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Restructuring the National Cancer Clinical Trials and Translational Research Enterprise

CTWG Informatics Initiatives Implementation Update to CTAC

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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CTWG and Related Clinical Trials Initiatives

- Establish a comprehensive database containing regularly-updated information on all NCI-funded clinical trials *(Doroshow)*
- Promote establishment of national clinical trial information technology infrastructures that are fully interoperable with NCI's cancer Biomedical Informatics Grid *(Speakman)*
- Achieve industry and FDA concurrence on standard Case Report Forms incorporating Common Data Elements *(Speakman)*
- Develop a credentialing system for investigators and sites *(Speakman)*
- Procurement of an enterprise-wide clinical data management system *(Speakman)*

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Rationale: Clinical Trials Reporting Program

- NCI has no electronic database for more than half of its clinical trials portfolio (> 20,000 patients accrued per year)
  - R01s, R21s, P01s, SPOREs etc.
  - Institutionally-supported using CCSG resources
- Currently available databases do not allow NCI and the broader cancer community to:
  - Identify toxicity trends for public safety,
  - Manage portfolio accountably by monitoring accrual, identifying gaps and duplicative studies
  - Effectively prioritize clinical trials

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CTWG Goals for Establishment of CTRP

- ***"Create a comprehensive database containing information on all NCI-funded clinical trials to facilitate better planning and management across clinical trial venues"***
- ***"Create, in partnership with the extramural cancer research community, a national cancer clinical trials information technology infrastructure fully interoperable with NCI's cancer Bioinformatics Grid to improve cost effectiveness and comparability of results across trials and sites"***
- **Predates enactment of FDA amendment act by >2 yrs**

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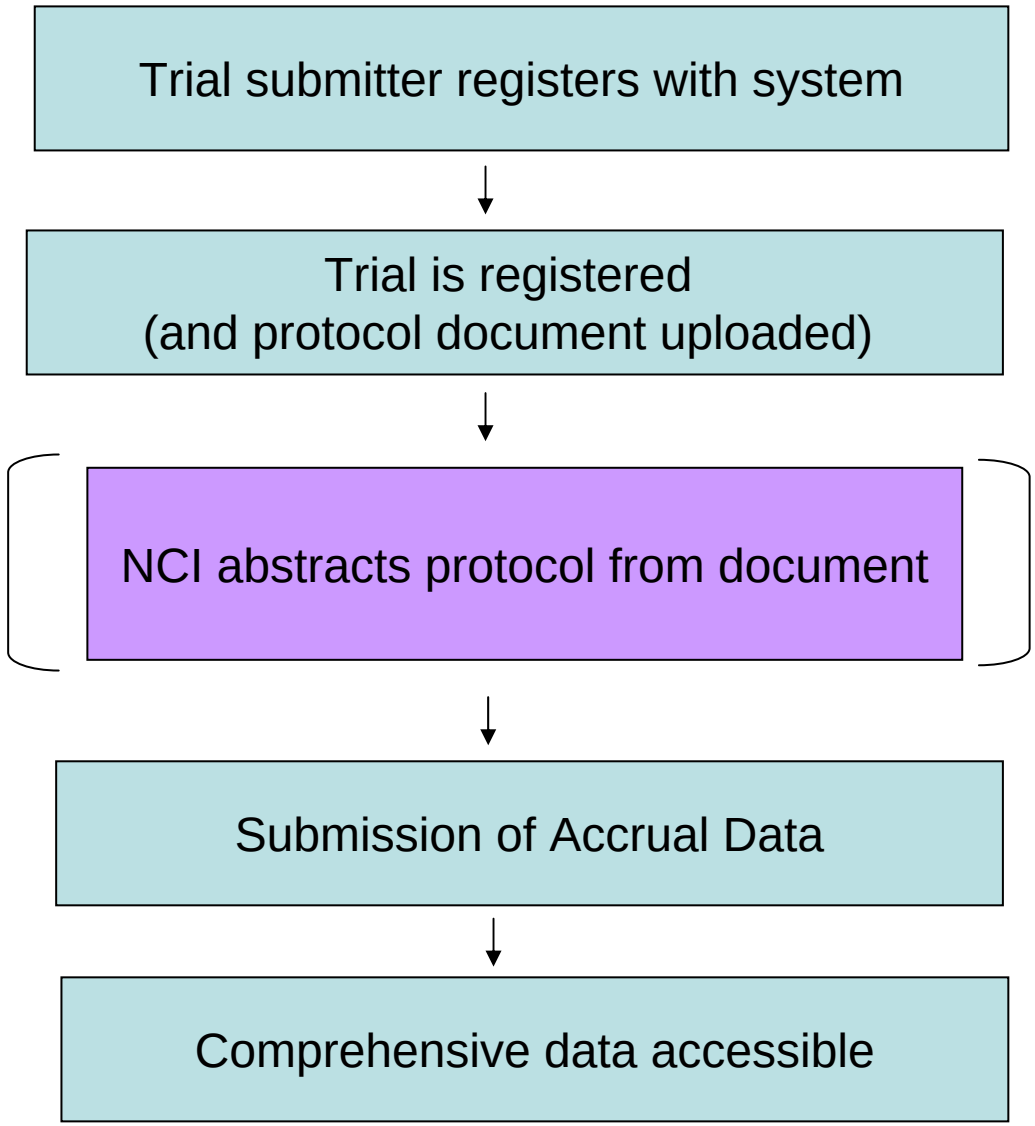
CTRP Database



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FDA Amendment Act and NIH policy

- FDA Amendment Act (FDAAA) of 2007
  - Requires registration of all applicable trials (Phase II/III) with ClinicalTrials.gov
  - Sets rules for determining "Responsible Party" for this activity
  - Penalties for non-registration include large fines and withdrawal of NIH funding
  - Substantive outcomes reporting requirements
  - NIH policy: It is no longer permissible for NIH institutes to register trials on behalf of Responsible Parties (*e.g.*, via any NCI system)
- NCI is not in control of these requirements
- Establishment of need for CTRP in CTWG Report pre-dates FDAAA

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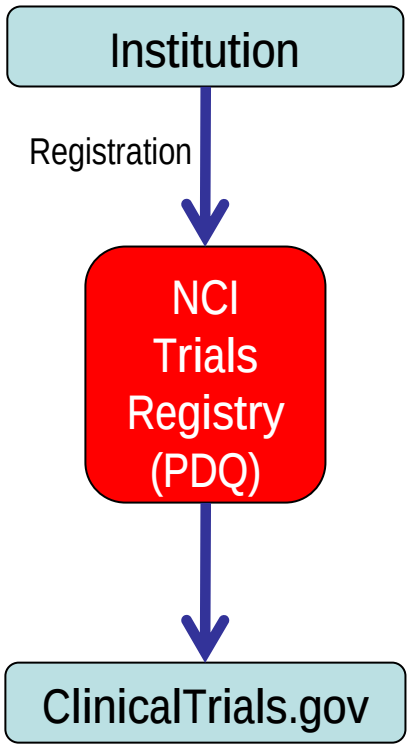
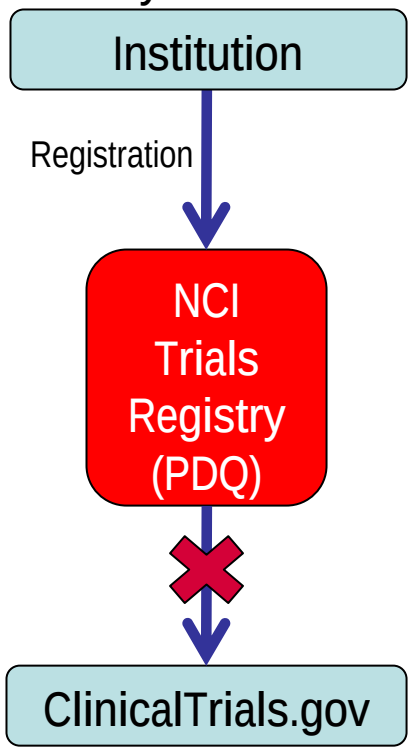
Value-Add of NCI CTRP Registration

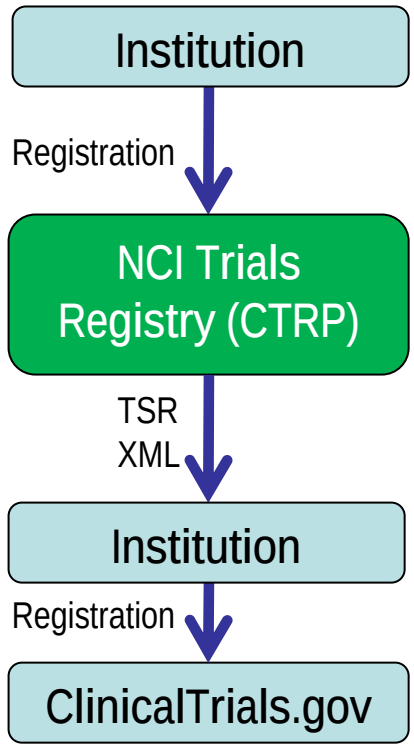
2005: Voluntary ClinicalTrials.gov registration from NCI Registry



2007: FDAAA requires registration and outcomes by Responsible Party. NIH policy prohibits registration by any Federal System



2009: CTRP enhanced to abstract information for ClinicalTrials.gov registration and return file to institutions for independent validation and submission



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CTRP Services to the Cancer Community

- Performs abstraction of data that may be suitable for Clinical Trials.gov reporting
  - 40 FTEs funded by NCI
- Provides a data file
  - Data can be uploaded to ClinicalTrials.gov so that dual entry for required elements is unnecessary
  - Data can be used for local data management
- Provide clinical trials management tools for Centers
- Generates Cancer Center “Summary 4” table
- Interoperable with commercial clinical trials systems; NCI will also work with Cancer Centers that have developed own in-house systems

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CTRP Reporting Capabilities

- This single portal will meet the NCI's and the cancer research community's current and future reporting needs

Feature	PDQ	CTRP
Basic search capability for protocol information		
Enhanced search capability for NCI's website (Cancer.gov)		
Complete and comprehensive listing of *all* NCI supported clinical trials		
Accrual data		
Patient level demographic data (CDUS abbreviated)		
Patient level outcome data (CDUS complete)		

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ClinicalTrials.gov Capabilities

- The information in ClinicalTrials.gov does not meet the NCI's or the cancer research communities' current and future needs

Feature	PDQ	CTRP	CT.gov
Basic search capability for protocol information			
Enhanced search capability for NCI's website (Cancer.gov)			
Complete and comprehensive listing of *all* NCI supported clinical trials			
Accrual data			
Patient level demographics (CDUS abbreviated)			
Patient level outcomes (CDUS complete)			

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CTRP Technology Capabilities

- The CTRP system utilizes a state-of-the-art design, developed around structured data that enables integration with Cancer Center systems to automate reporting requirements

Feature	PDQ	CTRP	CT.gov
Relational Database			
Web user interface			
Reporting capability			
Industry Standard Information to allow sharing of data			
Electronic reporting standardization aligned with FDA requirements			
Open design enabling information exchange with all internal NCI systems			
Open design enabling information exchange with Cancer Center clinical trial systems			

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Initial Registration / Reporting Requirements

	Pre-CTRP	CTRP
NCI Cooperative Group Trials	•Trial registration via NCI/CTEP Trial Registry	•Trial registration via NCI Trial Registry (CTRP); No change
NCI Investigational Drug Trials (N01/U01)	•CDUS Abbreviated*	No change
	•CDUS Complete**	No change
Other NCI-funded trials (R01, R21, P01, SPORE etc.) and other Institutional Interventional Clinical Trials	•Trial registration via NCI Trial Registry (PDQ; pre-2010) or CT.gov	•Trial registration via NCI Trial Registry (CTRP)
	•Annual reporting of list of trials and accrual for Summary 4	•Accrual data
	**Patient level accrual* ***Patient level outcomes, toxicity*	•Automated preparation of data for annual Summary 4 reporting

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Initial Reporting Specifications by Trial Funding Mechanism

Trial Type	Register	Accrual	Patient level demographics (CDUS Abbrev)	Patient level outcomes (CDUS complete)
Cooperative Group	Yes (No change)	Yes (No change)	Yes (No change)	Yes (No change)
Investigational Drug Trials (N01, U01)	Yes (No change)	Yes (No change)	Yes (No change)	Yes (No change)
Other NCI-funded grant (P01, R21, R01, SPORE etc.)	Yes	Yes		
Institutional Investigator-Initiated	Yes	Yes		
Industry	Yes	Yes		
Observational				

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Proposed Future Reporting Specifications by Trial Funding Mechanism *(input sought)*

Trial Type	Register	Accrual	Patient level demographics (CDUS Abbrev)	Patient level outcomes (CDUS complete)
Cooperative Group	Yes (No change)	Yes (No change)	Yes (No change)	Yes (No change)
Investigational Drug Trials (N01, U01)	Yes (No change)	Yes (No change)	Yes (No change)	Yes (No change)
Other NCI-funded grant (P01, R21, R01, SPORE etc.)	Yes	Yes	Yes	Yes
Institutional Investigator- Initiated	Yes	Yes	Yes	?
Industry	Yes	Yes	No	No
Observational	?	?	?	?

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CTRP Implementation

- Pilots at NCI-designated Cancer Centers
  - First for registration, now for accrual
  - Identify issues, estimate workload and refine implementation timeline
- Funding Cancer Centers via CCSG supplements
  - Pilot (n=5) and Early-Adopter Centers (n=19) funded in 2009
  - Budgeted for all Centers in 2010
- Support via phone and e-mail
  - For both Centers and vendors
- Communication:
  - Informational web site, mailing list, online forums
  - Weekly/monthly conference calls with Pilot & Early-Adopter sites
  - Regular updates to Cancer Center Directors and Administrators

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CTMS Steering Committee and CTRP Subcommittee

- caBIG Clinical Trials Management Systems (CTMS) Steering Committee
  - Chairs: Jan Buckner, M.D., (Mayo), Sorena Nadaf (UCSF)
  - Quarterly face to face meeting to provide extramural oversight for the implementation of *all* of the CTWG informatics initiatives
  - CTAC liaison: Dan Sargent, Ph.D.

- CTMS CTRP Subcommittee
  - CTRP Subcommittee: conference calls weekly on deployment strategy, reporting capability
  - Provide strategic guidance on efforts with CTRP
  - Identify and discuss potential or existing issues with the CTRP; recently expanded to include Center Directors

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Partnering with the clinical trials community

- Developing implementation and adoption timelines

Implementation Timeline	Technology	Cancer Community
Registration	Ready	2010
System Integration (caBIG Enterprise Services)	Ready	?
Accrual	Ready	?
Patient level demographics file loader format (CDUS abbreviated)	Q3 2010	?
Patient level outcomes (CDUS complete)	Q4 2010	?

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CTRO Metrics 3/4/10 (2032 Trials Submitted)

- Site-submitted Trials (excluding CTEP/DCP)
  - Original Submissions 1038
  - Abstracted 984
  - QC 605
  - Trial Summary Report Sent 418
  - Submitted Amendments 47
- CTEP/DCP Trials
  - Original Submission 994
  - Abstraction Started 872

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CTWG Initiative: Systems Interoperability and Harmonization

- Common IT Infrastructure
  - *"The CTWG endorses the universal adoption and deployment of a common, standards-based IT infrastructure for the management of clinical trials across the NCI-supported cancer enterprise that is fully interoperable with the caBIG architecture"*
- Intramural and Extramural
  - *"The long-term goal is for all clinical trial sites either to migrate to the caBIG architecture or to develop interfaces and other required enhancements such that their IT architecture is fully interoperable with the caBIG standards-based architecture"*

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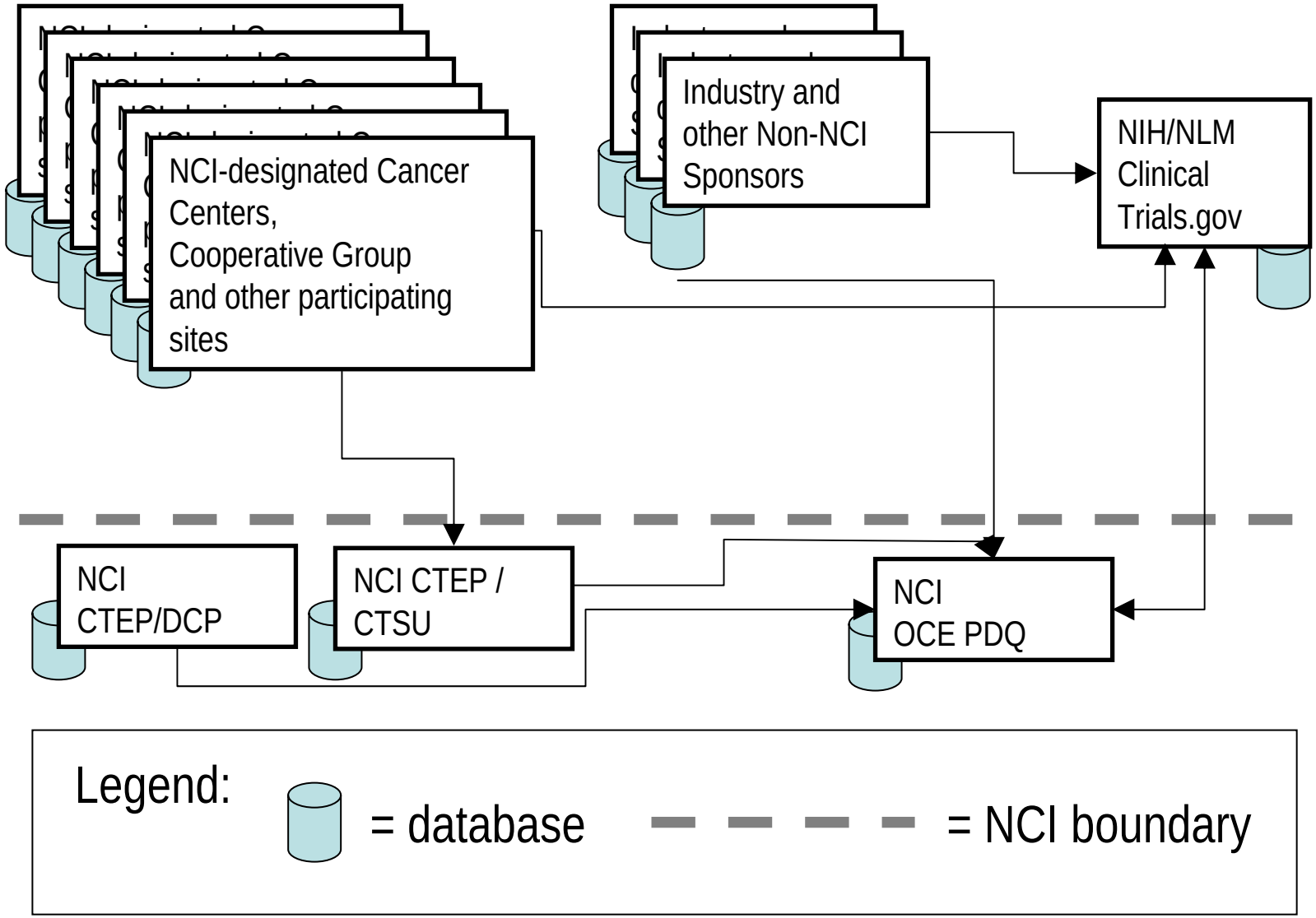
NCI Legacy Process



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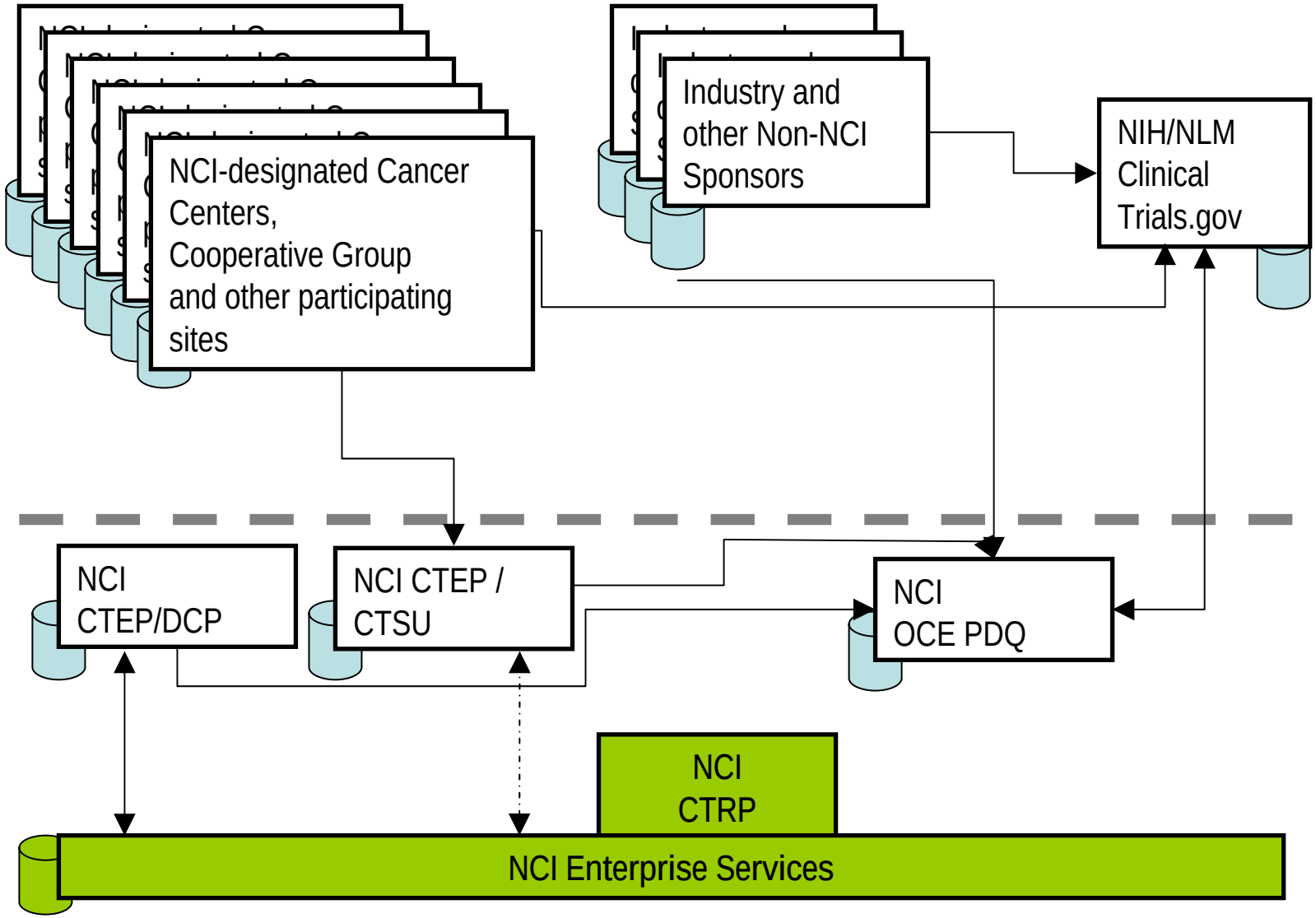
NCI Current/Near Term Process



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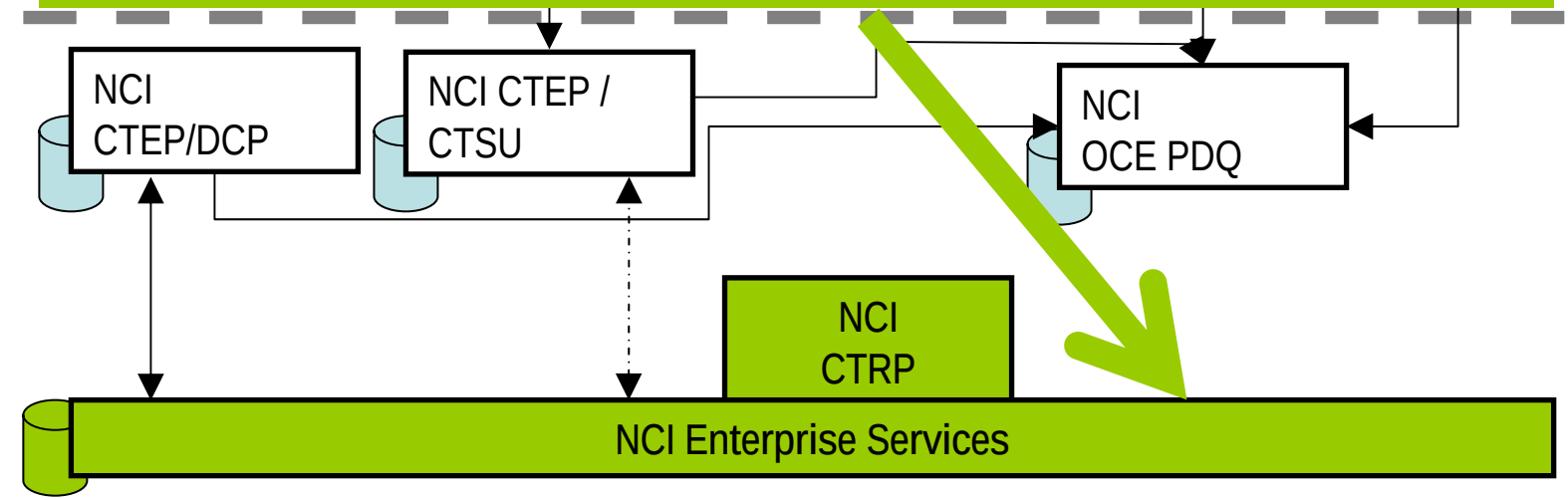
NCI Current/Near Term Process

NCI Enterprise Services (NES): a collection of single, enterprise-wide "sources of record" for key shared items of data, *e.g.*:

- Protocols
- Organizations
- People (e.g., PIs)
- Diseases
- Agents



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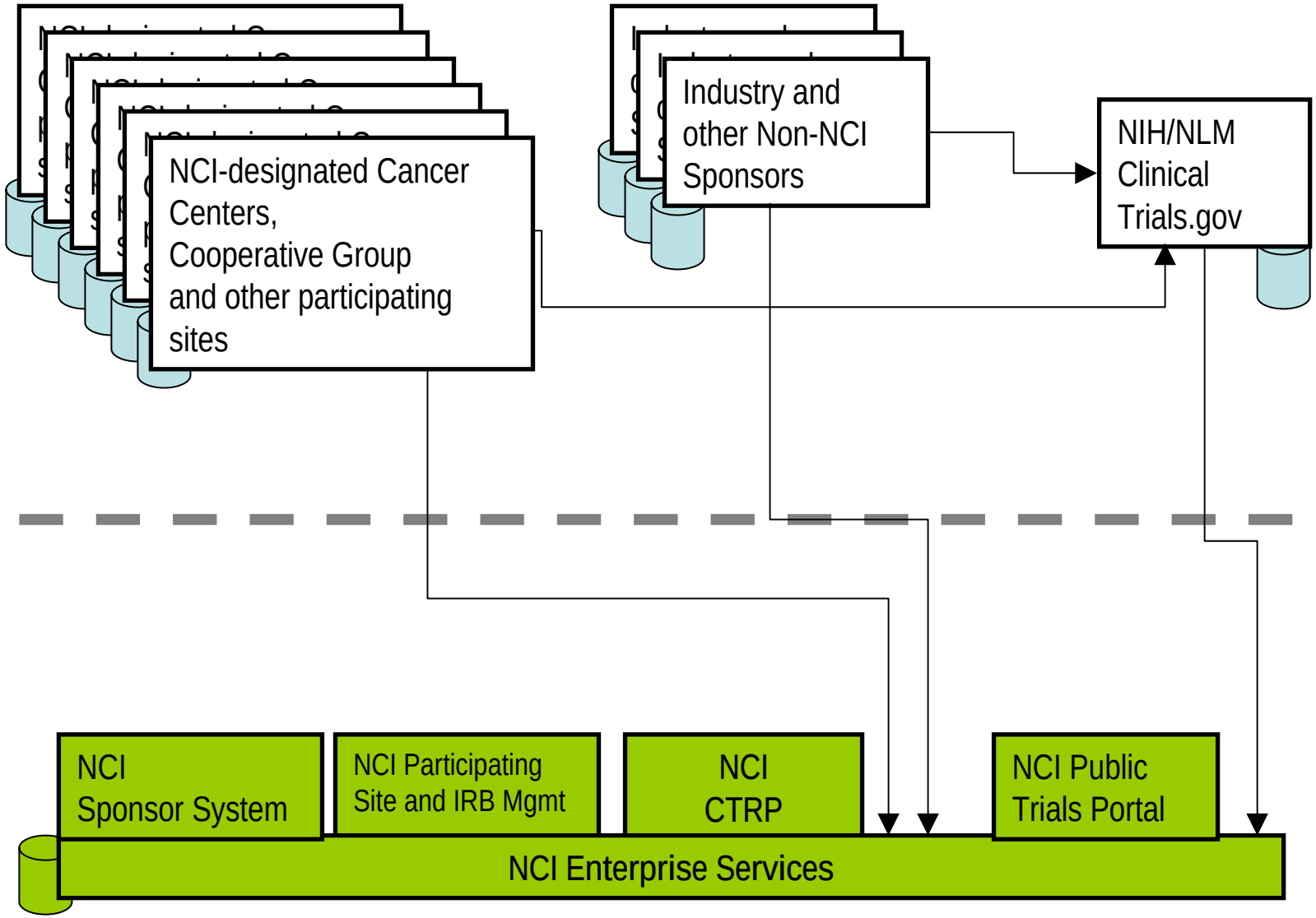
NCI Future Term Process



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Interoperable Infrastructure - Future

- NCI Divisions, Programs, Centers and Offices engaged in clinical trials activities (*e.g.*, CTEP, DCP, OCE, OCC) assembling integration plans
  - Recognizing that NCI's clinical trials operation is a production process, with many moving parts
- caBIG® Clinical Trials Applications have been re-engineered to leverage NCI Enterprise Services
  - Pre-curated data sources accessible by other applications
- Extramurally developed systems being re-engineered to leverage NCI Enterprise Services
  - First Cancer Centers, vendors engineering systems to leverage services for seamless reporting to CTRP

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Library of Standard Case Report Form Modules

Demography CRF Module

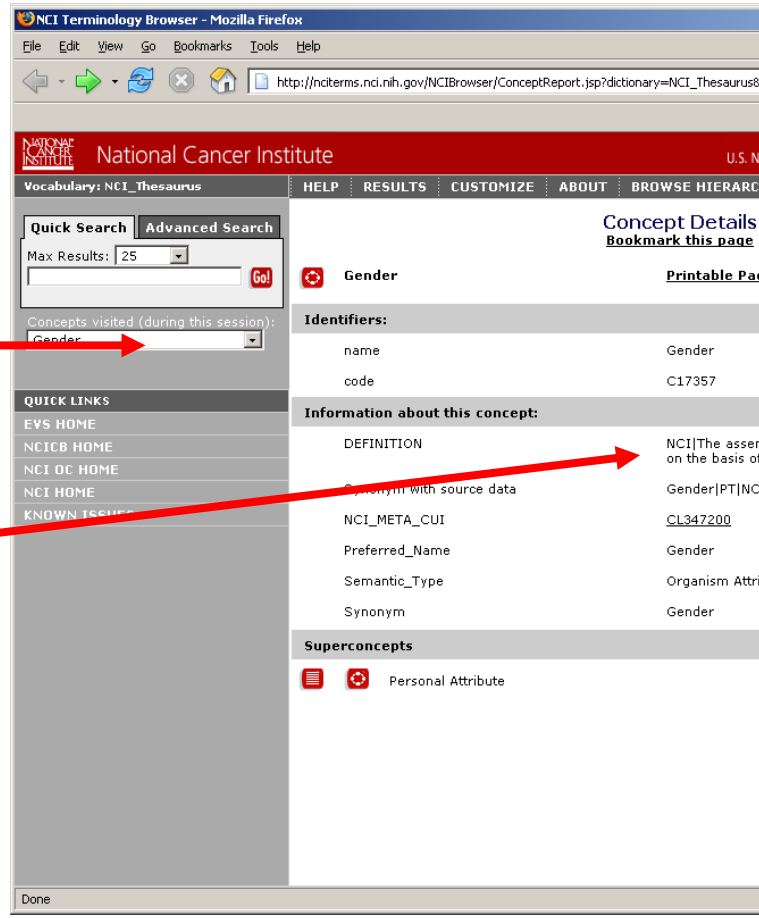
Patient Name: _____

Patient Gender (Check one):

- ☐ Male
- ☐ Female
- ☐ Unknown
- ☐ Not Determined

Patient Race (Check all that apply):

- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or other Pacific Islander
- ☐ White
- ☐ Unknown
- ☐ Not Reported



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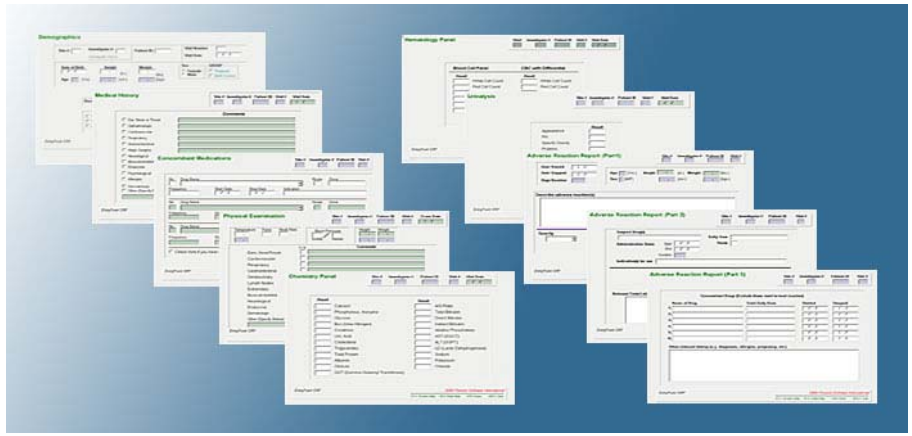
CTWG Initiative: Develop a Library of Standardized Case Report Form Modules

- Using Common Data Elements
- Reduction of time, cost and effort
- Standardized data capture, cross-trial analysis
- Maximize the capture of critically important data
- Simpler regulatory review
- Leveraging of:
  - past and current NCI standardization work
  - experience of what does and does not secure adoption



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Harmonization with Industry

- Clinical Data Acquisition Standards Harmonization (CDASH)
  - Initiative of Clinical Data Interchange Standards Consortium (CDISC)
- Common goal with NCI: harmonizing and standardizing data collection for clinical research
  - CDASH focus: elements that are common to all clinical studies
  - NCI focus: oncology studies
- NCI modules will include all CDASH “mandatory” questions, plus additional oncology content

CDASH Initiative

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CRF Module Harmonization Workflow

1	NCI CBIIT staff create CRF inventory
2	Working group aggregates and identifies key content, resolves discrepancies, harmonizes. *Change – expansion in working group membership to include named POC for all major internal and external clinical trial stakeholders*
3	Working group partitions content - mandatory, conditional, optional
4	Working group achieves consensus on final list of elements, assures adherence to data standards
5	Executive summary sent to CTROC
6	Module circulated for broad community review
7	Working group reviews and responds to changes from community review. *Change – POCs for all major internal and external clinical trial stakeholders provide formal approval of CRF elements prior to subsequent review*
8	CRF Subcommittee of the CTMS Steering Committee reviews and approves. *Change – newly formed subcommittee ensures review by critical external clinical trial stakeholders, e.g., NCI cooperative groups*
9	CTROC reviews and approves
10	Annual review cycle

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Case Report Form Modules – Status

Round	Work Groups	Status
1	Demography	Complete
2	Adverse Events; Participant ID; Enrollment; Registration; Protocol Violation; Medical History; Physical Examination	Broad community review complete – awaiting expanded workgroup review
3	Concomitant Agents; Study Agents; Prior and Post Therapy Agents; Drug Accountability; Lab Results; Outcomes; Extent of Disease/Staging	Broad community review complete – awaiting expanded workgroup review
4	Imaging; Off Treatment, Diagnosis; Footer/Header; Eligibility; Non-Agent Interventions; Vital Signs	Expanded workgroups to consider before broad community review
5	Any remaining elements	Convene after above

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Future

- Community adoption essential for success
- Plan for ongoing maintenance includes annual review of the total library of CRFs for necessary changes
- Modifications will be requested by, and changes will be vetted by, community and NCI

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CTWG Recommendation: Investigator and Site Credential Repository

- Simplify and speed trial initiation
  - Eliminate the need to endlessly reestablish credentials each time a trial is initiated (or annually in the case of CTEP)
- Facilitate rapid communication of:
  - new regulations and changes to the clinical research community
  - changes in the status of individual investigators and sites to sponsors
- Partner with relevant federal agencies, professional societies and trade associations
  - As appropriate, pursue links to clinical investigator community outside of cancer research
- Leverage FIREBIRD
  - Federal Investigator REgistry of Biomedical Informatics Research Data

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FIREBIRD

Interagency Oncology Task Force

FIREBIRD

- Product of the Interagency Oncology Task Force (IOTF) - NCI-FDA partnership
- Automates and centralizes “FDA 1572 Form” investigator registration process
  - Eliminates paper-based, manual process, need for wet signatures
  - Investigators register online with trial sponsors (NCI and/or commercial) via web interface to secure, central repository
  - Maintains accreditation information profile, can automatically be applied to multiple registrations and / or sponsors
  - Standardizes collection of registration information across multiple sponsors and FDA
- FIREBIRD has completed Operational Pilot, in limited production with NCI Division of Cancer Prevention

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2010 NCI Implementation

- Establish NCI/professional society/trade association partnership
  - Approach FDA, professional societies (*e.g.*, ASCO, AACR, AACI, ONS, SoCRA, ACRP), trade associations (*e.g.*, PhRMA, BIO)
- Form task force to define and establish credentialing criteria for both investigators and sites
  - Start with FDA 1571/1572 forms
  - Develop formal investigator and site credentialing process for oncology clinical trials, based on criteria established by task force
  - Incorporate/harmonize information from professional organizations that provide certification/training programs
- Establish and maintain data repository
  - Based on Federal Investigator Registry of Biomedical Informatics Research Data (FIREBIRD)
  - Incorporating NCI Enterprise Services (NES)

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CDMS Procurement

- NCI has purchased licensing rights for a commercial clinical data management system (CDMS) software product
- Will be made available free of charge to all organizations in the NCI Clinical Research Enterprise
  - (*i.e.*, all non-profit NCI-supported organizations conducting clinical trials)
- Can be used under license terms for all cancer trials
  - Not just NCI-sponsored trials
  - Including industry, investigator-initiated, etc.
- Cannot be used for non-cancer trials under license terms
  - If an organization wanted to extend the license to allow use in non-cancer trials, a business discussion between the organization and the vendor (not involving NCI) would be required

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CDMS Procurement: Purpose

- Respond to need expressed by Cooperative Groups for a single Remote Data Entry system
  - *"…a unique responsibility and opportunity to develop a uniform, paperless, RDE system for over 1700 trial sites, 30,000 new accruals per year, more than 100,000 patients in active follow up"*
- Deliver full-function clinical data management capability to entire NCI-supported clinical research community
  - Irrespective of ability to pay
- Allow researchers to share information
  - with other caBIG® compatible systems, within organizations, with other organizations and with NCI
- Cooperative Groups have agreed to use the CDMS' Electronic Data Capture (EDC) functionality
  - Optional use of other CDMS features/sub-components
  - Other organizations (*e.g.*, Cancer Centers, Consortia) may choose to use the CDMS

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CDMS Procurement: License

- NCI-hosted or locally hosted
- Unlimited-user, perpetual license, including:
  - On-site installation, administrator training, user training materials
  - Telephone / e-mail support
  - Periodic software upgrades
- Does NOT include:
  - Custom integration with existing / legacy systems
  - Migration of legacy data
  - Infrastructure for locally hosted option (system administration staff, hardware, *etc.*)
- Request for Letters of Intent, November 2009
  - Total LOIs received: 43
- Full implementation has been delayed because of vendor protests

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Communication: CDMS Mailing Lists

- Communications will be sent to
  - caBIG® ANNOUNCE mailing list (CABIG_ANNOUNCE@LIST.NIH.GOV)
  - caBIG® Clinical Trials mailing list (CABIG_CTMS-L@LIST.NIH.GOV)
  - caBIG ® Clinical Data Management System (CABIG_CDMS@LIST.NIH.GOV)
- Communications will come from
  - ncicabigcdms@mail.nih.gov

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Questions / Contacts on CDMS Procurement

- Questions regarding the contract, protests, etc.:
  - Louis Gilden, Contracting Officer , US Department of the Interior: louis.gilden@aqd.nbc.gov
- Questions regarding CDMS Procurement
  - George A. Komatsoulis, Ph.D., Deputy Director, NCI Center for Biomedical Informatics and Information Technology (CBIIT) at komatsog@mail.nih.gov
  - John Speakman, Associate Director, Clinical Trials Products and Programs, NCI Center for Biomedical Informatics and Information Technology (CBIIT) at john.speakman@nih.gov
- Questions regarding CDMS Deployment
  - Neesha Desai, CDMS Project Manager, NCI Center for Biomedical Informatics and Information Technology (CBIIT) at neesha.desai@nih.gov

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CTRP User Resources

- Trial registration website: https://trials.nci.nih.gov/registry/
  - Register trials with the NCI's CTRP, search CTRP registered trials
- CTRP informational website: http://www.cancer.gov/ncictrp
  - Resources include FAQs, Glossary, and a CTRP User's Guide
- CTRP Forum: https://cabig-kc.nci.nih.gov/CTMS/forums/viewforum.php?f=31
  - Ask questions of the CTRP team and other CTRP users
- CTRP-USERS-L@list.nih.gov – CTRP mailing list
- NCICTRP@mail.nih.gov – Program questions
- NCICTRO@mail.nih.gov – Clinical Trials Reporting Office

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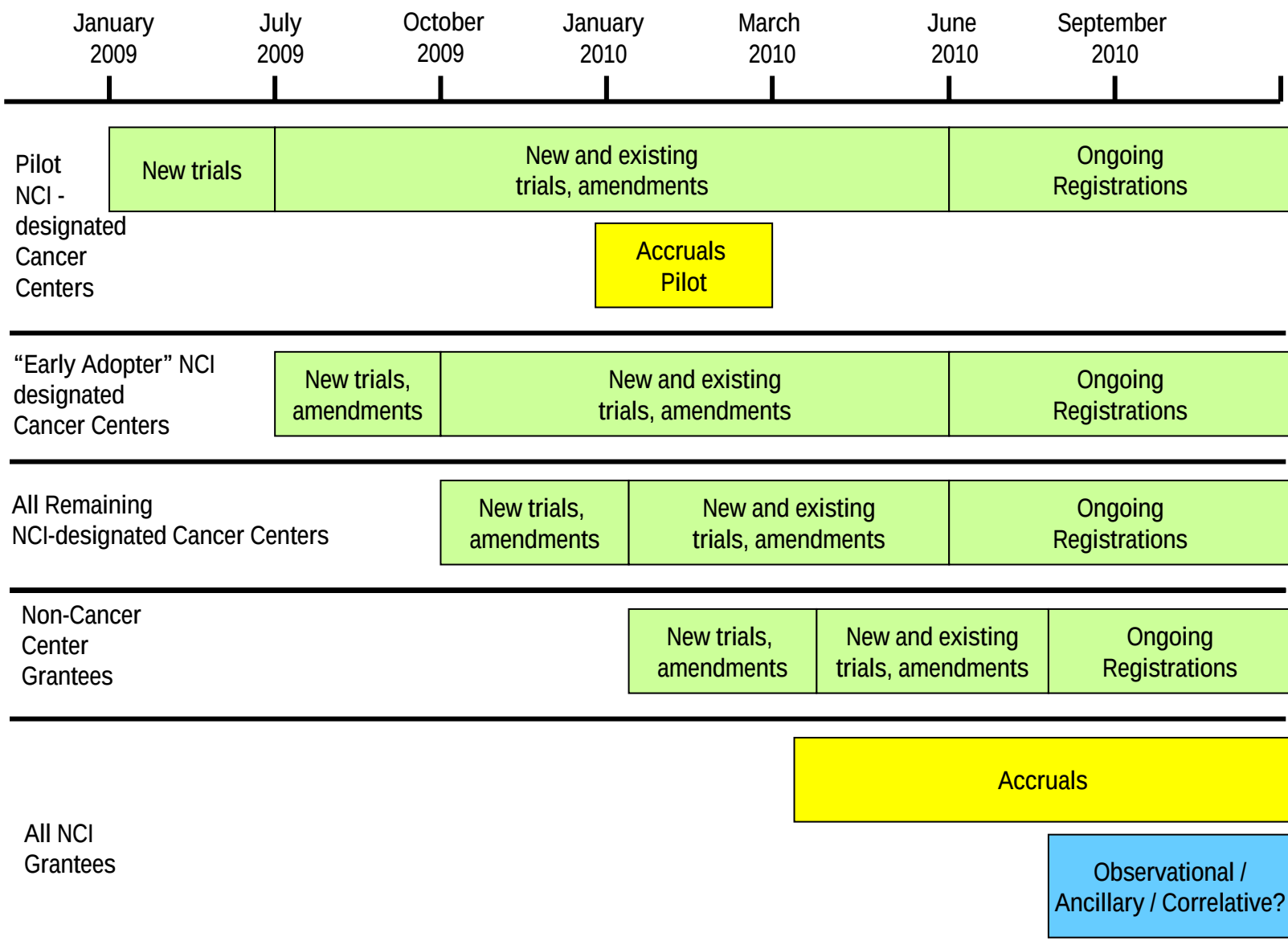
Cancer Center Adoption Timeline



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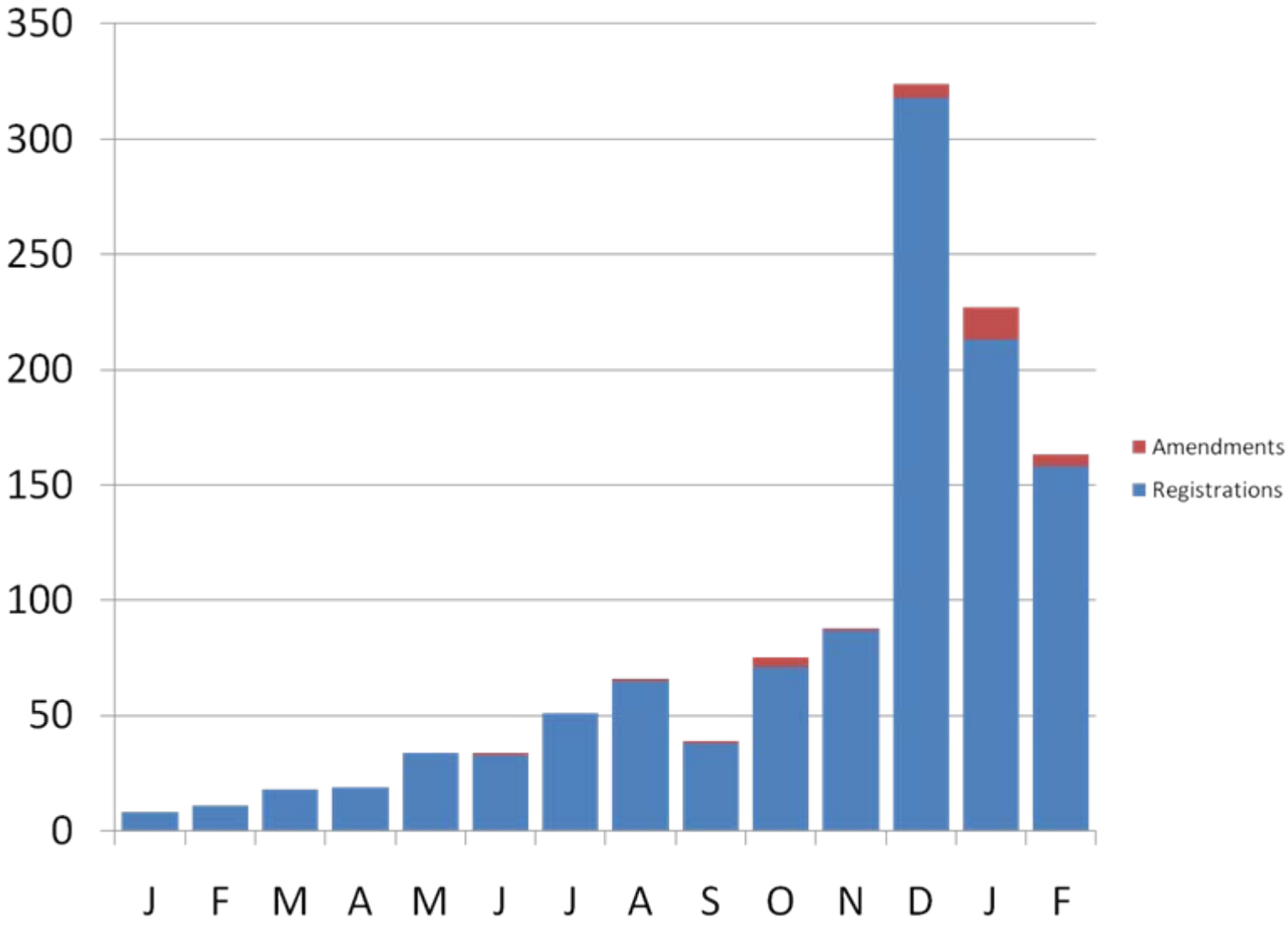
Monthly Submissions / Amendments from January 2009 Program Start



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Why not just take the data from ClinicalTrials.Gov into CTRP?

- Several key concepts are not structured in the ClinicalTrials.Gov specifications (*e.g.*, eligibility criteria)
- NCI, patients and physicians need data elements to be more finely grained for retrieval of trials
  - within conditions (*e.g.*, clinical stage, histological type, grade of tumor)
  - Other qualifiers (*e.g.*, again using cancer as an example, “unresectable”, “localized”, “recurrent”)
- CTRP Database enables investigators to update current data elements quarterly in near-real-time
  - ClinicalTrials.Gov waits until two years after study closure
- As the data elements relating to outcomes are finalized, NCI expects the scope of information needed will be much broader and more detailed