Standard Terms of Agreement for Research Trials (START) Clause Utilization and Impact Evaluation

NCI Clinical Trials and Translational Research Advisory Committee

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Genesis of START Clauses

- NCI Clinical Trials Working Group identified negotiation of clinical trial agreements as a key barrier to timely initiation of cancer clinical trials.

- CEO Roundtable on Cancer Life Sciences Consortium (LSC) identified standardization of key clinical trial agreement clauses as a top priority.

- NCI/LSC perception that final negotiated agreements generally contain clauses reflecting a relatively consistent set of key agreement concepts.

- Established partnership to develop commonly accepted clauses for clinical trial agreements between industry and academic medical centers.
START Clause Participants

NCI-Designated Cancer Centers
• U. of Arizona
• City of Hope
• U. of Chicago
• U. of Colorado
• Dana Farber
• Fox Chase
• Johns Hopkins
• Mayo Clinic
• Moffitt
• MD Anderson
• U. of Pittsburgh
• Roswell Park
• UNC Lineberger
• UCSF

LSC Member Companies
• AstraZeneca
• Eli Lilly
• GlaxoSmithKline
• Johnson & Johnson
• Novartis
• OSI Pharmaceuticals
• Pfizer
• Quintiles
• Sanofi-Aventis
• Schering Plough
  (2009, Merck)
• Wyeth
  (2009, Pfizer)
START Clause Development

- Solicited legal and business representatives from participants as expert consultants
- Analyzed 48 final negotiated clinical trial agreements provided by participants
- Greater than 67% convergence on vast majority of clause concepts
- Drafted proposed clauses based on these common concepts
- Obtained input on proposed clauses from legal and business representatives
- Refined proposed clauses based on input & disseminated
START Clause Implementation

- Public dissemination by NCI/LSC in Fall 2008

- Implementation requirements
  - START clauses intended only as a starting point for individual negotiations
  - No agreement or understanding among project participants to use any of the START clauses in their agreements
  - No recommendation or promotion of START clause use

- Evaluate impact of this initiative and the START clauses themselves on negotiations
Evaluation Methodology

• 14 participant Cancer Centers, 31 non-participant Cancer Centers
• 9 LSC member companies
• Interviews conducted individually with legal & business representatives of each organization
• Responses analyzed to identify common themes and individual variations
START Clause Evaluation

Findings

• Current negotiation environment

• Current perceptions about the START clauses

• Impact of the START clause process and the clauses themselves

• Emerging areas affecting clinical trial agreement negotiations
Company templates are nearly always the starting point for negotiations.

Perception that negotiation duration has decreased.

START clauses are perceived as an acceptable “middle ground”.

Language not “implemented” *per se* because already close to current practice or guidance.

Every organization uses master agreements.
  - ~40% of CTA negotiations fall under masters.
Negotiation Environment: Company Perspective

• Cancer Center initial positions are closer to the START clauses than in 2008
  – Negotiations are perceived as less confrontational
  – Negotiations are lengthy only in rare instances
  – Negotiations are more complex – but not longer
  – Cancer Centers have become more sophisticated

• START clauses parallel current company negotiation guidance, but not necessarily initial position

• 7/8 companies use CROs for negotiating oncology clinical trial agreements
Perception that negotiation duration is decreasing, however:

- Half of respondents perceive an increase in the complexity of negotiations
- Half of respondents perceive negotiations as still a barrier to getting trials quickly underway

Half of respondents perceive the company templates as distant from START clauses

START clauses would speed negotiations if used as a starting point
START Clinical Trial Agreement

Clauses

PART I:
COMPANY-SPONSORED
CLINICAL TRIAL AGREEMENT

1. Intellectual Property
2. Subject Injury
3. Indemnification
4. Data
5. Confidentiality
6. Publication Rights

PART II:
INVESTIGATOR INITIATED
CLINICAL TRIAL AGREEMENT

1. Intellectual Property
2. Indemnification
3. Data
4. Confidentiality
5. Publication Rights
Intellectual Property: Investigator-Initiated Agreement

START Clauses

• Invention definition
  • Conceived or reduced to practice
  • In performance of the study
  • Ownership follows US patent law

• Paid-up, non-exclusive license for all purposes

• Option to negotiate an exclusive, royalty-bearing license for all purposes
**Intellectual Property: Investigator-Initiated Agreement**

- **Company Stance**
  - Majority similar to START (6/8)
    - Significant Cancer Center pushback on the NERF license

- **Cancer Center Stance**
  - Definition: Majority similar to START (18/32)
    - Minority narrow the definition (14/32)
      - “conceived and reduced to practice”
      - Confidential company information, new use/formulation/methodology, patent infringement
  - License: Majority **dissimilar** to START (30/39)
    - Non-exclusive, royalty-free license for research only (23/39)
    - Direct to option to negotiate exclusive royalty bearing license (7/39)
Subject Injury: Company-Sponsored Agreement

START Clauses

• Company reimburses Research Institute
  • Treatment of study subject for
    – Adverse events
    – Illness
    – Bodily injury
  • Caused by treatment in accordance with the Protocol

• Exemptions
  • Failure to comply with agreement, protocol or instructions
  • Negligence or willful misconduct
Subject Injury: Company-Sponsored Agreement

• **Company Stance**
  – All **arrive** at START
    • 1st pass similar to START (3/6)
    • 2nd pass similar to START (3/6)

• **Cancer Center Stance**
  – All similar to START (37/37)
Subject Injury: Company-Sponsored Agreement

• Noteworthy areas of negotiation:
  • Exclude if patient fails to follow instructions
  • Exclude underlying or pre-existing conditions
  • Coverage for immediate or necessary treatment only
  • Association for the Accreditation of Human Research Protection Programs (AAHRPP) accreditation
  • Health Insurance Portability and Accountability Act
Indemnification: Investigator-Initiated Agreement

START Clauses

• Research Institution
  – Liabilities, damages, losses, claims and expenses

• Arising from claims caused by
  – Negligence or willful misconduct

• Company
  – Any and all losses

• Resulting from claims arising out of
  – Drug manufacturing defects
  – Company’s use or publication of Study Data

• Exemptions
  – Research Institution negligence or willful misconduct
Company Stance

- Majority arrive at START
  - 1st pass similar to START (2/7)
  - 2nd pass similar to START (4/7)

- Noteworthy deviations in initial position
  - No company indemnification – a walk away point (1/7)
  - No indemnification for company’s use or publication of Study Data
Cancer Center Stance

- ~50% similar to START (18/37)
- State law or institutional policy restricts indemnification (12/37)
- Minority receive fewer rights (7/37)
  - No indemnification for company’s use or publication of Study Data
  - No indemnification for manufacturing defects
  - No company indemnification
Impact of START Clause Process

- Identifying negotiation time as an important issue
- Provoking internal dialog and action
  - Altering expectations of negotiations
  - Analysis and optimization of negotiation
    - Implementing automated management systems
    - Parallel processing of different aspects of negotiations
    - Increasing personnel
    - Active monitoring of negotiation timeline
- **START clauses as benchmarking tool**
  - Corroboration of previously established guidelines
  - Development of guidelines/templates or initial negotiation stance
  - Identification of acceptable fallback position in negotiations
Timelines

• Nearly every organization is actively monitoring time to negotiate clinical trial agreements
  – Execution time estimate: 86-123 days (LSC Companies)
  – Negotiation time estimate: 30-60 days (Cancer Centers)

• Nearly half of Cancer Centers (19/36) perceive that negotiation time has decreased slightly
  – No change in negotiation time (11/36)
  – Increase in negotiation time (6/36)

• A significant number of Cancer Centers believe that negotiation duration is no longer an issue, but they are split on whether negotiations are more complex and intense
Emerging Issues

• **Biological Samples**
  – Respondents commented that negotiations surrounding biological samples are increasingly becoming an issue

• **Clinical Research Organizations/Contract Research Organizations (CRO)**
  – Cancer Centers stated that working with CROs lengthens negotiations and increases difficulty
Conclusions

• Both Cancer Centers and companies are focused on the issue of negotiation duration and managing the negotiation process

• START clauses are generally acceptable & overall represent the “middle ground”

• Cancer Centers perceive that company templates are more pro-company than START clauses

• START clause “implementation” is as successful as can be reasonably expected
"Negotiation in the classic diplomatic sense assumes parties more anxious to agree than to disagree."

- Dean Acheson
Potential Future Projects

- Standardized clauses covering use of biological samples and associated data generated from clinical trials
- Standardized clauses for clinical trial agreements between Cooperative Groups and companies
- Improved processes for clinical trial budget development