Introduction to the Clinical Trials Transformation Initiative

Pamela Tenaerts, MD, MBA
Executive Director
CTTI
May 19, 2016
Agenda

- Welcome and Introduction to the Clinical Trials Transformation Initiative
  - Pamela Tenaerts, CTTI

- Project Overview
  - Jonca Bull, FDA

- Project Recommendations and Tools
  - Beth Mahon, Janssen R&D

- Discussion
Disclaimer

The views and opinions expressed in this presentation are those of the individual presenters and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.

One of the presenters is an employee of Duke University. Salary support comes from pooled membership fees of the Clinical Trials Transformation Initiative and from an FDA Cooperative Agreement.
Clinical trials in crisis

REPORT TO THE PRESIDENT
TRANSFORMATION AND OPPORTUNITY: THE FUTURE OF THE U.S. RESEARCH ENTERPRISE
Executive Office of the President
President’s Council of Advisors on Science and Technology
NOVEMBER 2012

The changing structure of industry-sponsored clinical research: pioneering data sharing and transparency.
Kuntz RE

The changing structure of industry-sponsored clinical research: pioneering data sharing and transparency.
Kuntz RE

Biomedical Innovation: Identifying Challenges and Prioritizing Needs
Addressing This Need

To identify and drive adoption of practices that will increase the quality and efficiency of clinical trials

Public-Private Partnership
Co-Founded by FDA and Duke involving all stakeholders
70+ members
CTTI Strategic Plan

MISSION STATEMENT
To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

GOALS
Create recs & tools  Make data publicly available  Communicate broadly  Demonstrate impact  Characterize clinical trial landscape

AREAS OF STRATEGIC FOCUS
Systematic evidence generation  Patients as equal partners  Clinical trials designed with a focus on quality & efficiency  Trials addressing emerging public health concerns  Safe & ethical trials that are streamlined
CTTI’S UNIQUE APPROACH

MULTI-STAKEHOLDER

TRANSFORMING CLINICAL TRIALS
Practices (tools, recommendations, etc.) that improve the efficiency and quality of clinical trials

EVIDENCE BASED

IMPACT
Collaboration Towards Solutions

Better Streamlined
Fit for purpose
Clinical Trials

Government and regulatory agencies

Industry: pharma bio device CRO

IRBs

Clinical investigators

Patients / Patient advocacy groups

Academia

Industry trade / Professional organizations
CTTI Membership
Methodology

State Problem
- Issue Statement, Project Plan

Gather Evidence
- Literature Reviews, Multi-stakeholder Meetings, Surveys, Interviews

Find Solution
- Team Meetings, Multi-stakeholder Meetings

Refine Ideas
- Team Meetings, Multi-stakeholder Meetings

Action
- Workshops, Pilot Studies, Measure Impact
Evidence guides the journey to solutions

We use quantitative & qualitative research methods, selecting those best aligned with each project’s objectives, to:

- Identify/describe “what is going on” to gain a better understanding of a particular phenomenon
- Move beyond individual views to a more complete and objective understanding of the disincentives and motivators for change

Equipped with data, we then challenge assumptions, identify roadblocks, build tools and develop recommendations to change the way people think about and conduct clinical trials.
How CTTI Works

- **Engage & value** all stakeholders equally
- **Understand incentives** to maintain non-value added activities and have solutions that are mindful of those incentives
- **Plant the seeds for change** throughout all phases of a project
- **Develop actionable**, evidence-based, consensus driven recommendations
- **Create and share** knowledge, tools & resources to facilitate change that improves clinical trials
CTTI projects focus on streamlining and accelerating clinical trials, while ensuring the highest standards of quality and human subjects protection. We provide actionable, evidence-based, consensus-driven recommendations designed to:

- Accelerate study start-up times & streamline protocols
- Leverage new technologies to improve efficiency of clinical trials
- Enhance the quality of clinical trials without adding undue burden
- Identify streamlined strategies while meeting regulatory requirements
Better, Streamlined, Fit for Purpose Clinical Trials

- Change
- Build consensus
- Gather evidence
- Formulate recommendations
- Identify solutions
- Target problem areas in clinical trials
## Portfolio of CTTI Projects

<table>
<thead>
<tr>
<th>Completed projects</th>
<th>Investigational plan</th>
<th>Study start-up</th>
<th>Study conduct</th>
<th>Analysis and dissemination</th>
<th>Specialty areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Large simple trials • Uses of electronic data</td>
<td>• Central IRB • Site metrics</td>
<td>• Adverse event reporting • IND safety • Monitoring</td>
<td></td>
<td>• Long-term opioid data</td>
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<table>
<thead>
<tr>
<th>Current projects</th>
<th>Investigational plan</th>
<th>Study start-up</th>
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<th>Specialty areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Patient groups and clinical trials • Pregnancy testing • QbD • Trials based on registries • Remote Clinical Trials</td>
<td>• Central IRB advancement • GCP training • Informed consent • Investigator turnover</td>
<td>• Safety case studies • IND safety advancement</td>
<td>• State of clinical trials • DMCs</td>
<td>• Streamlining HABP/VABP trials • Pediatric Antibiotic trials • Unmet need in Antibiotic development • HABP/VABP pilot study</td>
</tr>
</tbody>
</table>

- **Recruitment**
Recruitment Project Team Members

**Team Leaders**
- Jonca Bull (FDA)
- Elizabeth Mahon (Johnson & Johnson)
- Patricia Furlong (Parent Project Muscular Dystrophy)

**CTTI Staff**
- Jamie Roberts
- Diane Willis
- Kimberley Smith

**Team Members**
- David Ciavarella (CR Bard)
- Beth Harper (Clinical Performance Partners)
- Grant Huang (VA)
- Leslie Kelly (Duke)
- Jim Kremidas (ACRP)
- Barbara LeStage (Patient Advocate)
- Claire Meunier (Michael J. Fox Foundation)
- Holly Massett (NIH)
- Kelly McKee (Lilly)
- Ashish Oza (St. Jude Medical)
- Anuja Rastogi (FDA)
Recommendations for Recruitment: Moving Recruitment Planning Upstream To Reduce Barriers to Participation

CTTI Recruitment Project Team
Jonca Bull, Food and Drug Administration
Beth Mahon, Janssen R&D

May 19, 2016
Framing the Issue: Lackluster Recruitment to Clinical Trials

Jonca Bull, MD
Director, Office of Minority Health, Food and Drug Administration

May 19, 2016
Critical Issues in Recruitment to CTs

**LACKLUSTER RECRUITMENT**
A staggering number of clinical trials fail to meet recruitment goals, leading to delays, early trial termination, or inability to draw conclusions at trial completion due to loss of statistical power.

**INADEQUATE SOLUTIONS**
Many explanations have been offered including poor study design, lack of patient engagement, insufficient staff time, inadequate attention to determine and identify available patients who meet eligibility criteria, and inadequate centralized site support.

**NEW PARADIGM NEEDED**
Solution ➔ CTTI project to identify recruitment challenges and develop actionable recommendations.
Clinical Trials Crisis: Low Site Enrollment Rates

- 13% Meet Targets
- 11% Exceed Enrollment Targets
- 37% Under Enroll
- 39% Fail to Enroll Even 1

Adapted from Tufts Center for the Study of Drug Development, 2012
Clinical Trials Crisis: \( \uparrow \) Trial Complexity = \( \uparrow \) Burden on All Stakeholders

On average, 20% of Phase II and 30% of Phase III protocols collect non-core data that are not associated with a primary or key secondary endpoint, regulatory compliance, or standard baseline assessments.

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<thead>
<tr>
<th>Endpoints</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>Primary</td>
<td>14.8%</td>
<td>9.4%</td>
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<tr>
<td>Key Secondary</td>
<td>38.3%</td>
<td>34.8%</td>
</tr>
<tr>
<td>Tertiary</td>
<td>27.8%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Exploratory</td>
<td>19.1%</td>
<td>26.1%</td>
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<thead>
<tr>
<th>Procedures</th>
<th>Core</th>
<th>Required</th>
<th>Standard</th>
<th>Non-core</th>
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<tbody>
<tr>
<td>Core</td>
<td>64.9%</td>
<td>4.6%</td>
<td>9.7%</td>
<td>20.7%</td>
</tr>
<tr>
<td>Required</td>
<td>4.6%</td>
<td>3.7%</td>
<td>7.1%</td>
<td>30.6%</td>
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</tbody>
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Adapted from Tufts CSDD Impact Report Vol 16, No 5, Sep/Oct 2014
Project Objective 1

Identify barriers and optimal approaches to patient recruitment

Understand barriers and solutions for identifying, engaging and enrolling patients

Summarize existing literature on barriers and solutions

Survey experts representing stakeholders to obtain their perceptions of identified barriers and solutions
Project Objective 2

Identify methods to move recruitment planning upstream in the study development process

- Identify and catalog current recruitment planning tools
- Identify key elements of recruitment plans and tools
Evidence Gathering

LITERATURE REVIEW (2013)

STAKEHOLDER SURVEY (2014)

LANDSCAPE SCAN (Jan-May 2015)

EXPERT MEETING (Nov 2015)
**Limited data** regarding how successful or unsuccessful trialists have been in overcoming barriers or how barriers have affected the outcome of trials.

Most strategies investigated were supported by only one or two studies.

Paucity of literature on retention barriers, strategies and promoters.
Survey Results: Key Findings
Perceived Barriers to Recruitment

81.1% Finding patients who meet eligibility criteria
67.4% Insufficient staff time for recruitment
65.6% Consent forms (e.g., length and complexity)
60.3% Protocol requirements (other than recruitment criteria)

Rated very/somewhat significant (by more than 50% of respondents)
Free Text Suggestions of Methods to Increase Clinical Trial Enrollment

Outreach, Relationships, Engagement & Partnerships (11)
- Partner with patient advocacy groups
- Build relationships
- Community outreach & engagement

Plan Appropriately (13)
- Make protocols less burdensome
- Target trials to patient locations
- Recruitment & retention research

Technology & Tactics (17)
- Use technology (including registries)
- Site-specific recruitment action plans
- Advertise & educate
Survey Results: Key Findings & Recurrent Themes

**Barriers** most often reported as problematic:

- **Eligibility criteria**
- **Insufficient staff time for recruitment**
- **Protocol requirements (other than I/E criteria)**
- **Complexity of consent forms**

**Patients** offer a valuable perspective to overcoming recruitment barriers.

**Stakeholders** are not engaged in the process

- Barriers are often *designed into* protocols (and must later be amended out) at significant cost (opportunity and economic)

A comprehensive recruitment strategy, rather than a single tool or solution, will be required to address the range of significant recruitment barriers identified
The key is making sure the trial is worth doing, that it asks an important question and that the endpoints are significant… After that, we can work on all kinds of recruitment strategies.”
Survey Findings: Published Online September 3, 2015
Analysis & Discussion

Industry: variable and siloed approaches to the development of recruitment plans

- Sponsors are the primary owners of the recruitment problem
  - Hence, efforts should start centrally with study design
- Tactics to enhance recruitment are often developed too late in the process of a clinical trial
  - Frequently reactive rather than proactive
  - Often to rescue

Inference:

- Need for a culture shift toward developing a recruitment plan from the earliest stages of clinical trial development
Sounds Great! But…..

What *is* a recruitment plan?

What are the necessary components?

What are the key features?

What **tools** are being used to create them?

Who is creating them?
Gathered recruitment planning tools from wherever we could find them

Major themes:
- Recruitment plans are illusive, typically study specific and tactic based
- Recruitment planning tools are likely abundant but often proprietary
- No single framework was available for planning recruitment as part of planning a study

Inference: **Need for a systematic framework for thinking about recruitment planning in parallel with trial design & development**
- Planning should touch a number of areas
  - Study question design & protocol development
  - Trial feasibility and site selection
  - Communications
Expert Meeting: Consensus

- Sponsors are the primary owners of the recruitment problem
  - Hence, efforts should start centrally with study design

- Tactics to enhance recruitment are often developed too late in the process of a clinical trial
  - Frequently reactive rather than proactive, often to rescue

- Consensus: **We need…**
  - A *culture shift toward developing a recruitment plan from the earliest stages of clinical trial development*
  - A *systematic framework for thinking about recruitment planning in parallel with trial design & development*

- Planning concerns fall into 3 main areas
  1. Study design & development
  2. Trial feasibility and site selection
  3. Communications
The Recommendations

Beth Mahon, JD
Associate Director, Global Clinical Operations - US Janssen R&D

May 19, 2016
<table>
<thead>
<tr>
<th>Trial Design &amp; Development</th>
<th>Identify and engage all stakeholders</th>
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<tr>
<td></td>
<td>Ensure the relevance of the scientific question to stakeholders</td>
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<td>Limit protocol complexity to reduce the burden of participation</td>
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<td>Develop realistic eligibility criteria</td>
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<td>Optimize data collection to only what’s necessary to maintain patient safety and answer the scientific question</td>
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<td><strong>Trial Feasibility &amp; Site Selection</strong></td>
<td>Conduct an evidence-based trial feasibility analysis</td>
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<td>Establish realistic metrics and milestones</td>
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<td>Develop an adequate budget and resources</td>
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<td></td>
<td>Ensure appropriate site selection</td>
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<td>Engage in suitable site performance monitoring</td>
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<td>Recruitment Communication Planning</td>
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<td>------------------------------------</td>
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<tr>
<td>Identify ALL stakeholders and partners</td>
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<td>Identify participant locations based on where participants may seek treatment &amp; relevant information</td>
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<tr>
<td>Develop and test tailored messages</td>
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<tr>
<td>Develop creative material and select appropriate channels for delivery</td>
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<tr>
<td>Develop a realistic communication budget</td>
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<td>Monitor and evaluate both the recruitment process &amp; performance with meaningful metrics</td>
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<tr>
<td>Embed recruitment intervention studies into clinical trials &amp; share the results to develop best practices</td>
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The Tools and Resources

CTTI website: http://www.ctti-clinicaltrials.org/

Recommendations, Tools and Figures can be found at http://bit.do/CTTI-Recruitment
Framework for Strategic Recruitment Planning

**TRIAL DESIGN & PROTOCOL DEVELOPMENT**
- Identify & engage all stakeholders
- Ensure the relevance of the scientific question
- Limit complexity to reduce burden
- Have realistic eligibility criteria
- Optimize data collection

**TRIAL FEASIBILITY & SITE SELECTION**
- Conduct evidence-based feasibility analysis
- Have realistic metrics & milestones
- Develop an adequate budget & resources
- Ensure appropriate site selection
- Engage suitable performance monitoring

**RECRUITMENT COMMUNICATION PLANNING**
- Identify and engage all stakeholders
- Identify where participants seek treatment & relevant information
- Develop & test tailored messages
- Develop creative material & select appropriate delivery channels
- Have a realistic budget
- Monitor & evaluate process & performance
- Embed recruitment intervention studies & share results
CTTI TOOLS FOR EFFICIENT AND EFFECTIVE CLINICAL TRIAL RECRUITMENT PLANNING

TOOL 1. DECISION TREE FOR OPTIMIZING PROTOCOL DESIGN

START

Is the scientific question relevant?

Identify and engage with stakeholders to ensure the question is relevant and meaningful; Make sure you are meeting the needs of the patients and providers according to their perception of the disease.

NO

YES

Eligibility Criteria: Are the I/E criteria carefully designed to ensure feasibility?

NO

YES

Procedural Burden: Have you minimized the procedural burden to only those necessary to answer the scientific question/endpoint?

NO

YES

Data Parsimony: Have you minimized the burden of data collection to only those necessary to answer the scientific questions/ endpoints?

NO

YES

Goal: a well-designed, minimally burden-some protocol that is poised to provide data to answer a meaningful scientific question.

Consult with stakeholders, ensure the criteria are feasible; Refine the eligibility criteria to broaden the available population; Eliminate any criteria that are not necessary for the safety of participants or relevant to directly answering the research question.

Solicit feedback from stakeholders regarding important outcomes, motivations, barriers, the schedule of events and feasibility of accomplishment based on disease burden and state, workflow as well as the perceived risk/benefit ratio.

Calculate the incremental cost (financial, time, effort) of each additional data element and its utility to answering the study question; Collect only the minimum data set necessary to address study endpoints and meet the needs of various stakeholders.
FIGURE 2. MONITORING RECRUITMENT PROCESS AND PERFORMANCE

- Develop testable interventions / tactics
- Secure stakeholder buy-in
- Define measurable goals
- Identify meaningful metrics for each goal
- Define success for each metric
- Identify the required data for each metric

Plan

- Embed testable recruitment interventions/tactics into trials
- Deploy testable recruitment interventions/tactics
- Collect process and performance data

Do

- Re-assess & revise
- Make necessary improvements
- Develop rapid tests of change
- Share knowledge & experience to facilitate adoption of best practices

Act

- Analyze collected process and performance data to measure and evaluate

Check

*Process: Did we do what we said we were going to do (e.g., deploy 3 paid ads in newspapers)?
Performance: What impact did the intervention have (e.g., increase enrollment by 10%)?
Tool #2: Stakeholder Identification and Analysis Tool

<table>
<thead>
<tr>
<th>STAKEHOLDERS &amp; RESOURCES</th>
<th>STRATEGY</th>
<th>TACTICS</th>
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<tbody>
<tr>
<td>Characteristic</td>
<td>Why this group is important to a successful trial (e.g., their role)</td>
<td>What do we need them to know and to do? What do we need to know about their current attitude(s) or concerns?*</td>
</tr>
<tr>
<td>Patients (diagnosed)</td>
<td></td>
<td>How and when should/can/will we engage them? How frequently will we need to communicate with them to maintain their engagement?</td>
</tr>
<tr>
<td>Patients (at risk)</td>
<td></td>
<td></td>
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<tr>
<td>Healthy persons</td>
<td></td>
<td></td>
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<tr>
<td>Families of patients</td>
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CTTI Recruitment Project Conclusions

Actionable solutions are needed since, without them, the promise of many trials will remain unfulfilled. It is time to move recruitment planning upstream and parallel to the clinical trial design process to ensure trial feasibility given the anticipated scientific, environmental, financial, time, and resource constraints.

Overall, recruitment must involve a critical level of thought that is more inclusive of all who might have influence on, or be influenced by, the development and implementation of a clinical trial.

The development of protocol elements must be done with attention paid to upstream activities that may have a downstream impact on recruitment.
Thank you.

With tremendous thanks to the CTTI Recruitment Project Team for all their efforts at making these recommendations possible

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