National Cancer Institute

NCI Experimental Therapeutics Clinical Trials Network(ETCTN) Clinical UM1 and U24 PK Resource

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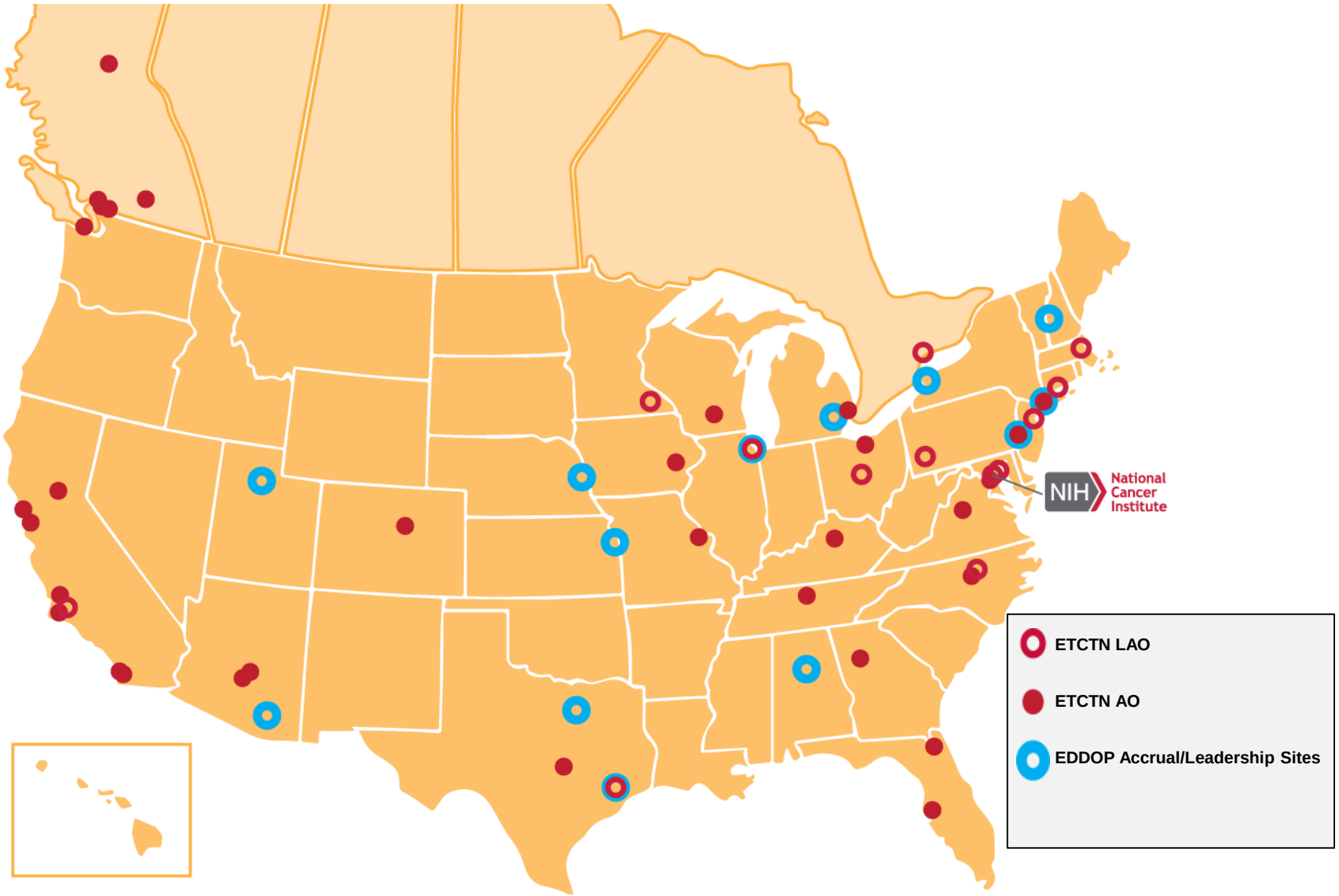
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Experimental Therapeutics Clinical Trials Network: Lead Academic (12) and Affiliated Organizations (41); Experimental Drug Development Opportunities Program (15)



Goals and Objectives of Experimental Therapeutics Clinical Trials Network

Research, development and improvement of cancer treatments

- Advance the clinical development of NCI-IND agents with early phase studies
  - ❖ *Complementary collaboration with pharma partners*
- Determine dose, schedule and sequence for NCI-IND agents and combination regimens
- Perform disease-specific activity studies of NCI-IND-agents and combinations
  - ❖ *Prioritize cancers and cancer subsets where industry is not investing*

Biomarker and cancer biology-driven studies using patient derived specimens

- Acquire high quality patient tumor specimens for correlative studies
- Incorporate fit-for-purpose PD/biomarker assays into ETCTN trials

Career enhancement for early career investigators

- Experience leading clinical trials in the ETCTN
- Play a significant role on the drug development Project Teams

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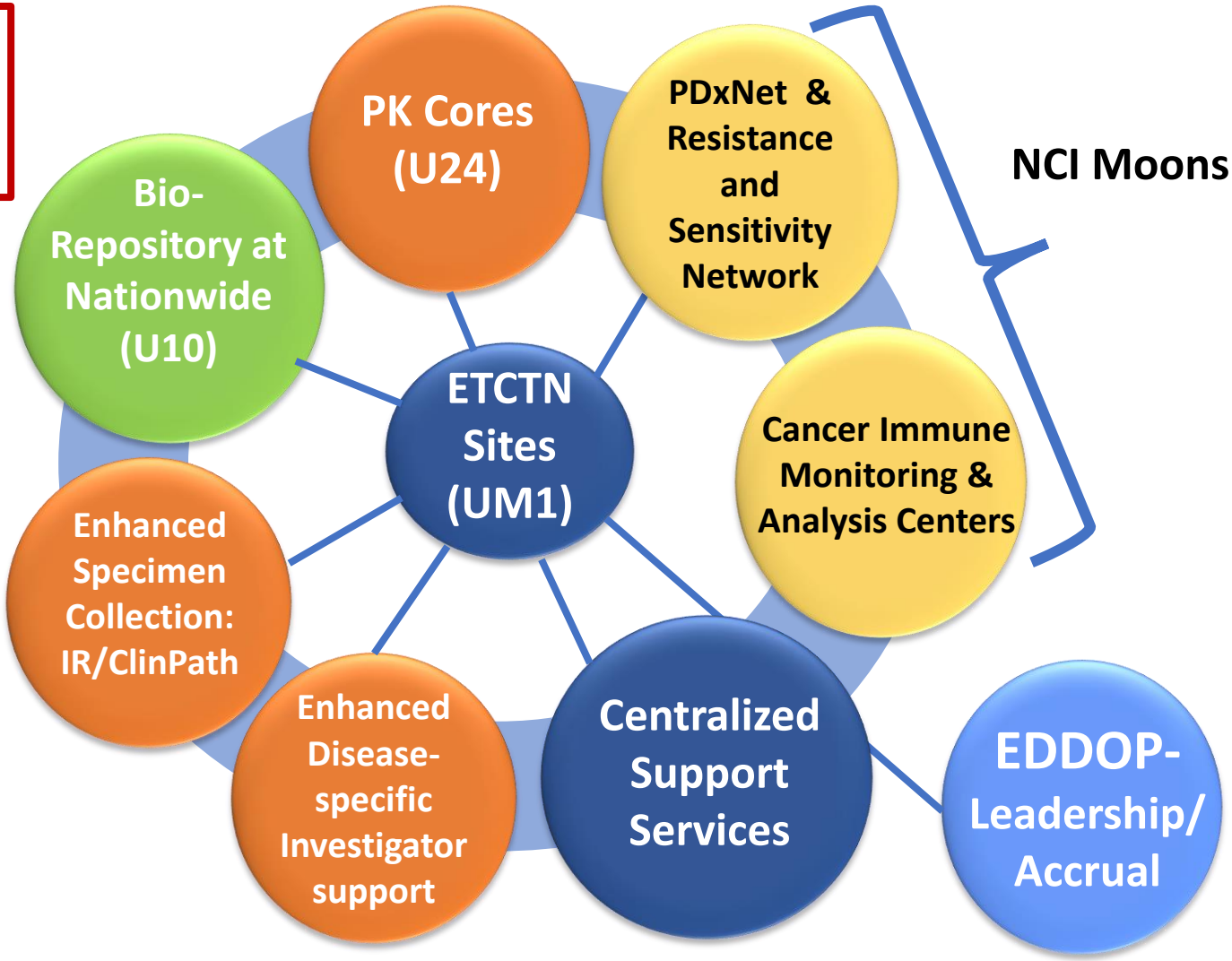
Proposed updates/changes to ETCTN Network

≈ 41 enrolling North American sites



- Affiliated organizations
- New ETCTN initiatives
- ETCTN biorepository (U10)
- Early drug development opportunities programs in NCI CCs (EDDOP) for accrual and leadership

ETCTN – Transformation to a Network Structure

- **Collaborative approach to clinical trial development and implementation**
  - Moved from mass solicitations to **extramural project teams** early in clinical development planning
  - Involve **disease-specific clinical** expertise from all sites
  - Enhance **study participation** across the network

- **Assuring Reproducible Translational Science**
  - Transformed the approach to **biomarkers** from laboratory developed tests (**LDTs**) to analytically **validated, fit for purpose bioassays**

- **Site Re-Organization and Infrastructure Support**
  - Moved from siloed sites to a **unified trials network** with centralized infrastructure support
  - Further enhanced **GCP principles** in all aspects of ETCTN trials
  - Addition of protocol authoring service, recently
  - Interventional Radiology Working Group

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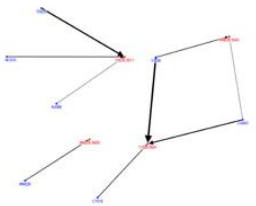
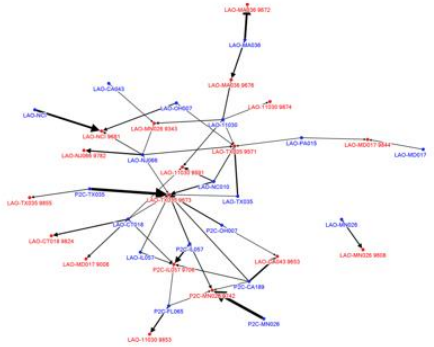
Accrual Network: Year 1 to Year 4

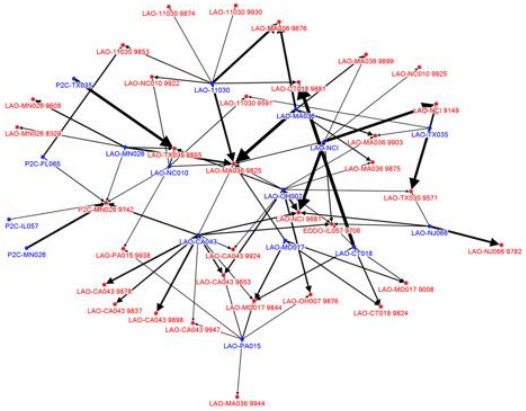
Year 1



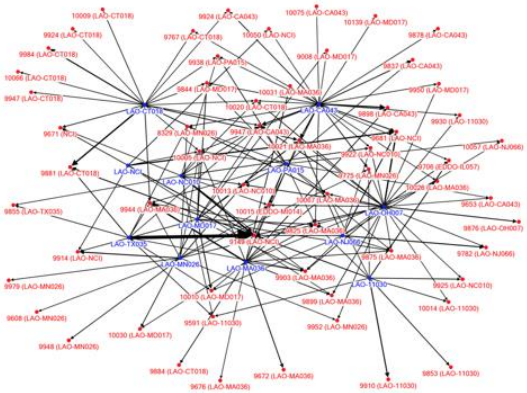
Year 2



Year 3



Year 4



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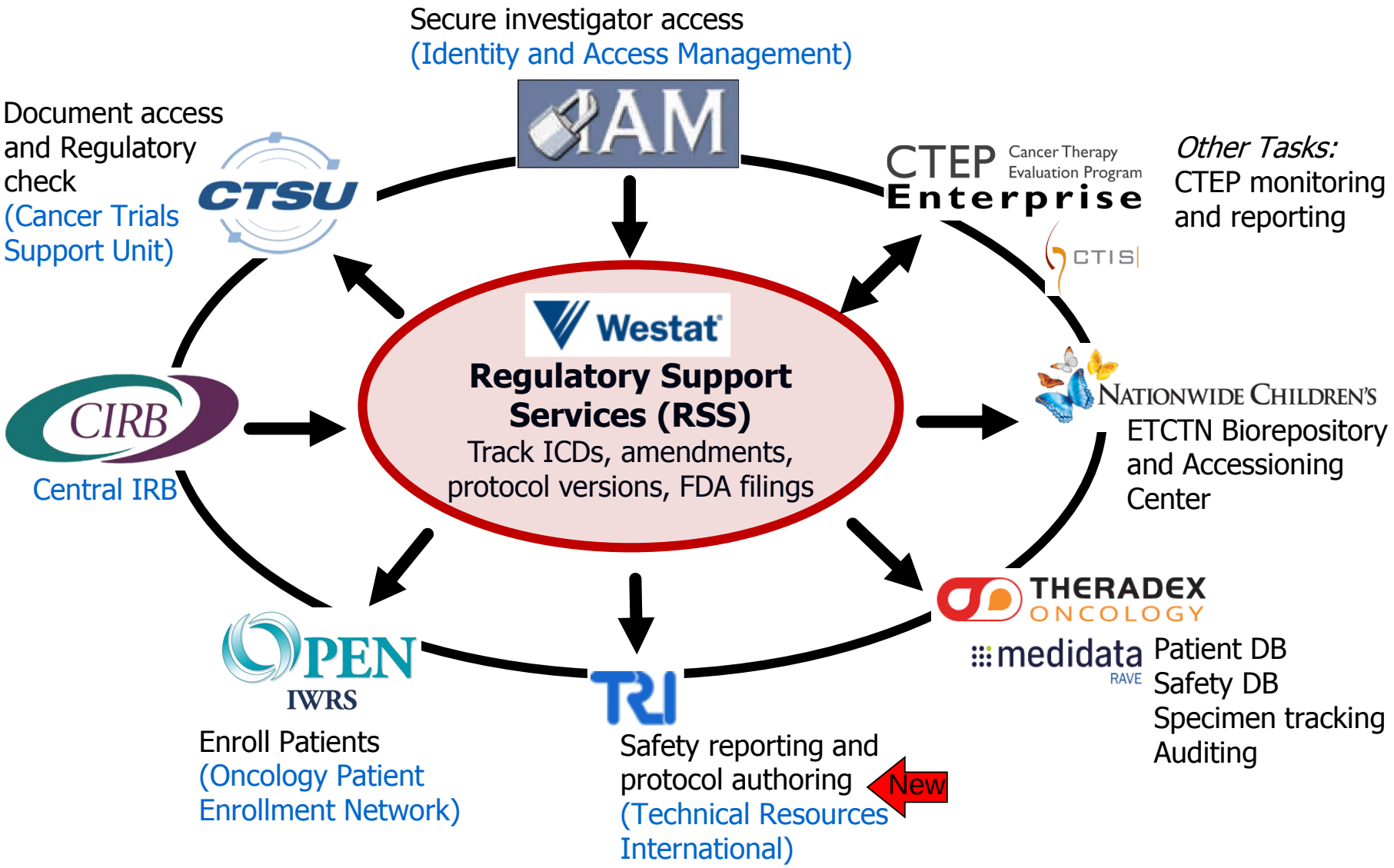
ETCTN central infrastructure support



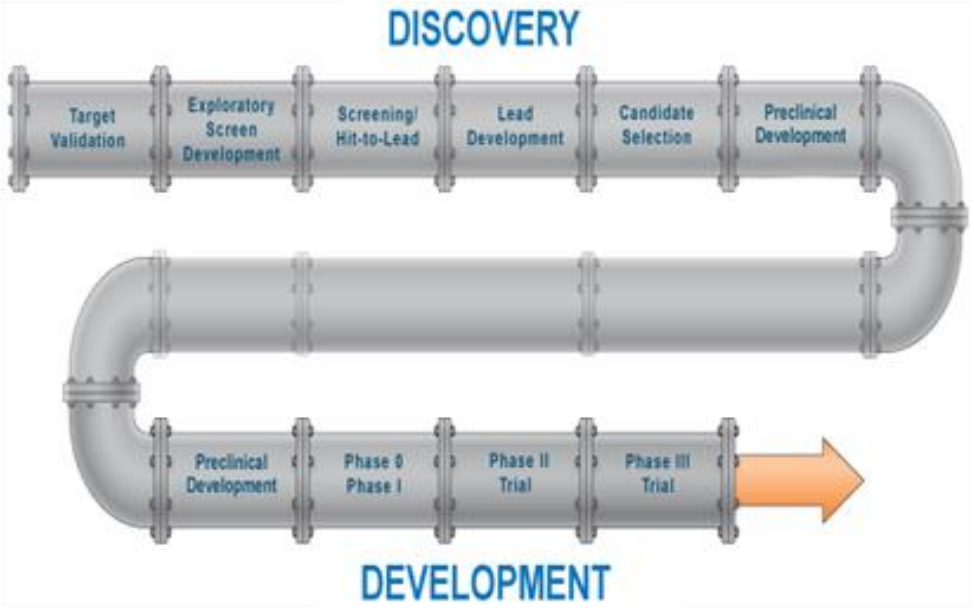
External review of Agents and Trials in the ETCTN

- **All agents come from the NExT (NCI Experimental Therapeutics) Pipeline**

  Review of applications

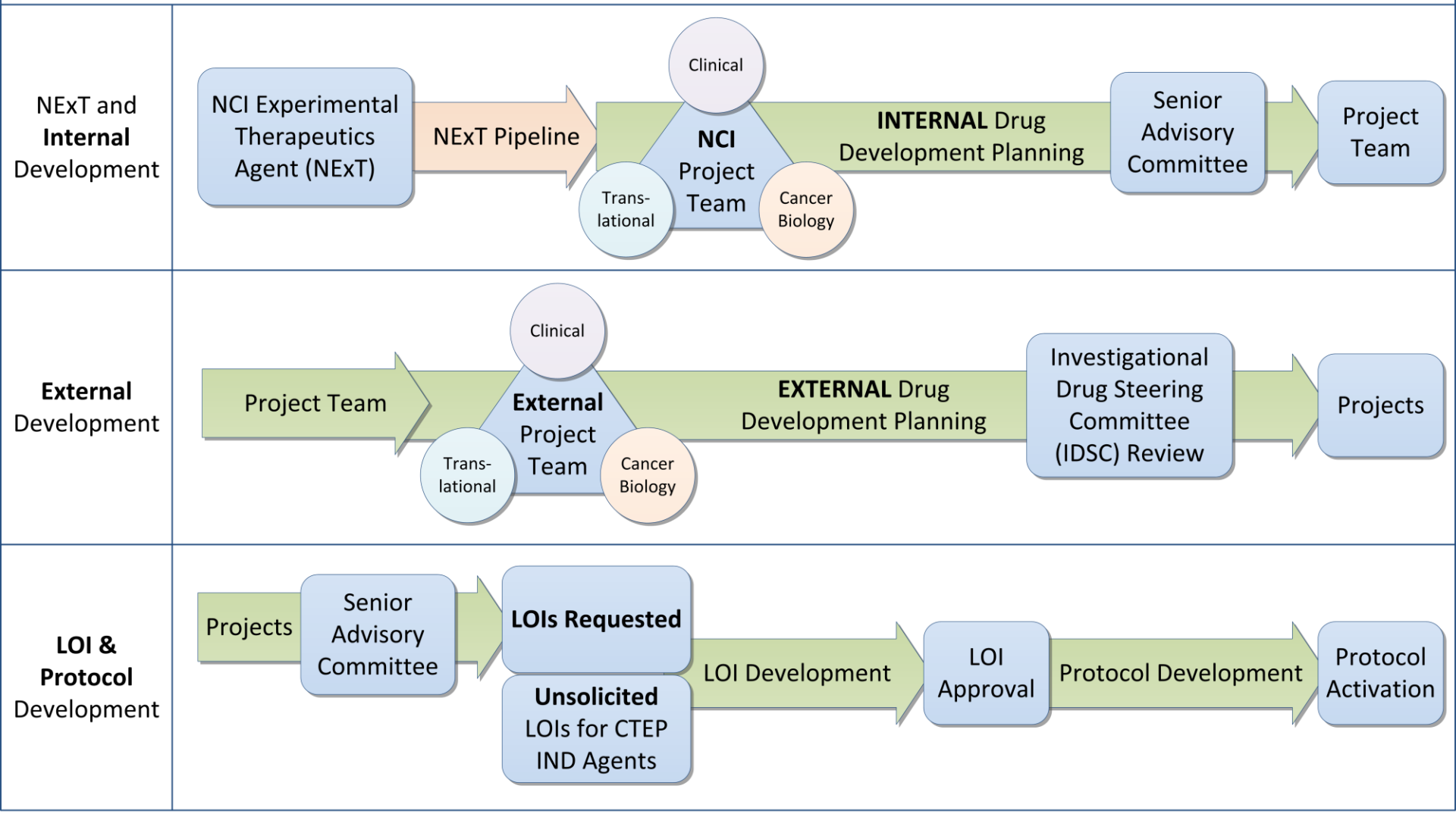
  by external experts

  (https://next.cancer.gov/)



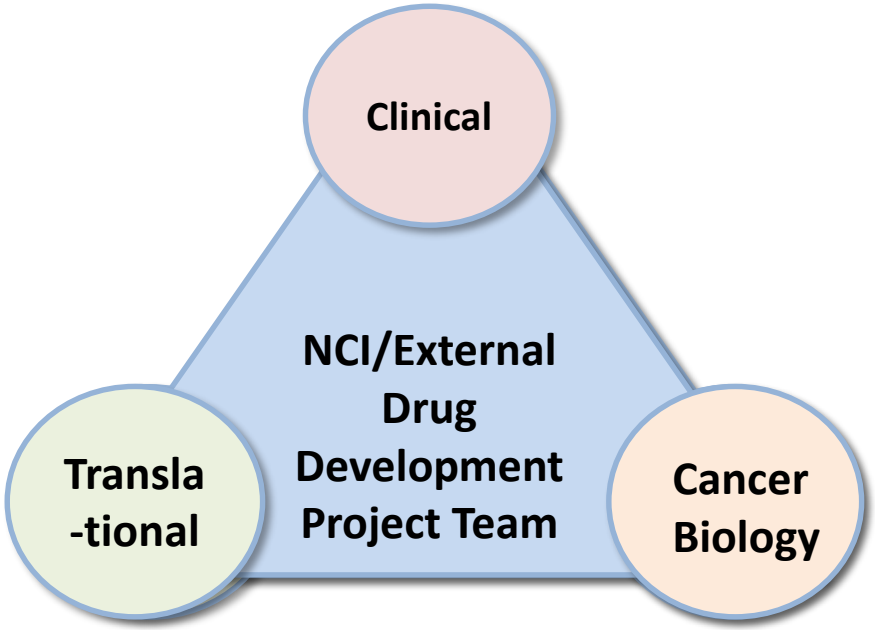
- **All trials proposed by drug development project teams are reviewed by Investigational Drug Steering Committee**
  - IDSC is composed of ETCTN PIs, external experts and NCTN members

ETCTN Core Protocol Development Processes



Parallel processes not shown include: Biomarker and assay development and review
Regulatory agreement development and sign-off (e.g. CRADA)
Additional levels of internal review

ETCTN drug development project teams

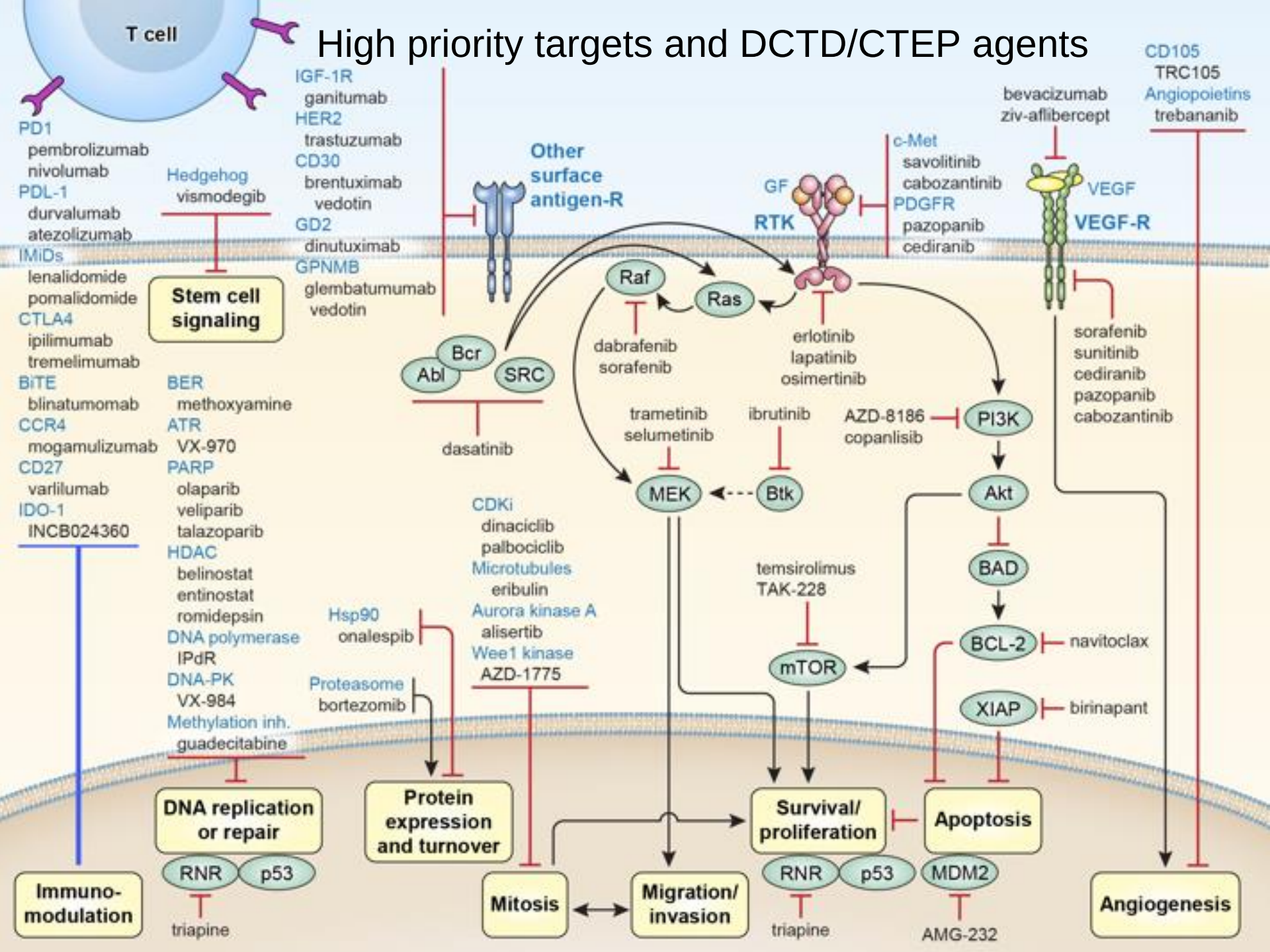


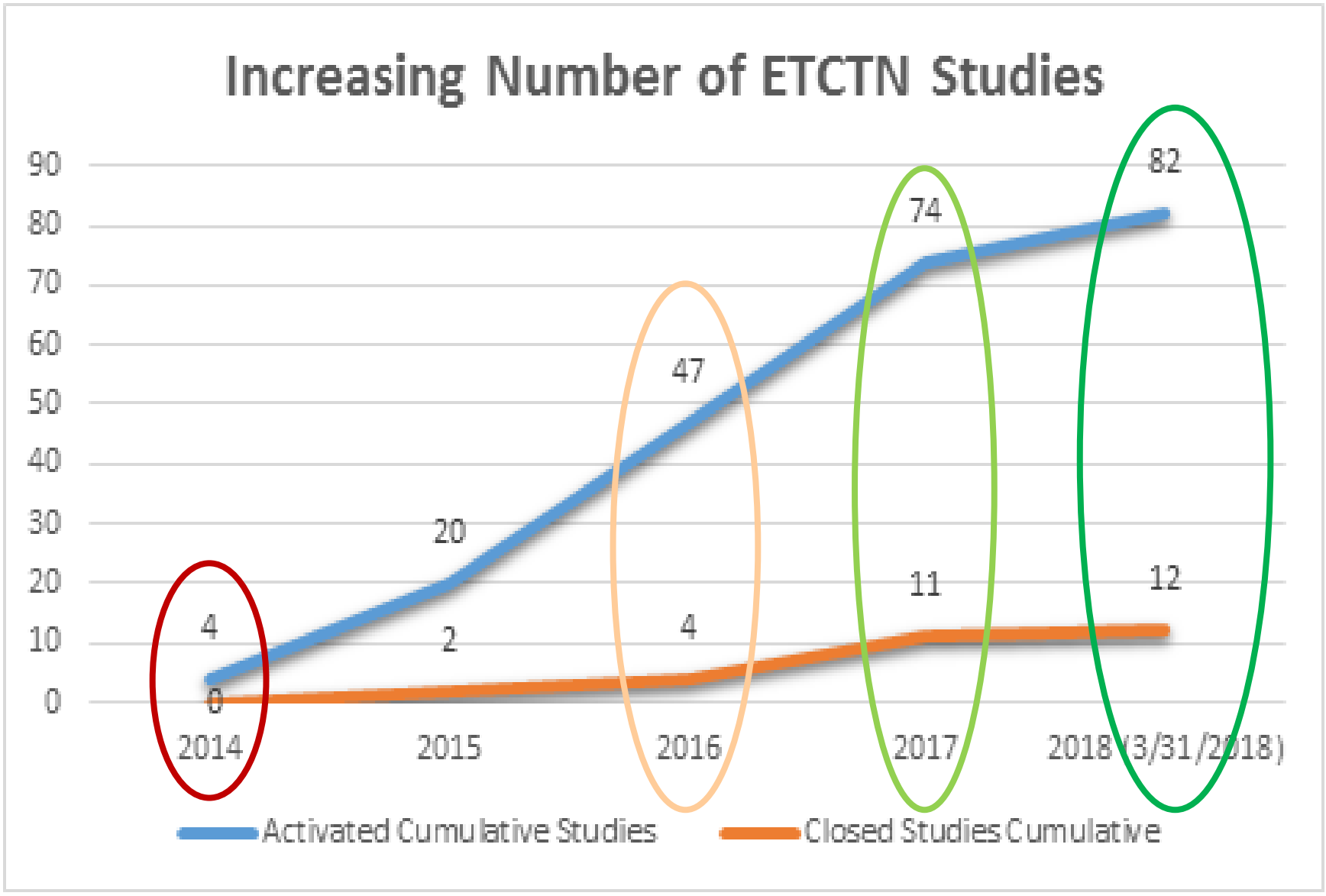
- Extensive extramural involvement
- Reflects heavy emphasis on early career development
- Drug development and CRADA negotiations occur in parallel
- Unsolicited LOIs accepted after Project Team deliberations

Drug development project teams (14):

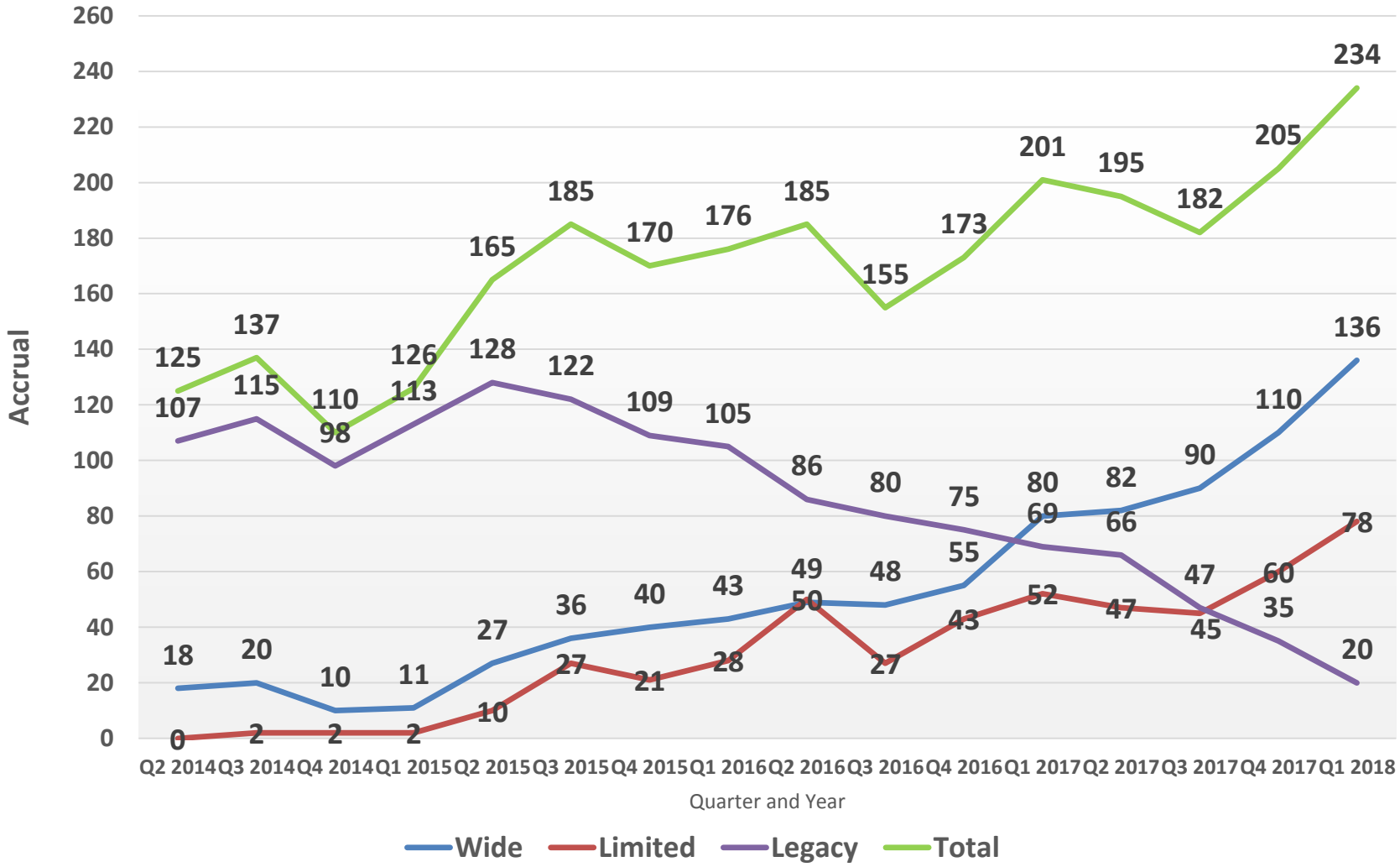
- AT13387 (onalespib) (HSP90i)
- Osimertinib (AZD9291, T790M EGFRi)
- M3814 (DNA-PKcs i)
- VX970 (ATRi)
- Durvalumab (PD-L1i)
- Atezolizumab (PD-L1i)
- T-VEC (Talimogene laherparepvec, oncolytic virus)
- AMG-232 (mdm2i)
- Anetumab ravtansine (BAY 94-9343, anti-mesothelin)
- Copanlisib (BAY 80-6946, PI3Ki)
- CB839 (glutaminase i)
- Ixazomib (proteasome i)
- Pevonedistat (NEDD8i)
- M3814 (DNA-PKi)
- 3 others starting

High priority targets and DCTD/CTEP agents




Increasing Number of ETCTN Studies
90
80
70
60
50
40
30
20
10
0
4
20
47
74
82
0
2
4
11
12
2014
2015
2016
2017
2018 (3/31/2018)
Activated Cumulative Studies
Closed Studies Cumulative

Quarterly ETCTN Accrual (Limited, Wide, Legacy and Total) Q2 2014 – Q1 2018



Career Enhancement and Development for Early Career Investigators (03.2014-01.2018)

Activity	Number of LOIs (% of total)
LOIs from Project Teams with early career PI's	45 (90)
Unsolicited/pre-solicitation LOIs with early career PI	60 (31)
Activated or transitioned ETCTN protocol with early career PI	44 (60)

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Duration of Award

- The duration of the ETCTN UM1 and U24 PK awards has been extended to **6 years.**

- **Q & A** regarding the FOAs will be posted on the CTEP website in the section related to the Experimental Therapeutics Clinical Trials Network.

- Due on **May 22, 2019, by 5:00 PM local time** of applicant organization

ETCTN transformation during the 2020-2025 award period:
Leveraging NCI resources to enhance drug development & productivity

1. Address the need to find rare or uncommon, molecularly defined subsets of patients – a challenge for phase 2 studies

2. Enhance requirements for **high quality biopsy material** for correlative studies

3. Improve ability to perform **validated biomarker assays** to characterize and monitor **molecularly defined subsets** of common or uncommon tumors (validation of integral/integrated biomarkers)

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1. Recruit rare or uncommon, molecularly defined subsets of patients

- **Lead and Affiliate Organizations will apply as teams**
  - **Encourage multiple PI applications**
  - LAOs to have a minimum of **one Phase 1 investigator**
  - LAOs and AOs to have a minimum number of **identified disease focused clinical investigators (DFCI)** responsible for accrual
    - **4** distinct disease-specific investigators **for each LAO**
    - **2** distinct disease-specific investigators **for each AO**
  - Award will provide **partial salary support** for each team member- NCI can provide academic credit through grant salary support
  - Funded co-investigators will have **performance criteria outlined in Terms of Award** for performance in opening studies and accrual

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1. Recruit rare or uncommon, molecularly defined subsets of patients (cont.)

Levels of Effort

- Each individual designated as a PD/PI (LAO and AO(s) PD/PI must commit a minimum of 1.2 person-months/calendar months of effort per year. This minimal effort level must be maintained throughout the entire project period.

- The designated DFCIs, Translational Scientist(s), Interventional Radiologist(s) and Research Pathologist(s) are expected to commit a minimum of 0.6 person- months/calendar months of effort each per year.

1. Recruit rare or uncommon, molecularly defined subsets of patients (cont.)

- **Disease Focused Clinical Investigators (DFCIs)**

- Disease-Focused Clinical Investigators (DFCIs) should be either the site Clinical Trial PI or Co-Investigator.

- LAO PD/PIs and AO site PD/PIs may serve also as Disease-Focused Clinical Investigators.

- Disease-Focused Clinical Investigators may be early career clinical investigators with senior mentorship support.

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1. Recruit rare or uncommon, molecularly defined subsets of patients (cont.)

- **Site Staff**

-Each LAO is required to have at least one Translational Scientist, one Interventional Radiologist, one Research Pathologist, and four Disease-Focused Clinical Investigators.

-Each AO is required to have one Interventional Radiologist and two Disease-Focused Clinical Investigators.

-The LAO and/or its AO(s) should identify at least one statistician with the skill and expertise in the design and monitoring of early phase clinical trials including adaptive and other designs for phase 1 and 2 trials to support the clinical activities of the site or consortium.

Level of Effort for Required Personnel

0.6 Calendar months equal 5% effort

NIH salary cap = $189,600

Assume 3 AOs per UM1 application

Each LAO is required to have one Translational Scientist (TS), one Interventional Radiologist (IR), one Research Pathologist (RP), and four Disease-Focused Clinical Investigators (DFCI) with a minimum of 0.6 person - months/calendar months of effort each per year.

4 DFCI +TS + IR + RP = 7 staff X 0.6CM (5% effort) = 35% effort

$189,600 X 35% = $66,360 + fringe benefits

Each AO is required to have one Interventional Radiologist (IR) and two Disease-Focused Clinical Investigators (DFCI) with a minimum of 0.6 person – months/calendar months of effort per year.

IR + 2 DFCI = 3 staff per AO X 0.6 CM (5% effort) = 15% effort

$189,600 X 15% = $28,440 per AO X 3 AOs = $85,320 + fringe benefits

Total for LAO with 3 AOs = $66,360 + $85,320 = $151,680 + fringe benefits

2. Improve the quality of biopsy specimens

- **Organize ETCTN-wide initiatives with ETCTN-funded investigators to improve biopsy quality**
  - **Partial salary support** for these team members will be provided
  - Funded investigators will have **performance criteria in the Terms of Award**

- **Lead academic organization (LAO) teams to include:**
  - An **Interventional Radiologist and Research Pathologist** for acquisition of high quality specimens

- **Each Affiliate (AO) team to include**
  - An **Interventional Radiologist** for acquisition of high quality specimens; **Research Pathologist** optional

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3. Enhance the use of biomarker assays to achieve precision medicine goals

- **Increase use of biomarker assay resources developed through NCI resources coordinated through the National Clinical Laboratory Network (NCLN)**
  - Pharmacodynamic Assay Development and Implementation Section (**PADIS**) lab and network
  - Cancer Immune Monitoring and Analysis Centers (**CIMACs**) for Immuno-Oncology (IO) studies
  - Molecular Characterization (**MoCha**) lab for genomic and transcriptomic evaluation
  - ETCTN **biorepository and accessioning** center
- **Scale back UM1 Biomarker Assay Development administrative supplements**
- **Consolidate ETCTN PK activities**
  - Two **U24-funded PK consortia**
  - **Remove funding** for PK assays from core ETCTN UM1 awards

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Additional goals for the ETCTN 2020-2025

- **Use of Moonshot^{SM} networks/centers** for preclinical work in support of clinical trials (e.g., Patient Derived Xenografts Network (**PDXNet**), Drug Resistance and Sensitivity Network (**DRSN**))

- **Broaden classes of agents** under NCI development (e.g., radiopharmaceuticals, cellular therapies, antibody drug conjugates (ADCs))

- Include **ePRO**'s in early phase ETCTN studies for safety and tolerability determinations

- Further development of **risk-based monitoring approaches**

- **Adoption of the ASCO/Friends broadened eligibility criteria:** age, viral, prior malignancy, organ function, brain metastasis

ASCO/Friends Broadening Eligibility

Does your LOI apply to YIA patients?

Include:

- ASCO/Friends recommendations to modernize eligibility : http://ascopubs.org/doi/full/10.1200/JC
- Clearly list the one responsible ETCTN Group on the LOI.

  → List "champions" or vice-chairs from other groups, such as COG

- Consider both groups (for example ETCTN and COG) to project accrual
- Approval from the corresponding PI at the time of LOI or concept submission
- The protocol title should reflect the target population
- Explanation of selection of eligibility age range

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ASCO/Friends Broadening Eligibility

Does your LOI apply to YIA patients?

Consider at this stage:

- Assent : will be reviewed by the NCI Early Phase CIRB
- Coordination between COG sites and ETCTN sites
- Not an excuse to prolong OEWG timelines
- Address any known safety/toxicity data obtained in patients < 18-yo (or if there are none available)
- Include dosing guidelines for patients < 18-yo
- Address age-appropriate dose modifications, supportive care and toxicity monitoring

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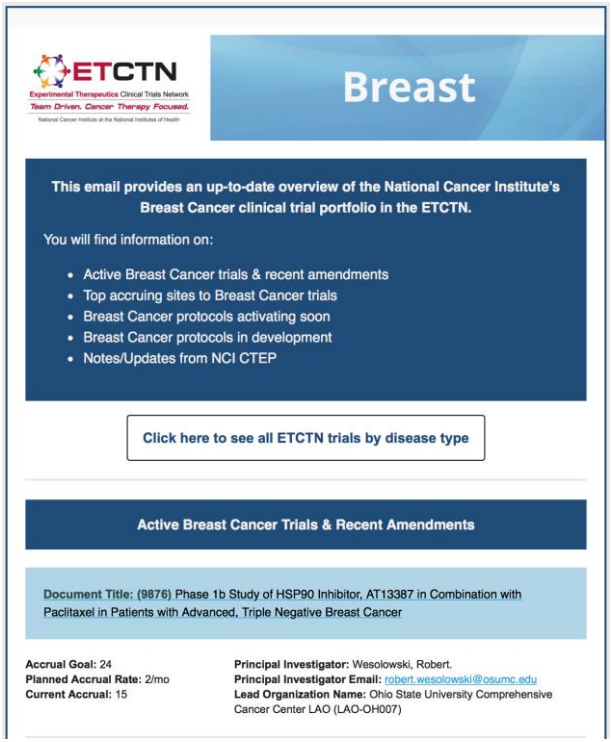
CTEP activities to support ETCTN tracking, site activation and accrual

Activity	Description
Corrective Action Plans (CAPs)	Study chairs of slow accruing trials provide reasons for slow accrual and propose strategies to improve within 6 months; -Including 6 month OEWG re-review; -3-month follow-up to track progress of CAP
Champion Surveys	UM1 award PIs are asked to identify disease-specific site champions for recently activated trials
Slow Accrual Surveys	Send online queries to ETCTN PIs asking to report potential reasons why a trial is slow accruing
Disease-specific Newsletters	Monthly newsletters sent to ETCTN PIs based on their disease specialty, to provide update and easy access to each disease portfolio of trials
Monthly Review of Portfolio Accrual	Categories of trials' progress based on accrual increase, number of activated sites, and time open; trials flagged as 'red' are addressed at CTEP IDB meeting every 6 weeks to develop strategy to improve accrual
Trial-specific Materials	Develop CIRB-approved patient materials for trials, and physician fact sheets
Trial promotion	On Twitter and other platforms

Monthly disease-specific email newsletters



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National Cancer Institute at the National Institutes of Health

Breast

This email provides an up-to-date overview of the National Cancer Institute's Breast Cancer clinical trial portfolio in the ETCTN.

You will find information on:

- Active Breast Cancer trials & recent amendments
- Top accruing sites to Breast Cancer trials
- Breast Cancer protocols activating soon
- Breast Cancer protocols in development
- Notes/Updates from NCI CTEP

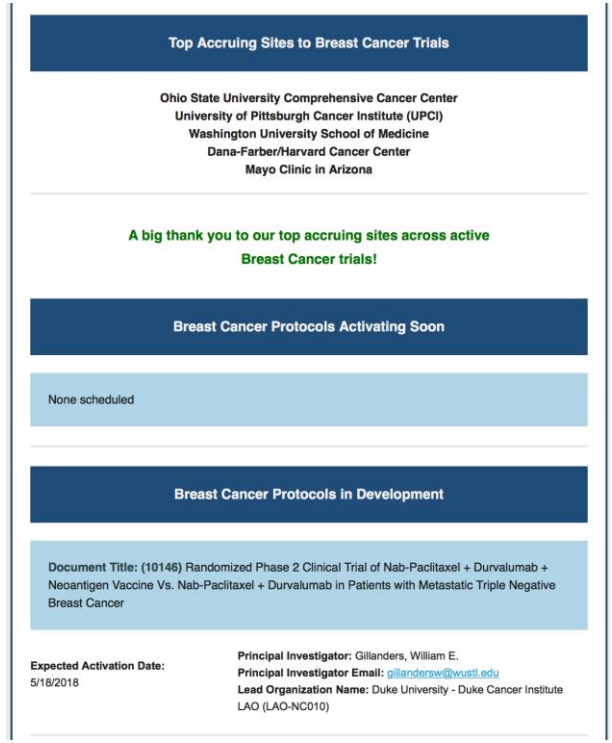
Click here to see all ETCTN trials by disease type

Active Breast Cancer Trials & Recent Amendments

Document Title: (9876) Phase 1b Study of HSP90 Inhibitor, AT13387 in Combination with Paclitaxel in Patients with Advanced, Triple Negative Breast Cancer

Accrual Goal: 24
Planned Accrual Rate: 2/mo
Current Accrual: 15

Principal Investigator: Wesolowski, Robert.
Principal Investigator Email: robert.wesolowski@osumc.edu
Lead Organization Name: Ohio State University Comprehensive Cancer Center LAO (LAO-OH007)



Top Accruing Sites to Breast Cancer Trials

Ohio State University Comprehensive Cancer Center
University of Pittsburgh Cancer Institute (UPCI)
Washington University School of Medicine
Dana-Farber/Harvard Cancer Center
Mayo Clinic in Arizona

A big thank you to our top accruing sites across active Breast Cancer trials!

Breast Cancer Protocols Activating Soon

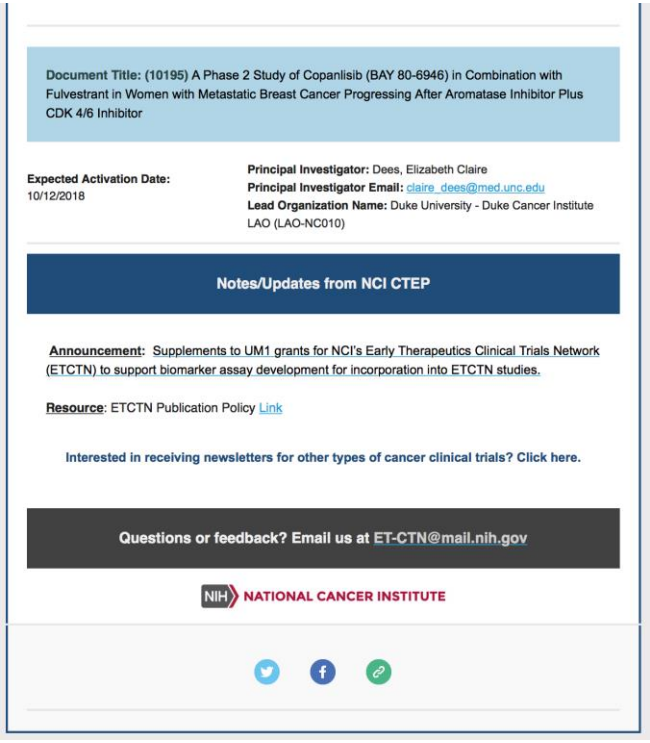
None scheduled

Breast Cancer Protocols in Development

Document Title: (10146) Randomized Phase 2 Clinical Trial of Nab-Paclitaxel + Durvalumab + Neoantigen Vaccine Vs. Nab-Paclitaxel + Durvalumab in Patients with Metastatic Triple Negative Breast Cancer

Expected Activation Date:
5/18/2018

Principal Investigator: Gillanders, William E.
Principal Investigator Email: gillandersw@wustl.edu
Lead Organization Name: Duke University - Duke Cancer Institute LAO (LAO-NC010)



Document Title: (10195) A Phase 2 Study of Copanlisib (BAY 80-6946) in Combination with Fulvestrant in Women with Metastatic Breast Cancer Progressing After Aromatase Inhibitor Plus CDK 4/6 Inhibitor

Expected Activation Date:
10/12/2018

Principal Investigator: Dees, Elizabeth Claire
Principal Investigator Email: claire_dees@med.unc.edu
Lead Organization Name: Duke University - Duke Cancer Institute LAO (LAO-NC010)

Notes/Updates from NCI CTEP

Announcement: Supplements to UM1 grants for NCI's Early Therapeutics Clinical Trials Network (ETCTN) to support biomarker assay development for incorporation into ETCTN studies.

Resource: ETCTN Publication Policy Link

Interested in receiving newsletters for other types of cancer clinical trials? Click here.

Questions or feedback? Email us at ET-CTN@mail.nih.gov

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Human Subjects System (HSS) Instructional Videos

Overview: https://www.youtube.com/watch?v=8s7xRT9mW10

Human Subjects and Clinical Trials Forms Walkthrough: https://www.youtube.com/watch?v=nz9NWFhYOG8

Accessing the Human Subjects System: https://www.youtube.com/watch?v=laBXeNqglto

You can also search YouTube using the phrase: "NIH Human Subjects System"

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

The Experimental Therapeutics Clinical Trials Network (ETCTN) Pharmacokinetic Resource Laboratories U24

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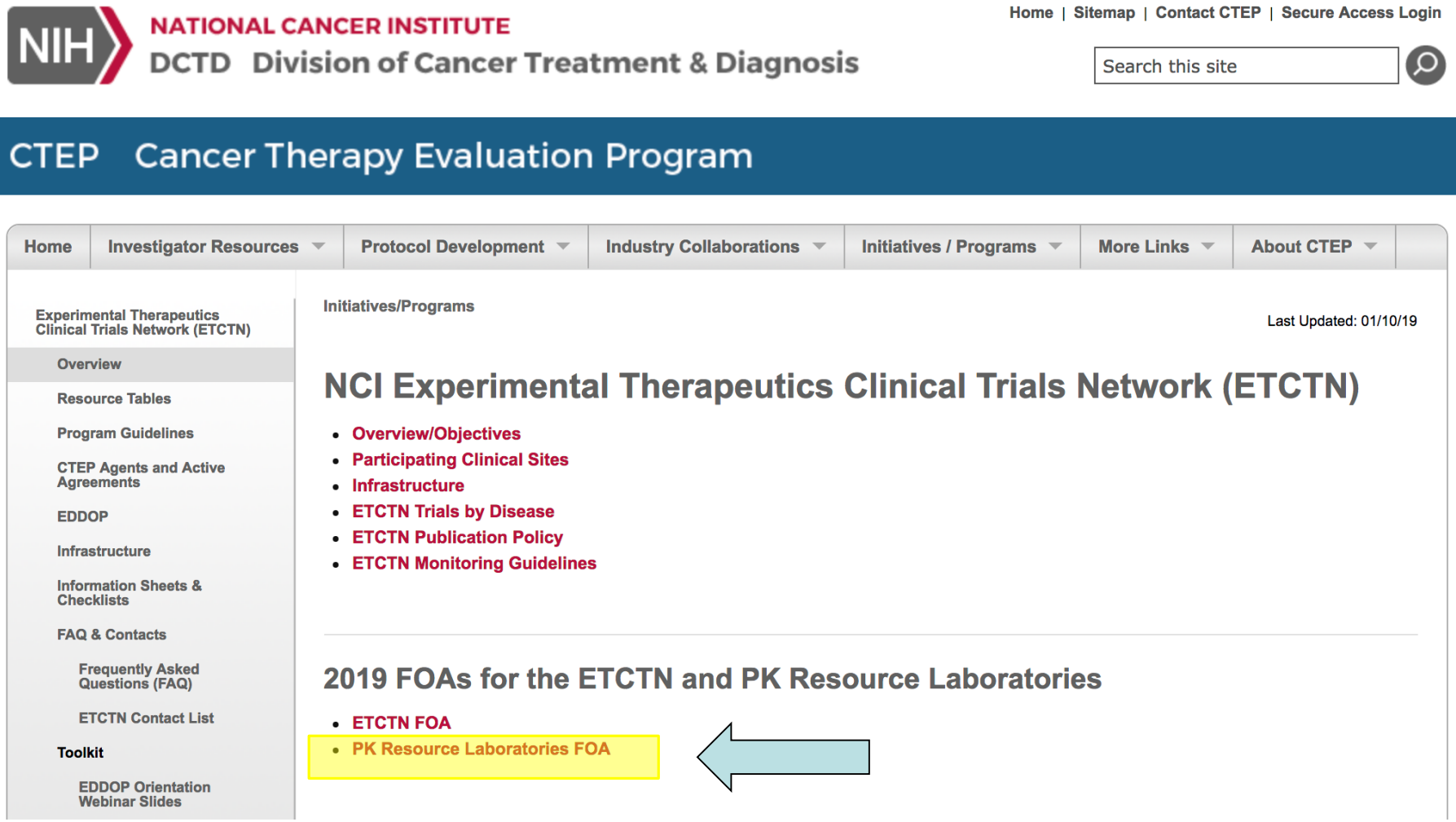
Consolidation of Pharmacokinetics Research and Development in the ETCTN (PK)

What's new?

- Up to two **U24-funded PK consortia in FY2020**
  $750,000 *total funds;* direct costs limited to $320,000/year

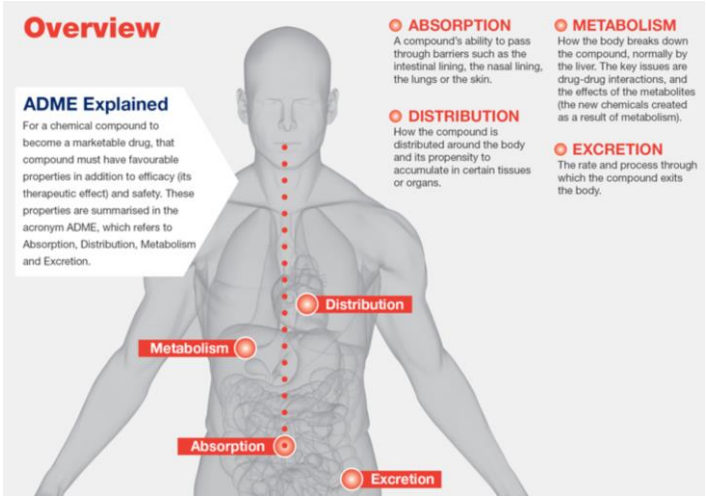
- **Core** ETCTN UM1 awards no longer include funding for PK

This FOA seeks U24 cooperative agreement applications from multidisciplinary groups that will conduct **all pharmacokinetic studies** for ETCTN early phase clinical trials filed to the IND applications in DCTD/CTEP (NCI)



Pharmacokinetics

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion



- Parameters include but are not limited to:
  - area under the curve (AUC)
  - maximum agent concentration (Cmax)
  - clearance (CL),
  - half-life,
  - volume of distribution
  - PK assay development

- All drugs and biologics show inter- and intra-individual variability in PK measures and parameters. (See FDA clinical pharmacology guidance: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm064982.htm)

Goals

- To advance the clinical development of NCI-IND agents through achieving **comprehensive understanding of pharmacokinetic behavior** of these agents studied in ETCTN protocols.

- To create **Pharmacokinetics Resource Laboratories** (PK Laboratories) that
  will support the Experimental Therapeutics Clinical Trials Network (ETCTN)

- To organize specimen **collection and subsequent analysis** of pharmacokinetic endpoints, drug-drug interactions, cytochromes P450 (CYP) interactions, and food effects

- To assure the availability of physicians, clinical pharmacologists, nurses and scientists who have the **appropriate expertise in pharmacokinetic studies** for early drug development and translational research

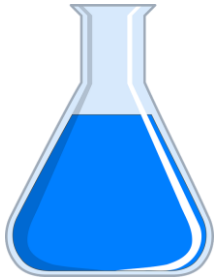
The intent is for the PK experts to be an integral part of a collaborative drug development group

Area(s) of expertise

- Technical and clinical evaluation of assays for study drug(s) PK that are quality assured/quality controlled and standardized for use in plasma and/or tumor tissue
- Evaluation of drug-drug interaction risk for each drug and its active metabolites in relationship to other therapeutics and concomitant medications
- Definition of PK sampling strategies, limited sampling strategies and population PK
- Evaluation of PK in plasma and tissue
- Timely reporting to the study team and to NCI of the results of PK analyses.

Expectations

- **Infrastructure** to support PK studies for ETCTN clinical trials from trial initiation through clinical development of NCI-IND agents
- **Engagement** of multidisciplinary clinical and pharmacology experts
- Ability to perform biostatistical/computational **data analysis**, interpretation, and compartment modeling for PK studies
- Extensive experience in PK studies **for early phase clinical trials**
- Specific capabilities:



- Performing PK analysis in high quality specimens in the context of clinical trials
- Established Standard Operating Procedures **(SOPs) for data quality and laboratory quality** control, including institute quality control for reagents and technologies for ETCTN PK studies
- Conducting PK studies according to Good Laboratory Practice **(GLP) principles**
- Providing **preliminary data** to inform the design and conduct of PK studies for investigational drugs;
- Evaluating PK data from early phase experimental therapeutic clinical trials using single or combinations of novel NCI CTEP IND agents;
- Serving as **PK resource centers within the ETCTN** for collaborative validation studies, statistical and computational analyses, data management, and coordination of ETCTN pharmacokinetic studies; and
- Providing technical and scientific expertise to **CTEP Project Teams** related to PK activities in the drug development plan
- Ability to **accept and transfer specimens** from clinical trials both nationally and internationally

PD(s)/PI(s) Responsibilities

- Overseeing **all the activities** of the ETCTN PK laboratory
- Determining overall **research strategy** for ETCTN pharmacokinetic studies for early phase clinical trials
- Ensuring **timely** completion of PK analyses and reporting their results
- Ensuring **timely** preparation, presentation, and publication of PK results and research findings
- Ensuring **compliance** with the applicable rules for the conduct of clinical research

Due on **May 22, 2019, by 5:00 PM local time** of applicant organization

National Cancer Institute

The Experimental Therapeutics Clinical Trials Network (ETCTN)

Interventional Radiology Working Group (IRWG)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

ETCTN Interventional Radiology Working Group (IRWG)

- **Purpose:** Maximize the efficient acquisition of IR-guided biopsy samples that are sufficient for molecular analysis.

- **Members to Date:**
  - Meet via telecon as needed

- **All ETCTN sites welcome**

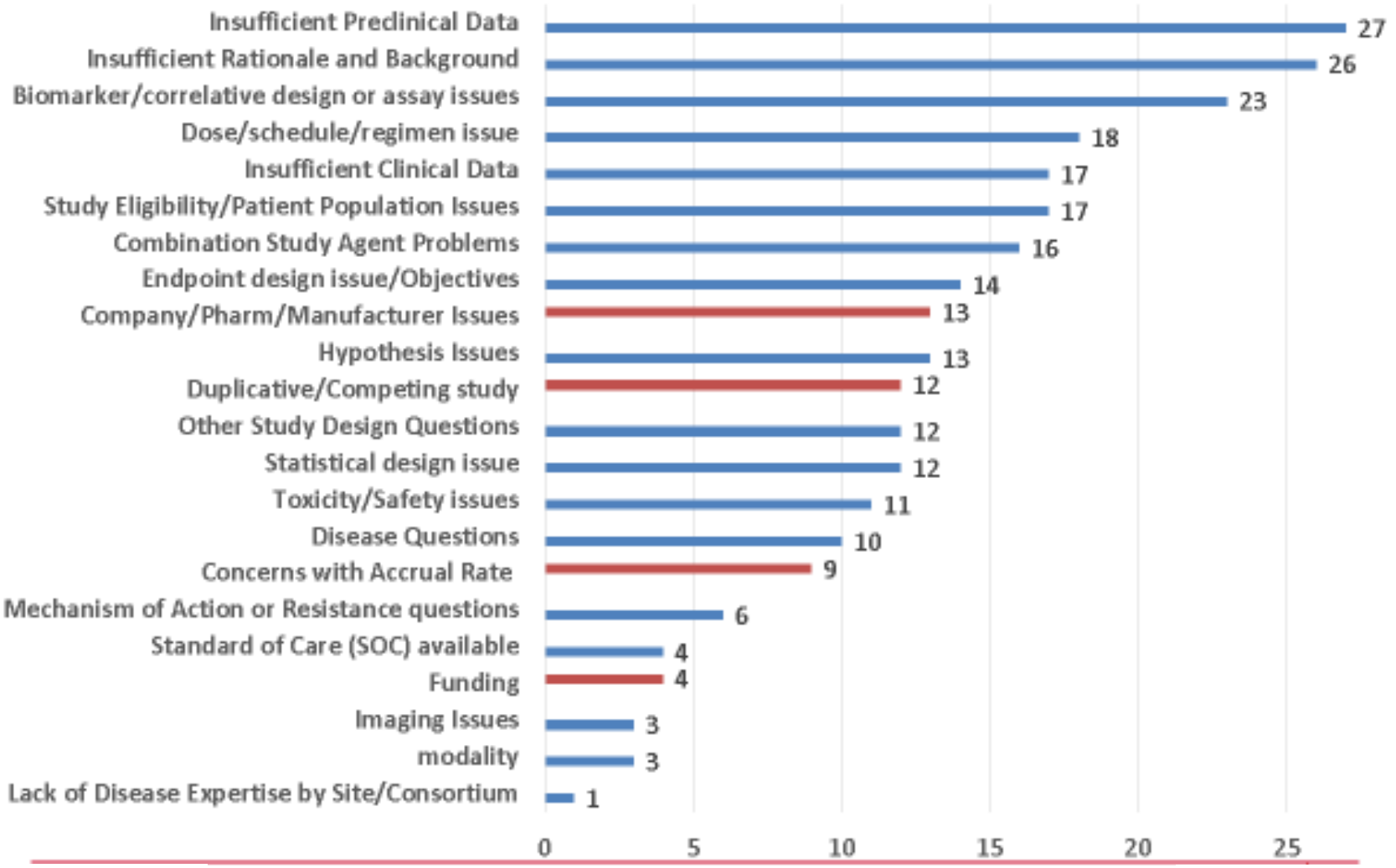
- **For more information**
  - ETCTN@mail.nih.gov

Mayo	Atwell	Thomas
	Kurup	Anil
	Lim	Vun-Sin
	Adjei	Alex
PMH/Moffitt/BCCa/VCU	Siu	Lillian
	Choi	Junsung
	Beecroft	Robert
	Martin	Montgomery
	Strife	Brian
Yale	LoRusso	Patricia
	Kim	Kevin
	Hafez	Navid
JHU	Carducci	Michael
	Hong	Kelvin
	O'Mara	Daniel
DFCC/Harvard	Shapiro	Geoff
	Silverman	Stuart
	Shyn	Paul
MDACC/Colorado	Meric-Bernstam	Funda
	Tam	Alda
	Sabir	Sharjeel
	Sheth	Rahul
	Johnson	David
NCI	Shankar	Lalitha
	Ivy	Percy
	Arnaldez	Fernanda

National Cancer Institute

Backup Slides

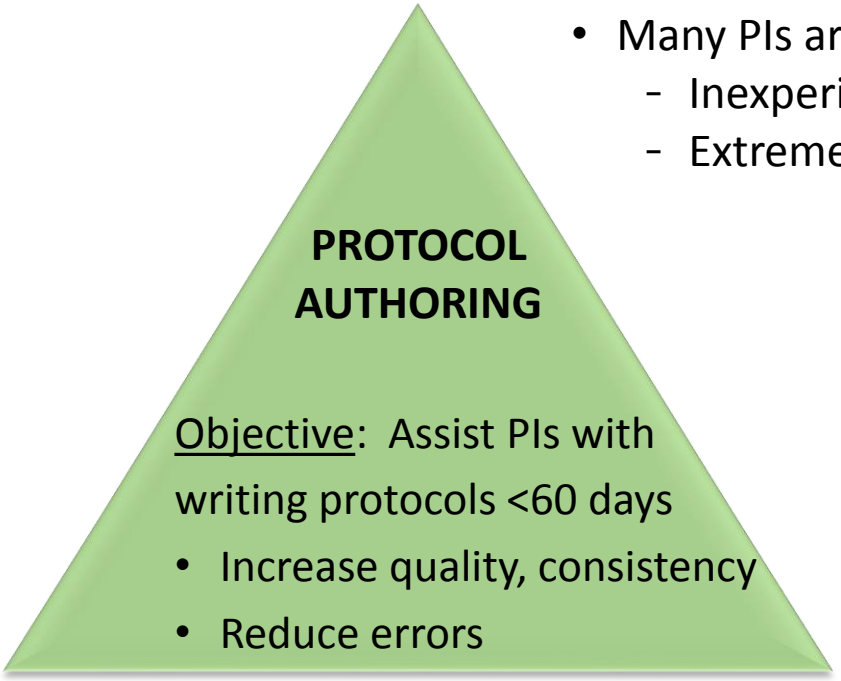
Reasons for LOI disapproval



Protocol authoring decision: Triangulation of evidence

Grant PI interviews

- Many PIs are early career investigators
  - Inexperienced in writing protocols
  - Extremely busy schedules



OEWG timeline analysis

- Long activation delays due to multiple revisions post-PRC (median=4 rounds)

CIRB data review

- 50% of protocols required multiple CIRB reviews
- Median of 26 stipulations/protocol
  - Poorly written
  - Inconsistent w/ templates

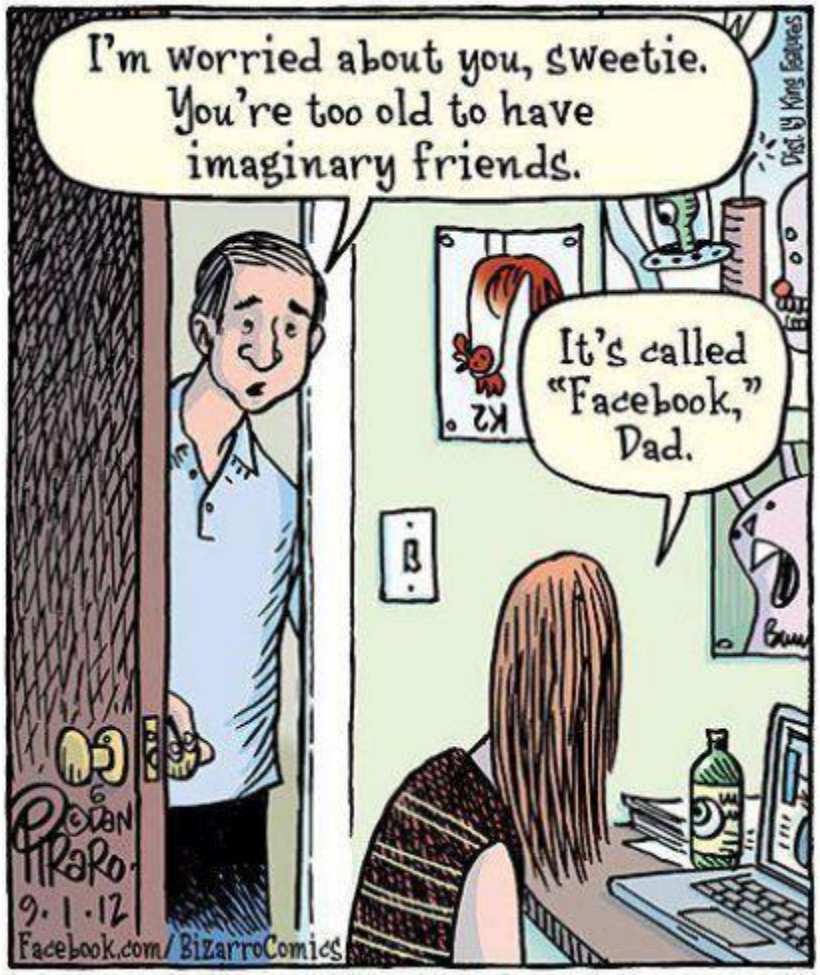
ETCTN External Program Review

- **Reviewers were recruited from government and pharma, both nationally and internationally in January 2018**

  Greg Reaman, FDA, USA
  Eric Rubin, Merck & Co., USA
  Janet Dancey, NCIC & ORI, Canada
  Ian Walker, CRUK, UK

- **Review questions included:**
  - Have **phase 1 /2 trials opened** at an adequate rate?
  - Are trials answering **important questions and optimally designed**?
  - Were steps taken to adapt to cancer **precision medicine** challenges?
  - Does the program conform to **GCP standards**?
  - Is **team science** promoted? Is this a collaborative, interactive research network?
  - Are adequate clinical research opportunities provided for **early career investigators**?

- Reviewers **responded positively to all questions**, thought the program **achieved its goals and objectives,** and provided additional **input for future endeavors.**


I'm worried about you, sweetie. You're too old to have imaginary friends.
It's called "Facebook," Dad.
Dist. by King Features
K2
B
Dan Piraro
9.1.12
Facebook.com/BizarroComics