From Principles to Practice

Ethics of Participant Consent in Clinical Trials

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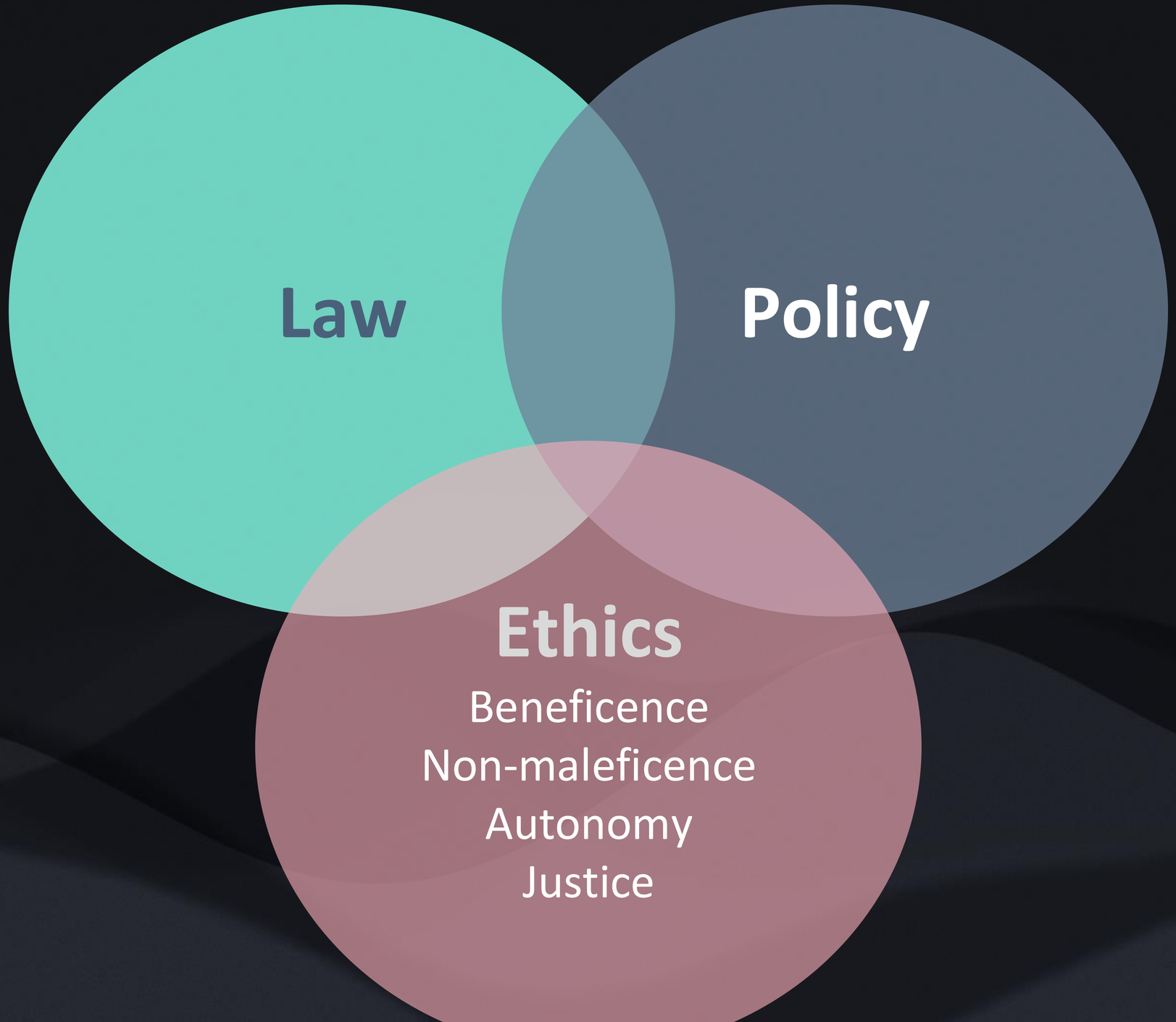
Objectives

- To review the foundations of patient consent in clinical trials

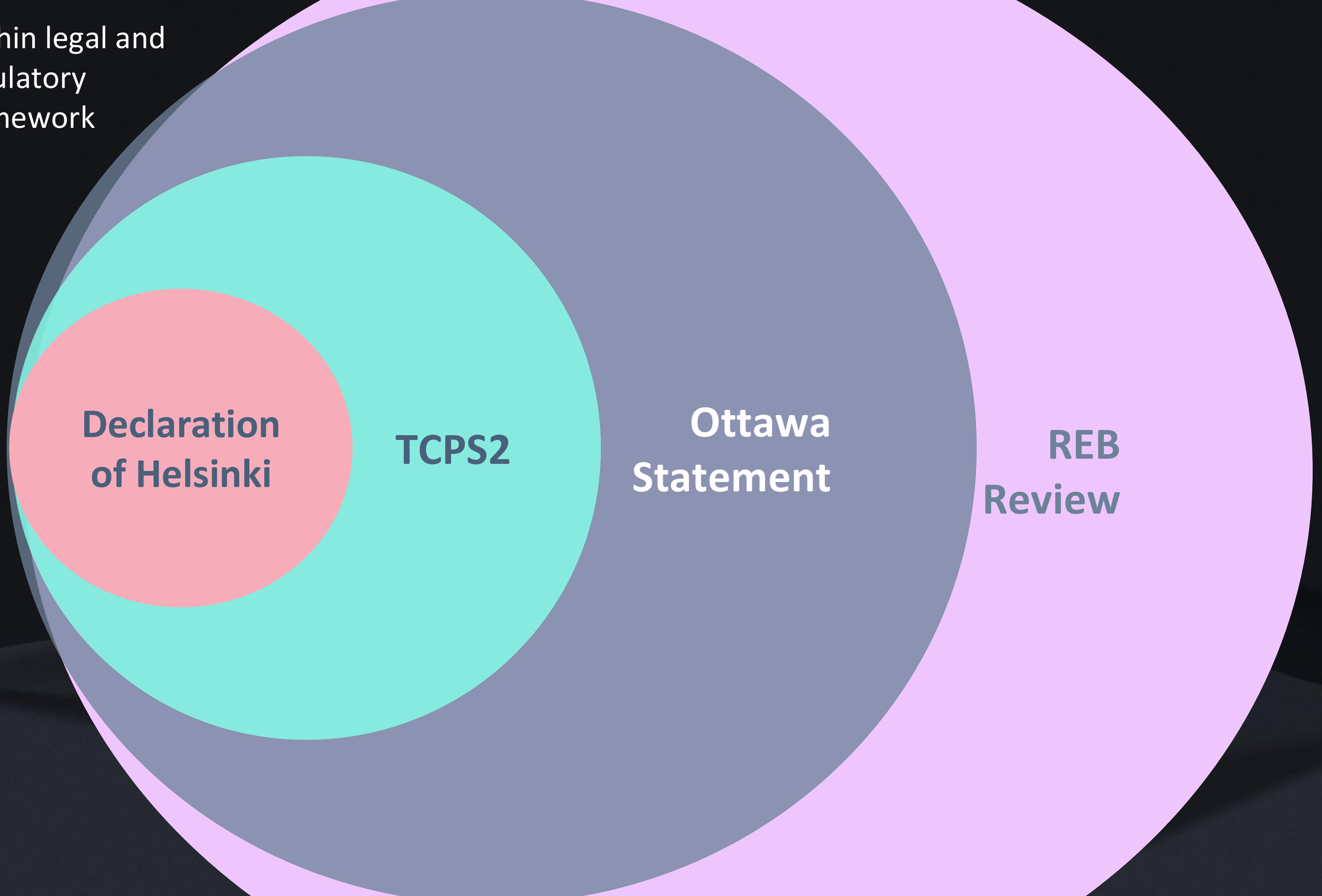
- To provide an overview of the ethics, policy, and practice of consent in clinical trials

- To identify gaps, uncertainties, and inconsistencies in consent policy and practice

Fundamentals of Consent in Health Research


Law
Policy
Ethics
Beneficence
Non-maleficence
Autonomy
Justice

Within legal and regulatory framework



WMA Declaration of Helsinki (1964; 2024)

Ethical Principles for Medical Research Involving Humans

- Influenced by the Nuremberg Code (1947), itself a direct response to Nazi atrocities in WW2
- **Non-legally binding** declaration internationally; wide influence on national and regional legislation and regulation
- Considered **morally binding** for physician-researchers
  - a minimum standard of research ethics
  - overriding national/regional policy/law
- ***The physician must commit to the primacy of patient health and well-being and must offer care in the patient's best interest***

Declaration of Helsinki

What does it say about consent?

Free and informed consent is an essential component of respect for individual autonomy

The **right to refuse or withdraw** consent; **withdrawal will not adversely affect patients from receiving the standard of care**

Consent from a qualified individual, independent of the treating physician

Consent is required for collection, processing, storage, secondary use **of biological material and identifiable or re-identifiable data**

Research on incapable patients should only be done if incapacity is a necessary characteristic of the research group

- Should only be included if likely to benefit or it is minimal risk
- Consent must be obtained as soon as possible from legally authorized representative of an incapable patient, if possible, from the patient
- **Seek assent** for research if incapable, and respect dissent of incapable patients

Consent should be documented on paper or electronically; or otherwise formally witnessed

The elements of 'informed' consent

- aims
- methods
- anticipated benefits, risks, compensation
- researcher qualifications
- funding and COIs
- privacy protections
- treatment of injury/compensation

Research activities must be **clearly distinguished from clinical care**

How to withdraw from the research

Individual obtaining consent needs to **ensure the information is understood**

Option of being **informed about general research outcomes**

TCPS2

Ethical Conduct for Research Involving Humans

- Joint policy of 3 Canadian federal research agencies: CIHR, NSERC, SSHRC (2001, 2010, 2018 TCPS2)
- Institutions which receive funding from these bodies are expected to adhere to the TCPS2 as a **condition of funding**
- Three core ethical principles
  - **Respect for Persons**
  - **Concern for Welfare**
  - **Justice**

TCPS2

What does it say about consent?

- **Article 3.1 - Consent shall be given voluntarily**
  - a) Consent shall be given voluntarily — voluntariness respects human dignity and the right to choose
    - REBs and researches should consider the potential for **undue influence**, **coercion, or incentives** may undermining voluntariness
  - b) Consent can be withdrawn at any time without need a reason
    - Practical considerations may prevent this
    - There should be no disadvantage or reprisal for withdrawing; any payment due prior should be given
  - c) If a participant withdraws consent, the participant **can also request the withdrawal of their data** or human biological materials
    - The consent process should be clear about circumstances that do not allow withdrawal of data or biological materials

TCPS2

What does it say about consent?

- **Article 3.3 - Consent shall be an ongoing process**
  - Consent is a process from initial contact to the end of participant involvement
  - Researchers have **an ongoing duty** to provide participants with all information relevant to their ongoing consent to participate in the research
  - Participant **capacity may change** over time;
    - If participants' capacity changes, consent should be obtained directly from them

TCPS2

What does it say about consent?

- **Article 3.2 - Consent Shall Be Informed**
  - Researchers should provide to prospective participants full disclosure of all information necessary for making an informed decision
  - Need for adequate time and opportunity to assimilate the information, ask questions, discuss, and consider participation
  - large list (items A - L) of informed consent requirements

TCPS2

What does it say about consent?

- **Article 3.5 - Consent shall Precede Collection of, or Access to, Research Data**
  - **Research can begin only after** participants or their authorized third parties have provided their consent
  - Consent is not required when having conversations with potential participants/communities that may be involved in the research about the design or conduct of the research

Ottawa Statement

Ethical Design and Conduct of Cluster Randomized Trials (2012)

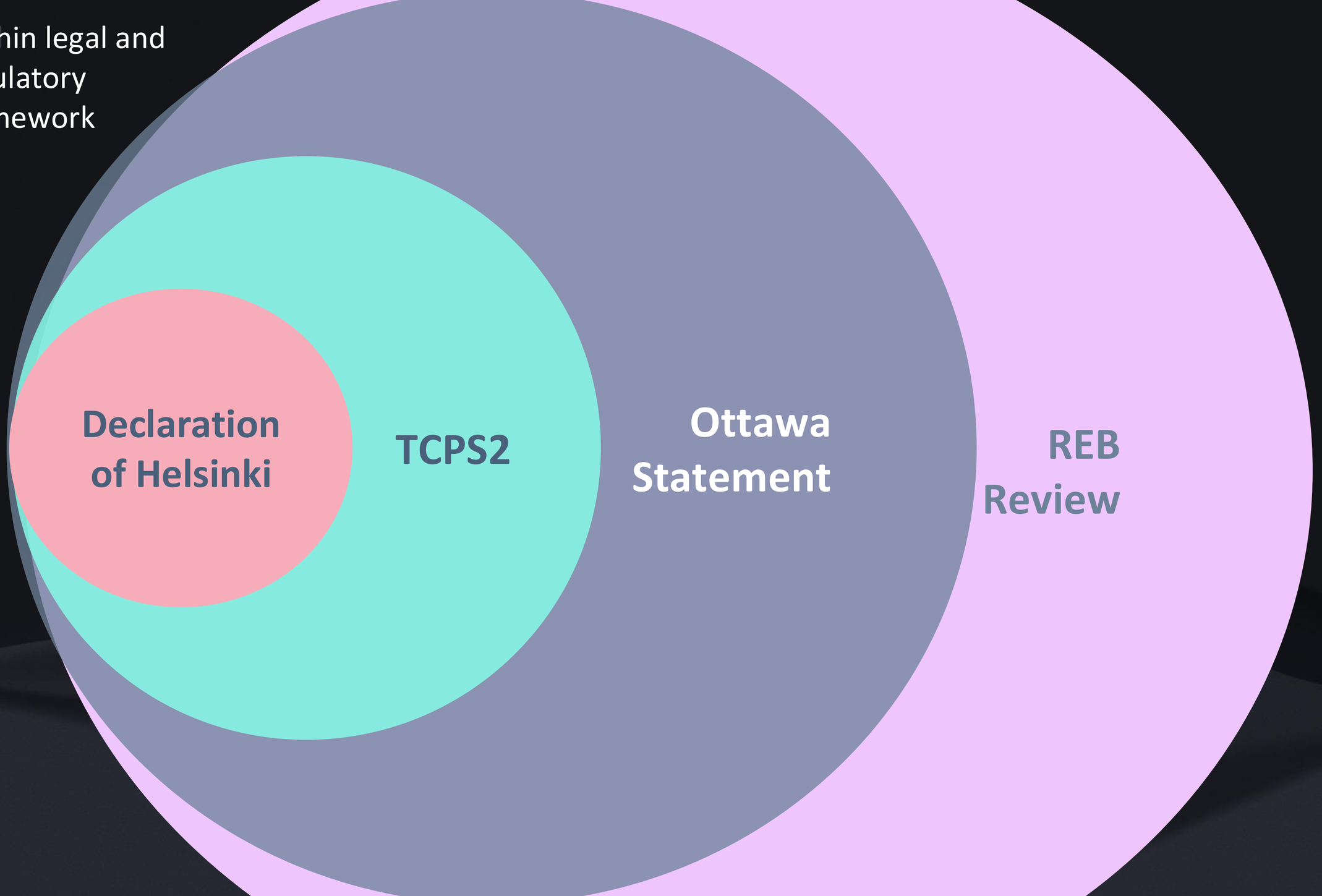
- Result of CIHR-funded mixed-methods project to explore unique aspects of cluster RCTs
- **Neither legally nor morally binding**; aims to influence policy-makers, REBs, researchers
- Specific issues relevant to consent in cluster trials:
  - Role of ‘gatekeepers’ in providing access to clusters
  - Unique challenges to ‘consent’ for entire populations

Ottawa Statement

Ethical Design and Conduct of Cluster Randomized Trials

- Researchers must obtain informed consent from human research participants in a CRT, unless a waiver of consent is granted by a REC under specific circumstances.
- Researchers must obtain informed consent from professionals or other service providers who are research participants unless conditions for a waiver or alteration of consent are met
- Gatekeepers cannot provide proxy consent on behalf of individuals in a cluster
- If there is a gatekeeper who possesses legitimate authority to make decision upon a cluster's behalf, researchers should seek their permission to enroll the cluster
    - This does not replace need for individual consent

Within legal and regulatory framework



Alteration of consent

Declaration of Helsinki

What does it say about alterations of consent requirements?

S. 28	Those persons incapable of giving free and informed consent are in situations of particular vulnerability and are entitled to the corresponding safeguards. In addition to receiving the protections for the particularly vulnerable, those incapable of giving consent must only be included if the research is likely to either personally benefit them or if it entails only minimal risk and minimal burden.
S.30	If no such representative is available and if the research cannot be delayed, the research may proceed without informed consent provided that the specific reasons for involving participants with a condition that renders them unable to give informed consent have been stated in the research protocol and the research has been approved by a research ethics committee. Free and informed consent to remain in the research must be obtained as soon as possible from a legally authorized representative or, if they regain capacity to give consent, from the participant.
S. 32	A research ethics committee must approve the establishment and monitor ongoing use of such databases and biobanks. Where consent is impossible or impracticable to obtain, secondary research on stored data or biological material may be done only after consideration and approval of a research ethics committee.

TCPS2

Alteration of consent requirements - Article 3.7A, 3.7B, & 3.8

- 3.1 Consent Shall be Given Voluntarily
- 3.2 Consent Shall be Informed
- 3.3 Consent Shall be an Ongoing Process
- 3.5 Consent Shall Precede Collection of, or Access to, Research Data

Researchers must clearly describe the nature and extent of proposed alterations and justify the need for alteration of consent requirements at the level of the REB

Participant risk is more heavily weighted when including patients without a standard informed consent (concern for welfare)

TCPS2

Alteration of consent requirements - Article 3.7A, 3.7B, 3.8, 5.5

- **Article 3.7A - Alterations to Consent Requirements**
- If the REB is satisfied that that following conditions have been satisfied
  - the research involves **no more than minimal risk** to the participants
    - *"Research in which the probability and magnitude of possible harms implied by participation in the research are no greater than those encountered by participants in those aspects of their everyday life that relate to the research."*
  - the alteration to consent requirements is **unlikely to adversely affect the welfare of participants**
  - **it is impossible or impracticable** (see Glossary) to carry out the research and to address the research question properly, given the research design, if the prior consent of participants is required;
  - in the case of a proposed alteration, **the precise nature and extent of any proposed alteration is defined**; and
  - a **plan to provide a debriefing that may also offer participants the possibility of refusing consent** and/or withdrawing data and/or human biological materials (further defined in 37B)

TCPS2

What does it say about consent?

- **Article 3.7B - Debriefing in the Context of Alterations to Consent Requirements**
- Debriefing must be a part of all research involving an alteration to consent requirements whenever it is possible, practicable and appropriate.
- Participants in such research must have the opportunity to refuse consent and request the withdrawal of their data and/or human biological materials whenever possible, practicable and appropriate

TCPS2

What does it say about consent?

- **Article 5.5A - Secondary Use of Information for Research Purposes**
- The REB may allow research for secondary use of identifiable information if all requirements are met:
  - *Identifiable information is **essential** to the research;*
  - *the use of identifiable information without the participants' consent is **unlikely to adversely affect the welfare** of individuals to whom the information relates;*
  - *the researchers will take appropriate **measures to protect the privacy of individuals** and to safeguard the identifiable information;*
  - *the researchers will **comply with any known preferences** previously expressed by individuals about any use of their information;*
  - *it is **impossible or impracticable** to seek consent from individuals to whom the information relates; and*
  - *the researchers have obtained any other necessary permission for secondary use of information for research purposes.*

Ottawa Statement

Alterations of consent

- When participants' informed consent is required, but recruitment of participants is not possible before randomization of clusters, researchers **must seek participants' consent for trial enrollment as soon as possible after cluster randomization**—that is, as soon as the potential participant has been identified, but before the participant has undergone any study interventions or data collection procedures.
- A REC may approve a waiver or alteration of consent requirements when
  - (1) the research is not feasible without a waiver or alteration of consent
  - (2) the study interventions and data collection procedures pose no more than minimal risk

Declaration of Helsinki	TCPS2	Ottawa Statement	REB policy/judgements
Those persons incapable of giving free and informed consent are in situations of particular vulnerability and are entitled to the corresponding safeguards. In addition to receiving the protections for the particularly vulnerable, those incapable of giving consent must only be included if the research is likely to either personally benefit them or if it entails **only minimal risk and minimal burden.**	research involves **no more than 'minimal risk'**; alteration to consent is unlikely to affect the welfare of participants.	A REC may approve a waiver or alteration of consent requirements when the study interventions and data collection procedures pose **no more than minimal risk**	What constitutes **'minimal risk?'** What does it mean to "**adversely affect the welfare**" of a potential participant?
Where consent is **impossible or impracticable to obtain,** secondary research on stored data or biological material may be done only after consideration and approval of a research ethics committee.	…**it is impossible or impracticable** (incapable of being put into practice due to a degree of hardship or onerousness that jeopardizes the conduct of the research); it does not mean mere inconvenience.) to carry out the research and to address the research question properly, given the research design, if the prior consent of participants is required;	A REC may approve a waiver or alteration of consent requirements when the research is **not feasible** without a waiver or alteration of consent	What is **feasible**? What is **impracticable**?
	Researchers who have not obtained consent from participants for secondary use of identifiable information shall only use such information for these purposes if they have satisfied the REB that **identifiable information is essential to the research**		When **is identifiable information "essential"** to the research?
	the plan to **provide a debriefing** (if any) that may also offer participants the possibility of refusing consent and/or withdrawing data and/or human biological materials, shall be in accordance with Article 3.7B.		What constitutes **adequate debriefing?**

From principles to practice

Ethics of Participant Consent in Clinical Trials

- Clinician-researchers are **morally bound** to protect the rights of potential research participants

- Researchers **must operate within legal/regulatory requirements** which apply to their jurisdiction and are relevant to the research

- **Free and informed consent is one of the key protections** of participants; if consent is altered, **participant welfare** is more heavily weighted

- Policies provide detailed guidance on consent processes, but still have substantial gaps, resulting in ***inconsistent*** **interpretation by REBs,** impeding research

Thank you!

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