NCI Update: Modernizing Informed Consent

Clinical Trials and Translational Research Advisory Committee (CTAC)

November 6, 2024

NIH NATIONAL CANCER INSTITUTE

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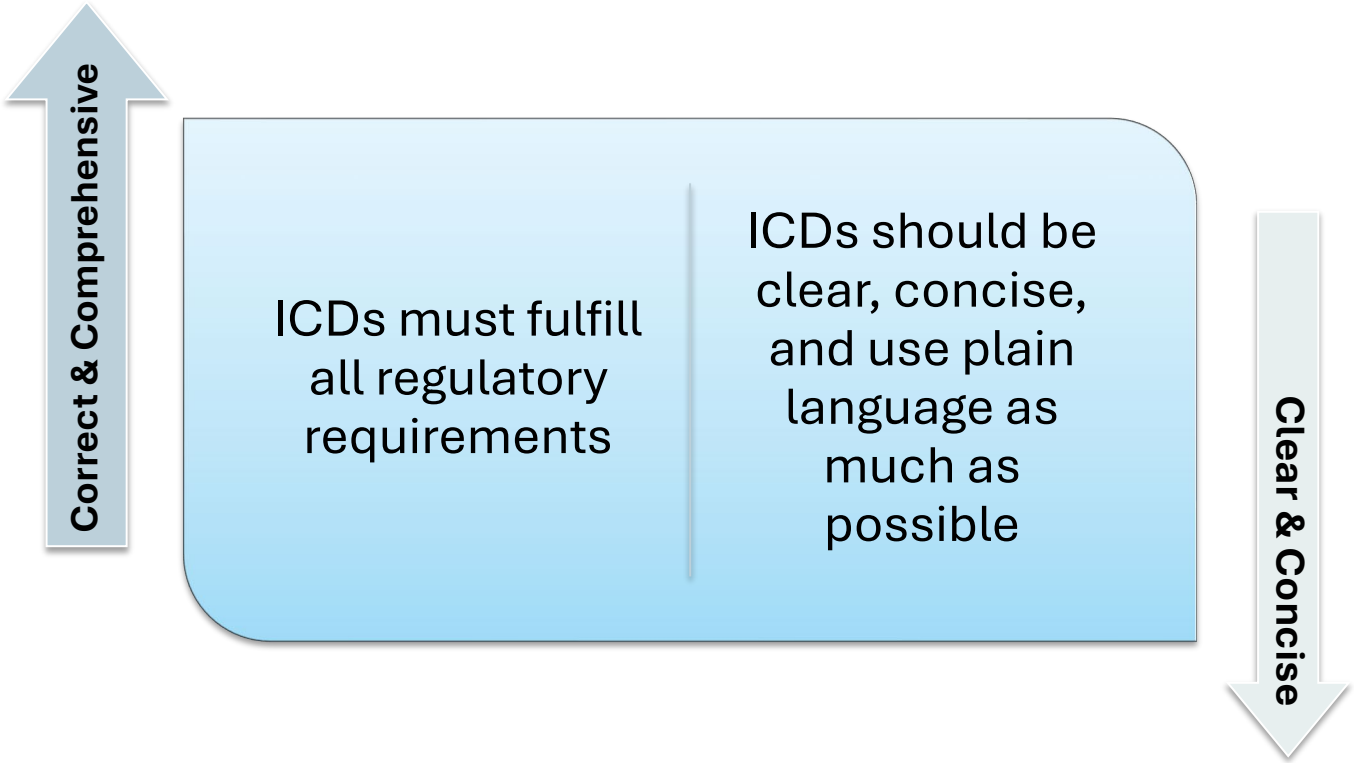
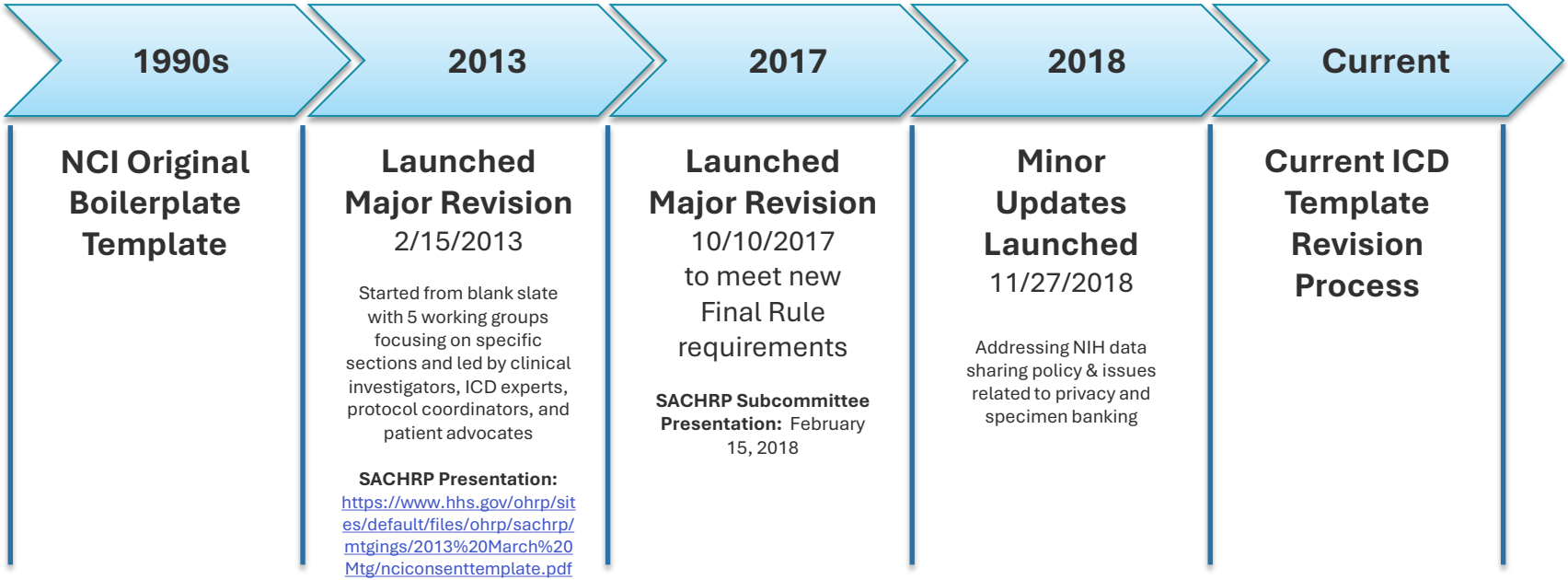
Informed Consent Documents (ICDs): A Challenging Balance



NCI Informed Consent Document Template Development History



Reviewers providing feedback for revisions include individuals at NCI and across HHS with

Patient Advocates	Clinical Research Professionals	Plain Language Experts
Clinicians and Investigators	Ethics Experts	Regulatory Experts

NCI Informed Consent Template Audiences

- Primary audience for template: Researchers & research staff who write and edit informed consent documents (ICD)

  Current template includes:

  - Instructions to ICD authors
  - “Required” text to be used in ICDs
  - “Example” text that can be adapted for a specific trial (per Phase, Intervention Type, etc.)

- Primary audience for trial-specific ICD: Patients & caregivers considering participation
  - Includes required text & adapted text from the template
  - Also supports site staff conducting consent to facilitate overall consent process

Brief Overview of Informed Consent Requirements and Considerations

Overview Crosswalk of General Required Elements for Informed Consent from ICH GCP, 21 CFR 50 (FDA-regulated trials), and 45 CFR 46.116 (Common Rule)

Required Element	ICH GCP	FDA CFR 21	Revised Common Rule
Key Information			X
Trial involves research	X	X	X
Purpose	X	X	X
Probability for random assignment	X		
Procedures	X	X	X
Subject responsibilities	X		
What is experimental	X	X	X
Risks to subject	X	X	X
Risks to fetus/infant	X	X	X
Benefits	X	X	X
Alternative / usual course	X	X	X
Trial-related injury	X	X	X
Compensation / payment	X		
Cost	X	X	X
Voluntariness and Right to Withdrawal	X	X	X

Required Element	ICH GCP	FDA CFR 21	Revised Common Rule
Medical records access	X	X	
Confidentiality of records and if published	X	X	X
New findings & informing	X	X	X
Contacts	X	X	X
Potential for stopping participation	X	X	X
Duration	X	X	X
Number of participants	X	X	X
Unforeseeable risks		X	X
Withdrawal consequences and procedures		X	X
Clinicaltrials.gov language		X	
Identifiable information / specimens			X
Commercial profit			X
Return of research results			X
Whole genome sequencing			X

ICH E6(R2) Good Clinical Practice: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
21 CFR 50: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guide-informed-consent
45 CFR 46: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/revised-common-rule-regulatory-text/index.html#46.116

Overview Crosswalk of General Required Elements for Informed Consent from ICH GCP, 21 CFR 50 (FDA-regulated trials), and 45 CFR 46.116 (Common Rule)

Category	Requirement	ICH GCP	FDA CFR 21	Revised Common Rule
Biospecimens	Types of research			X
	Identifiable information / specimens			X
	Period of time			X
	Unknown future research			X
	Return of results			X
	Contacts			X
Additional Requirements	ICD must have sufficient information but not be lists of isolated facts			X
	Have IRB approval and comply with GCP and ethical principles	X		
	Communication and documentation of any changes	X		
	No coercion	X		X
	No waiving of legal rights or releasing from liability for negligence	X		X
	Provide all information including IRB approval	X		
	Understandability of consent	X		X
	Time for consideration	X		X
	Consent before participation	X		X
	Written documentation of consent	X		X
	Reading the consent to subject unable to read	X		X
	Patient receives a copy of the consent	X		X
	Subject should sign to the degree possible	X		

Modernized Informed Consent Process

- Goal is to modernize the informed consent process by moving toward risk-based, modularized, dynamic forms & procedures

- Informed consent must conform to ICH GCP, 21 CFR 50 (covering FDA-regulated trials) and 45 CFR 46.116 (Common Rule)

- Revised Common Rule sections on consent for biospecimen collection and use along with NCI emphasis on “data sharing” for clinical data & specimens presents new research opportunities, but with challenges on how to best to provide clear/concise consent language

NCI ICD Template: Modularized Approach

- Revised Common Rule **requires** a Key Information section (2-3 pages) to provide a succinct overview of the trial for discussion with patients

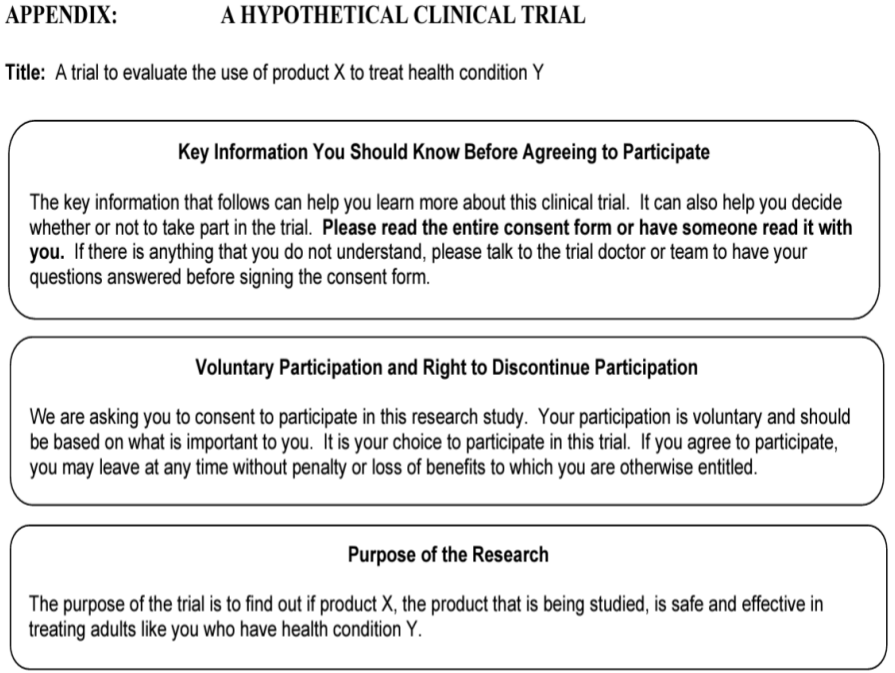
- Patients interested in participating after review of Key Information continue with full consent discussion that complies w/ regulatory requirements

- Need for a site's local context provided by NCI CIRB processes:
  - Only permissible **deletion** for local boilerplate language is reproductive language specific for faith-based institutions
  - Permissible **additions** related to Local Contact information, State & Local laws, and Institutional Policy related to research as allowed in NCI CIRB Quickguide
  - NCI CIRB offers Remote Consent as an option that any site can elect to use

FDA and OHRP Draft Guidance on Key Information

- HHS Office of Human Research Protections (OHRP) & FDA jointly issued draft guidance on "Key Information and Facilitating Understanding in Informed Consent" on March 1, 2024
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/key-information-and-facilitating-understanding-informed-consent-guidance-sponsors-investigators-and

- Proposed guidance, with an FDA proposed rule, would harmonize FDA and Common Rule consent requirements and offer suggestions on approaches to Key Information section



APPENDIX: A HYPOTHETICAL CLINICAL TRIAL

Title: A trial to evaluate the use of product X to treat health condition Y

Key Information You Should Know Before Agreeing to Participate

The key information that follows can help you learn more about this clinical trial. It can also help you decide whether or not to take part in the trial. **Please read the entire consent form or have someone read it with you.** If there is anything that you do not understand, please talk to the trial doctor or team to have your questions answered before signing the consent form.

Voluntary Participation and Right to Discontinue Participation

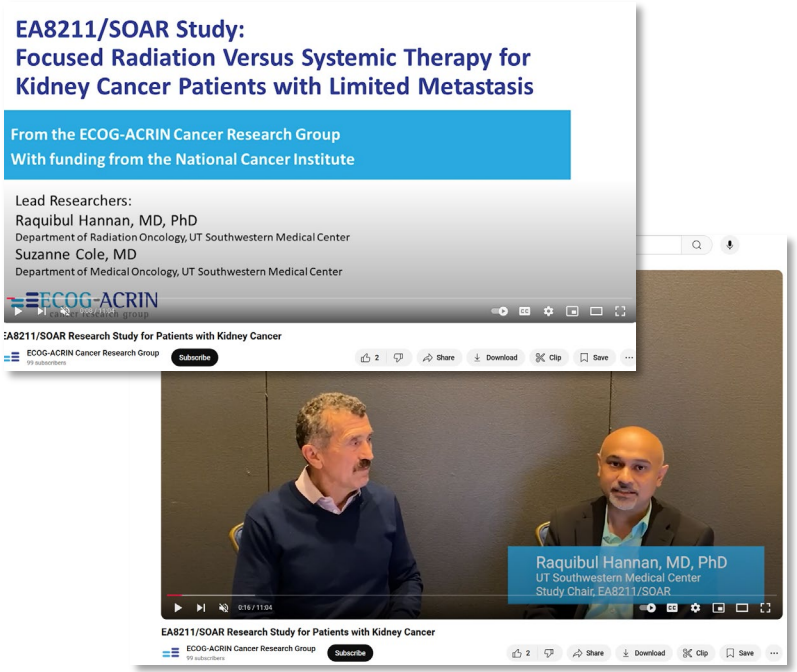
We are asking you to consent to participate in this research study. Your participation is voluntary and should be based on what is important to you. It is your choice to participate in this trial. If you agree to participate, you may leave at any time without penalty or loss of benefits to which you are otherwise entitled.

Purpose of the Research

The purpose of the trial is to find out if product X, the product that is being studied, is safe and effective in treating adults like you who have health condition Y.

Additional Options for Trial-Specific Education

NCI CIRB approves trial-specific patient educational materials to supplement consent discussion



Lead Organizations also provide trial-specific resources for site staff to facilitate discussions

Ongoing ICD Template Revisions

NCI Efforts to Improve the Informed Consent Template

- DCTD/CTEP. with DCP & others at NCI, oversees & periodically revises NCI Template
  - Led by Andrea Denicoff, RN, MS, ANP and Grace Mishkin, PhD, MPH
  - Incorporates input from a wide range of stakeholders to improve clarity
  - Allows response to changing science & research opportunities

- Latest revision is currently underway and includes:
  - Reducing length of Key Information section
  - Streamlining content based on feedback on what areas are most relevant to patients
  - Improving usability of template by putting “example” text in a separate document
  - Streamlining information related to risks of standard of care

- Ongoing efforts to streamline consents based on complexity & risk

ICD Template Length and Example Text

- By streamlining sections as much as possible and moving the “Example Text” out of the main template to a separate document, the template has been shortened from 51 pages to less than 25

- Separating out Example Text will also facilitate making changes with more relevant examples based on changing science and trial designs without requiring an update to the entire template

Proposed Key Information Section Changes to Further Streamline and Emphasize Modularity of the ICD

- Combined 3 short Key Information sections for new beginning of Key Information
- Minor changes to move/consolidation information to improve clarity
- Added a clear start and end to the Key Information section with textboxes

- **Challenge:** Since template is intended for hundreds of trials conducted across thousands of sites, simple or minimal formatting is easiest to implement by the full range of sites when they add their local context.

Potential Change: Streamlining References to Standard of Care Commercial Agent Risks

Excerpts from 6 Pages of SOC Risk Tables in Typical Lung Trial Consent

following current NCI ICD template instructions

Possible Side Effects of Cisplatin (Table Version Date: August 6, 2021)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions
OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Cisplatin, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
RARE, AND SERIOUS
In 100 people receiving Cisplatin, 3 or fewer may have:
• Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness • Seizure

Description of SOC Risks in the Pragmatica-Lung Consent

If you are in Group 1 - (Usual Treatment): You and your doctor will choose a usual treatment that is right for you. Talk with your doctor about the risks and side effects of the specific usual treatment that you would receive. Your doctor will discuss in more detail the risks of the drugs you will be receiving and will let you know how common and serious the side effects are for those drugs. In general, side effects from chemotherapy for lung cancer may include the following:

- Fatigue, mood changes, hair loss, easy bruising and bleeding
- Infection, anemia which may cause tiredness, or may require blood transfusion
- Nausea, vomiting, constipation, diarrhea
- Appetite changes, weight changes, urine and bladder changes and kidney problems
- Mouth, tongue, and throat problems such as sores and pain with swallowing
- Peripheral neuropathy or other nerve problems, such as numbness, tingling, and pain
- Skin and nail changes such as dry skin and color change

You should also talk with your doctor about potential changes in sexual function and fertility problems that might be side effects of the usual treatment you decide on.

Informed Consent Process Improvement: Challenges

- Required elements are drawn from federal regulations & must be adequately addressed at time of consent

- FDA and OHRP released a draft guidance with recommendations for the "Key Information" section,[1] (as required by revised Common Rule 2018) but all required language must still be provided elsewhere in the consent

- Unfortunately, complex trials – especially those that involve additional correlative research and multiple optional studies – require longer and more complicated consent documents

1. Draft Guidance Document: "Key Information and Facilitating Understanding in Informed Consent Guidance for Sponsors, Investigators, and Institutional Review Boards." March 2024. https://www.fda.gov/media/176663/download

Informed Consent: Discussion

Are there other issues you think should be considered as we explore making changes to the standard of care risk list tables?

We appreciate your feedback and suggestions for consideration as the revision continues!