

Progress Through Partnership: Integrating Stakeholders into the Clinical Research Process

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CTTI - PATIENT GROUP AND CLINICAL TRIALS EXPERT
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Background

- Translation is a team sport. No single player can bring new treatments all the way to the finish line.
- Relevant communities and stakeholders should be included as partners, not “subjects” or “consumers”.
- Early engagement of affected or interested parties is critical to success.
- Patient groups, NIH, industry and others increasingly recognize the need for partnership.

Partnership across the spectrum of the clinical research enterprise

- Make sure that the research questions matter to patients
- Ensure feasible protocols with acceptable burden
- Promote stakeholder input into consent language
- Include patients in implementation and safety oversight
- Improve dissemination through communication with relevant communities

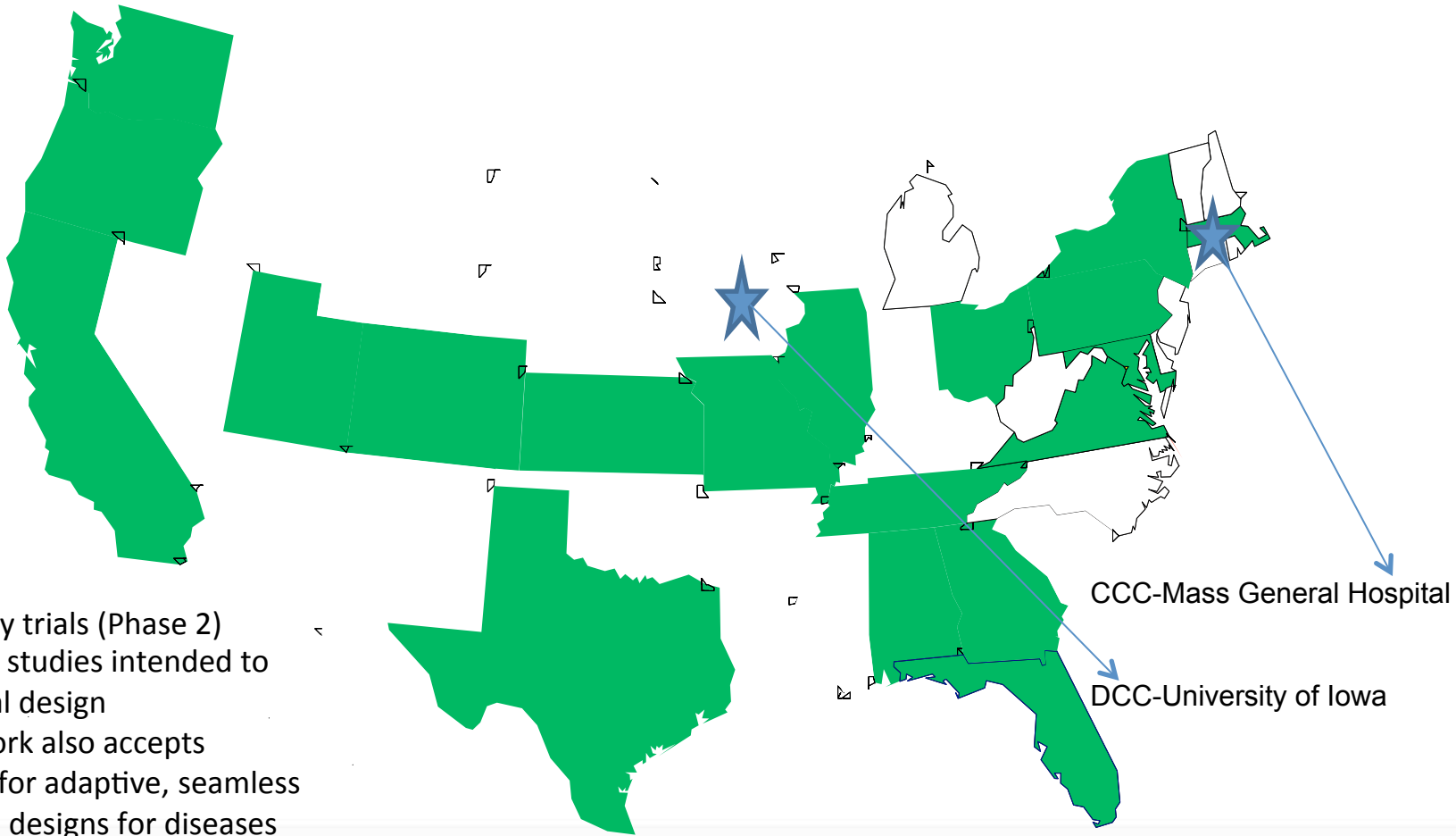
NEURONEXT - CLINICAL TRIALS NETWORK FOR NEUROLOGICAL DISORDERS

EXAMPLE FOR PATIENT ENGAGEMENT ACROSS THE
PROJECT LIFESPAN

NCATS

NeuroNEXT

Clinical trial network for neurological disorders



- Exploratory trials (Phase 2)
- Biomarker studies intended to inform trial design
- The Network also accepts proposals for adaptive, seamless Phase II/III designs for diseases with prevalence of <5,000 in US

NeuroNEXT goals

- **Test promising therapeutics in Phase 2 clinical trials**
 - Use biomarkers when available
 - Provide results that allow for Go/No go decisions
- **Accelerate drug development through an established clinical trials infrastructure**
 - Respond flexibly to opportunities as they arise
 - Share expertise between disease areas
- **Decrease the time/cost between trial design and trial completion**
 - Use a central IRB, and standing master trial agreements
- **Coordinate public/private sector efforts**
 - Test best therapeutics, whether from academic or industry investigators
 - **leverage NINDS' existing relationships with academic investigators and patient advocacy groups**

Working with patients and communities

- All NeuroNEXT Protocol Working Groups include a patient representative to provide input on the protocol as well as the informed consent from the very beginning.
- The Steering Committee for each study includes a patient representative.
- The Data and Safety Monitoring Board has a patient representative.

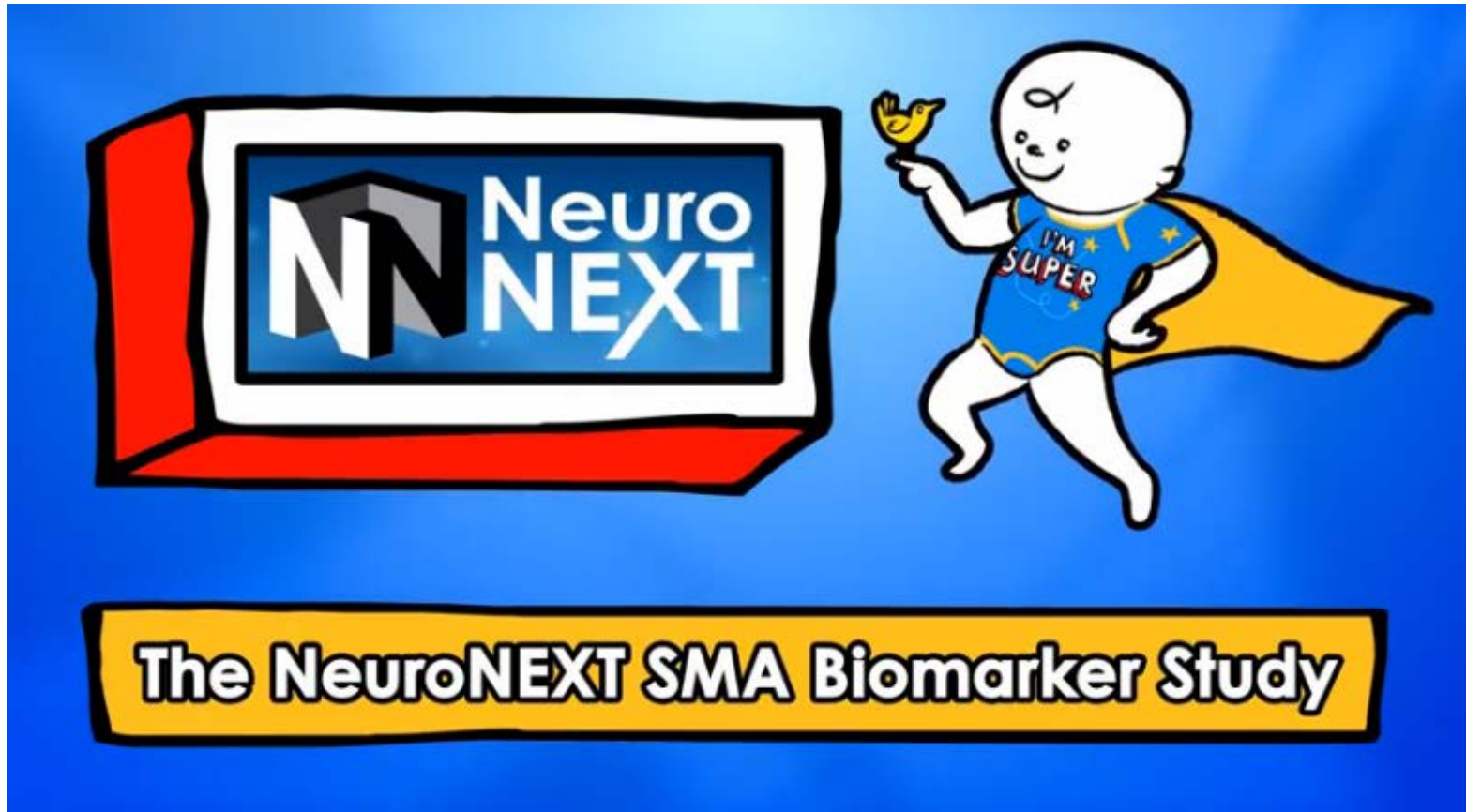
Example: NeuroNEXT study NN101

- Spinal Muscular Atrophy (SMA) Biomarkers in the Immediate Postnatal Period of Development
 - PI: Stephen Kolb MD PhD
 - Ohio State University
- This study was done in collaboration with Families of SMA (providing travel funding).
- Families and stakeholders were included from the onset

Protocol Working Group

- Family and patient representatives provided critical input on
 - Travel feasibility
 - Protocol burden
 - Length of visits
 - Recruitment and consent material

Video



NeuroNEXT Study: NN 102

- Secondary and Primary pRogressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis – SPRINT-MS
 - PI: Robert Fox
 - Cleveland Clinic
 - This study is supported by Medicinova and the National Multiple Sclerosis Society as part of a private-public partnership with the NIH.
 - Patient representatives are included in protocol working group, steering committee and DSMB

NeuroNEXT contact

Dr. Elizabeth McNeil

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Stroke

NINDS/NIH

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www.neuronext.org

Lessons learned

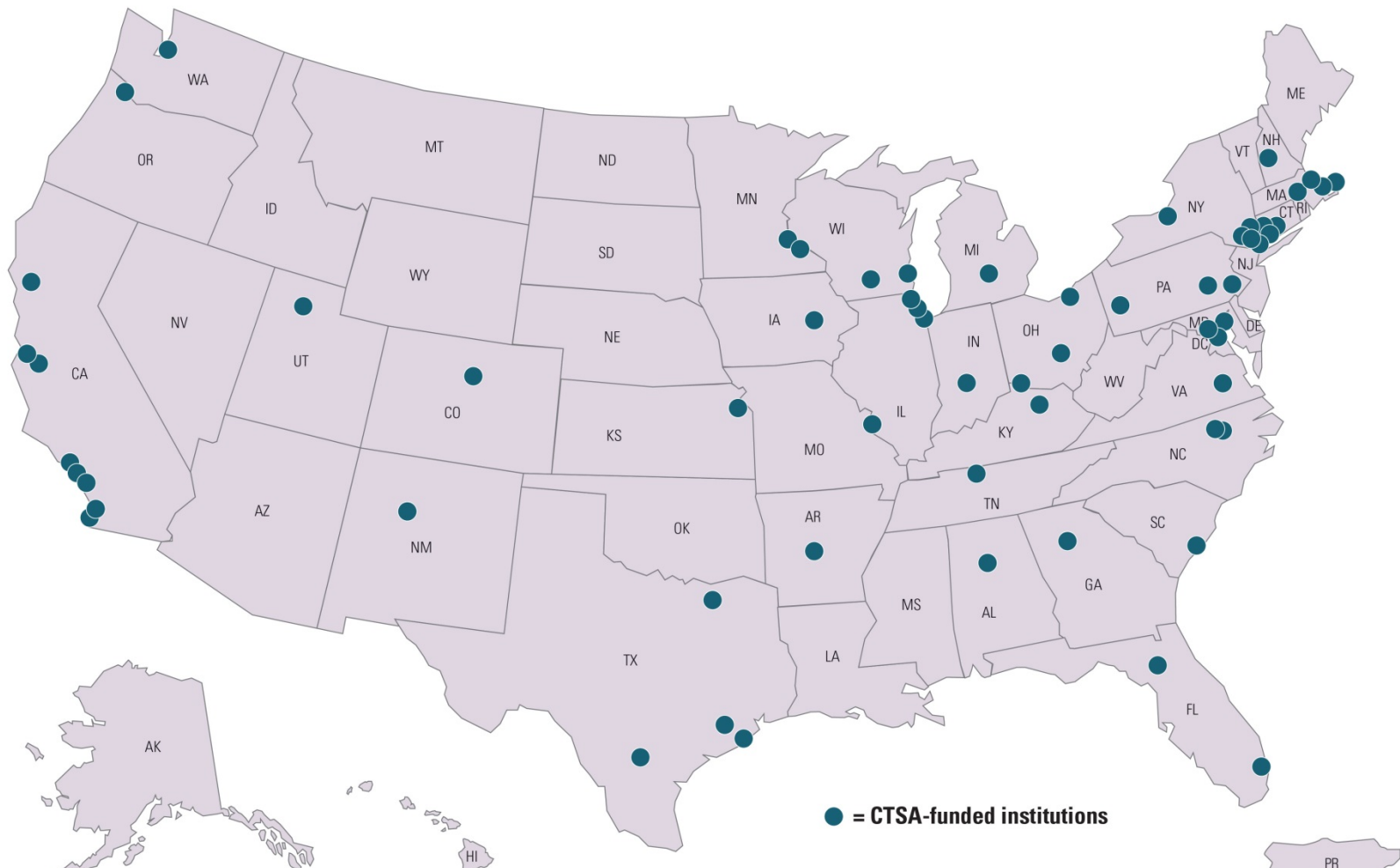
- We need best practices in this somewhat uncharted territory
- Establish transparent way of inviting patient representatives
- No need for scientific expertise for patient representative, but need enough information to be an equal partner
- Consider all issues related to patient representative participation (time, cost, work, travel, needs)

THE CLINICAL AND TRANSLATIONAL SCIENCE AWARD PROGRAM

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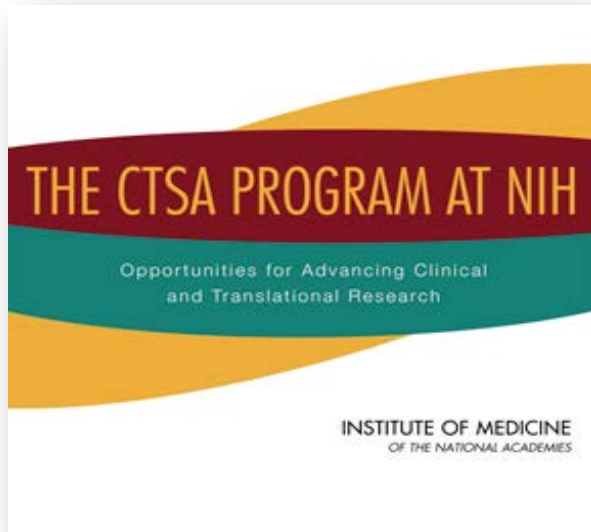
Clinical and Translational Science Awards (CTSA) Program Sites (n=62)

- National consortium of medical research sites
- Work together to improve the way clinical translational research is conducted nationwide
- Provide training for clinical translational researchers



IOM Report on the CTSA Program

Recommendations



- IOM CTSA Report released June 2013
- Report includes 7 recommendations
 1. Strengthen leadership of the CTSA program by NCATS
 2. Reconfigure and streamline CTSA consortium
 3. Build on the strengths of the individual CTSA's across the spectrum of research
 4. Formalize and standardize clear, consistent, and novel metrics
 5. Advance innovative education and training models with a focus on team science, leadership, and entrepreneurship
 6. Ensure community engagement in all phases of research
 7. Strengthen translational research relevant to child health

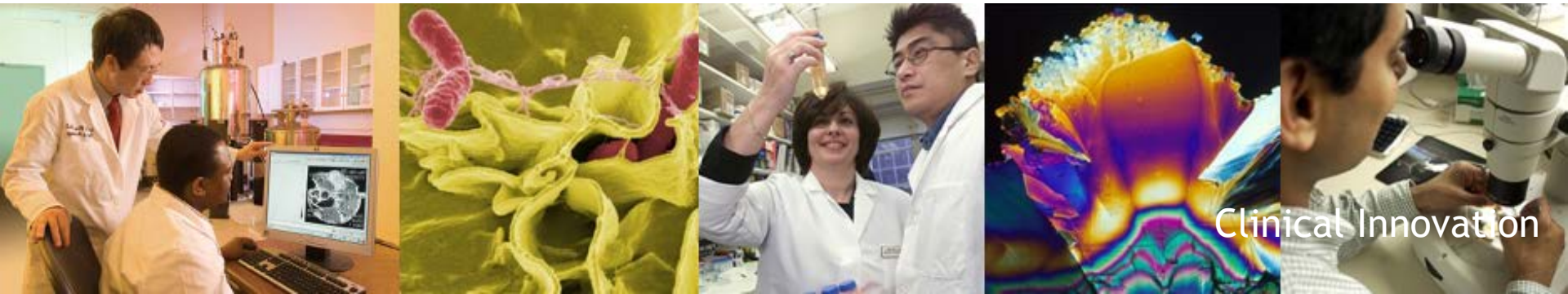
NCATS Director Statement: Institute of Medicine Report on the CTSA Program at NIH

June 25, 2013

In 2006, recognizing the need for a "new vision" for translational and clinical science, the National Institutes of Health (NIH) established the [Clinical and Translational Science Awards \(CTSA\)](#) program. The institutions supported by the CTSA program have been transformative to the science and culture of those academic centers across the country, providing expertise, capacities, training and collaborations to advance clinical translational science as a discipline across the translational spectrum.

NCATS Division of Clinical Innovation Strategic Goals

1. Train, develop and cultivate future leaders in translational science;
2. Innovate translational science;
 1. Engage patients and communities in every phase of the translational process;
 2. Promote the integration of special and underserved populations in translational research across the lifespan.
 3. Innovate processes to increase the quality and efficiency of translational research, particularly of multi-site trials;
 4. Advance the use of modern informatics in translation;
3. Communicate effectively with internal and external audiences using clear, timely, and consistent messages;
4. Measure success of the CTSA program through a set of common metrics;
5. Partner effectively with NIH and other stakeholders;



Clinical Innovation

RARE DISEASES CLINICAL RESEARCH NETWORK (RDCRN)

- A Model for Collaborative Rare Diseases with patient advocacy groups as partners

NCATS

RDCRN: Background Information

- Established in 2003
- Expanded in 2009
- Each Consortium: multiple diseases/ investigators / sites collaborative clinical research Involving Patient Advocacy Groups (PAGs)
- Consortium awardees receive no more than \$1.25 M Total Cost/year U54 awards
- 3rd cycle (renewal- 2014):
 - 22 distinct multi-site Clinical Research Consortia and a central Data Management and Coordinating Center (DMCC)

Special Features

- *The RDCRN is unique in its approach to addressing rare diseases as a group. Each consortium studies a group of minimum three related rare diseases.*
- *The direct involvement of PAGs as research partners is a major feature of this network.*
- Collaboration with 10 NIH ICs

About RDCRN

- Each consortium conducts at least two multi-site clinical studies (including one longitudinal study), has a training program, pilot project program
- Collectively, the RDCRN is studying 200 rare diseases in natural history and clinical trials at 240 clinical sites located in the US and in 14 countries.
- There are more than 90 active protocols.
- 29,000 patients have enrolled in clinical studies.
- There have been 174 trainees.
- There are 2,290 collaborative consortium members.
- There are 98 PAGs as research partners, collectively formed a Coalition (CPAG).

<http://rarediseasesnetwork.epi.usf.edu/>

NIH
ORDR/NCATS, NCI, NHLBI,
NIAID, NIAMS, NICHD, NIDCR,
NIDDK, NIMH, NINDS, ODS

**Dystonia
Coalition**

**Coalition of Patient
Advocacy Groups
(CPAG)**

**Porphyria Rare Disease Clinical
Research Consortium**

PAG

**North America Mitochondrial
Diseases Consortium**

**Primary Immune Deficiency
Treatment Consortium**

**Developmental Synaptopathies
Associated with TSC, PTEN
And SHANK3 Mutations**

**The Frontotemporal Lobar
Degeneration Clinical
Research Consortium**

**Inherited Neuropathies
Consortium**

**Nephrotic Syndrome
Study Network**

**Rare Lung Diseases
Consortium**

**Lysosomal
Disease Network**

**Rare Kidney
Stone Consortium**

**Vasculitis Clinical
Research Consortium**

**Clinical Research in ALS & Related
Disorders for Therapeutic Development**

**Autonomic Disorders
Consortium**

**Sterol and Isoprenoid
Diseases Consortium**

**Rett, MECP2 Duplications
and Rett-Related
Disorders Consortium**

**Brittle Bone Disorders
Consortium**

**Chronic Graft Versus
Host Disease**

**The Data Management and
Coordinating Center**

**Urea Cycle Disorders
Consortium**

**Brain Vascular
Malformation Consortium**

**Genetic Disorders of
Mucociliary Clearance**

**Consortium of Eosinophilic
Gastrointestinal Disease Researchers**



- Collaborative Clinical Research
- Centralized Data Coordination and Technology Development
- Public Resources and Education
- Training



CPAG

Coalition of Patient Advocacy Groups

Collectively, the Coalition of Patient Advocacy Groups (CPAG) represents the perspective and interests of all patient advocacy organizations associated with the clinical research consortia. Through collaboration, patient advocacy groups and researchers can make faster progress toward new treatment options and cures, which can improve the lives of all persons and families affected by a rare disease. [Learn More >](#) | [CPAG Committee Roster](#)

News

Featured Links

- [NORD](#)
- [NIH Office of Rare Diseases](#)
- [Genetic and Rare Diseases Information Center \(GARD\)](#)
- [Genetic Alliance](#)
- [AARDA](#)
- [OOPD/FDA](#)

Rare Diseases Advocacy Groups

Click on a Rare Diseases Network Consortium to see corresponding advocacy groups:

[Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium \(ARTFL\)](#)



[Autonomic Rare Diseases Clinical Research Consortium](#)



[Brain Vascular Malformation Consortium](#)

[Brittle Bone Disorders \(BBD\)](#)



[Chronic Graft Versus Host Disease Consortium \(cGVHD\)](#)



[Consortium of Eosinophilic Gastrointestinal Disease Researchers \(CEGIR\)](#)

[CREATE: Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium](#)

[Developmental Synaptopathies Consortium \(DSC\)](#)



[Dystonia Coalition](#)



[Genetic Disorders of Mucociliary Clearance Consortium](#)



[Inherited Neuropathies Consortium](#)



[LDN Lysosomal Disease Network](#)



[NEPTUNE: Nephrotic Syndrome Rare Disease Clinical Research Network](#)



[North American Mitochondrial Diseases Consortium](#)



[Porphyrias Consortium](#)



[Primary Immune Deficiency Treatment Consortium \(PIDTC\)](#)



[Rare Kidney Stone Consortium](#)

[Rare Lung Diseases Consortium](#)

[Rett Syndrome, MECP2 Duplications, & Rett-related Disorders Consortium](#)



[STAIR: Sterol and Isoprenoid Diseases Consortium](#)



[Urea Cycle Disorders Consortium](#)



[Vasculitis Clinical Research Consortium](#)

Coalition of Patient Advocacy Groups (CPAG)

- Each RDCRN consortium has direct involvement of patient advocacy groups (PAGs)
 - Advise on operations, activities and strategy
- Collectively, CPAG represent all PAGs associated with the RDCRN
 - Meets via monthly call
 - Influences the direction of the RDCRN as a whole

RDCRN Program Contact:

Rashmi Gopal-Srivastava, Ph.D.
Director, Extramural Research Program, ORDR
(*Program Director, RDCRN*)
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NEW THERAPEUTIC USES PROGRAM

A FRAMEWORK FOR PPP

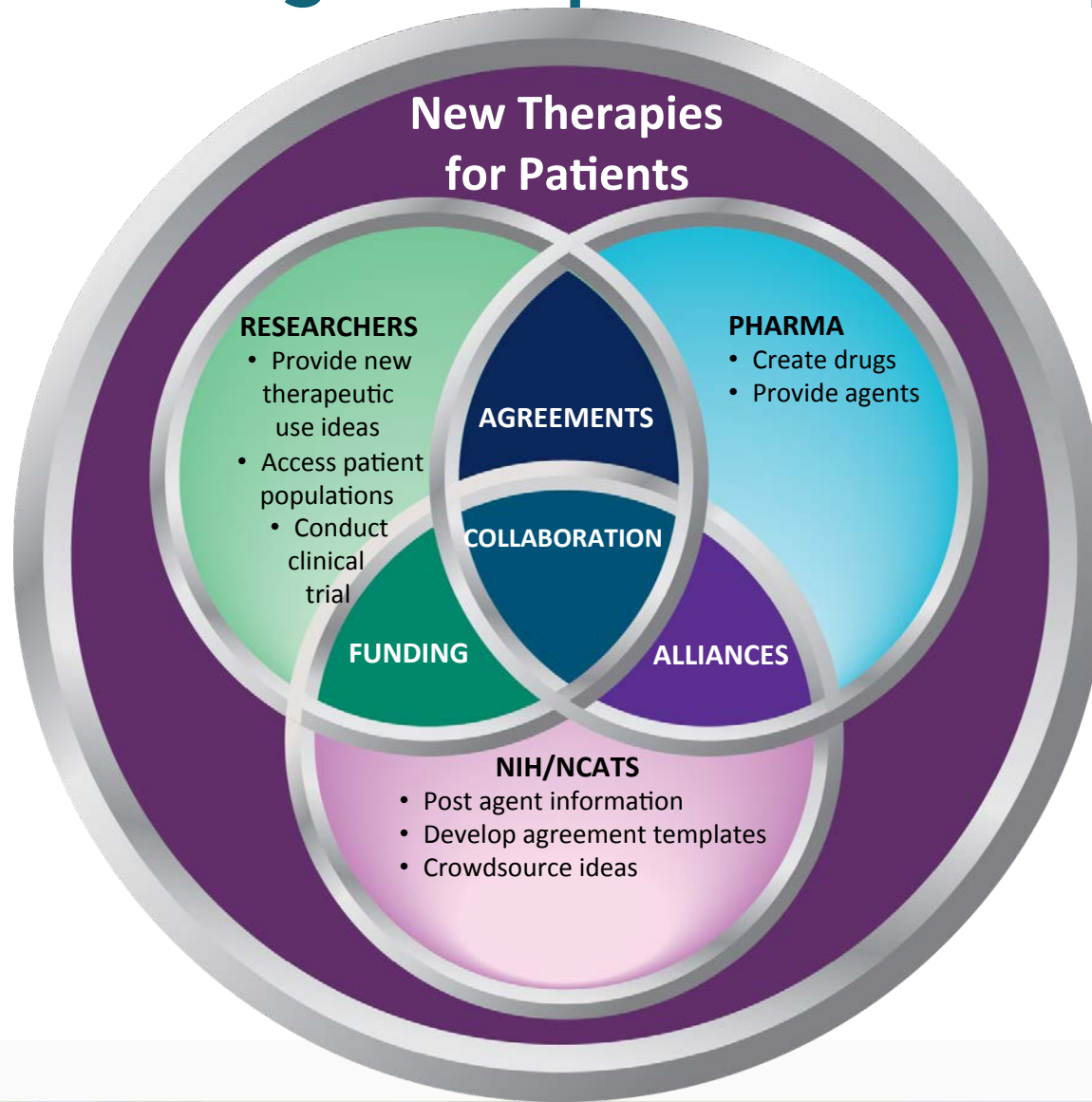
NCATS

NCATS: NTU Program

The current initiative:

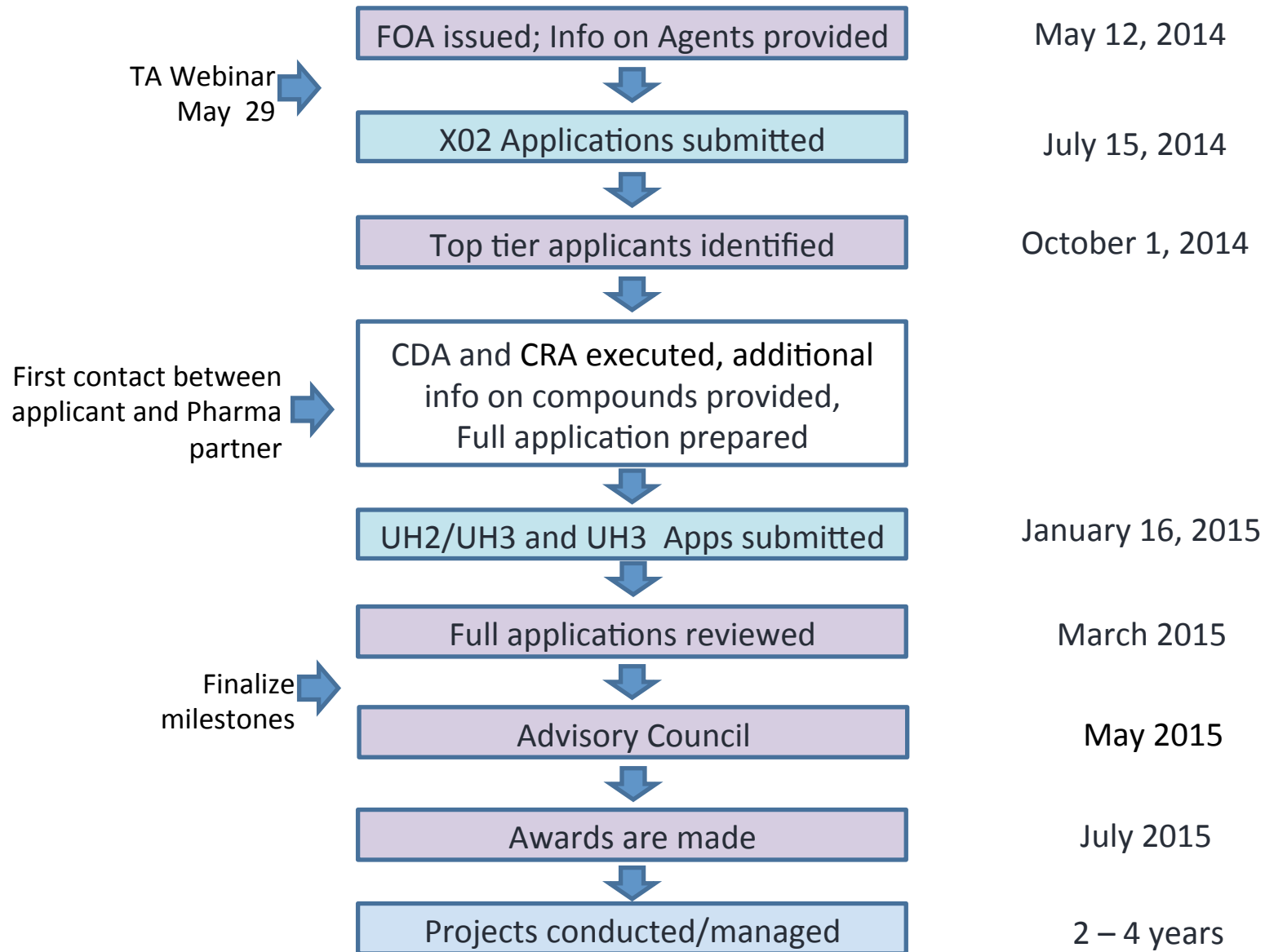
- Allows investigators to propose new therapeutic uses for Agents from pharmaceutical company partners across a broad range of human diseases
- Expands the program to include pediatric indications
 - **NIH provides:** template partnership (confidential disclosure and collaborative research) agreements, review, funding, and oversight
 - **Pharmaceutical partners provide:** Agents, in kind support, and pertinent data
 - **Academic researchers provide:** deep understanding of disease biology, new concepts to test, and access to patients

Accelerating Therapeutic Development



Agents: Criteria for Selection

- Mechanism of action for each Agent must be known and selective
- Pharmacokinetics are suitable to explore the mechanism in a new indication
- Phase 1 clinical trial has been completed
- Safety profile is understood
- Pre-clinical and clinical Agent and placebo will be provided for studies
- Availability of data/information for regulatory documents to enable an investigator to file an Investigational New Drug (IND) application



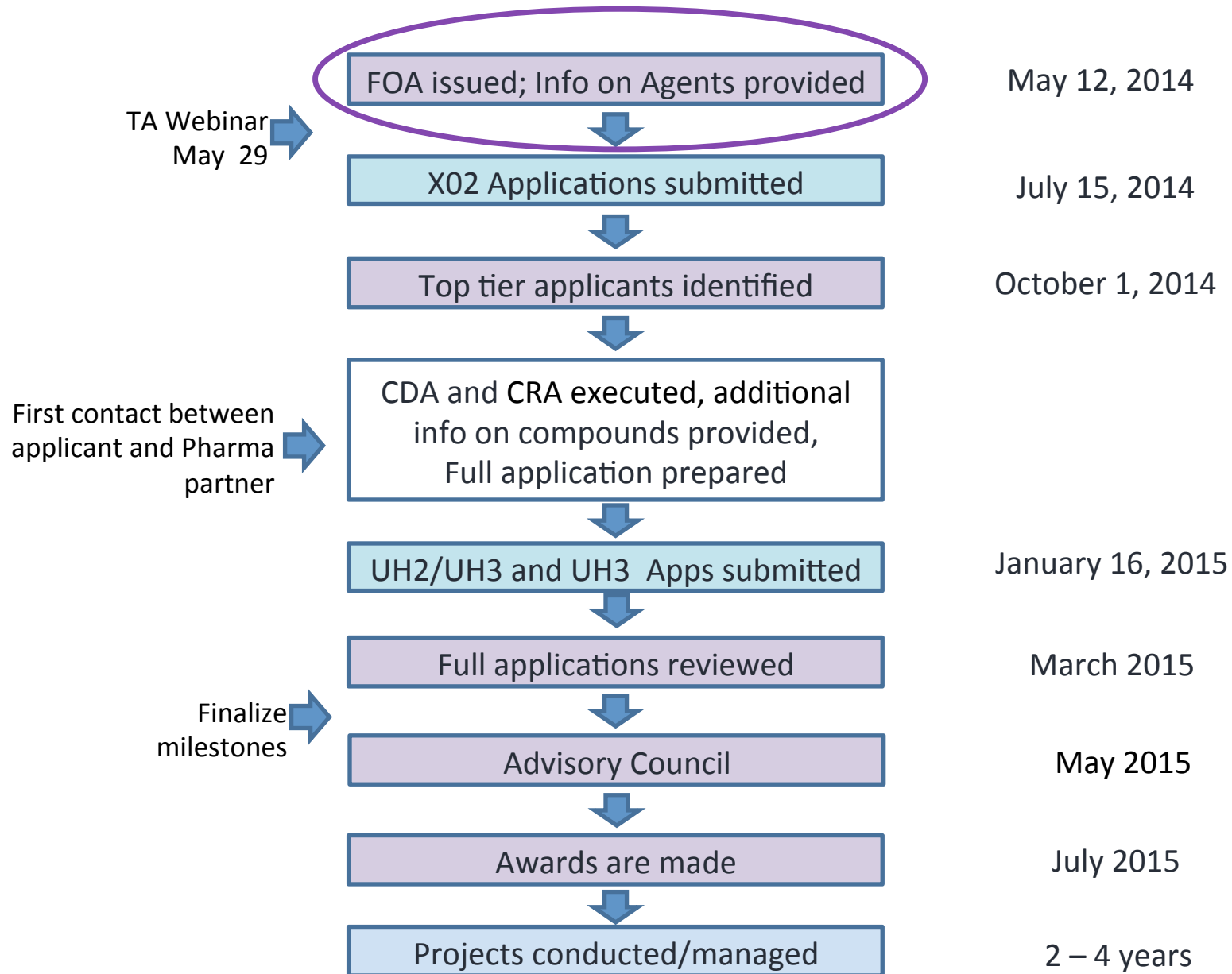


Table of Agents for Adult Indications

Code Number & Link to More Information	Mechanism of Action	Original Development Indication(s)	Route of Administration Formulation Available (CNS Penetrant±)
RWJ-445380	Cathepsin S Inhibitor	Psoriasis, Rheumatoid Arthritis	Oral
SAR114137	Cathepsin S (CTSS) Inhibitor	Chronic Pain (OA pain, neuropathic pain, chronic low back pain)	Oral (might be CNS penetrant)
CNTO 888 Carlumab	Chemokine (C-C motif) Ligand 2 (CCL2) Selective human IgG1 Kappa Monoclonal Antibody	Idiopathic Pulmonary Fibrosis	Intravenous (i.v.) (No)
AZD9291	Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Sensitizing and T790M Resistance Mutations Inhibitor	Non-Small Cell Lung cancer (NSCLC)	Oral (Unknown)
SAR110894	Histamine H3 Receptor Antagonist	Symptomatic treatment of Alzheimer's disease	Oral (Yes)
JNJ-31001074 Bavisant	Histamine Type 3 (H3) Receptor Antagonist	Attention Deficit Hyperactivity Disorder	Oral (Yes)
AZD4017	11-Beta Hydroxysteroid Dehydrogenase Type 1 (11 β -HSD1) Inhibitor	Diabetes	Oral (Low)
AZD2014	Mammalian Target of Rapamycin (mTOR) Serine/Threonine Kinase (dual TORC1 and TORC2) Inhibitor	Solid Tumors	Oral (Unknown)

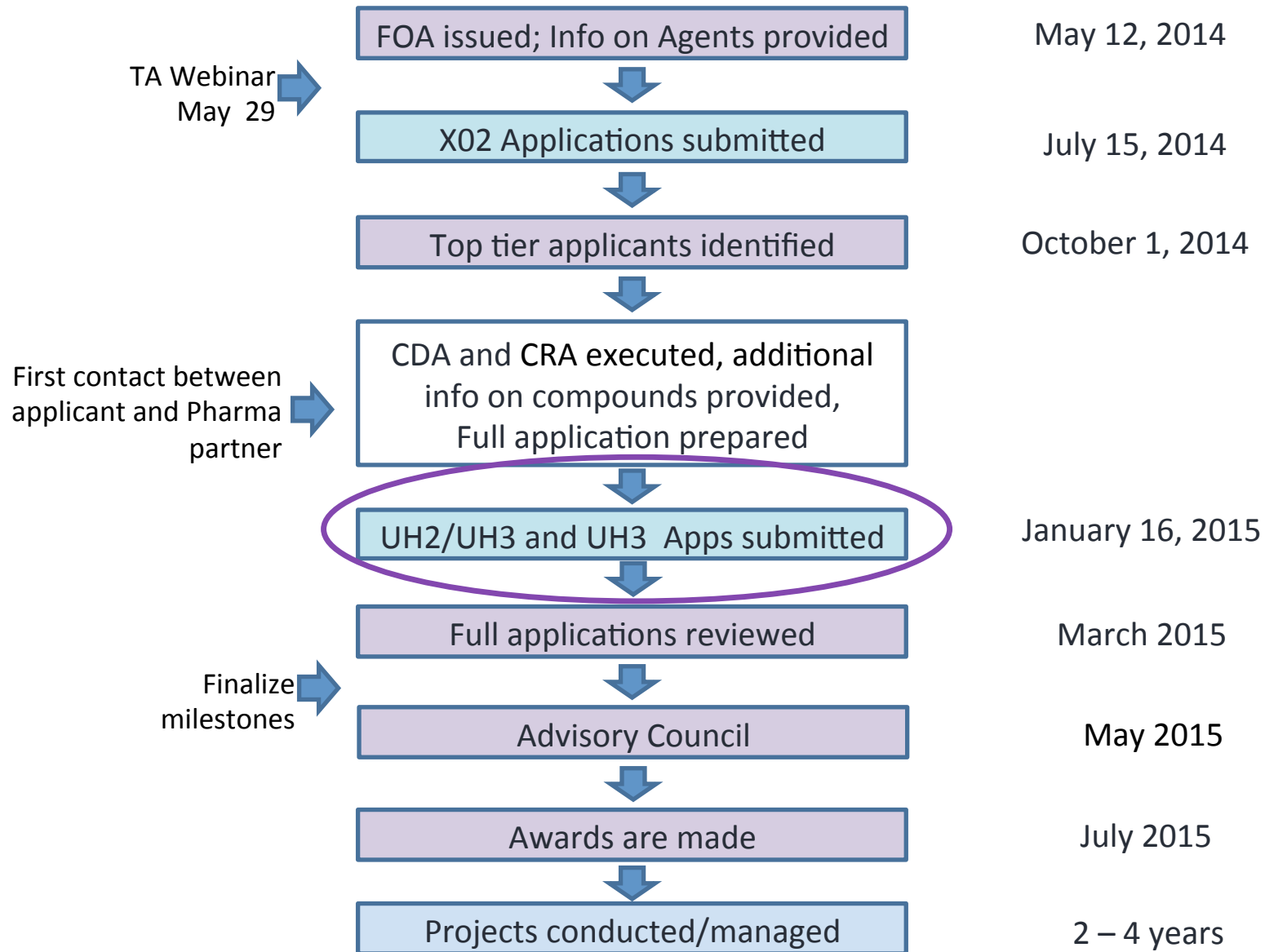
AstraZeneca	AZD2624
Mechanism of Action	Neurokinin-3 receptor, tachykinin receptor 3 (NK3R; TACR3) antagonist; http://www.ncbi.nlm.nih.gov/gene/6870
Overview	<p>AZD2624 is a potent human NK3R antagonist (K_i of 2 nM; calcium flux IC_{50} of 2.6 nM) with >100-fold selectivity over a panel of 184 other receptors, enzymes and ion channels, including NK2R, NK1R and cholecystokinin 2 receptor (CCK2R). The major human metabolite has only slightly weaker human NK3R antagonist potency (calcium flux IC_{50} of 9.0 nM) with selectivity of >10-fold to NK2R. In gerbils, AZD2624 significantly reversed senktide-induced suppression of locomotor activity by both the intraperitoneal and oral routes with ED_{50} values of 0.48 mg/kg and 1.1 mg/kg, respectively.</p> <p>From consideration of in vitro data and in vivo findings in pre-clinical species, AZD2624 is anticipated to demonstrate low CNS exposure at therapeutic doses.</p>
Safety/Tolerability	<p>AZD2624 has been administered orally in single doses up to 80 mg and multiple doses up to 30 mg twice daily (BID) for 7 days or 40 mg every day (QD) for 6 days in healthy volunteers, and also at 40 mg QD for 28 days in schizophrenia patients. The most common AEs in excess of placebo were headache, abdominal discomfort, eye pain, somnolence and upper respiratory tract infection, all mild to moderate, as well as an apparent primary pharmacology, mechanism-based reduction in serum testosterone in males.</p> <p>Preclinical studies of up to 3 months duration have been performed.</p>
Additional Information	<p>Clinically significant, transient, reversible, and asymptomatic reductions in total serum testosterone have been noted at doses/exposures estimated for primary target engagement in male subjects. Testosterone and LH lowering have also been seen with other NK3R antagonists (talnetant [GlaxoSmithKline] and osanetant [Sanofi]; ref). NK3R antagonism-induced lowering of hypothalamic GnRH pulsatility is the suspected cause. The effect of AZD2624 on female gonadal hormones is not known.</p> <p>AZD2624 at 40 mg QD for 28 days was not found to be effective in schizophrenia patients.</p>
Suitable for and Exclusions	<p>Until further data are available, AZD2624 is considered not suitable for administration in pregnant or lactating women or in women who are trying to conceive. Conception while on treatment must be avoided. Since interaction with the metabolism of oral contraceptives cannot be excluded, trial protocol will require the use of alternative highly effective forms of contraception.</p> <p>Monitoring for reductions in total serum testosterone should be included in male patients.</p> <p>Suitable for study in indications, sub-populations and/or endpoints that are manifestly distinct from those previously studied for this compound or mechanism of action.</p>
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD2624&Search=Search
Additional Characteristics: CNS Penetration/Pediatric Diseases	<p>AZD2624 has low CNS penetration and, thus, is probably not suitable for a CNS indication.</p> <p>Pediatric disease projects cannot be supported at this time.</p>
Publications	http://www.ncbi.nlm.nih.gov/pubmed/20937004

UH2/UH3 vs. UH3 Application

- The decision of whether to submit a UH2/UH3 or UH3 application should be made by the investigators based on the existing data on the Agent as it relates to the proposed new therapeutic use
- UH2/UH3 supports a two-stage approach in adults, including feasibility studies (pre-clinical or Phase 1b trials; up to 1 year) prior to a Phase 2a trial
- UH2/UH3 for pediatric indications supports a two-stage approach, including a longer feasibility stage (up to 2 years) to cover required pre-clinical toxicity studies
- UH3 supports implementation of Phase 2a trials (no feasibility studies needed)

Approach section

Describe a plan for the involvement of Patient Advocacy Groups (PAGs) in the project. If PAGs are not included, provide a rationale for their exclusion.



Take-home messages

- Our understanding of what causes diseases creates unprecedented opportunities for translation
- The process currently takes too long
- Partnership among the stakeholders in the clinical research enterprise is critical to accelerate progress
- We need to develop, demonstrate and disseminate effective models of collaboration, considering
 - Incentives
 - Risk/benefit