Informing the Renovations to the ICH E6 GCP Guideline for Good Clinical Practice

Survey Findings

FINAL Report
March 16, 2020

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1. PURPOSE OF RESEARCH

The Clinical Trials Transformation Initiative (CTTI)—a public-private partnership between Duke University and the US Food and Drug Administration—independently conducted (1) a global online survey, (2) qualitative, in-depth telephone interviews, and (3) an open comment platform, to provide opportunities for stakeholders affected by ICH E6 GCP to identify areas in ICH E6 GCP that are of greatest need for renovation, to suggest realistic ways for renovation, and to describe their experiences with implementing ICH E6 GCP. All participants reviewed ICH E6 (R2).

In this report, CTTI provides the final findings from the survey to ICH for their consideration as they renovate ICH E6 GCP. The in-depth interview findings report and open comment opportunity report are provided as separate documents.

2. SURVEY FINDINGS

2.1 Participant characteristics

A total of 327 stakeholders responded to all survey questions and were included in the final sample (410 individuals opened the survey but did not complete it). Participants were from 39 countries and represented every region of the world. However, most participants' locations of employment were in Europe and Central Asia (n=193; 59%), primarily European countries, and North America (n=98; 30%) (**Table 1**).

Table 1. Participants' Geographic Location of Employment (n=321*)

Region/Country	No. (%)
East Asia and Pacific	**21 (6.5)**
Australia	16 (5.0)
China	1 (0.3)
Japan	4 (1.2)
Europe and Central Asia	**193 (60.1)**
Austria	3 (0.9)
Belgium	6 (1.9)
Bulgaria	1 (0.3)
Croatia	1 (0.3)
Czechia (Czech Republic)	4 (1.2)
Denmark	5 (1.6)
Estonia	2 (0.6)
Finland	4 (1.2)
France	7 (2.2)
Germany	56 (17.4)
Greece	3 (0.9)
Hungary	2 (0.6)
Ireland	10 (3.1)
Italy	9 (2.8)
Netherlands	7 (2.2)
Norway	4 (1.2)
Poland	1 (0.3)
Portugal	5 (1.6)
Romania	3 (0.9)
Serbia	2 (0.6)
Slovakia	3 (0.9)

Slovenia	3 (0.9)
Spain	9 (2.8)
Sweden	4 (1.2)
Switzerland	11 (3.4)
Turkey	1 (0.3)
United Kingdom	27 (8.4)
Latin America and Caribbean	**3 (0.9)**
Argentina	1 (0.3)
Colombia	2 (0.6)
Middle East and North Africa	**4 (1.2)**
Iraq	1 (0.3)
Israel	2 (0.6)
Lebanon	1 (0.3)
North America	**98 (30.5)**
Canada	48 (15.0)
United States of America	50 (15.6)
South Asia	**1 (0.3)**
Sri Lanka	1 (0.3)
Sub-Saharan Africa	**1 (0.3)**
Tanzania	1 (0.3)

*Data are missing from 6 participants.

Participants conducted research in 153 countries worldwide (**Table 2**).

Table 2. Geographic Location of Participants' Research[a]

Country	No. (%)
East Asia and Pacific	**97 (29.7)**
Australia	72 (22.0)
Cambodia	3 (0.9)
China	40 (12.2)
Indonesia	14 (4.3)
Japan	41 (12.5)
Laos	1 (0.3)
Malaysia	18 (5.5)
Maldives	1 (0.3)
Marshall Islands	1 (0.3)
Mongolia	1 (0.3)

Country	No. (%)
Myanmar	3 (0.9)
New Zealand	47 (14.4)
Papua New Guinea	1 (0.3)
Philippines	16 (4.9)
Singapore	27 (8.3)
South Korea	35 (10.7)
Taiwan	30 (9.2)
Thailand	27 (8.3)
Vietnam	12 (3.7)
Europe and Central Asia	**230 (70.3)**
Albania	4 (1.2)
Andorra	3 (0.9)
Armenia	2 (0.6)
Austria	69 (21.1)
Azerbaijan	3 (0.9)
Belarus	12 (3.7)
Belgium	78 (23.9)
Bosnia and Herzegovina	6 (1.8)
Bulgaria	30 (9.2)
Croatia	26 (8.0)
Cyprus	8 (2.4)
Czechia (Czech Republic)	55 (16.8)
Denmark	71 (21.7)
Estonia	27 (8.3)
Finland	50 (15.3)
France	89 (27.2)
Georgia	8 (2.4)
Germany	134 (41.0)
Greece	39 (11.9)
Greenland	2 (0.6)
Hungary	51 (15.6)
Iceland	14 (4.3)
Ireland	73 (22.3)
Italy	93 (28.4)

Country	No. (%)
Kazakhstan	3 (0.9)
Kosovo	2 (0.6)
Kyrgyzstan	3 (0.9)
Latvia	21 (6.4)
Liechtenstein	3 (0.9)
Lithuania	25 (7.6)
Luxembourg	11 (3.4)
Malta	4 (1.2)
Moldova	9 (2.8)
Monaco	3 (0.9)
Montenegro	1 (0.3)
Netherlands	80 (24.5)
North Macedonia (Formerly Macedonia)	3 (0.9)
Norway	53 (16.2)
Poland	69 (21.1)
Portugal	45 (13.8)
Romania	40 (12.2)
Russia	48 (14.7)
Serbia	18 (5.5)
Slovakia	31 (9.5)
Slovenia	23 (7.0)
Spain	80 (24.5)
Sweden	73 (22.3)
Switzerland	69 (21.1)
Tajikistan	1 (0.3)
Turkey	29 (8.9)
Turkmenistan	1 (0.3)
Ukraine	32 (9.8)
United Kingdom	112 (34.3)
Uzbekistan	1 (0.3)
Vatican City	1 (0.3)
Latin America and Caribbean	**59 (18.0)**
Argentina	39 (11.9)
Bahamas	1 (0.3)

Country	No. (%)
Barbados	1 (0.3)
Belize	1 (0.3)
Bolivia	2 (0.6)
Brazil	38 (11.6)
Chile	27 (8.3)
Colombia	21 (6.4)
Costa Rica	4 (1.2)
Cuba	3 (0.9)
Dominica	1 (0.3)
Dominican Republic	3 (0.9)
Ecuador	7 (2.1)
El Salvador	2 (0.6)
Guatemala	5 (1.5)
Guyana	1 (0.3)
Honduras	1 (0.3)
Jamaica	2 (0.6)
Mexico	38 (11.6)
Nicaragua	1 (0.3)
Panama	5 (1.5)
Paraguay	4 (1.2)
Peru	11 (3.4)
Uruguay	5 (1.5)
Venezuela	10 (3.1)
Middle East and North Africa	**42 (12.8)**
Algeria	2 (0.6)
Bahrain	2 (0.6)
Egypt	10 (3.1)
Iran	1 (0.3)
Iraq	1 (0.3)
Israel	30 (9.2)
Jordan	4 (1.2)
Kuwait	2 (0.6)
Lebanon	6 (1.8)
Morocco	2 (0.6)

Country	No. (%)
Oman	1 (0.3)
Qatar	5 (1.5)
Saudi Arabia	8 (2.4)
Syria	1 (0.3)
Tunisia	4 (1.2)
United Arab Emirates	6 (1.8)
Yemen	3 (0.9)
North America	**170 (52.0)**
Canada	119 (36.4)
United States of America	122 (37.3)
South Asia	**44 (13.5)**
Afghanistan	1 (0.3)
Bangladesh	6 (1.8)
India	43 (13.1)
Nepal	2 (0.6)
Pakistan	6 (1.8)
Sri Lanka	5 (1.5)
Sub-Saharan Africa	**49 (15.0)**
Benin	2 (0.6)
Botswana	1 (0.3)
Burkina Faso	1 (0.3)
Cameroon	4 (1.2)
Central African Republic (CAR)	1 (0.3)
Congo, Democratic Republic of the	3 (0.9)
Cote d'Ivoire	2 (0.6)
Ethiopia	4 (1.2)
Gabon	1 (0.3)
Gambia	4 (1.2)
Ghana	8 (2.4)
Guinea	1 (0.3)
Kenya	13 (4.0)
Liberia	1 (0.3)
Malawi	4 (1.2)
Mali	1 (0.3)

Country	No. (%)
Mozambique	3 (0.9)
Namibia	2 (0.6)
Nigeria	6 (1.8)
Rwanda	4 (1.2)
Senegal	2 (0.6)
Seychelles	1 (0.3)
Sierra Leone	3 (0.9)
South Africa	37 (11.3)
Sudan	3 (0.9)
Tanzania	9 (2.8)
Uganda	10 (3.1)
Zambia	5 (1.5)
Zimbabwe	5 (1.5)

[a] The regional headers represent the total number of participants and percentage of the study population who conduct research in one of the countries in that region. The country subheaders represent the total number of participants and percentage of the study population who conduct research in that country.

Participants were affiliated with a wide range of organizational types. The most common were university/academic research centers affiliated with a hospital/medical center (n=132; 40%), pharmaceutical biotechnology companies (n=61; 19%), and commercial contract research organizations (n=44; 14%) (**Table 3**).

Table 3. Participants' Organizations (n=327)

Type of Organization	No. (%)
University/academic research center affiliated with a hospital/medical center	132 (40.4)
Pharmaceutical company or biotechnology company	61 (18.7)
Contract research organization (commercial/for profit)	44 (13.5)
Hospital/medical center not affiliated with a university/academic research center	21 (6.4)
University/academic research center not affiliated hospital/medical center	20 (6.1)
Governmental organization that regulates medical products	14 (4.3)
Non-governmental organization or not-for-profit organization	12 (3.7)
Private research site	8 (2.4)
Governmental organization that does not regulate medical products	5 (1.5)
Patient advocacy group	2 (0.6)
Private foundation	2 (0.6)

Type of Organization	No. (%)
Trade/professional organization	1 (0.3)
Not affiliated with a specific organization	1 (0.3)
Prefer not to respond	4 (1.2)

Participants represented many research roles. The most common were (1) principal investigator, coinvestigator, subinvestigator, site investigator (n=77; 24%), (2) quality assurance/quality control personnel (n=65; 20%), (3) clinical operations personnel (n=57; 17%), and (4) clinical research associate/research coordinator/study nurse (n=45; 14%) (**Table 4**).

Table 4. Participants' Main Role in Research (n=327)

Research Role	No. (%)
Principal investigator, co-investigator, sub-investigator, site investigator	77 (23.5)
Quality assurance/quality control personnel	65 (19.9)
Clinical operations personnel	57 (17.4)
Clinical research associate/research coordinator/study nurse	45 (13.8)
Regulatory affairs personnel	21 (6.4)
Data analyst	12 (3.7)
Monitor	10 (3.1)
Inspector	9 (2.8)
Data manager	6 (1.8)
Government regulator	4 (1.2)
Laboratory personnel	4 (1.2)
Pharmacist	3 (0.9)
Ethics review/Institutional Review Board personnel	1 (0.3)
Medical provider (healthcare provider who delivers medical care to study participants)	1 (0.3)
Data collector	1 (0.3)
Patient advocate	1 (0.3)
Prefer not to respond	10 (3.1)

Participants' time involved in research ranged from less than 1 year to more than 20 years (**Table 5**).

Table 5. Length of Time Participants Have Been Involved in Research (n=327)

Length of Time	No. (%)
Less than 1 year	2 (0.6)
1 year to less than 5 years	24 (7.3)
5 years to less than 10 years	38 (11.6)
10 years to less than 20 years	108 (33.0)
20 or more years	151 (46.2)
Prefer not to respond	4 (1.2)

Nearly all participants (n=289; 88%) conduct phase I, II, or III clinical research on medicinal products (drugs, vaccines, and biologicals). Participants also reported conducting other kinds of clinical research, as well as social and behavioral sciences research and epidemiological research (**Table 6**).

Table 6. Type of Research Conducted by Participants (Current and Past)

Type of Research	No. (%)[a]
Phase I, II, or III clinical research on medicinal products (drugs, vaccines, and biologicals)	289 (88.4)
Observational clinical research	186 (56.9)
Phase IV: Post-marketing/post-approval clinical research on medicinal products	182 (55.7)
Epidemiological research	112 (34.3)
Other clinical research not on medicinal products	74 (22.6)
Diagnostic studies	73 (22.3)
Other clinical research on medicinal products	68 (20.8)
Social science and behavioral research	46 (14.1)

[a] Participants selected all that applied.

About one-third of participants (n=106; 32%) reported that they use mobile applications for the remote capture of efficacy or safety outcomes data for regulatory decision making. About two-thirds (n=203; 62%) reported using routine health care data (including hospital data, registries, national clinical data sets, medical records, administrative data) for capture of efficacy or safety outcomes data for regulatory decision-making.

Nearly all participants (n=304; 93%) received training on ICH E6 GCP. Most participants said they regularly rely on it in their research role (n=258; 79%) (**Table 7**).

Table 7. Participant Engagement With ICH E6 GCP (n=327)

Type of Engagement	No. (%)
Received training on ICH GCP	304 (93.0)
How often rely on GCP to do research role	
Regularly	258 (78.9)
Occasionally	41 (12.5)
Rarely	15 (4.6)
Never	2 (0.6)
Prefer not to respond	11 (3.4)

2.2 Principles of ICH

Figure 1 presents participants' recommendations for revising the ICH E6 GCP principles, ranked in order of need. **The top 5 principles identified by participants as needing renovation are**:

1. Systems with procedures that assure the quality of every aspect of the trial should be implemented. ADDENDUM Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems (n=94; 29%).
2. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist (n=92; 28%).
3. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s) (n=89; 27%).
4. Freely given informed consent should be obtained from every subject prior to clinical trial participation (n=86; 26%).
5. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. ADDENDUM This principle applies to all records referenced in this guideline, irrespective of the type of media used (n=84; 25%).

The top 5 principles participants believed did not need renovations are:

1. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial

should be initiated and continued only if the anticipated benefits justify the risks (n=258; 79%).

2. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society (n=256; 78%).
3. Clinical trials should be scientifically sound and described in a clear, detailed protocol (n=256; 78%).
4. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirement(s) (n=255; 78%).
5. A trial should be conducted in compliance with a protocol that has received prior IRB/independent ethics committee (IEC) approval/favorable opinion (n=252; 77%).

Figure 1. Participant recommendations for revising the ICH E6 GCP principles

ICH E6 GCP PRINCIPLE

Revision needed	Revision NOT needed	No comment

Systems with procedures that assure the quality of every aspect of the trial should be implemented. ADDENDUM Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Freely given informed consent should be obtained from every subject prior to clinical trial participation.

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. ADDENDUM This principle applies to all records referenced in this guideline, irrespective of the type of media used.

The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

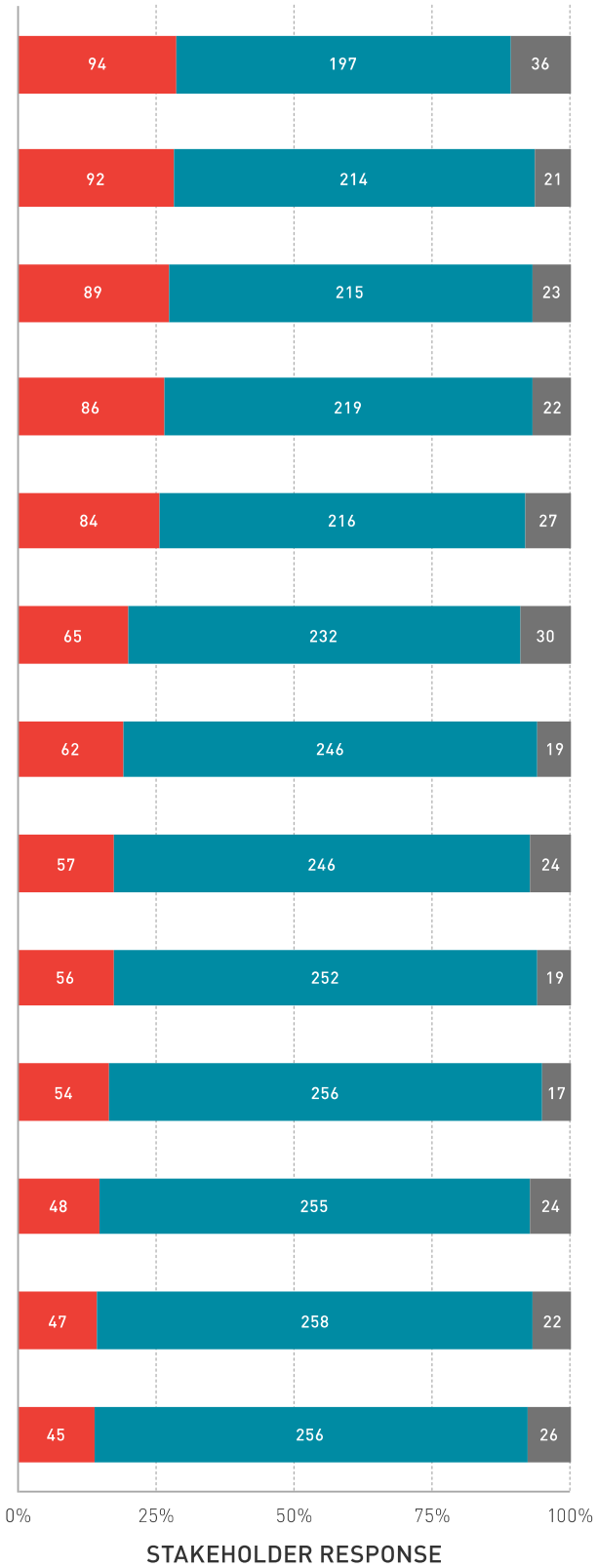
A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.



2.3 Sections of ICH

Figure 2 presents participants' recommendations for renovating the ICH E6 GCP topics, by section.

The top 10 sections/topics that participants reported needing renovation are:

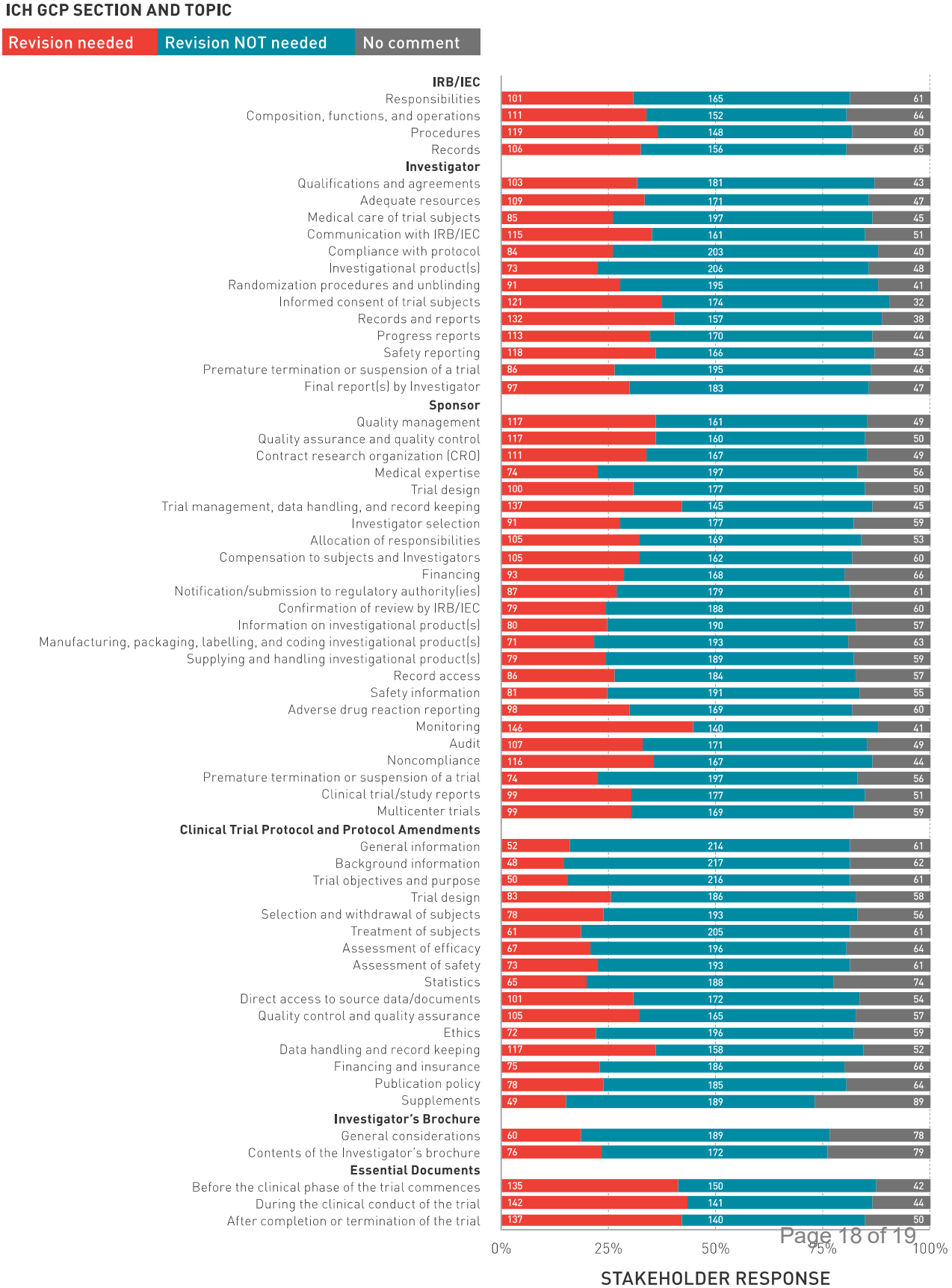
1. Sponsor: Monitoring (n=146; 45%)
2. Essential documents: During the Clinical Conduct of the Trial (n=142; 43%)
3. Essential documents: After Completion or Termination of the Trial (n=137; 42%)
4. Sponsor: Trial Management, Data Handling, and Record Keeping (n=137; 42%)
5. Essential documents: Before the Clinical Phase of the Trial Commences (n=135; 41%)
6. Investigator: Records and reports (n=132; 40%)
7. Investigator: Informed Consent of Trial Subjects (n=121; 37%)
8. IRB/IEC: Procedures (n=119, 36%)
9. Investigator: Safety Reporting (n=118; 36%)
10. Clinical Trial Protocol and Protocol Amendments: Data Handling and Record Keeping (n=117; 36%) together with Sponsor: Quality Management (n=117; 36%) and Quality Assurance and Quality Control (n=117; 36%)

The top 10 sections/topics that participants reported not needing renovation are:

1. Clinical Trial Protocol and Protocol Amendments: Background Information (n=217; 66%)
2. Clinical Trial Protocol and Protocol Amendments: Trial Objectives and Purpose (n= 216; 66%)
3. Clinical Trial Protocol and Protocol Amendments: General Information (n=214; 65%)
4. Investigator: Investigational Product(s) (n=206; 63%)
5. Clinical Trial Protocol and Protocol Amendments: Treatment of Subjects (n=205; 63%)
6. Investigator: Compliance with Protocol (n=203; 62%)
7. Investigator: Medical Care of Trial Subjects (n=197; 60%)
8. Sponsor: Medical Expertise (n=197; 60%)
9. Sponsor: Premature Termination or Suspension of a Trial (n=197; 60%)

10. Clinical Trial Protocol and Protocol Amendments: Assessment of Efficacy (n=196; 60%) and Ethics (n=196; 60%)

Figure 2. Participants' recommendations for renovating the ICH E6 GCP sections and topics



3. METHODS

3.1 Recruitment

CTTI leadership established relationships with organizations that have robust global professional networks that would be willing to forward the survey invitation to those networks. The CTTI advisory group members also identified specific groups in which to send the survey invitation, and CTTI staff conducted internet searches to identify research networks to contact. We sent a recruitment email to all these groups with a link to the online survey, and also requested that recipients forward the recruitment email to others who might be interested in completing the survey. The initial response from stakeholders residing in North America, Europe, and Australia was strong, but there were few participants from other parts of the world. Therefore, we conducted a second wave of recruitment, focusing on stakeholders who were part of research networks in ICH member countries, specifically Brazil, China, South Korea, Japan, and Singapore. We also reached out to research networks that conduct research in Africa. CTTI also posted the survey link on Twitter and LinkedIn.

3.2 Data collection

We administered the online survey via Qualtrics. The purpose of the survey was to (1) identify areas of ICH E6 GCP that participants believe are and are not in need of renovation, and (2) identify a diverse group of individuals globally to invite for follow-up, in-depth interviews. Participants were asked to complete the survey on their own, because as the survey was not designed for participants to combine their answers and respond as a group. The survey was offered in English only, the official language of ICH. Survey participants were asked to (1) answer demographic questions such as the location(s) of their research, type of institution, and role in research, and (2) review a list of the ICH E6 GCP principles and sections and indicate whether they believe that the topic is or is not in need of renovation, or if they have no comments.

The survey was conducted from August 15 to September 20, 2019.

3.3 Participant eligibility

Individuals were eligible to take part if they self-reported that (1) they are involved in research in some way in a professional capacity, (2) have access to a computer and a reliable internet connection, and (3) read English.

3.4 Data analysis

We used descriptive statistics to describe the survey findings.

3.5 Ethics

The Duke University Health System Institutional Review Board (IRB) determined that the research is exempt from further IRB review.

4. STUDY TEAM

- **Principal Investigator**: Amy Corneli, PhD, MPH, CTTI Lead Social Scientist; Associate Professor,
  Departments of Population Health Sciences and Medicine, Duke University School of Medicine
- **Team Leads**:
  - Annemarie Forrest, RN, MS, MPH, CTTI Director of Projects
  - Pamela Tenaerts, MD, MBA, CTTI Executive Director
  - Teresa Swezey, PhD, MA, CTTI Assistant Social Scientist; Clinical Trials Project Leader, Department of Population Health Sciences, Duke University School of Medicine
- **Interviewer**: Teresa Swezey, PhD, MA
- **Qualitative Data Analysts**:
  - Teresa Swezey, PhD, MA
  - Carrie Dombeck, MA, CTTI Research Associate; Research Program Leader, Department of Population Health Sciences, Duke University School of Medicine
- **Statistician**: Li Lin, MS, Senior Biostatistician, Department of Population Health Sciences, Duke University School of Medicine
- **Research Assistant**: Adora Nsonwu, Clinical Research Specialist, Department of Population Health Sciences, Duke University School of Medicine