Clinical Research Ethics

UTM Pharmaceutical Panel
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Leading with Innovation
Serving with Compassion

ST. MICHAEL'S HOSPITAL

A teaching hospital affiliated with the University of Toronto

Outline

- Educational and Employment Background
- Regulatory Affairs Overview
- Clinical Research Overview
- Research Ethics Board
- Research Ethics Coordinator

Education

- Bachelor of Science (Biology)
  - University of Toronto Mississauga
- Regulatory Affairs and Quality Operations Post-graduate Diploma
  - Seneca College

Employment

- Regulatory Affairs Associate
  - sanofi-pasteur
- Research Ethics Coordinator
  - St. Michael's Hospital
    - SMH is a U of T affiliated teaching hospital

What is Regulatory Affairs?

- Division within a pharmaceutical company that ensures compliance with regulations and laws established by government and international agencies.
  - In Canada: Health Canada (HC)
  - U.S.: Food and Drug Administration (FDA)
  - International: International Conference on Harmonization (ICH)
- regulated industries (pharmaceuticals, banking, insurance, etc.)
- Health Canada Divisions:
  - Therapeutic Products Directorate (TPD)
  - Medical Devices Bureau (MDB)
  - Biologics and Genetic Therapeutic Directorate (BGTD)
  - Natural Health Products Directorate (NHPD)

What is Regulatory Affairs?

- The pharmaceutical industry is the most regulated of all industries.

- RA professionals are the primary communication link between the company and regulatory bodies (i.e. Health Canada) and they are responsible for ensuring that the company is compliant with national and international regulations and laws

- In the pharmaceutical industry, RA professionals have expertise in the legal and regulatory environments, as well as in ***clinical research protocols.***

The Importance of Regulations

- If we do not abide by regulations then we have nothing but chaos leading to failure.

- Changes in regulations effect:
  - clinical trials process
  - regulatory strategies: deciding what trials are needed (equivalence, non-inferiority, randomized, etc.)
  - post-marketing surveillance
  - protocol development
  - drug manufacturing and QC, QA testing, etc., etc.,

- New areas evolve as science changes: stakes are high; drug approvals--as well as delays or failures--are featured prominently in the media and can make or break a company

RA Associate

- Creating, planning and executing drug submissions, amendments and annual reports for regulatory authorities (Health Canada and FDA) as well as international health authorities (EMEA)

- Coordinates, prepare and submits responses to Health Authority questions to both ensure the company progress in various areas: investigational new drug, product/establishment license, regulatory inspection and communication, adverse drug reaction reporting, Labeling and **Clinical Trials**

- International Markets: work with regulatory contacts at foreign distributors to facilitate preparation of marketing application and post-approval submission documents

- Provide regulatory advice/support to internal functional departments and product development teams: R&D, manufacturing, marketing, sales, QA, Clinical development.

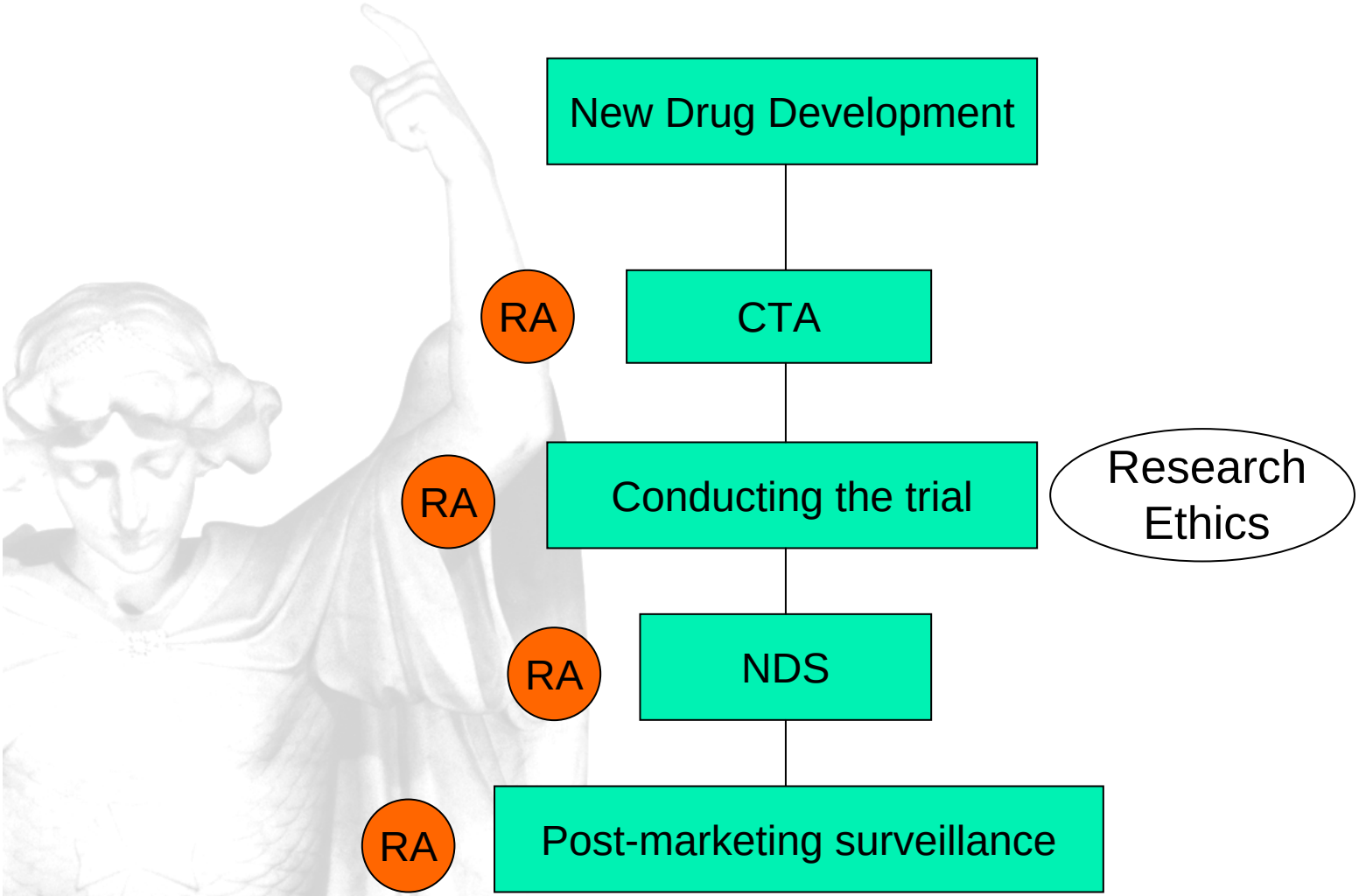
- Conversely, RA professionals can also work for Health Canada as a review of regulatory submissions!

Clinical Research

- Clinical Investigations (trials) of a new or existing drugs, biologics, devices or surgical interventions in human subjects with the intent to discover potential beneficial effects and/or determine its safety and efficacy

- Clinical trials are only conducted after approval is obtained by Health Canada through the RA department. They are conducted in phases to gather data for a New Drug Submissions

- Final step includes post marketing surveillance, which monitors and evaluates a drug's safety after it is available on the market especially when a company receives reports of serious adverse drug reactions (SAEs).



What is 'Research Ethics'?

- Research Ethics involves identifying, analyzing and resolving ethical issues surrounding patient protection when conducting clinical trials

Some Key Issues:

- **Safety** of each research participant:
  - accomplished by carefully considering the **risk/benefit ratio** using all available information (previous research, standard of care, SAEs, consequences, individual patient data) and continually monitoring the research as it proceeds.
- **Informed Consent** from each participant:
  - obtained in writing after the participant has had the opportunity to carefully consider the risks and benefits and to ask any pertinent questions = Informed
- **Privacy and confidentiality**
  - protection of patient information
- **Clinical equipoise**
  - A state of genuine uncertainty on the part of the expert medical community (investigator) about the comparative therapeutic merits of a clinical trial

Brief History of Research Ethics

Nuremberg Code (1948)

- Established in 1948, states "The **voluntary consent** of the human subject is absolutely essential" clearly indicating that subjects should give consent and that the benefits of research must **outweigh the risks (beneficence)**.
- Nuremberg Code was the first international document which advocated voluntary participation and informed consent

Declaration of Helsinki (1964)

- 1964, the World Medical Association established recommendations for medical doctors in research involving human subjects.
- The Declaration governs international research ethics and defines rules and is the basis for Good Clinical Practices used today.

Belmont Report (1979)

- The Report is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects.
- 3 basic principals: Respect for Persons, Beneficence, Justice

Main ethical principles

Three primary ethical principles for research with human subjects:

1. **Respect for Persons (Autonomy):** refers to the obligation on the part of the investigator to respect each participant as a person capable of making an informed decision regarding participation in the research study. The investigator must ensure that the participant has received a full disclosure of the nature of the study, the risks, benefits and alternatives, with an extended opportunity to ask questions.

2. **Beneficence:** refers to the obligation on the part of the investigator to attempt to maximize benefits for the individual participant and/or society, while minimizing risk of harm to the individual.

3. **Justice:** which demands equitable selection of participants, i.e., avoiding participant populations that may be unfairly coerced into participating, such as prisoners and institutionalized children.

Research Ethics Board (REB)

- An independent group of professionals designated to review and approve clinical trial protocols including all related documentation.
- The primary role of the Research Ethics Board is to protect patients entering research trials within a given institution
- It is also the REB's responsibility to ensure that studies adhere to Health Canada regulations.

Research Ethics Board (REB)

- The REB will determine whether the scientific question or hypothesis is appropriate to warrant the use of human subjects and that the proposed study and conduct of their research demonstrates:
  - respect for human dignity
  - respect for voluntary and informed consent
  - respect for vulnerable persons
  - respect for privacy and confidentiality
  - respect for welfare and rights of research subjects by balancing harms and benefits through minimizing harm and by maximizing beneficence.

Research Ethics Board (REB)

The TCPS (Article 1.3) states that an REB must consist of *at least 5* individuals:

- two members have broad expertise in the methods or in the areas of research that are covered by the REB;
- one member is knowledgeable in ethics;
- one member knowledgeable in the relevant law
- one member has no affiliation with the institution, recruited from the community served by the institution.

membership requirements are designed to ensure the expertise, multi-disciplinary and independence essential to competent research ethics review

Current Regulations and Guidelines

- Tri-Council Policy Statement (TCPS)
- Health Canada Food and Drugs Act
- ICH GCP
- CIHR Best practices
- Catholic Health Association Ethics Guide

SMH REB

The SMH REB consists of:

- ~25 Doctor's
- 3 Legal representatives
- 5 community members
- Clinical Ethicists
- **3 Coordinators**

VOLUNTEERS!

Role of an REB Coordinator

- Review of new clinical and non-clinical research protocols involving humans as research subjects
  - Sponsor initiated vs. Investigator initiated
  - Full board vs. Delegated/Expedited

Role of an REB Coordinator

- Reviewing and Editing of study related documentation
  - Consent forms
  - Posters/Advertisements
  - Letters to participants
  - Scripts
  - Patient Brouchures
  - Etc.

Informed Consent

The voluntary verification of a patient's willingness to participate in a clinical trial, along with the documentation thereof. This verification is requested only after complete, objective information has been given about the trial.

Informed Consent

What are the components of an ethically valid informed consent for research?

- Purpose and Description of the Research
- Potential Harms
- Potential Benefits
- Confidentiality and Privacy
- Potential Costs/Reimbursement
- Compensation for Injury
- Participation and Withdrawal
- Consent

Role of an REB Coordinator

- Educating Investigators on the Ethical conduct of studies
- SOP and guideline development
- On-going review of long-term studies
  - ~1200 open studies at SMH; ~350/year
- Serious Adverse Events/ ongoing monitoring
- TAHSN Research Ethics Committee

Challenges

- Change, Change, Change
  - The regulatory framework is constantly changing
- Diversity of Medical Research
  - Novel therapies, devices, procedure, etc., are always being developed
- Commute!

Summary

- Attention to detail
- Sense of Urgency
- Strong written communication skills
- Excellent facilitation/liaising skills
- Sound Scientific knowledge
- Proficient Organizational skills

Example Study

- Disease: Barrett's Esophagus
  - Dysplasia; earliest form of pre-cancerous lesion
- Device: Cryospray
  - Freezes cells so they can be easily scraped away
- Patient Population:
  - can have either 'high grade' or 'low grade' dysplasia
- Ethical concern:
  - A subset of patients with high grade dysplasia may be inoperable; any perforation of the esophagus can be fatal
- Result:
  - Patients at high risk excluded from the study

Questions?