

**The CTSA Program and Rare Disease Research**  
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Oregon Health & Science University

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**Disclosures**

**None**



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**Outline**

- CTSA Program: Introduction and Relevance to Rare Disease Research
- CTSA Resources for Rare Disease Researchers (Local)
- CTSA Regional/National Networks
- CTSA CC-CHOC Rare Disease Workgroup
- Challenges in Rare Disease Research with Possible Solutions, Many Involving CTSA
- Distributed Biobank Project as Example



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### Background: Impetus for the CTSA Program



Former NIH Director Zerhouni & others: To ensure new discoveries lead to improved public health, clinical science must evolve to better:

- ❑ Implement biomedical discoveries.
- ❑ Develop, test, bring new prevention strategies into medical practice more rapidly.
- ❑ Catalyze change - lower barriers between disciplines.
- ❑ Encourage creative, innovative approaches.

**CTSA** Clinical & Translational Science Awards

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### Goals for the CTSA Consortium

The CTSA consortium, developed since 2006, funded by NIH NCRR has the following five goals:

- Training and Career Development of Clinical and Translational Scientists
- Building National Clinical and Translational Research Capability
- Enhancing Consortium-Wide Collaborations
- Enhancing the Health of our Communities and the Nation
- Encouraging T1 Translational Research

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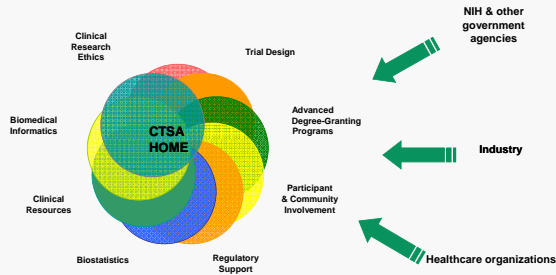
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### Each CTSA Institution is a home for clinical and translational science



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**CTSA Resources for Researchers: Local**

- CTSA provide numerous resources for researchers:
- Study design/biostatistics/informatics
- Clinical Resources (formerly GCRCs), Core Labs Often
- Community Engagement
- Contracting/Partnerships with Industry
- IRB/Ethics & Regulatory Assistance
- Enrollment and Retention Strategies
- Education and Training in Many of These Areas
- However resources vary between sites:
- Limited funding: some resources with "fee for service"
- Standardization not mandated so sites differ in resources
- Rare disease research (RDR) not generally a focus

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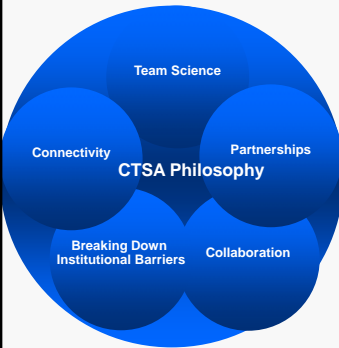
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**Guiding Principles of the CTSA Consortium**



Nice overlap between CTSA Philosophy & what's needed for successful RD research

**Collaborations to improve rare diseases research**

**Partnerships: essential role of PAGs to facilitate research**

**Establish best practices across research consortia for translation of basic discoveries into practice (in rare diseases)**

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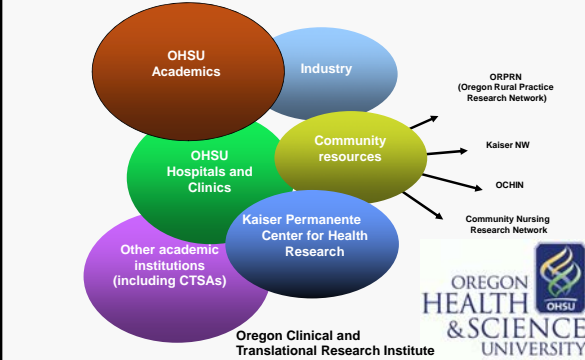
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**Local Partnerships/Networks in CTSA: OCTRI Example**



Oregon Clinical and Translational Research Institute

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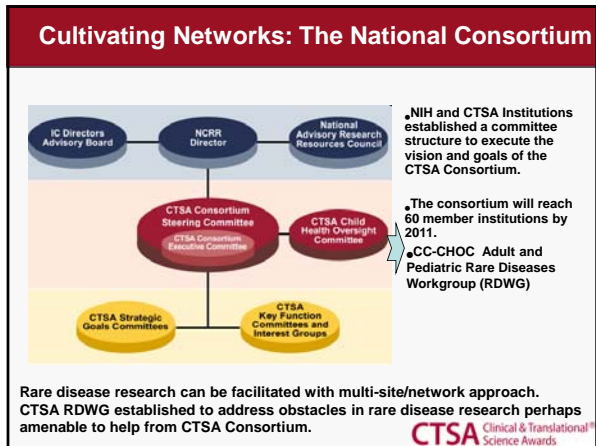
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- ### CC-CHOC RDWG Goals
- (Originally child health oriented, now all ages).
  - Increase translational research in rare diseases at members' home CTSA sites.
  - Build partnerships across CTSA sites: no single site sees enough affected pts. to make rapid progress alone. Single site rare disease research (RDR) may be harder now than ever.
  - Bring new investigators into RDR.
  - Encourage development infrastructure to facilitate multi-site research, education, training.

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- ### CC-CHOC RDWG
- Rare diseases a CC-CHOC priority since 1<sup>st</sup> meeting
    - Identify pressing RDR issues
    - Discover opportunities
    - Identify gaps in systematic study of rare diseases, determine how CTSA Program/expertise/resources might help address gaps
    - Many rare diseases not covered in existing networks
  - Collaborative partners
    - NCRD, CTSA supplement grants
    - NIH Office of Rare Disease Research
    - NIH Rare Disease Clinical Research Networks
    - FDA Office of Orphan Products Development
    - NHGRI, NBSTRN/ACMG
    - NORD, Genetic Alliance, Patient Advocacy Groups, etc.

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**CC-CHOC RDWG (2)**

- **Barriers/Challenges/Issues**
  - Biorepositories exist, but little coordinated information about rare disease specimen collections (when we began)
  - How to involve industry/advocacy partners
- **RDWG Goals:**
  - Platform for communication, collaborative research, education and training in RDR
  - Platform for locating, providing resources to rare disease researchers, trainees



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- What are some of the unique challenges inherent in rare disease research, as well as some of the solutions (emphasis on those involving CTSA's)?

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**Challenges in Rare Disease Research**

**Challenge 1:** Difficult to enroll subjects w/ rare disorders in clinical research. How to enroll from distant sites with limited research infrastructure?

**Possible Solutions:**

- 1) Simplify eligibility criteria leading to simplified data collection and subjects being enrolled in a single visit. Web-based CRFs; data collection from home by subject, parent, or home site.
- 2) Develop CTSA-wide network(s) for RDR

But: How to encourage collaborative participation in clinical research for rare disorders? How would collaborating investigator receive academic credit?

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**Challenge 2:** Scores of rare disease registries, many different formats/software & outcome measures, not tied to biobanks, with incompatible mechanisms for data collection, encoding, storage, access/sharing.

**Possible Solutions:**

- 1) Define common standard for software/platform, format, CRFs, data entry, outcomes/endpoints. Modify it for specific (rare) disease of interest. Ongoing progress in this area.
- 2) Develop universal protocol/ICF template for natural history/registry/biobank studies for rare disorders. Boilerplate language for ICFs/protocols to address main issues in RDR (ie collection and storage of DNA).

RDWG members agreed to submit examples. Rare disease toolkit/reference library posted on CTSA RD wiki  
<https://www.ctsawiki.org/wiki/display/Peds/Adult%20and%20Pediatric%20Rare%20Diseases%20Workgroup>

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**Challenge 3:** Difficult to find rare disease registries, natural history studies, biobanks, clinical research protocols, clinical trials, patients, investigators.

**Possible Solutions:**

- 1) Add ALL clinical research protocols to [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Request "rare disease" and "CTSA" fields be added to facilitate searching.
- 2) Use GeneTests website <http://www.geneclinics.org>, which already has diagnostics (including research), clinics, disorder reviews, resources, link to [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Add information re: registries, longitudinal/natural history studies, biobanks, investigators, etc.
- 3) NIH ORDR developing a registry of registries/biobanks

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**CC-CHOC RDWG: Progress**

- **Planned Educational/Training Symposium**
  - RDWG members worked with NIH RDCRN PI's, esp. Peter Merkel on NIH R13 conference grant, development of agenda for this RDCRN/CTSA Rare Disease Symposium (CCRRD)
- **Collaboration with NICHD-funded Newborn Screening Translational Research Network (NBSTRN)**
  - RDWG members serve on planning/standing committees
- **2<sup>nd</sup> RFA for RDCRN suggested including CTSA resources where available**
- **Successful Grant Application: CTSA Administrative Supplement for Rare Disease Biobanking (DBRD)**

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**Rare Diseases Provide Ideal Substrate for Working Out CTSA Collaborative technology**

**Premise of Distributed Biobanks for Rare Diseases (DBRD)**

- Rare diseases research is limited without collaborations between multiple institutions.
- Rare disease researchers motivated to develop CTSA infrastructure for collaborative research.
- Rare disease Use Cases can test CTSA technology for sharing samples, data, training on a small scale.
- Functionality required for RDR mirrors on a small scale what will be required for large cohort studies.

Thanks to Jennifer Puck, MD  
Funding: NCR: USCF  
CTSA Supplement Grant

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**DBRD Activities**

**1. Assemble Rare Disease Use Cases**

- a) Severe combined immunodeficiency (SCID): *how is genotype related to outcome following BMT?*  
Jennifer Puck, UCSF  
Luigi Notarangelo, Harvard  
Mort Cowan, Primary Immune Deficiency Treatment Consortium (RDCRN)  
Kate Sullivan, CHOP, US Immunodeficiency Network (Immune Deficiency Foundation, NIAID)
- b) Down syndrome: *what genetic factors influence severity of cognitive impairment?*  
Priya Kishnani, Duke  
Stephanie Sherman, Emory  
Cheryl Maslen, OHSU

**Scientific questions determine what data and samples are collected**

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**DBRD Activities, (cont.)**

**2. Governance**

- a) Biobank best practices, SOPs for sample handling, tracking  
Prohibitive cost central sample collection dictated local (or regional) storage  
Samples from patients with rare diseases irreplaceable, need to be salvaged even if not collected by ideal guidelines  
Prospective standardization essential
- b) Legal, ownership issues  
Physician investigators have large investment in their sample and data collections and insist on some control over their use
- c) Human subjects issues (archived & prospective collections)

**Keeping samples at their original site could be an acceptable way to make them available on a collaborative basis. Virtual warehouse.**

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**DBRD Activities, continued**

3. **Informatics** (*R. Wynden et al., The integrated data repository: ontology mapping and data discovery for the translational investigator. J Biol Informatics 2010*)

- a) Extract sample tracking data and sample associated clinical data from local databases.
- b) Transform data into standard formats in a secure database that substitutes codes for subject identifiers.
- c) Extract a de-identified data summary for each available sample to constitute a sample index at each site.
- d) Make the sample index available to be queried by pre-qualified viewers over a secure informatics grid.

4. **Implement a 2-step process for rare disease researchers**

- a) Initial de-identified query to find potential appropriate samples
- b) Collaboration established between sample holders and investigators

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**DBRD Remaining Challenges**

1. Ethics and research regulation policies vary between institutions.  
Two IRBs came to different conclusions about the need to re-consent subjects with Down syndrome in order to have their samples used in multisite studies.

2. HIPAA and institutional protections require security for inter-site electronic grid queries, but mechanisms to review and monitor access not yet established at CTSA sites.

3. Scaling up to accommodate users at many CTSA sites will require a generalized protocol.

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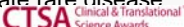
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**Conclusions**

- Significant challenges inherent in rare disease clinical research.
- CTSA Program includes many resources for investigators studying rare diseases.
- CTSA Program should facilitate multi-site research on rare disorders; that promise not yet realized.
- CTSA RDWG developing additional resources for rare disease researchers, also working towards building infrastructure to allow multi-site RDR & training across CTSA's.
- Outstanding opportunities for collaboration exist between CTSA Program & ORDR, NHGRI, FDA, RDCRN, NBSTRN, other Research Networks, Professional Societies, PAGs, Industry, others.
- Tremendous opportunity to accelerate rare disease research in CTSA era.



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