Educational Series Webinars

- Monthly, usually last Wednesday
- Attendees are asked to join DIA
- If you'd like to present or have suggestions for topics, please contact emuella.flood@astrazeneca.com

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Demystifying Submissions of eCOA Documentation for Ethics Review: Are We Making Submissions More Difficult Than Necessary?

September 18, 2019

Moderator	Sue Vallow, RPh, MBA, MA	Executive Director, Patient Centered Outcomes – Global Oncology, Novartis Pharmaceuticals
Presenters	Steve Raymond, PhD	Chief Scientist, Scientific Affairs ERT
	Art Gertel	CEO MedSciCom, LLC
	Olivier Chassany, MD, PhD	Deputy Director of Patient-Centered Outcomes Research Paris-Diderot University and INSERM
	David Forster, JD, MA, CIP	Chief Compliance Officer WIRB-Copernicus Group

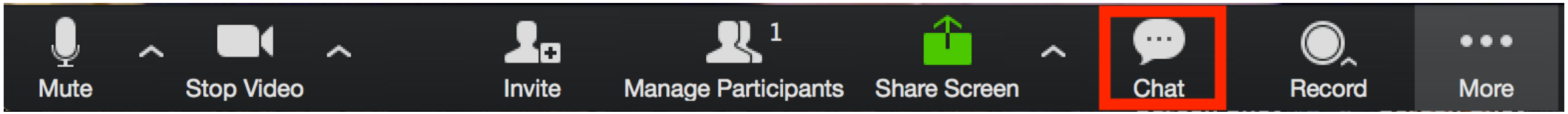
Housekeeping Items

Please ensure to place your phones and other devices on mute (but not on hold)

Housekeeping Items: Continued

- We'll be recording today's presentation and the recording will be available via the DIA and ePRO Consortium websites.

- To ask a question, please use the "chat" feature in the meeting controls and **direct your question to the moderator, Sue Vallow**.



Questions will be answered at the end of the webinar.

Disclaimer

- The views and opinions expressed in the following slides are those of the individual presenters and should not be attributed to their respective organizations/companies, the U.S. Food and Drug Administration or the Critical Path Institute.

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Biographies

Sue Vallow, RPh, MBA, MA – Executive Director, Patient Centered Outcomes – Global Oncology, Novartis Pharmaceuticals
Sue is an outcomes researcher with over 20 years of expertise in the development and validation of patient-reported outcome measures (PROMs) and is keenly interested in bringing the patient perspective forward with the effective use of PROMs and technology. She has held PRO leadership positions in pharma, consulting and with an eCOA Provider and is active in industry-wide patient-focused initiatives, including the Critical Path Institute's PRO Consortium and ePRO Consortium. She has presented at many patient-centered conferences and is a co-author of more than 20 peer-reviewed papers and more than 70 research posters and presentations.

Steve Raymond, PhD – Chief Scientist, Scientific Affairs, ERT Corporation
Steve introduced electronically administered patient self-assessments into pivotal clinical trials in 1994. He was a co-founder of Personal Health Technologies Corporation (PHT) in 1993 and served as their Chief Scientist and Quality Officer from 1997 until 2015 when PHT was acquired by eResearch Technology (ERT) where he now serves as Chief Scientist in the Department of Scientific Affairs. He holds a BS degree in Physiology from Stanford University and a PhD in Biology with a specialization in Neurophysiology from MIT, where he was a faculty researcher in the Departments of Biology, Electrical and Computer Engineering and the Research Laboratory of Electronics.

Biographies: Continued

Art Gertel

After 35 years serving in the pharmaceutical and related industries, Art established an independent consultancy in 2012: MedSciCom, LLC. He provides independent and collaborative strategic regulatory consulting - applying drug/device development, medical writing, bioethics, and DSMB expertise. Art brings over forty years of increasingly senior-level positions in the Pharmaceutical industry and leadership roles in professional organizations, as well as with collaborative efforts focusing on the improvement of the research, development, review, and approval of new therapeutics and diagnostics. He is a Registered Agent to US FDA. He is Past President of the American Medical Writers Association (AMWA), and a Fellow of both AMWA and the European Medical Writers Association (EMWA).

Olivier Chassany, MD, PhD, HDR

Professor Olivier Chassany is a specialist physician in gastroenterology and liver diseases by training. He is Deputy Director of Patient-Centered Outcomes Research, Paris-Diderot University and INSERM (French National Institute of Health and Medical Research). As a professor of therapeutics, he teaches therapeutics, methodology management, and ethics of clinical research, including critical reading of publications and patient-reported outcomes. Involved in Ethics Committees since 1989, he has been vice-chair and chairman of a Parisian Ethics Committee (agreed as US Institutional Review Board) (1998-2012). He has been expert of regulatory agencies (ex-Afssaps, EMA, French HTA) and member of several committees and working groups of the French drug Agency (ex-Afssaps) from more than 20 years (1994- 2014).

Biographies: Continued

David Forster, JD, MA, CIP

Mr. Forster joined Western IRB (WIRB) in 1996 and is currently the Chief Compliance Officer for the WIRB-Copernicus Group (WCG). Mr. Forster co-chairs the Secretary's Advisory Committee on Human Research Protections (SACHRP) Sub-Committee on Harmonization. He previously served a four-year term as a member of SACHRP and was previously a member of the SACHRP Sub-Committee on Inclusion of Individuals with Impaired Decision-Making in Research. Mr. Forster served on the Certified IRB Professional (CIP) Council and also served on the World Health Organization Quality Management and Evaluation Advisory Committee. Mr. Forster also plays an active role in the Harvard Multiregional Clinical Trials Work Group.

About Critical Path Institute

- Established in 2005 by the University of Arizona and the U.S. Food and Drug Administration (FDA)
- An independent, non-profit organization
  - Dedicated to implementing FDA's Critical Path Initiative
  - Enables pre-competitive collaboration that includes regulatory input/expertise
- Funding for this, publication, press release, etc. was made possible, in part, by the Food and Drug Administration through grant (U18 FD 005320). Views expressed in written materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.
- Support for the ePRO Consortium comes from membership fees paid by members of the ePRO Consortium (https://c-path.org/programs/epro/).

ePRO Consortium

- The Electronic Patient-Reported Outcome (ePRO) Consortium was established by the Critical Path Institute (C-Path) in 2010. Along with C-Path, the members of the ePRO Consortium are firms that provide electronic data collection technologies and services for capturing patient-reported outcome (PRO) and other clinical outcome assessment (COA) data in clinical trials.

- The mission of the ePRO Consortium is to advance the science of clinical trial endpoint assessment by collaboratively supporting and conducting research, designing and delivering educational opportunities, and developing and disseminating best practice recommendations for electronic collection of clinical outcome data.

Agenda

1. Introduction
2. Nature of the Burden: Specificity of Requirements
3. Ethical Considerations
4. European Perspective
5. Suggested Best Practices
6. Conclusion

Are We Making Submissions for Ethics Review Unnecessarily Cumbersome?

Objective: Demystify a common request from sponsors and CRO's to submit ***all written material*** to ethical committees that is to be presented to the Subject

The mystery:

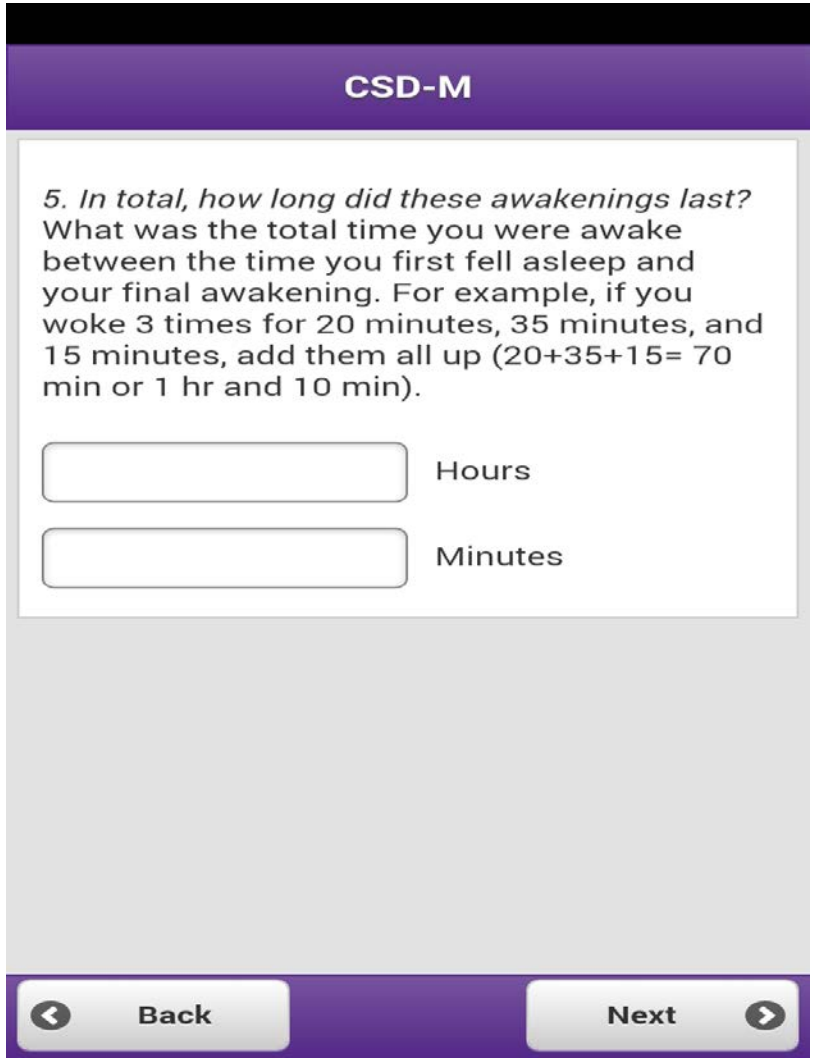
Does the ethical obligation that patients be fully informed in deciding whether to participate in a clinical trial require that such written material include:

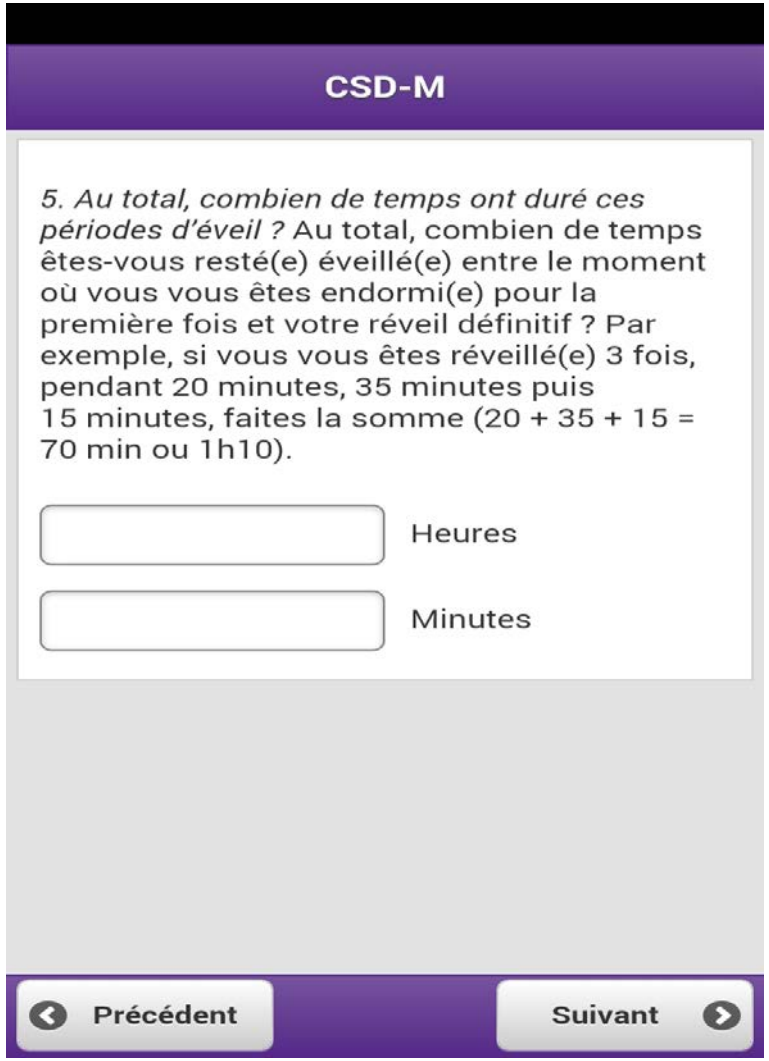
- all screenshots of eCOA questionnaires, diaries….
- Screenshots of error messages and control buttons for the electronic application
- All translations of the above from the final version of the electronic application

Why delve into this mystery? Why does it matter?

- The burden on sponsors, eCOA providers and IRBs is substantial, and delays study start
- The request may not match with the intention of GCP
- The relevance of such materials to the patients' decision is questionable

Scope of the task: A Screenshot Page





English to French
One "page" per item in a questionnaire, PRO instrument or diary

Scope of the Request: "All Screenshots"

How many items? How many pages?

An example of familiar instruments validated for a context of use and a daily and weekly diary might include about 200 items:

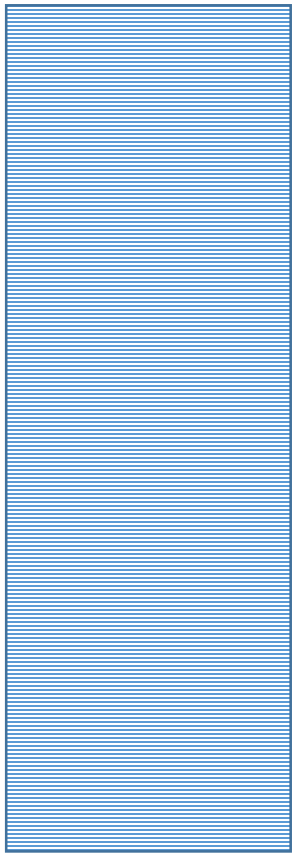
SF-36 (42 items), EQ 5D (6 items), EORTC QLQ C30 (33 items), PRO-CTCAE (~25 items selected), FACIT (14), HAQ-DI (26), Daily Diary (20 items); Weekly Diary (10 items)

"Stem" and "response options" in English:

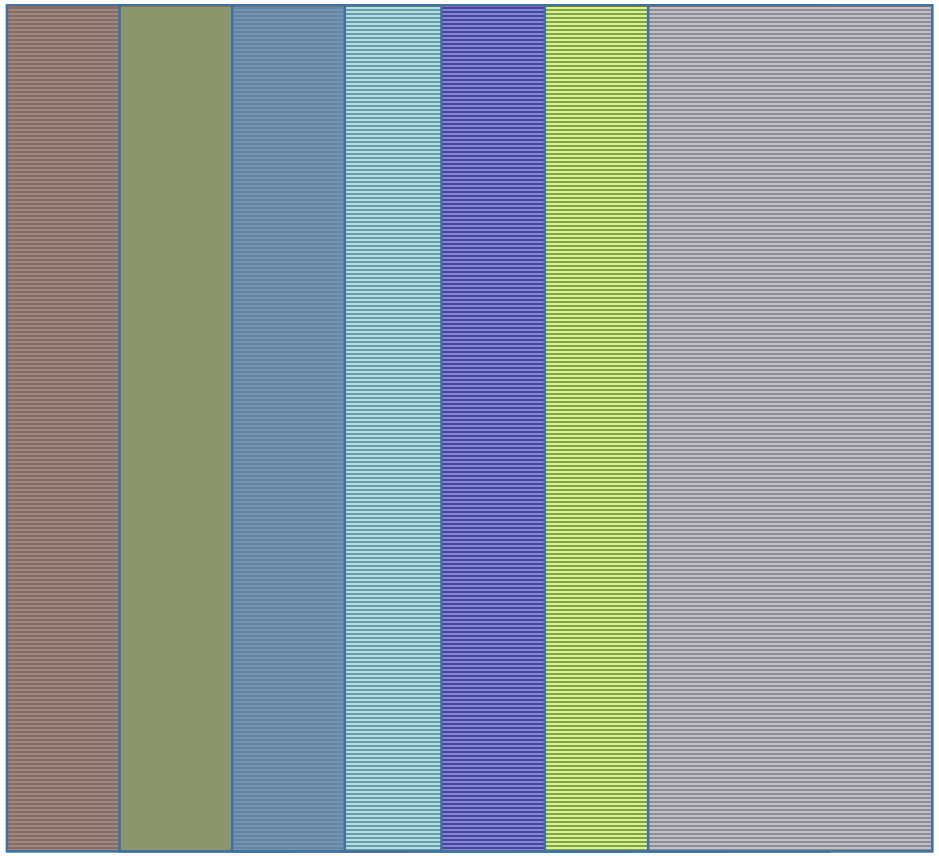
- Match the content of the paper specifications, which ARE usually included in the protocol
- Need to match the final protocol and be ready for translation into the applicable languages for a global study

Screenshots in English + 40 translations

English



200 pages



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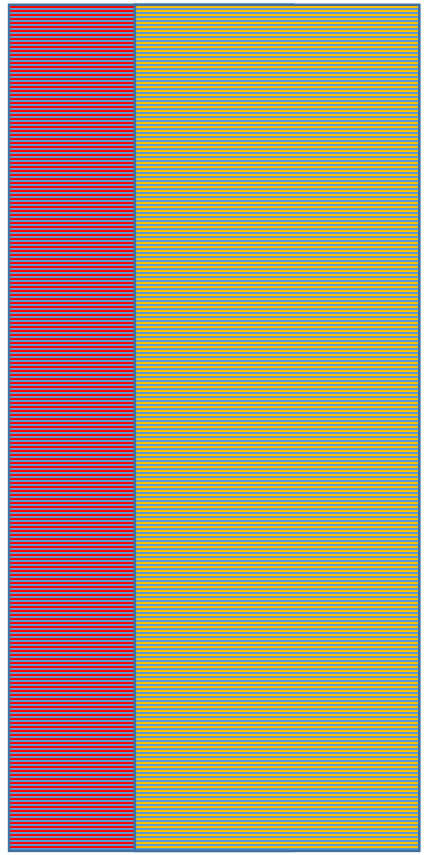
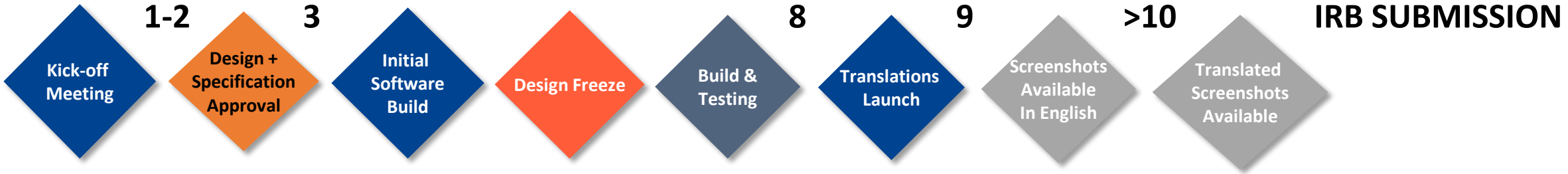


8,000 pages screenshots per Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) in 30 countries

Delay and Timing

The Timeline from study start to validated eCOA application



Final screenshots are only available after:

- Final protocol with COA questionnaires and Diaries (Week 3)
- Complete programming and design of screens in English (Week 8-9)
- Complete sequencing, scheduling of screens and instructions in English (Week >10)
- All translations of English screens/ forward/ backward/ approved
- Shoot all the screen shots
- Send (massive) files to IRB/ IEC (Week 12)

If the Protocol changes: Do much of the above AGAIN

Conclusion: A big task and a delay of 2 - 3 months

What really is required by GCP?

Demystification by looking closely at the language of GCP:

- "written information" is requested, not "written materials." Throughout GCP it's "…Information to be *provided* to the subject" (e.g., to be received)
- The context for information that needs to be supplied in the Subjects' language applies to the decision to enroll (informed consent, advertisements)
- GCP does mention operational forms (diaries and evaluation checklists) to be shown to or used for capturing responses from subjects, but not in the context of "written information to be provided to the subject."

[*Some textual quotations from ICH EG R2 Harmonized GCP support this interpretation as follows*]

Citations from ICH GCP bearing on “written information”

3.1.2 The IRB/IEC should obtain the following documents:

trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator’s current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

2 “written information”
GCP Section 4: Informed Consent

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. The communication of this information should be documented.

3 “Written Information” Informed Consent If Subject Cannot Read

4.4 Communication with IRB/IEC (continued)

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject….

By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject’s legally acceptable representative

4 The Listing of "Written Information" Informed Consent

4.4 Communication with IRB/IEC

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- *[Itemized list from a to t – none of which has any mention of PRO measures or inclusion of subject diaries or evaluation checklists. 20 items]*

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

5 Confirmation of Review by IRB/IEC to be obtained by sponsor

5.11.1 (c) The sponsor should obtain from the investigator/institution: (a) The name and address of the investigator's/institution's IRB/IEC. (b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations. (c) Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

- *[Note: written informed consent for(s) and any other written information to be provided to subjects is again a single item, not 2 items].*

6 "8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL"

ePRO CONSORTIUM
CRITICAL PATH INSTITUTE

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.1	**INVESTIGATOR'S BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	**INFORMATION GIVEN TO TRIAL SUBJECT**		X	X
	- **INFORMED CONSENT FORM** (including all applicable translations)	To document the informed consent		
	- **ANY OTHER WRITTEN INFORMATION**	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X

Interpretation of GCP and rationale for not supplying screenshots, operational controls, in all translations

GCP Language: "Any written information to be provided…" does not mention PRO, clinician interviews, or diaries used to capture information from subjects.

Protocol is intended to include such measures for evaluation by IRB IEC:

- Title, content (suitability for scientific purpose and" sensitivity"), administration plan (burden)
- Protocol in English (or possibly translated), but not in every subject's language, and only for IRB/IEC review, not to be "received" to a subject. Available EARLY.
- Ethical concerns of burden and content can be reviewed by IRB from the protocol materials

Ethical relevance

- programming, translations complete → delay, which IRBs are encouraged to avoid
- thousands of pages to be sent, quality controlled (QC'd), read, provided, and archived by Sponsor and IRB →
  - Expense, effort and possibly distraction, which IRBs are charged to minimize
  - Ethical purpose? importance to subject ? Any benefit from the effort to review?

Demystification: Review and approval of therapies seems to be unnecessarily delayed

Proposal: A best practice that is compliant with intent of GCP

Submit conventional paper versions of eCOA and PRO measures as PDF documents in English (or IRB/IEC preferred “protocol language”) for review by IRB as part of each version of the protocol

And submit in the protocol a description of any device to be used to display and capture the records (usability, security, privacy)

- Can be submitted early, appropriate for IRB/ IEC mission
- Supports evaluation of scientific relevance, burden to subjects, and protection of patient rights

Ethical Considerations

Data integrity is not the only concern when conducting clinical studies.

Study participants must be assured of basic protections.

Ethical Considerations

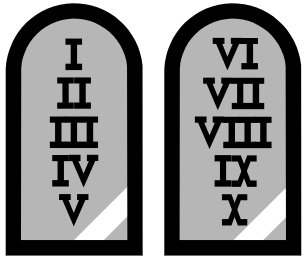
Challenge:

If the content of written materials included in the study protocol submitted to the Ethics Committee, remains consistent with that presented to the subject prior to, and during, the clinical study, is there a need to provide screenshots?

If the screenshots are not provided to the Ethics Committee, are clinical study subject protections compromised?

Codified Ethical Principles

Codified Ethical Principles



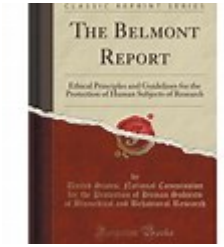
Ten Commandments
(7th Century BCE (?))

Nuremberg Code
(1949)

Declaration of Helsinki
(1964-2013)

FDA

US Food & Drug
Administration



The Belmont Report
(1974)

NIH
National Institutes of Health

Human Subject Protections –Office of Human Subjects Research, NIH (OHSR)
(2000)

Regulation (EU) No. 536/2014 (2014)

ICH
harmonisation for better health

ICH E6 (R2) – GCP (2015)
[FDA: 2018]

Codified Ethical Principles

Association of the British Pharmaceutical Industry

Pharmaceutical Industry Trade Association

Important Distinction
(a reminder from the Belmont Report)

Practice vs. Research

"Practice":

Interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide:

- ✓ diagnosis
- ✓ preventive treatment or therapy
- ✓ to particular individuals

"Research":

Activity designed to:

- ✓ test a hypothesis
- ✓ permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge
- ✓ Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

Prior to Enrollment into the Study…

Reliance on, and confidence in, "Learned Intermediaries":

- ✓**IRB/EC** vetting and approval of study protocol
- ✓**Sponsor** ethical responsibilities re: compliance with protections articulated in Codified Ethical Principles
- ✓**Principal Investigator (PI)** responsibility and accountability in context of Hippocratic Oath, GCP (and other applicable regulatory requirements) compliance, and "contract" (e.g., FDA Form 1572)

However…there are institutional and societal protections which must be applied and enforced.

Basic Principles for All Medical Research

What do we protect?

Principle	Nuremberg	Helsinki	Belmont	NIH	EU	ICH*
Life & health	✓	✓	✓	✓	✓	✓
Self-determination (including DISSENT)	✓	✓	✓	✓	✓	✓
Privacy		✓		✓	✓	✓
Confidentiality		✓		✓	✓	✓
Informed decision-making	✓	✓	✓	✓	✓	✓
Vulnerable groups	✓	✓	✓	✓	✓	✓

***NOTE: ICH E6(R2) – GCP, has been adopted by FDA**

Basic Principles for All Medical Research

How do we protect?

Principle	Nuremberg	Helsinki	Belmont	NIH	EU	ICH*
Adhere to Generally-Accepted Scientific Principles	✓	✓	✓		✓	✓
Require thorough knowledge of scientific literature	✓	✓	✓		✓	✓
Base study on laboratory & animal data	✓	✓			✓	✓
Require study protocol		✓			✓	✓
Review by Ethics Committee		✓	✓	✓	✓	✓
Site staff must be scientifically qualified & trained	✓	✓			✓	✓
Assessment of predictable risks/burdens & foreseeable benefits	✓	✓			✓	✓

***NOTE: ICH E6(R2) – GCP, has been adopted by FDA**

Basic Principles for All Medical Research

How do we protect?

Principle	Nuremberg	Helsinki	Belmont	NIH	EU	ICH*
Provide option for surrogate or delayed consent		✓	✓	✓	✓	✓
Prevent intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion	✓	✓	✓	✓	✓	✓
Duty & responsibility for ascertaining the quality of consent rests upon each individual who initiates, directs or engages in the research	✓	✓			✓	✓
Provide adequate facilities	✓	✓		✓	✓	✓
Allow unfettered withdrawal (per Subject/Investigator)	✓	✓		✓	✓	✓
Prevent selection bias	✓	✓	✓		✓	✓
Provide adequate medical care					✓	✓

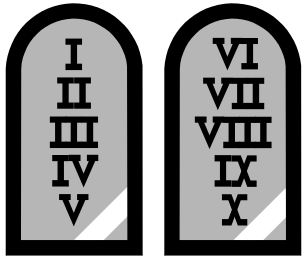
***NOTE: ICH E6(R2) – GCP, has been adopted by FDA**

Other Considerations

Unintended Consequences:

If the initiation of a clinical study is delayed due to the administrative burden of required review of information that does not bear on subject protection, this might deprive patients of timely and, potentially beneficial, intervention.

If the screenshots are not provided to the Ethics Committee, are clinical study subject protections compromised?



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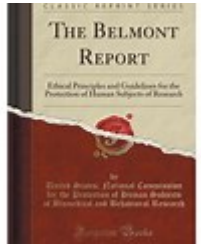

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European Perspective

Apart the issue of COA/eCOA, the European regulation landscape of clinical research is still heterogeneous!

Not enforced yet, waiting for the unique European portal for submission

European Regulation on medicinal products	French law "Jardé"
Interventional trial *(i.e., phase 1 to 3)*	Interventional (except drugs)
Interventional trial with minimal intervention *(i.e., post approval trials)*	Interventional at minimal risk (except drugs)
Observational studies on drugs are outside the scope and remain under each national regulation!	Observational (drugs included)

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC - https://ec.europa.eu/health/human-use/clinical-trials/regulation_en
LOI n° 2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine. https://www.legifrance.gouv.fr

Does the European Regulation on clinical trials on drugs (i.e., interventional) require anything in the EC submission dossier for COA/eCOA?

- No, it does not describe in detail the submission dossier beyond essential documents (i.e., protocol, Investigator Brochure, information and Consent form).
- Translation of the European Regulation in the French law does not mention CRF, or any COA questionnaire (whether paper or electronic) to be part of the submission dossier.
- European regulation is supposed to harmonize the process across European countries. So other European countries should have (or may be have not !) the same submission dossier, i.e., no mention of CRF or COA in the dossier.
- In practice, it happens that French EC do ask to review questionnaires (paper or electronic) …

Arrêté du 2 décembre 2016 fixant le contenu, le format et les modalités de présentation du dossier de demande d'avis au comité de protection des personnes sur un projet de recherche mentionnée au 1° de l'article L. 1121-1 du code de la santé publique portant sur un médicament à usage humain. JORF n°0284 du 7 décembre 2016. https://www.legifrance.gouv.fr

Risk-based approach of the French law Jardé: an attempt by the legislator not accepted by EC

It adapts the EC review process to the risks of the study: is it working? Not really

Type of study	Interventional at minimal risk	Observational	Observational with only questionnaires or interviews
Expedited review	Expedited review (by a few members of the EC, not in a plenary session): not currently endorsed by a majority of EC		**"Super" expedited review** (no formal review by EC): has been abandoned as EC refused not to review studies which may be at risk!
Dossier	No mention in the decree of the necessity to submit COA in the dossier	The decree specifies that **questionnaires should be part of the dossier!**	"Light" dossier with no COA to be submitted

Arrêté du 21 décembre 2018 fixant le format du résumé du protocole d'une recherche impliquant la personne humaine mentionnée au 3° de l'article L. 1121-1 du code de la santé publique ne comportant que des questionnaires ou des entretiens.
https://www.legifrance.gouv.fr/eli/arrete/2018/12/21/SSAP1835310A/jo/texte

EC submission dossier for observational studies adding only questionnaires or interviews

"Light" dossier with no protocol but a synopsis: from a draft to the official decree…

Draft decree describing the short synopsis (Nov 2017)

Main objective of the research:
Secondary objective (s):
Methodology of questionnaires / interviews
- Questionnaires
  Administration mode:
  □ internet, □ phone, □ face to face ….):
- Interviews
  □ Semi-directive
  □ Face to face
  □ By phone
Location of the research:
Estimated number of respondents:
Estimated duration of the research:
Inclusion criteria:
Exclusion criteria:
- Nature of the questions asked:
  □ Demographic information
  □ Health data
  □ Other

Attempt (probably by some EC) during consultation to introduce in the decree (Oct 2018) the sentence :

B. Attach the questionnaire or the interview guide

Published decree (Dec 2018): longer synopsis but no questionnaire required…

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ

Arrêté du 21 décembre 2018 fixant le format du résumé du protocole d'une recherche impliquant la personne humaine mentionnée au 3° de l'article L. 1121-1 du code de la santé publique ne comportant que des questionnaires ou des entretiens

NOR : SSAP1835210A

B. – **Méthodologie des questionna**
– questionnaire (s)
Modalités de passation :
– questionnaire administré par : □
– questionnaire administré en : □ u
Type de questionnaires : □ validé □
– si validé, indiquer l'origine de la
– si non validé, justifier :
Commentaire libre (si besoin pour pr
questionnaires) :
– entretien (s)
Modalités de réalisation :
– □ entretien individuel □ entretien
– entretien réalisé en : □ face à fac
– entretien réalisé : □ une fois ; □
Type d'entretien : □ directif ; □ sen

B. - Methodology of the questionnaires / interviews:

Questionnaire (s)
Administration mode:
- mail Internet, phone, face to face, other (explain, list):
- administered: once; several times (specify the number):
Type of questionnaires: validated / not validated
- if not validated, justify:

Interview (s):
- individual interview / focus group
- face to face, video conference, phone, other (explain, list):
- realized: once; several times (specify the number):
Type: directive; semi-directive; non-directive
Transcript of verbatim: no / yes
If recording: audio; video; Respect for the right to the image

Has there ever been an EC that has indicated that an electronic PRO measure has represented a risk to the patient?

- Yes, for some members of French EC, questionnaires are risky (they can destabilize patients), even more when the questionnaire is "**non validated.**"
- For some EC, a questionnaire under development should be categorized as an interventional trial, i.e., a simple qualitative study on 15 participants to generate the concepts should go under the process of a full interventional trial!)

Recent (July 2019) typical negative appraisals of French EC on studies adding only questionnaires or interviews

Qualitative study

"Indeed, although the subject of the research is interesting, it is not admissible at the scientific and ethical level: it seems difficult to obtain results on only about 15 subjects (besides it is not known what are hypotheses for the sample size). Semi-structured interviews are planned but interview guide is not provided. No statistical methodology is provided…"

Observational study with patient-reported outcome questionnaire

"The version of the questionnaire, as presented to the patient on screen, was not submitted to the EC"

French EC review is definitely not driven by a risk-based approach

	Interventional trials on drugs (European regulation - ER)	Interventional trials except drugs (French Law Jardé)	Interventional trials at minimal risk except drugs (French Law Jardé)	Observational study	Observational study with only questionnaires / interviews
Potential risk	+ to +++ (Ph 1)	++	+	0	0
EC review	**When the ER will be in place, EC will only review information / consent form ***		**In practice EC do spend a lot of time on these dossiers with minimal or no risk, and ask a lot of questions (e.g. on questionnaires) and sometimes give a negative appraisal (but are not able to discuss if the use of a placebo in a phase 1 trial is ethical…)**		
Submission of COA	No	No	No	**Yes**	No

* The Competent Authority, i.e. French Drug Agency ANSM will review the scientific aspects and methodology of the trial

What have we learned from these past years of updating the European regulation on clinical research?

- Attempts to “simplify” the law of clinical research are considered suspect, even when justified by a clever risk-based approach
- EC (at least French EC) are reluctant to endorse the risk-based approach in the management of clinical research and acknowledged internationally by all other stakeholders (EMA, FDA, regulators, sponsors, and probably patient organizations)

Conclusion: Need for better European regulation harmonization and EC training: utopia?

- Need to train EC members to the notion of risk added by the research in general and especially about the absence of risk in the majority of situations where questionnaires are completed by patients, clinicians or caregivers.
- Still need to harmonize the requirements of EC submission across European countries (especially studies which are outside the scope of the European regulation, i.e., observational studies with COA/eCOA)
- Still need to harmonize the review process of European EC (within countries and across countries) - we've been talking about it for more than 20 years ☺

Suggested Best Practices

- ICH
- FDA Information Sheet “Recruiting Study Subjects”
- Risk-based approach

ICH

- 3.1.2 The IRB/IEC should obtain the following documents:
- trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator’s current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

FDA Guidance on IRB Review

- FDA Information Sheet “Recruiting Study Subjects”
- Principal US guidance addressing IRB review of materials other than the consent form.
- Concentrates on recruitment, with an emphasis on recruitment as the beginning of the consent process.

FDA Guidance on IRB Review

- “An IRB is expected to review all the research documents and activities that bear directly on the rights and welfare of the subjects of proposed research. The protocol, the consent document and, for studies conducted under the Investigational New Drug (IND) regulations, the investigator's brochure are examples of documents that the IRB should review. The IRB should also review the methods and material that investigators propose to use to recruit subjects.”

FDA Guidance on IRB Review

- “FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process. Advertisements should be reviewed and approved by the IRB as part of the package for initial review.”

Substance:

- “FDA expects IRBs to review the advertising to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol.”

FDA Guidance on IRB Review

Procedure:

- "The IRB should review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the IRB should review the final audio/video tape."
- "The IRB may review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording. The review of the final taped message prepared from IRB-approved text may be accomplished through expedited procedures. The IRB may wish to caution the clinical investigators to obtain IRB approval of message text prior to taping, in order to avoid re-taping because of inappropriate wording."

Application of the Guidance to eCOA Review

- Application of the guidance to eCOA review using a risk-based approach
- Substance: The IRB reviews recruitment materials to ensure they are not unduly coercive or influential. eCOAs are not recruitment materials, and it is very unlikely that they will be unduly coercive or influential
- Rather, the IRB should review simply for accuracy and consistency with the protocol.

Application of the Guidance to eCOA Review

- Process: FDA recommends that IRBs review the final versions of print and recorded ads to ensure they are consistent with the original approval. The goal is to ensure that no changes have been made that introduce undue coercion or influence
- Given that eCOAs are highly unlikely to be unduly coercive or influential in the first place, this process is very unlikely to achieve any additions in human subject protection

Conclusion

- For this reason, we argue that it should not be necessary for the IRB to review final versions of eCOAs, as the underlying reason for IRB review is distinct from recruitment.
- Clearly, the review of different translations is not necessary, particularly as a requirement before the study can be approved.
- From a risk-based approach, IRB review of a paper copy of an eCOA is sufficient to ensure that the rights and welfare of subjects are protected.

Conclusion:
What should be submitted to IRBs/IECs

- Content and wording of PRO measures that the subject completes on the eCOA system, including the time and event schedule, and suggested time required for completion, to be submitted in English in paper layout.

- Descriptions of devices to be used in the study including regulatory approvals, summary of training for the subject on the device, privacy and security protections, and summary of administrative functions in order to implement the PRO measures on the eCOA system.

- Description of the processes followed to ensure appropriate translations are being obtained.

Conclusion:
What should *not* be Submitted to IRBs / IECs

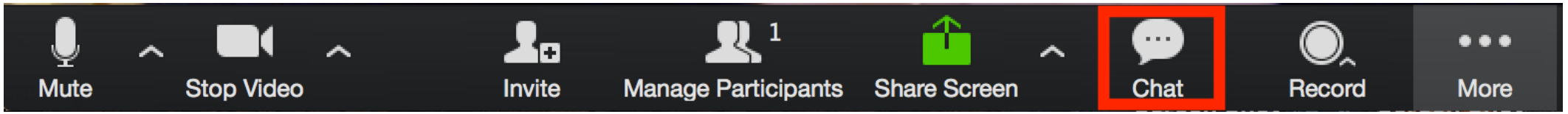
- Screenshots of ePRO questionnaires as they appear on the devices, and their translations.

- Administrative screens that may appear before or during the PRO measures, screens that appear to direct the patient to complete items or advance to the next screen, rules for moving from one screen to the next or to submit questionnaires, and their translations.

- Actual devices for review by the IRB/IEC

Q & A

To ask a question, please use the “chat” feature in the meeting controls and direct your question to the moderator, Sue Vallow.



On behalf of the DIA Study Endpoints Community and the ePRO Consortium, thank you for attending this webinar!