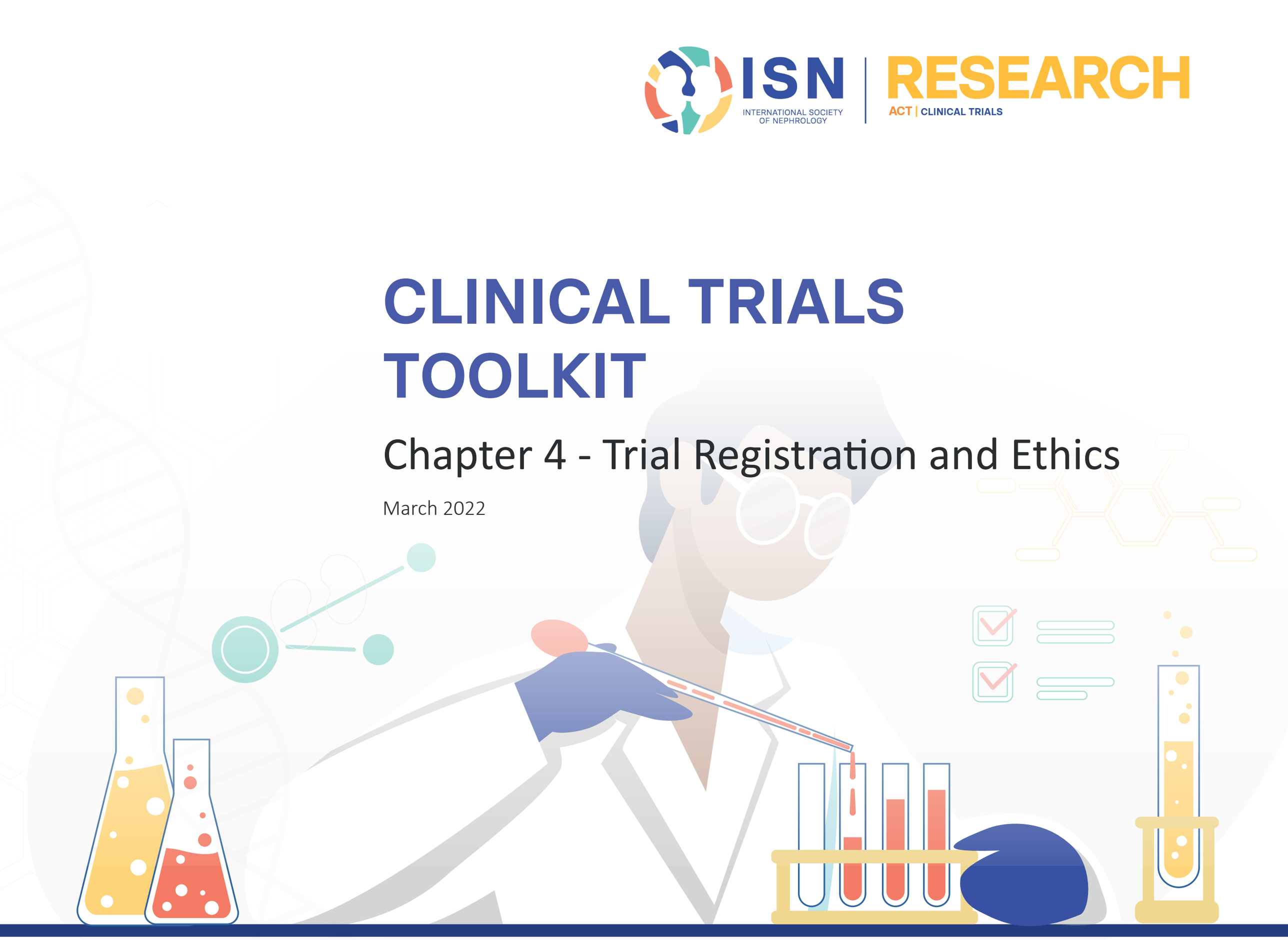
ISN INTERNATIONAL SOCIETY OF NEPHROLOGY | RESEARCH
ACT | CLINICAL TRIALS

CLINICAL TRIALS TOOLKIT

Chapter 4 - Trial Registration and Ethics

March 2022



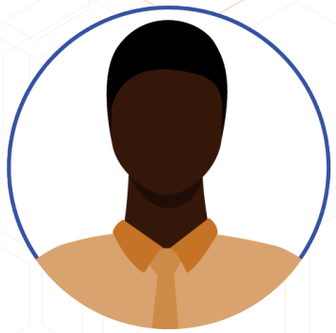
4. TRIAL REGISTRATION AND ETHICS

By M.D. Ph.D. Augusto Cesar Soares dos Santos Junior (Brazil) and M.D. Brendan Smyth (Australia).

The text below is a transcript of the concepts described in the ISN-ACT Clinical Trials Toolkit. The characters and background story were added to the text to illustrate common research methods used in clinical trials. The names used refer to fictional characters making no reference to actual persons.

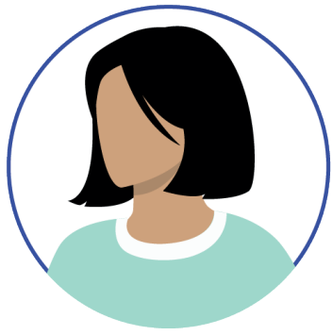
4.1 INTRODUCTION

Members of ISN's first Emerging Leaders Program (ELP) initially discussed the idea of launching a multicenter clinical trial at one of their preliminary meetings. The ISN developed the ELP to help shape its vision of global, equitable access to kidney health. It provides early-career professionals in kidney health with an opportunity to work alongside international experts to gain the experience needed to take up a leadership role in kidney care.



Dr. Leonard, a scientist based in Ghana, was one of the 12 young leaders selected to join the first ISN-ELP cohort. An early-career professional, Dr. Leonard is also a successful researcher with several publications in scientific journals.

His proposal to initiate a multicentric trial involving patients with rare kidney diseases was greeted with enthusiasm by other cohort members. **Dr. Samantha**, based in China, was pleased to participate in the group. As a scientist interested in studying patients with congenital nephrotic syndromes, she was excited by the prospect of an international collaboration to increase the feasibility of clinical trials involving rare kidney diseases.



Dr. Samantha and Dr. Leonard began considering the best way forward in such a trial: How would it work? An international multicentric study would need to navigate different regulatory policies in trial registration and ethics in multiple countries. Where would they start?

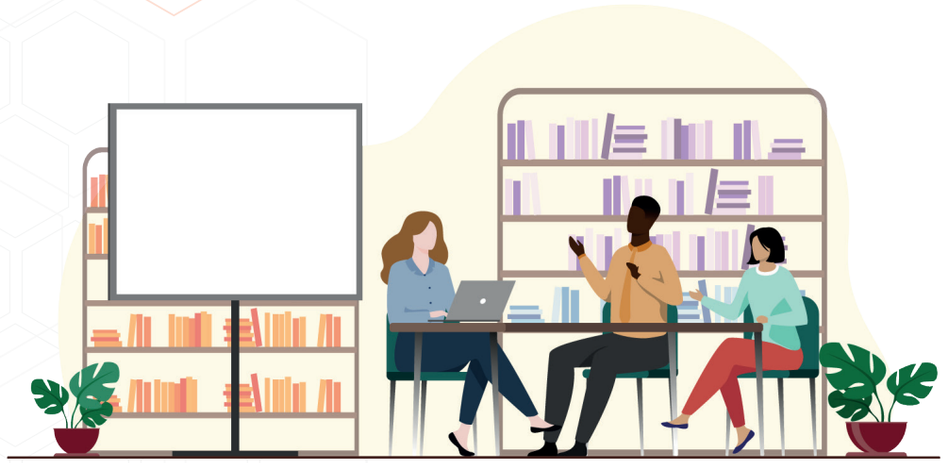
Meanwhile, **Ms. Harris**, an entrepreneur with an MBA from Imperial College London, was already outlining a plan to implement the project. She was selected for the ELP cohort thanks, in part, to her experience innovating within healthcare systems.

4.2 WHAT IS TRIAL REGISTRATION?

Dr. Leonard had experience tackling regulatory issues involving clinical trials before and wanted to make sure everyone knew the current guidelines. Ms. Harris took notes while Dr. Leonard explained:

"The International Committee of Medical Journal Editors (ICMJE) introduced a policy on trial registration in 2004. Since then, several international organizations and some countries came up with related policies and laws on the registration of any publicly and privately supported clinical trials conducted with patients."

Aware that Ms. Harris' experience was in business rather than research, Dr. Samantha added:



"Trial registration involves submitting descriptive information of a prospective clinical trial, such as the study protocol, including design, recruitment information, eligibility criteria, conduct, and administrative elements, to a web-based registry, readily accessible to the public. Trial registration must take place before the first patient is recruited, and regular updates on protocol changes and trial results should be provided."

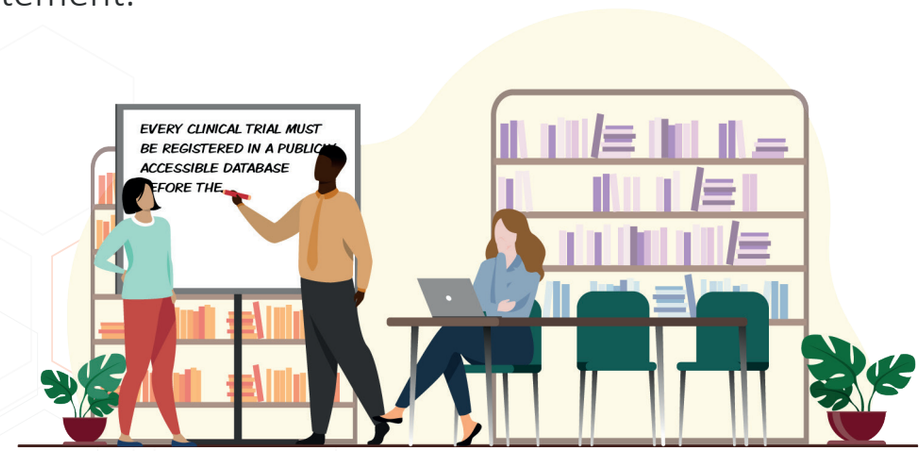
4.3 WHY IS THIS IMPORTANT?

With her business background, Ms. Harris quickly grasped that trial registration could increase the efficiency of drug and device development by:

- Preventing trial duplication.
- Providing information about ongoing clinical trials to potential participants, researchers, and referring clinicians, encouraging trial recruitment.
- Helping to identify potential design problems early in the research process, thus improving the quality of clinical trials and clinical research practice.

- Ensuring transparency and helping to avoid selective reporting and publication bias.

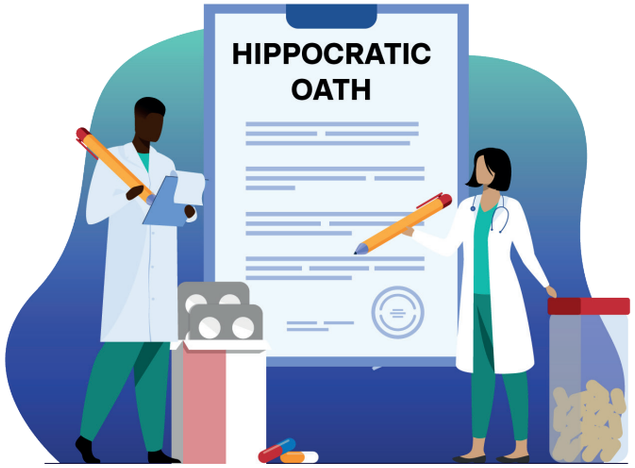
Ms. Harris realized that trial registration was also an ethical obligation when Dr. Leonard wrote, “Every clinical trial must be registered in a publicly accessible database before the first subject is recruited” in capital letters on the whiteboard, explaining that the principle was issued by the Declaration of Helsinki, the World Medical Association’s best-known policy statement.



4.4 ETHICS

As a specialist in medical ethics, Dr. Leonard continued to share his expertise with the team:

“Medical ethics is a set of values that applies to the practice of clinical medicine and in scientific research. It’s not a new concept: Hippocrates, the father of medicine, was the first to define them in the Hippocratic Oath written in the 5th century B.C.; the dictum ‘Primum non nocere’ (Latin), ‘First, do no



Harm’ is centuries old. History shows, however, that these ‘oaths’ have often been ignored in human research: Edward Jenner tested the smallpox vaccine on his son and neighbors, the “Tuskegee Study” in the early 1900s was conducted on subjects unaware of their diagnosis of syphilis and deprived of treatment once it was available, the Nazis did brutal experiments on prisoners during the Second World War. And it’s not only the underprivileged or marginalized who have suffered. In 1966, Henry Beecher’s seminal report in the *New England Journal of Medicine*[1] called out 22 studies by leading universities for being unethical or questionably ethical’ and contributed to the development of modern ethical regulations.”

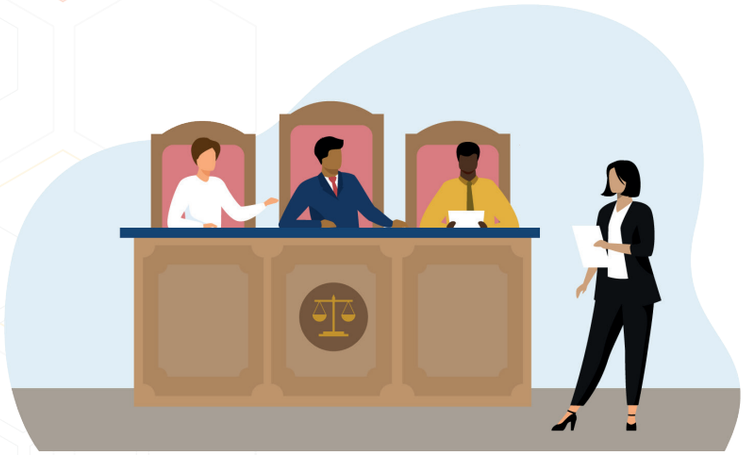
4.5 PRINCIPLES OF MEDICAL ETHICS

This background was fascinating to Ms. Harris, who asked: “Who is responsible for assessing a clinical trial from the ethical perspective?”

Dr. Samantha took the lead to explain:

“To ensure medical research is ethical, a formally designated, independent group of trained professionals needs to oversee institutions carrying out research, especially when human subjects are involved. These professional committees are commonly known as the Institutional Review Board (IRB) or Ethical Review Board (ERB). Their role is to ensure that all research performed at an institution upholds the principles of medical ethics so that participants are protected from undue risks.”

Ms. Harris realized that each ISN-ELP member involved in the multicentre research would have to submit a project to their local IRB or ERB, so she added this vital step to the project schedule. Dr. Samantha continued:



“Medical ethics is based on four prima facie principles: respect for autonomy; beneficence (doing good); non-maleficence (not doing any evil or harm); and justice.”

Respect for autonomy acknowledges the dignity and freedom of every person. It means getting informed consent from research subjects or their legally authorized representatives. Beneficence and non-maleficence require researchers to maximize benefits and minimize harm during research. Research-related risks must be reasonable considering the expected benefits or should provide net benefits to the patient. In a clinical trial setting, no patient should suffer because of taking part, and no patient should be denied known effective treatment, which relies on objective evidence rather than subjective belief. Justice requires equality and fairness in selecting, recruiting, and treating research subjects.

Dr. Samantha then briefly addressed possible decisions after a project has been submitted to the IRB or ERB. She explained:

“Depending on the risks a participant may be exposed to; a research proposal can fall into one of three categories:

1. **Exempt of review**: A research activity may be declared exempt if considered low-risk for participants. This would include:
    - Research conducted in established or commonly accepted educational settings, involving standard educational practices
    - Research using anonymous or no-risk tests, surveys, interviews, or observations

- Most research involving public officials
- Research involving the collection or study of existing data if it is publicly available or if subjects cannot be identified

2. **Expedited review**: a research activity may qualify for this category if it involves minimal risk to participants, does not include intentional deception, does not employ sensitive populations or topics, and has appropriate informed consent procedures. Examples are research involving the collection of physical data through non-invasive methods, which include height and weight, ECG (electrocardiogram), MRI (Magnetic Resonance Imaging), ultrasound, moderate exercise, blood, or other body fluids.

3. **Full board review**: Research requires full board review when it is deemed to involve more than minimal risks or involves protected populations such as children, prisoners, or disabled people. This category includes projects that use procedures that are personally intrusive, stressful, or potentially traumatic (stress can be physical, psychological, social, financial, or legal).

Dr. Leonard, Dr. Samantha, and Ms. Harris were excited about the start of this collaborative venture. After the discussion, all members of the first ISN-ELP cohort were confident that they understood the reasons for registering their clinical trials as well as the importance of obtaining appropriate ethical approval in all jurisdictions. With these important initial steps, they looked forward to designing and running their own clinical trials to help shape the future direction of kidney care.

Don’t miss the next chapter in July 2022!

Notes

1 https://www.nejm.org/doi/full/10.1056/NEJM196606162742405

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