NCI Pediatric Early Phase Clinical Trials Network (PEP-CTN)

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Pediatric Early Phase Clinical Trials Network (PEP-CTN)

- Dedicated component focused on early phase clinical trials is key element of NCI pediatric drug development program
- Requirements for early phase clinical trials distinctive from phase 3 clinical trial requirements (i.e., distinctive from COG)
  - Limited institutions
  - Intensive data collection
  - Close study monitoring
  - Detailed pharmacokinetic (and pharmacodynamic) sampling
  - Rapid development and activation of protocols using standard templates

Setting (1)

- NCI has supported pediatric phase 1 program since early 1990s
- COG Phase 1 Consortium productive over most recent funding period
  - 15 new trials approved by CTEP
  - Evaluations of range of novel therapies: checkpoint inhibitors, antibody-drug conjugates, molecularly targeted agents, oncolytic viruses, DDR modulators
  - Effective incorporation of PK and imaging

Setting (2)

- Increased agent opportunities through Title V of the FDA Reauthorization Act (FDARA) of 2017
- Directs FDA to create list of molecular targets substantially relevant to the growth and/or progression of pediatric cancers
- “Molecularly targeted pediatric cancer investigation"
  - To be performed if the product is intended for treatment of an adult cancer and directed at a molecular target that FDA determines to be "substantially relevant" to a pediatric cancer
  - Designed to yield clinically meaningful pediatric clinical data

Settings (3)

- Research Opportunities
- Targeted agents primarily developed for adult cancer targets
- Pediatric specific targeted agents (agents targeting oncofusions)
- Agents modifying DNA damage response
- Immunotherapy (including antibody-drug conjugates)

Setting (4)

- Increasing options for “first in children” clinical trials
- Agents in (or entering) COG phase 3 trials
  - Selumetinib (ACNS1831 and ACNS1833) veliparib (ACNS1721)
  - Temsirolimus (ARST1431)
  - Blinatumomab (AALL1331 and AALL1731)
  - Brentuximab vedotin (AHOD1331 and ANHL12P1)
  - ^{131}I-MIBG (ANBL1531)
  - Inotuzumab ozogamicin (AALL1732)

Settings (5)

- Opportunities for improvements
- Prioritization process: slow, diffuse, with lack of transparency
- Study design: dose finding less common, phase 1-2 studies more common
- Enhancements to meet increasing regulatory requirements & expectations
- Enhancements to expand genomic characterization for eligibility

Pediatric Early Phase Clinical Trials Network (PEP-CTN)

CTEP-NCI

PEP-CTN Operations & Biostatistics

Pharma-Biotech

PEP-CTN Core Institutions

Phase 2 Expansion Institutions

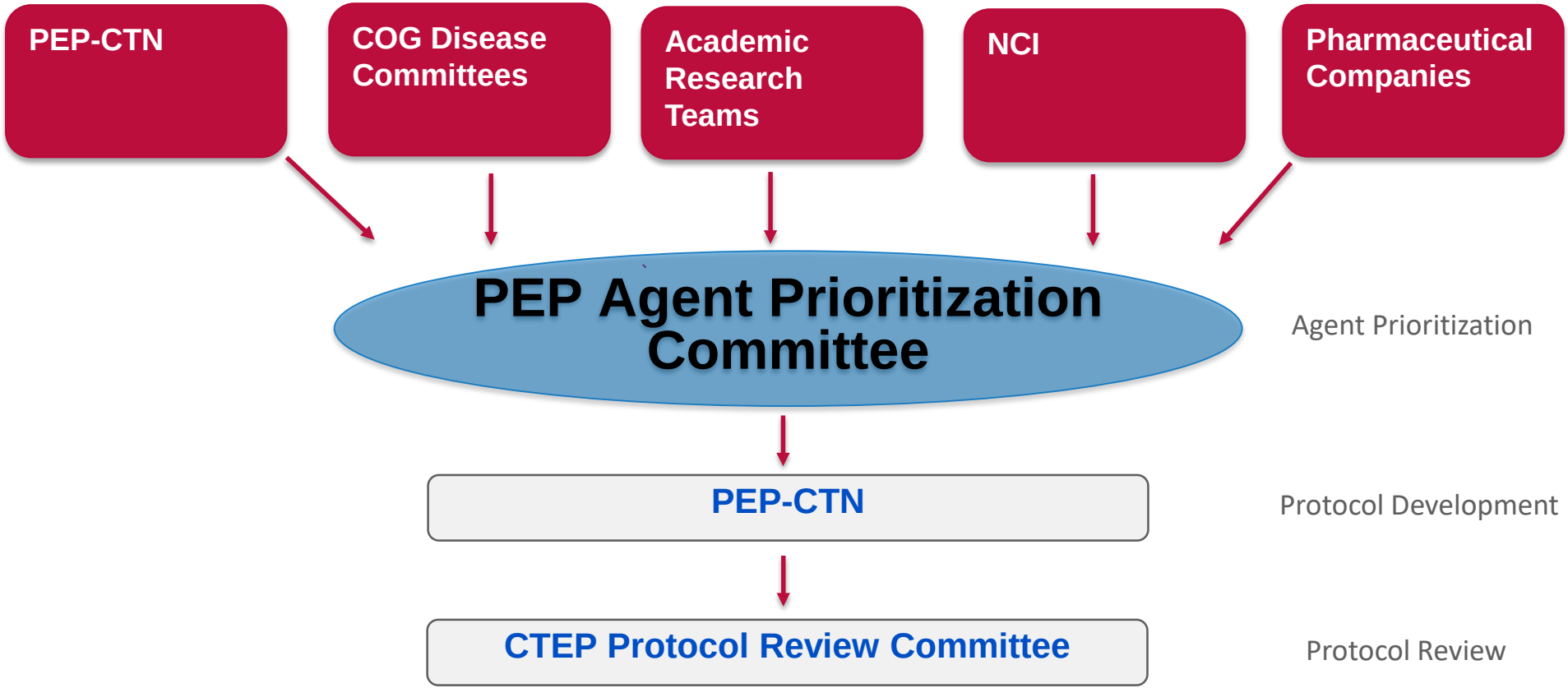
Changes Incorporated into PEP-CTN

- Pediatric Early Phase Clinical Trials Network (PEP-CTN)
  - Core institutions for conducting phase 1 studies with intensive PK and monitoring (same institutions as existing COG Phase 1/Pilot Consortium)
  - Additional institutions credentialed for participation in phase 2 studies
  - Allows seamless phase 1 to phase 2 expansion
- Application of central monitoring to supplement onsite auditing
- Integration of genomics into PEP-CTN
- Single portal for agent prioritization through Pediatric Early Phase (PEP) Agent Prioritization Committee

PEP Agent Prioritization Committee (APC)

- Include key stakeholder representation in APC for robust single point of prioritization:
  - PEP-CTN leadership
  - COG representatives
  - NCI
  - FDA
  - Independent researchers
  - Advocates

Pediatric Early Phase Agent Prioritization Committee



PEP Agent Prioritization Committee

- Accepts and reviews applications that provide agent information and rationale for prioritization for testing in children with cancer
- Committee decision options: Proceed to protocol development or defer pediatric development at this time
- Approved agents move immediately to protocol development
- Advantages
  - Single portal for entry of agents to PEP-CTN
  - Incorporates range of stakeholders for robust decision-making
  - Accelerates pace of agents moving into testing in children with cancer

Central Remote Monitoring

- Require inclusion of a specific monitoring plan in all PEP-CTN protocols.
- Describe specific central monitoring procedure to include at a minimum:
  - Source data verification of patients at each enrolling site [e.g., for informed consent, eligibility, first two courses of treatment (drug administration and AEs), and any other key data items]
  - Tracking of source data verification (through Medidata Rave),
  - Timeliness of data submissions and query resolutions, and
  - Factors that may trigger more frequent monitoring or on-site audits.

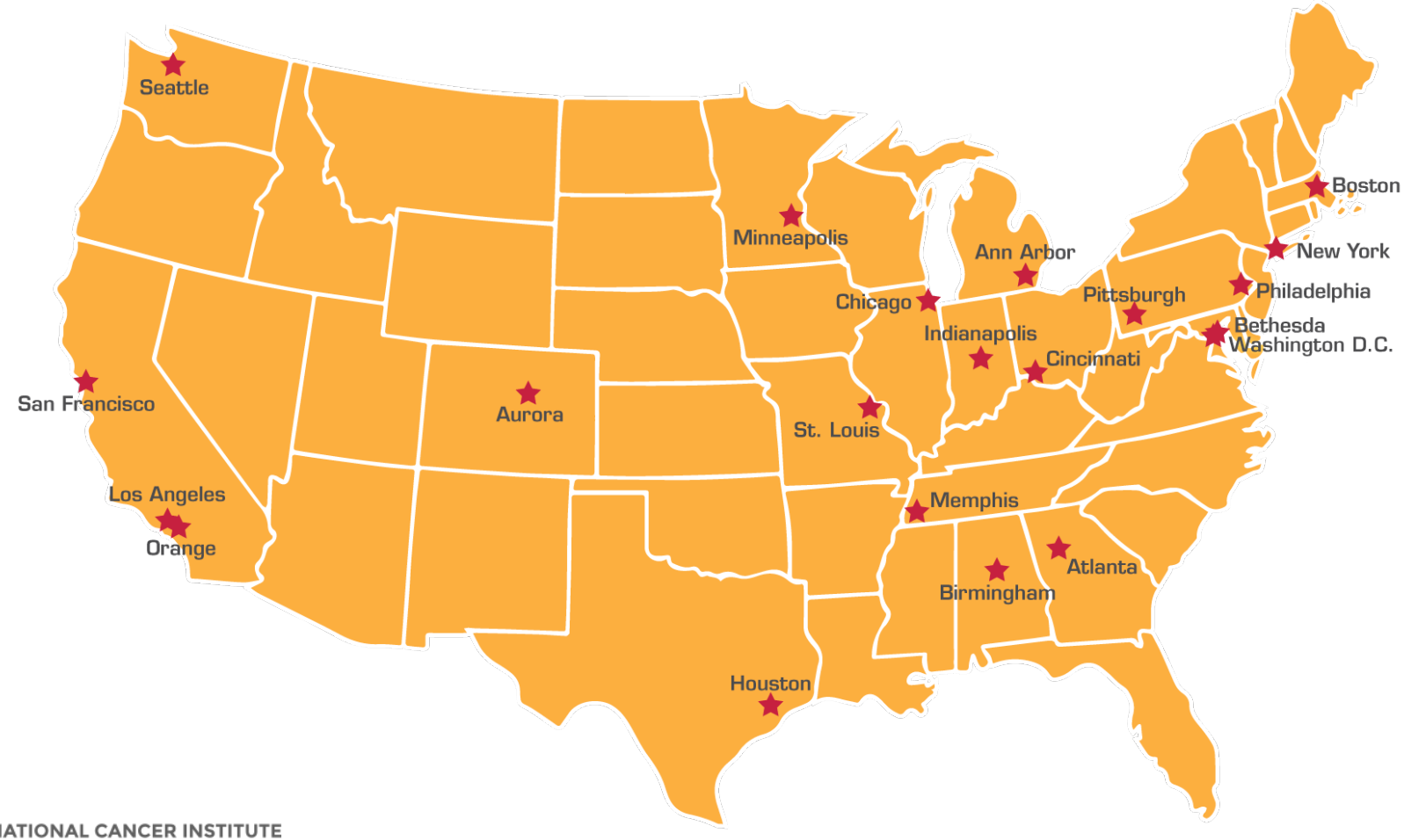
Three Key Organizational Entities/Functions (1)

- PEP-CTN Operations and Data/Statistics Center (ODSC) with responsibilities including:
  - Clinical trial protocol development;
  - Data Management/Analysis;
  - Quality Control/Quality Assurance including central data monitoring;
  - Statistical design and analysis of early phase clinical trials;
  - Regulatory affairs and compliance;
  - Managing tissue acquisition, tissue shipping, and tissue storage; and
  - Logistical management for PEP-CTN operations, including teleconferences, electronic communications, meetings, etc.

Three Key Organizational Entities/Functions (2)

- PEP-CTN Member institutions:
  - "Core Member Institutions" for participation in all PEP-CTN clinical trials and for the support of PEP-CTN clinical research activities;
  - Phase 2 expansion and pilot institutions for participation in selected clinical trials.

PEP-CTN Core Member Institutions



Three Key Organizational Entities/Functions (3)

- PEP-CTN Translational Research Program:
  - Genomics and translational biology for PEP CTN clinical trials
  - Pharmacokinetics program for PEP-CTN clinical trials
  - Imaging for PEP-CTN clinical trials

Pharmaceutical-Biotech Advisory Committee

- PEP-CTN to establish committee of pharmaceutical and biotech company representatives
  - Provide insight on how to enhance the ability of PEP-CTN to collaborate with industry
  - Forum for making PEP-CTN capabilities more visible to industry

Summary

- PEP-CTN strives to be the clear choice for “first-in-children” evaluations of promising anticancer agents
- Timely agent prioritization and protocol development for rapid, seamless phase 1-2 clinical trials of promising agents
- Incorporation of requisite genomic and pharmacology studies
- Rigorous adherence to regulatory expectations
- Valued partner for pharmaceutical and biotech companies
- Accelerator of the discovery of new, more effective treatments for children with cancer

QUESTIONS???

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