THE CSR SIMPLIFICATION PROJECT
CREATING A CLEAR, COMPLIANT & CONCISE CSR

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for the CSR Simplification Team
Today’s Agenda

Background & Introduction

Overview of Project Results

Implementation

Next Steps
Challenge: Can we focus & simplify CSRs?

Create: A clear & concise document that reports results & key messages

VS

Current: A comprehensive document containing all study information

- Paper-based legacy
- Extensive background, introduction & rationale from protocol
- Complete description of study design & conduct from protocol
- SAP copied in from protocol
Project Overview

Analysis:

• Who is the primary **customer** for the CSR?
• What is the **Health Authority Reviewer** looking for?
• Do our CSRs **facilitate or hinder** the Reviewer?
• Are we taking advantage of / **leveraging technology** to make it easier for the Reviewer? For us?
• Are we using (all) our **resources** effectively?
• Disclosure!

**Benchmarking**
(CROs, Pharma, Transcelerate)

**Critical review of SOP, documentation, procedures. Benchmarking**

**Recommendations made to SOP co-owners & leadership**
√ Endorsed

**SOP & Resource roll-out (Dec ‘17)**
Training & communications to stakeholders
Benchmarking

Internal and external feedback from key industry leaders

CORE reference

Alignment with TransCelerate CPT format

- Reviewers do not read front to back
- Synopsis <5 pages
- Bullet text instead of prose
- Not a manuscript
- CSR <100 pages
- Only key results described in CSR body
- Freezing sections to limit editing
- Tables are final before used in text
- 100 table limit/CSR
- Leveraging technology
- Functional area focus during review
- Using a coordinating reviewer per function
- Proactive approach to disclosure
- Internal and external feedback from key industry leaders
- CORE reference
- Alignment with TransCelerate CPT format
Guiding Principles

Build on Industry & Our Best Practices

- Embrace focused authoring principles
  - No distracting redundancies or unnecessary descriptions
- Leverage electronic environment
  - Build on structured authoring initiatives
- Leverage the Core Protocol Template (CPT):
  - Re-use reviewed & approved text from protocol
    - Protocol is only 1 click away!
  - Maximize immutable text
  - Minimize customization

Benefits Team

- Compliant
  - ICH E3, FDA, CFR, CORE Reference
- Time
  - Reduce author time
  - Reduce reviewer time
  - Reduce QC time
- Reduce potential for error
- Build on existing initiatives to simplify documentation
- Applicable for most studies

Benefit the Agency Reviewer

- Concise / focused document to help reviewer “see” the results & key messages
Key Categories

- Focused authoring
- Use text instead of tables
- 5-page target

- Numbering system for TLFs
- TLF insertion tool
- Country-specific Module 5
- Minimize need to redact

- CORE template adopted
- Focused authoring
  - Streamline 4-9
  - Focus 10-12
  - Clarify Section 13

- Clarify reviews
- Clarify roles
- Clarify expectations
- Reduce unnecessary work

Synopsis
Template
TLFs
Appendix
Process
Project Results: Synopsis

noun

a brief summary or general survey of something. "a synopsis of the accident"
synonyms: summary, summarization, précis, abstract, outline, digest, rundown, roundup, abridgment

"the synopsis was so intriguing that I just had to buy the book"

• an outline of the plot of a book, play, movie, or episode of a television show.
Synopsis

- 5-page target
  - Provide information required for disclosure
- No tables or figures
  - Except as required by template
- Bullet or number lists to summarize information
  - Re-use from CSR results summaries
- Primary & secondary endpoints
  - Summarize secondary analyses only if key to results
Synopsis: Before & After

Original
- Lots of white space & partial pages
- 14 tables!
- Text repeats information in the tables
- Methods and Results described together
- Detailed descriptions of additional endpoints
- Paragraphs

27 pages

After
- Reformatted
- 1 AE table
- Briefly summarized key methods & analyses
- Key messaging for efficacy & safety information
- Primary & secondary endpoints
- Bullet lists

4 pages
Project Results: CSR Template

- CORE for Section 9
- Streamlined Sections 4-9
  - Link to protocol
- Focused Sections 10-12
- Clarified Section 13
CORE Adopted for Template Sections 9.4 - 9.8

9.4 Treatments
  9.4.1 Treatments Administered
  9.4.2 Identify of Investigational Products
  **9.4.3 Avoidance of Bias in the Study**
    - 9.4.3.1 Methods of Assigning Participants to Treatment Groups
    - 9.4.3.2 Blinding
  9.4.4 Selection and Timing of Doses for Each Participant
  9.4.5 Intervention Compliance
  9.4.6 Prior and Concomitant Therapy

9.5 Study Assessments and Procedures
  9.5.1 Planned Measurements and Timing of Assessment
  9.5.2 Appropriateness of Measurements
  **9.5.3 Pharmacokinetic and Pharmacodynamic Measurements**
    - 9.5.3.1 Analytical Methods
    - 9.5.3.2 Pharmacokinetic Methods
  9.5.4 Other Measurement Methods

9.6 Data Quality Assurance

9.7 Changes in the Conduct of the Trial

9.8 Changes in Planned Analyses
  9.8.1 Changes in the Conduct of the Study
  9.8.2 Changes in the Planned Analysis
  9.8.3 Changes Following Study Unblinding and Post-hoc Analyses

FORMER TEMPLATE

9.4 Treatments
  9.4.1 Treatments Administered
  9.4.2 Identify of Investigational Products
  **9.4.3 Dose Selection & Timing of Dose**
  9.4.4 Trial Blinding/Masking
  9.4.5 Randomization or Treatment Allocation
  9.4.6 Concomitant Medications

9.5 Clinical Procedures/Assessments
  9.5.1 Measurements Assessed & Timing
  9.5.2 Appropriateness of Measurements
  **9.5.3 Drug Concentration Measurements**
    - 9.5.3.1 Analytical Methods
    - 9.5.3.2 Pharmacokinetic Methods
  9.5.4 Blood for Planned Genetic Analysis
  9.5.7 Pharmacodynamic Methods

9.6 Data Quality Assurance

9.7 Changes in the Conduct of the Trial

9.8 Statistical Analysis Plan

9.9 Changes in Planned Analyses

NEW (CORE) TEMPLATE
Template Sections 4 through 9 (1 of 2)

General principal: Maximize use of standard / pre-approved text.

- Sections 4, 5, & 6
  - Use standard template text & link to protocol
- Sections 7 & 9.1
  - Summarize information from protocol
- Sections 8, 9.3, & 9.4
  - Use verbatim text from protocol
- Sections 9.2, 9.5, 9.6, & 9.7
  - Link to the protocol
- Section 9.8
  - Summarize information not in protocol / SAP

4 List of Abbreviations
5 Ethics (IEC, Ethical Conduct, Subject Information)
6 Investigators & Trial Administrative Structure
7 Introduction
8 Objectives & Hypothesis
9 Investigational Plan
  9.1 Overall Study Design and Plan
  9.2 Discussion of Study Design
  9.3 Selection of Study Population
  9.4 Treatments
  9.5 Study Assessments and Procedures
  9.6 Data Quality Assurance
  9.7 Statistical Analysis Plan
  9.8 Changes in the Conduct of the Study or Planned Analyses
**Template Sections 4 through 9 (2 of 2)**

**Original CSR:**
1. List of Abbreviations p1-3 (2+ pages)
2. Ethics p3-4 (2 pages)
3. Investigators & Trial Administrative Structure p4-5 (1 page)
4. Introduction p6-7 (1.5 pages)
5. Objectives & Hypothesis p7-10 (4 pages)
6. Investigational Plan
   - 9.1 Overall Study Design and Plan p11-12 (1.5 pages)
   - 9.2 Discussion of Study Design p12-14 (2 pages)
   - 9.3 Selection of Study Population p14-19 (5 pages)
   - 9.4 Treatments p19-24 (5+ pages)
   - 9.5 Study Assessments and Procedures p24-32 (7 pages)
   - 9.6 Data Quality Assurance p33 (0.75 pages)
   - 9.7 Statistical Analysis Plan p35-48 (13 pages)
   - 9.8 Changes in the Conduct of the Study or Planned Analyses p33-35,48 (3+ pages)
7. TOTAL: 48 pages

**New Template:**
1. List of Abbreviations p1-3 (2+ pages)
2. Ethics p4 (0.5 page)
3. Investigators & Trial Administrative Structure p4 (1 para)
4. Introduction p4-5 (0.5 page, 3 para)
5. Objectives & Hypothesis p5-7 (2.5 pages)
6. Investigational Plan
   - 9.1 Overall Study Design and Plan p7-8 (1 page)
   - 9.2 Discussion of Study Design p8 (1 para)
   - 9.3 Selection of Study Population p8-10 (3 pages)
   - 9.4 Treatments p10-12 (2+ pages)
   - 9.5 Study Assessments and Procedures p12 (0.5 page)
   - 9.6 Data Quality Assurance p12-13 (0.5 page)
   - 9.7 Statistical Analysis Plan p13 (1 para)
   - 9.8 Changes in the Conduct of the Study or Planned Analyses p13-14 (1 page)
7. TOTAL: 14 pages
10 Study Participants

10.1 Disposition of Participants

10.2 Protocol Deviations

10.3 Subjects ... Prematurely Unblinded

10.4 Subject Populations Analyzed

10.5 Demographic and Other Subject Characteristics

10.6 Measurements of Treatment Compliance

11 Pharmacodynamic, ... Efficacy Evaluation and Results

11.x Efficacy Summary

12 Safety Evaluation

12.1 Extent of Exposure

12.2 Adverse Events

12.3 Clinical Evaluation of Laboratory Tests

12.4 Vital Signs, Other...

12.5 Subjects at Increased Risk...

12.6 Safety Summary

11 Efficacy and Other Evaluations

11.1 Efficacy Results

11.2 Immunogenicity Results

11.3 PK/PD/Other Results

11.4 Results of Statistical Considerations....

11.5 Efficacy Results Summary

12 Safety Evaluation

12.1 Adverse Events

12.2 Serious Adverse Events

12.3 Clinical Laboratory Evaluation

12.4 Vital Signs, Other....

12.5 Safety Summary
Template Sections 10-13 (2 of 2)

General Principles: **Text in the results section should provide a clear/concise interpretation of key (primary, secondary) endpoints & should not just repeat data from tables/figures.** Summaries (data without interpretation) and conclusions (overall key messages for safety and efficacy) are reused directly in the synopsis.

<table>
<thead>
<tr>
<th>Section</th>
<th>Requirements</th>
</tr>
</thead>
</table>
| 10 Study Participants | ✓ Suggested text provided  
 ✓ Use of consort diagram when possible.  
 ✓ Further assessment of deviations/analysis exclusions  
 ✓ Additional headers suggested in 10.4 Demographics |
| 11 Efficacy/Immunogenicity/PK/PD | ✓ Present results that support the key messaging  
 ✓ Structure subsections (primary, secondary, etc.)  
 ✓ Required **Efficacy Summary** (bullet format) |
| 12 Safety | ✓ Focus text on difference or similarity between groups  
 ✓ Narratives compiled in the appendix  
 ✓ Required **Safety Summary** (bullet format) |
| 13 Discussion and Conclusions | ✓ Discussion is not mandatory  
 ✓ Don’t fill with repeating results & summary statements  
 ✓ **Conclusions presented in bullet format** |
Project Results: Focused Authoring & Simplification

1. a center of activity, attraction or attention
   a point of concentration
2. directed attention, emphasis
3. a state or condition permitting clear
   perception or understanding

1. to reduce to basic essentials
2. to diminish in complexity
3. to make more intelligible
Use a focused writing style for all CSR content.

- Methods are described in Section 9 and **not repeated** in Sections 10-12
- Data from in-text tables or figures are **not repeated** in the text
  - Text provides an interpretation of data
- No ‘roadmap’ text!
  - No text telling the reader what is in each sub-section.
    - *Information available via side navigation bar!*
- Every word in the text is **needed**
  - Add pertinent information
  - For correct grammar
## Be Concise

<table>
<thead>
<tr>
<th>Tip</th>
<th>Original Text</th>
<th>Being Concise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep table references parenthetical</td>
<td>Table 10-3 presents subject medical history conditions with an incidence rate of &gt;5% in 1 or more group. OR As shown in Table 10-3, medical history conditions…</td>
<td>Medical history conditions were balanced across all groups [Table 10-3].</td>
</tr>
<tr>
<td>Avoid repetition</td>
<td>Group 1 had a mean systolic blood pressure of 15.8 mm Hg at Week 1 and Group 2 had a mean systolic blood pressure of 13.2 mm Hg at Week 1.</td>
<td>The mean systolic blood pressure at Week 1 was 15.8 mm Hg in Group 1 and 13.2 mm Hg in Group 2.</td>
</tr>
<tr>
<td>Remove roadmaps</td>
<td>Sec. 11.1.1 discusses the primary efficacy analysis of the change in JRS score for each treatment group. Sec. 11.1.2 discusses the secondary and Sec. 11.1.3 discusses the exploratory efficacy analyses.</td>
<td>No text needed: Rely on the navigation bar</td>
</tr>
</tbody>
</table>

From: *Using a Focused Authoring Strategy to Create a Message Driven Deliverable* by E Brown & K Jochman, AMWA 2 Nov (2-3:30)
Simplifying the CSR: Reduce/Eliminate Unnecessary Steps

Section 4: List of Abbreviations

- The list serves as the *first appearance in text*!
  - Abbreviations *are not spelled out again* in later sections of the CSR.
  - Unused abbreviations *are not deleted* from the list.
  - Create a standard list for the program or therapeutic area.

Section 14: Tables & Figures

- Includes all tables & figures supporting Sections 10-12
  - Tables/figures used in Sections 10 – 12 are not deleted from Section 14
- Standard numbering for Section 14
  - Examples: 14.1 (Demographics), 14.2 (Efficacy)
  - Reduces need to renumber if new presentations added
Simplifying the CSR: TLF Insertion

- Old process was fully manual, time-consuming, inefficient, & dated
- The link for each TLG was manually cut & pasted into the document

Identified solution

- Reduces the need for extensive manual intervention
- Automates the TLG exchange between document authoring & programming
Implementation

- Communication
- Training
- Reinforce
Implementation

- **Buy-in**
  - Senior management
  - Therapeutic areas (TAs)
  - Functional areas

- **Communicate, communicate, communicate**
  - Across TAs, programs, & projects
  - Across functional areas
    - Clinical, Statistics, Regulatory, Safety, etc…

- **Tools**
  - Templates
  - User guides
  - Slide decks

- **Training**
  - All MWs
    - All groups
    - All TAs

Reinforce!
How Do These Changes Affect Me?

- For collaborative authors:
  - Be aware of overall changes to section numbering and content
  - Utilize focused authoring strategies
  - Resources for specific content questions: CSR template, CSR Guidance Document, Lead MW

- For reviewers:
  -期待 streamlined organization and focused text.
  - Focus review on subject matter expertise: ensure key messages and scientific content are properly communicated
  - Engage management and peers during FAR for additional feedback on key issues/concerns

- Change management
  - Lead MW will direct team regarding the need to update in-progress CSRs. No impact to overall timelines.
  - If changes are needed, expect requests for focused review of updates as needed
Next Steps

- Continue to monitor
  - Continue to reinforce
- CSR as part of Structured Content Management (SCM)
CSR is a Component of Structured Content Management
SCM offers the promise of single source, component-based platform for authoring, review, and approval of related compendium of documents.
Content Reuse: Protocol (CPT) & Clinical Study Report

**Components Reused:** 43

**Diagram:**
- TEE CPT
  - Schema
  - Objectives/Endpoints
  - Study Treatment
- CSR
  - Imported components

**Export/Import Process:**
- Export
- Import
- xml
THANK YOU!
Making documents intelligent

Current State

✓ Flat structures
✓ Cannot exploit information
✓ Reuse via copy/paste
✓ Little or no Standards
✓ Inefficient to recreate same across documents
✓ Quality & consistency

Future State

✓ Structured content across docs
✓ Ability to exploit information
  ✓ Reuse
  ✓ Downstream uses
✓ Standards driven
✓ Text mining, analytics
✓ AI to leverage knowledge from the content
✓ Regulatory agencies efficiencies
Protocol is the Primary Source for Clinical Trial Content

### Objectives and Endpoints

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
</tr>
</tbody>
</table>

#### 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, unused, and unverifiable data. This section is a summary of the planned statistical analysis of the primary and secondary endpoints.

##### 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>

##### Safety Analyses

All safety analyses will be performed on the Safety Population.

<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>
Data Flow and Content Reuse Across Three Clinical Documents

Significant amount of clinical content:
- Begins in the protocol
- Is reused downstream
- If “standard holder” then content can be shared with other documents in a “source and target”
Simplifying an Inclusion Criterion for a CSR

6. Have a calculated creatinine clearance at time of screening ≥50 mL/min, based on the Cockcroft-Gault equation which is as follows:

\[
\text{Clcr (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (in kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad \text{for males and}
\]

\[
\text{Clcr (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (in kg) \times 0.85}}{72 \times \text{serum creatinine (mg/dL)}} \quad \text{for females}
\]

Additional details are available in the study protocol [16.1.1].