DIA 2017 GLOBAL ANNUAL MEETING JUNE 18-22 | CHICAGO

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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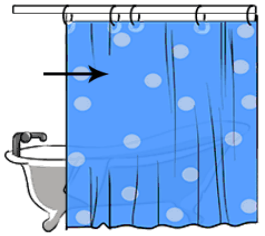
What is CORE Reference?

- 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.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS
E3

Current Step 4 version
dated 30 November 1995

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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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
  Hamilton S, Bernstein AB, Blakely G, et al Research Integrity and Peer Review 2016

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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'~~

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What is CORE Reference?

Version 1.0
03-May-2016

2. SYNOPSIS

<Deliberate wider line spacing below to allow optimal presentation of ICH E3 2012 Q&A text>

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:

Comment [A28]: Per ICH E3 2012 Quesitons & Answers (Q & A) Point 2 for CSR synopsis: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf which updated this ICH E3 instructional text to state '*Since the synopsis will be used as a stand-alone document within a Common Technical Document, it should be written so that it can be understood and interpreted on its own, i.e. without the other sections of a CSR*'.
Clarification is added to this effect, and to remind that 'other' documents should not be referenced either.

Comment [A29]: Per ICH E3 2012 Q & A Point 2 which updated ICH E3 instructional text to state the synopsis can be longer than 3 pages if it needs to be.
Awareness comment pending finalisation of ICH guidance: An example of '10 pages' (see also [updated since 2012 Q & A] ICH M4E_R2: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2__Step_2.pdf) is described as acceptable for more complex studies, with the proviso that 10 pages is not an absolute requirement or limit, but should not need to be exceeded considerably.

ICH E3 text | *ICH E3 2012 Q&A text* | CORE Reference text | [Right margin comment=RATIONALE]

24

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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

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Utility Survey

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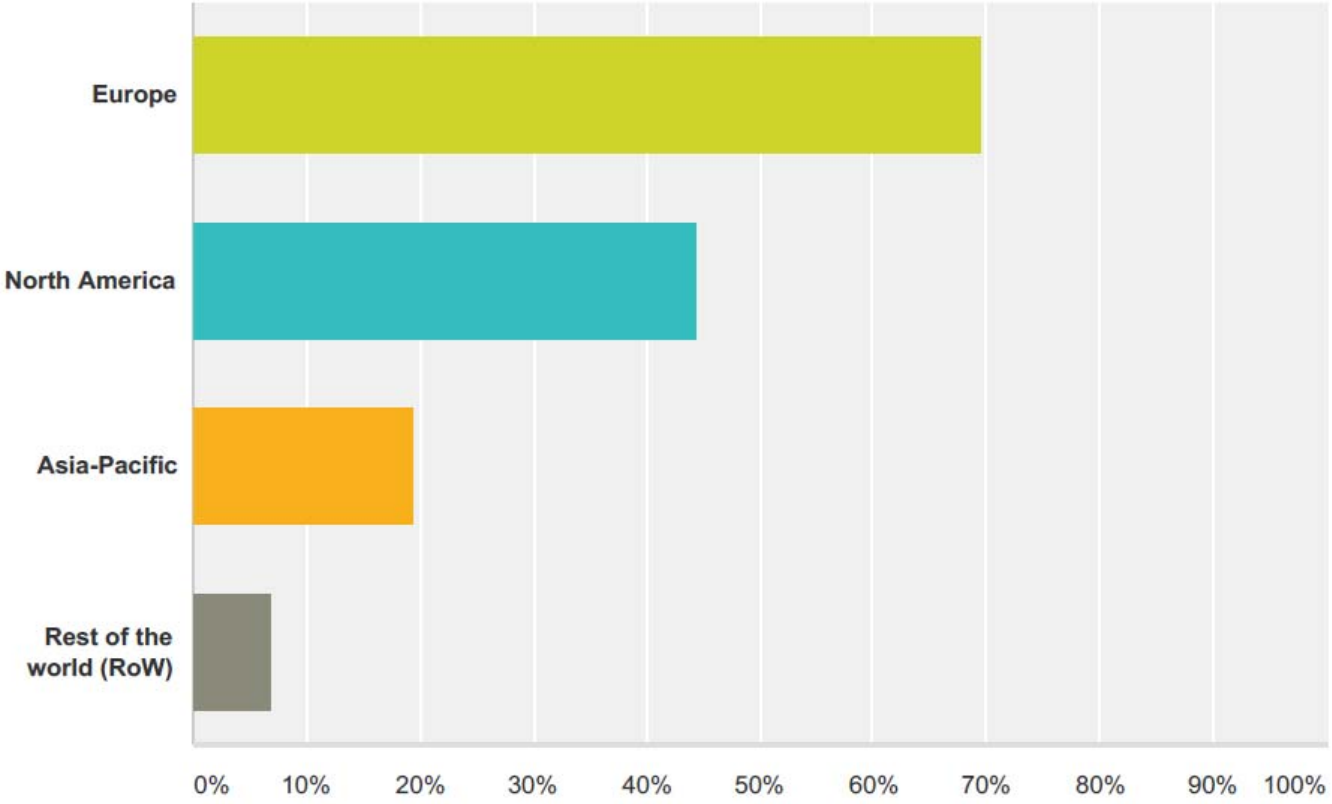
CORE Reference Utility Survey - 1

- Where are your primary client locations?



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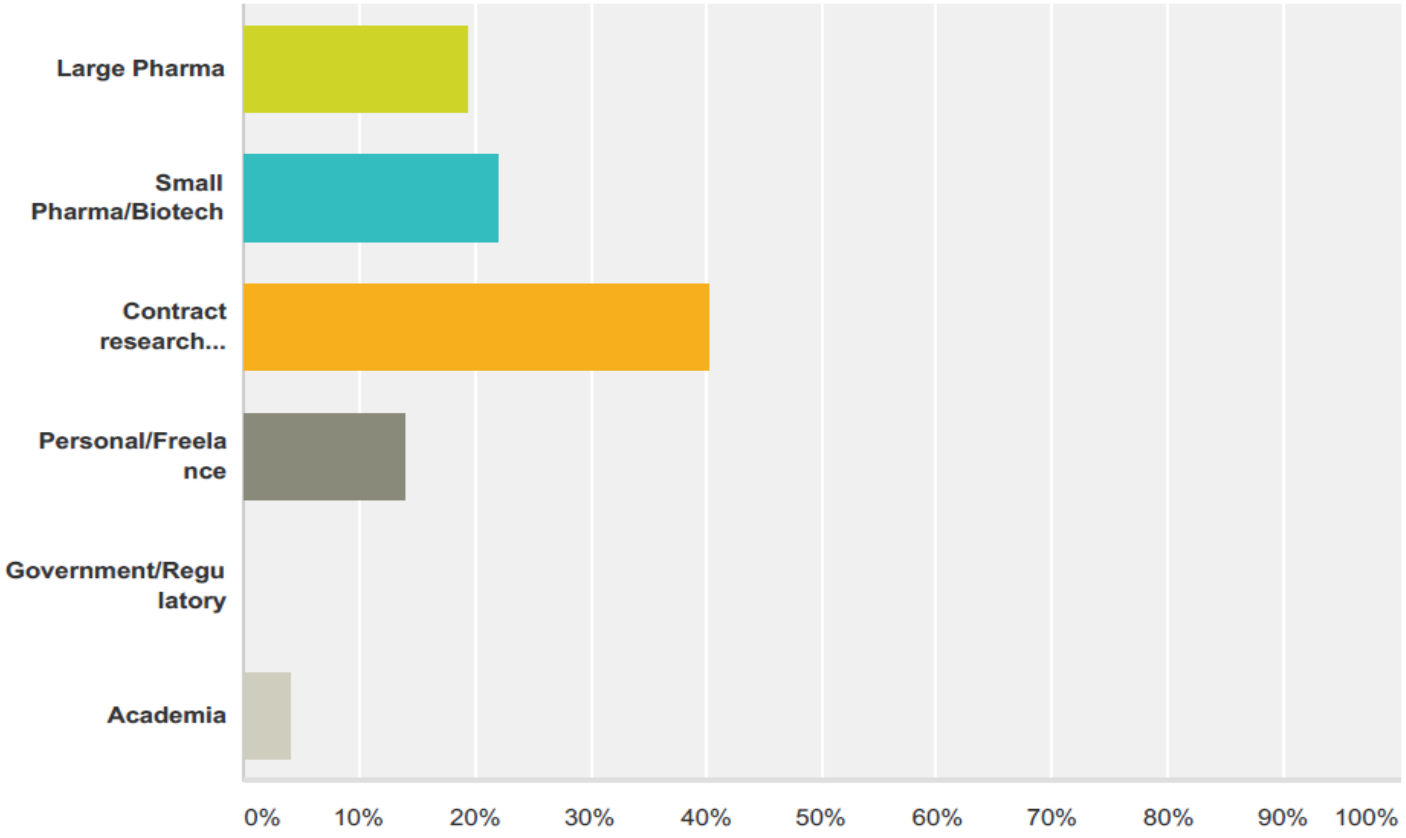
CORE Reference Utility Survey - 2

- What type of organisation do you work for?



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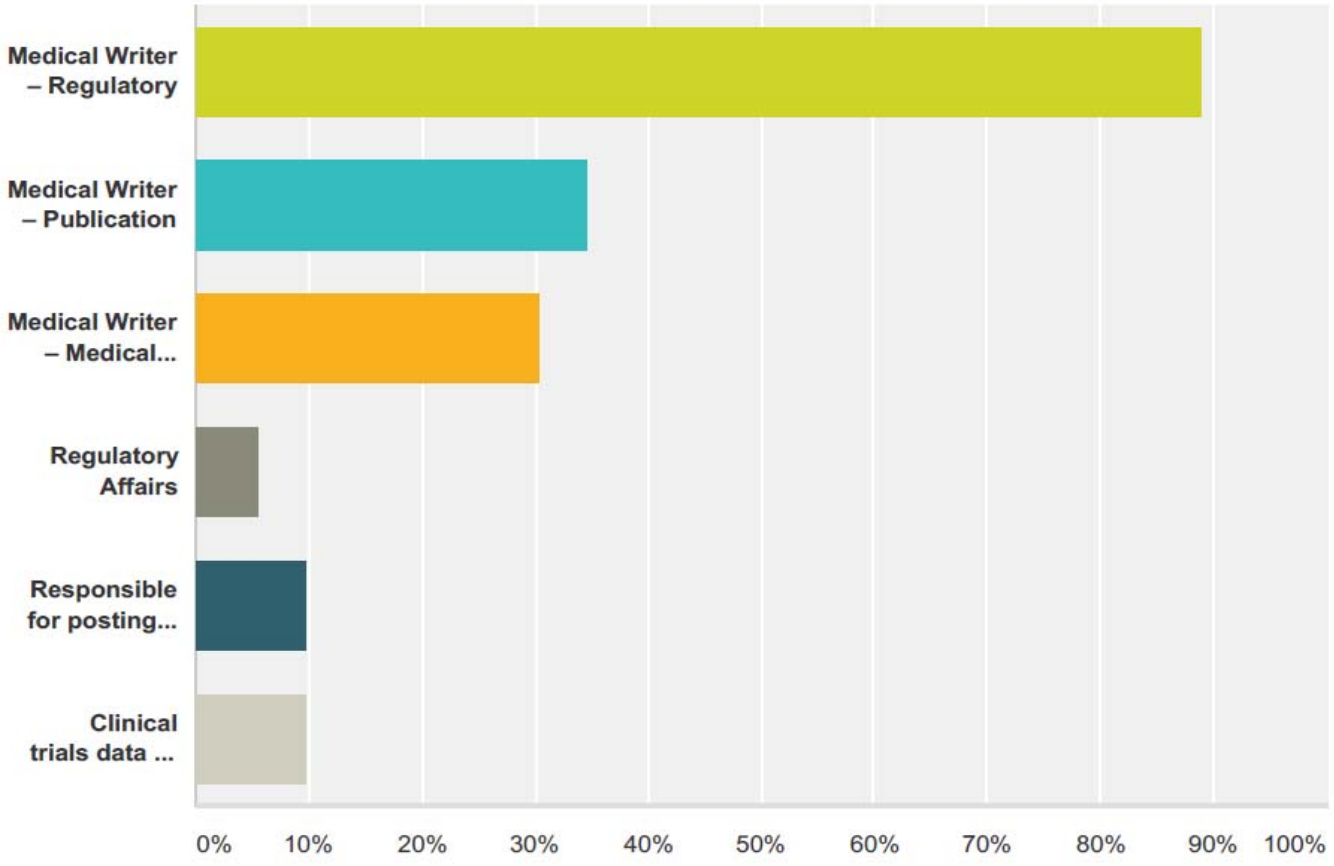
CORE Reference Utility Survey - 3

- What is your role?



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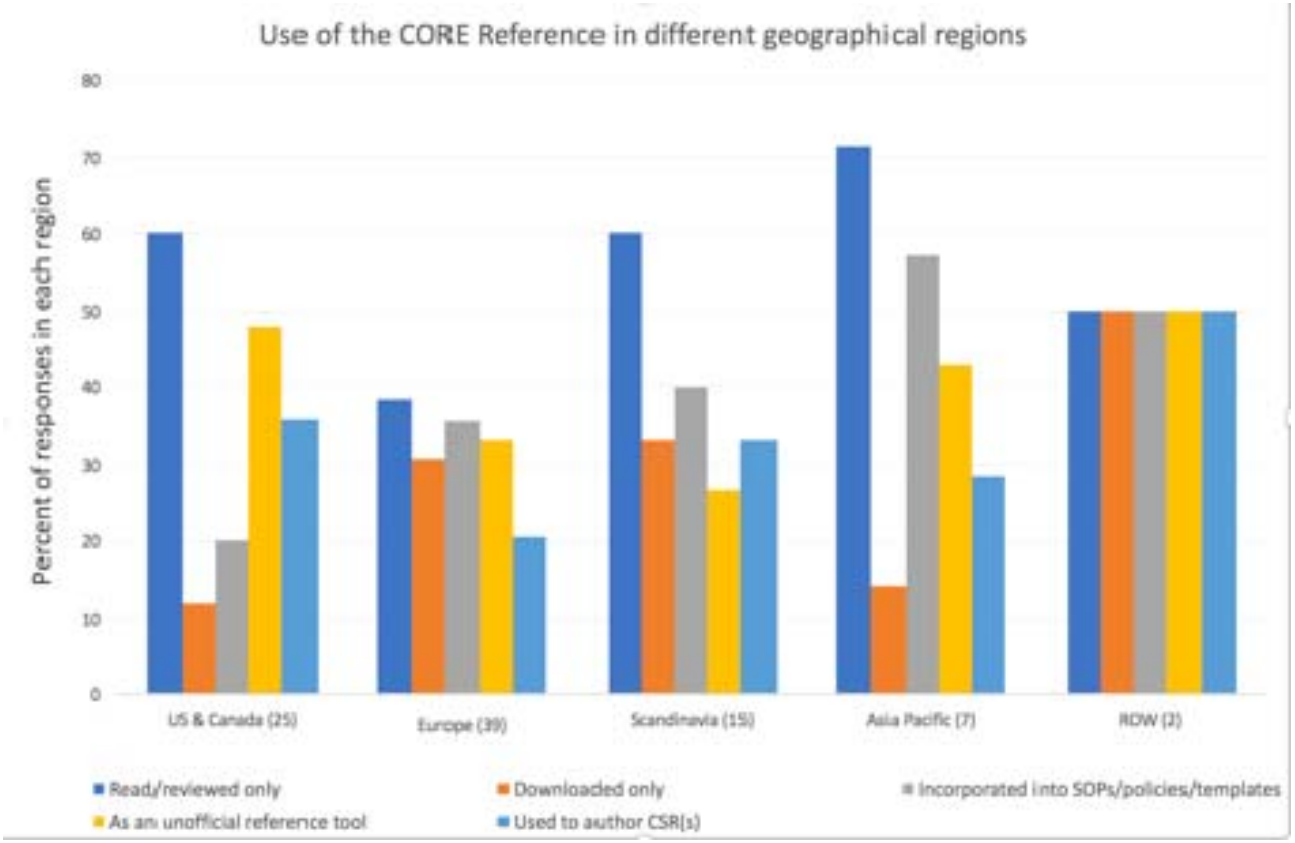
Regional Differences in use/adoption of CORE Reference



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Audience Poll

1. What region do you prepare documents for?

   A. US
   B. Europe
   C. Asia-Pacific
   D. Other

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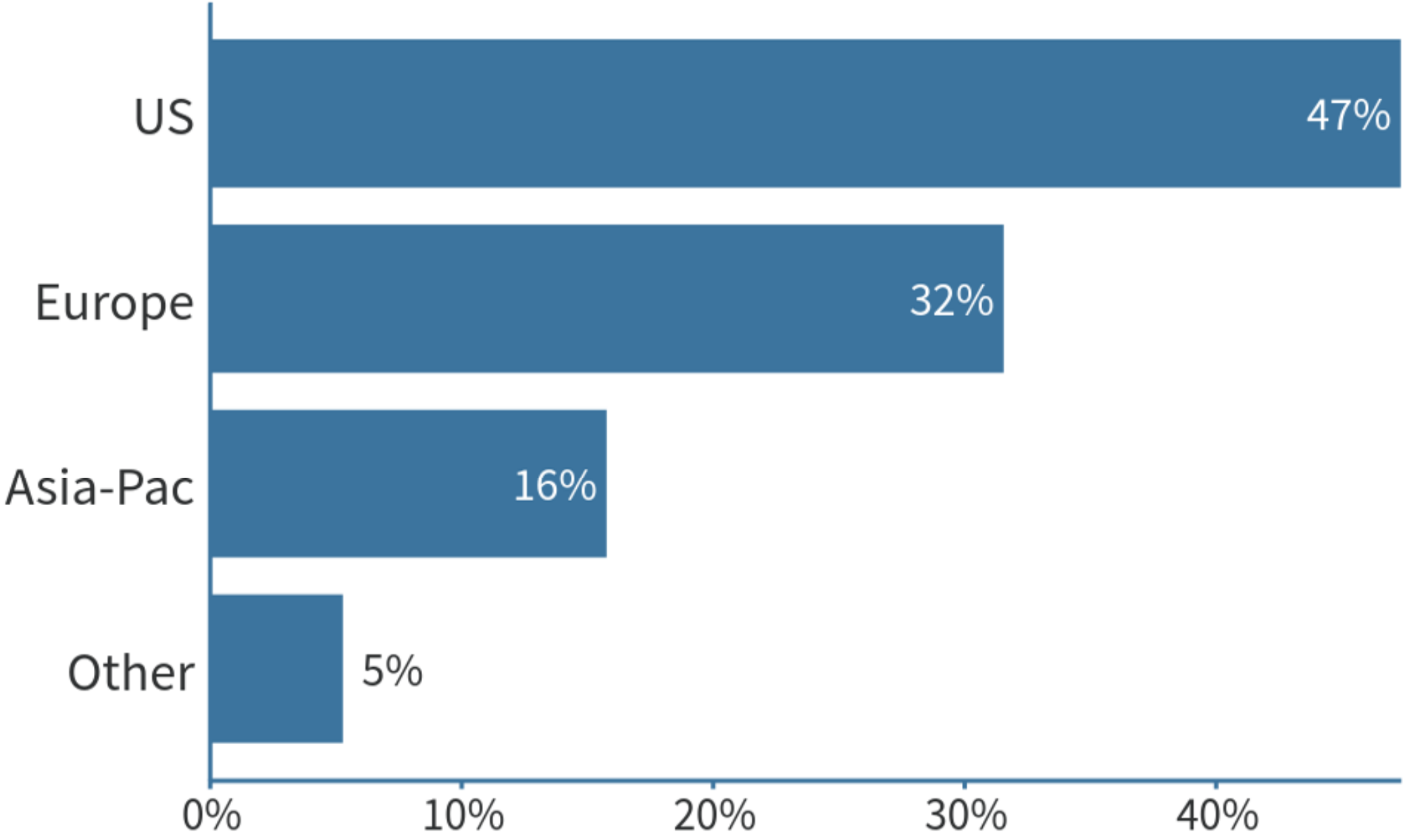
What region do you prepare documents for?

When poll is active, respond at **PollEv.com/dia03**

Text **DIA03** to **22333** once to join



Audience Poll

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

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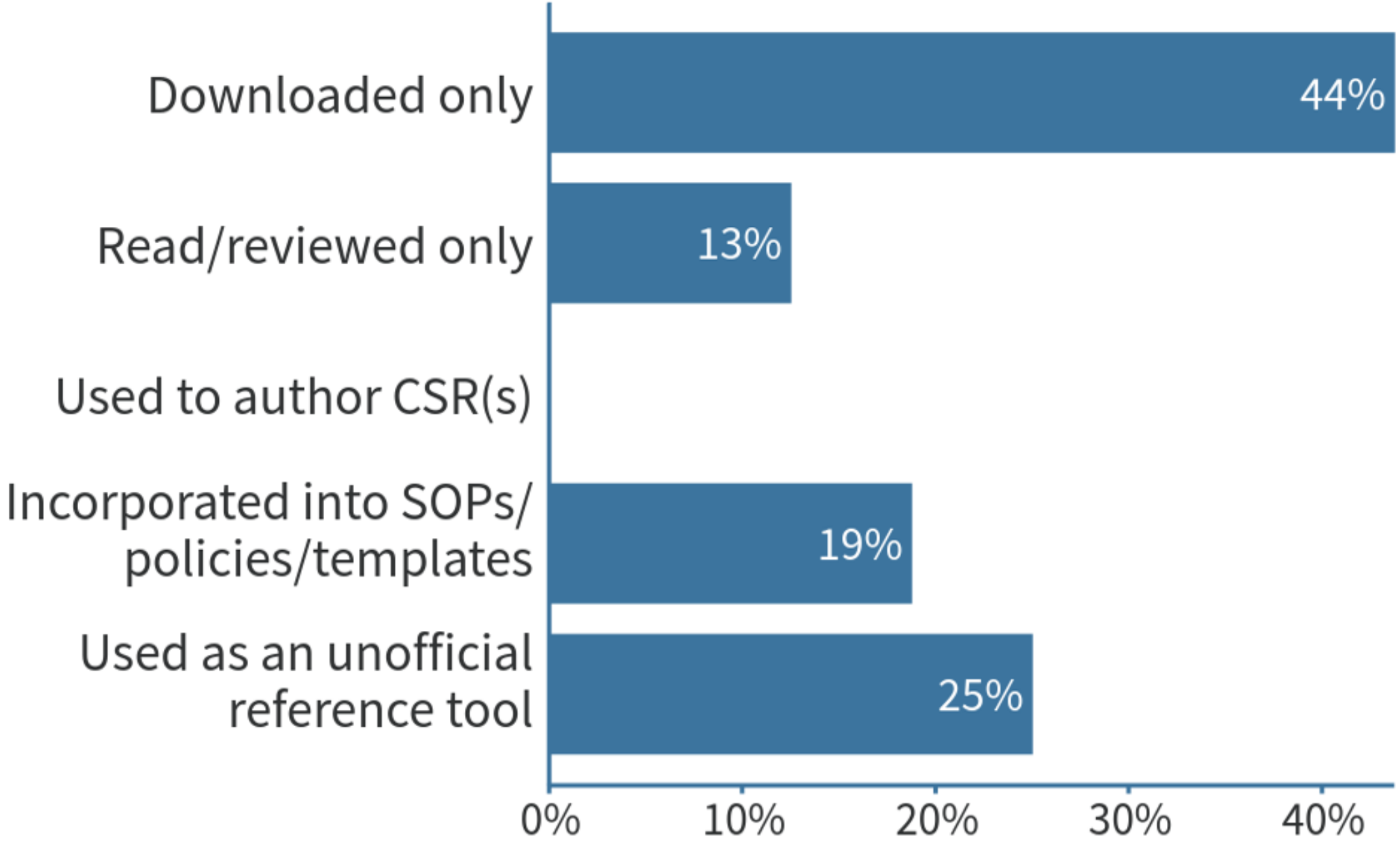
Have you used CORE Reference?

When poll is active, respond at **PollEv.com/dia03**

Text **DIA03** to **22333** once to join



Audience Poll

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

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What have been the greatest challenges to the adoption of CORE References (experienced by you/your company)?

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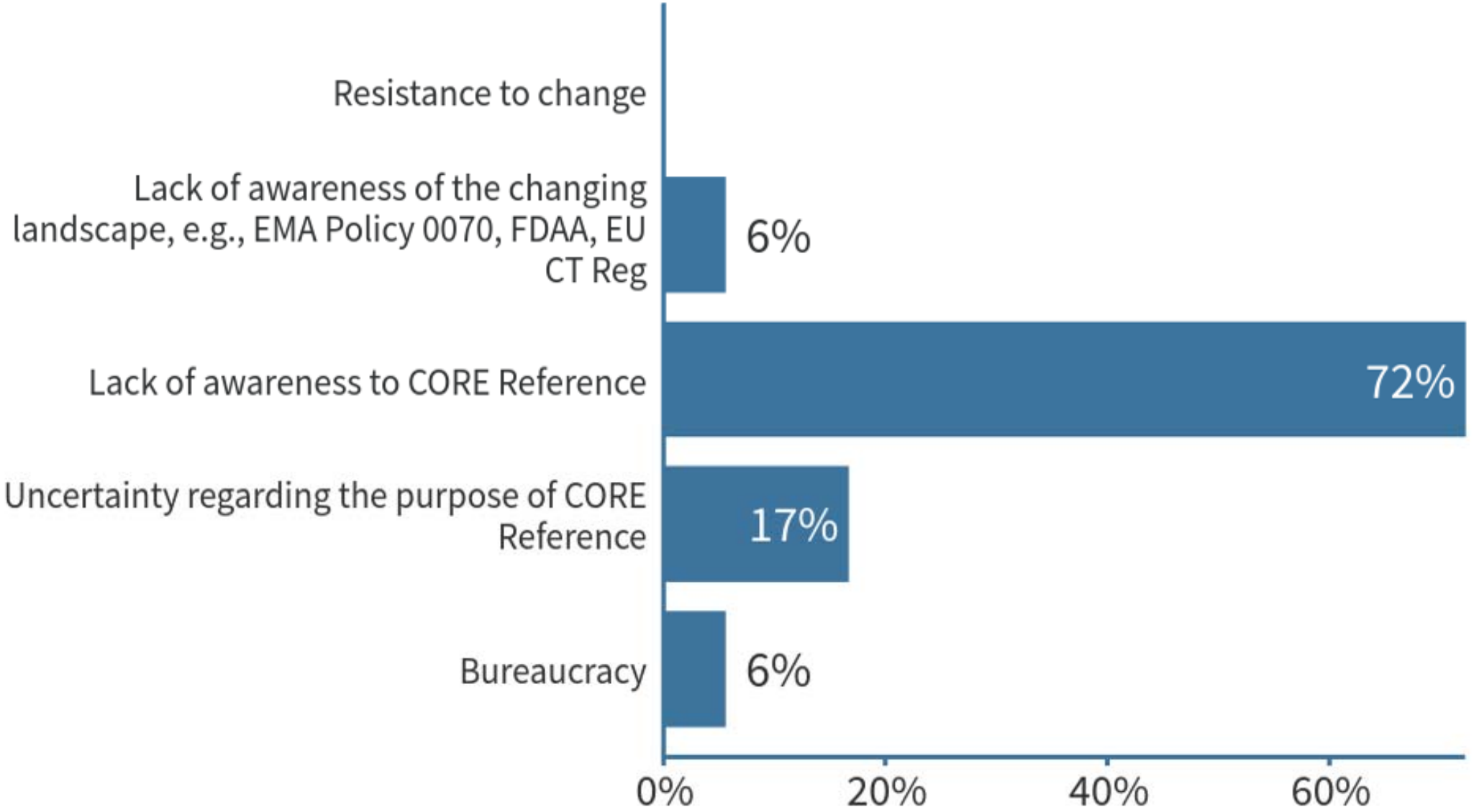

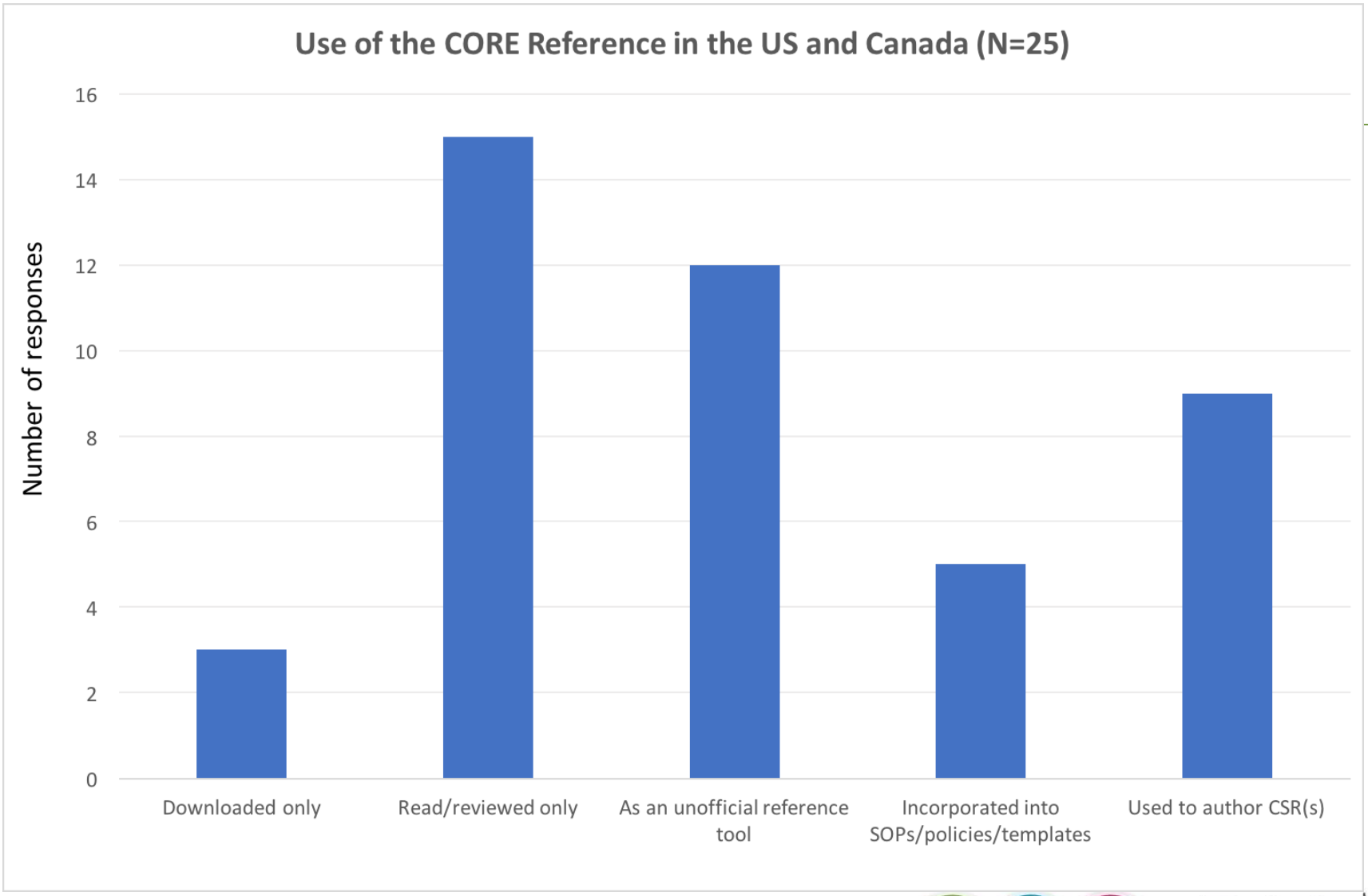

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North American Adoption (N=25)

- 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

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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.

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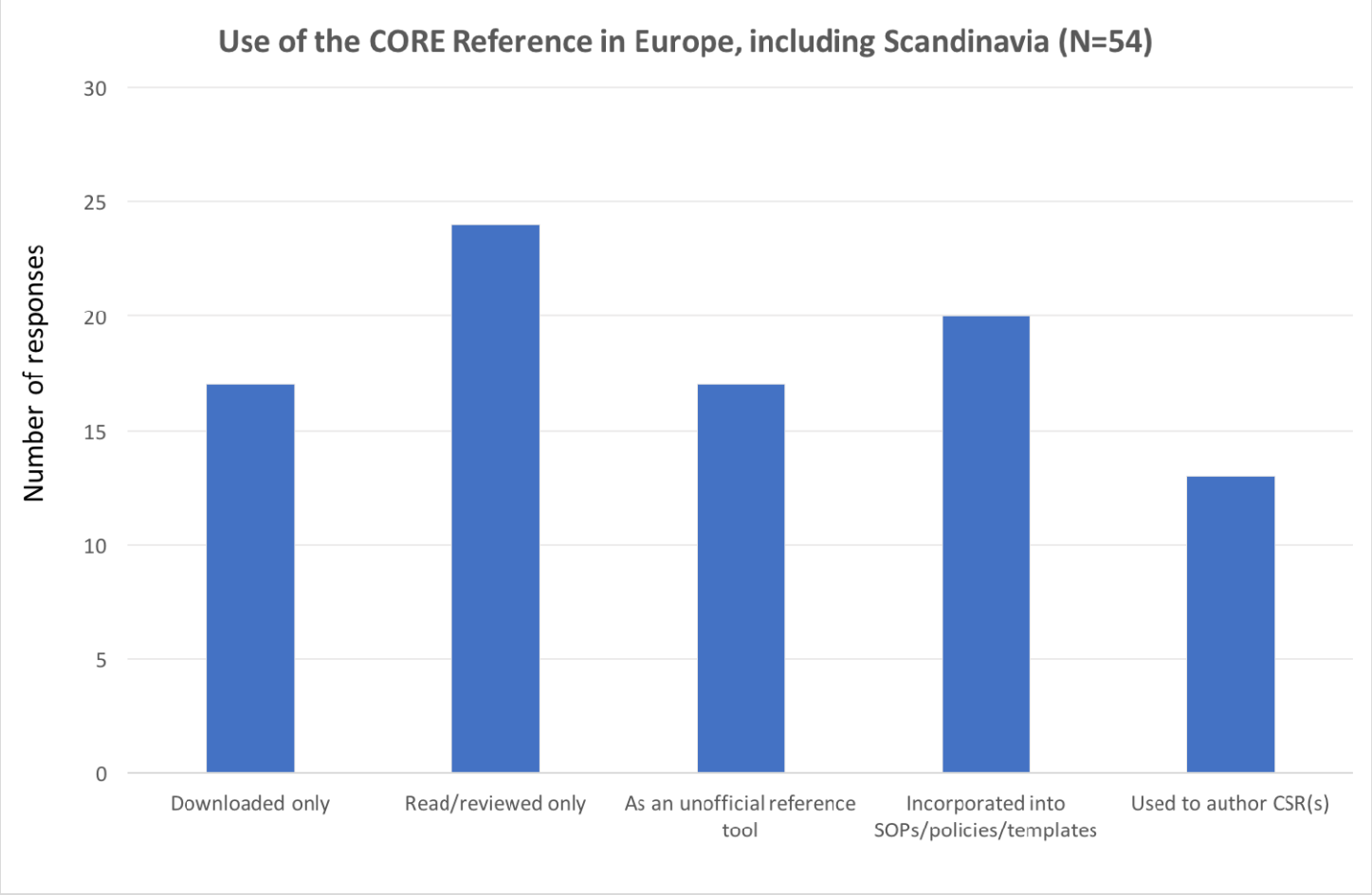
Regional Differences in use/adoption of CORE Reference



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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Director

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

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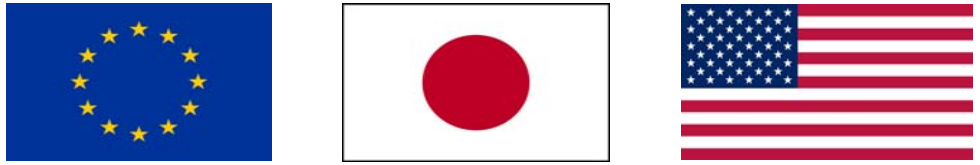
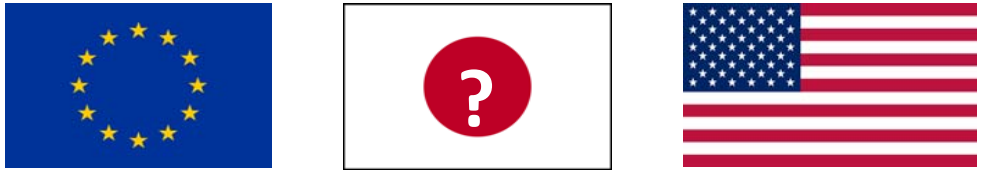
DIA is international…

- ICH is international – founding representatives



- CORE Reference Guidelines are international…

  …but what happened to Japan?



- Can we **drive insights** from this session **into action?**

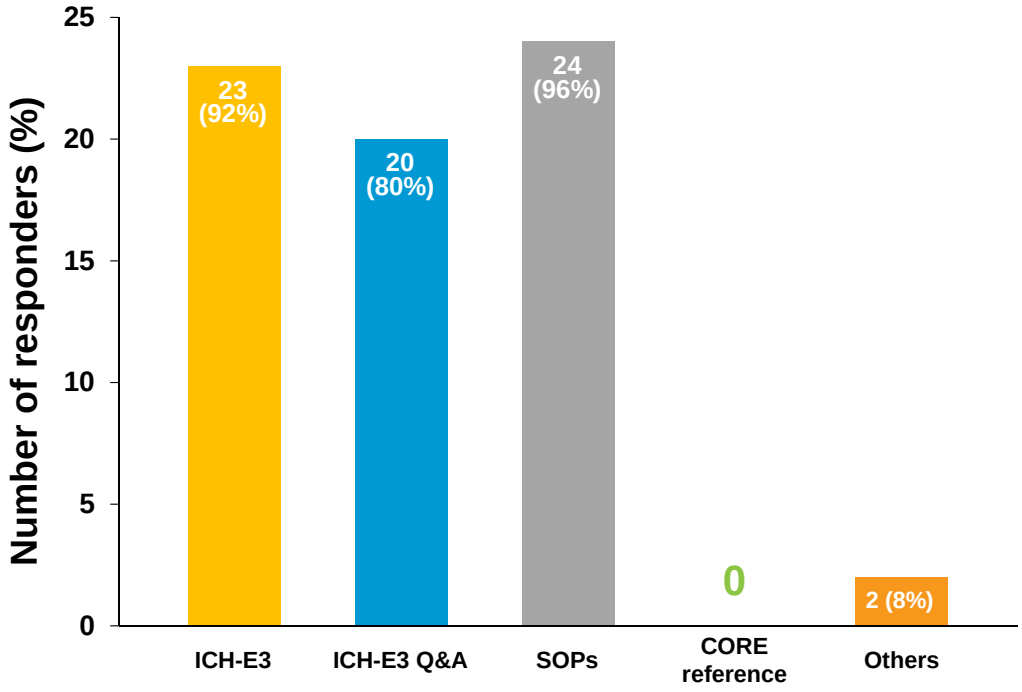
  (enhance future international guideline development)

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

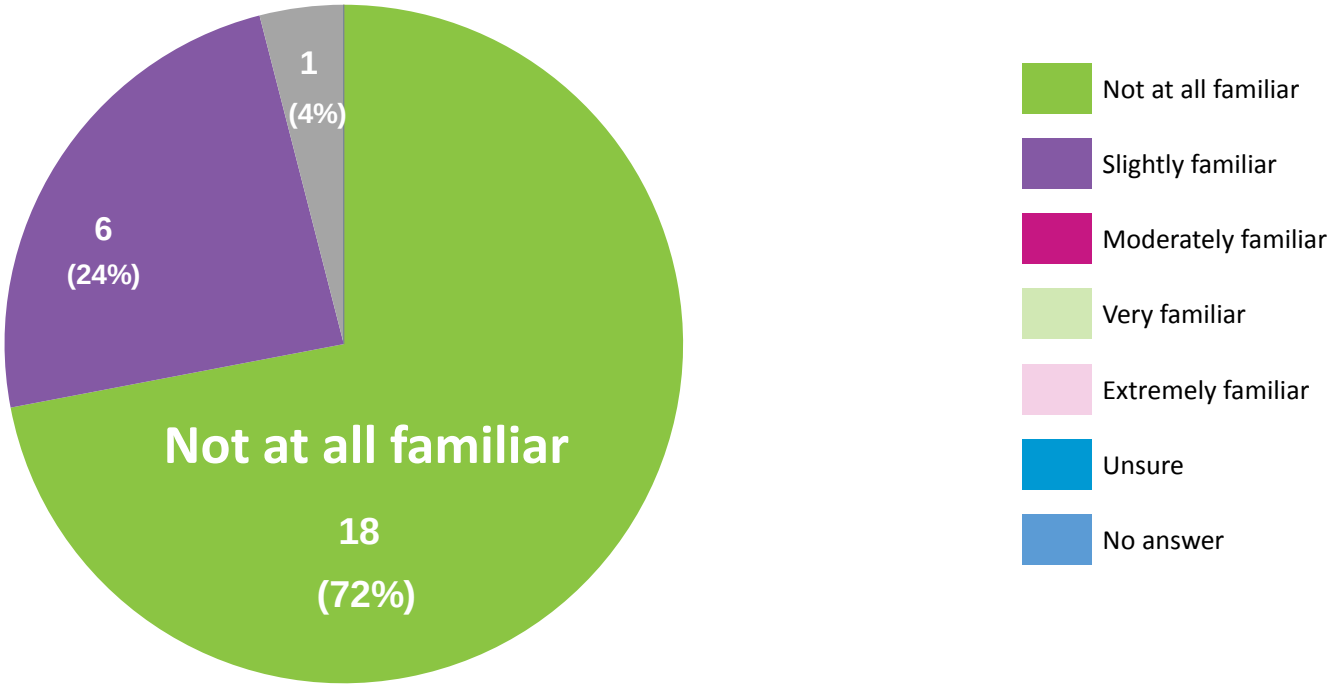


Multiple answers allowed
No answer 1, Others: Yaku-shin No.335 (1 May 1996). ICH-E1, E9, E10, etc.

N=25 responding companies

Low awareness of CORE in Japan

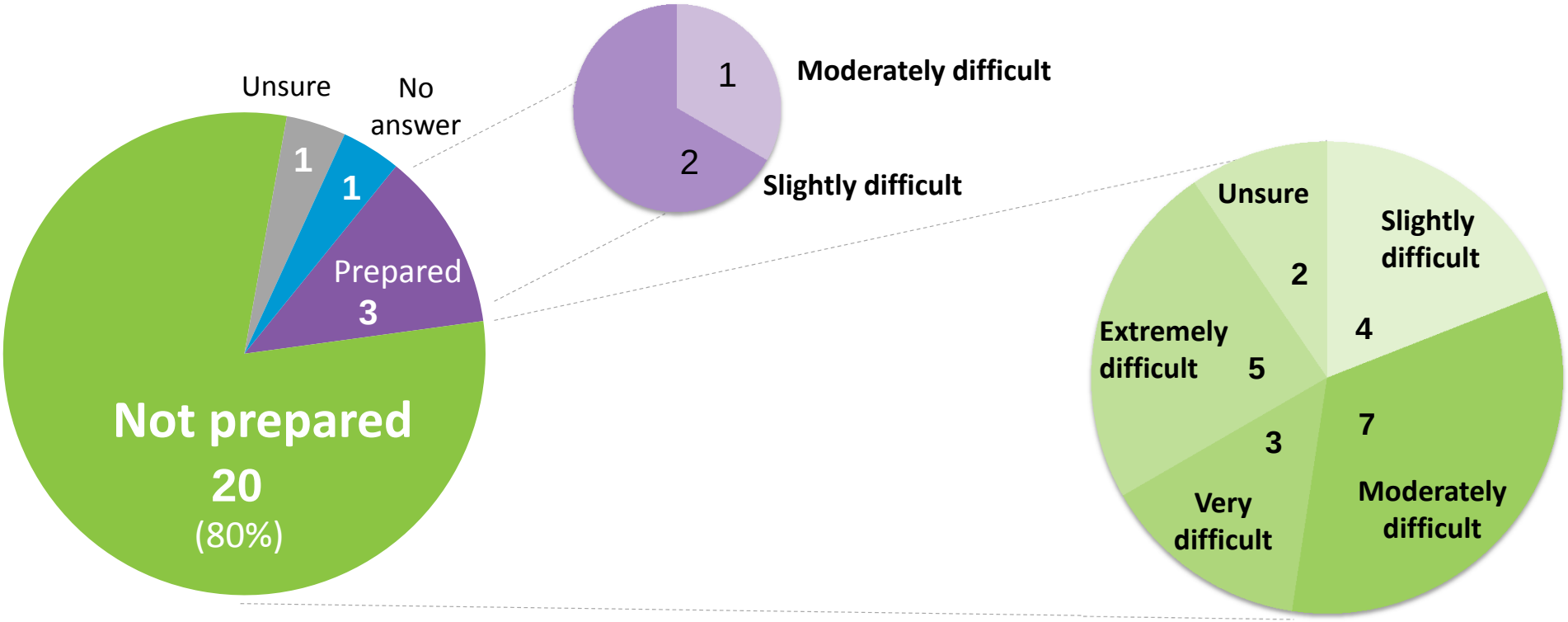
- Familiarity with CORE Reference



N=25 responding companies

Minimal experience in redacting CSRs in Japan

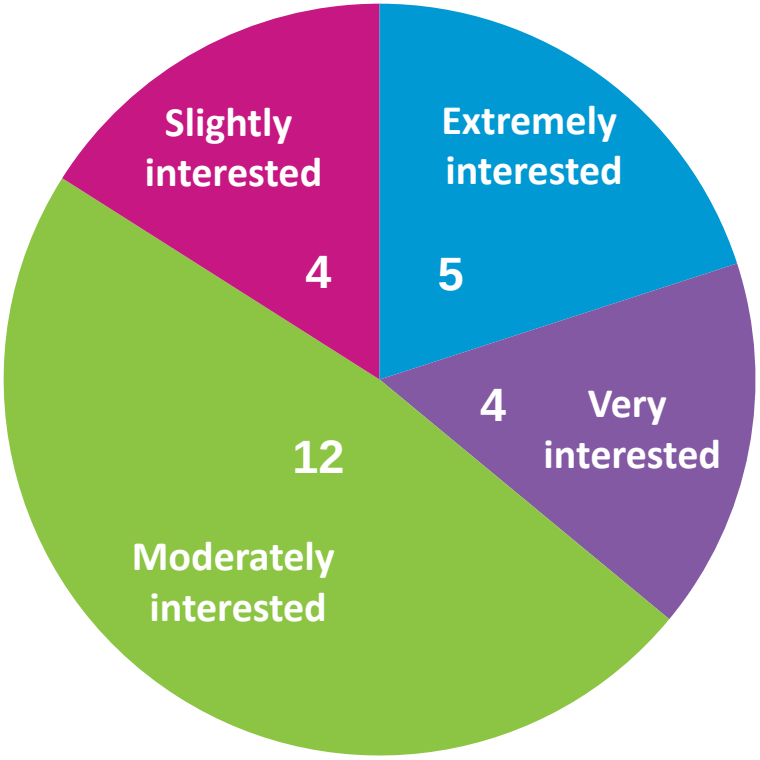
- Redacted CSR experience and level of difficulty experienced or expected



N=25 responding companies

Clear interest in Japan for learning more about CORE

- Interest in attending an educational seminar on CORE



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

Acknowledgements

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