Regulatory Standards & Contracts

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Objectives

- To define the clinical trial regulations and guidelines that apply to research
- To define and understand the Canadian regulatory standards
- To understand additional considerations for international research collaboration
- To describe the basic content of research contracts

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Clinical Trial Regulations and Guidelines

HISTORY

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Nuremburg Code

- 1946 -1949 Nuremburg Trials, World War II International military tribunal
- Nazi's who conduct "medical science" experiments
- 1947 Judgment included a set of ethical standards for medical research = Nuremburg Code
- Detailed 10 standards physicians must conform to when conducting research with human subjects

Declaration of Helsinki

- Medical progress is based on research which rests in part on human subject experimentation
- Purpose of medical research is to improve treatments and understanding of disease
- Medical research involves risks and burdens
- Medical Research must therefore be subject to ethical standards

Declaration of Helsinki

Protocol

- Written protocol is required
  - Design and procedures clearly formulated
- Research must be scientifically sound and based on a thorough knowledge of scientific literature and other relevant information
- Protocol should contain statement of ethical considerations involved and state compliance with the Declaration of Helsinki

Declaration of Helsinki

Ethics Review

- Ethics review required for:
  - protocol (initially and continually)
  - serious adverse events
  - potential conflicts of interest
  - incentives for subjects
- Research Ethics Board (REB) should be independent of investigator

Declaration of Helsinki

Subjects

- Subjects must be volunteers and informed participants
- Well-being of human subject comes before interests of science and society
- Some populations need special protections
- Protect privacy and confidentiality of subjects

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Declaration of Helsinki

Informed Consent

- Informed consent must address:
  - Research aims and methods, sources of funding, any possible conflicts of interest, benefits and risks, right to refuse and withdraw
- Consent should be obtained in writing
- Subject incompetent—legally authorized representative can provide consent
- Caution recommended if subject has an dependent relationship with the investigator

Declaration of Helsinki

Publications

- Accurate
- Publish negative and positive results
- Declare funding sources, institutional affiliations and any conflicts of interest
- Studies not conducted in accordance with the Declaration of Helsinki should not be accepted for publication

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Tri-Council Policy Statement (TCPS)

- Policy statement for Canadian Granting Agencies:
  - CIHR-Canadian Institute for Health Research (formerly MRC)
  - NSERC-Natural Sciences & Engineering Research Council
  - SSHRC (Social Sciences and Humanities Research Council)
- Granting agencies will only fund individuals and institutions which certify compliance
- Not currently force of law in Canada

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TCPS

Guiding principles, respect for:

- Human dignity
- Free & informed consent
- Vulnerable persons
- Privacy and confidentiality
- Justice and inclusiveness
- Balancing harms and benefits

ICH – GCP

- 1996 International Conference on Harmonization, Good Clinical Practice (ICH-GCP)
- International ethical and scientific quality standard for the design and conduct of clinical trials in human subjects as well as for the recording and reporting of clinical trial data
- Describes the responsibilities of those conducting clinical trials

ICH – GCP

- Applies to regulatory agencies / pharmaceutical companies of ICH regions (Japan, US, and EU)
- Follow when conducting a trial
  - Intended for regulatory submission
  - Any trial under a Clinical Trials Application (CTA) in Canada
- ICH-GCP applies to all trials

ICH – GCP

- ICH Topic E6 basic structure
  1. Glossary
  2. Principles
  3. Research Ethics Boards (REBs)
  4. Investigator Responsibilities
  5. Sponsor Responsibilities
  6. Protocol/Amendments
  7. Investigator Brochure
  8. Essential Documents

ICH – GCP

Principles

- Conducted in accordance with the ethical principles that have their origin in the DOH
- Foreseeable risks and inconveniences should be weighed against the anticipated benefit for the subject and society
- Rights, safety, and well-being of trial subjects are the most important considerations

ICH – GCP

Principles

- Available nonclinical and clinical information on an investigational medicinal product (IMP) should be adequate to support the proposed clinical trial
- Clinical trials should be scientifically sound and described in a clear, detailed protocol
- A trial should be conducted per protocol following institutional research ethics board (REB) approval/favourable opinion

ICH – GCP

Principles

- Medical care given to, and medical decisions made on behalf of subjects, should always be the responsibility of a qualified physician or, when appropriate, a qualified dentist
- Clinical trial personnel should be qualified by education, training, and experience
- Freely given informed consent should be obtained from each subject prior to participation

ICH – GCP

Principles

- Clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification
- Confidentiality should be ensured
- IMP should be manufactured, handled, and stored in accordance with good manufacturing practices (GMP)
- Systems with procedures that assure the quality of every aspect of the trial should be implemented

REB Responsibilities

- Responsibilities
  - Ensure rights, safety, and well-being of all subjects (emphasis on vulnerable populations)
  - Obtain
    - Protocol / amendments
    - Informed consent and updates
    - Recruitment procedures
    - Investigator Brochure or Product Monograph
    - Safety information
    - Payments and compensation
    - Qualified Investigator CV ++ other documents

REB Responsibilities

- Responsibilities
  - Review and approve / favourable opinion
  - Conduct continuing review at minimum annually
  - Ensure informed consent requirements have been met depending on trial type
- Composition, Functions, and Operations
  - Consist of a reasonable number of members who collectively have appropriate qualifications and experience
    - At least 5 members
    - At least one member whose primary area of interest is in a non-scientific area

REB Responsibilities

- Procedures
  - Detailing composition and authority (e.g. signing)
  - Scheduling of meetings and conducting reviews
  - Providing expedited review and approval / favourable opinion of minor changes in ongoing trials
  - Ensuring that no subject is enrolled prior to approval / favourable opinion
  - Specifying that deviations, adverse drug reactions, and new information be reported
  - Maintaining records

Investigator Responsibilities

- Qualifications and agreements
- Adequate resources
- Delegation of Duties
- Medical care of trial subjects
- Communication with REB
- Compliance with protocol
- Investigational Medicinal Product (IMP)
- Randomization / unblinding

Investigator Responsibilities

- Informed consent of trial subjects
- Records and reports
- Progress reports
- Safety reporting
- Premature termination or suspension
- Final report

Sponsor Responsibilities

- Quality assurance and quality control
- Contract Research Organization (CRO)
- Medical expertise
- Trial design
- Trial management, data handling, and record keeping
- Investigator selection / responsibilities

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Sponsor Responsibilities

- Financing
- Notification / submission to regulatory authority(ies)
- Confirmation of local REB approval / favourable opinion
- Information on IMP e.g. labeling
- Record access
- Safety information, adverse drug reaction reporting

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Sponsor Responsibilities

- Monitoring & auditing
  - Central and on-site
- Noncompliance
- Premature termination or suspension
- Clinical trial / study reports

Health Canada Food and Drug Regulations

CANADIAN REGULATORY STANDARDS

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Health Canada

- Health Products and Food Branch of Health Canada (HPFB):
  - Clinical Trials Regulations for Drugs
    - Therapeutic Products Directorate (TPD)
    - Biologics and Genetic Therapies Directorate (BGTD)
      - Blood and blood products; cells, tissues, and organs; gene therapies; radiopharmaceuticals
  - Natural Health Products
  - Medical Devices

Health Canada

- Health Canada Food and Drug Act (FDA)
- Food and Drug Regulations (FDR), Division 5 “Drugs for Clinical Trials Involving Human Subjects”
  - Came into force on September 1, 2001
  - Includes GCP (C.05.010)
  - Applies to all Phase I to Phase IV clinical trials

Health Canada

Key Points for Sponsors

- CTAs will be filed for trials which involve unmarketed agents, or marketed agents, where one or more of the following is different from the Health Canada Notice of Compliance (NOC):
  - Indication(s) and clinical use
  - Target patient populations(s)
  - Route(s) of administration
  - Dosage regimen(s)

Health Canada

Key Points for Sponsors

- CTAs are not required to be filed for clinical trials involving marketed agents where the investigation is to be conducted within the parameters of the approved NOC.
- For example, clinical trials involving Patient Reported Outcomes (PRO's), and surgical trials typically do not require a CTA

Health Canada

Key Points for Sponsors

- Example….Metformin
- Phase III randomized trial of metformin versus placebo on recurrence and survival in early stage breast cancer
- Use not covered in Product Monograph for Metformin therefore a Clinical Trial Application (CTA) was filed with Health Canada

Health Canada

Key Points for Sponsors

- CTA submissions include
  - Protocol, consent, drug information, investigator brochure, ++ required forms
- 30 day review period by Health Canada

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Health Canada

Key Points for Sponsors

- Health Canada will issue either…
  - No Objection Letter (NOL) = trial can proceed
  - Or Clairfax = additional information must be submitted to Health Canada
- Complete guidance from Health Canada is available detailing the CTA submission process and required documentation
- Pre CTA meetings with Health Canada can be arranged

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Health Canada

Key Points for Sponsors

- Clinical Trials Require…
  - Compliance with ICH – GCP Topic E6
  - Submission and approval of changes to the protocol / consent
  - Drug labeled specifically for the trial
  - Reporting of serious adverse events
  - Submission of safety data upon request
  - Notification of premature trial discontinuation or significant events
  - Health Canada may inspect sponsors and/or sites participating on clinical trials

Considerations

INTERNATIONAL

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US Federal Regulations

- US Code of Federal Regulations (CFR); Title 45, Part 46, Protection of Human Subjects
- Governs research funded by the US National Institutes of Health (NIH) or agencies (e.g. Oncology – NCI)
- OHRP (US Office of Human Research Protection) ensures compliance with the code

US Food and Drug Administration

- Applicable to studies conducted in Canada where trial is being directly under a US IND
- IND required in US when…
  - IMP is not marketed or
  - IMP is marketed but one of the following conditions exist
    - Intention to submit trial to FDA as a well-controlled trial
    - Intention to change labeling as a result of trial results
    - Indication / dose etc… involves a significant increase in risk

US Food and Drug Administration

- Regulations and processes to consider when filing a US IND
  - CFR Title 21, Section 312
  - Requirements for labeling, safety reporting, investigators, REB review, etc…
  - Completion of FDA 1572 by Qualified Investigator
  - Completion of Financial Disclosure form

US Food and Drug Administration

- Other factors to considers…
  - IND is drug specific
  - Once an IND is in place, trials are filed to the IND
  - FDA have 30 days to comment but no formal approval is given
    - Note: May issue a clinical hold
  - Versus Canada….each trial has a unique CTA and NOL and the drug is filed under a Drug Master File (DMF)

European Union

- Regulations governing clinical trials in the EU are provided in Directive 2001/20/EC
- Addresses GCP implementation in clinical trials with select nuances
- Partnerships require legal representatives in the EU
- Should be defined in trial contracts

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European Union

- Responsibilities include…
  - Regulatory submission
  - Oversight including audit / monitoring
  - Safety reporting
  - Aspects of drug including relevant GMP requirements

Summary

REGULATORY ROAD MAP

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What Regulations and Guidelines Apply to Which Trials in Canada?

- Declaration of Helsinki / International Conference on Harmonization Good Clinical Practice
  - Yes, these ethical principles apply to all trials
- Tri Council Policy Statement (TCPS)?
  - Yes if funded by Canadian agency

What Regulations and Guidelines Apply to Which Trials in Canada?

- Health Canada Clinical Trials Application (CTA)? - Yes if new indication including…
  - Licensed drug but not in an approved disease or stage
  - Licensed drug but in a new schedule or dose
  - Licensed drug but in a new combination
- Office for Human Research Protection rules? - Yes if drug or funding is provided via NIH
- US FDA? - Yes if a US Investigational New Drug (IND) is filed

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What Regulations and Guidelines Apply to Which Trials in Canada?

	DOH ICH-GCP	Local REB	TCPS	Health Canada CTA	OHRP	US FDA
All Human Trials	X	X				
Canadian agency funding	X	X	X			
+ new indication	X	X		X		
US government funding	X	X			X	
Under US IND	X	X				X

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CONTRACTS

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Contract Requirements

- Good Clinical Practice 1.17 Contract:

  A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

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Contract Requirements

GCP	Contract/Agreement	Investigator / Site Files	Sponsor Files
8.2.4	**Financial Aspects of Trial** To document financial agreement between Site and Sponsor	Yes	Yes
8.2.5	**Insurance Statement** To document that compensation to subject(s) for trial-related injury will be available	Yes	Yes
8.2.6	**Signed Agreements between** Involved Parties To document agreements	Yes	Yes

Legal Entity & Signing Authority

- Legal Entity
  - Determine legal entity of sponsor, Investigator centre, Institution
  - NCIC CTG legal entity is Queens University
- Signing Authority
  - Determine who is authorized to sign
  - NCIC CTG signatory is Director of Queens Office of Research Services and NCIC CTG Group Director

Common NCIC CTG Contracts & Agreements

- Bilateral Confidential Disclosure and Limited Use Agreement
  - Agreement between sponsor and company
  - Signatories intend to hold discussions and exchange information
- Clinical Trials Agreement (CTA)
  - Signatories intend to conduct a clinical research study according to protocol
  - Agreement between sponsor and company
  - Roles and Responsibilities are detailed

Common NCIC CTG Contracts & Agreements

- Participating Centre Agreement (PCA)
  - Agreement between sponsor and Investigator centre
  - Signatories intend to conduct a clinical research and responsibilities are specified
  - NCIC CTG has PCA with each Investigator centre that covers all research conducted; Renewable every 5 years
  - If Trial Specific PCAs are required this can cause delays in trial activation and accrual

Common NCIC CTG Contracts & Agreements

- Clinical Trials Agreement (CTA); Collaborating Partner
  - Agreement between sponsor and Intergroup partner
  - Signatories intend to conduct a clinical research study according to a protocol
  - Roles and Responsibilities are detailed

Common NCIC CTG Contracts & Agreements

- Tumor Tissue Data Repository (TTDR), Clinical Trial Tissue Access Agreement
  - Agreement between sponsor and Investigator
  - Contract to access trial specific clinical database held by NCIC CTG as well as tissue samples collected for the clinical trial
  - Investigator applies to NCIC CTG to conduct a research project related to the database/tissue and an agreement is signed

Common NCIC CTG Contracts & Agreements

- Data Sharing Agreement
  - Agreement between sponsor and Investigator
  - Results of a study have been published
  - Investigator applies to NCIC CTG to conduct additional research project on the database and an agreement is signed
  - NCIC CTG provides a partial anonymized database to the Investigator for the project

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Roles & Responsibilities

- Protocol and protocol amendments
- Case Report Forms
- Informed Consent Form
- Investigational Medicinal Product
- Correspondence with Health Authorities
- Serious Adverse Event Reporting
- Safety Monitoring
- Research Ethics Board Approvals/Ethics
- Audit and Monitoring

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Roles & Responsibilities

- Site and Investigator Selection
- Trial and Investigator Centre Initiation
- Investigator Meetings
- Data Management
- Trial Close Out
- Statistical Analysis and Report
- Communication
- Other (ie Trial Master File retention)

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Contract Negotiations

- Communication
  - Legal team discussing aspects of trial conduct
- Roles and Responsibilities
  - Management of expectations
  - Agreement to timelines and deliverables
  - Discussion over on-site monitoring strategies and different costs associated

Contract Negotiations

- Indemnification (NCIC CTG sample)
  - CTG shall indemnify Company, its trustee, directors and personnel and hold it harmless from any liability, cost, or expense, including legal fees, arising out of, or in connection with, any injury to a person (including death) arising from Company's Study Drug used in this Study to the extent such injury relates directly to any negligent act by CTG and its employees pertaining to the activities to be carried out pursuant to the obligations of this Agreement.

Contract Negotiations

- Similarly…Company shall indemnify and hold harmless CTG, its trustees, directors and personnel and those Participating Centres, Participating Investigators, and their respective trustees, directors and personnel (the "Indemnitee(s)") from any liability, cost, or expense, (including reasonable legal fees and expenses), including without limitation claims arising from bodily injury, including death, (individually, a "Claim") arising in connection with or arising out of: (i) the use of the Study Drug in the Study, etc….

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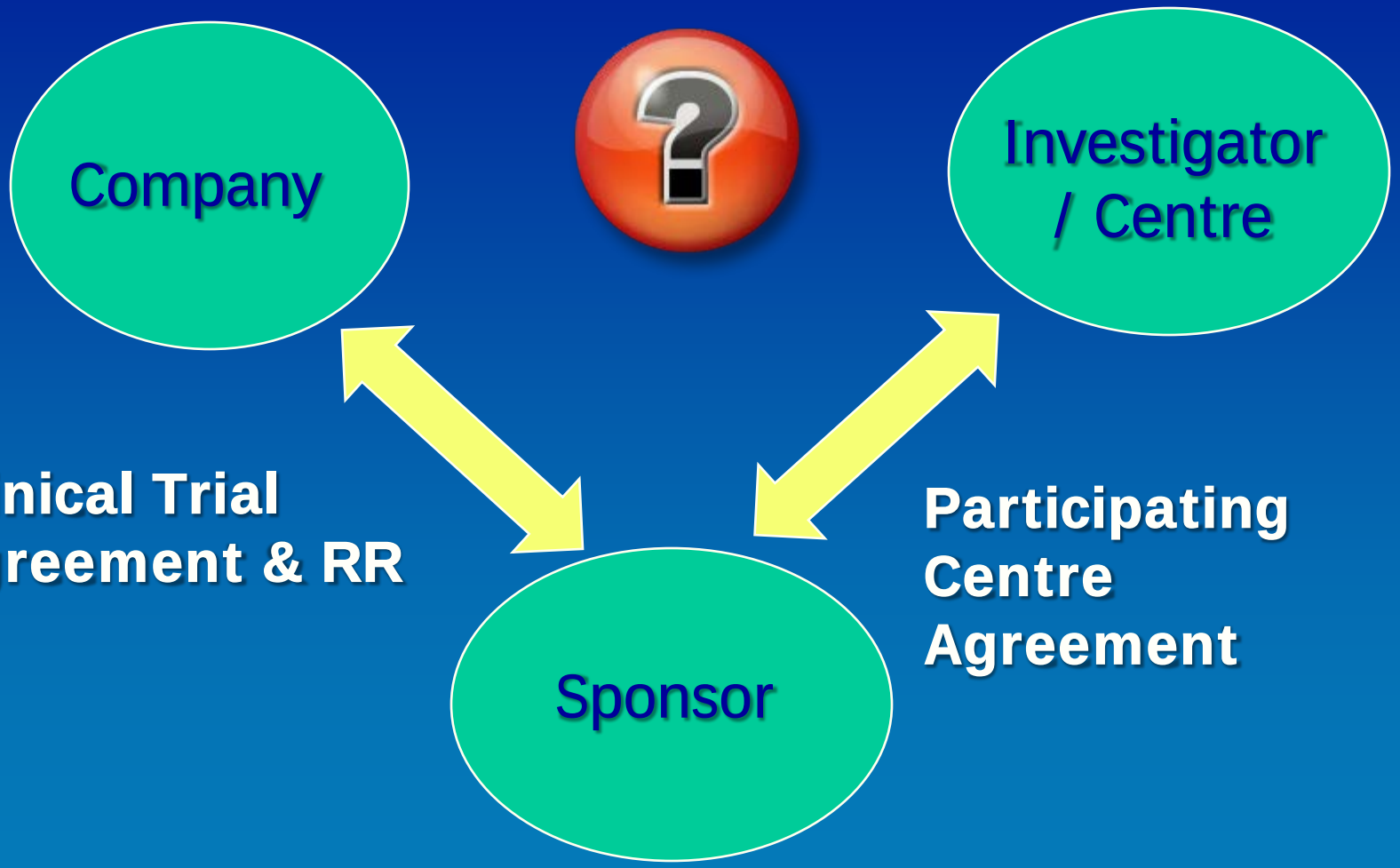
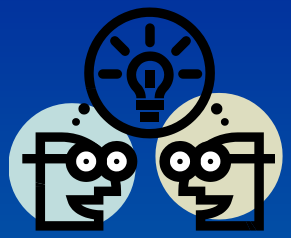
Contract Negotiations



Contracts and Trial Timelines



#1 Bilateral Confidential Disclosure and Limited Use Agreement

#2 Clinical Trial Agreement & RR

#3 Trial Specific Participating Centre Agreement

#4 Clinical Trials Agreement; Collaborating Partner & RR

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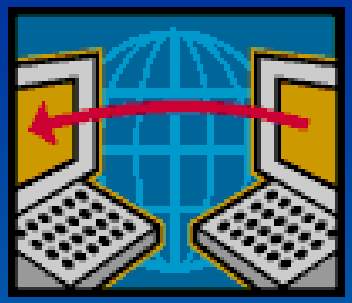
Contracts and Trial Timelines

New England Journal of Medicine



#5 Data Sharing Agreement

#6 Tumor Tissue Data Repository (TTDR)

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Investigator Perspective

- Pharmaceutical sponsored trial in which Investigator participates
  - Agreement between Investigator Institution and pharma partner
  - Details responsibilities of Investigator team in delivering the trial from an Institutional perspective
- Investigator initiated clincial trial
  - Investigator has clinical trial agreement with pharma partner to provide agent and funding
  - Investigator has submitted CTA to Health Canada
  - Investigator now responsible for delivering to pharma partner and regulatory authority from both the Investigator and Sponsor levels

Summary Contracts

- Consult with legal entity and ensure authorized signatories are aware of the research project
- Determine what type of contract and definition of roles and responsibilities will be required
- Communication with legal team during contract negotiations is important
- Contracts address more than finance and ensure expectations are clear throughout the life of a project

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