Launching CONNECTS: A Partnership Between Research Triangle Institute, Vanderbilt University Medical Center, and NHLBI
Sonia Thomas, DrPH RTI and Gordon Bernard, MD VUMC

September 11, 2020
Collaboration of 34+ Networks and 1,000+ Sites
Website nhlbi-connects.org
Why a CONNECTS collaborative?

Current unprecedented and urgent public health crisis
  • Assemble expertise and resources in a nimble fashion
  • Ensure appropriate geographic reach and expertise
  • Enable resource deployment when and where needed

This collaborative transcends what any individual network may do alone

“The whole is greater than the sum of its parts”
• **Overarching Purpose:**
  - Test host-directed therapies for COVID-19 via rapid, efficient, collaborative adaptive platform trials aimed at helping to prevent infection, slow or halt disease progression, and speed recovery

• **Strategic approach:**
  - Fully integrate major NHLBI networks under one organizational umbrella to ensure efficiencies; standardization; collaboration; and sharing of control groups (as appropriate), resources, and data
  - Nimbly shift studies as needed, based on new knowledge and changing pandemic clinical landscape

• **Expectation:**
  - Innovative model of seamless collaboration; all set aside their own “team jerseys” to join an All-Star Team
CONNECTS Is Part of a Larger Ecosystem

Strategic direction, oversight, and key partnerships:

- NHLBI-directed
- In collaboration with BARDA; Operation Warp Speed; and as appropriate, other ICs (e.g., NIAID, NINDS)
- Engage clinical trials/networks, other NIH ICs, Clinical Data Interchange Standards Consortium
- Trials are aligned with, or formally part of, NIH ACTIV (e.g., ACTIV-4)
NHLBI COVID-19 Clinical Studies Framework

COVID-19+ Progression

Prevention
Outpatient
Asymptomatic
Outpatient
Symptomatic
Emergency
Department
Hospital
Vent/CPAP-free
Hospital
ICU
Conva-
lescence
Recovered

Point of Care Diagnostics

Host-Directed Therapeutics Clinical Trials

Patient Registry and Long-term Follow up

Cohort of Cohorts

REDs-IV-P Sero-surveillance

Community-Based Research Consortium
CONNECTS Is a Research Collaborative

A community promoting collaboration, harmonization, and sharing of scientific expertise and resources.
Steering & Executive Committee Chairs

Steering Committee

Clyde Yancy, Chair
(Northwestern University)

Serpil Erzurum, Vice-Chair
(Cleveland Clinic)

Diane Nugent, Vice-Chair
(CHOC Children’s Hospital)

Executive Committee

Robert Harrington, Co-Chair
(Stanford University)

Amy Patterson, Co-Chair
(NHLBI)
CONNECTS and ACTIV Clinical Trials

NCATS Clinical Trials
- ACTIV 1a: Immunomodulators: TNFa v. SOC
- ACTIV 1b: Immunomodulators: CTLA-4 + SOC
- ACTIV 1c: Immunomodulators: CCR2/5 Inhibition + SOC

NIAID Clinical Trials
- ACTIV 2: Outpatient mAbs
- ACTIV 3: Inpatient mAbs
- ACTIV 5: Inpatient POC mAbs

NHLBI CONNECTS Clinical Trials
- ACTIV 4A: Anticoagulant Inpatient
- ACTIV 4B: Anticoagulant Outpatient
- ACTIV 4C: Anticoagulant Conval
- C3PO: Convalescent Plasma
- Other Host Directed Therapeutics: TBD
Designing New Studies

Gordon Bernard, MD
CONNECTS ACC Science Unit PI
Vanderbilt University Medical Center
Our Immediate Goal: Design and Implement Master Protocol Driven Adaptive Clinical Trials

Outpatient Master Protocols

Inpatient Master Protocols

Recovering Master Protocols

Some remain asymptomatic and/or recover without requiring hospitalization or intensive care

Exposed → Infected → Asymptomatic → Symptomatic/Mild → Hospitalized/Moderate → Intensive Care Unit/Severe → Recovering → Recovered

Passive Immunity Therapeutics
Anticoagulation Therapeutics
Immunomodulatory Therapeutics
Host Tissue Therapeutics
Leveraging Network Expertise for Master Protocol and Agent Prioritization leadership groups

Progress to Date

• All network-nominated experts are currently engaged by the ACC.

• Experts are serving as members in Master Protocols and Agent Prioritization committees.

• Additional nominations are always welcome

Nominated Expert Areas of Expertise

- Biostatistics: 15
- Adaptive Trial Design: 34
- Master Protocols: 17
- Clinical Science: 18
- COVID-19 Characteristics & Risk Assessment: 16
- Passive Immunization/Neutralizing Antibodies: 8
- Anticoagulation: 1
- Immunomodulation: 16
- Host tissue response-directed: 13
- Deep phenotyping: 11
- Precision medicine: 5
- Use of biospecimens: 6
- Drug prioritization: 2
- Other: 14

Number of Experts
Master Protocol Committee Structure:
Drafting and harmonization of master protocols across patient stages

Master Protocol Development Committee

Outpatient Master Protocol Subcommittee
- Outpatient Immunomodulatory Appendix Working Group
- Outpatient Host Tissue Response Appendix Working Group
- Outpatient Passive Immunity Appendix Working Group
- (Outpatient Anticoagulant Appendix Working Group)

Inpatient Master Protocol Subcommittee
- Inpatient Immunomodulatory Appendix Working Group
- Inpatient Host Tissue Response Appendix Working Group
- Inpatient Passive Immunity Appendix Working Group
- (Inpatient Anticoagulation Appendix Working Group)

Recovering Master Protocol Subcommittee
- Recovering Immunomodulatory Appendix Working Group
- Recovering Host Tissue Response Appendix Working Group
- Recovering Passive Immunity Appendix Working Group
- (Recovering Anticoagulation Appendix Working Group)

Develop master protocols with a standard of care arm
Develop appendices to master protocols with therapeutic domain-specific content/arms
Statistical Design Concepts for COVID-19

• What are the most informative/statistically powerful outcomes?
  • Proposal: An ordered scale that includes clinically relevant and patient-centered features, that combines both safety and efficacy information, and that encompasses information pertinent across all settings and disease severities.

• What types and levels of evidence are needed to stop a trial?
  • Proposal:
    • Sequential design with frequent looks based on calendar time and a range of expected accrual rates rather than enrollment so that decisions can be made in a timely way.
    • Bayesian interim analysis methods incorporating a skeptical prior for efficacy, an uninformative prior for inefficacy/harm, and setting the acceptable level of evidence posterior probability such as $\geq 0.95$. 
Agent Prioritization Committee Structure:
Review and prioritization of potential nominated therapeutics

- Immunomodulatory Agent Working Group
- Host Tissue Response Agent Working Group
- Passive Immunity Agent Working Group
- Anticoagulation Agent Working Group
Overarching Agent Prioritization Committee

### Workstreams Groups

<table>
<thead>
<tr>
<th>Immunomodulatory</th>
<th>Passive Immunity</th>
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</thead>
<tbody>
<tr>
<td><strong>Host-tissue Response</strong></td>
<td><strong>Anticoagulation</strong></td>
</tr>
<tr>
<td>Michael Matthay(^1)</td>
<td>Judith Hochman</td>
</tr>
<tr>
<td>Marie-Carmelle Elie(^2)</td>
<td>Thomas R. Martin</td>
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<tr>
<td>Clark Files(^3)</td>
<td>Chad Miller</td>
</tr>
<tr>
<td>Macky Neal(^4)</td>
<td>Duane Mitchell</td>
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<td>Richard Becker</td>
<td>Thomas Ortel</td>
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<td>Jeffrey Berger</td>
<td>Liise-Anne Pirofski</td>
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<td>Javed Butler</td>
<td>Todd Rice</td>
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<tr>
<td>Ivor Douglas</td>
<td>Paul Ridker</td>
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<tr>
<td>Serpil Erzurum</td>
<td>Wes Self</td>
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<tr>
<td>Michael Felker</td>
<td>Chris Seymour</td>
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### Additional Members

- Neil Aggarwal – NIH/NHLBI
- Gordon Bernard – CONNECTS ACC VUMC Science Unit PI
- Ann Farrell – FDA, DNH, CDER/FDA
- Mary J. Homer – Chief, RNC, BARDA
- Zorina Galis – NIH/NHLBI
- David Goff – Committee Co-Chair, NHLBI Dir, DCVS
- James Kiley – Committee Co-Chair, NHLBI Dir, DLD
- Andrei Kindzelski - NIH/NHLBI
- Tony Punturieri – NIH/NHLBI
- Thomas R. Martin                  |
- Thomas Ortel                      |
- Liise-Anne Pirofski               |
- Todd Rice                         |
- Paul Ridker                       |
- Wes Self                          |
- Chris Seymour                     |

Workstreams Chairs: \(^1\) Immunomodulatory; \(^2\)Proposed Passive Immunity; \(^3\)Host-tissue Response; \(^4\)Proposed Anticoagulation.
Nominations can and should come from multiple places.
**Science Unit Support of Agent Prioritization: Summary Packages**

**Elements of a Summary Package**

- **Mechanism of action**: Informs hypotheses related to drug efficacy and potential side effects
- **Safety considerations**: Informs exclusion criteria and trial surveillance needs
- **Explanation of the drug's protein target in the context of COVID-19 disease**: Informs hypothesis related to drug efficacy and potential side effects
- **Timing of intervention**: Informs where along the COVID-19 disease progression spectrum the drug is likely to have efficacy and be feasible to administer
- **Pharmacology assessments**: Informs dosing regimen and potential drug interactions
- **Preclinical data**: Animal or human models establish disease mechanism, define patient population, and inform clinical trial endpoints
- **Prior studies in other coronavirus outbreaks**: Informs trial design, including feasibility
- **Pharmacogenomic considerations**: Genetic variants that may alter an individual’s response to drug therapy
Process for Agent Prioritization:
Flow for filtering therapies into Master Protocols

60 Agents

Survey of Agent Prioritization Committee
- One-pagers grouped, reviewed and scored by therapeutic area (10-25 agents per reviewer) leveraging all nominated experts/NLHBI program.

Feasibility Assessment and Working Group Review
- Review of priority agents, confirming NHLBI interest, non-redundancy with other trials, and access to therapeutics
- Deeper dive detailed assessment packages provided to Working Groups
  *current development is immunomodulatory and host tissue agents*

Deliberation
- Therapeutic domain Working Groups will have live group discussion of candidates for further prioritization, producing candidates for recommendation to the Steering Committee

Recommendation to SC for Assignment to Master Protocol Arms
- Factor in practical and logistical details for each agent
- Assignment into master protocol arms based on common features

Agent Prioritization Committee recommends final selections to Steering Committee

Master Protocols

9/4 meeting

9/9 group meeting

Complete
Final selected therapies will be incorporated into master protocols

**Intervention features**

- Type (e.g. small molecule, biologic, device, behavioral)
- Therapeutic domain/target host response
- Route of administration (e.g. IV, oral, inhaled)
- Disease phase where therapy is most likely to have efficacy
- Duration of intervention
- Safety profile (for eligibility criteria and monitoring)

- **Outpatient Master Protocol**
- **Inpatient Master Protocol**
- **Recovering Master Protocol**
Study Implementation

Sonia Thomas, DrPH
CONNECTS ACC PI
RTI International
Forming Study Implementation Teams

Team composition determined by expertise, site populations. Registered sites will be activated based on geographic distribution of disease activity.
Forming Study Implementation Teams

CONNECTS Participating Networks & Sites

CONNECTS Participating Networks & Sites

Network A
Network B
Network C
Disease Activity

Team composition determined by expertise, site populations. Registered sites will be activated based on geographic distribution of disease activity.
ACC: Supporting CONNECTS Studies

START-UP

- Concept & Design
  - Subject Matter Experts
  - Agent Prioritization
  - Design & Endpoint Harmonization

- Resourcing
  - Pharmaceutical Partnering
  - Supply Availability Tracking
  - Site Case Load/Study Engagement Tracking

- Regulatory
  - Supplemental Regulatory Expertise
  - Harmonization Focus

- Tools & Systems
  - Data Standards & Harmonization Guidance
  - Tools Sharing

IMPLEMENTATION

- Recruitment & Retention
  - Target Population Enrollment Tracking
  - Community Engagement

- Resourcing
  - Additional Site/Network Engagement
  - Supply Identification & Reallocation

- Monitoring
  - Milestone Tracking
  - Coordinated DSMB Reporting

INTERPRETATION & DISSEMINATION

- Analysis
  - Subject Matter Experts
  - Interpretation Harmonization

- Data & Biospecimen Repositories
  - Biospecimen Inventory Reporting
  - BD Catalyst Liaison and Consulting

- Dissemination
  - Collaborative Publication Guidance
  - Harmonized Reporting Standards

RESEARCH COLLECTIVE
Centralized community and information sharing hub for enhancing collaboration and support
Common Data Elements (CDE) Principles

• **Principle 1: Build on existing trials**
  • Curate CDEs from protocols and CRFs of existing COVID-19 studies

• **Principle 2: Build on existing standards and NIH CDE resources**
  • Prioritize data elements in existing standards

• **Principle 3: Enable multiple types of analysis**
  • Across- and pooled- studies, epidemiological studies

• **Principle 4: Allow room for innovation**
  • Minimize CDE burden
  • Classify CDEs as “Core” or “Recommended”
Common Data Elements and Data Transfer Activity

• Common Data Element Manual
  • What is measured
  • How it is measured and recorded

• Review of draft protocols and CRFs

• Up-front data transfer planning and coordination
  • To ACC for study enrollment dashboard and Biorepository Database
  • To BioData CATALYST for data sharing
Centralized Information Portal

• **Site ID tools**
  Map-based and searchable by network, by study, and by site characteristics

• **Study Enrollment**
  Real-time through data transfer from study DCC

• **Study Milestones**
  Efficient, seamless reporting to NHLBI
Call for Sites!

• Regional Site Consortiums (networks of community hospitals)
• Sites in areas with projected hot-spots
• “Spoke sites” that can be led by teams from strong academic hubs
• Existing National/International consortiums

• Current need:
  • Inpatient, outpatient, and post-hospital recovering for anti-thrombotics

• Please email to both:
  activ4siteenroll@pitt.edu
  info@nhlbi-connects.org
Collaboration of 34+ Networks and 1,000+ Sites