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Council of
Academic Hospitals
of Ontario

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de l'Ontario

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August 24, 2009

Re: Statement of Principles to be Considered When Negotiating a Clinical Study Agreement Version 2.0

Dear Colleagues,

On behalf of the Clinical Studies Agreement (CSA) Steering Committee at the Council of Academic Hospitals of Ontario (CAHO), I am pleased to share with you a draft copy of Version 2.0 of the "*Statement of Principles to be Considered When Negotiating a Clinical Study Agreement*" (Statement of Principles). In September 2007, CAHO released the inaugural version of this document. At that time, the committee decided that the Principles document should become a "living document" that evolves (and hopefully improves) with time to address the needs of academic institutions and our research partners in the pharmaceutical and devices industries.

Over the last two years, the Statement of Principles has been utilized by a range of industry and academic organizations, and we have received positive feedback on its value in expediting the negotiation of clinical study agreements. We have also received a number of suggestions for improving the document.

In August 2009, the CSA Steering Committee met and updated the Statement of Principles in light of the feedback we received. Enclosed you will find a draft copy of Version 2.0 with all of the changes tracked in the document for ease of identification. The Steering Committee is hoping to get broad input on this document. We welcome your comments on all the proposed revisions, as well as any additional suggestions that you may have. **Please submit your feedback to CAHO at info@caho-hospitals.com by October 1, 2009.**

Following receipt and review of comments, the CSA Steering Committee will release Version 2.0 of the Statement of Principles in Fall 2009.

We look forward to hearing from you.

A handwritten signature in black ink, appearing to read 'Arthur Slutsky', is written in a cursive style.

Arthur Slutsky, MD
Chair, Clinical Studies Agreement Steering Committee
Council of Academic Hospitals of Ontario



Statement of Principles to be Considered When Negotiating a Clinical Studies Agreement

Living Document

As of August 24, 2009

Version 2 - DRAFT

Introduction

Collaboration of academic institutions with pharmaceutical and/or device companies is important as a means of facilitating co-operative research and advancing science. A key aspect of any such collaboration is the contract between the parties, which defines the relevant ethical, financial and academic issues. Engaging in the negotiations to develop a contract can be challenging since each institution and each company often appear to have unique needs; however, on closer inspection, there are common principles that underlie all such contracts.

In recognizing the potential benefits that would accrue from harmonization across multiple institutions, a CAHO Steering Committee was formed to draft working principles for consideration when academic institutions negotiate with industry. This resultant principles document sets out the recommended minimum standard requirements for Ontario academic hospitals when negotiating a clinical study agreement. The working committee that developed this document appreciated that there would still be variations in the contract requirements across institutions. For example, certain institutions may require somewhat shorter deadlines, additional rights of disclosure, or greater amounts of insurance. To assist academic institutions in determining acceptable variations, an accompanying document of best practices has also been provided, entitled, "Clinical Trial Agreement Best Practices for Agreements with Private Industry Sponsors".

Representatives from Ontario Cancer Research Network (OCRN), Ontario Academic Hospitals' Research Institutes and their contract offices (including legal counsel) collaborated to draft this document, facilitated by the Council of Academic Hospitals of Ontario (CAHO) (see below for Steering Committee members). They based this document on a document of clinical trial agreement principles developed by the Clinical Study Agreements Working Group (CSAWG). CSAWG is made up of contract administration representatives from several Toronto-area hospitals, including: Centre for Addiction and Mental Health, Mount Sinai Hospital, St. Michael's Hospital, Sunnybrook Health Sciences Centre, The Hospital for Sick Children, and University Health Network.

Please note that the principles in this document are not meant to be used as contract language but rather to express the general concept that is to be included in the contract. This document cannot provide any substitute for consulting a lawyer and no legal advice is provided in this document.

Recognizing the evolving nature of the clinical trial agreements environment, this is a "living document" and as such will be periodically reviewed and revised as appropriate. Should you have any feedback, please forward your comments to the Council of Academic Hospitals of Ontario, at info@caho-hospitals.com.

The members of the Steering Committee included:

- **Arthur Slutsky**, Vice President, Research, St. Michael's Hospital; Chair
- **Michelle Moldofsky**, Manager, Contracts Office, The Hospital for Sick Children
- **Laurel Evans**, Business Services Coordinator, St. Michael's Hospital
- **Karen Arts**, Director Business Development, Ontario Cancer Research Network
- **Sarah Lampson**, Clinical Trial Agreements and Contracts Specialist, Hamilton Health Sciences
- Tamara Birkenheier, Research Contracts Specialist, Mount Sinai Hospital
- Paul Macpherson, Grants and Contracts Services, University Health Network
- Valerie Sales, Director, Clinical Studies Resource Centre, University Health Network
- Ron Heselgrave, Head, Research Ethics Board
- Deidre Henne, Director, Internal Audit and Research, Hamilton Health Sciences
- Marie Lynch, Chief Governance and Corporate Services and Chief Privacy Officer, St. Joseph's Healthcare Hamilton
- Sandi Machado, Manager, Grants and Contracts Office and Clinical Research Administration, Lawson Health Research Institute
- Marisa Akow, Director, Research Administration, Ottawa Health Research Institute
- Connie Day, Associate Vice President, Medical Administration, Credit Valley Hospital
- Samuel Ludwin, Vice President, Research Development, Kingston General Hospital
- Sharyn Szick, Administrative Director, University of Ottawa Institute of Mental Health Research
- Joe Gilbert, Vice President, Research, London Health Sciences Centre

***Bolding** indicates Working Group members.

As of January 2007

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Superior Principles

- ❑ Study subjects are volunteers offering themselves for human experimentation. Their safety must not only be, but must be seen to be, the overriding principle of the contract.
- ❑ All parties will comply with all applicable federal and provincial laws, regulations and Health Canada guidelines; with ICH GCP and the Declaration of Helsinki; and the parties to whom it is applicable will comply with the TriCouncil Policy Statement. Among other things, these laws, regulations, and guidelines have as their purpose to protect the well-being of study subjects.
- ❑ The study subjects are drawn from the general public and have submitted themselves to experiment in good faith.
- ❑ The results, whether positive or negative, should be published within a reasonable time of completion of the study. The trial should be registered in a public registry (which meets the ICMJE criteria) in order to permit publication in peer-reviewed journals.

Publication

Naming of authors

- ❑ If authorship is included in the contract, authors should be named in accordance with established authorship guidelines of the International Committee of Medical Journal Editors (ICMJE) [or other recognized journal]

What can be published by Institution/Investigator?

- ❑ site results can be published by Institution/Investigator; sponsor may delete its confidential information not including data/results or study methods sufficient for the requirements of an academic journal
- ❑ access to all site-specific data will be provided to the site
- ❑ consideration should be given to providing access to aggregate multi-site data

When can Institution/Investigator publish site results?

- ❑ Following occurrence of the first of the following:
 - After publication of multi-site data, or
 - After sponsor indicates it will not publish multi-site data, or
 - After completion or abandonment of study at all sites plus
 - An 18 month delay (after database lock); plus
 - A period of no more than 120 days for sponsor's review of the manuscript including, if needed, sponsor's delay of the manuscript for the purpose of filing proprietary protection (e.g., for sponsor's review of the manuscript up to 60 days and for sponsor's delay of the manuscript for the purpose of filing proprietary protection, if needed, an additional 60 days)

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Right of sponsor to copy and distribute site publications

- sponsor's right is subject to
 - permission of publishing journal if required
 - acknowledgement of authorship
 - no use of institution/investigator name for endorsement purposes

Right of Institution/investigator to name sponsor in a site publication

- right to name sponsor in accordance with customary scientific practice as set out in ICMJE guidelines

Intellectual Property

(This is a context-specific component of any agreement)

Ownership of data

- permissible:
 - Owned by sponsor
 - Owned by institution
 - Owned jointly by sponsor and institution

Use of data by institution/investigator if owned by sponsor or jointly owned

- May be used by institution/investigator for
 - performance of study
 - publication
 - for internal
 1. administrative
 2. academic purposes
 3. research purposes
 4. study subject care/clinical purposes

Use of data by sponsor if owned by institution

- May be used by sponsor for regulatory submissions; other uses require permission of institution

Use of data by sponsor or institution if jointly owned

- May be used for any legitimate purpose

Ownership of inventions

- Subject to negotiation on a study-by-study basis; options include
 - Sponsor ownership
 - Institution ownership
 - Joint ownership by sponsor and institution

Use of inventions by institution if inventions owned by sponsor

- Non-exclusive royalty-free perpetual licence to be used by institution/investigator for non-commercial, internal
 - administrative
 - academic purposes
 - research purposes
 - study subject care/clinical purposes

Use of inventions by sponsor if owned by institution

- At discretion of Institution to negotiate on commercially reasonable terms to use for commercial purposes

Confidentiality

Exceptions to confidentiality of information defined as confidential

These are exclusions to confidential information:

- at the time of disclosure the information is already generally available to the public;
- after disclosure the information becomes generally available to the public (including through publication in accordance with the terms of the study agreement), except through breach of the study agreement by the Institution or Investigator;
- the information can be demonstrated to have been in the Institution's or Investigator's possession prior to the time of disclosure by Sponsor, and was not acquired directly or indirectly from Sponsor under an obligation of confidentiality;
- the information becomes available to the Institution or Investigator from a third party which is not legally prohibited from disclosing such information, provided such information was not acquired directly or indirectly from Sponsor under an obligation of confidentiality;
- the information can be documented to have been independently developed by Institution personnel who did not have access to Sponsor's information

Nature of confidentiality obligation

- recipient of confidential information (clarify that recipient is party to the agreement) to maintain information in confidence using same degree of care as recipient uses with its own confidential information and not less than a reasonable standard of care
- access by personnel with need to know
- to Institution's/Investigator's staff with a need to know and to the Institution's REB

Permitted disclosures of confidential information

Confidential information may be disclosed by Institution or Investigator

- when required to be disclosed by law, regulation or legal process
- to potential study subjects during the recruitment process or to study subjects who are or were enrolled in the Study, or their lawful representatives, in order to obtain and maintain informed consent or as the information relates to their health, safety or diagnosis;
- when otherwise permitted by agreement

Term of obligation of confidentiality

- Obligation survives termination/expiration of agreement but must have an end date, which is expected to be no more than 10 years
- If Institution/Investigator is required to return all confidential information to sponsor on termination of agreement, Institution/Investigator may retain a copy (i) as required by law, regulation or in accordance with the provisions of ICH Good Clinical Practices or Health Canada Guidelines; (ii) as necessary to exercise site publication rights; and (iii) for legal record-keeping purposes

Privacy

- all parties agree to comply with applicable privacy legislations
- no disclosure by recipient except in accordance with consent or as required by law
- also applies to study subject's biological samples/materials
- Sponsor's right to access records for monitoring/audit does not entitle Sponsor to a copy of personal health information
- Sponsor will notify Institution (or Investigator, if Investigator is the health information custodian) of any breaches of privacy by Sponsor or its representatives

Indemnification

Indemnitees

- A party including its/his/her trustees, directors, officers, affiliates, employees, agents, appointees (including Investigator and sub-investigators), students (if applicable), sub-contractors (if applicable), each being a separate indemnitee

Indemnitor has obligation to indemnitees to

- Indemnify and hold harmless¹

¹ Institution insurer and Investigator's defence provider have stated they will not cover for claims brought outside Canada. Institutions will have to make a risk management decision if institutions are asked to defend sponsor. Some Institutions won't agree to defend sponsors. If Institution does agree to defend sponsor as well as indemnify and hold harmless, Institution may indicate that Institution's obligation to defend applies within Canada only. See comment regarding governing law/jurisdiction (note 2).

Sponsor's indemnification and hold harmless

- To the extent the claims arise out of or are caused by
- ❑ Conduct of study (anything required by the protocol, including without limitation injury to study subjects arising from administration of study drug/device/placebos/comparators or study procedures)
 - ❑ Sponsor's negligence, error, omission or intentional wrongdoing; including without limitation breach of clinical trial agreement and/or failure to conduct study in accordance with applicable laws
 - ❑ Sponsor's use of results (if this is included in limitation of liability, the hospital may consider not including in indemnity)

Institution cross-indemnification and hold harmless

- ❑ Some institutions will offer on behalf of Institution employees and agents only, excluding licensed physicians and their employees and agents (*Note: the insurer of many hospitals does not provide coverage for or indemnification on behalf of physicians for clinical work*)
- ❑ To the extent that claim arises out of or is caused by Institution's
 - Negligence, error, omission or intentional wrongdoing; including without limitation breach of clinical study agreement or failure to conduct study in accordance with protocol and/or failure to conduct study in accordance with applicable laws
- ❑ Investigators are not expected to provide an indemnification²

Deleted: , but may be asked to provide a statement accepting responsibility for his/her own actions and the actions of those for whom he/she is in law responsible.

Indemnification is expected to be provided directly by Sponsor either in the clinical trial agreement or in a separate indemnification/insurance/warranties agreement made with Institution/Investigator

- ❑ If the clinical trial agreement is between sponsor's agent contract research organization (CRO) and Institution/Investigator, Sponsor must at minimum provide written confirmation/representation to Institution/Investigator that CRO has authority to bind Sponsor to the agreement as a principal.

Indemnification exclusions

- ❑ Provided that the failure causes the claim, the following are acceptable exclusions from the indemnification obligations:
 - The indemnitee's negligence, error, omission or intentional wrongdoing
 - Failure to comply with applicable law/rules and regulations
 - Breach of the agreement

² The CAHO hospitals cannot speak for Investigators but note that Investigators may be asked to provide a statement accepting responsibility for his/her, and for those for whom he/she is in law responsible, own negligence, error, omission or intentional wrongdoing; including without limitation breach of clinical study agreement or failure to conduct study in accordance with protocol and/or failure to conduct study in accordance with applicable laws. Investigators retain the right to refuse to provide such a statement of liability.

- o Failure to follow the protocol (except for deviations due to medical necessity)

Indemnification conditions

- If there is a cross-indemnification from the Institution, conditions must be reciprocal
- Indemnitor's control over defense and right to settle must not include admission of liability on behalf of an indemnitee without that indemnitee's prior written consent
- Provision of prior written notice of the claim must have reasonable time lines associated

Study subject reimbursement (medical care of study subjects)

- Sponsor will reimburse institution/investigator/subject as applicable for costs of reasonable medical expenses required due to injury arising
 - o From study drug/device/materials
 - o From protocol procedures
- Reimbursement may be denied by sponsor to the extent that
 - o government sponsored insurance pays for treatment
 - o the injury is caused by Institution/Investigator negligence
- The subject's private insurance provider should not be responsible for payment
- Subjects should not be excluded due to own negligence

Insurance

- physicians will maintain membership in the CMPA or equivalent (Note: As this is a defence fund rather than insurance, it does not have specified minimum coverage amounts)
- Sponsor must have general liability, product liability and/or clinical trial insurance coverage
- Institution must have general liability coverage
- For interventional clinical trial it is expected that there will be a minimum coverage of \$5M, per occurrence and in the aggregate. (Note: The appropriate minimum will be subject to risk assessment, determined according to the circumstances)

Limitation of Liability of Institution/Investigator

Deleted: /No Warranties

- If included, limitation of liability for indirect/consequential damages must be reciprocal and must exclude those arising out of indemnification obligations.
- Institution and investigator accept no liability for use of results or intellectual property by sponsor or third parties (if this is covered in Sponsor's indemnity, the hospital may consider not including this limit of liability)

Deleted: <#>Institution and investigator disclaim warranty for ownership, merchantability, or fitness for a particular purpose of the results.¶

No Warranties/Disclaimer

- Institution and investigator disclaim warranty for ownership, merchantability, or fitness for a particular purpose of the results.
- Institution and investigator do not make a guarantee to meet recruitment goals.

Comment [MM1]: This was moved. It is not new.

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Comment [MM2]: This is new. The suggestion was that there should be an exclusion of liability for recruitment of subjects.

Disclosure of Existence of Contract & Use of Name

- Institution/Investigator have rights to disclose in customary reports of research funding:
 - Existence of agreement
 - Name of parties
 - Global amount of funding provided (for annual financial report purposes)
 - Name of study or protocol (Note: Can use the name published in a public registry or the parties can agree upon the study name)
- Sponsor has rights to disclose
 - Existence of agreement
 - Global amount of funding provided
 - Name of study or protocol
 - Names of institution and investigator, except for endorsement purposes
- No party has a right to use another party's name in any way that suggests advertising or an endorsement (of a product, service, study etc.) by that other party, without that other party's prior written permission

Parties' Rights and Obligations

Compliance with applicable laws, regulations and guidelines

- Adverse event reporting obligations and rights of Sponsor and Institution/Investigator to be set out (including, in event Sponsor fails to do so, right of Institution/Investigator to report SAEs and results required to protect the health of study subjects directly to regulatory authorities, data safety monitoring board, study subjects or their lawful representatives, participating centres, and their research ethics boards, and applicable steering committee)
- Warranty by sponsor re study drug/device that study drug/device shall be free of defects, and the manufacture, packaging and labeling of study drug/device shall be in full compliance with any requirements and specifications of Health Canada, and with Good Manufacturing Practices

Conflict of study documents

- Protocol versus agreement
 - Agreement prevails
- Prior confidentiality agreement
 - Study agreement supersedes

Force majeure

- If included, applies to all parties

Dispute Resolution and Governing Law/Jurisdiction

Dispute resolution

- If there is a dispute resolution clause, binding arbitration shall not be used in disputes that may involve subject safety issues
- If jurisdiction included in dispute resolution clause, needs to follow principle of governing law/jurisdiction.

Governing law/jurisdiction

- Governing law/jurisdiction is expected to be a Canadian province and the federal laws/courts applicable therein. Any exceptions will require a risk-assessment by the Institution/Investigator³.

Termination

Termination events

- All parties have the following rights to terminate the study agreement:
 - for breach of contract on written notice, with a reasonable correction period
 - for study subject safety reasons, right to suspend the study immediately on written notice and to terminate the study agreement if such reasons are not resolved within a reasonable period
 - For withdrawal of regulatory approval, immediately on written notice
- There is a mechanism to terminate
 - for inability of investigator to perform study for reasons beyond his/her control and no acceptable alternative investigator available, on written notice after reasonable efforts made to find alternative

Events on termination

- Parties cooperate to wind up study in safe and efficient manner
- Payment by sponsor of amounts owing for work performed to date of termination plus non-cancellable obligations incurred prior to notice of termination
- except in event of termination for safety reasons, sponsor to continue to supply study drug in quantities sufficient to safely wind up study

³ Institution insurer and Investigator's defence provider have stated they will not cover for claims brought outside Canada. This limitation in coverage affects both governing law/jurisdiction and Institution's ability to defend sponsor. See comment regarding defending sponsor (note 1).

Survival of rights/obligations following completion or termination of agreement

- survival of specified contract clauses
 - confidentiality (for the stated period)
 - indemnification
 - insurance to be maintained by parties as necessary to cover obligations incurred under study agreement
 - warranties
 - publication/publicity
 - provisions relating to payment of any amounts that may be payable following termination (not always limited to payment of per patient fees)
 - survival
- if a study subject is benefiting from the study drug (as reasonably determined by subject's physician) and subject to appropriate regulatory approvals, consideration should be given to keeping the subject on the drug until the end of protocol timelines or until the drug is commercially available.

Additional Principles – For Contracts with Contract Research Organizations

- Sponsor is expected to be a party to the study agreement among CRO, institution and investigator and to accept obligations under the agreement. In the event the sponsor is not a party to the study agreement;
 - CRO must take full responsibility for payment, or sponsor must take full responsibility for payment through legally binding means;
 - Sponsor must enter into a legally valid agreement with institution and investigator setting out the following responsibilities:
 - Indemnity
 - Insurance
 - Drug/device warranty (if applicable)
 - Sponsor's role in the study and compliance with applicable law, regulations, GCP, Health Canada guidelines and customary ethics.
- If sponsor is not party to the study agreement among CRO, institution and investigator but has obligations under the agreement, sponsor must provide a legally valid representation letter that it is principal to CRO's agent and is bound to sponsor's obligations under the contract, and that institution/investigator can enforce those obligations directly against sponsor.