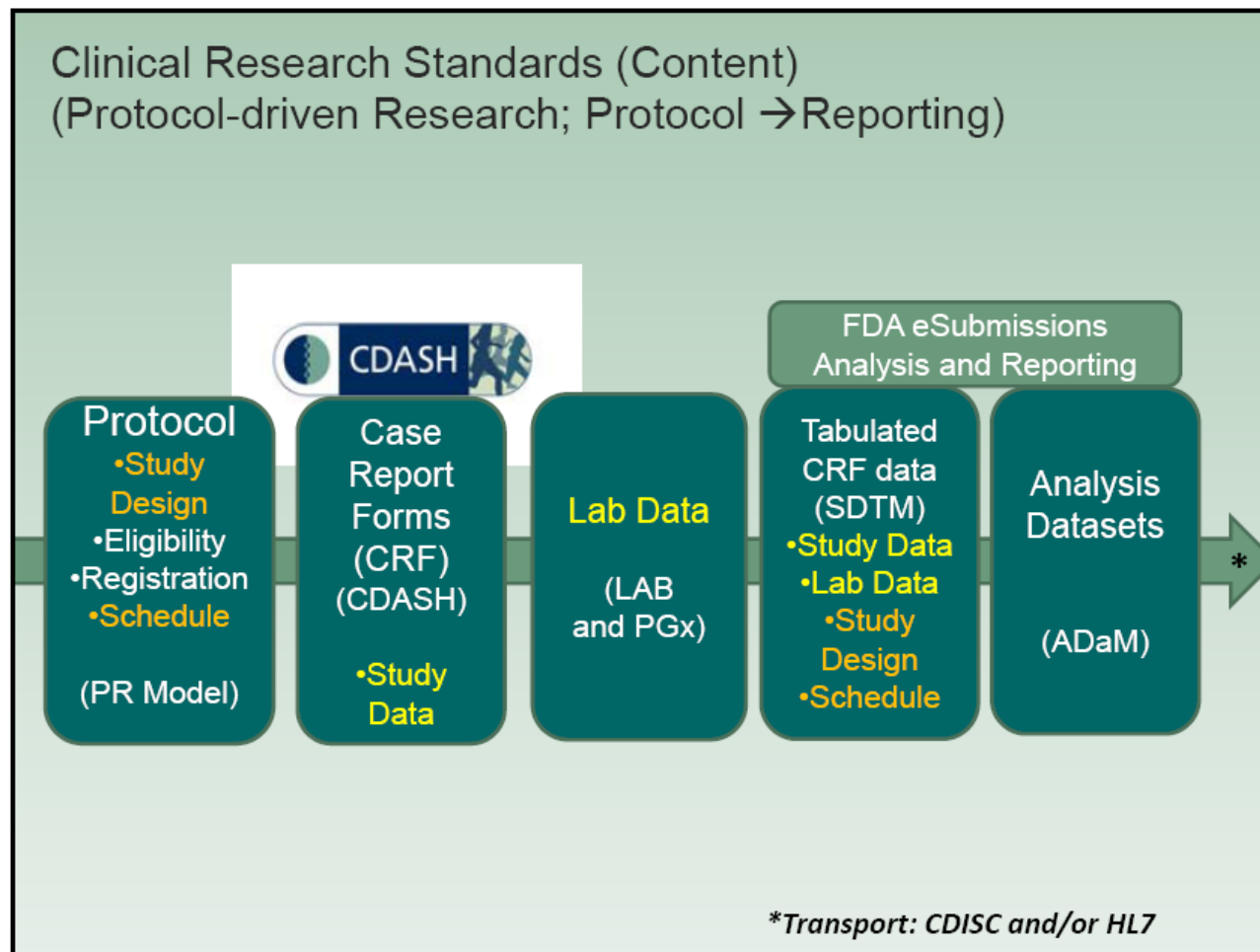


PRM: Benefits & Efficiencies

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

Extend Standards End-to-End: Part 2



Missing anything?

Extend Standards: Displays/Reporting

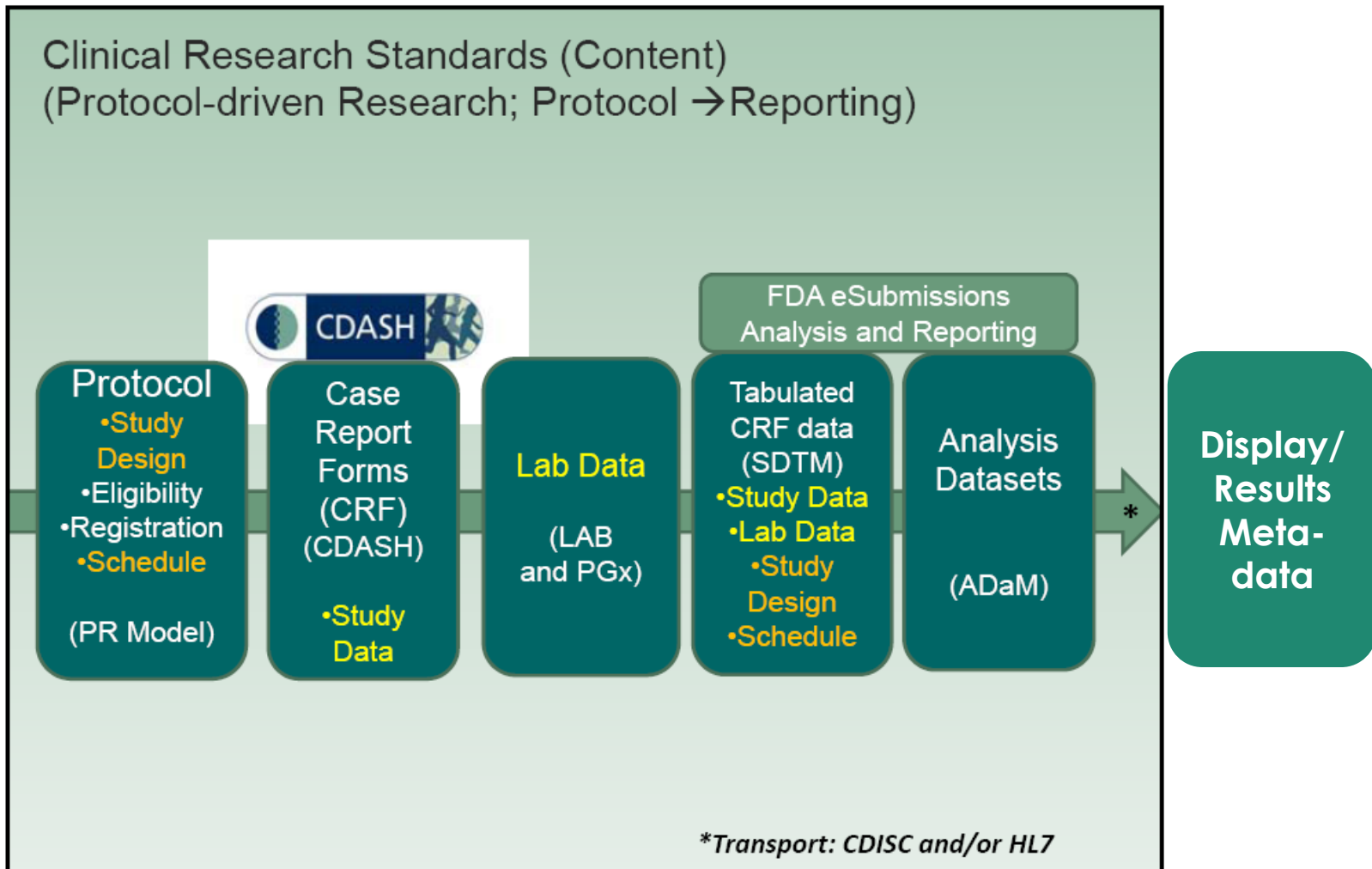
Standards not extended to reporting

Fewer papers/presentations using standards effectively

Many displays are common across numerous studies

Focus of FDA Working Group 5

Standards Now Truly End-to-End



Implementation Plan



Company Size Matters!

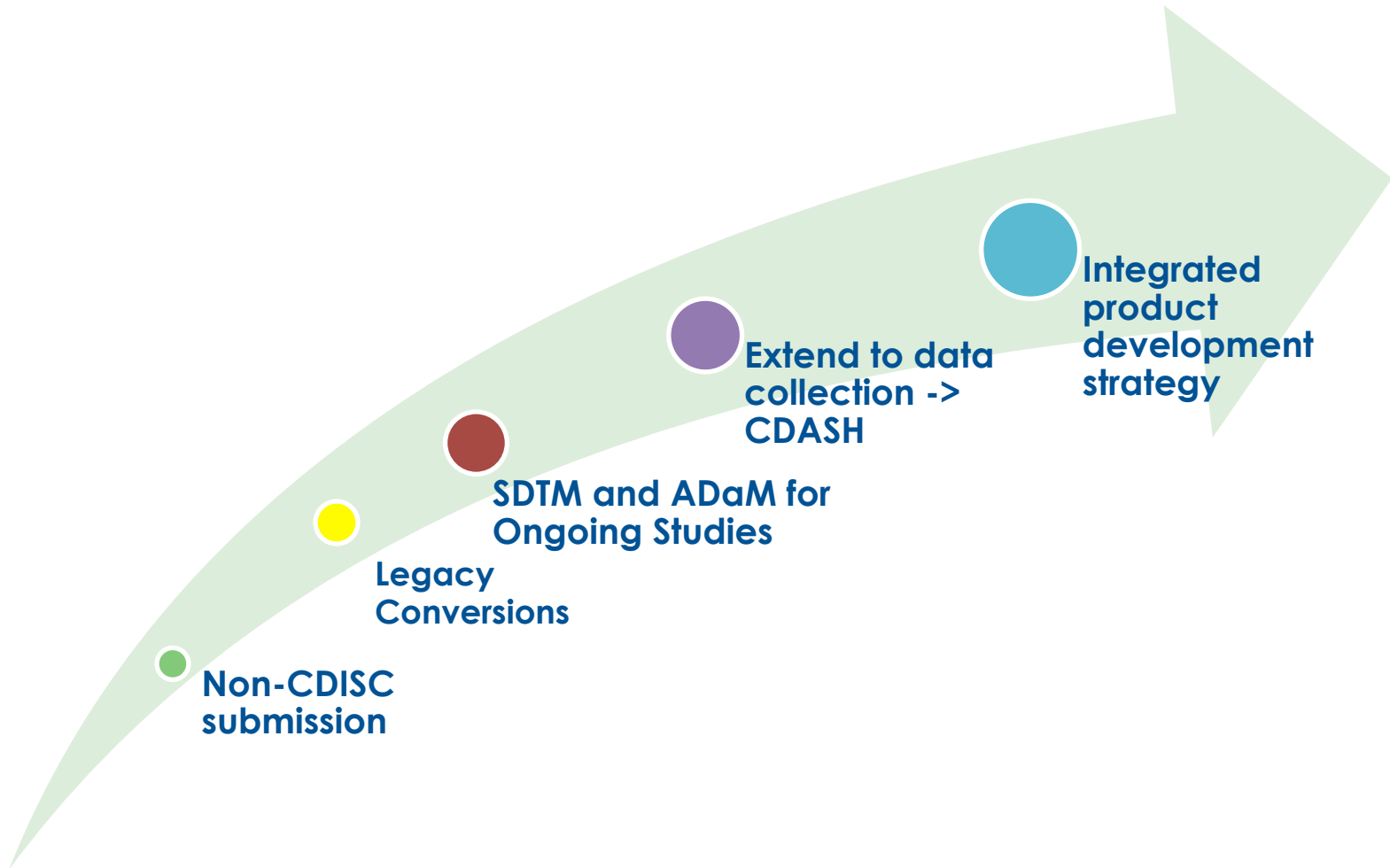
- Size and diversity of skill sets
- Resources available



Business Model

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

Implementation Strategy



When to Implement

Non-CDISC submission

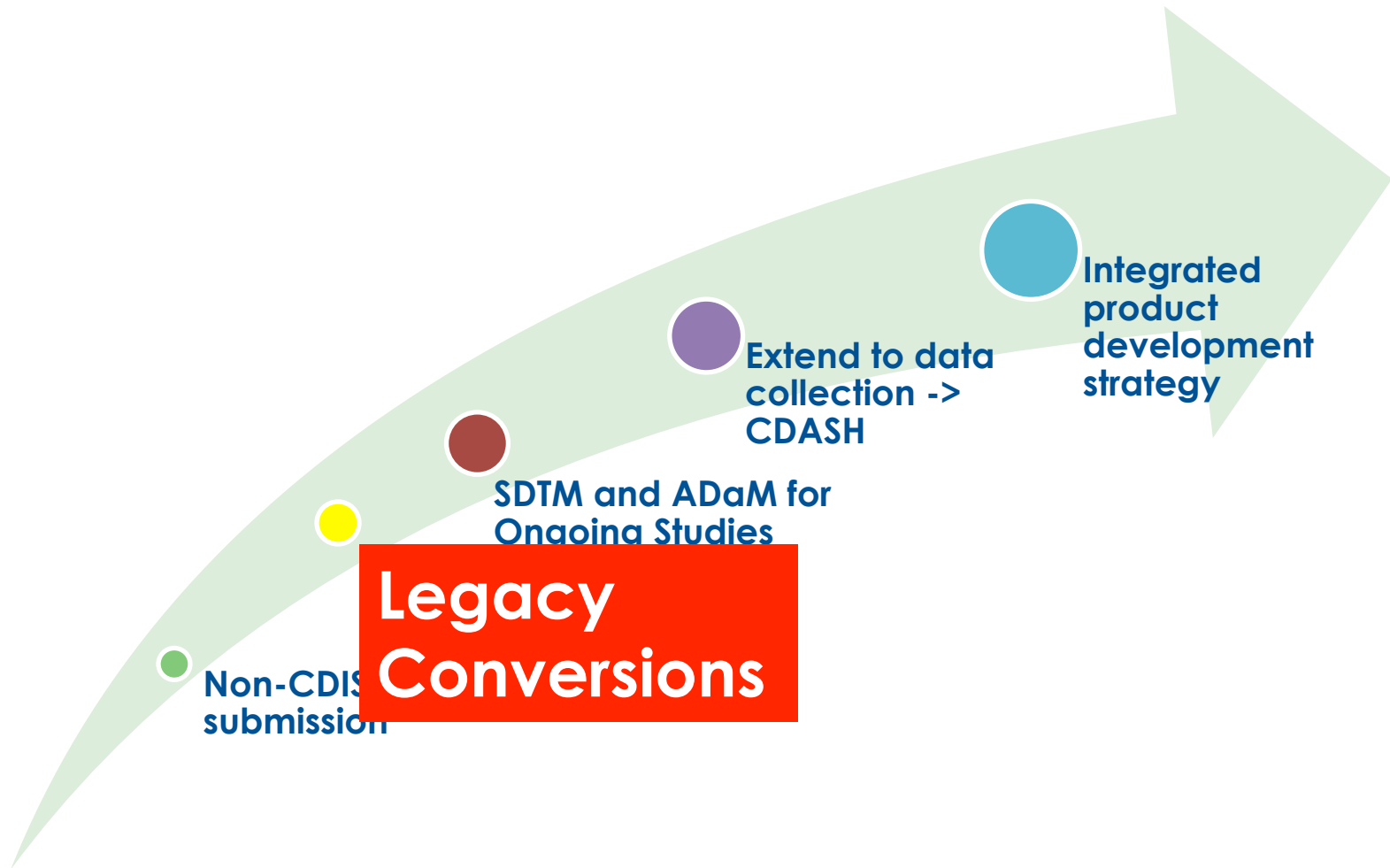
Legacy conversions for all studies

SDTM and ADaM only for Phase III

SDTM and ADaM for all studies

End to End plan

Implementation Strategy



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

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

Legacy Conversion Post Phase III

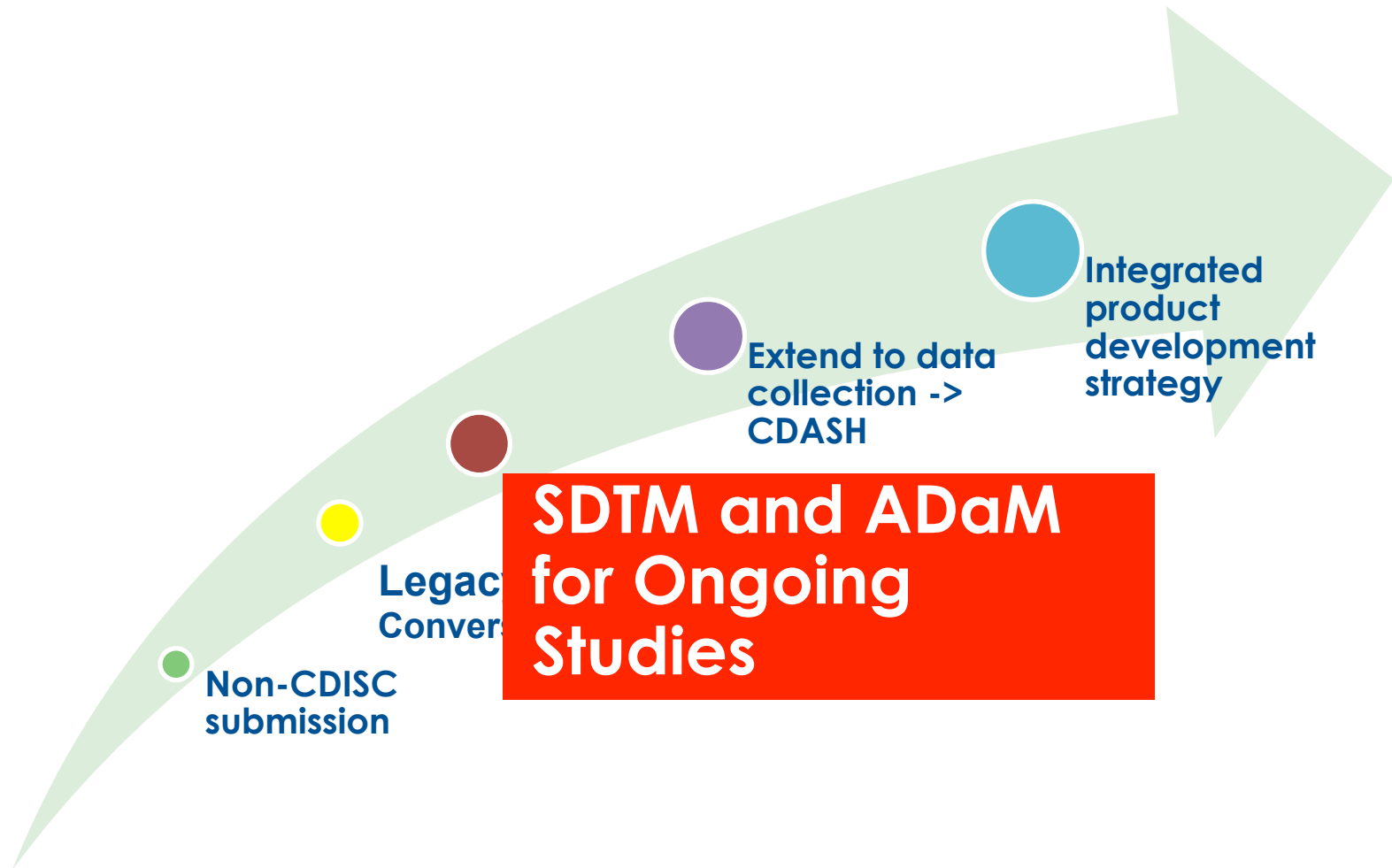
Not a
good
strategy
if:

- 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

Implementation Strategy



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

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

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

SDTM/ADaM: Hybrid Strategy

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

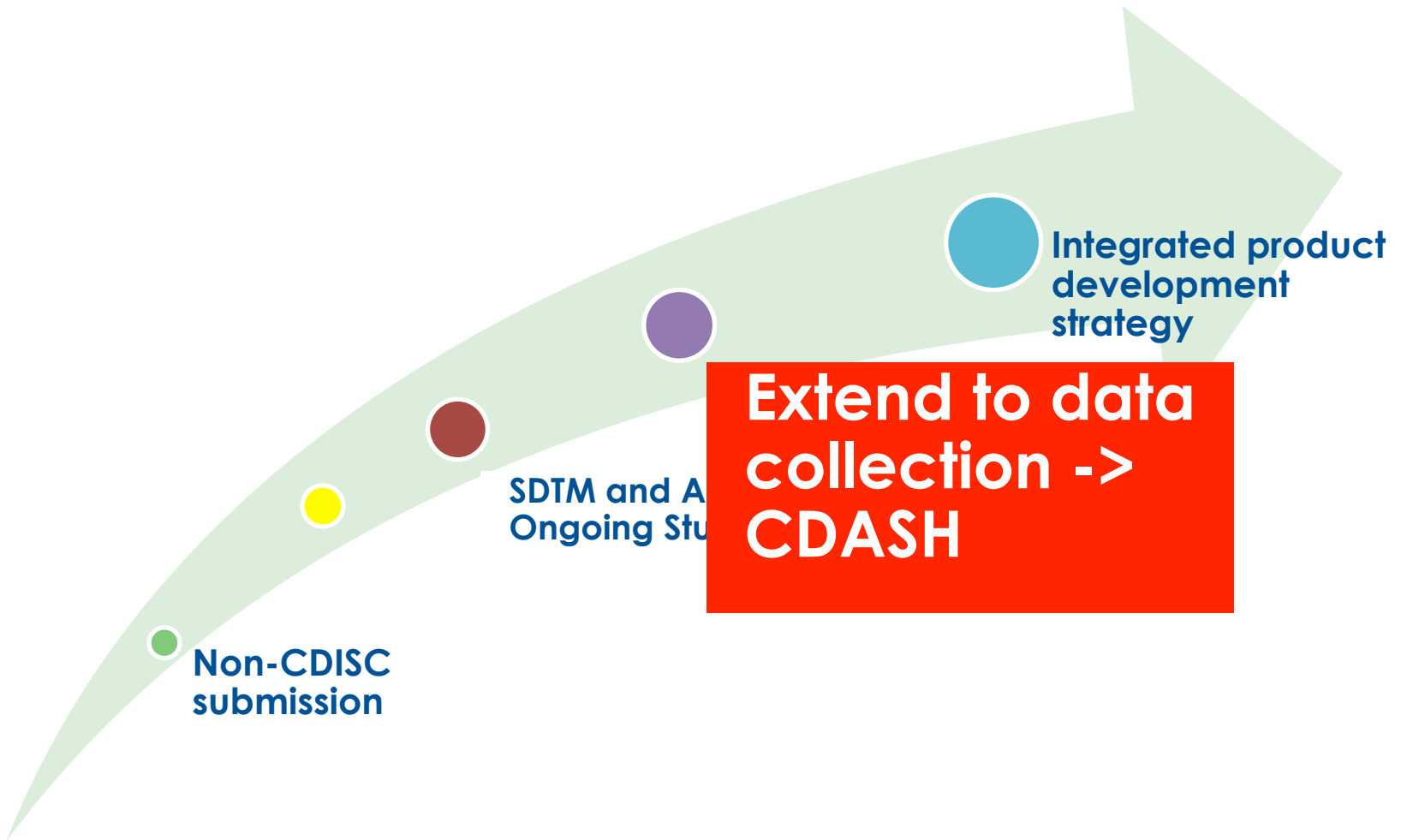
Advantages

- 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

Implementation Strategy



SDTM and ADaM + CDASH



Same advantages as
SDTM/ADaM Strategy



Extends standards to
data collection



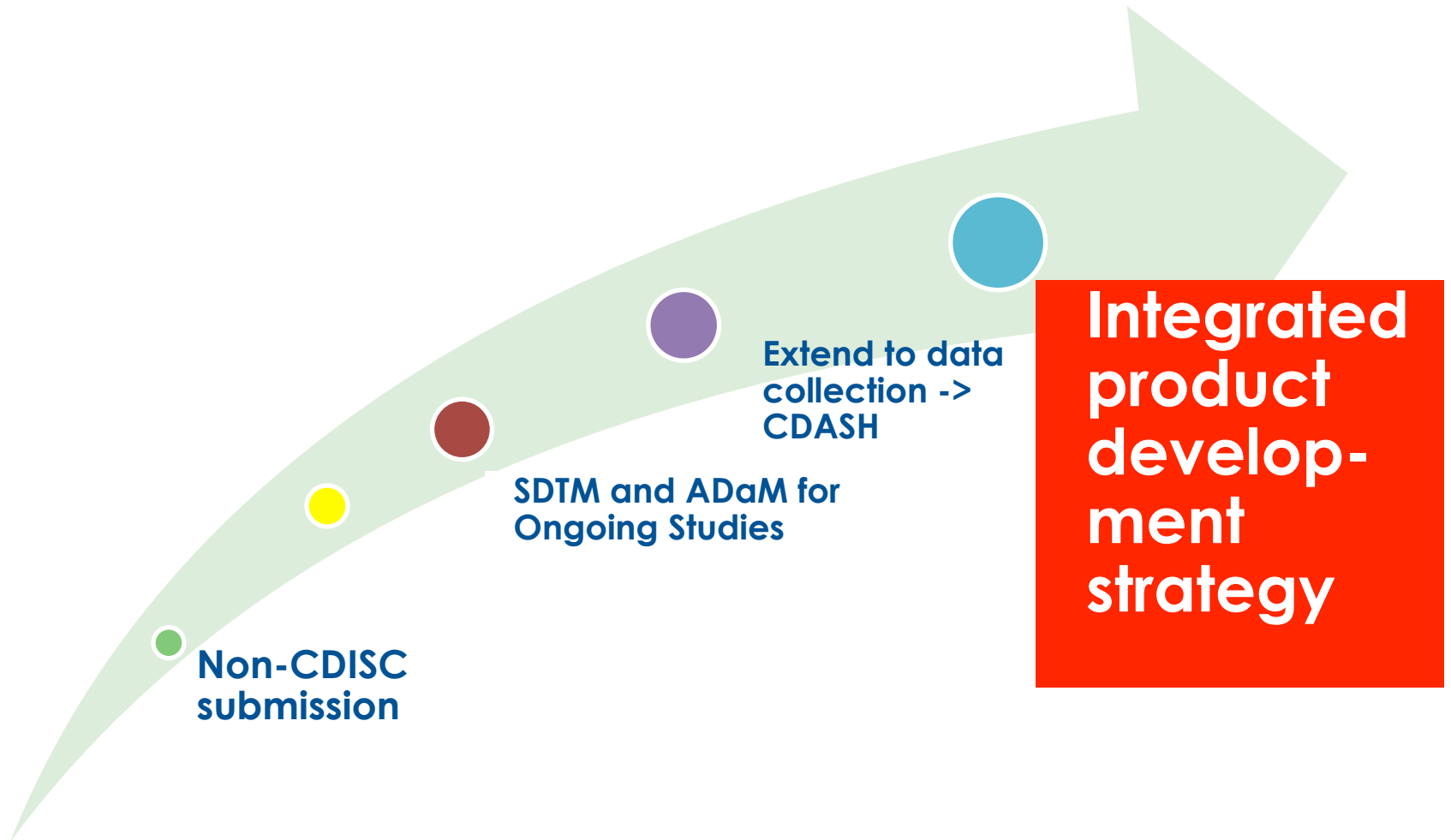
Global library of data
collection elements

SDTM and ADaM + CDASH

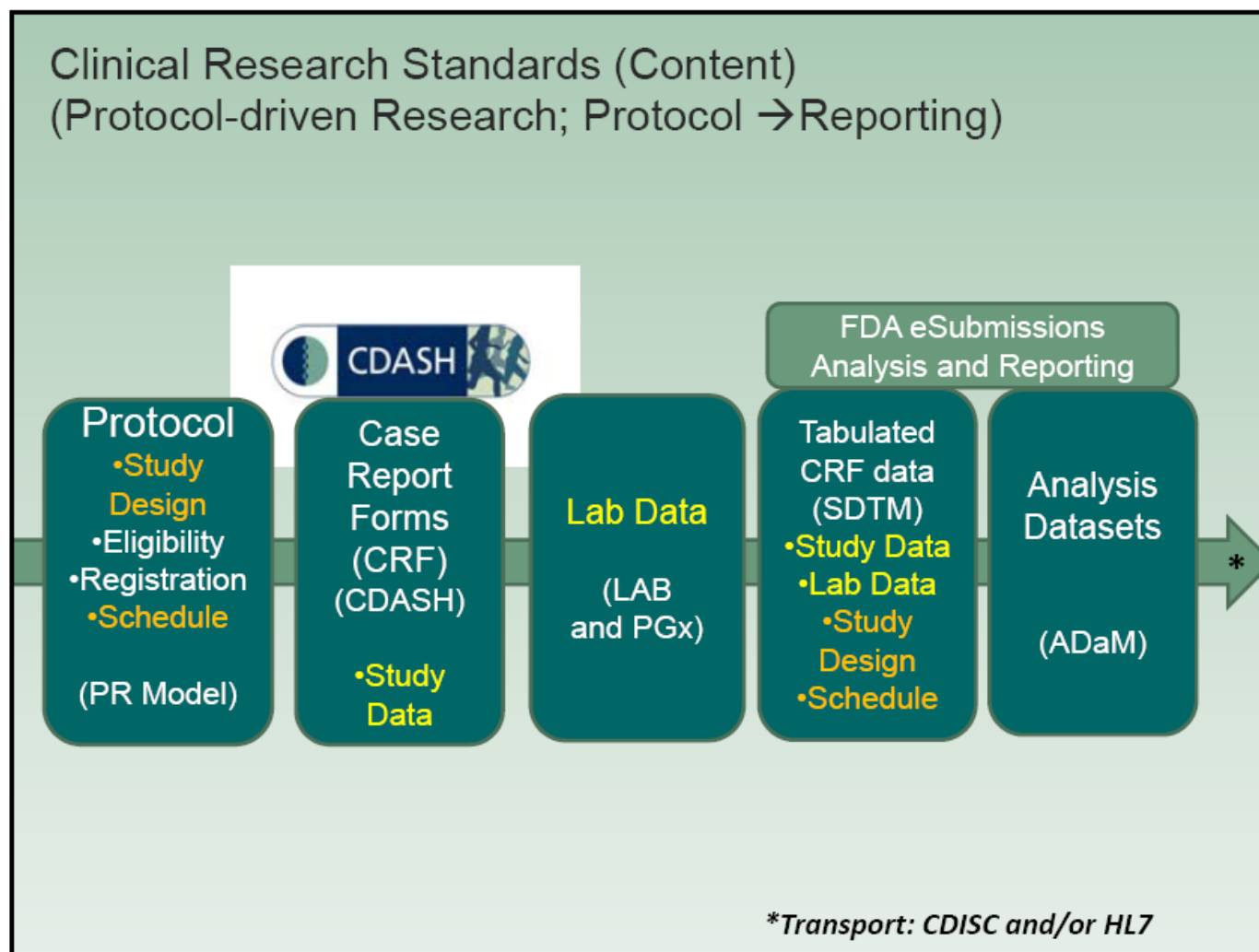
Advantages

- 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

Implementation Strategy



End-to-End Standards Implementation



End-to-End Standards Implementation

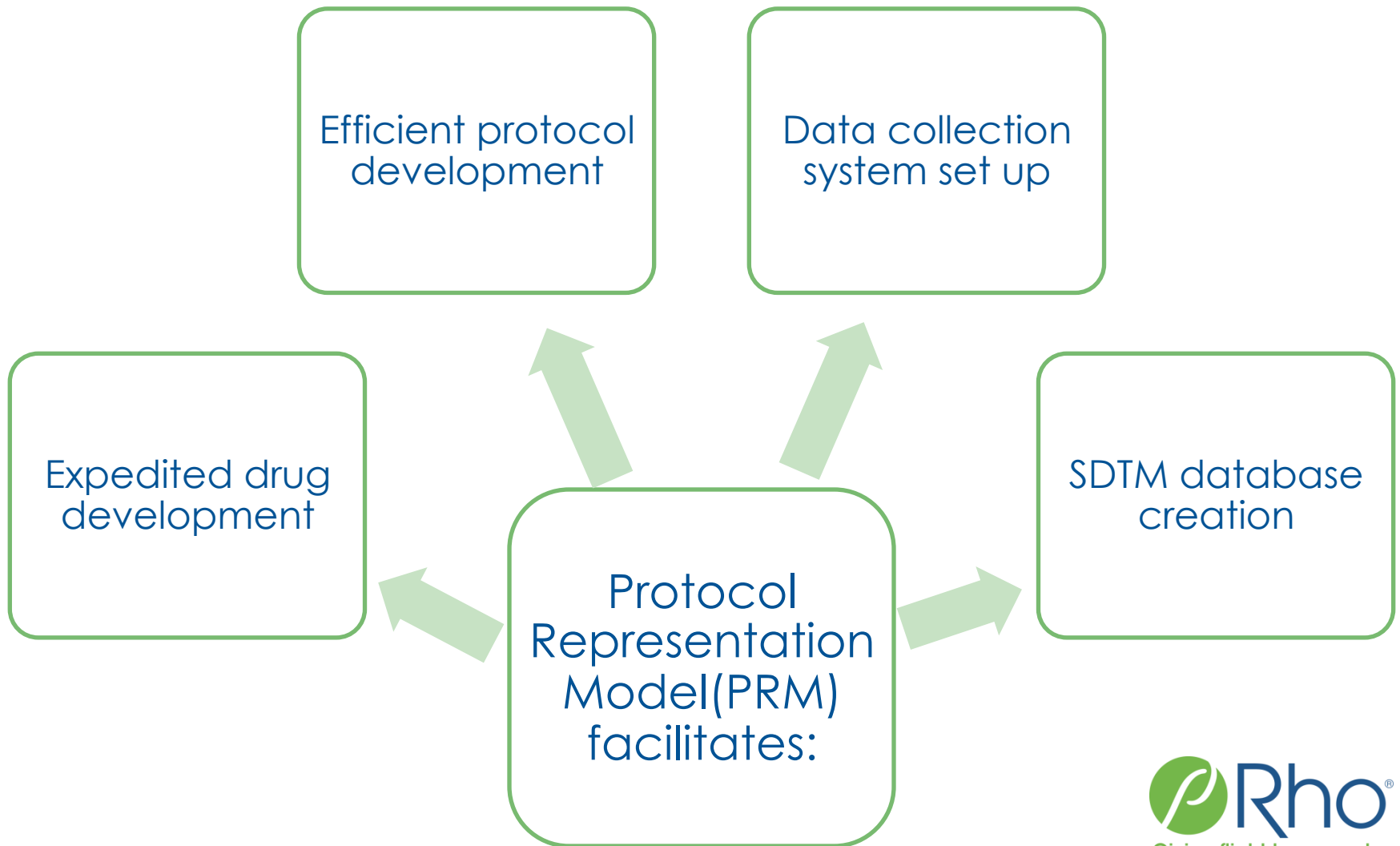
Extend standards implementation
all the way upstream

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

End-to-End Standards Implementation



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)

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

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”

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.”

Q&A

Send questions or comments to:

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