



Therapeutic Products Directorate

Direction des produits thérapeutiques

Health Products and Food Branch

Direction générale des produits
de santé et des aliments



13 – Essential Elements in Clinical Trial Assessment

**Presentation to APEC Preliminary Workshop
on Review of Drug Development
in Clinical Trials**

**Celia Lourenco, PhD,
Manager, Clinical Group I
Office of Clinical Trials
Therapeutic Products Directorate**

Slide 1

L1

Lourenco; 28.01.2008



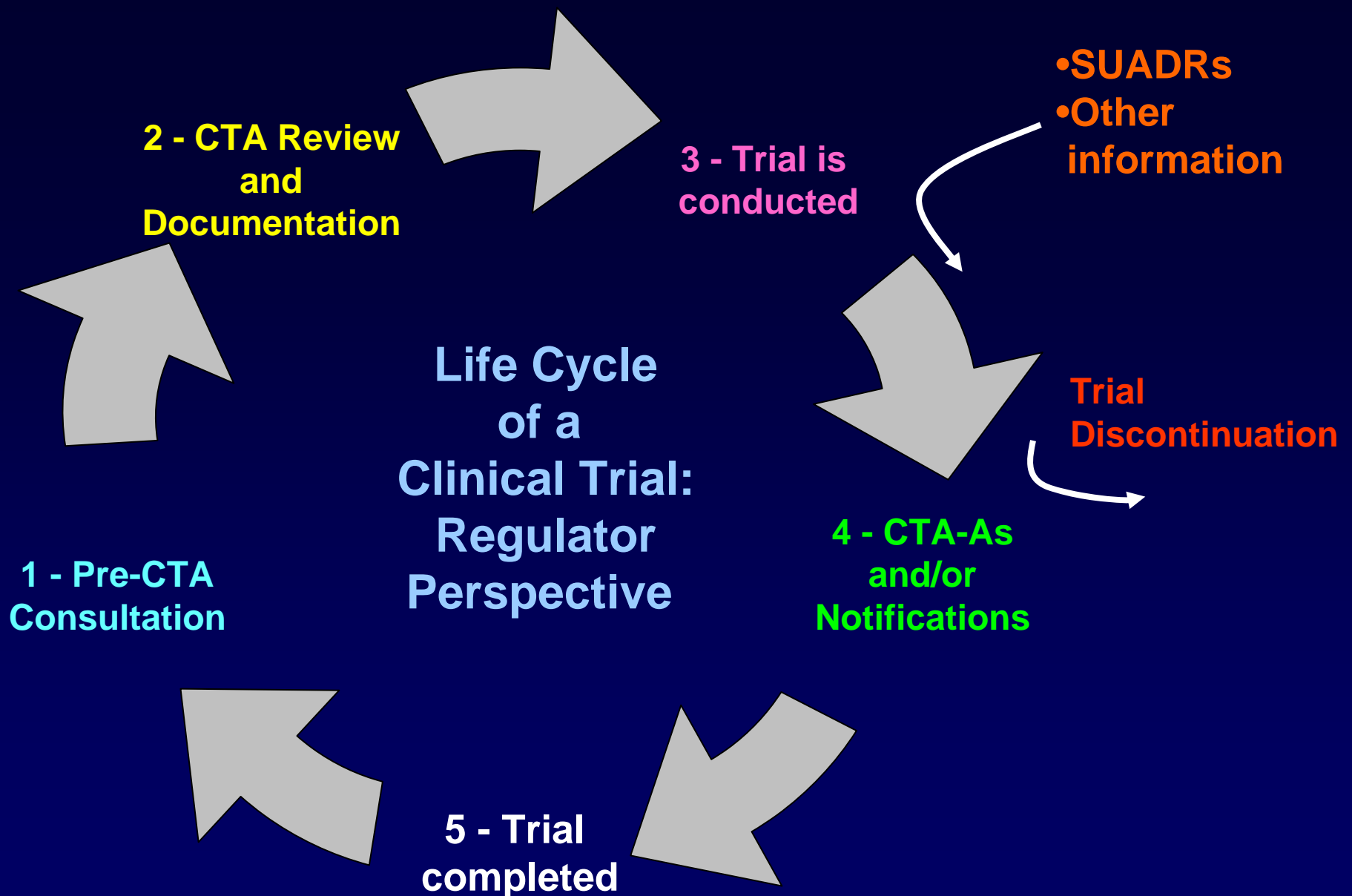
Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop

Overview

- Sufficient evidence (safety, efficacy, and quality)
- Enabling regulatory framework
- Good review practices when assessing a clinical trial
- Challenges & strategies
- Lessons learned from the Canadian experience

Sufficient Evidence

- Sufficient evidence signifies a positive benefit-to-risk ratio based on a sum of all of the following:
 - Acceptable Quality (CMC) for the phase of development
 - Acceptable supporting nonclinical and clinical data (as applicable) for the phase of development, type of drug and/or disease target
 - Acceptable protocol and informed consent form for the proposed trial
 - Maintenance of the positive benefit/risk ratio during the conduct of the trial through safety monitoring of the trial as well as other ongoing trials with the drug ('product life-cycle' approach)



Regulatory Framework must be Enabling of Sound Benefit / Risk Assessment

Regulatory Framework

- Regulations must aim to protect clinical trial subjects and enable sound benefit / risk assessment, without unduly restricting research and access
- Regulatory requirements should take into consideration the global context
- Globalization: adopt international guidelines where possible
- Address regional-specific issues by developing region-specific guidelines
- Guidance documents on process, format, and content, of clinical trial applications should be available

Good Review Practices Overview

- Regulatory expertise
- Scientific expertise
- Time management
- Documentation
- Systematic approach to review
- Review of subsequent information – life cycle approach

Good Review Practices (1)

- Regulatory expertise:
 - Know the applicable regulations
 - Know the applicable guidelines
 - Know the difference between regulations and guidelines
 - Regulations are mandatory requirements
 - Guidelines are supported by regulations but allow flexibility in requirements when acceptable scientific rationales are presented
 - Check prior decisions that were precedence-setting and ensure consistency
 - Use a case-by-case approach for infrequent scenarios

Good Review Practices (2)

- Scientific expertise (CMC):
 - Know the principles of CMC and GMP for pharmaceuticals or biologics
 - Know the basic quality requirements and considerations for the type of drug product and clinical trial stage in question (quality is linked to clinical application)
 - Consult with colleagues and read the latest literature related to the product area

Good Review Practices (3)

- Scientific expertise (clinical):
 - Know how the disease is treated and the clinical practice guidelines relevant to the disease area
 - Read the latest literature on the disease
 - Compare the information with the background and rationale provided by the sponsor
 - Consult with internal or external experts in the disease area as needed
 - If unclear about the rationale for the study, ask the sponsor for additional information

Good Review Practices (4)

- Time management:
 - A good review takes time, therefore, do the preliminary assessment as soon as possible taking into consideration the time available
 - Prioritize applications that may present problems following initial overview / screen
 - Major issues should be communicated to the sponsor as early as possible to allow time for discussion and resolution
 - Strive for issuing requests for additional information once the entire data package has been reviewed

Good Review Practices (5)

- Documentation:
 - Documentation of the review of the clinical trial should be accurate and concise, including information about the drug, sponsor and manufacturer, protocol number, title of the study, and the regulatory tracking number(s) assigned to the clinical trial application
 - Templates filled out by the sponsor can be used in preparing the review report

Good Review Practices (6)

- Documentation (continued):
 - Both the clinical and quality (CMC) review reports should include a section where the reviewer summarizes the essential quality and clinical elements in the proposed clinical trial presented by the sponsor, along with the reviewer's comments and thought processes in the analysis of the information
 - The reviewer's recommendation should be clearly supported by a scientific and/or clinical assessment of the overall benefit-to-risk ratio

Good Review Practices (7)

- Documentation (continued):
 - Any deficiencies identified during review should be described along with the outcome of all discussions with colleagues, managers, experts, or communications with the sponsor to resolve the deficiencies
 - All communications with the sponsor (e.g., faxes, letters, emails, records of telephone conversations) should be appended to the review report

Good Review Practices (8)

- Documentation (continued):
 - Review reports should be signed by the reviewer and dated along with the recommendation for disposition of the clinical trial in line with the applicable regulations:
 - The clinical trial application **is** considered to comply with section C.05.006(1)(a) of the Food and Drug Regulations, and a **No-Objection-Letter** is recommended
 - The clinical trial application **is not** considered to comply with section C.05.006(1)(a) of the Food and Drug Regulations, and a **Not-Satisfactory-Notice** is recommended for the following reasons:

Good Review Practices (9)

- Electronic documents:
 - Review reports should be saved electronically on a shared drive for ease of access and reference when subsequent applications, such as amendments, are filed by the sponsor
 - The investigator's brochure should also be kept electronically for quick access if needed (such as when a safety issue arises through serious ADR reporting)

Good Review Practices (10)

- Approach to review is a systematic approach:
 - Review of the dossier should begin with an assessment of the prior experience with the drug, including nonclinical data
 - The CMC data requirements should always be linked to the clinical trial context in question
 - Nonclinical data has greater impact on initial trials as compared to later development confirmatory trials, but is still important with regards to safety at later stages (e.g., results of long-term carcinogenicity, reproduction toxicity, fetal development, fertility studies, etc.)
 - The proposed trial should be supported by the quality (CMC) package and nonclinical program, as well as by previous human studies as applicable

Good Review Practices (11)

- Approach to review of the Protocol:
 - Study design, population, sample size, dosage regimen, treatment duration, and the safety and efficacy variables must be valid, supported by data, and make scientific and clinical sense
 - Close attention should be paid to the safety monitoring, which should be appropriate for the drug, trial, and subject population
 - Check for measures to prevent adverse events (e.g., appropriate eligibility criteria and laboratory or other safety assessments), **as well as** measures to manage AEs should they arise (e.g., rescue medication, drug discontinuation, etc.), **and** measures to manage potential AEs after study termination (e.g., dose tapering to avoid drug withdrawal symptoms)

Good Review Practices (12)

- Approach to review of the Protocol:
 - The need for oversight by an independent data safety monitoring board (DSMB)
 - pivotal trials, trials with drugs that have the potential to induce unacceptable toxicity, trials where mortality is the primary endpoint, etc.
 - The level of safety monitoring and risk mitigation measures should be commensurate with the risk of the drug under the conditions of the trial

Good Review Practices (13)

- Statistical considerations:
 - Ensure the study design, including control group, are acceptable
 - Validated primary endpoint
 - Sample size calculation takes into account:
 - Multiplicity in primary endpoints
 - Acceptable margins of clinical significance in non-inferiority trials and superiority trials
 - Interim efficacy analysis
 - Planned statistical tests and interim analyses should be described and justified

Good Review Practices (14)

- Informed consent review:
 - Purpose of the trial, and that it involves research
 - Visits, tests, and procedures
 - Potential risks are explained; AEs listed
 - Anticipated benefits
 - Alternate available treatment options are described
 - Subject's right to withdraw at any time
 - Access to medical records by regulatory authorities
 - Vulnerable subjects
 - Consent by a caregiver
 - Consent by parent / legal guardian
 - Assent
 - REB also reviews the consent form from a safety and ethical perspective

Good Review Practices (15)

- Overall approach to review:
 - The review should aim to identify the major issues, which would lead to a clinical trial rejection

“See the forest through the trees!”
 - Major safety issues are paramount
 - Regulatory issues can present dilemmas, but a patient-centred benefit/risk approach should be used, when applicable
- Integrate the findings from the entire body of scientific, nonclinical, and clinical evidence provided by the sponsor, but check also the literature, and the serious unexpected ADRs that have been reported to the regulator for the drug under study (“product life-cycle”)

Good Review Practices (16)

- Review of amendments:
 - The amendment should be supported by a sound rationale from the sponsor
 - Protocol text changes should be clearly identified
 - Changes to CMC should be supported by the necessary data
 - Review should assess
 - overall impact on safety, including monitoring
 - altered statistical analyses plans, including interim analyses
 - impact on evaluation of efficacy
 - impact on informed consent form
 - any SUADRs that have been reported

Good Review Practices (17)

- Review of notifications:
 - Changes to the protocol or CMC should be clearly identified, and include a rationale for the notification
 - Assess impact on:
 - safety of trial subjects, including monitoring
 - evaluation of efficacy
 - informed consent form
 - A review of SUADRs may be warranted

Good Review Practices (18)

- Review of SUADRs:
 - Integrate clinical trial reports with post-market reports
 - Epidemiological approach to the review
 - Baseline prevalence / predisposition of the patient population
 - Total number of subjects treated and duration of treatment
 - Recognize the limitations in the data presented in ADRs (e.g., comorbidities, concomitant medications, insufficient follow-up)
 - But remember the “precautionary principle”: if concerned about a potential signal, pursue further

Good Review Practices (19)

- Review of SUADRs:
 - Check the potential mechanism of action
 - Do other drugs in the same class display similar ADRs?
 - Is there dependence on time, dose?
 - Is there evidence from de-challenge ↔ re-challenge?
 - Check the investigator's brochure, previous protocols filed for the drug, and the literature

Good Review Practices (20)

- Review of SUADRs:
 - The review should determine:
 - Potential causality
 - Whether the qualified investigators and the trial subjects should be informed of new risk information
 - Whether any new risk mitigation measures are required
 - Whether the clinical trial documents should be revised
 - Whether the study should be discontinued
 - Findings are discussed with colleagues, managers, etc., and discussed with the sponsor to determine the acceptable course of action

Good Review Practices (21)

- Premature discontinuations should include a sound rationale from the sponsor and indicate:
 - The impact on planned or ongoing trials
 - That all investigators, including those of other ongoing trials, have been informed
 - That all left-over trial drug has been retrieved
- The review is aimed at assessing:
 - Impact on the safety of trial subjects from the discontinued trial, as well as patients in ongoing or planned trials
 - Impact on informed consent forms
 - Whether the sponsor fulfilled the regulatory requirements as stated above

Challenges

- A variety of types of clinical trials signifies that a small group of clinical reviewers have to cover a broad knowledge base on different disease areas, which has the potential to lead to ill-informed decisions: “**ignorance of ignorance**”
- Increased complexity in science, types of products, and treatment of disease (e.g., gene therapies, product combinations, nanotechnologies)
- Despite the degree of complexity, reviewers have a short time frame to arrive at a review recommendation

Strategies (1)

- Always approach a review with a perspective of safety
 - Regulatory requirements must be met
 - Alternate approaches to guidelines could be acceptable, however, the reviewer should ask for a rationale from sponsors if there is inconsistency between the sponsor's proposal and the guidelines
- Question your knowledge, and discuss issues with colleagues and managers: **do not work alone!**
- Maintain, and make use of, internal expertise or established external expertise such as scientific advisory committees

Strategies (2)

- Review the decisions by other regulators
- Discuss issues or concerns with sponsors
- Others will also be reviewing the trial, including, but not limited to:
 - REBs
 - Qualified investigators
 - DSMB
- Record decisions for future reference
- Keep-up with the science

New Clinical Trial Regulations: Canadian Experience (1)

- New regulations typically go through extensive internal and external consultations before implementation
- But once implemented, they still need to be interpreted for:
 - The sponsors who have to meet the regulatory requirements
 - The public servants who have to put the regulations into practice
 - New stakeholder groups that may surface
- Important to:
 - Develop and release guidance documents at the time of implementation of the regulations
 - Be aware and address new scope of the regulations

Canadian Experience (2)

- Division 5 of the Canadian regulations is only 6 ½ years old; previous regulations were from the early 60's:
 - Main changes brought by new regulations were:
 - Incorporating GCP into regulations
 - Broader scope, encompassing off-label trials
 - Inspection program
- Although the regulations appear fairly straightforward, it can be a challenge to translate regulations into practice
- Impact of new regulations is really measured after they are implemented and have been in effect for some time (e.g., RIAS – 3-5 years)

Canadian Experience (3)

- Implementation of the inspection program:
 - Utilized a phased-in approach starting with a confidence-building voluntary phase (January 1, 2002)
 - Mandatory phase with 2% of clinical trials inspected and trials chosen using a risk-based approach (started January 1, 2003)
 - Interpretation of:
 - Record-keeping requirement of 25 years
 - Labelling of drug products
 - Who can act as the importer
- Lack of clarity over the interpretation of the regulations can lead to inconsistency, and requesting unnecessary information or insufficient information from sponsors

Canadian Experience (4)

- Regulations impact more than just the pharmaceutical company sponsor
 - Qualified investigators / institutions and their staff
 - Research ethics boards
 - Subjects and patients
 - Health care and access to drugs
 - Investigators / Institutions as sponsors
 - Other research groups (e.g., positron-emitting radiopharmaceuticals)
- When implementing new regulations, need to ensure that downstream effects are initially considered, and measured by consulting with all affected stakeholders, in order to make informed decisions on how to move forward

Regional / Global Impact

- When developing regulations, consider:
 - What are the disease areas of interest (what can your population offer)?
 - What can your health care system offer?
 - What is the status of investigator/institution-driven research in your country?
 - What frameworks are in place for ethical review of human research and protection of clinical trial subjects?
 - What are sponsors looking for in your country?
- Prepare your regulatory framework, and scientific expertise accordingly

**If not there already,
you are on a path to success!**

- Consulting with other regulators
 - Looking for best practices
 - Looking for lessons learned

Thank You!