CLINICAL TRIALS TRANSFORMATION INITIATIVE

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Conduct of Clinical Trials: Drugs and Medical Devices

Pamela Tenaerts, MD, MBA
Executive Director
Pamela.Tenaerts@duke.edu

Disclaimer

- The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.
- The presenter is an Employee of Duke University. Salary support comes from pooled membership fees of the Clinical Trials Transformation Initiative and from FDA Cooperative agreement. Is an independent director on the board of TRxAde, Inc and on the Board of the Society of Clinical Trials and sits on the DiMe scientific leadership board.

Agenda:

- Medical Product Development
- Ethical Conduct of Research
  - Good Clinical Practice(GCP - ICH E6)
  - Human Subjects Research Protection (HSRP)
  - Data Monitoring Committees
  - Bioresearch Monitoring (BIMO)
- Clinical Trials Registration & Results Reporting (clinicaltrials.gov)
- Patients Organization’s role medical product development

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Public-Private Partnership
Co-founded by Duke University & FDA

Involves all stakeholders
- Approx. 80+ members
- Participation of 400+ more orgs

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

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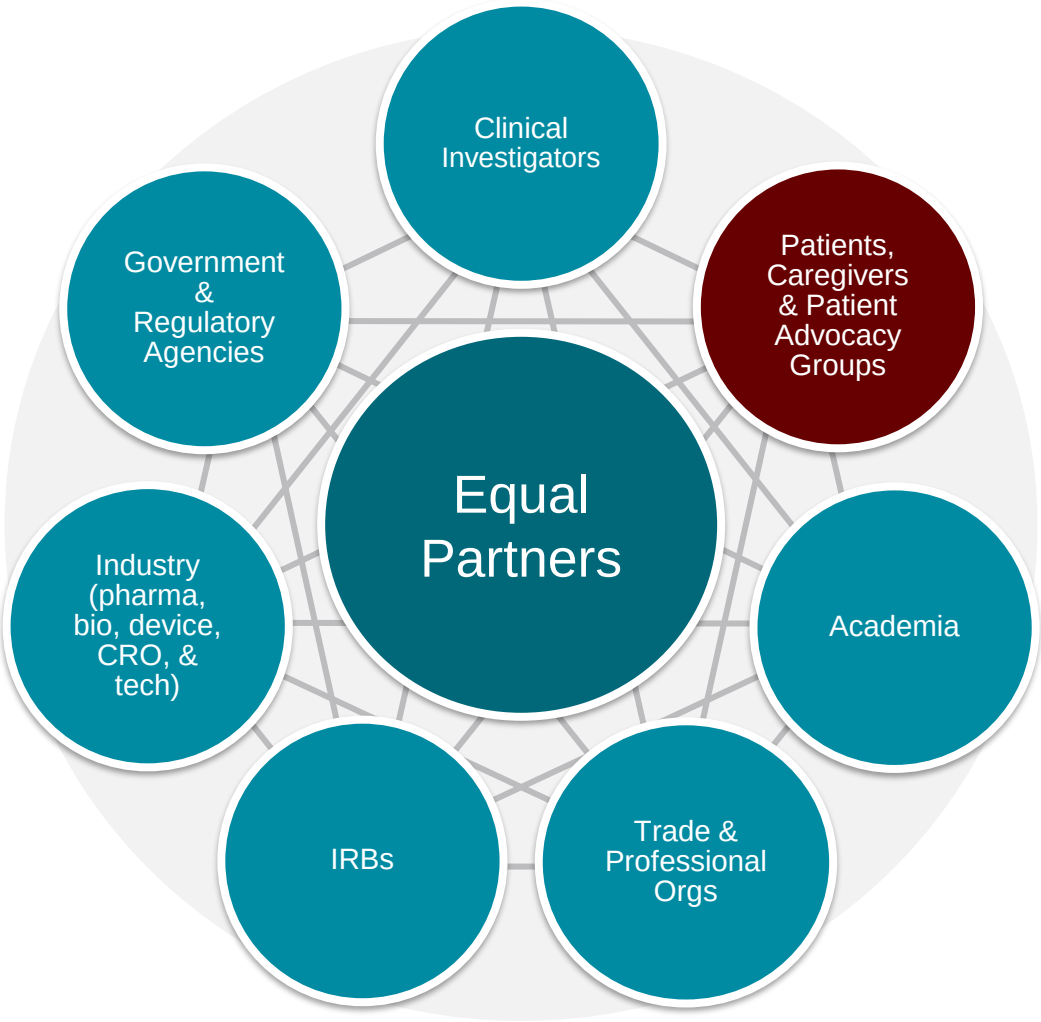
Clinical Trials Stakeholders



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CTTI Membership

*Version: June 26, 2020

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CTTI Activities

Quality

- Quality by Design
- Informing the Update of ICH E6
- Diversity
- Analysis of ClinicalTrials.gov
- Recruitment
- Planning for Pregnancy Testing
- State of Clinical Trials Report
- Monitoring

Patient Engagement

- Patient Group Engagement
- Patient Engagement Collaborative

Investigators & Sites

- Investigator Community
- Investigator Qualification
- Site Metrics

Digital Health Trials

- Novel Endpoints
- Feasibility Studies Database
- Digital Health Technologies
- Decentralized Clinical Trials
- Engaging Patients and Sites

Novel Clinical Trial Designs

- Trials in Health Care Settings
- Real-World Data
- Registry Trials
- Master Protocols
- Antibacterial Drug Development
- Large Simple Trials
- Using FDA Sentinel for Trials

Ethics & Human Research Protection

- Single IRB
- Data Monitoring Committees
- Informed Consent
- Safety Reporting

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Medical Product Development

Patient Group Engagement Across the Clinical Trial Continuum*

Patient groups have potential to enhance the quality and efficiency of clinical trials by providing:

- Financial support for research
- Natural history data
- Input on relevance of research to patients
- Access to translational tools
- Help defining eligibility criteria
- Input on meaningful endpoints & PROs
- Advocacy for policy & funding issues†
- Education to patient community†

- Support to sponsors around key regulatory meetings
- Support preparing submissions for newborn screening for rare diseases
- Informing regulators on benefit-risk†
- Public testimony at regulatory meetings†

Discovery & Preclinical‡ → **Phase 1 - 3** → **Regulatory Review** → **Postapproval**

- Benefit-risk & patient-preference studies
- Protocol design & study feasibility input
- Study recruitment & retention strategy input
- Increased awareness about trials
- Participant feedback on trial experience
- Input on informed consent content & processes
- Peer advocates for participants†
- Clinical trial networks†
- Data and Safety Monitoring Board members†

Phase 1-3 activities and …

- Support interpreting & disseminating study results
- Collaboration on post-marketing studies & surveillance initiatives
- Support developing access strategy & preparing for value or health technology review

**Updated 2018; adapted from Parkinson's Foundation materials | †Patient group activities typically undertaken independently or with partners other than sponsors | ‡Includes early planning for trials*

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Clinical Trials

- Clinical trials are an integral part of new product discovery and development
- Required by Regulatory Authorities (the Food and Drug Administration) before a new product can be brought to the market.

> Research studies in which one or participants are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

https://grants.nih.gov/policy/clinical-trials/definition.htm

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Duration of Development (drugs)

Examples of the Duration and Size of Drugs Successfully Completing Clinical Trials

Drug Name	Treatment for	Years in Clinical Trials	Number of Study Volunteers
Allegra	Seasonal allergy relief	2	3,600
Celebrex	Rheumatoid arthritis	3	13,000
Lipitor	High cholesterol	2.5	20,000
Prilosec	Ulcers, GERO	4	4,000
Viagra	Erectile dysfunction	2.5	3,000
Vibativ	Skin infection	7.2	1,794
Vioxx	Osteoarthritis	4	10,000
Zocor	High cholesterol	2.5	20,000
Zytiga	Prostate cancer	5.3	1,195

Source: CISCRP

Phases of Clinical Trials

- Phase I trials: Researchers test a drug or treatment in a small group of people (20–80) for the first time. The purpose is to study the drug or treatment to learn about safety and identify side effects.
- Phase II trials: The new drug or treatment is given to a larger group of people (100–300) to determine its effectiveness and to further study its safety.
- Phase III trials: The new drug or treatment is given to large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it with standard or similar treatments, and collect information that will allow the new drug or treatment to be used safely.
- Phase IV trials: After a drug is approved by the FDA and made available to the public, researchers track its safety in the general population, seeking more information about a drug or treatment's benefits, and optimal use.

Characteristics of Clinical Trial Phases

	Phase 0 "Exploratory"	Phase I	Phase II	Phase III	Phase IV
Description	First-in-man early trial to determine if drug engages its expected target	Initial safety evaluations, determine safe dosage range, identify common side effects, study toxicity profile of the drug	Begin to explore efficacy while maintaining safety	Final confirmation of safety and efficacy	Any trials conducted after FDA approval of the drug
Number of subjects	10-15 healthy volunteers	20-80 healthy volunteers	100-300 volunteers with the targeted medical condition	1,000-3,000 subjects with the targeted medical condition	Number of subjects depends on trial endpoints
Dose	Single, low dose (<1% of dose calculated to produce a clinical effect)	• Single dose • Single ascending dose • Multiple ascending dose	Multiple dose trials, often conducted against placebo	Multiple dose trials, ascending doses	Variable
Endpoints	Not expected to show clinical effect or significant adverse effects. Helps to choose between competing chemical analogs for further study.	Escalation of dose ends when unacceptable side effects occur; the previous dose is considered the maximum tolerated dose.	Explores clinical effects against the targeted condition, and reveals the less-common side effects	Confirms clinical efficacy of the drug against the targeted condition and evaluates safety and side effects	Confirms clinical efficacy and safety and explores other possible drug uses; may be required as a condition of drug approval
Timing	Can be conducted with prior approval while final IND review is pending	Together with Phase 0 trials, first clinical trials conducted in an IND process	Conducted after report to FDA of results of Phase I trials	Conducted after report to FDA of results of Phase II trials	Conducted after release of the drug by the FDA for marketing

Abbreviations as in Table 3.

Drugs, Devices, and the FDA: Part 1
March 2016 JACC Basic to Translational Science 1(3):170-179
DOI: 10.1016/j.jacbts.2016.03.002

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Ethical conduct of Research
Good Clinical Practice & Human Subjects Research Protection

- Adherence to the principles of good clinical practice (GCP), including human subject research protection (HSRP), is universally recognized as a critical requirement to the ethical conduct of research involving human subjects.
- Participants (vs subjects) in clinical trials
  - An individual who participates in a **clinical trial** either as a recipient of the investigational product(s) or as a control. The term "**subject**" is part of the federal regulation and may be used interchangeably with **participant**

Good Clinical Practice (ICH E6)

- Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects
- The objective of ICH GCP guidance is to provide a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.
- This guidance should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

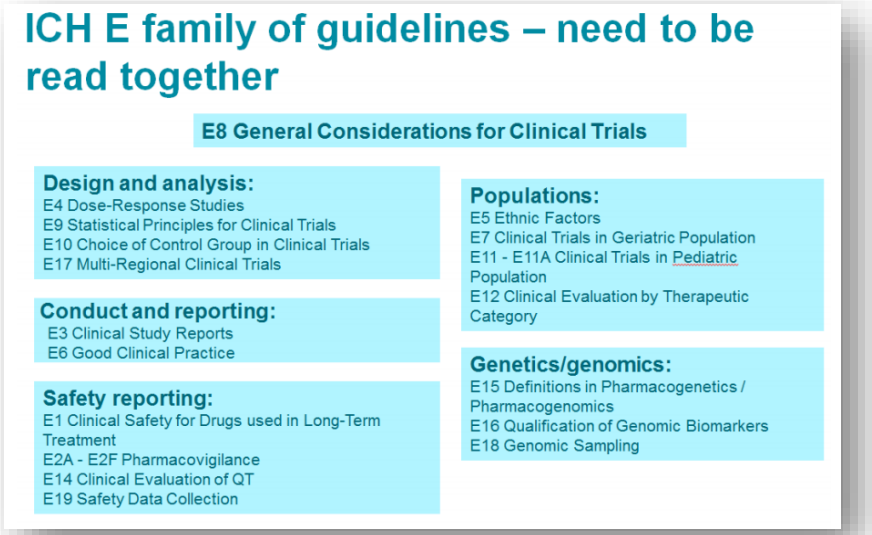
https://www.fda.gov/media/93884/download

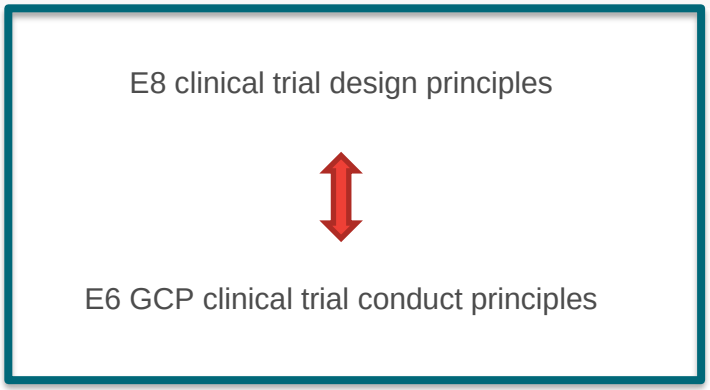
ICH

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- Since 1990, a unique harmonisation effort to:
  - Improve efficiency of **new drug** development and registration process
  - Prevent duplication of clinical trials in humans and minimize use of animal testing ---without compromising safety and effectiveness

ICH E6: A Global Standard for Clinical Trial Conduct

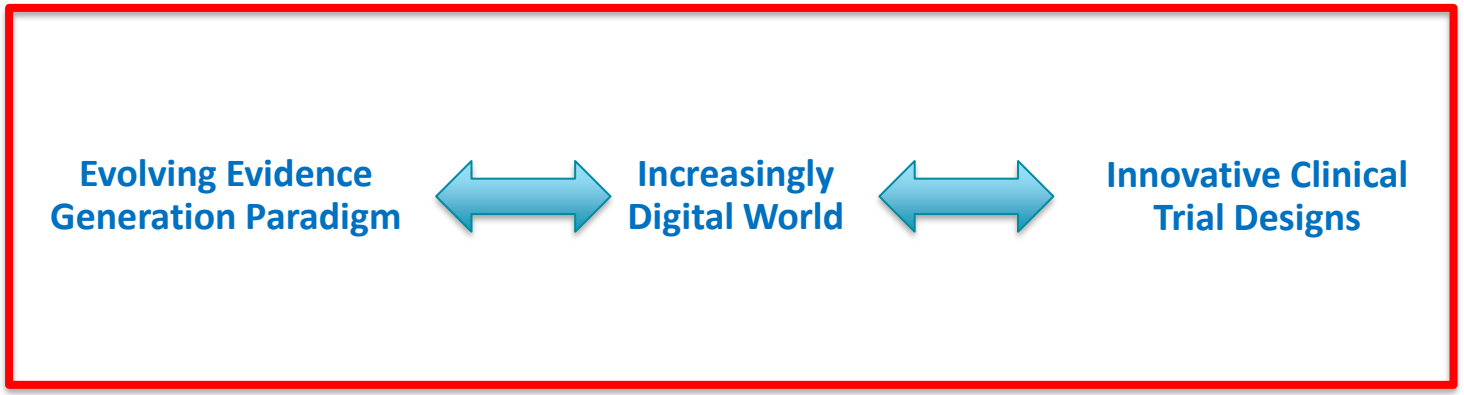
- **E6: Good Clinical Practice (GCP) – finalized in 1996**
  - Describes the responsibilities and expectations of stakeholders in the conduct of clinical trials.
  - GCP covers aspects of monitoring, reporting, and archiving of clinical trials
  - Addenda for essential documents and investigator brochures
- **E6(R2) – finalized in 2016**
  - Addendum to encourage implementation of improved and more efficient approaches to GCP, while continuing to ensure human subject protections
  - Updated standards for electronic records





ICH E6: An Important Global Standard

Global Clinical Trials



Overview of ICH E6(R3) Revisions

- Annex 1 – Interventional Clinical Trials
  - Considers principles as they relate to the use of unapproved or approved drugs in a controlled setting with prospective allocation of treatment to participants and collection of trial data
- Annex 2 – Non-traditional Interventional Clinical Trials
  - Considers principles as they relate to the use of non-traditional clinical trial designs such as pragmatic clinical trials and decentralized clinical trials, as well as those trials that incorporate real-world data sources

Human Subject Protection

Data Monitoring Committees

DMC definitions

- **Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB)** – A group of individuals who review accumulating trial data by treatment group in order to monitor patient safety and efficacy, ensure the validity and integrity of the trial, and make a benefit-risk assessment.
- **External DMC** – An independent group of individuals that conducts these activities outside of the sponsor organization.
- **Internal DMC** – A group of individuals that conducts these activities within the sponsor organization.
- **Data Coordinating Center (DCC)** – A group whose role is to facilitate the collection and quality control of trial data as specified in the protocol
- **Statistical Data Analysis Center (SDAC)** – A group whose role is to prepare statistical analyses of accumulating data, and prepare and present reports of data to the DMC; this group may be within or separate from the organizational structure of the DCC

Data Monitoring committee (DMC)

- DMCs traditionally have been used to monitor masked, randomized, controlled, multicenter trials that evaluate interventions intended to reduce major morbidity or mortality, whether sponsored by industry, government, or other entities.
- Use of DMCs is not dependent entirely on study size or study phase, but rather on the nature and extent of risk to trial participants.
- DMCs add transparency, and their use may enhance the credibility of trials among both patients and clinicians.
- DMCs typically oversee the conduct of a single trial but they are occasionally asked to review multiple related trials.
- The criteria for when a DMC is necessary are not well defined, and may vary substantially depending on the type of sponsor and their perceived need for independent trial monitoring and oversight.

Role of the DMC

- DMCs should be used when there is a need to periodically review the accumulating unmasked safety and efficacy data by treatment group, and advise the trial sponsor on whether to continue, modify, or terminate a trial based on benefit-risk assessment.
- DMC members should be independent of the trial sponsor and should be provided with adequate resources and flexibility to perform their role of assessing benefit-risk (e.g., performing ad hoc analyses as needed, having full access to accumulating unmasked study data).
- The rationale for use of a DMC, and the roles, responsibilities, and operational structure of the DMC, should be addressed in a Charter agreed to by the sponsor and the DMC members prior to patient enrollment.
- The DMC and the SDAC preparing reports for the DMC should have access to all accumulating study data by treatment group beginning at trial initiation. The SDAC should have the flexibility and resources to perform additional analyses that may be requested by the DMC.

DMC Composition

- Clinician(s) with expertise in the medical area under study, and statistician(s) knowledgeable about clinical trials and statistical monitoring plans are essential members of a DMC.
- Bioethicists and patient advocates may make important contributions to some DMCs. Other types of expertise may be needed in some trials (e.g., pharmacology, toxicology, behavioral science).
- DMC members should have experience in clinical research, and preferably clinical trials.

Bioresearch Monitoring (BIMO)

FDA uses Compliance Program Guidance Manuals (CPGM) to direct its field personnel on the conduct of inspectional and investigational activities. The CPGM's described below form the basis of FDA's Bioresearch Monitoring Program. The purpose of each program is to ensure the protection of research subjects and the integrity of data submitted to the agency in support of a marketing application.

- CPGM for Clinical Investigators
- CPGM for Sponsors, Contract Research Organizations, and Monitors
- CPGM for Institutional Review Boards [1.02 MB]

Observations: Common Clinical Investigator (US: 600 OUS: 179)

- Failure to follow the investigational plan; protocol deviations
- Failure to comply with Form FDA 1572 requirements
- Inadequate and/or inaccurate case history records; inadequate study records
- Inadequate accountability for the investigational product
- Inadequate subject protection; informed consent issues
- Safety reporting; failure to report and/or record adverse events
- Failure to comply with 21 CFR part 56 (IRB) requirements.

https://www.fda.gov/media/136797/download

Observations: IRB (US:140)

- Failure to have minutes of IRB meetings in sufficient detail to show attendance at the meeting; vote actions, quorum issues
- Failure to conform to membership criteria listed in 21 CFR 56.107; membership list
- Failure to conduct initial and/or continuing review of research
- Inadequate written procedures for prompt reporting of non-compliance, suspension or termination
- Failure to prepare and maintain documentation of IRB activities; inadequate copies of research proposals and related documents

https://www.fda.gov/media/136797/download

Observations: Sponsor/Monitor/CRO (US: 108 OUS: 5)

- Failure to select qualified investigators and/or monitors, ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan. (General responsibilities of sponsors)
- Failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; accountability for the investigational product.
- Failure to bring non-compliant investigators into compliance

https://www.fda.gov/media/136797/download

Clinical Trials.gov

Deborah A. Zarin, M.D. Director, ClinicalTrials.gov February 2018

Key Clinical Trial Reporting Requirements

Reporting Requirement	ICMJE Policy (Effective in 2005)	FDAAA & Regulations (Effective 2007 & 2017)	Final NIH Policy (Effective 2017)
What	Registration*	Registration & results reporting	Registration & results reporting
Scope	Clinical trials (any)	Applicable clinical trials	Clinical trials (NIH-funded)
Phase	All	Not Phase 1 and device feasibility	All
Intervention Type	All	Drug, biological, & device products regulated by the FDA	All (including behavioral interventions)
Enforcement	Refusal to publish	Criminal proceedings and civil penalties (up to $10,000/day); loss of HHS funding	Withholding/loss of NIH funding

*ICMJE policy also: (1) **expects** compliance with results reporting requirements and (2) **encourages** results reporting for all other trials

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Other Clinical Trial Reporting Policies

- **World Health Organization (WHO)** considers registration to be a “scientific, ethical and moral responsibility” and states that there is an ethical imperative to report results
- **European Union (EU)** requires registration and results reporting of certain European Medicines Agency (EMA)-regulated drug and biologic clinical trials
- **Center for Medicare and Medicaid Services (CMS)** requires NCT Number for coverage of routine costs of qualifying clinical trials
- **U.S. Department of Veterans Affairs (VA)** requires registration and results reporting of clinical trials funded by the VA Office of Research & Development
- **Patient-Centered Outcomes Research Institute (PCORI)** requires registration and results reporting for interventional studies that it funds

ClinicalTrials.gov Reporting Volume

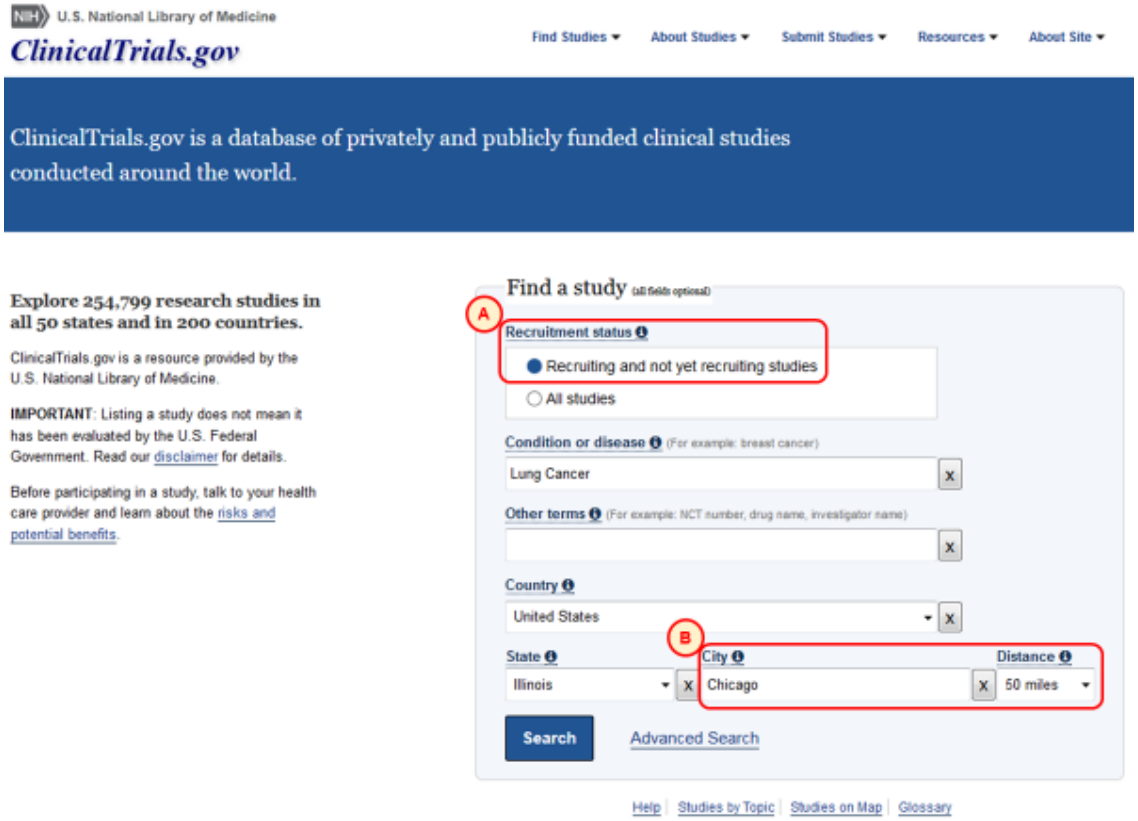
(as of 5 February 2018)

- Registration
  - 265,000 study records (including observational)
  - 600 submissions/week
  - 17,500 data providers (sponsors and investigators)
- Summary Results Reporting
  - 30,000 records with results posted
  - 140 submissions/week
  - 3,000 data providers
- Usage Stats
  - 244M hits per month
  - 171M page views per month
  - 93K unique visitors per day

Homepage - ClinicalTrials.gov Updates

A. Search for all studies or only those that are or will be recruiting participants

B. Search for studies within a certain distance of a city



Search Results - ClinicalTrials.gov Updates

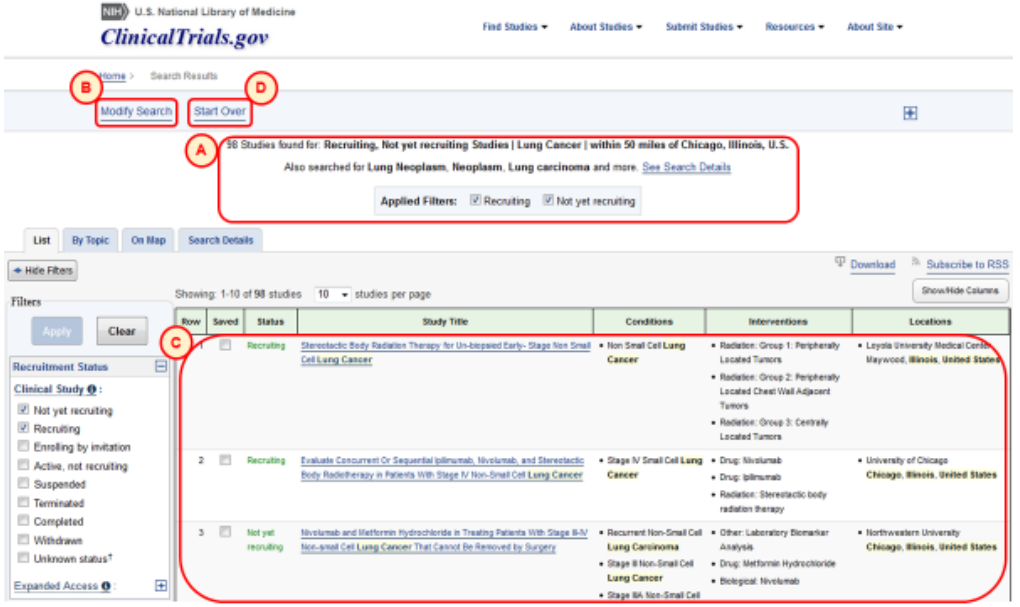
A. Search summary

- Number of study records found meeting criteria
- Synonyms used
- Filters applied

B. Modify search

C. List of study records

D. Start over option

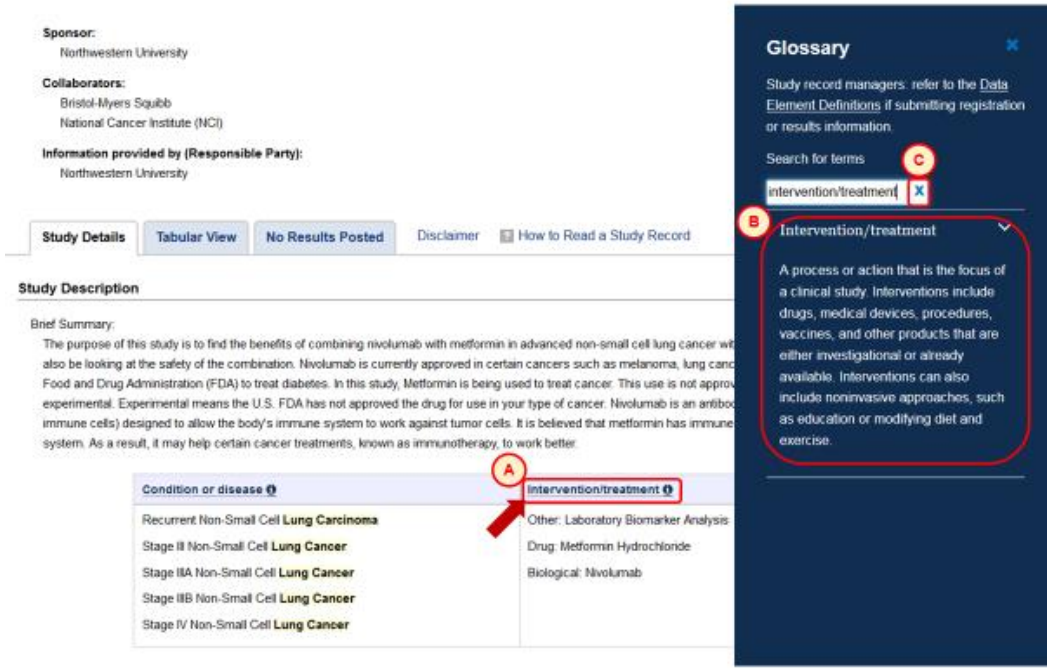


Glossary - ClinicalTrials.gov Updates

A. Icons to help identify when a glossary entry is available

B. Description of term

C. Search box



Patients in product development

Patient Group Engagement Across the Clinical Trial Continuum*

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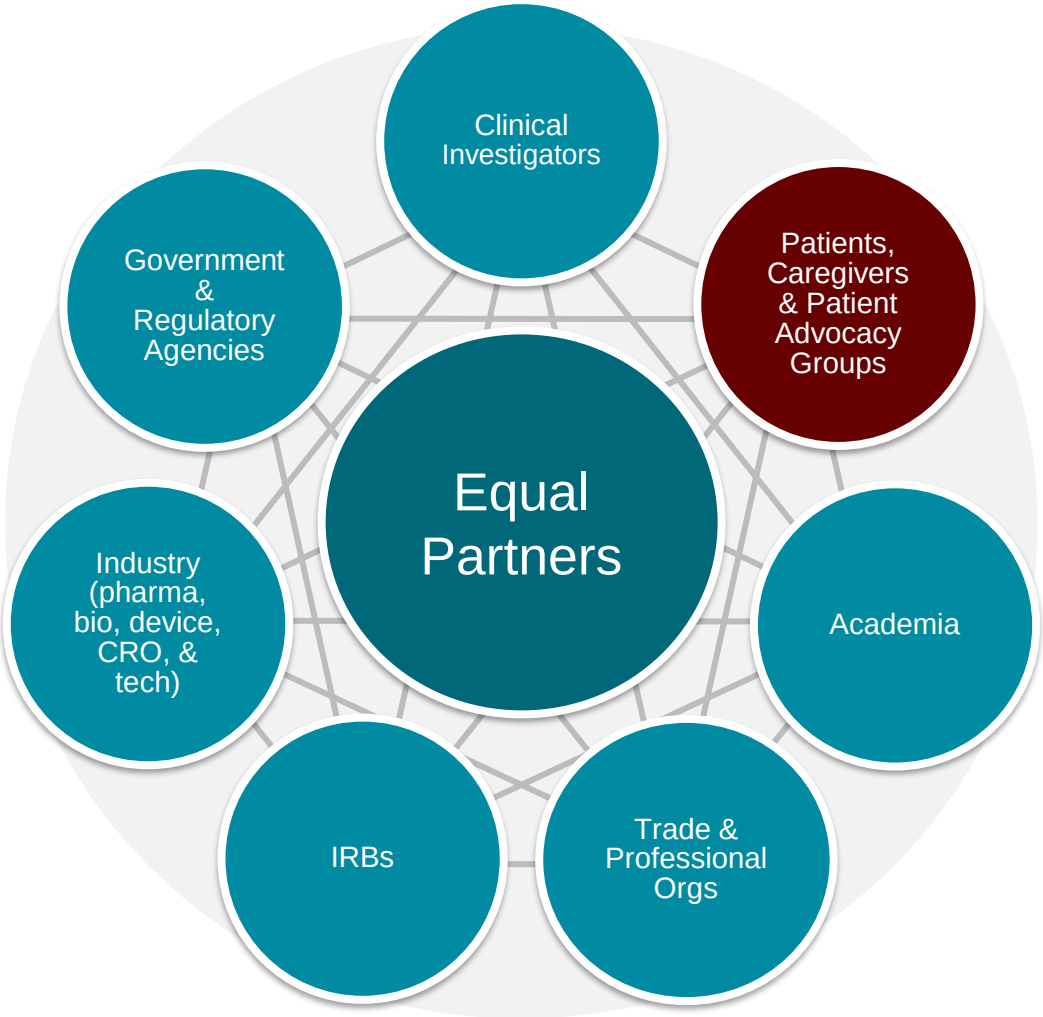

- CDRH/CBER 2019 draft guidance: "FDA believes medical device clinical investigations prospectively designed with input from patient advisors may help to address common challenges."
- ICH E8(R1) 2019 draft: "Clinical study design is best informed by input from a broad range of stakeholders, including patients and treating physicians."

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Patient Engagement at CTTI

Normed (no question) inclusion of patients as equal partners into every aspect of clinical trial (reform)

- Full integration into the Steering Committee in 2015
- Individual patients reimbursed for time on CTTI activities including projects

Patient/caregivers on project teams have played critical role in shaping projects

Co-founded Patient Engagement Collaborative with FDA

Almost all CTTI recommendations to date include a recommendation to involve all stakeholders, particularly patients, in the process

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CTTI Resources Developed for Engaging Patient Groups in Clinical Trials

Identifying Best Practices	Describing Value & Impact
▶ Recommendations: Effective Engagement with Patient Groups Around Clinical Trials ▶ Implementation resources • Patient Group Organizational Expertise and Assets Evaluation • Assessment of Patient Group Internal Aspects • Assessment of Patient Group External Relationships	▶ Economic model to quantify the financial value of patient engagement ▶ Online prioritization tool for identifying high-value engagement opportunities

All resources freely available at
https://www.ctti-clinicaltrials.org/projects/patient-groups-clinical-trials

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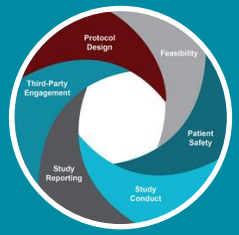
CTTI Patient Engagement Resources

- **Economic Model:**
  https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/new_ctti_resource_26feb2020_final.pdf
- **Prioritization Web Tool:**
  https://prioritizationtool.ctti-clinicaltrials.org/
- **Recommendations: Realizing the Value of Effective Patient Group Engagement**
  https://www.ctti-clinicaltrials.org/projects/patient-groups-clinical-trials



Quality by Design (QbD)

Mobile Clinical Trials

Patient Engagement Collaborative

Additional Resources for Engaging Patients in Clinical Trials

Patient Engagement Collaborative

Patient Engagement Collaborative (PEC) brings together diverse representatives from the patient community to meet with the FDA several times a year and discuss how to achieve more meaningful patient engagement in medical product development and other regulatory discussions. The PEC, launched in December 2017, is a joint effort of CTTI and the FDA.

FDA U.S. FOOD & DRUG ADMINISTRATION

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THANK YOU.

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Webinar recording & slides available at:

https://www.ctti-clinicaltrials.org/briefing-room/webinars

www.ctti-clinicaltrials.org

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