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E6(R3) GCP Expert Working Group Vision & Engagement:

Lessons Learned from Public Input & Stakeholder Feedback

E6(R3) Expert Working Group
International Council for Harmonisation
of Technical Requirements
for Pharmaceuticals for Human Use

May 18 & 19, 2021

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Purpose

The aim of this presentation is to share with you:

- ICH E6 Good Clinical Practice (GCP) stakeholder engagement plan and activities
- How the Expert Working Group (EWG) collected and analyzed input from all stakeholders to inform their work

Engagement is Essential to Inform EWG Work

- **Acknowledging the wide impact of E6 and the many stakeholders who are affected by this guideline, the ICH Management Committee approved an engagement plan* for the E6(R3) EWG.**
- **The engagement plan includes:**
  - Public engagements, such as today's web conference, and publishing updates. As a part of the EWG continuous transparency and engagement efforts, the EWG published draft, work-in-progress principles
  - Direct EWG engagement with academic experts during the EWG meetings as the work on the guideline proceeds

*ICH E6 Summary Engagement Plan - https://admin.ich.org/sites/default/files/2020-05/E6-R3_PublicEngagemenSummary_2020_0421.pdf

EWG Stakeholder Engagement

Nominated stakeholders that engage directly with the EWG as the work evolves

Organization Name	Representative Name
Society of Clinical Trials (USA)	Pamela Tenaerts, MD*
Network of Networks (Canada)	Lisa Johnston, RN
Patients' and Consumers' and Healthcare Professionals Working Parties (EU)	Martin Landray, PhD
Brazilian Society of Clinical Research Professionals (Brazil)	Vivienne Castilho, PharmD
Chinese Pharmaceutical Association (China)	Haiyan Li, MD
Research Group on ICH GCP Renovation (Japan)	Kenichi Nakamura, MD, PhD

*** Pamela Tenaerts has subsequently left this role; a replacement will be announced.**

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Stakeholder Representative Input

- As the EWG worked on developing E6(R3), areas and language were identified for review by stakeholder representatives
- Stakeholder representatives were invited to select EWG meetings to provide insight, input, and review
- Stakeholder representatives were also asked to review certain drafts, language, and phrases as a way to test the language for clarity, conciseness, and focus
- Stakeholder representatives provided valuable perspectives from an external reader point of view

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Stakeholder Representative Input

- **Stakeholder representatives provided valuable insight and input addressing key areas, such as:**
  - Highlight the importance of well-designed and conducted clinical trials
  - Clarity on the scope of E6
  - Encourage risk-based approaches across clinical trial processes
  - Consider the flexibilities needed for the use of technological tools
  - Address the digital data ecosystem
  - Consider innovative clinical trial designs, such as decentralised trials, trials in healthcare settings, adaptive trial designs, etc.

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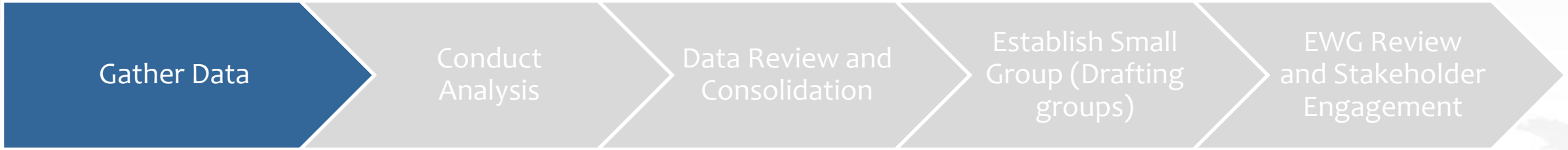
E6(R3) development is informed by the results of an extensive analysis of stakeholder input and by consistent engagement with stakeholders

E6(R3) EWG Analysis

Process for Analyzing Stakeholder Input

- **Goals of this analysis**
  - Identify opportunities for improvement in E6(R3)
  - Provide potential options on how and where to apply the modifications

E6(R3) EWG Analysis
Gather Data



- **Analysis is comprised of two approaches:**
  - An analysis of stakeholder comments on E6(R2)
  - An analysis of select ICH guidelines to help align between relevant guidelines whenever appropriate

References Used to Inform the Analysis

Stakeholder Comment Analysis

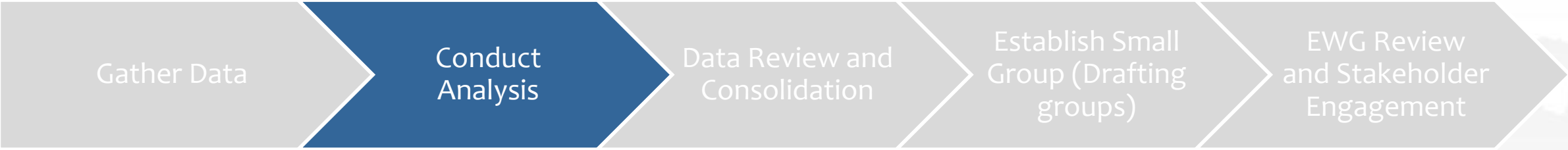
- **Academic Responses**
  - Open letter & published articles
- **CTTI "Informing the Renovations to the ICH E6" Project**
  - Stakeholder Survey, In-depth Interviews, Open Comments
- **Public Engagement Materials**
  - Americas Engagement Meeting
  - Europe Engagement Meeting
  - Japan Engagement Meeting

ICH Guideline Analysis

- **All Efficacy Guidelines + M11**
- **Peer-review publications**

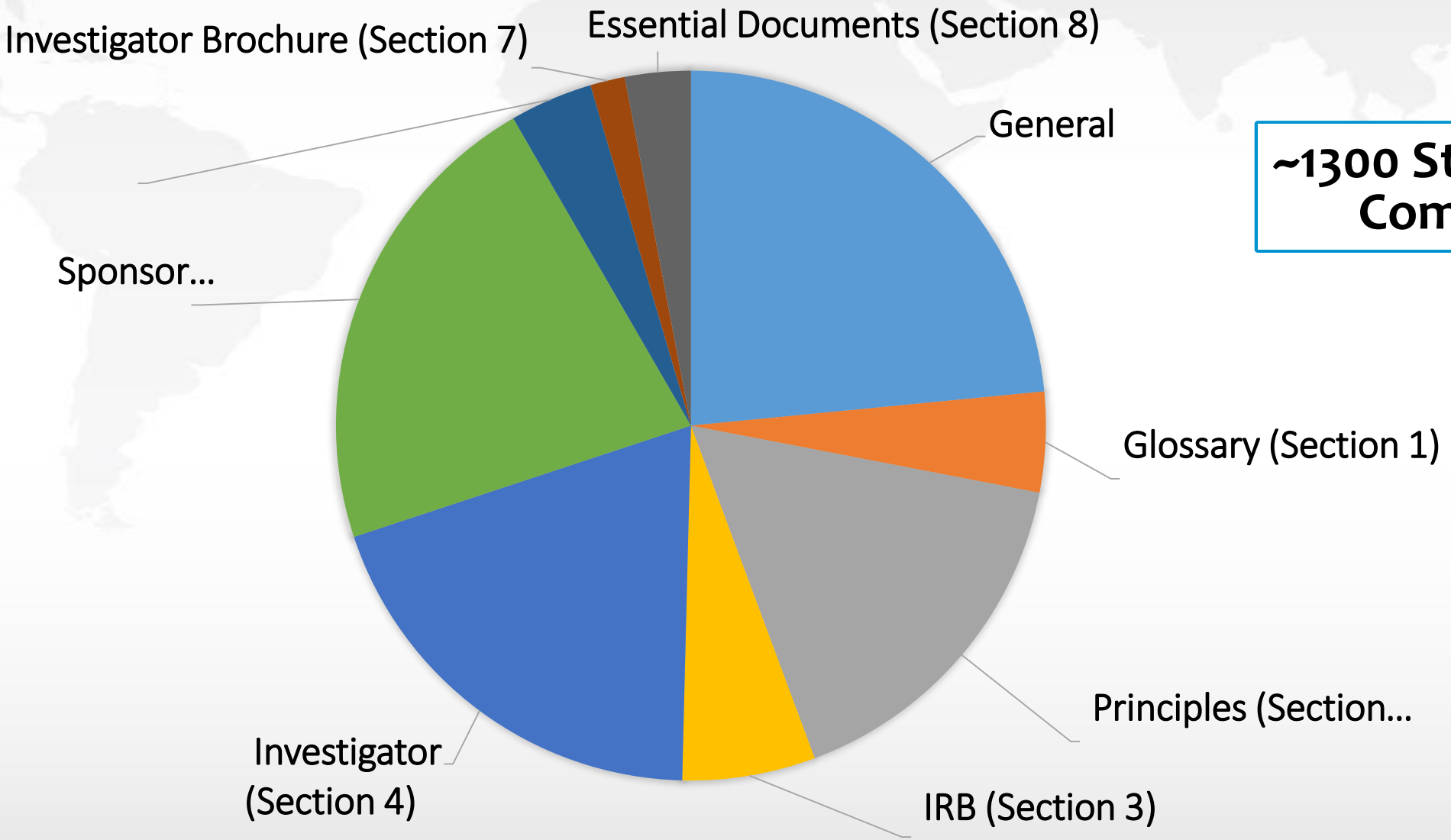
E6(R3) EWG Analysis

Conduct Analysis



What did the analysis of the data tell us?

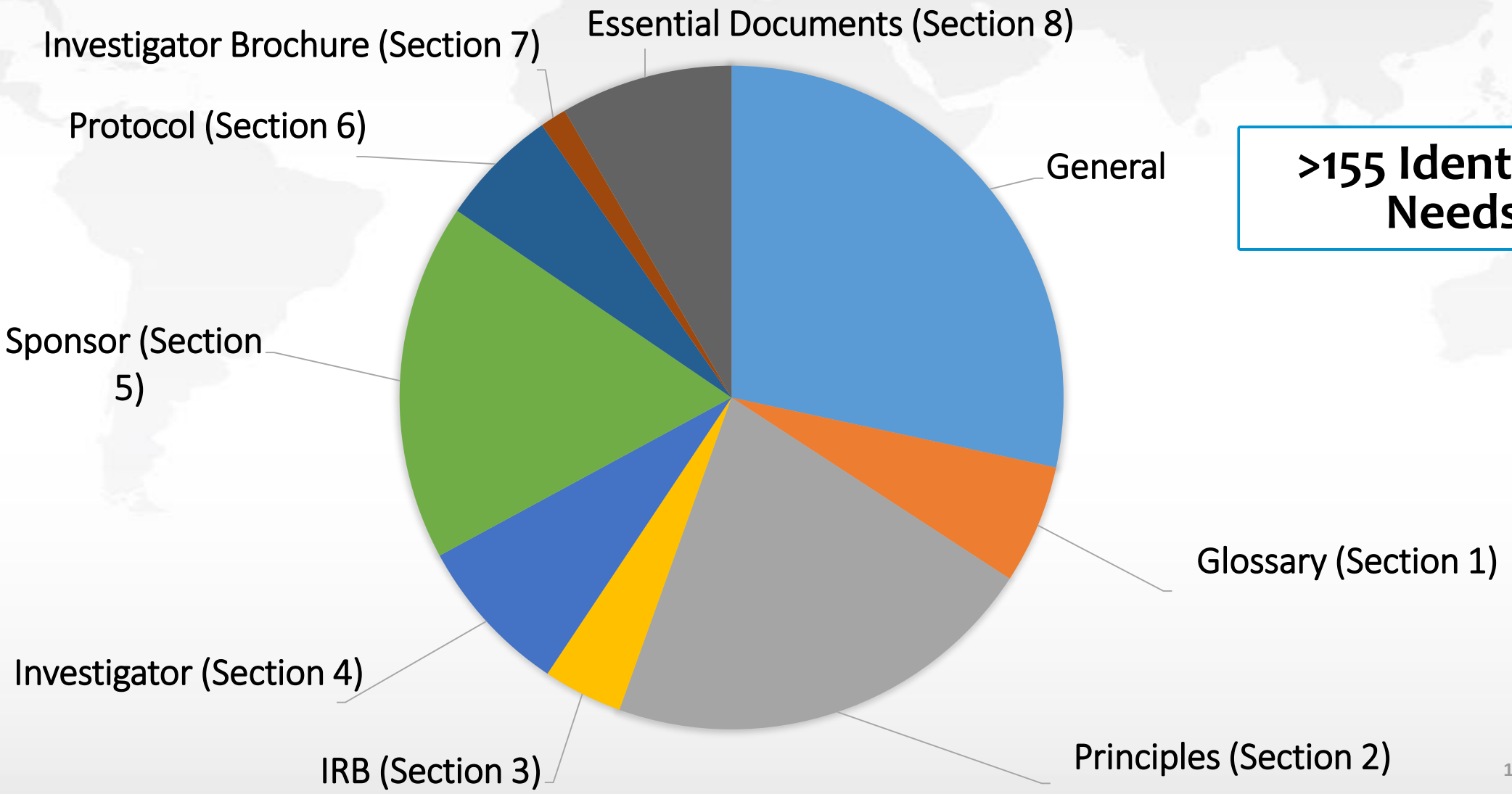
Public Comments
Sections of Stakeholder Interest



~1300 Stakeholder Comments

Comparing ICH Guidelines

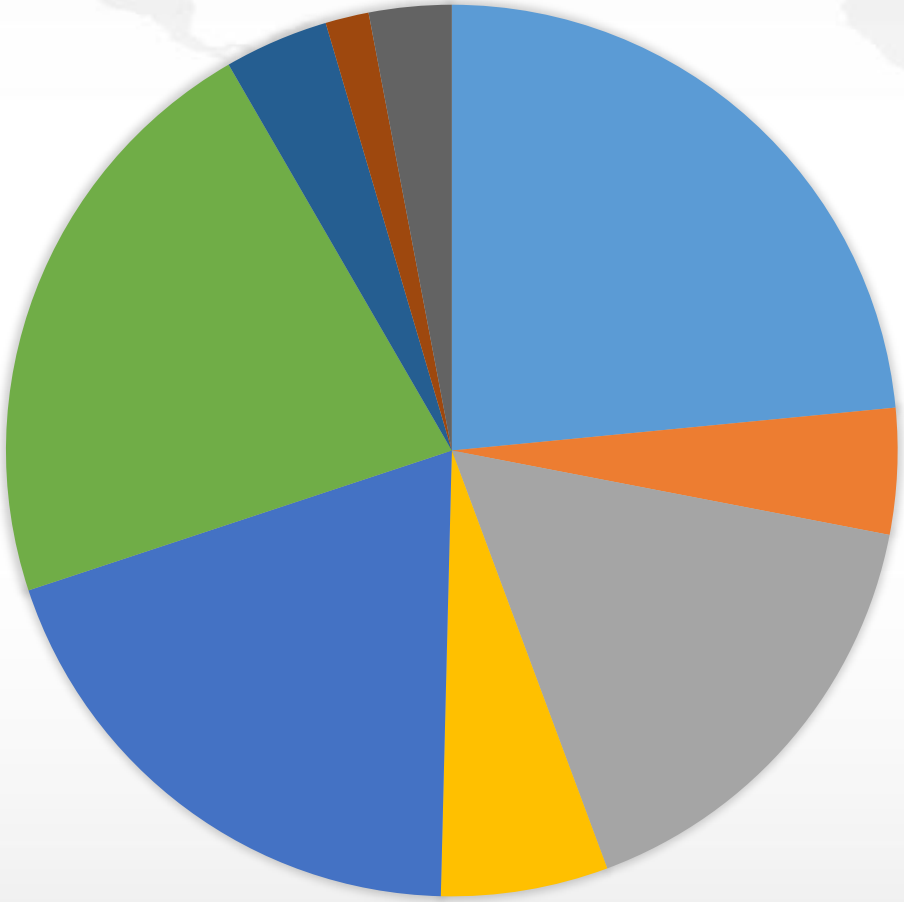
Opportunities for Clarity and Consistency



>155 Identified Needs

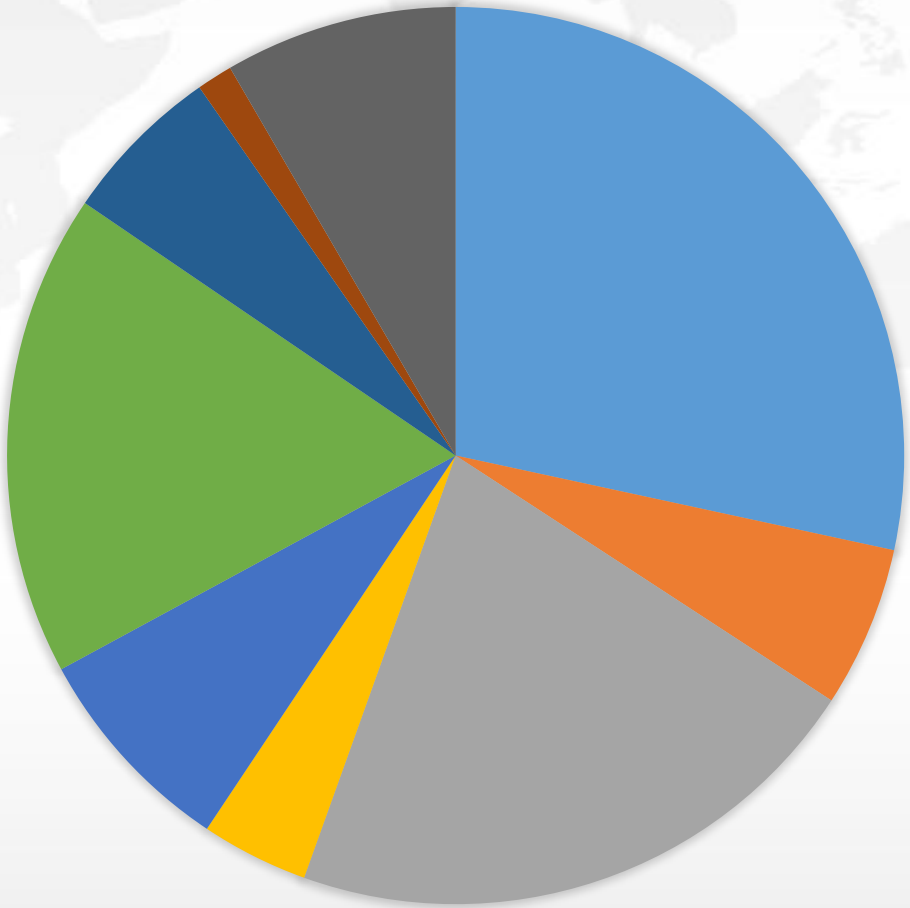
Comparing Areas of Focus

PUBLIC COMMENTS



General
Glossary
Principles
IRB
Investigator
Sponsor
Protocol
IB
ED

COMPARING ICH GUIDELINES



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High-level Themes from the Findings

- Scope of E6 guideline could be further clarified
- Stakeholder engagement should inform E6(R3) revisions
- Provide additional discussion of purpose of GCP; difference between research and clinical care
- More emphasis should be placed on critical to quality factors and a proportional approach to clinical trial conduct
- E6 internal consistency and consistency between E6 and E8 should be ensured

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High-level Themes from the Findings

- Consider if/how/where participants can take a more active role in GCP process
- Consider including return of trial results to participants
- Clarify/update adverse event reporting recommendations
- ICH E6(R3) should include considerations for new technologies and clinical trial designs
- Some areas lack detail (e.g., data management and the protocol sections)

E6(R3) EWG Analysis
Consolidation the Analysis

What did we find after pooling the data?

Missing Key Features in Light of E8 Revisions

- **Patient engagement**
- **Decrease burden for sites and participants**
  - E.g., by involving stakeholders and planning trials closer to real life of participants and researchers
- **Critical to quality factors**
- **Proportionality**

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Considerations for Responsibilities

- Clarifying investigator and sponsor responsibilities in new trial types (e.g., decentralised clinical trial settings)
- Increasing amount of investigator systems
- Contracts and agreements – clarification of requirements in relation to investigator or sponsor responsibilities (complex trial landscape)
- Acknowledgement of the diverse knowledge now required for trials
- Prequalification and performance evaluation of vendors/CROs

Considerations for Data Management

- **Systems and Data, missing/lack of details regarding**
  - Data Management and Statistical Analysis (5.5)
  - Adding text to bridge between E6 and E9 and include essential documents regarding these processes
  - New technology and data types (e.g., wearables, artificial intelligence)
  - More process and dataflow driven
  - IT security, user management and validation

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Considerations for Monitoring

- **Clarify some emerging themes and different types of quality control by different sponsor representatives to ensure data quality and sponsor oversight such as:**
  - Source data and metadata review versus source data verification
  - Medical monitoring versus centralised monitoring
  - Remote monitoring, use of platforms
- **Clarify requirements for review of site systems and for other prequalification activities**

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Areas Needing Additional Clarification

- **Protocol**
  - New trial designs
  - New systems
  - New data types
  - Additional information in some sections where little or no text
- **Essential Documents**
  - Digital documents and their retention
  - Highlight importance of recordkeeping in an ongoing manner

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Areas Needing Additional Clarification

- **Safety – clarity required regarding review of potential safety data**
- **Use of data monitoring/adjudication committee and their processes**
- **Informed consent**
  - Consideration for different patient populations (e.g., assent)
  - Potential for use of data collected outside the trial

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Examples of Proposed Minor Updates

Proposed Minor Updates (e.g., additional sentences):

- Documentation of screen failures
- Procedure for rescreening
- Timely review of safety parameters
- Documentation of what can be directly entered into the case report form (or other systems)
- Translation quality of important documents
- Procedure for site termination including informing Health Authorities
- Independence of the monitor from the site

Note: A large number of other areas have been identified

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How to Prioritize Those Topics?

Initial Prioritized Sections

- **Data Management / Data Governance**
- **Responsibilities**
- **Monitoring**
- **Informed Consent**
- **Safety**
- **Protocol**
- **Essential Documents**

First Topics for Drafting

- **Data Management / Data Governance**
  - 233 stakeholder comments
  - E.g., digital data flow
- **Responsibilities**
  - 170 stakeholder comments
  - E.g., responsibilities of the concerned parties in relation to new technology
- **Monitoring**
  - 69 stakeholder comments
  - E.g., different types of monitoring, on-site, central, and remote

E6(R3) EWG Analysis

Establishing Small Group (Drafting Groups)

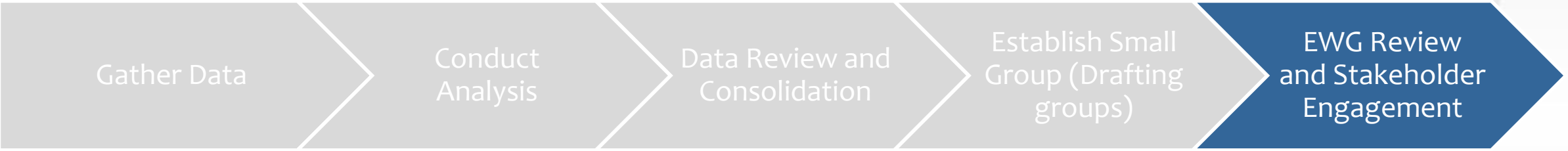
- **Small Groups**
  - Subset of full EWG
  - Divided into drafting groups to facilitate topic discussion with full EWG and leads drafting a specific topic / section
  - Regularly meet to ensure that cross-section topics are addressed and considerations applicable throughout the guidelines are aligned

Draft Overarching Considerations

Topic/Issue	Writing Group Considerations
New technologies, tools, and methodologies	Review and consider updating language in (sub)section to be inclusive of current and future advances in trial technologies, tools, and methodologies. Media neutral to allow for electronic documentation activities.
Participant engagement	Review (sub)section to identify any areas where participant engagement can or should be sought.
Risk assessment, critical to quality factors, and proportionality	Review and consider updating each (sub)section to provide additional guidance on topics associated with risk assessment, critical to quality factors, and proportionality.
Flexibility for new trial designs	Consider if and how language accommodates new types of trials designs (e.g., platform trials, decentralised trials, umbrella trials, trials in healthcare settings).
Flexibility for trials being conducted in exceptional circumstances	Determine whether (sub)section has any considerations related to trials being conducted in exceptional circumstances (e.g., during public health emergencies).
ICH Guideline consistency	Review each (sub)section to ensure consistency with other E6 sections and relevant ICH guidelines.
Paediatrics	Consider issues related to paediatric populations (e.g., assent, age-appropriate lab values and clinical measurements).
Principles	Ensure that (sub)section is consistent with the spirit and aim of the associated principle.
Documentation practice	Consider if and how good documentation practice can be applied across all documents relevant to the (sub)section (e.g., version control, signatures are unambiguous). Consider the timeliness of the documentation.
Minor edit	Consider changing “written” to “documented” throughout (sub)section; Consider changing “human subject/subject” to “participant” throughout (sub)section.

E6(R3) EWG Analysis

EWG Review and Stakeholder Engagement



- **EWG Review and Stakeholder Engagement**
  - Small group will regularly consult the full EWG
  - EWG will provide stakeholder representatives with updates on progress of drafting groups
  - EWG will prioritize opportunities to engage stakeholder representatives
  - EWG will agree on the proposed concepts and draft text

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In Summary

- Information collected from the input analysis will continue to inform the work to develop E6(R3)
- The EWG will continue to engage with stakeholder representatives to maximize clarity and relevance of E6(R3)
- The EWG is committed to the development of E6(R3), which provides a future proofed document while still protecting trial participants and ensuring the reliability of results

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Questions / Discussion