Förderung von Qualität in der Patienten-orientierten Forschung - ein vergleichender Blick in die USA

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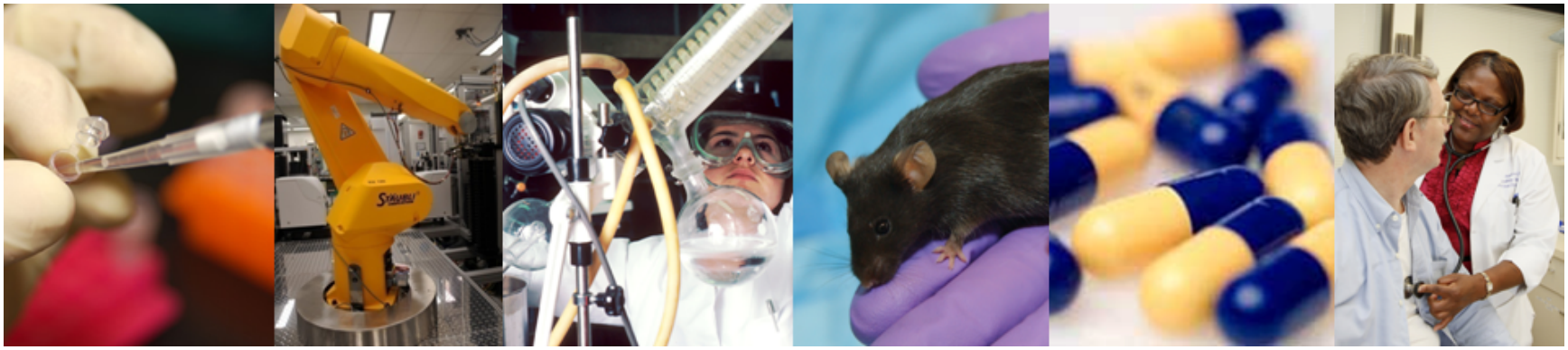
NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

DFG WORKSHOP „QUALITÄTSKRITERIEN PATIENTEN-ORIENTIERTER FORSCHUNG ALS GRUNDLAGE FÜR ERKENNTNISGEWINN“
3. UND 4. MÄRZ IN BONN

NCATS

NIH National Center for Advancing Translational Sciences

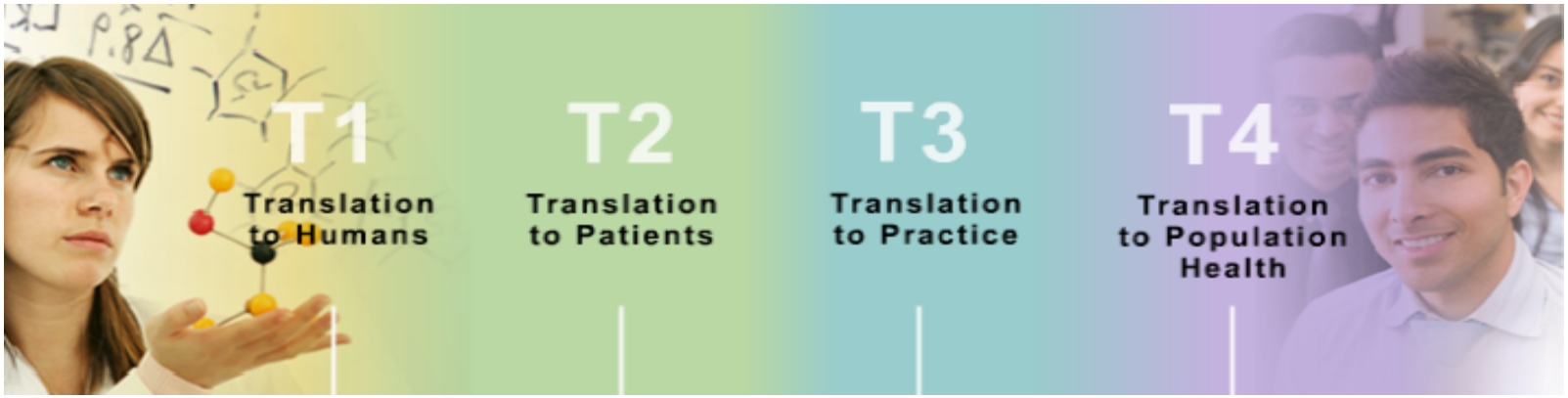
The National Center for Advancing Translational Sciences (NCATS) Mission



Katalyse innovativer Methoden und Technologien zur Entwicklung und Prüfung neuer diagnostischer und therapeutischer Ansätze für ein breites Spektrum von Erkrankungen.

Translation

Translation beschäftigt sich mit dem Prozeß, Beobachtungen aus dem Labor oder der Klinik in Behandlungen umzusetzen, die die Gesundheit von Individuen oder der Bevölkerung verbessern.



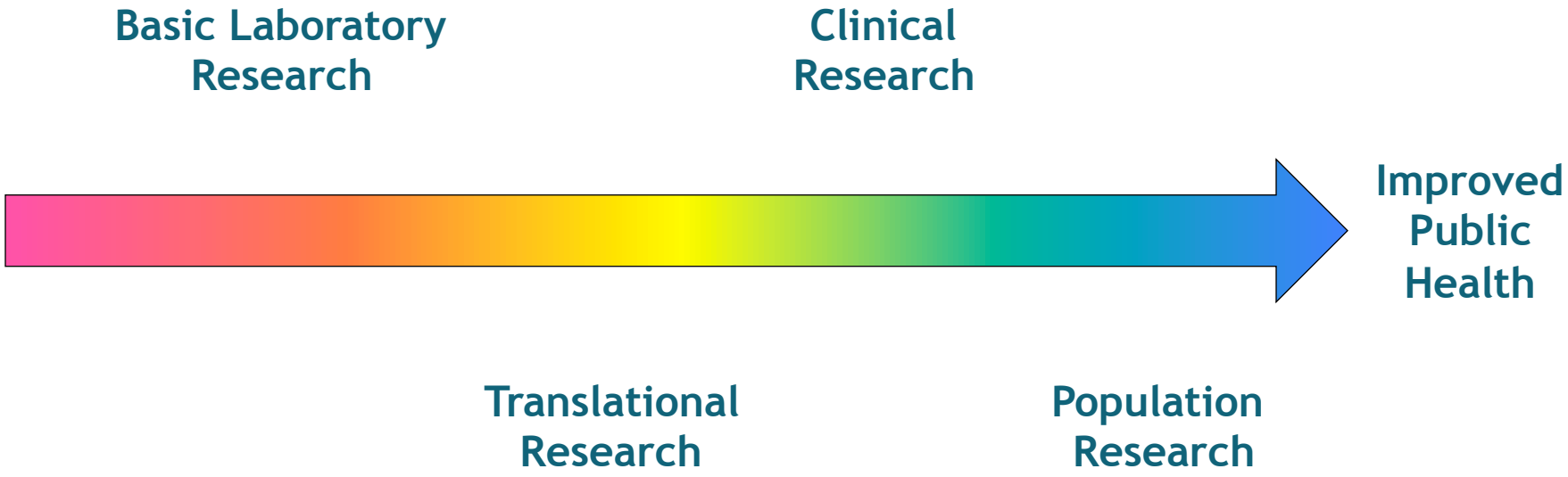
Hintergrund

- Translation ist ein Mannschaftssport. Keiner der Spieler kann eine neue Behandlungsmöglichkeit eigenmächtig zum Ziel bringen.
- Relevante Interessengruppen sollten als aktive Partner, und nicht als “Subjekt” oder “Konsumer” einbezogen werden.
- Frühzeitige Einbeziehung aller interessierter Gruppen ist ein kritischer Erfolgsfaktor.
- In den vereinigten Staaten erkennen die National Institutes of Health (NIH), Patientengruppen und Industrie zunehmend die Notwendigkeit von partnerschaftlicher Zusammenarbeit.

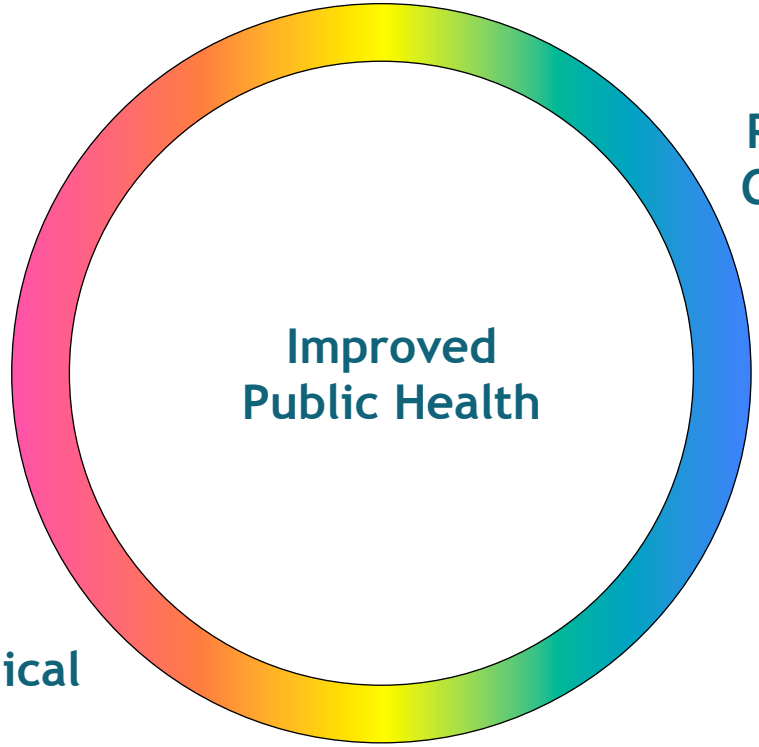
Community engagement

- Die Einbeziehung von Patienten alleine reicht nicht aus.
- Relevante Interessengruppen sollten systematisch in die Forschung integriert werden.
- Center for Disease Control (CDC) Definition für “communities”
  - Patienten, Famlienangehörige, Patiententgruppen, gemeinnützige Vereine, Kliniker, klinische Forscher, niedergelassene Ärzte, geographische oder kulturelle Gruppen, die Öffentlichkeit

Standard Model

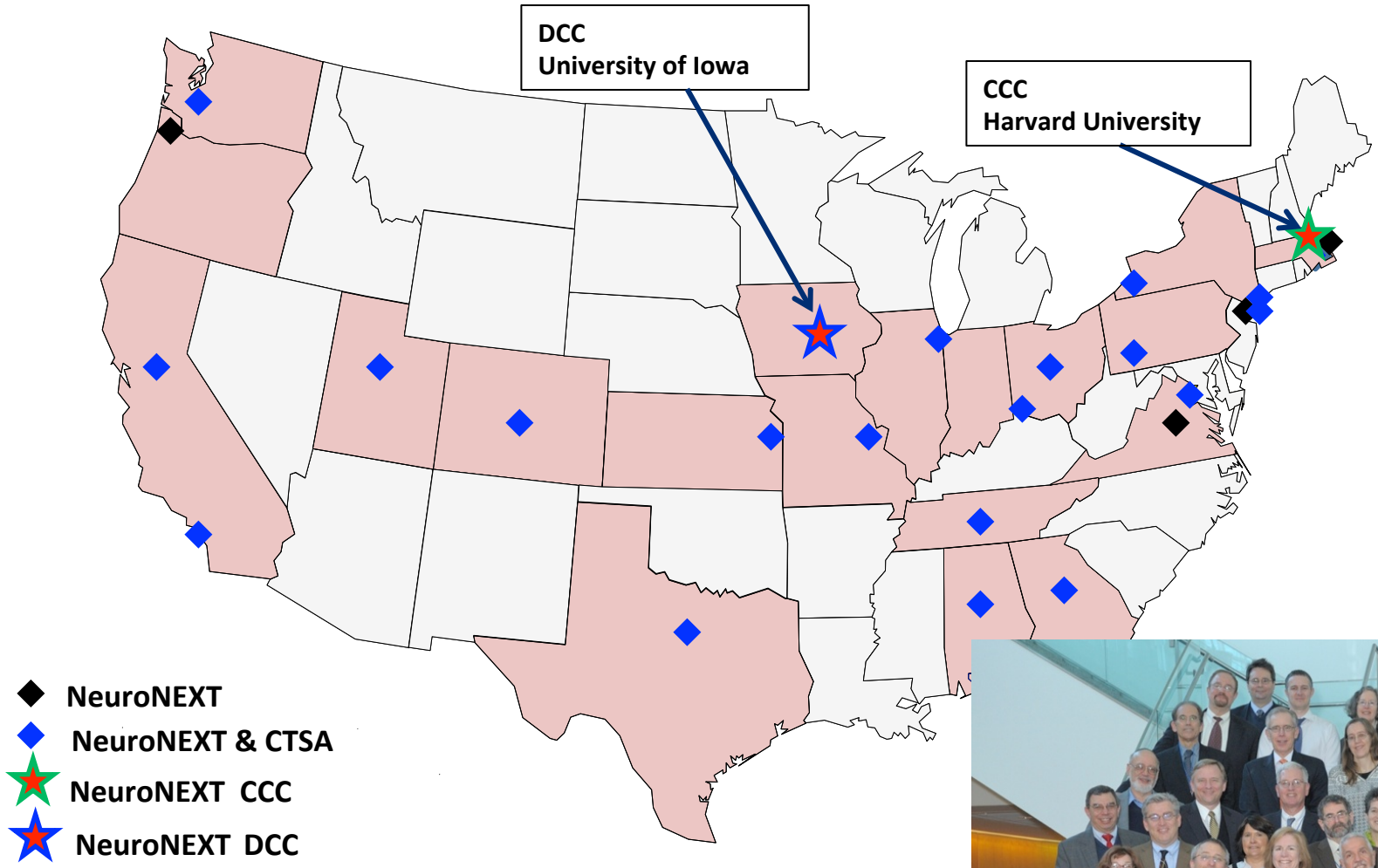


The Way It Should Work



NeuroNEXT

NIH-gefördertes Netzwerk für Phase 2 Studien neurologischer Erkrankungen



- Phase 2 Studien vielversprechender Therapien
- Schnellerer Fortschritt durch Infrastruktur
- Koordination von Private-Public Partnerships

NeuroNEXT goals

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

NeuroNEXT

- Patienteneinbeziehung in allen Projektphasen
  - Ist das Konzept relevant für die Betroffenen?
  - Ist das Protokoll durchführbar und patientenfreundlich (Patienten als Mitglieder von Protokollarbeitsgruppen)?
  - Ist das Informationsmaterial verständlich?
  - Ist der Rekrutierungsplan angemessen?
  - Ist die Studienüberwachung adequat (Patienten als DSMB Mitglieder)?
  - Ist es wahrscheinlich, daß die Ergebnisse Einfluß auf die Praxis haben?

Erfolgskriterien - Beispiel NeuroNEXT study NN101

- Spinal Muscular Atrophy (SMA) Biomarkers in the Immediate Postnatal Period of Development
  - Stephen Kolb MD PhD, Ohio State University
- Partnership with device company
- Patientenorganisation (Families of SMA) war von Anfang an einbezogen
  - Reiseunterstützung für Studienteilnehmer
  - Information für Familien
- **Ergebnis**
  - Studie erfolgreich abgeschlossen
  - Schneller als geplant

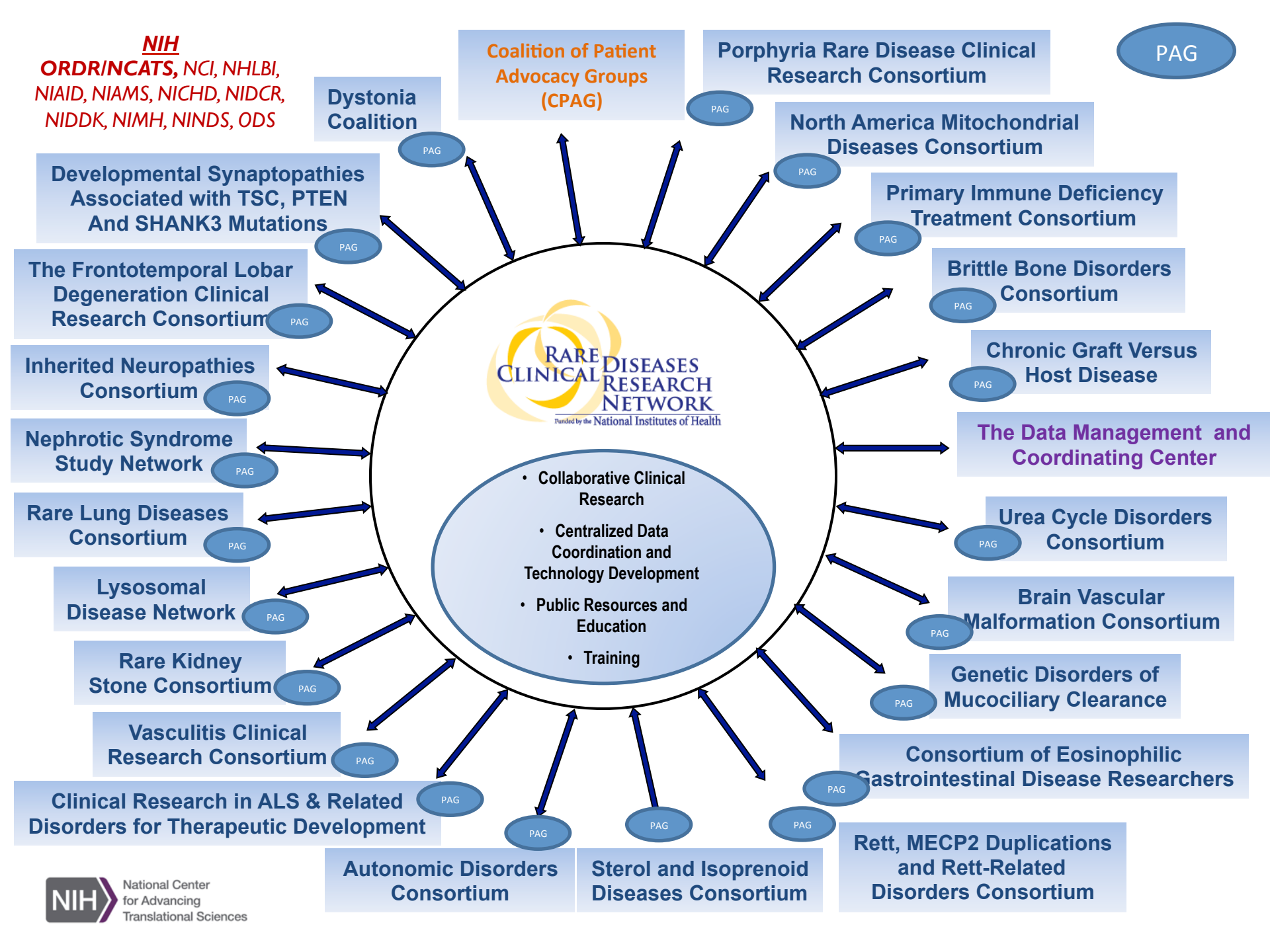
RARE CLINICAL DISEASES RESEARCH NETWORK

Initiative of the National Center for Advancing Translational Sciences (NCATS)

- Jedes Consortium führt mindestens zwei multizentrische Studien durch, hat ein Trainingprogram, und eine Initiative für “pilot projects”
- Kollektiv untersuchen die RDCRNs über 200 seltene Erkrankungen an 240 Universitäten und Kliniken in den USA und 14 Ländern
- 29,000 Patienten haben an den Studien teilgenommen
- 174 Forscher sind ausgebildet worden
- Die Konsortien haben 2,290 kollaborative Konsortiummitglieder
- 98 PAGs nehmen als Forschungspartner teil, und bilden gemeinsam die CPAG Koalition (Coalition of Patient Advocacy Groups)

http://rarediseasesnetwork.epi.usf.edu/ -

Program Contact: Rashmi Gopal-Srivastava PhD, gopalr@mail.nh.gov


NIH
ORDR/NCATS, NCI, NHLBI, NIAID, NIAMS, NICHD, NIDCR, NIDDK, NIMH, NINDS, ODS
PAG
Coalition of Patient Advocacy Groups (CPAG)
Porphyria Rare Disease Clinical Research Consortium
Dystonia Coalition
North America Mitochondrial Diseases Consortium
Developmental Synaptopathies Associated with TSC, PTEN And SHANK3 Mutations
Primary Immune Deficiency Treatment Consortium
The Frontotemporal Lobar Degeneration Clinical Research Consortium
Brittle Bone Disorders Consortium
Inherited Neuropathies Consortium
Chronic Graft Versus Host Disease
RARE CLINICAL DISEASES RESEARCH NETWORK
Funded by the National Institutes of Health
Nephrotic Syndrome Study Network
The Data Management and Coordinating Center
• Collaborative Clinical Research
• Centralized Data Coordination and Technology Development
• Public Resources and Education
• Training
Rare Lung Diseases Consortium
Urea Cycle Disorders Consortium
Lysosomal Disease Network
Brain Vascular Malformation Consortium
Rare Kidney Stone Consortium
Genetic Disorders of Mucociliary Clearance
Vasculitis Clinical Research Consortium
Consortium of Eosinophilic Gastrointestinal Disease Researchers
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
NIH National Center for Advancing Translational Sciences

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

FARA Friedreich's Ataxia Research Alliance

Patient Registry

- Über 2200 aktive Patienten registriert
- Aus über 65 Ländern
- Top Five Länder– United States (60%), Canada, United Kingdom, Brasilien, Australien, Spanien

Erfolgreich für klinische Forschung und Studien

- 7 klinische Studien; 9 Beobachtungsstudien
- Teilnehmer wurden in Stunden bis Tagen angeworben, nicht Monaten

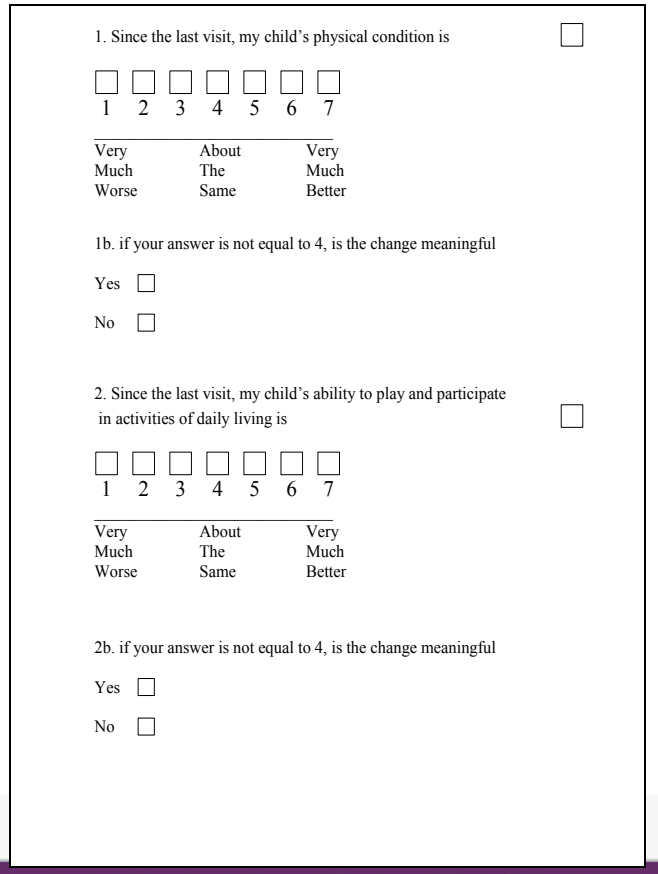
Patient Centered Outcomes Research Institute

- Patient powered research networks
  - Patientengruppen
    - Erhalten Forschungsmittel
    - Sind Teil des Führungsteams
  - Forschungsprojekte haben elektronische Patientenportals
  - Elektronische Klinikdaten werden direkt für die Forschung genutzt
- Entwicklung von innovativen Methoden zur Patienteneinbeziehung
- Nutzung klinischer Daten zur Forschung

Klinische Endpunkte

- **Feasible in population**
- **Acceptable burden**
- **Applicable to a wide range of population**
- **Reliable**
- **Sensitive to change**
- **Meaningful**

Clinically meaningful change?



1. Since the last visit, my child's physical condition is ☐

☐ ☐ ☐ ☐ ☐ ☐ ☐
1 2 3 4 5 6 7

Very Much Worse	About The Same	Very Much Better

1b. if your answer is not equal to 4, is the change meaningful

Yes ☐

No ☐

2. Since the last visit, my child's ability to play and participate in activities of daily living is ☐

☐ ☐ ☐ ☐ ☐ ☐ ☐
1 2 3 4 5 6 7

Very Much Worse	About The Same	Very Much Better

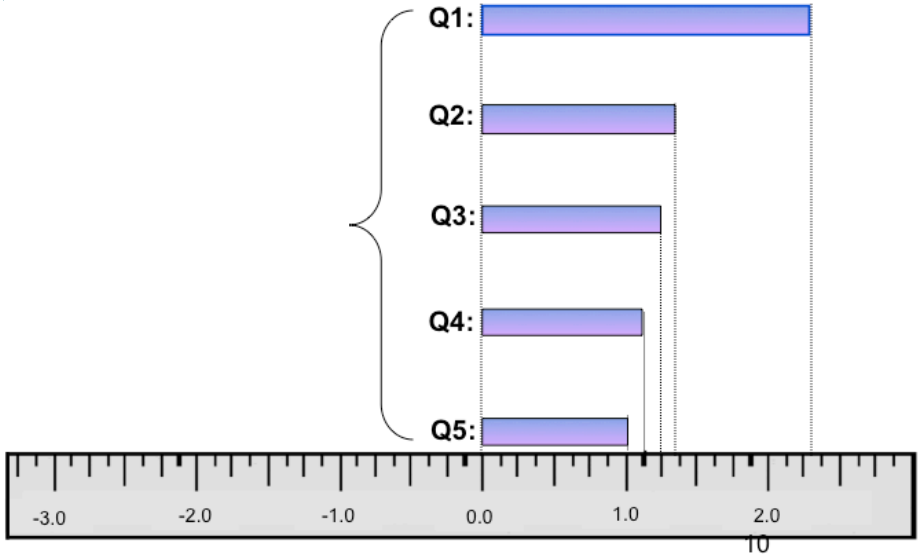
2b. if your answer is not equal to 4, is the change meaningful

Yes ☐

No ☐

PROMIS and NeuroQoL

- Measures constructs across lifespan
- Based on robust psychometric methods (Rasch analysis – Item Response Theory)
- Validity and reliability established
- Flexible (paper, computer, mobile device)
- CAT option (computer assisted testing)



PROMIS®

Dynamic Tools to Measure Health Outcomes from the Patient Perspective

About PROMIS® | Measures | Science | Software | What's New | Related Resources | PROMIS® For You | Search

- PROMIS Methodology
- Pediatric Methodology
- Selected Publications
- Presentations
- Public Use Data
- Origins of PROMIS
- Legacy Scales & Items
- Qualitative Item Review
- Calibration Testing
- Validity Studies

ɔmes Measurement Information System (PROMIS),
al Institutes of Health (NIH), is a system of highly
ible, precise, and responsive assessment tools
sure patient-reported health status.

Res

Provides efficient, reliable
valid assessments of adult
child (pediatric) self-reported
health

- PROMIS Instruments Selected References
- PROMIS In Research

Clinicians

data about the effect of
hat cannot be found in
traditional clinical measures

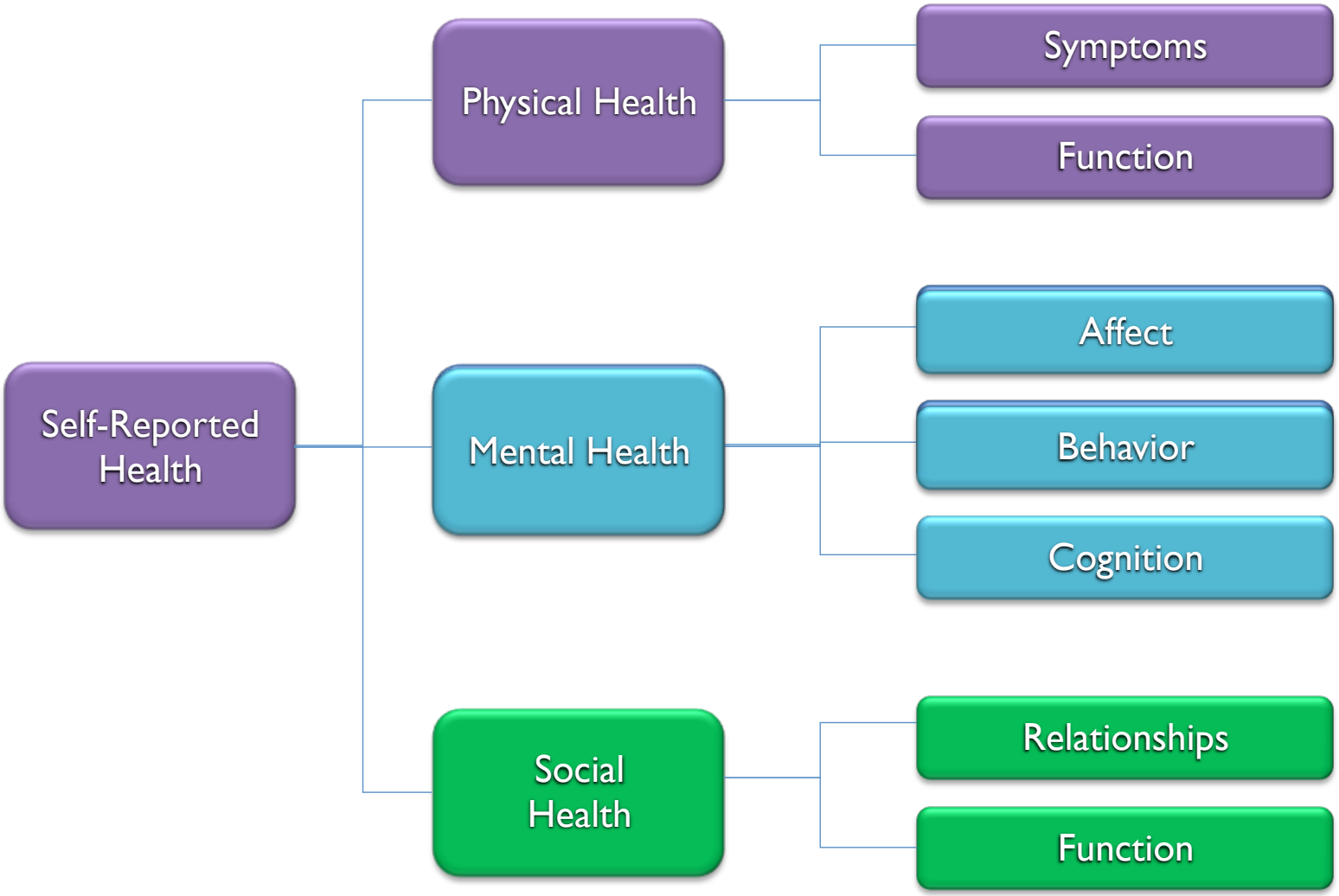
- PROMIS for Clinicians
- Select Publications
- Computer Adaptive Test (CAT) Demonstration

Patients

Measures what you are able to do and how you feel

- More on PROMIS
- What Patient Reported Outcomes (PROs) are
- PROMIS Measures

PROMIS Domain Framework



NIH Assessment Tools

- ***NIH Toolbox*** ***www.nihtoolbox.org/default.aspx***
  - *Assessment of Neurological and Behavioral Function*
- ***Neuro-QOL*** ***www.neuroqol.org/default.aspx***
  - *Quality of Life in Neurological Disorders*
- **The *EXAMINER*** ***http://examiner.ucsf.edu***
  - *Neurobehavioral Evaluation and Research*
- ***Phen-X*** ***www.phenx.org***
  - *Consensus Measures for Phenotypes and Exposures*
- **PROMIS®** **www.nihpromis.org**
  - *Patient-Reported Outcomes Measurement Information System*

Common Data Elements – Data Standards

- There are no widely used data standards
  - Investigators re- create data standards that exist already
- Meta-analyses across studies often require extensive data re-formatting
- Multitude of data formats
  - creates barriers to data sharing
- Common data elements (CDEs) could accelerate rare disease drug development

www.**commondataelements**.ninds.nih.gov

cde.nih.gov

Common data elements (CDEs)

- are uniform formats by which clinical data can be **systematically collected, analyzed** and **shared**
- require the **identification of common variables**, names, definitions, and operational meta-information so that case report forms can be standardized and legacy data sets can be mapped to CDEs.
- Example

Marital/Partner Status

☐ Never Married/Single
☐ Married
☐ Domestic Partnership
☐ Separated
☐ Divorced
☐ Widowed

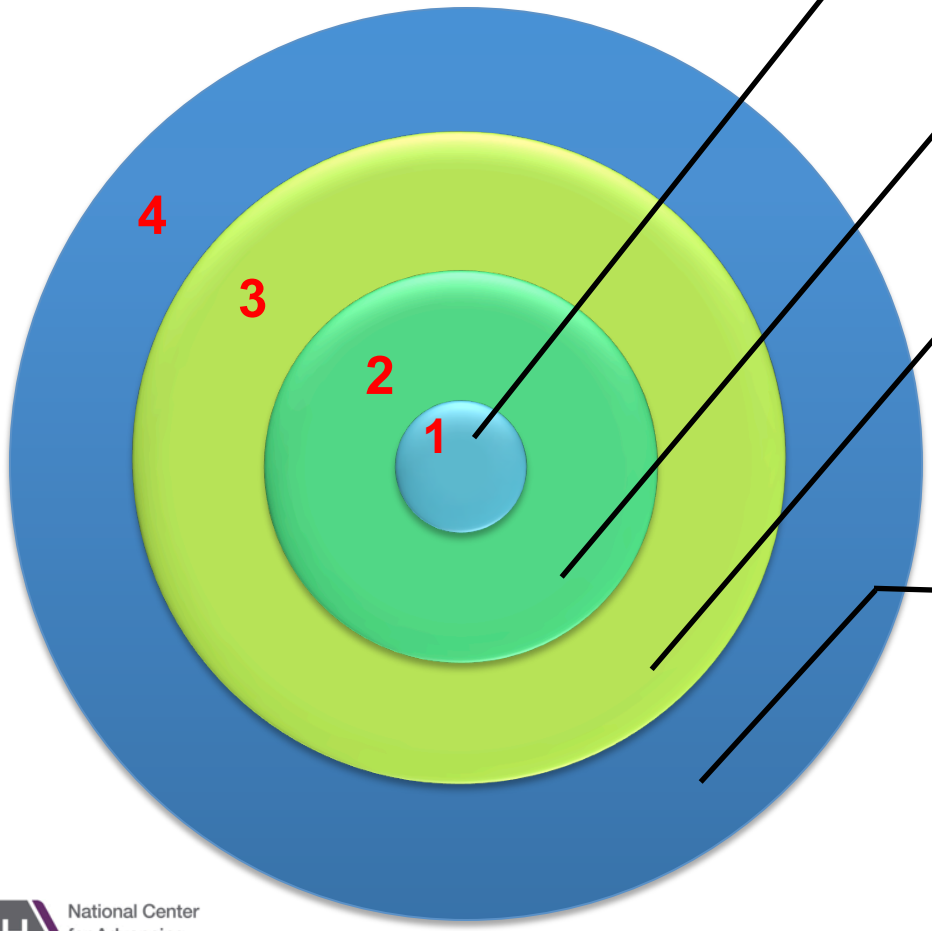
Appearance on paper/electronic case report form

CDE Name	Definition / Description	Code List / Permissible Values	Definitions for Codes / Permissible Values	Data Type	Guidelines/ Instructions	Other Notes	References
Marital/ Partner status	Current marital/ partner status	Never married; Married; Domestic partnership; Divorced; Separated; Widowed;	Never Married = A person who has never been married or whose only marriages have been annulled. Married = A person currently joined in matrimony. Classify common law marriage as married. Includes married couples living together and not living together. Domestic partnership = A person who is a member of an unmarried couple, including same sex couples, living together in longstanding relationships, that are registered or licensed.	Char	Choose the current marital status of the participant/ subject	No additional notes available	caBIG CDE Public ID = 2188083

Appearance as single row in data dictionary

CDEs are not encouraging unnecessary data collection

Modular Approach:



1. "General" Core CDEs

Relevant across neuroscience clinical research

2. Disease-specific Core CDEs

Should be used in all studies for this disease

3. Disease-specific Supplemental CDEs

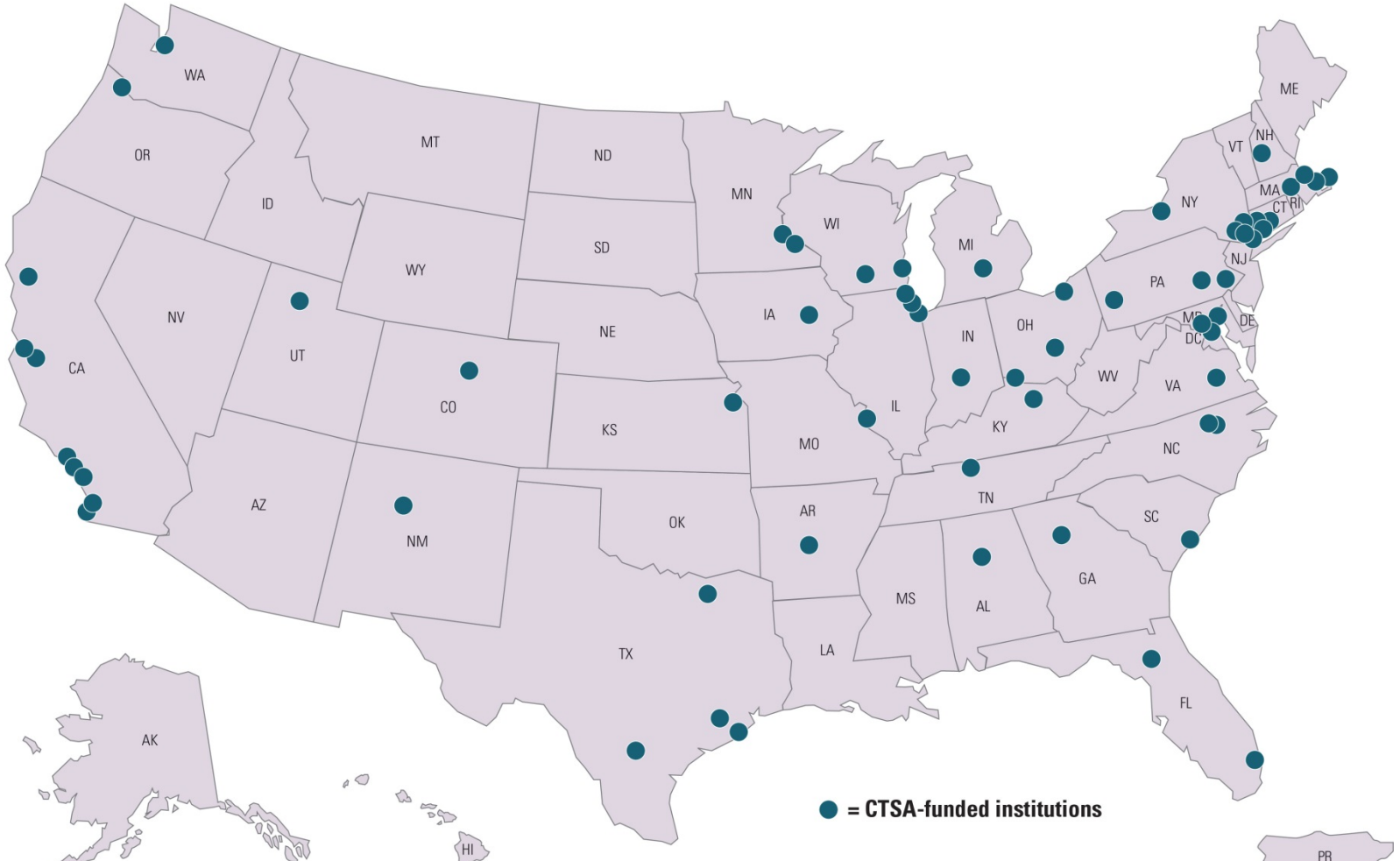
Extended set that are "common", but supplemental, i.e. not required - Choose from a "menu"

4. Disease-specific Exploratory CDEs

Not yet validated, or under development

Clinical and Translational Science Awards
(CTSA) Program Sites (n=62), 472 million p.a.

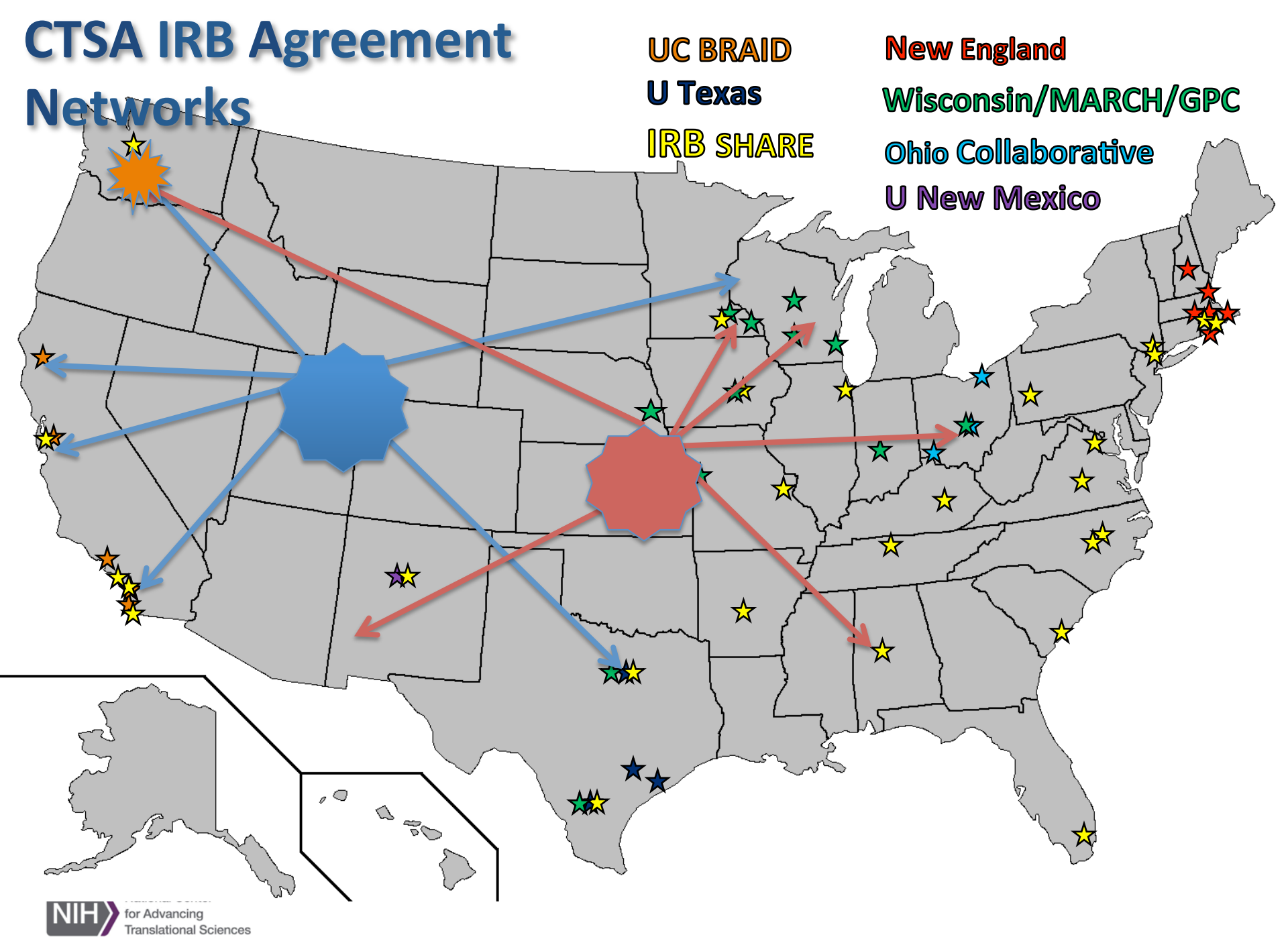
- US Nationales Konsortium medizinischer Forschungszentren,
- die gemeinsam Translation verbessern,
- und die die nächste Generation translationeller Forscher ausbilden



Multizentrische Studien

- Das Problem:
  - Multizentrische Studien sind ein kritischer Schritt in der Translation
  - Das gegenwärtige System is ineffizient:
    - IRB approval and subcontracting between institutions delays start-up
- Die Lösung:
  - NCATS is funding an initiative to build national trial support centers that
    - Centralize IRB review, and
    - Streamline contracting

CTSA IRB Agreement Networks



NIH for Advancing Translational Sciences

Value of Reliance Agreement and Network:

- Doctors at Mass Eye and Ear in Boston realized that they could learn more about the nature of blast-related ear injuries by studying victims of the Boston marathon bombing.
  - Harvard CTSA already had an IRB reliance network in place.
    - With 7 other hospitals, rapid IRB approval was obtained to study a large number of ear injuries from the same blast, and to observe patients as they healed
    - See a video: http://catalyst.harvard.edu/programs/regulatory/

Improving Efficiency: Participant Recruitment

- The problem:

  Slow recruitment delays most NIH-funded trials

- The approach:

  NCATS funds initiative to build national recruitment capacity using data from the Electronic Health Record (EHR) to identify potential trial participants meeting entry criteria (i2b2/SHRINE)

Trial planning phase → **Trial implementation phase**

Data-driven site selection

Feasibility analysis

Privacy and IRB compliant recruitment plan

Funded expert staff to help implement

"Enhancing Clinical Research Professionals' Training and Qualification"

Background

- Competency-based training for research personnel involved in executing clinical trials is inconsistent or absent

Aims

1. Standardize training in Good Clinical Practices (GCP) across the CTSA network ***(Phase 1)***
2. Develop a competency-based, clinical research professionals' training curriculum ***(Phase 2)***

Scope

- All 62 CTSA hubs awarded supplements

Evolving the Program to Transform Clinical Translational Science

CTSA Hubs

TIC:
Trial Innovation Centers
Central IRB
Contracting
Budgeting
Other support PRN

RIC:
Recruitment Innovation Centers
Feasibility Assessment
Recruitment Plan and Implementation

Multi-site Study funded by NIH IC or others

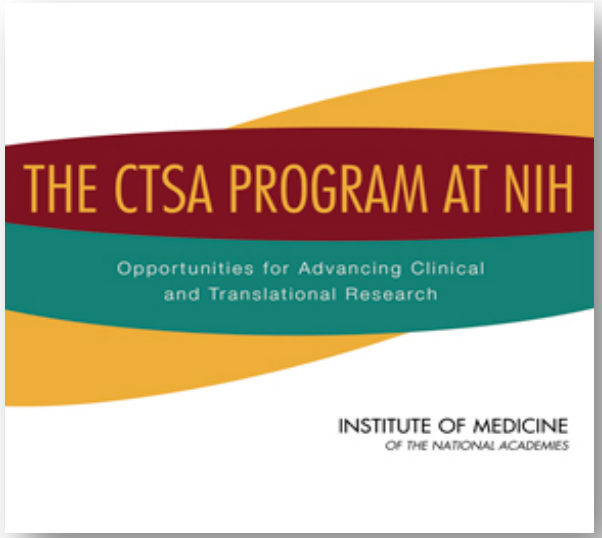
Clinical Lead

Stats/Data Management

No need to re- build trial components each time

IOM Report on the CTSA Program

Recommendations

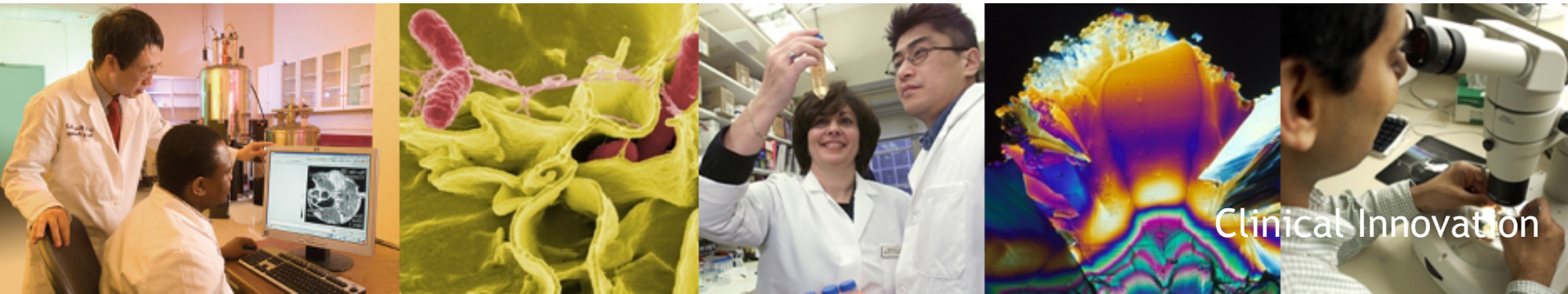


- IOM CTSA Report released June 2013
- Report includes 7 recommendations

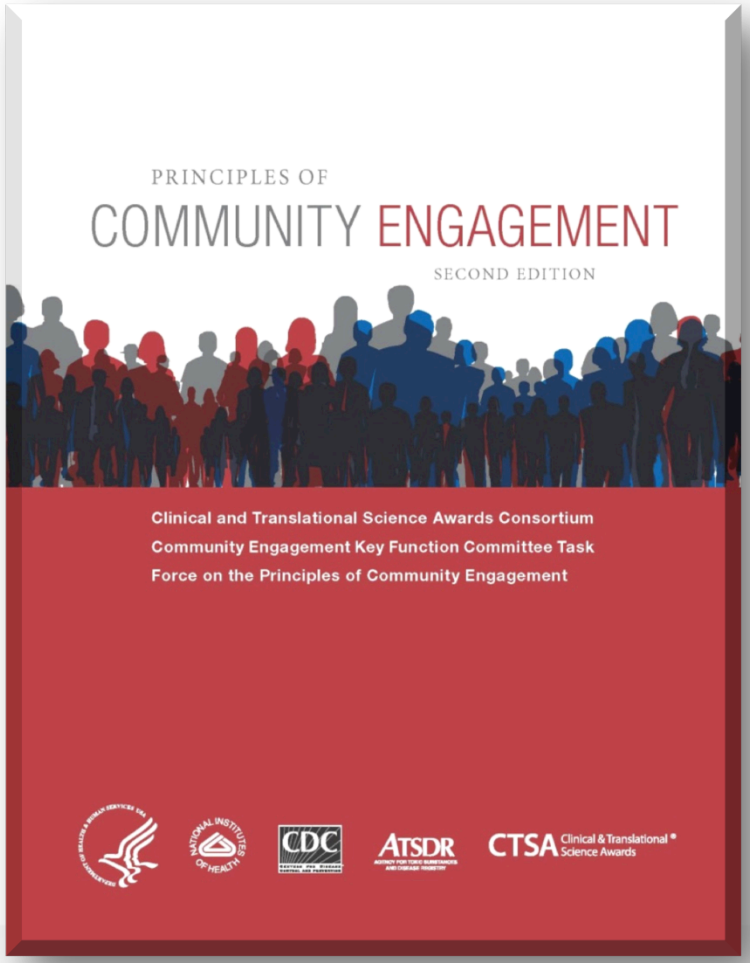
1. Strengthen leadership of the CTSA program by NCATS
2. Reconfigure and streamline CTSA consortium
3. Build on the strengths of the individual CTSAs across the spectrum of research
4. **Formalize and standardize clear, consistent, and novel metrics**
5. Advance innovative education and training models 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 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. Integrate **informatics** between clinical care and research



CTSAs



- Zusammenarbeit mit CDC und anderen Organisationen
- Transparente Methoden um Patienten als gleichgestellte Partner zu identifizieren
- Patienten brauchen ausreichende Informationen, aber keine wissenschaftlich Erfahrung
- Planung für adequate Unterstützung von Patientenvertretern (Zeit, Kosten, usw.)

Example: Community Engagement Studios

- Structured process of eliciting project-specific input
- May be used in any phase of translational research

- Stakeholders selected based on researchers' needs
- An experienced core team identifies stakeholders and prepares them for engagement; reduces burden to researcher

Joosten, et al. (in press). Community Engagement Studios: A Structured Approach to Obtaining Meaningful Input from Stakeholders to Inform Research. *Academic Medicine*.

Clinical trial recruitment before and after Community Engagement Studio

African American Women
Needed for Research Study

This study will look at how muscles absorb glucose (sugar) and how the body regulates your blood pressure.

You may qualify if you:

1. Are an African American, and
2. Have high blood pressure or borderline high blood pressure,
3. Are overweight, and
4. Are between the ages of 18-60 years, and
5. Have high triglycerides, high cholesterol, or high blood sugar, and
6. Do not smoke.

This study will require a screening visit, four clinic visits, two study days, study medications, and blood and urine collections.

Participants will be compensated for their time.

If you would like to learn more about this study, contact
Ginnie Farley
ginnie.farley@vanderbilt.edu.
Vanderbilt University

Date of IRB Approval: 6/10/2010

6/2/10

VANDERBILT UNIVERSITY
Institutional Review Board

Before: No participants enrolled after 3 months of active recruitment

African American Women
Needed for Research Study

You can help with this important clinical study that will test if a drug improves blood sugar levels and blood pressure.

This study is conducted
at Vanderbilt University Medical Center.

Requires a screening visit, study medication, 3 study days, and blood and urine collection.

Participants will be compensated.

You may qualify if you are :

Overweight
Age 18-60 years
Have borderline or high blood pressure
High cholesterol
High blood sugar levels
And do not smoke

For more information PLEASE CALL 615-689-1033 (Davalynn Johnson)
Davalynn.a.johnson@vanderbilt.edu

After: Targeted enrollment reached ahead of schedule; 100% retention in randomized, blinded, placebo controlled trial with 10 study visits

Take-Home Messages

- Das derzeitige Tempo in der Translation kann nicht mit den gegenwärtigen Möglichkeiten mithalten
- Wir kennen Tausende von Erkrankungen, können jedoch nur ungefähr 200 behandeln
- Die Probleme des 21ten Jahrhunderts können nicht mit den Methoden des 20ten Jahrhunderts gelöst werden.
- Der Prozeß dauert zu lange
- Das traditionelle akademische Modell ist im Begriff sich zu erneuern
- Partnerschaft mit Patienten, Klinikern, Industrie, HMOs und anderen, sowie die internationale Zusammenarbeit sind kritische Erfolgsfaktoren.