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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Brent Miller, Ph.D.

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**
  - http://restructuringtrials.cancer.gov/files/StClauses.pdf
- **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**

Negotiation Environment: Common Perspective

- **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***

Negotiation Environment: Cancer Center Perspective

- **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

Indemnification: Investigator-Initiated Agreement

- **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

Indemnification: Investigator-Initiated Agreement

- **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**