National Cancer Institute's Implementation of the NIH Clinical Trials Stewardship Policies

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NIH NATIONAL CANCER INSTITUTE

November 1, 2017

PRESENTATION OUTLINE

PART 1. NIH STEWARDSHIP OVERVIEW

- NIH STEWARDSHIP GOALS
- HUMAN SUBJECTS RESEARCH
- NIH-FUNDED CLINICAL TRIALS

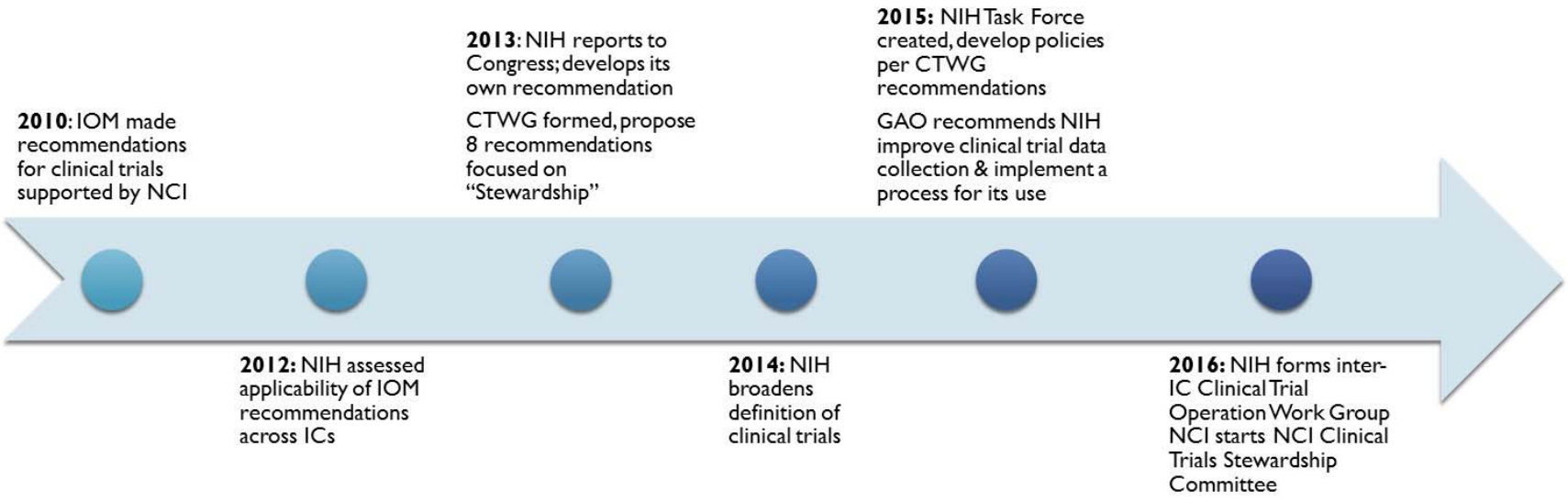
PART 2. NCI CLINICAL TRIALS STEWARDSHIP ACTIVITIES

- IMPLEMENTATION & COMMUNICATION

PART 1. NATIONAL INSTITUTES OF HEALTH

REFORMS AND INITIATIVES

NIH PROPOSES A "STEWARDSHIP" APPROACH



2016: NIH ANNOUNCES 1ST SERIES OF REFORMS & INITIATIVES

Opinion

VIEWPOINT

Toward a New Era of Trust and Transparency in Clinical Trials

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Supplemental content

Clinical trials are the most publicly visible component of the biomedical research enterprise, from the potential human application of novel laboratory findings to the generation of robust evidence about treatments or preventive interventions in routine clinical care. These trials are also the point at which biomedical research most directly engages human participants—dedicated volunteers who trust investigators to uphold the highest standards of scientific rigor and ethical oversight. While clinical trials have evolved and improved over time—producing impressive advances in diagnosis, treatment, and prevention—there are still major challenges. Therefore, fundamental changes are needed to reflect science and society's movement to increase efficiency, accountability, and transparency in clinical research.

As the largest public funder of clinical trials in the United States, currently investing more than $3 billion each year, the National Institutes of Health (NIH) takes its stewardship of the nation's clinical trial enterprise very seriously. Therefore, NIH must ensure that supported trials investigate a mission-relevant question that is of high priority, do not needlessly duplicate previously conducted trials (in contrast to providing needed replication), and have the highest likelihood to advance knowledge and improve health. To achieve this goal, a number of challenges in the design, efficiency, and reporting of clinical trials need to be addressed.[1,2] For example, too often clinical trials are overly complex, have small sample sizes, rely on surrogate end points that lack clinical relevance, have unrealistic accrual rates, and have inadequate budgets. Of particular concern is the existence of trials from which the results are never published or data submitted to a public database.[3,4]

Therefore, the NIH has launched a multifaceted effort to improve the quality and efficiency of clinical trials, an effort that is focused on a variety of key points along the "lifespan" of a clinical trial (eFigure in the Supplement). These initiatives will reengineer the process by which clinical investigators develop ideas for new trials, how NIH reviews and selects clinical trials for support and oversees the progress of the research, and how results and aggregate data are shared broadly and rapidly. Specifically, these changes are aimed at enhancing the application and award processes, increasing NIH's ability to assess the merits and feasibility of clinical trial applications, improving oversight and transparency, and increasing the sharing of clinical trial results. In combination, these initiatives are intended to ensure rigor and efficiency in the US clinical trial enterprise.

As a crucial first step, NIH will require Good Clinical Practice (GCP) training for investigators and NIH staff responsible for conducting or overseeing clinical trials. The aim is to help ensure that all involved in the clinical trial enterprise have the appropriate knowledge about the design, conduct, monitoring, recording, analysis, and reporting of clinical trials. While GCP training on its own may not be sufficient, it provides a consistent and high-quality standard.

Another important change at the beginning of the clinical trial lifecycle is a new NIH policy that will require all applications for clinical trials to be submitted in response to clinical trial–specific Funding Opportunity Announcements (FOAs). This will mean that applications including one or more clinical trials will no longer be accepted in response to parent funding announcements, which are broad FOAs that allow researchers to submit investigator-initiated applications without specific elements appropriate to describe and evaluate a trial. Under this policy, NIH trial applications will need to contain specific information about protocols and other information necessary for effective peer and programmatic review. In addition, clinical trial–specific FOAs will include review criteria that focus on the rationale, design, and operational and analysis plans, all of which will inform assessments of proposed studies.

Peer review of NIH clinical trial applications must be conducted by study sections with appropriate expertise, such as clinical trialists, biostatisticians, and pharmacologists, as well as the basic science experts needed to evaluate the scientific rigor of relevant preclinical data provided. The advisory councils of NIH's institutes and centers (ICs) also will be responsible for ensuring that clinical trials supported by their respective ICs address these important priorities. After funding decisions have been made, terms specific to clinical trial research will be incorporated into Notices of Award to remind awardees of their responsibilities, including timely sharing of research results.

Inconsistent information submitted to the NIH for clinical trial applications and to the US Food and Drug Administration (FDA) under the investigational new drug (IND) application process has long been recognized as a source of delays and inefficiencies. To assist NIH-funded investigators to plan their studies in a way that is also consistent with the FDA IND process, the NIH is encouraging the use of a clinical trial protocol template that was developed through a collaboration between NIH and FDA[5] and that meets International Council for Harmonisation (ICH) E6 Good Clinical Practice Guidance.[6] Use of the protocol template will help ensure that investigators prepare protocols that contain all the information necessary to enable efficient and timely review by institutional review boards (IRBs) and to be in compliance with FDA IND application regulations.

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Hudson KL, Lauer MS, Collins FS..
JAMA.2016;316(13):1353–1354.

ADDRESSING CHALLENGES IN DESIGN, EFFICIENCY, AND REPORTING OF CLINICAL TRIALS

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Trial Reporting in ClinicalTrials.gov — The Final Rule

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H., and Sarah Carr, B.A.

Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA) expanded the legal mandate for sponsors and others responsible for certain clinical trials of FDA-regulated drug, biologic, and device products to register their studies and report summary results information to ClinicalTrials.gov,[1] which is managed by the National Library of Medicine at the National Institutes of Health (NIH). The statute expanded registration requirements and provided a legally defined timeline with specific requirements for the systematic reporting of summary trial results. Although statutory components took effect before 2010, the FDAAA directed the Department of Health and Human Services (HHS) to issue regulations regarding certain statutory provisions and to consider possible expansion of the requirements through rulemaking.

The registry currently has more than 224,000 study records, 23,000 of which display results information. Compliance with the results-reporting requirements, however, has been low across many sectors of the clinical research enterprise.[2] We believe this low compliance to be due, in part, to the ambiguity of some statutory requirements. The details provided in the final rule should help increase accountability within the clinical research enterprise; going forward, investigators, sponsors, and the general public will be better able to evaluate what information is required to be submitted and, in general, whether compliance has been achieved.

After issuing a Notice of Proposed Rulemaking (NPRM) in November 2014,[3,4] HHS received nearly 900 comments from individuals and organizations, including companies, trade associations, academic institutions, patient advocacy groups, and members of the general public.[5] After careful consideration of these comments, HHS developed the final rule, which was made publicly available on September 16, 2016. Simultaneously, the NIH issued a complementary final policy, under which NIH-funded awardees and investigators will be expected to submit registration and results information for all NIH-funded clinical trials, whether or not the trials are covered by the FDAAA requirements.[6]

Here, we summarize and highlight key points about the final rule (see box).

BACKGROUND

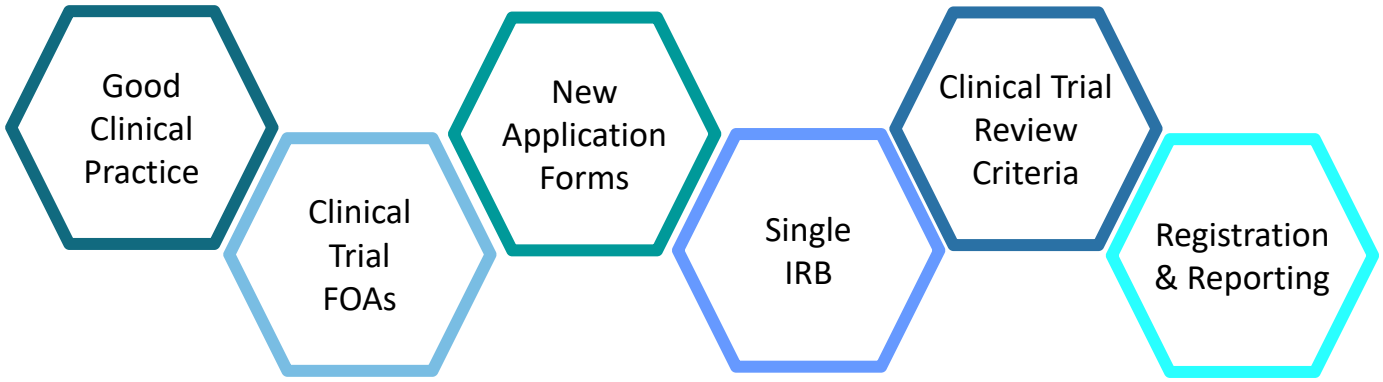
The FDAAA established legal requirements for sponsors and designated principal investigators (i.e., responsible parties) to report specified clinical trial information for certain applicable clinical trials to ClinicalTrials.gov. In addition to registration, the statute established a system and mandate for reporting summary results information within certain time frames, independent of decisions about journal publication. Under the statute, responsible parties, including, for example, grantee institutions, could be held accountable for noncompliance, with the potential for substantial civil monetary penalties, the withholding of grant funding from HHS agencies, and criminal proceedings.

The goals of the final rule are to clarify the requirements for the regulated community, interpret ambiguous key statutory provisions, and make decisions about additional reporting requirements necessary to further the goals of the statute. As a result, after a period of education and outreach to inform the regulated community of its obligations and ways of fulfilling them, the public will be better able to determine from the ClinicalTrials.gov website (https://clinicaltrials.gov) which trials are subject to the rule; whether and when results information is due; in general, whether there is compliance with the requirements; and whether certain enforcement actions have been taken.

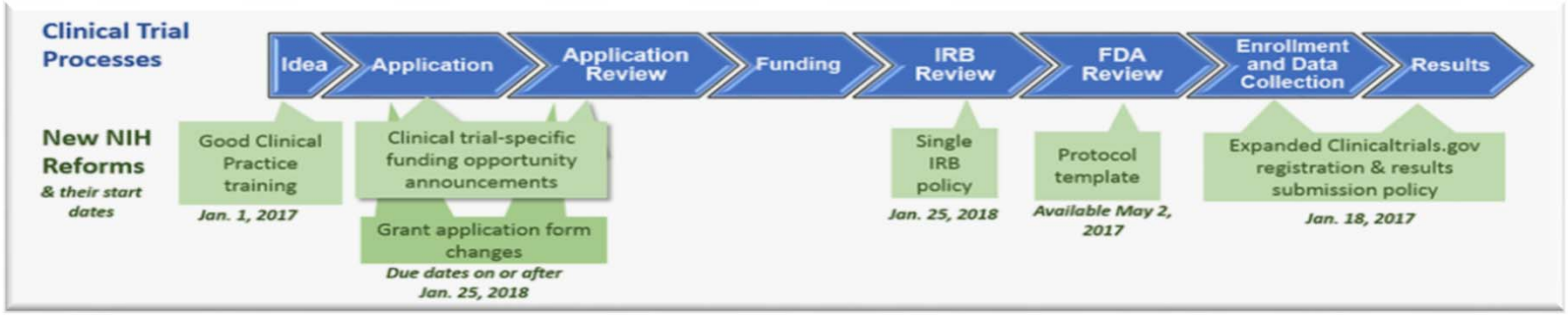
Registration requirements established under

Deborah A. Zarin, M.D., Tony Tse, Ph.D., *et. al.,*
N Engl J Med 2016; 375:1998-2004 November 17, 2016

NIH POLICY CHANGES TO ENHANCE STEWARDSHIP



NIH POLICY CHANGES THROUGHOUT THE CLINICAL TRIAL LIFE CYCLE



Ensure Public Trust

- ✓Scientific Rigor
- ✓Transparency
- ✓Ethical Oversight

POLICIES FOR ***ALL*** RESEARCH INVOLVING HUMAN PARTICIPANTS

- ✓ Use of a single Institutional Review Board (IRB) for multi-site studies
- ✓ New forms to collect human subjects information

- NEW PHS HUMAN SUBJECTS AND CLINICAL TRIAL FORM
- FORMS E APPLICATION PACKAGE
- AVAILABLE NOW

SINGLE INSTITUTIONAL REVIEW BOARD (sIRB)

NOT-OD-16-094: All domestic multi-site studies will use sIRB for ethical review required of non-exempt humans subjects research protocols

Must include a plan that describes:

- The use of a sIRB selected to serve as the IRB of record
- How communications between sites and sIRB will be handled

Standardized agreements have been developed that allow institutions to rely on a sIRB

- NCATS Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Platform

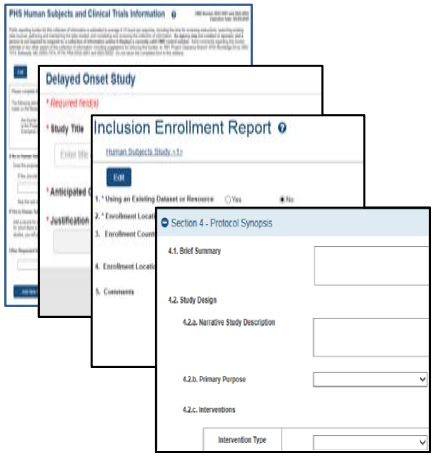
There are exceptions…

New Application Forms
January 25, 2018

CHANGES TO THE APPLICATION PACKAGE

(NOT-OD-17-062: FORMS-E Application Guide & Package)

PHS Human Subjects and Clinical Trials Information Form



- Consolidates information from multiple forms
- Incorporates structured data fields
- Collects human subjects, inclusion enrollment, and clinical trial information at the study-level
  (e.g., Protocol Synopsis, Statistical Plan,)
- Includes a Clinical Trials Questionnaire

https://grants.nih.gov/policy/clinical-trials/new-human-subject-clinical-trial-info-form.htm

New Application Form January 25, 2018

CLINICAL TRIAL QUESTIONNAIRE

Does the study…

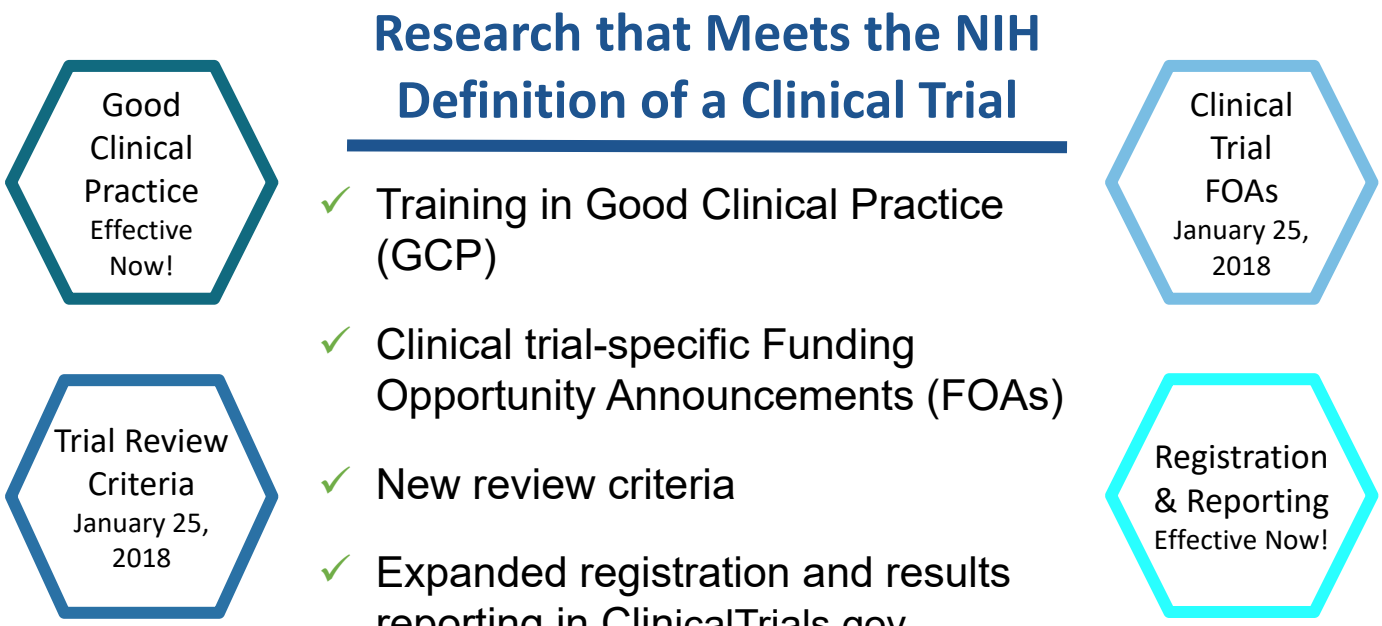
1. Involve one or more human subjects?
2. Prospectively assign human subject(s) to intervention(s)?
3. Evaluate the effect of intervention(s) on the human subject(s)?
4. Have a health-related biomedical or behavioral outcome?

If "yes" to ALL – its a clinical trial

NOTE:

- Select right NIH FOA
- Write research strategy and human subjects sections
- Comply with appropriate policies

NIH POLICIES CHANGES FOR CLINICAL TRIALS



ICH – GOOD CLINICAL PRACTICE TRAINING

Who:	All NIH-funded investigators and NCI staff involved in the *conduct, oversight or management* of clinical trials
What:	Both are expected to receive Good Clinical Practice training
Why:	To assure the safety, integrity, and quality of clinical trials
How:	Through a class or course, academic training program, or certification from a recognized clinical research professional organization (NIAID, NIDA, and CITI courses available)

Clinical Trial-Specific Funding Opportunity Announcements

NOT-OD-16-147: All clinical trial applications **MUST** be submitted to an FOA that allows clinical trials

- Clinical Trial - Not Allowed
- Clinical Trial - Optional
- Clinical Trial – Required
- No Independent Clinical Trial – K grants

Trial Review Criteria January 25, 2018

REVIEW CRITERIA FOR CLINICAL TRIALS

Clinical Trial FOAs January 25, 2018

NOT-OD-17-118: FOAs that accept clinical trials will include new review criteria

Scored Review Criteria

- ✓ Significance
- ✓ Investigator
- ✓ Innovation
- ✓ Approach
- ✓ Environment

Additional Review Criteria

- ✓ Study Timeline

Registration & Reporting

Effective Now!

Dissemination of NIH-Funded Clinical Trial Information

NOT-OD-16-149

Who: All investigators conducting clinical trials funded in whole or in part by the NIH regardless of trial phase

What: Sponsors need to register* and report results** of trials in ClinicalTrials.gov

Why: Increase the availability of information about clinical trials and their results to the public in a timely manner

*within 21 days of 1st patient enrollment
**no later than 1 year after trial's primary completion date

PART 2. NATIONAL CANCER INSTITUTE'S STEWARDSHIP ACTIVITIES

NCI STEWARDSHIP GOAL

In 2016, NCI launched an institute-wide effort to achieve:

"Effective oversight and management across multiple NCI Divisions, Offices, and Centers for ensuring quality of the clinical trial, safety of research participants, reliability of data, and appropriate stewardship of funds."

IMPLEMENTATION PLANNING GROUPS & ACTIVITIES

(Help to work through implementation)

NIH CLINICAL TRIALS OPERATION WORK GROUP (CTOW)

- Central point of contact and communication for NIH Policies
- Help OER work through implementation issues (e.g., Training on FOA writing)

NCI'S CLINICAL TRIALS STEWARDSHIP COMMITTEE (NCTSC)

- Consists of representatives across NCI
- Guides the development of NCI's specific Clinical Trials Stewardship Initiative
- Creates a unified set of Standard Operating Procedures for oversight

NCI'S OFFICE OF COMMUNICATION AND PUBLIC LIAISON (OCPL)

- Tracking and communicating NIH updates to NCI staff
- Outreach to the oncology scientific community
- Establishing new employee orientation materials

CRUCIAL 1st STEP: DEVELOPING NCI-SPECIFIC FOAS

(34 Clinical Trial Allowed FOAs)

NCI IS NOT PARTICIPATING IN NIH CLINICAL TRIAL-REQUIRED PARENT R01 & R21

FOA	NCI–*Specific* CLINICAL TRIAL (CT) FOA
New Investigator-initiated Clinical Trials (R01)	Yes: CT Required DCTD & DCCPS-DCP
NCI Clinical and Translational Exploratory/Developmental Studies (R21)	Yes: Reissue as CT Optional
NCI Small Grants Program for Cancer Research (R03)	Yes: Reissue as CT Optional
NCI Program Project Applications (P01)	Yes: Reissue as CT Optional
NCI Specialized Programs of Research Excellence (P50)	Yes: Reissue as CT Required

NCTSC NEXT STEP: BETA TESTING TOOLS USED BY NCI STAFF TO MONITOR NCI-FUNDED TRIALS

FOCUS: UNIFYING PROGRAM OFFICIER AND GRANTS MANAGEMENT REVIEWS OF PROGRESS REPORTS:

METHOD: Utilizes a risk-based approach to review and monitoring of trials

PROCEDURE:

1. Identify resource risk elements associated with the intervention, study design, trial features, readiness for activation, etc.
2. Resource risk classification determines the frequency in reporting progress to NCI
3. Create a Clinical Trial Management Plan based on resource risk classification

OCPL EFFORTS: DEVELOPING RESOURCES FOR RESEARCHERS

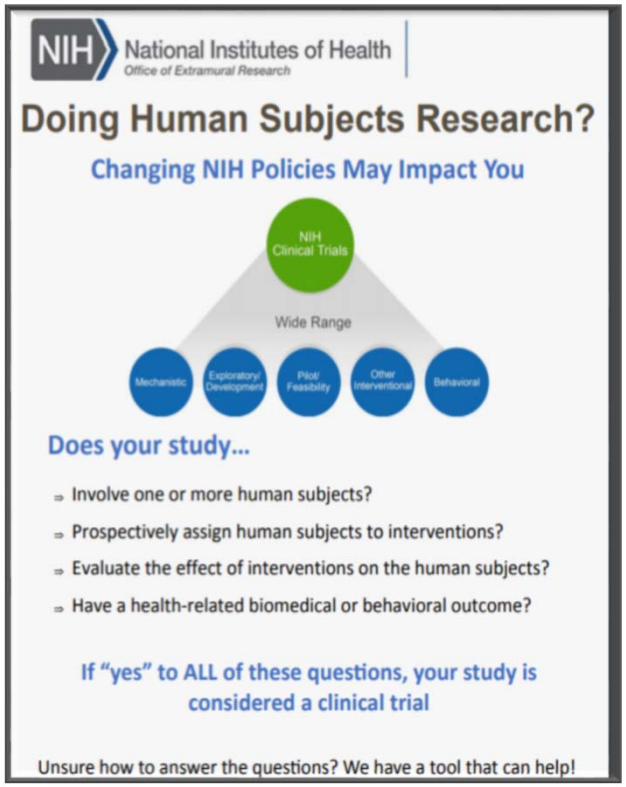
August 11, 2017

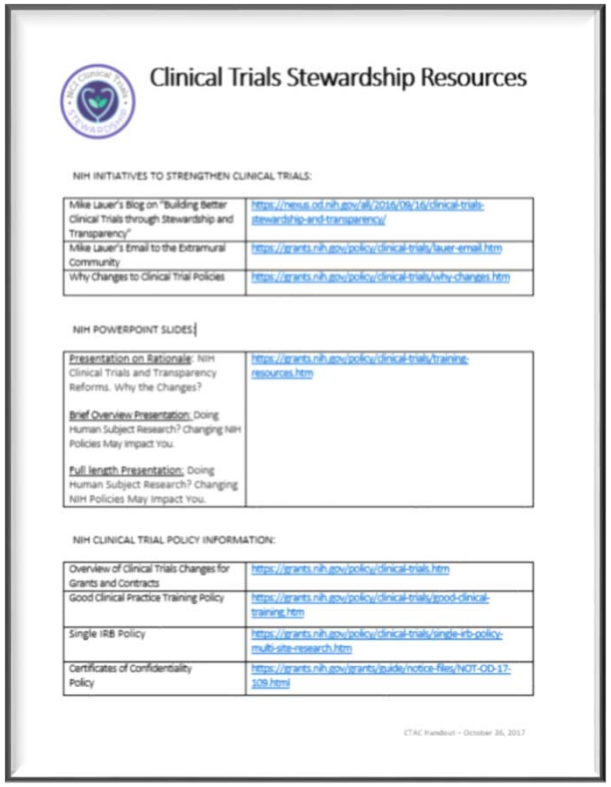
- NIH OER notified all grantees by email
- Provided web page resource: Clinical Trial Requirements for NIH Grantees and Contractors web page
- NIH resource for more info: https://grants.nih.gov/policy/clinical-trials.htm

Mid-November 2017

- NCI Divisions, Offices and Centers will notify NCI grantees by email along with the broader community (advocates and other organizations)
- Will provide an NCI-specific web page resource
- Grantees can contact their PDs, etc.

ADDITIONAL MATERIALS





Clinical Trials Stewardship Resources

NIH INITIATIVES TO STRENGTHEN CLINICAL TRIALS:

Mike Lauer's Blog on "Building Better Clinical Trials through Stewardship and Transparency"	https://nexus.od.nih.gov/all/2016/09/16/clinical-trials-stewardship-and-transparency/
Mike Lauer's Email to the Extramural Community	https://grants.nih.gov/policy/clinical-trials/lauer-email.htm
Why Changes to Clinical Trial Policies	https://grants.nih.gov/policy/clinical-trials/why-changes.htm

NIH POWERPOINT SLIDES:

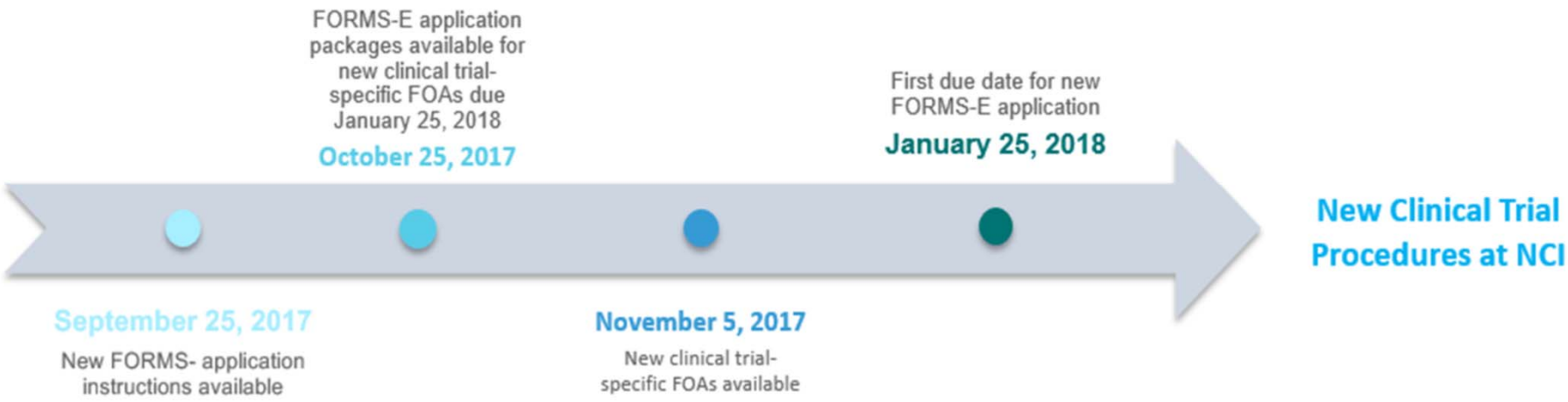
Presentation on Rationale: NIH Clinical Trials and Transparency Reforms. Why the Changes? Brief Overview Presentation: Doing Human Subject Research? Changing NIH Policies May Impact You. Full length Presentation: Doing Human Subject Research? Changing NIH Policies May Impact You.	https://grants.nih.gov/policy/clinical-trials/training-resources.htm

NIH CLINICAL TRIAL POLICY INFORMATION:

Overview of Clinical Trials Changes for Grants and Contracts	https://grants.nih.gov/policy/clinical-trials.htm
Good Clinical Practice Training Policy	https://grants.nih.gov/policy/clinical-trials/good-clinical-training.htm
Single IRB Policy	https://grants.nih.gov/policy/clinical-trials/single-irb-policy-multi-site-research.htm
Certificates of Confidentiality Policy	https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html

CTAC Handout – October 26, 2017

KEY DATES TO REMEMBER



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NCI CLINICAL TRIALS STEWARDSHIP COMMITTEE

DCCPS: Stephanie Land, Kathleen Castro, Wynne Norton

DCP: Ann O'Mara, Linda Parreco, Leslie Ford

DCTD: Roy Wu, Vikram Devgan, Jan Casadei, James Zwiebel, Peter Ujhazy, Rosemary Wong, Dan Xi, Mostafa Nokta, Rebecca Huppi, Eileen Resnick, Karen Said

DEA: Chris Hatch, Shamala Srinivas

CCCT: LeeAnn Jensen, Gisele Sarosy

GMO: Crystal Wolfrey

SBIR/STTR: Andrew Kurtz

OA: Marla Jacobson, Donna Perry-Lalley, MaryAnne Golling

OCPL: Rhonda DeJoice, LaTonya Kittles, Kelly Lawhead, Sara Johnson

Emmes: Chris Williams

THANK YOU FOR YOUR ATTENTION

Questions?

NATIONAL CANCER INSTITUTE

www.cancer.gov

www.cancer.gov/espanol