Driving International Awareness and Use of Regulatory Writing Guidelines: Case Studies of the Clarity and Openness in Reporting (CORE) Reference Guidelines

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Driving International Awareness and Use of Regulatory Writing Guidelines: Setting the Scene

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What is CORE Reference?

- **Clarity**: CSRs must be clear, well-written, and free of ambiguity.

- **Openness**: Health Authorities and the public require transparency, and public disclosure of clinical regulatory documents with CSRs being among the first for public disclosure.

- **Reporting E3-based**: CSRs must serve the interests of regulatory reviewers by promoting reporting per ICH.
METHODS

- BWG: 9 authors with about 200 years industry experience
  - 6 have headed one or more Medical Writing department
  - 1 statistician
  - 1 clinical pharmacologist
  - 1 overall regulatory and strategic advisor

- Comprehensive Stakeholder Review
  - 5 member Health Canada review team (Celia Lourenco)
  - 18 member DIA CORE Review Task Force (Chair, David Clemow)
  - Academic and Principal Investigator (Todd E. Pesavento, MD)
  - Patient Advocate (David Gilbert)

- Methods published in a peer-reviewed journal
Background to CORE Reference

- May 2014 – May 2016

- Preface 20 pages: Assumptions, References

- Body: NOT a template, content suggestions
  - Incorporates ICH E3 and ICH E3 2012 Q & A
  - Provides clarifications on how to interpret ICH guidance, including rationale
  - Encourages **you** to make informed choices for authoring **your** CSR – ‘one-size-fits-all’
What is CORE Reference?

2. SYNOPSIS

A brief stand-alone synopsis without cross-reference to other sections of the CSR or other documents (usually limited to three pages, although longer is acceptable for more complex studies) that summarises the study should be provided. In addition to a brief description of the study design and critical methodological information (what was actually done), the synopsis should provide a summary of all relevant results [e.g., if there are multiple endpoints, consider limiting to primary and secondary] obtained during the study, as well as other critical information, including data on the study population, disposition of subjects, important protocol deviations and treatment compliance. The synopsis should include numerical data to illustrate results, not just text or p-values (consider presenting results as summary tables to reduce the amount of text in the synopsis). The conclusions should exactly match the overall conclusions in the body of the report. The use of a tabular format synopsis is not mandatory.

An example Synopsis follows:
Challenges

- Regulatory Authority buy-in and participation
- Stakeholder buy-in and participation
- Recognition of need for “User’s Guide”
- Commitment by members of the Budapest Working Group to a long development cycle and many hours of hard labor
Utility Survey
Where are your primary client locations?

- Europe: 70%
- North America: 40%
- Asia-Pacific: 20%
- Rest of the world (RoW): 10%
What type of organisation do you work for?

- Large Pharma
- Small Pharma/Biotech
- Contract Research
- Personal/Freelance
- Government/Regulatory
- Academia
What is your role?

- Medical Writer – Regulatory: 80%
- Medical Writer – Publication: 30%
- Medical Writer – Medical...: 40%
- Regulatory Affairs: 10%
- Responsible for posting...: 20%
- Clinical trials data...: 10%
Regional Differences in use/adoption of CORE Reference
Audience Poll

1. What region do you prepare documents for?

A. US
B. Europe
C. Asia-Pacific
D. Other
What region do you prepare documents for?

- US: 47%
- Europe: 32%
- Asia-Pac: 16%
- Other: 5%

When poll is active, respond at PollEv.com/dia03
Text DIA03 to 22333 once to join
2. Have you used CORE Reference?

A. Downloaded only
B. Read/reviewed only
C. Used to author CSR(s)
D. Incorporated into SOPs/policies/templates
E. Used as an unofficial reference tool
Have you used CORE Reference?

- Downloaded only: 44%
- Read/reviewed only: 13%
- Used to author CSR(s): 19%
- Incorporated into SOPs/policies/templates: 25%
- Used as an unofficial reference tool: 25%

When poll is active, respond at PollEv.com/dia03. Text DIA03 to 22333 once to join.
3. What have been the greatest challenges to the adoption of CORE References (experienced by you/your company)?

A. Resistance to change
B. Lack of awareness of the changing landscape, e.g., EMA Policy 0070, FDAA, EU CT Reg
C. Lack of awareness to CORE Reference
D. Uncertainty regarding the purpose of CORE Reference
E. Bureaucracy
What have been the greatest challenges to the adoption of CORE References (experienced by you/your company)?

- **Resistance to change**: 6%
- **Lack of awareness of the changing landscape, e.g., EMA Policy 0070, FDAA, EU CT Reg**: 6%
- **Lack of awareness to CORE Reference**: 72%
- **Uncertainty regarding the purpose of CORE Reference**: 17%
- **Bureaucracy**: 6%

When poll is active, respond at PollEv.com/dia03
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North American Adoption (N=25)

- 12% have only downloaded
- 60% have read/reviewed
- 48% use as an unofficial reference tool
- 20% have incorporated into SOPs/policies/templates
- 35% have used to author CSRs
Relative North American Adoption (% response)

Compared to either Europe or Asia Pacific, North Americans seem to have proportionately slightly greater use of CORE Reference as an informal reference tool and to author CSRs.

Speculation:
- The lower rate of formal incorporation into policies and procedures may reflect a more cumbersome bureaucracy in the US-based companies.
- Proportionately higher numbers of responders from North America were affiliated with CROs. Thus, they may not be able to directly drive adoption among their clients.
Driving international awareness and use of regulatory writing guidelines

Case studies of the Clarity and Openness in Reporting (CORE) reference guidelines

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Regional Differences in use/adoption of CORE Reference

Use of the CORE Reference in Europe, including Scandinavia (N=54)

- Downloaded only: 16
- Read/reviewed only: 26
- As an unofficial reference tool: 16
- Incorporated into SOPs/policies/templates: 23
- Used to author CSR(s): 12

Number of responses
EU Adoption, including Scandinavia (N=54)

- 32% have downloaded CORE
- 44% have read/reviewed CORE
- 32% have used CORE as an unofficial reference tool
- 37% have incorporated CORE into SOPs/policies/templates
- 24% have used CORE to author CSRs
Relative Europe Adoption

Compared to North America and Asia Pacific, proportionately more Europeans (incl. Scandinavia) have downloaded CORE Reference and incorporated CORE into SOPs/policies/templates.

Speculation:

- Europe/EMA is leading the world in public disclosure of clinical study documents

- EMA has
  - Issued Policy/0070 that mandates CSR disclosure
  - Issued Guidance on implementing Policy/0070

- Regulation (EU) No 536/2014
Benefits of CORE Reference

- In-house training tool: for new **and experienced** writers
- Clinical trial results postings: clinicaltrials.gov and EudraCT
  - **Reporting Period** - Synopsis
  - **Endpoints** – Synopsis, Section 8.2 ‘Endpoints’, Sections 11.1.1/.2/.3 ‘Primary/Secondary/Exploratory Endpoints’, as applicable
  - **Removal of a subject from treatment vs Removal of a subject from the study** – Section 9.3.3 ‘Removal of Subjects from Therapy or Assessment’, Section 11.2.2 ‘Handling of Withdrawals, Discontinuations or Missing Data’
  - **Adverse events** – Section 12.1.1 ‘Brief Summary of Adverse Events’, Section 12.1.2 ‘Most Frequently Reported Adverse Events’, Section 12.1.3 ‘Categorisation of All Adverse Events’
Thank You

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Join the conversation #DIA2017
Driving international awareness and use of regulatory writing guidelines

Case studies of the Clarity and Openness in Reporting (CORE) reference guidelines

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DIA is international...

- ICH is international – founding representatives
  
  ![EU flag](image1) ![Japan flag](image2) ![US flag](image3)

- CORE Reference Guidelines are international…
  …but what happened to Japan?

  ![EU flag](image1) ![Japan flag](image2) ![US flag](image3)

- Can we **drive insights** from this session **into action**?
  (enhance future international guideline development)
Engaging Japan in international guidelines

► Japan is a key market
  • ICH, large, fastest aging, “going global”

► CORE Reference team DID try!
  • 2 English email attempts to PMDA, no response

► Purpose of study
  • To investigate awareness of CORE Reference in Japan

► Method overview
  • CSR staff in JPMA companies (73 companies)
  • Online 10-question survey (19 July 2016 to 1 August 2016)
  • Email reminder, but no financial incentives
  • *Response rate = 34% (25 companies)*
Japanese writers DO use international guidelines

Guidelines used to prepare a CSR

- ICH-E3: 23 (92%)
- ICH-E3 Q&A: 20 (80%)
- SOPs: 24 (96%)
- CORE reference: 0
- Others: 2 (8%)

Multiple answers allowed
No answer 1, Others: Yaku-shin No.335 (1 May 1996), ICH-E1, E9, E10, etc.

N=25 responding companies
Low awareness of CORE in Japan

Familiarity with CORE Reference

- Not at all familiar: 18 (72%)
- Slightly familiar: 6 (24%)
- Moderately familiar: 1 (4%)
- Very familiar: 0
- Extremely familiar: 0
- Unsure: 0
- No answer: 0

N=25 responding companies
Minimal experience in redacting CSRs in Japan

- Redacted CSR experience and level of difficulty experienced or expected

Not prepared
- 20 (80%)

Prepared
- 3

Unsure
- 1

Moderately difficult
- 1

Slightly difficult
- 2

Extremely difficult
- 5

Very difficult
- 3

Slightly difficult
- 4

Moderately difficult
- 7

N=25 responding companies
Clear interest in Japan for learning more about CORE

Interest in attending an educational seminar on CORE

- 12 Moderately interested
- 5 Extremely interested
- 4 Very interested
- 4 Slightly interested

N=25 responding companies
Conclusions (insights) and implications (actions)

**Conclusions**
- Based on this sample, Japanese staff responsible for CSRs:
  - Do use international guidelines (that they are aware of!)
  - Have low awareness of CORE Reference
  - Are interested in becoming more aware about CORE Reference

**Implications**
- From these evidence-based insights, how do we drive action to help future guideline developers?
Conclusions (insights) and implications (actions)

1. Why do I need this guideline?

**CORE example**
Educate Japanese pharma companies that if they “go global”, they will need redacted CSRs

2. Who could be the local champions of this guideline?

**CORE example**
Involve Japan’s medical writing community – developers or connectors (eg, PMDA)

3. What resources are needed to ensure guideline uptake?

**CORE example**
Education seminars customized to Japan’s needs
Thank you

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