Introductions

Common Protocol Template Expert

Mitzi Allred
Merck & Co. Inc (MSD Global)
Head, Clinical Content Standards
Integration and Innovation Lead, TransCelerate Biopharma
Common Protocol Template Workstream
AGENDA

Overview of TransCelerate (5 Minutes)

Common Protocol Template: Rationale, Development, Benefits (15 Minutes)


Benefits across Stakeholders (5 Minutes)

Case Study: Embedding the Technology-Enabled CPT and Extending it to Extract Data for Downstream Processes (15 minutes)

Q&A (15 Minutes)
Overview of TransCelerate
TransCelerate:
A Not-for-Profit Entity Created to Foster Collaboration

Our Shared Vision:
To improve the health of people around the world by accelerating and simplifying the research and development of innovative new therapies.
The Reach of our Global Membership is Expanding

Membership is available to biopharmaceutical research and development organizations that engage in innovative discovery, development and manufacturing of new medicines*.

There are over 1,000 people from Member Companies that design and develop TransCelerate solutions.

* to be eligible for membership, companies must meet specified eligibility criteria.
External Collaboration play a critical role in achieving the future state

As a single stakeholder organization, we understand the value of robust collaboration with key stakeholders* across the R&D ecosystem which provide unique and important insights and perspectives.

<table>
<thead>
<tr>
<th>INVESTIGATOR SITES*</th>
<th>RESEARCH AND CRO COMMUNITY*</th>
<th>PATIENT ADVOCACY GROUPS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Logo]</td>
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<table>
<thead>
<tr>
<th>OTHER ASSOCIATIONS*</th>
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<td>![Logo]</td>
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<table>
<thead>
<tr>
<th>HEALTH AUTHORITIES*</th>
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<td>![Logo]</td>
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<td>![Logo]</td>
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<td>![Logo]</td>
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</tbody>
</table>

* Representative organizations, not exhaustive
Common Protocol Template: Rationale and Development
Why a Common Protocol Template?

Patient Advocate

“Just because ‘subject’ is in the regs, doesn’t mean you have to use it. Patients think of ‘subject’ as a verb, and who wants to be subjected to something? Please use ‘trial participant’ instead.”

Investigator

“Patient recruitment is challenged by the complexity of protocols. Sponsors do the same things too many different ways. Just make it the same!”

FDA

“If you have standards without traceability, then you aren’t really CDISC compliant.”

Heard at a June 2015 DIA meeting…
The Common Protocol Template Potentially Benefits Many Stakeholders

### Near Term Benefits to Sites
- Protocols streamlined and organized with an investigator focus
- Reduced burden on sites working on multiple studies

### Near Term Benefits to Sponsors
- Reduction in redundant protocol content
- Enabling of therapeutic area standards
- Improved conduct of the study and quality of data collected

### Potential Future Benefits to Sites
- Opportunity to harmonize additional documentation
- Enable consistency of some case report forms

### Potential Future Benefits to Sponsors
- Automation of downstream processes and reuse of content
- Enabling of therapeutic area standards in additional TAs
- Enabling collaborative clinical trials

### Near Term Benefits to Regulators
- Protocols streamlined, increased consistency between sponsor protocols to ease review

### Potential Future Benefits to Regulators
- Increased ease of data interpretation and ability to compare protocols (improves input on protocol design).
- Increased use of data standards enabling end-to-end use of metadata and traceability

### Near Term Benefits to Patients
- Improved access to protocol information
- Getting medicines faster, for participants & future patients

### Potential Future Benefits to Patients
- Improved access to protocol information
- Getting medicines faster, for participants & future patients

### Potential Future Benefits to IRBs
- Enabler for automation of IRBs submissions
- Increased consistency between sponsor protocols: easier review and faster approval

### Potential Future Benefits to IRBs
- Enabler for automation of IRBs submissions
- Increased ease of data interpretation and ability to compare protocols (improves input on protocol design),
- Increased use of data standards enabling end-to-end use of metadata and traceability
Common Protocol Template is Intended to Prepare for the Future State

- A common protocol template structure with harmonized language
- Streamlined content enables identification of critical information for end users
- Begin working towards model endpoint definitions to align with Clinical Data Interchange Standards Consortium (CDISC) Therapeutic Area (TA) data standards.
- TA Libraries available

- Reconnect processes (protocol, eCRF, development)
- Transformation of the design process
  - Analytics-driven trial design, modelling, scenario planning
- Role-based access to protocol information (Principal Investigator [PI], Ethics, Participants)
- Connection to other systems
The “Must Haves” in development of the CPT

<table>
<thead>
<tr>
<th>Structure must...</th>
<th>Content must...</th>
<th>Endpoints must...</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Be streamlined</td>
<td>✓ Develop common wording</td>
<td>✓ Map to an objective</td>
</tr>
<tr>
<td>✓ Be consistent</td>
<td>✓ Align with GCP, ICH, &amp; EU requirements</td>
<td>✓ Support use of CDISC TA Standards</td>
</tr>
<tr>
<td></td>
<td>✓ Allow for all phases and study types</td>
<td></td>
</tr>
</tbody>
</table>

“Just make it the same!”
- Investigators and Site Coordinators of the SCRS Site Advocacy Group pled for consistent organization of protocols across sponsors
The Common Protocol Template is NOT....

- A training document for protocol writing teams.
- A training document for inexperienced sites.
- A document for internal contracting of downstream actions within the sponsoring organization.
- An enrollment feasibility document (specifically referring to the Synopsis section).
- An exposition of the Sponsor’s development program.
- A substitute for or duplicate of the Investigators’ Brochure or Statistical Analysis Plan (SAP).
- Intended to meet the needs of any possible reader, but specifically written to meet the needs of investigative sites and regulatory reviewers.
How was the CPT Developed and Who is Using it?

- **17 Member Companies participated**
- **Advisory Committee informed early direction**
  CDISC, FDA, PhUSE, NCI-EVS. (EMA attended as an observer)
- **Review of content by key stakeholder groups**
  Site Advocacy Group: Investigator & Site Coordinator input via SCRS (2015)
  CRO Forum: Input from multiple CROs through partnership with ACRO (2016)
  FDA’s CPT Working Group: reviewed V002: Group is being reactivated to give additional input to TransCelerate

**Collaboration NIH-FDA Joint Protocol Template, 2016-2017**

Learned from NIH-FDA public comment exercise
Simplified TOC, moved sections and sub-sections, harmonized subsections
Prioritized sections for the user: investigator & reviewers
Treatment v. Study Agent = Study Intervention

**User and Member Company Feedback**

http://www.transceleratebiopharmainc.com/assets/common-protocol-template/

*Over 6,000 Downloads of from TransCelerate website!*
Member Companies (MC’s), other sponsors, academic institutions, health authorities, major cancer centers. Across all major global regions.

[Your feedback is welcome and valued! Use the “Talk to Us” button on the CPT Assets page of the TransCelerate website]
The ICH (International Council for Harmonization) Assembly has similarly established a working group to develop a Clinical electronic Structured Harmonized Protocol (CeSHarP).
CPT Structure:
Core Template and Libraries,
Basic Word Edition,
Technology Enabled Edition
What Does the CPT Look Like?

**Libraries** group and store point and click content used to populate the template

**Endpoint Definitions** modeled for TAs/indications

A sustainable **Governance Model** is in development

**Core Protocol Backbone**
- Common Level 1 & 2 Headings
- Common text
- Used across all phases
- Focus on investigators

**Appendices**
- Non-study specific info, items triggered by event

**Common Protocol Template and Guidance**

**Governance Model**

Core streamlined, focused on site needs

**Common Text** can be used “as is”-relevant across study types

**Appendices** to apply as applicable

Implementation Toolkit Materials
What does the CPT Look Like? Basic Word Edition

Word documents; No installation needed.

Locate the Basic Word Edition files on the TransCelerate CPT Website

Under" Common Protocol Template Tools and Resources," click on the blue bar “Basic Word Edition Template and Guidelines” to reveal all of the available resources. To download the CPT BWE, click on “Basic Word Edition Core Template.”

Participant and Therapeutic Area Libraries are also available. To download any of the files, click on the file and “Save As” to add the files to your desktop or local drive.

Start authoring your protocol.

<table>
<thead>
<tr>
<th>File</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Getting started with the CPT Basic Word Edition</td>
<td>Step-by-step guide for starting with the Basic Word Edition of the CPT</td>
</tr>
<tr>
<td>Basic Word Edition Core Template</td>
<td>MS Word enabled format and content template for the protocol, containing a common heading structure, common text, suggested text, and all CPT libraries. Includes a prerequisite analyzer to assess the environment prior to installation. Requires installation of template and add-ins on your workstation.</td>
</tr>
<tr>
<td>CPT Types of Text and Style Conventions</td>
<td>Defines color coding used within the CPT to distinguish common, suggested, example, and instructional text</td>
</tr>
</tbody>
</table>

**Participant and Therapeutic Area Libraries**

**Participant Libraries**
- Healthy Volunteer Library
- Patient Library
- Pediatric Library

**Therapeutic Area Libraries**
- Alzheimer's Library
- Asthma Library
- Breast Cancer Library
- COPD Library
- Diabetes Library
- Diabetic Kidney Disease Library
- Prostate Cancer Library
- Rheumatoid Arthritis Library
- TQT Library
What does the CPT Look Like? Basic Word Edition

Instructional text provided as red hidden text available by toggling paragraph marks

**2. Introduction**

++ Overall, this section should be short (recommend 2 to 3 pages) and may be started with an overview description of the study intervention, its class, and intended use as well as the study population.

++ Consider that the entire protocol will be subject to public disclosure and be accessed.

++ Be as much as possible, reference the investigator's brochure, package, and other relevant documents. Do not duplicate information available elsewhere.

**Example text**

XXX is a novel, potent, and selective long-acting inhaled β2 adenoreceptor agonist that is being developed for once-daily treatment of asthma and COPD.

**End of example text**

Phase 4 studies of FDA-approved drugs delineate additional information including the drug's risks, benefits, and optimal use.

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What Does the CPT Look Like? Tech-Enabled Edition
It still looks like paper….but its not!

The Technology Enabled Edition of the Common Protocol Template (CPT) avoids media breaks by capturing structured and unstructured information in variables available for export and reuse downstream.
CPT Resources Available for Download

http://www.transceleratebiopharmainc.com/assets/common-protocol-template

Basic Word Edition
- A document-based template and associated libraries for use across phases and study types
- Use as-is or modify current format template to reflect CPT content
  ✓ Common Protocol Template; ✓ Common SAP; ✓ Common CSR

Tech Enabled Edition (eTemplate)
- An MS Word-based template with add-ins
- Automation to leverage “point and click” text
- Capture of protocol-level metadata to facilitate content reuse
  ✓ eCPT; coming 2019: eSAP, eCSR

Implementation Toolkit
- Roadmap of activities to support implementation
- Materials tailored for various audiences
- Template evaluation tools and FAQs
  ✓ Coming 2019: eSuite Implementation Toolkit

<table>
<thead>
<tr>
<th>CPT</th>
<th>Common SAP</th>
<th>Common CSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic Word Edition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Q4 2018</td>
<td>Q4 2018</td>
<td></td>
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<tr>
<td>Tech Enabled Edition</td>
<td></td>
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<tr>
<td>✓ Q4 2018 (for Member Companies)</td>
<td>Q4 2018 (for Member Companies)</td>
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<tr>
<td>Implementation Toolkit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✓ Q4 2018</td>
<td>Q4 2018</td>
<td></td>
</tr>
</tbody>
</table>
The Next Release is Coming Soon

<table>
<thead>
<tr>
<th>CPT v6</th>
<th>Common SAP</th>
<th>Common CSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>• New libraries: CV-Safety, Vaccines</td>
<td>• New Template created with a hybrid Sprint/CPT Model</td>
<td>• New Template created by CPT CSR Subteam</td>
</tr>
<tr>
<td>• New CPT core content</td>
<td>• Incorporates draft ICH Guidance on estimands</td>
<td>• Lean approach</td>
</tr>
<tr>
<td>– Device trials</td>
<td>• FDA and EMA interested in reviewing it</td>
<td>• Adjustments from (but maps to) ICH and CORE</td>
</tr>
<tr>
<td>– EU Clin Trial Regulation analysis and alignment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Robust statistical content and other FDA feedback</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Improved Tech Enabled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Libraries can be stored in a central location, and users can work with these files offline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Previous versions of the CPT can be viewed in the Read-only mode</td>
<td></td>
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</tbody>
</table>
Protocol is the Primary Source for Clinical Trial Content

### 9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, traced, and questionable data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

#### 9.4.1. Efficacy Analyses

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Statistical Analysis Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td>Exploratory</td>
<td>[Will be described in the statistical analysis plan finalized before database lock]</td>
</tr>
</tbody>
</table>

#### 9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Statistical Analysis Methods</th>
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</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
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<tr>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td>Exploratory</td>
<td>[Will be described in the statistical analysis plan finalized before database lock]</td>
</tr>
</tbody>
</table>
Data Flow and Content Reuse Across Clinical Documents

Significant amount of clinical content:
- Begins in the protocol
- Is reused downstream

- TEE CPT
  - Schema
  - Objectives/Endpoints
  - Statistical Methods

- SAP
  - Direct Reuse
  - Edited Reuse

- CSR
  - New Topics
Benefits Across Stakeholders
Value Proposition – Why Use?

Quality
- The expertise of 19 sponsors companies has been tapped to develop the template with input from regulators, sites, CROs and an IRB – the work has been done for you.
- The template includes TA –specific libraries based on sponsor best practices.
- Stakeholders have the opportunity to suggest revisions; the template will be maintained and updated over time.
- Broad adoption will help drive greater efficiency for investigators, sites, sponsors, and regulators.

Efficiency
- Sponsors can spend less time on low-value customization, and reduce time managing template maintenance.
- The template is easy for authors to use.
- Sponsors can adopt in a phased approach, and can choose to use either the Word version or Tech-Enabled version. You don’t have to go “all in” at the outset.

Compliance
- The template is supported by FDA, and Health Authority feedback to date has been unanimously positive.

Quality + Efficiency + Compliance = Value

Harmonization

Value
Case Study: Embedding the Technology-Enabled CPT and Extending
Align with Structured Content Approach
Focus on Reuse Aligning with the Tech-Enabled

Why would anyone worry about managing and reusing content?

YOU CAN’T AFFORD NOT TO

Create structure from unstructured content using reuse conventions and information design

Content redundancies across documents lead to inefficiencies and risk...

Build on current authoring tools and guides such as the TransCelerate CPT

...same content repeatedly reviewed and approved

High probability of errors
What Was Done to Make it Work?

TransCelerate CPT Content

Tech-Enabled CPT Merged with Authoring Tool

Company Protocol Content

Content Design Model

TA-Specific Libraries
# Protocol Library Content Development

## TransCelerate CPT to Company Content Library Comparison

### High level mapping of section headers

All team members, not just lead reviewer(s), were asked to review all sections.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TransCelerate Heading</strong></td>
<td><strong>Section in Table of Contents</strong></td>
<td><strong>Comments - including:</strong></td>
<td><strong>Suggested Path Forward</strong></td>
<td><strong>Lead Reviewer(s)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TransCelerate</strong></td>
<td><strong>Merck Template</strong></td>
<td>GAPs (TC template is missing) / Comparison of Standard Text / Other differences</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title Page</td>
<td>Introduction</td>
<td>MRM: TC does not include IndicoCT Number; TC does not include study site terminology; Total File Binder; TC binder includes instructions on how to add page numbers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table of Contents</td>
<td>Table of Contents</td>
<td>MRM: add Table of Contents; MRM: add ASMEs, Kress</td>
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<td></td>
<td></td>
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<tr>
<td>Synopsis</td>
<td>MRM: Use TC template summary. Text Section 3 and Section 4 Objectives and Endpoints in sync automatically.</td>
<td>MRM: Use TC template summary. Text Section 3 and Section 4 Objectives and Endpoints in sync automatically.</td>
<td></td>
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</tr>
<tr>
<td>1. Objectives and Endpoints</td>
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</tbody>
</table>

### Different wording:
Can we accept CPT model text/instructions?

### CPT has content that Company does not:
Can we accept CPT model text/instructions?

### CPT is missing content that Company has:
Do we need it? Does it or can it exist elsewhere?

Team members provided comparison comments and suggested path forward.

Suggested Lead Reviewer(s)
What are the Content Reuse Opportunities for Our Company?

Content Reuse Opportunities

- Protocol
- CSR
- CTD
- TLFS
- Patient Datasets
- eSource
- Data Collection
- SAP
- MDR Metadata Repository
- Libraries
  - Objectives/Endpoints
  - Inclusion/Exclusion
  - Data Standards

Analytics

Content reuse opportunities
End-to-End Data Flow opportunities
Protocol Reuse

Protocol – General – Stakeholder Owned Text -26-32 Stakeholders

35% (CPT Content)

Protocol – System Inserted Content –TA or compound related

30% (Library)

Protocol – Content Controls for User selected Text

19% (Library)

Protocol – De Novo Areas

16%

Average time from Study Approval to Protocol Approval
Year 2018 = 34 days (down ~23 days from 2017)

…the use of structure library text, the control to deliver the immutable text and the governance to ensure change aligned to TA

✓ Speed
✓ Consistency
✓ Quality
<table>
<thead>
<tr>
<th>Compound Number</th>
<th>Number of Participants</th>
<th>Tertiary Objective(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Number</td>
<td>Enrollment Target</td>
<td>Tertiary Endpoint(s)</td>
</tr>
<tr>
<td>Protocol Title</td>
<td>Planned Number of Arms</td>
<td>Sex of Participants</td>
</tr>
<tr>
<td>Protocol Short Title</td>
<td>Arm Name</td>
<td>Planned Minimum Age of Subjects</td>
</tr>
<tr>
<td>Acronym</td>
<td>Study Intervention Name</td>
<td>Planned Maximum Age of Subjects</td>
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<tr>
<td>Approval Date</td>
<td>Intervention Type</td>
<td>Exclusion Criteria Medical Conditions</td>
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<tr>
<td>Sponsor Name</td>
<td>IMP and NIMP</td>
<td>Exclusion Criteria Prior Concomitant Therapy</td>
</tr>
<tr>
<td>Sponsor Legal Address</td>
<td>Sourcing</td>
<td>Exclusion Criteria Prior Concurrent Clinical Study Experience</td>
</tr>
<tr>
<td>Agency ID</td>
<td>Packaging and Labeling</td>
<td>Exclusion Criteria Diagnostic Assessment</td>
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<tr>
<td>Regulatory Agency Number</td>
<td>Current Former Names Aliases</td>
<td>Exclusion Criteria Other</td>
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<td>Data Monitoring Committee</td>
<td>Dosage Formulation</td>
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<tr>
<td>Intervention Model</td>
<td>Route of Administration</td>
<td></td>
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<tr>
<td>Primary Purpose</td>
<td>Dosage Level</td>
<td></td>
</tr>
<tr>
<td>Study Phase</td>
<td>Unit Dose Strength</td>
<td></td>
</tr>
<tr>
<td>Masking</td>
<td>Primary Objective(s)</td>
<td>*Sponsor Status = Commercial</td>
</tr>
<tr>
<td></td>
<td>Primary Endpoint(s)</td>
<td>*Trial Type = Intervventional</td>
</tr>
<tr>
<td></td>
<td>Secondary Objective(s)</td>
<td>*Responsible Party = Sponsor</td>
</tr>
<tr>
<td></td>
<td>Secondary Endpoint(s)</td>
<td>*Healthy Volunteer = HLTSUBJ1</td>
</tr>
</tbody>
</table>

*These variables do not appear in template text but are included in export with values populated.
Reuse Statistics: Disclosure Elements & Intra-document Content Reuse

Disclosure Elements
Number of variables in protocol to be reused for transparency (per CPTv5 disclosure alignment; N=33) (eg, Compound Number, Brief Title, Primary Purpose)

• Title page n=8 (25%)
• Synopsis n=13 (40%)
• Body Sections 3-9 = n=21 (64%)

Intra-document Content Reuse
Number of variables with intra-document content reuse within protocol (this is minimal, n=2) (eg, Compound Number, Protocol Title)

Number of variables with intra-document content reuse within CSR (expect this to be minimal, n=13) (eg, CSR Identification Number, Study Initiation Date, Report Date)
Reuse Statistics: Protocol to CSR Content Reuse (Projected)

- **Overall ~40% Reuse Expected**
  - Body Sections 5-9: 35%
  - Synopsis Content: 50%
  - Title Page Content: 43%

- **Overall ~17% Reuse Expected**
  - CSR Sections 1-9 Expected to Have Exact Reuse: 70%
  - Title Page and Synopsis Content: 100%

- **Overall ~34% Reuse Expected**
  - CSR Sections 1-9 Expected to Have Derivative Reuse: 100%

Looks at CSR content broken down into L1/L2 header units with counts of expected reuse from protocol to CSR according to type of reuse (e.g., exact [content used as is], and derivative [editing/rework expected]).

The bar graph percentages represent a breakdown of the overall % reuse illustrating greater detail.
Key Benefits & Lessons Learned

- More efficient reuse of established content from a library (by development stage, TA, product, etc.)
- Increased consistency and quality of content
  - Pre-population of established content in protocol, based on criteria (e.g., study development stage, therapeutic area)
- Content can be shared across document types
  - Content reuse is powerful, but complex in practice – adjustments likely need to be made to existing templates to optimize reuse
- Authors must understand content reuse and its implications (write once, use many…)
- Governance structure is important to set up early on
  - Content reuse is best managed centrally
Questions?