NCATS CTSA Program
Trial Innovation Network

Jane C. Atkinson, D.D.S.

Director, Trial Innovation Network
“Clinical trials in this country take too long, cost too much and too often don’t give us the answers we need to take care of our patients. Other than that, the system works great.”

—Rob Califf, M.D.
Chair of Board, Patient-Centered Research Foundation
Former FDA Commissioner
Former Duke CTSA PI
Founding Director of Duke Clinical Research Institute and Clinical Trials Transformation Initiative (CTTI)

Why a Trial Innovation Network?

- Cycle time for testing a clinical hypothesis (funding of clinical intervention concept to completion of test of therapeutic hypothesis) in an adequately powered study can easily be >10 years
- Time from approval/funding to start of clinical study can easily be two years
- Time for recruitment of participants can easily be 3-5 years
- Large percentage may be ultimately futile due to inability to recruit, and/or results being irrelevant by time study is completed due to science having moved on

Enormous losses to health and lives of patients, careers of investigators, and advancement of science and medicine
The CTSA Trial Innovation Network (TIN)

➢ A national laboratory to study, understand and innovate the process of conducting multisite clinical trials and studies

➢ A collaborative ‘test space’ within NCATS’ CTSA Program composed of three components:
  • Trial Innovation Centers (TICs)
  • Recruitment Innovation Center (RIC)
  • CTSA Institutions

➢ Goal: To develop, demonstrate effectiveness of, and disseminate scientific and operational innovations that dramatically increase the efficiency and effectiveness of clinical studies
  • Critical to bringing new interventions to patients and communities
  • Critical to renaissance/flourishing of clinical investigation as a career path
The TIN addresses these scientific translational issues on NCATS’ to-do list (highlighted in red)

➢ Predictive toxicology
➢ Predictive efficacy
➢ Derisking undruggable targets/untreatable diseases
➢ Data interoperability
➢ Biomarker qualification process
➢ Harmonized IRBs
➢ Patient recruitment
➢ Flexible “JIT” clinical research studies

➢ Electronic Health Records for research
➢ Clinical diagnostic criteria
➢ Clinical outcome criteria (e.g., PROs)
➢ Adaptive clinical trial designs
➢ Shortening time of intervention adoption
➢ Methods to better measure impact on health (or lack thereof)
Trial Innovation Network
A Part of the Larger CTSA Program
Trial Innovation Network Awardees

Trial Innovation Centers

➢ Center for Innovative Trials in Children and Adults
  • Institutions: Duke University and Vanderbilt University Medical Center
  • Principal Investigators: Daniel Benjamin, Jr., M.D., Ph.D. (Duke) / Gordon R. Bernard, M.D. (Vanderbilt)

➢ Utah Trial Innovation Center
  • Institution: University of Utah
  • Principal Investigator: Jonathan Dean, M.D.

➢ Johns Hopkins -Tufts Trial Innovation Center
  • Institutions: Johns Hopkins University and Tufts University
  • Principal Investigator: Daniel Hanley, M.D. (Johns Hopkins)

Recruitment Innovation Center

➢ Improving Clinical Trial Education, Recruitment and Enrollment at CTSA Hubs
  • Institution: Vanderbilt University Medical Center
  • Principal Investigators: Paul A. Harris, Ph.D. / Consuelo H. Wilkins, M.D.
Unique Characteristics of the Trial Innovation Network

- Imbeds a scientific hypothesis specific to the conduct of the trial within the overall science of the individual trial or longitudinal study it supports
- All projects have operational, design or statistical hypotheses, such as testing methods to find, enroll and retain special populations or developing new, less-burdensome trial endpoints
- Disease-agnostic
- Focused on multi-center studies
How the TIN innovates the design and execution of clinical trials/studies

Trial Designs
• Use novel study designs
• Have compelling scientific endpoints
• Use Quality by Design methodology
• Limit trial complexity
• Optimize data collection
• Have realistic budgets

Data Driven Approaches
• Use EHR-based cohort discovery and site selection tools
• Model recruitment to minimize amendments

Recruitment Planning
• Engage stakeholders in study design (via Community Engagement Studio)
  • Develop tailored messages and recruitment materials
  • Evaluate recruitment; modify strategies as needed

TIC and RIC Collaboration
The TIN at 24 Months: Developed Integrated Website for Proposal Submission

https://trialinnovationnetwork.org/
After proposal submission to TIN website

- All proposals receive an initial consultation.
- Some proposals request a comprehensive consultation for the development of an NIH application. One of the three TICs will be the data coordinating center in the application, and the trial will use all applicable TIN services.
- Other proposals request selected resources (either pre-application or post award). These may include:
  - Single IRB for a funded multisite clinical trial or study
  - Recruitment plan development and study feasibility assessments
  - Recruitment materials for funded studies
  - Community Engagement Studio service, a consultative method that allows meaningful involvement of diverse groups of stakeholders in the planning and implementation of research
  - Electronic Health Record (EHR) cohort assessments
  - Statistical support with design and other study parameters
Snapshot of Current Work

<table>
<thead>
<tr>
<th>Service</th>
<th>Current Support</th>
<th>Pending Activation/Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Consultation</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Comprehensive Consultations</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Recruitment Materials</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Feasibility Assessment</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>R&amp;R Plan</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Community Engagement Studio</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Cohort Discovery</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Standard Agreements</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>CIRB</td>
<td>38</td>
<td>15</td>
</tr>
</tbody>
</table>
Trial Innovation Network - Progress to Date

J. Michael Dean, M.D., M.B.A.
University of Utah School of Medicine
Trial Innovation Network
Where We Are Today*

1st Submission To Network
10/26/16

Number Submitted
147

CTSA Institutions Submitting
45

CTSA Institutions Involved
64

*As of 9/28/2018
Communication Opportunities

- **Webinars**
  - LT Monthly: >150 average attendance with all 64 CTSA represented on at least one call
  - Collaboration webinars: 40 held and attended by 187 different institutions (62 CTSA sites)
  - Monthly Open Forums

- **Newsletters (>400 distribution)**
- **Zoho recruitment listserv (>150 distribution)**
- **FAQs**
- **Dashboard**
Targeted Operations

**Standard Agreements**
- Umbrella CDA = 57/64 CTSA
- FDP CTSA = 63/64 CTSA

**Central IRB**
- Studies supported: 38
- Participating sites: 458

**Recruitment/ Retention Support**
- Apps for clinicians & participants
- Tools for identifying competing studies
- Cohort discovery & EHR alerts


Iterations

- Revised proposal requirements/process:
  - Prior discussion with NIH PO not mandatory
  - Accelerated time to first contact - now in 5 days

Using the Trial Innovation Network to Plan Your Trial

- Submit Study Proposal
- Contact Investigator
- Conduct Consultation
- Summary Recommendations
- Pre-Application Project
- Complete Comprehensive Consultation
- Grant Application Submitted

Illustrated timeline is approximate and may be subject to change based on the responsiveness and needs of the research team and current number of active proposals.

(Funded studies will have an abbreviated timeline)
Streamlining

CIRB
All of the TIN multisite single IRBs utilize NCATS’ SMART IRB Reliance Agreement

Investigators
Use SMART IRB to enable single IRB review

Get Started

SMART IRB is a platform designed to ease common challenges associated with initiating multisite research and to provide a roadmap for institutions to implement the forthcoming NIH Single IRB Review policy, which will take effect January 25, 2018. Freely available for institutions and investigators, SMART IRB is an integrated, comprehensive platform that allows flexibility in the size and scope of collaboration to enable IRB reliance for multisite studies across the nation, regardless of funding status.

https://smartirb.org/
HOW IT WORKS: Human Research Protections involves more than just an IRB reviews
HOW IT WORKS: CIRB Review vs. Local Site Review Responsibilities

Responsibility given to the CIRB

- IRB
- HIPAA Privacy Review

- Conflict of Interest Review

- Ancillary Reviews
- Institutional Policy Verification
- State/Local Law Verification
- Resources Verification
- Training & Qualifications Verification

All other study-specific reviews are completed by the local institution ("local context / local considerations")
CIRB REVIEW ISN’T NEW: Why does it feel so difficult?

An IRB Landscape Change

- The NIH and OHRP sIRB mandates place a spotlight on reliance:
  - From 2-page MOU to 23-page master reliance agreement
  - Increasing proportion of institution’s research portfolio
- Academic IRBs are now requiring local documentation for ceded studies
- Academic sIRBs depend upon local site to provide local knowledge
- Site coordination is a largely unanticipated (unfunded)
WHAT ARE THE TIC CIRBS DOING TO HELP?

**Education**
- For Relying HRPPs/IRBs
- For Study Teams

**Infrastructure**
- Common Indemnification Language
- Common Processes
- Common IT platform (IREx)
IRB Reliance Exchange (IREx):

A common portal to standardize sIRB review processes, local context, and metric collection

Basic Reliance Documentation
- sIRB agreement completion (SMART IRB)
- Reliance/cede decisions

Advanced Reliance Documentation
- Study-specific local considerations from site HRPPs/IRBs
- Site differences in study conduct and attestations
- CIRB approval documents for each site
IRB Reliance Exchange (IREx):

- 214 partner institutions
- >90% have relied on >1 study in IREx
- 42 States
- >1500 users: including HRPP/IRB, Coordinating Center, and Study Team staff
- studies in progress:
  - 77 39 Trial Innovation Network (TIN) studies
  - 38 Non-TIN studies
As of 8\textsuperscript{th} Oct 2018

<table>
<thead>
<tr>
<th>Overview</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TIC CIRB studies</td>
<td>38</td>
</tr>
<tr>
<td>Studies with CIRB approval</td>
<td>26</td>
</tr>
<tr>
<td>Sites participating in at least 1 TIC CIRB study</td>
<td>217</td>
</tr>
<tr>
<td>Average number of sites per study</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(range: 3-65)</td>
</tr>
<tr>
<td>Site Reliances and Approvals</td>
<td></td>
</tr>
<tr>
<td>Total sites on TIC studies</td>
<td>458</td>
</tr>
<tr>
<td>Total cede decisions indicated</td>
<td>347</td>
</tr>
<tr>
<td>Sites with approval from TIC CIRB</td>
<td>252</td>
</tr>
</tbody>
</table>

* Time from CIRB submission to approval does not include time for local reviews and cede decisions
Current State

• Site coordination requires significant time
  • Time required to get a site ready for CIRB submission and approval is highly variable and significant
  • Preliminary data show range of 1 to >200 days

• CIRB review for relying sites is quick
  • Median time from TIC CIRB submission to approval for relying sites is 14 days.
Innovation is our middle name

Some areas of innovation:

1. Process innovations and testing, to improve clinical trials

2. Development of continuous improvement processes driven by performance metrics

3. Innovations in study design and recruitment
Consuelo H. Wilkins, MD, MSCI
Executive Director, Meharry-Vanderbilt Alliance
Vision and purpose

Our goal is to positively impact human health by improving participant enrollment and retention in multi-center clinical trials.

Achieving this goal will require sophisticated informatics-based recruitment tools and novel engagement approaches to accelerate recruitment and retention.
RIC National Community Advisory Board

Pam Pimentel / Co-Chair
Guadalupe Campos
Irvin Cohen
Broderick Crawford
David Hahn
Grant Jones / Co-Chair
J. Stephen Mikita
Danielle Pardue
Yolanda Vaughn
Mysha Wynn
RIC Services & Model For Innovation

- Recruitment planning & Feasibility assessment
- Community Engagement Studios
- EHR Cohort Assessment
- EHR Workflow Assessment / Consultation
- Competing Trials Assessment
- Participant Compensation Assessment

RIC Recommends Existing Tools & Service Offerings
Proposes New Innovations
Site Feasibility: Leveraging CTSA Informatics Teams
# Recruitment & Retention Toolkit

## Comprehensive Resource Library
- Educational Videos
- Templates
- Guides
- Checklists
- Best Practices
- Tutorials

## Contributors:
- Advocacy Organizations
- Academic Institutions
- Government
- Nonprofit Organizations
- Private Sector
- Public-Private Sector

## Filters for refined searching
- Search by Contributor:
  - All Institutions
- Filter results by content type:
  - Educational Videos
  - Recruitment News
  - Recruitment Plan
  - Study Promotional Material
  - Tutorials and Guides
- Filter results by study phase:
  - Planning
  - Startup
  - Conduct
  - Closeout
- Filter results by tag:
  - enter search term...

## Open submission

### RECRUITMENT & RETENTION TOOLKIT METRICS
<table>
<thead>
<tr>
<th># of institutions</th>
<th># of resources</th>
<th># of downloads/views</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>56</td>
<td>5369</td>
</tr>
</tbody>
</table>
Medical discoveries are not possible without volunteers like you. Researchers need your help! Health research changes people’s lives every day, but many studies end early because there are not enough volunteers. We help by matching you with research studies. Researchers need both healthy people and people with all types of conditions. Everyone can be the perfect research match!

Join Now
Marcus participated in a clinical trial. Hear why he thinks everyone should. We’ll find ways to get and keep people healthy faster, if we work together.
Accelerating Minority Recruitment: *FasterTogether*

Develop, Demonstrate and Disseminate Innovation to Enhance Minority Recruitment & Retention in Clinical Trials

Focus on Meaningful Engagement

Promoting Inclusivity

Los descubrimientos médicos no serían posibles sin voluntarios como *usted*. ¡Los investigadores necesitan su ayuda! La investigación sobre la salud cambia la vida de las personas a diario. Sin embargo, muchos estudios finalizan antes de tiempo porque no hay...
Participant Perspective: Return of Value

2,554 Participants
59% women, 62% % minorities

<table>
<thead>
<tr>
<th>Value of information that could be returned</th>
<th>Mean Rating (1-7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How I may respond to medications based on my genetics.</td>
<td>6.30 (1.21)</td>
</tr>
<tr>
<td>How genetics affect my risk of getting a medical condition.</td>
<td>6.28 (1.26)</td>
</tr>
<tr>
<td>How my lifestyle affects risk of getting a medical condition.</td>
<td>5.98 (1.43)</td>
</tr>
<tr>
<td>Information about clinical trials near me.</td>
<td>5.81 (1.47)</td>
</tr>
<tr>
<td>Information about how researchers are using my data.</td>
<td>5.77 (1.48)</td>
</tr>
<tr>
<td>My Ancestry.</td>
<td>5.70 (1.64)</td>
</tr>
</tbody>
</table>

Preliminary data: Wilkins, Mapes, Jerome, Villalta, Pulley, Harris Sept 2018