PREGTRIAL

Inclusion of PREgnant and lactatinG people in clinical TRIALs

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Centre universitaire de santé McGill
Institut de recherche

McGill University Health Centre
Research Institute

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CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

DISCLOSURES

- Operating funds: Canadian Institute of Health Research, Heart and Stroke Foundation of Canada
- Support from FRQS – Chercheur Boursier Clinicien Junior 2
- Speaking honoraria: Htaq biomedical, GEMOQ, ASMIQ
- Gender inclusive language: use of terms “pregnant or breastfeeding woman” and “pregnant or lactating person” interchangeably

PRESCRIBING IN PREGNANCY & LACTATION: THE CURRENT STATE

- Delays in childbearing + advances in chronic disease management → pregnancy with complex medical issues
- **70%** of pregnant women take > 1 medication
- **91%** of FDA-approved drugs between 1980 and 2010 had insufficient data for use in pregnancy
- Most drugs enter breastmilk <**5-10%** but lack of or delays in PK studies → premature breastfeeding discontinuation or inappropriate cessation of necessary medication during lactation

This is UNequitable and UNsafe

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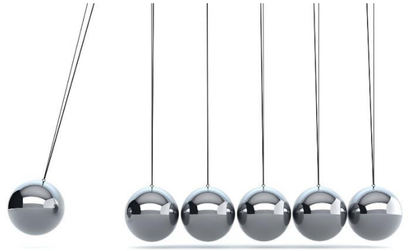
Daw JR, et al. Clin Ther 2012;34:239-49 e2.

Scime NV et al. Acta Obstet Gynecol Scand 2023;102:420-9.

Knight M, et al. MBRRACE 2021 report



HOW DID WE GET HERE?

Thalidomide crisis	FDA classification	Advocacy for inclusion in trials
•Toxicity testing • Fear of prescribing/testing drugs in pregnancy • Pregnant women as “vulnerable group”	• Guidance for health professionals • Balance of risks and benefits	• WHO • ICH • FDA • Tri-council policy statement / Health Canada

CONSEQUENCES OF INERTIA – SUBOPTIMAL CHRONIC DISEASE CARE THROUGHOUT THE PERIOD OF REPRODUCTION

Diabetes care in women of childbearing potential

- Metformin:
  - Observational meta-analyses show safety – 2003
  - Clinical trial for GDM – 2008
  - Clinical trial for DM2 – 2020
  - Post-marketing surveillance study of kids – 2023
  - *Still not in many guidelines as an option to continue throughout pregnancy*
- Novel diabetes drugs:
  - GLP-1 agonist, sglt2 inhibitors have changed the landscape of diabetes care
  - Trials have not included pregnant/lactating, and minimally include reproductive aged females
  - *Women are not prescribed these pre-conception, during pregnancy, during breastfeeding, inter-pregnancy intervals*

Kyriakos G, et al. Curr Cardiol Rev 2020;16:258-65.
Muller DRP, et al. Front Endocrinol (Lausanne) 2023;14:1215356.

OBSTACLES TO CHANGE

Barriers exist at various levels:

- Drug companies
  - Legal risk, delays in study roll-out
  - “vulnerable group”
- Clinicians
  - Lack of knowledge / comfort enrolling pregnant patients
- Researchers
  - Ethical complexities of inclusion
  - Resources / tools / processes
  - Insufficient funding (amount and time)
  - Challenges with enrollment and retention
- Patients
  - Fear, misunderstanding about trials in general and drugs in pregnancy and lactation
  - Informed consent has often been inadequate

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How to address these barriers within Canada

"Designing for Dyads": published proceedings from multidisciplinary workshop

KEY ACTION ITEMS

- Canada-centric guidance
- Resources for REB review
- Consenting models and consent forms
- Decision aids
- Public awareness
- Harmonized dashboard
- Tools for recruitment
- International collaboration & data sharing
- Infrastructure to capture long-term outcomes with mandated public reporting
- Sustainable training programs

Kelly, … Dayan et al, JOGC 2025 online

Global action plan for clinical trial ecosystem strengthening

Global action plan for clinical trial ecosystem strengthening. Geneva: World Health Organization; 2025. https://doi.org/10.2471/B09338. Licence: CC BY-NC-SA 3.0 IGO.

Action 3

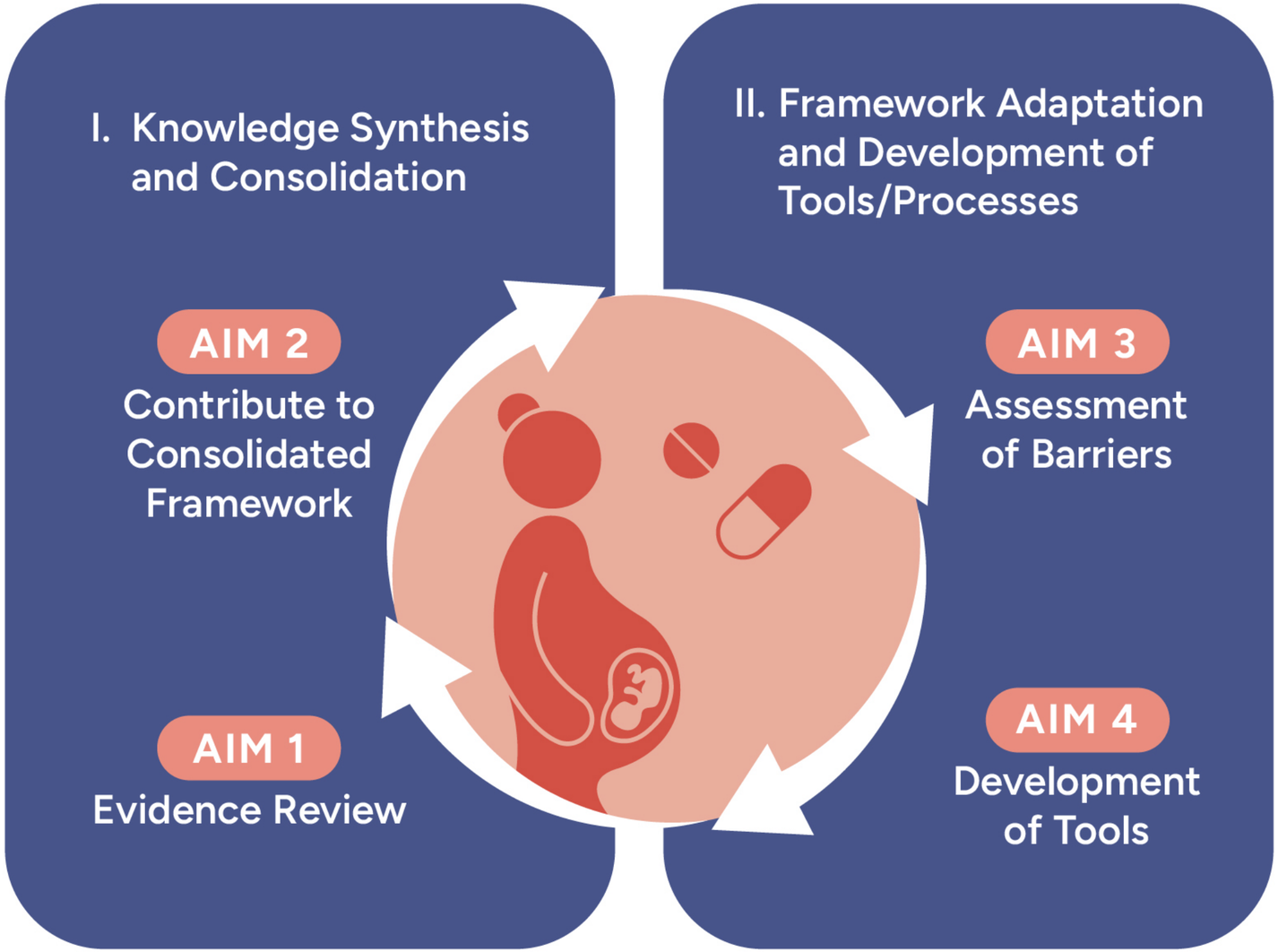
Address barriers to clinical trials in under-represented populations

To enable equitable participation in clinical research and trials, especially in under-represented populations, such as children, pregnant and lactating women and older people, actions require a multifaceted approach to transform guidelines, policies, and practices to ensure trials are designed to reflect the heterogeneity of those who will ultimately use or benefit from the intervention being evaluated and are conducted in diverse settings, including all major population groups the intervention is intended to benefit, with a particular focus on underrepresented populations. Specific measures include:

- where necessary, modifying existing normative frameworks for the ethical and regulatory oversight of research in order to avoid systematic exclusions from research, including clinical trials
- developing guidance to facilitate the responsible inclusion of populations that have been historically excluded from research, and strengthening capacities to conduct case-by-case analyses that are needed to implement the guidance
- prioritizing research and trials addressing evidence gaps and unmet health needs of under-represented populations
- developing tailored engagement, recruitment and retention strategies that address logistical and financial barriers and that increase outreach and inclusion of under-represented populations by integrating clinical research and trial activities at the point-of-care and in communities (see also Action 7).

Successful actions should lead to increased inclusion and balanced representation of populations in clinical trials, aligned with all major population groups that the intervention is intended to benefit.

KNOWLEDGE TO ACTION APPROACH



Synthesize data on clinical trials of vaccines

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KNOWLEDGE TO ACTION APPROACH

Collaborate with Health Canada on ICH E21 document

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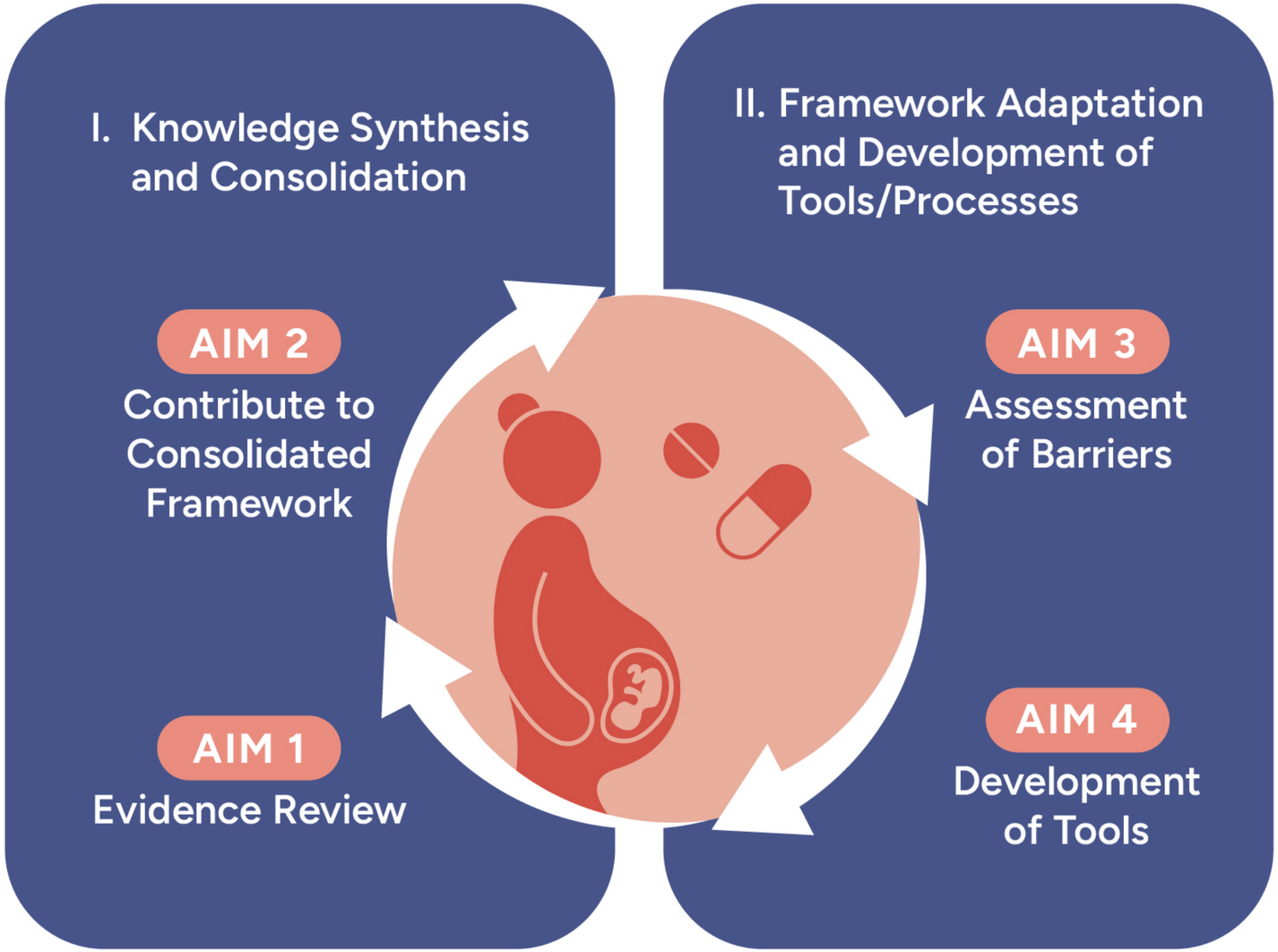

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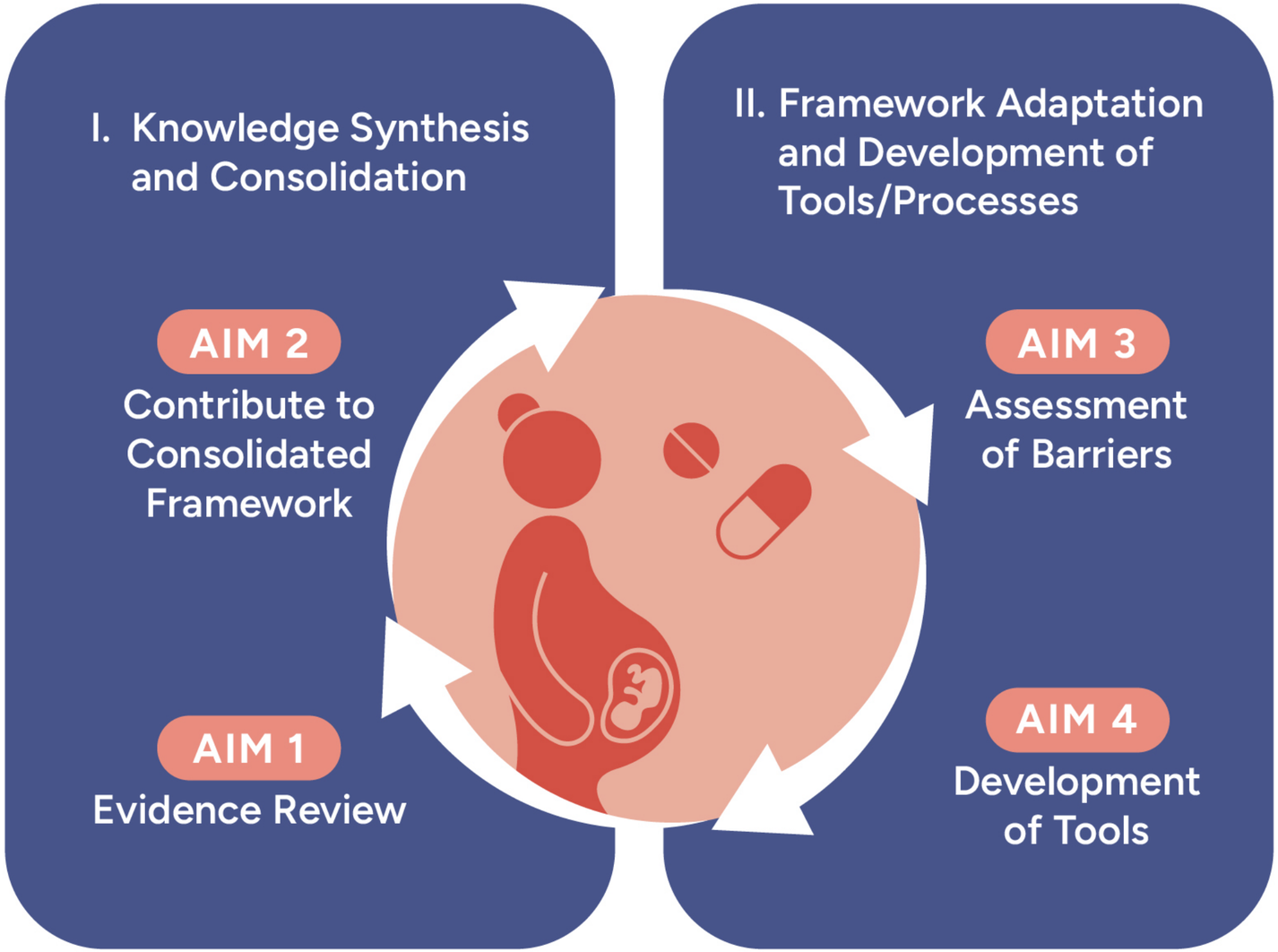

Surveys of investigators / REBs – in development

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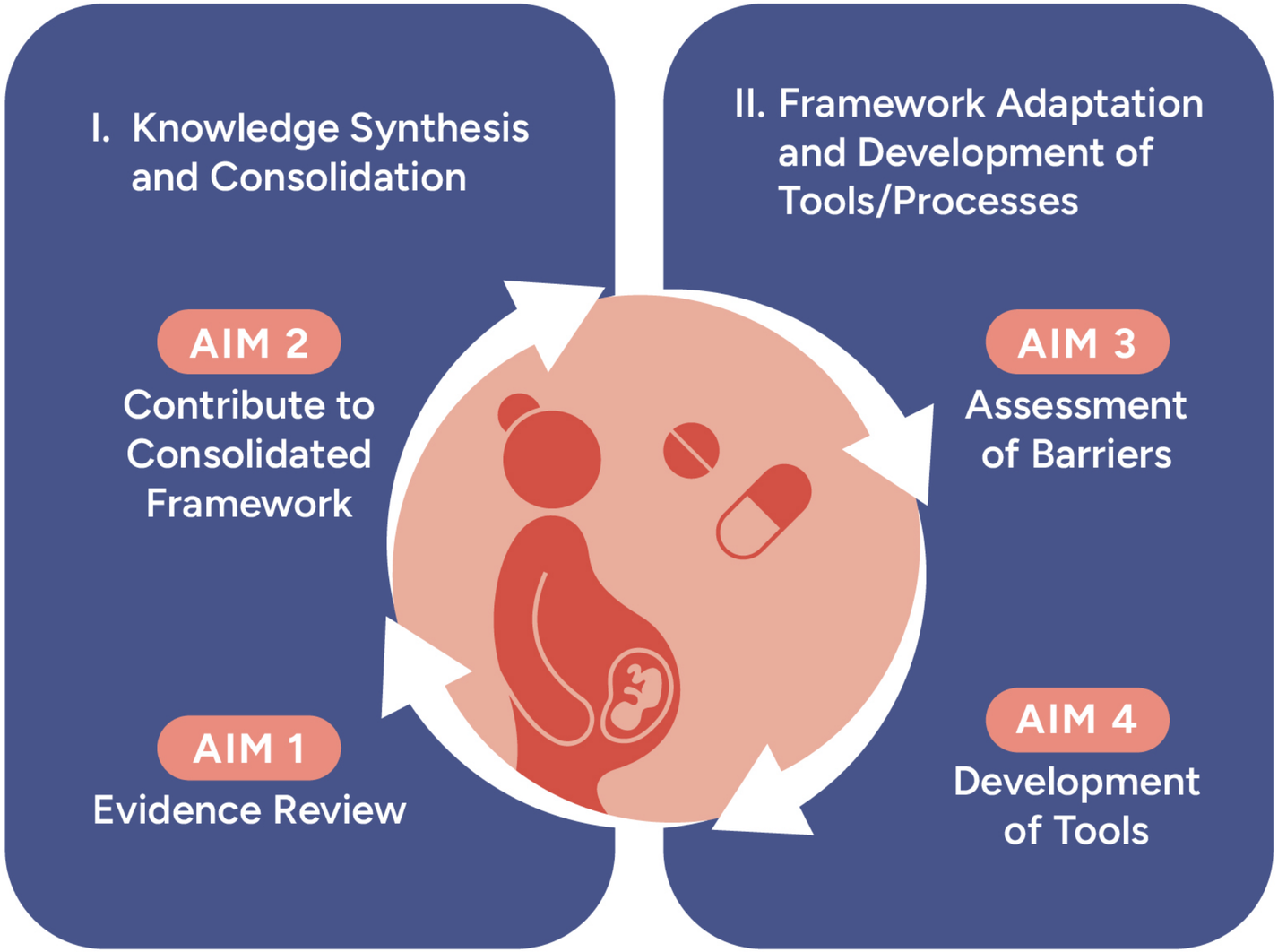

Surveys of investigators / REBs – in development

Develop tools such as ICF, toolkits for researchers

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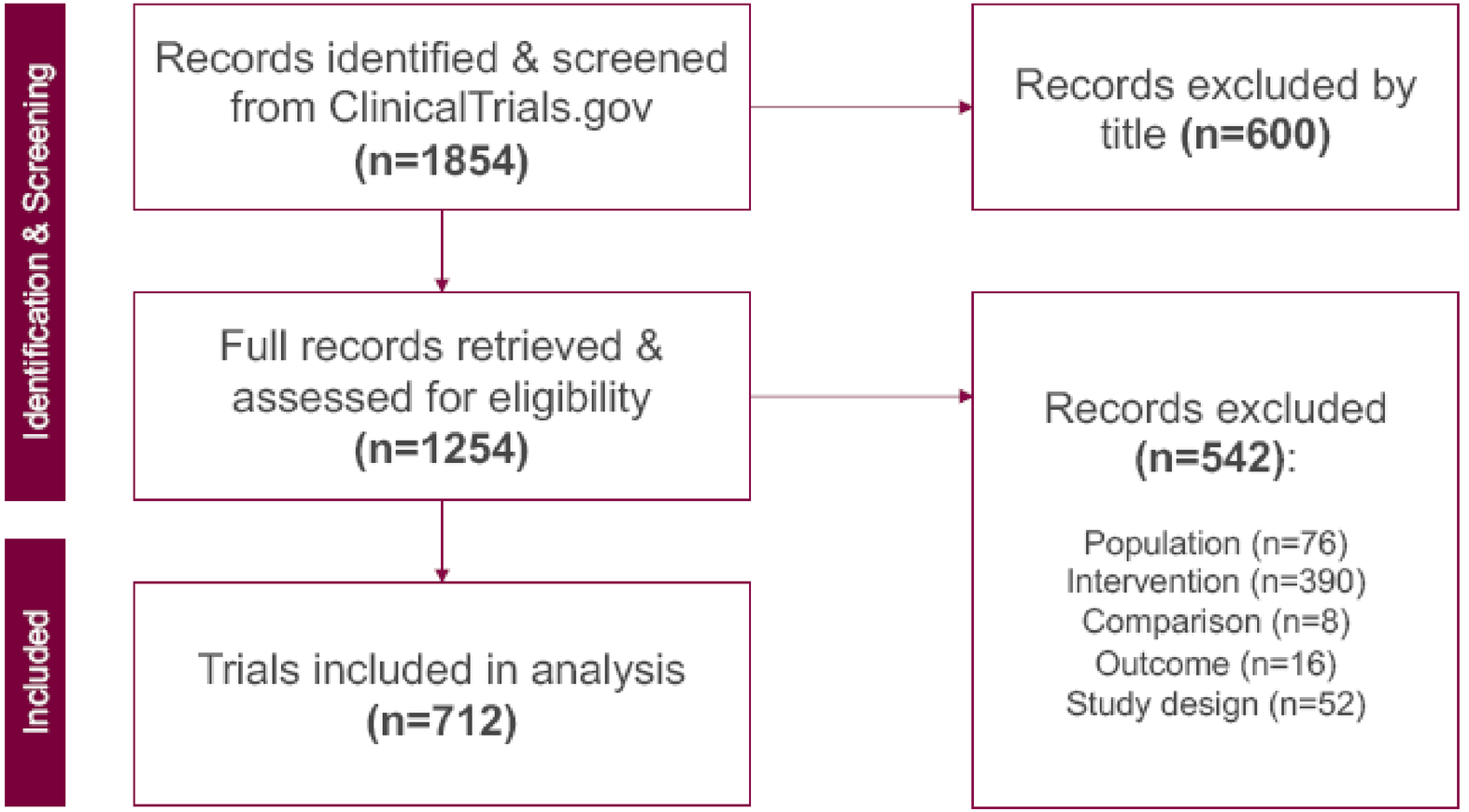
1. Knowledge synthesis

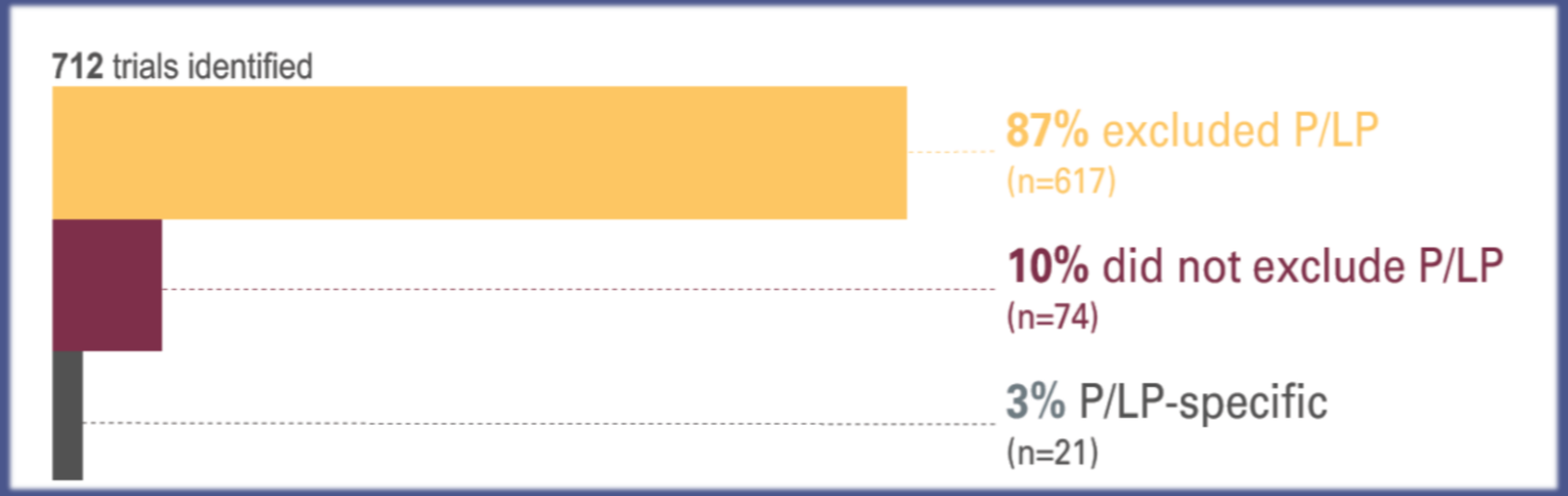
Review of registered vaccine trials from 2015 – 2025 on clinicaltrials.gov



C/O NCCMT

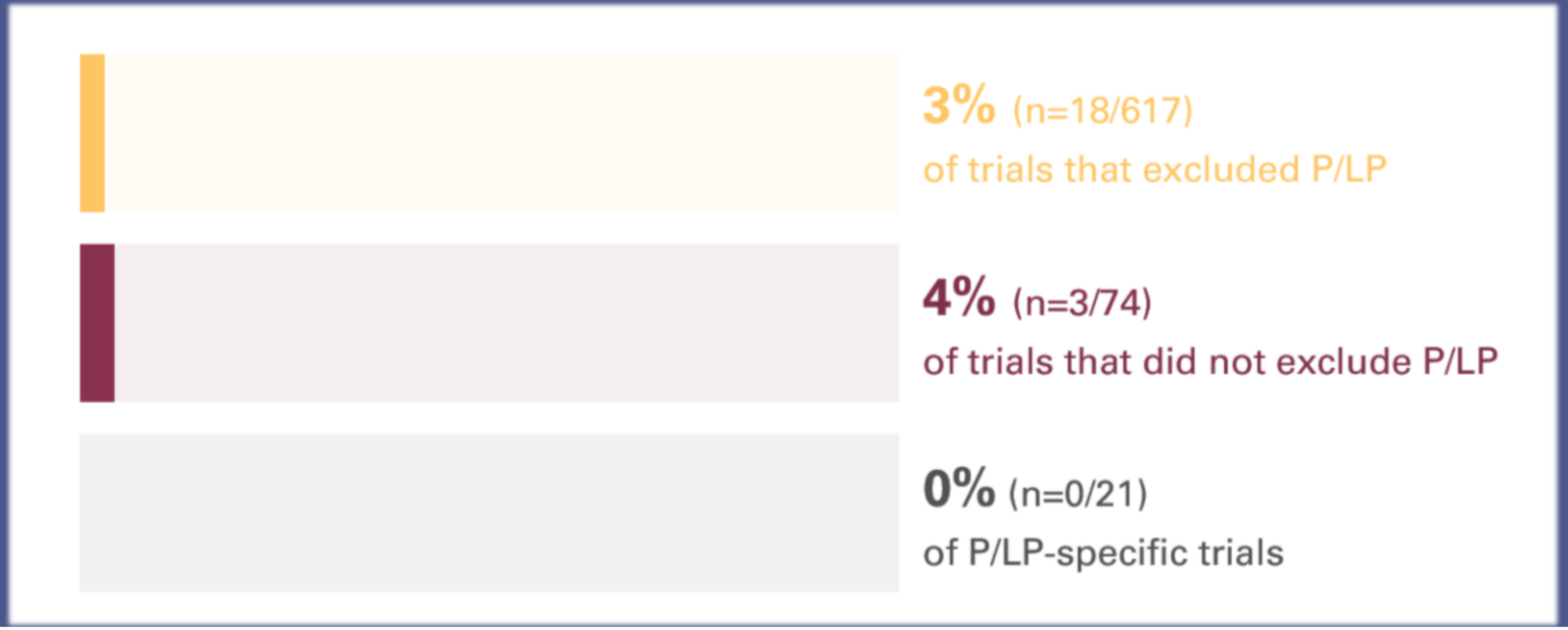
KEY FINDINGS

- **Overall:**



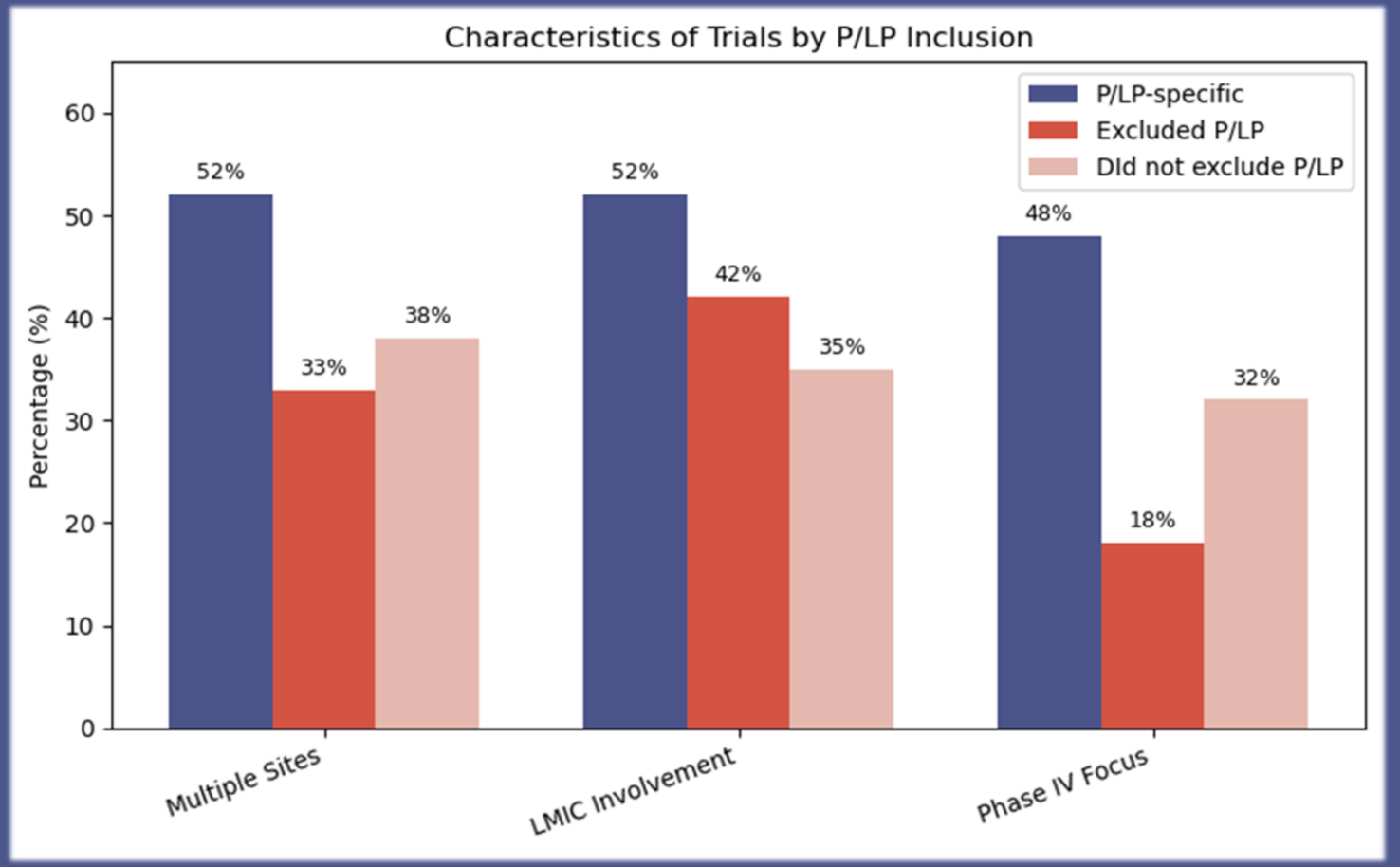
**2 trials that did not exclude P/LP mentioned contraception in the inclusion criteria*

- **In Canada:**



KEY FINDINGS

- P/LP-specific trials more often had:
  - multiple sites
  - involved low- and middle-income countries
  - focused on safety/adverse events and post-marketing surveillance (Phase IV)



Funding was from industry in 40% of trials excluding P/LP, 30% in studies that did not exclude P/LP and 24% in P/LP specific trials

2. Consolidated frameworks: E21 guideline

- International Council for Harmonization (ICH) guidelines aim to create consensus between regulators and industry on scientific and technical requirements for drug registration
- ***E21 = Efficacy guideline #21***
  - ***This global harmonised guideline will address scientific and high-level regulatory principles to ensure the appropriate inclusion and/or retention of pregnant and breast-feeding individuals in clinical trials***
  - The working group list for E21 includes
  - *regulatory members* from USA, EU, Brazil, Egypt, Canada, Japan, China, UK, Saudi Arabia, Chinese Taipei, and Switzerland;
  - *industry members* from Europe (EFPIA), North America (BIO, PhRMA), Japan (JPMA), and international associations (IGBA, IFPMA);
  - *the WHO*.

https://www.ich.org/
c/o Lindsay Patrick, Health Canada

2. Consolidated frameworks: E21 guideline

How we are contributing to E21

Public consultation: *Webinar in summer 2025 including Health Canada representatives for E21 and consolidated feedback from pediatricians, OBGyn/Ob-med, epidemiologist, bioethicist, international policy makers patient partners and other stakeholders.*

Our goal is to co-develop an abridged statement specific to Canadian setting (anticipated in 2027)

4) Tools / processes – develop an adapted ICF template in collaboration with CanReview

- Address a commonly described barrier
- Focus on implementing E21 guidance by integrating concepts and phrases into the ICF template in relevant sections
- Extract qualitative data from ICFs of trials that have included P/LP

Template Annotation: CanReview x E21 guidelines example

4.3 Recruitment and Retention of Pregnant Individuals in Clinical Trials

The general principles for recruitment outlined in ICH E6(R3) apply for clinical trials including pregnant individuals.

Pregnancy is a time when social and/or family interests are enhanced compared to the health of a non-pregnant individual. Such interests may influence a pregnant individual's autonomy and either unduly encourage or deter their participation in a clinical trial.

E21 guidelines

Emphasize family in decision making

Are there choices other than being in this study?

Explain the alternative options applicable to the study population, and their important potential benefits and risks. Refer to suggestions below as applicable.

You do not have to take part in this study in order to receive treatment or care. You may have other options as part of clinical care or other research studies may be available.

You can discuss these options with your health care provider or your study doctor before deciding whether or not to participate in this research project.

If applicable, state if there are no alternative therapies available.

Suggestion for studies using healthy volunteers:
You do not have to take part in this study.

CanReview template

ICF Collection & Categorization

CT categories

- vaccine (n=7)
- communicable disease (n=6)
- non-communicable disease (n=5) trials.

ClinicalTrials.gov ID	URL	Study Title	Study Status	Study's Completion Year	Total n	Condition researched
NCT02717494	https://clinicaltrials.gov/study/NCT02717494	Safety and Immunogenicity of Anti-Pneumococcal Vaccines in HIV-Infected Pregnant Women	COMPLETED	2019	347	Vaccine
NCT03589768	https://clinicaltrials.gov/study/NCT03589768	Study on the Safety and Immunogenicity of Boostrix Vaccine in Pregnant Malian Women and Their Infants	COMPLETED	2020	399	Vaccine
NCT06551506	https://clinicaltrials.gov/study/NCT06551506	The Immunology and Safety of Maternal RSV Vaccination (ABRYSVO), Infant Nirsevimab (BEYFORTUS) Immunization, or Both Products	ACTIVE_NOT_RECRUITING	2026	181	Vaccine
NCT03746665	https://clinicaltrials.gov/study/NCT03746665	Maternal Immunization With MenAfriVac™	UNKNOWN	2021	200	Vaccine
NCT03969641	https://clinicaltrials.gov/study/NCT03969641	Safety of RIV4 Versus IIV4 in Pregnant Women	COMPLETED	2021	384	Vaccine
NCT04589312	https://clinicaltrials.gov/study/NCT04589312	Maternal Pertussis Wholecell Responses (WoMANPOWER)	COMPLETED	2023	181	Vaccine
NCT04556526	https://clinicaltrials.gov/study/NCT04556526	A Study of a 2-dose Ebola Vaccine Regimen of Ad26.ZEBOV Followed by MVA-BN-Filo in Healthy Pregnant Women	COMPLETED	2025	4031	Vaccine
NCT03671967	https://clinicaltrials.gov/study/NCT03671967	PipEracillin Tazobactam Versus MERoPENem for Treatment of Bloodstream Infections Caused by Cephalosporin-resistant Enterobacteriaceae (PETERPEN)	RECRUITING	2026	1084	Communicable disease
NCT04793152	https://clinicaltrials.gov/study/NCT04793152	Vancomycin Dosing for Serious MRSA Infections: A Non-inferiority Randomized Trial of Trough Level Versus AUC/MIC (TAUC)	RECRUITING	2029	700	Communicable disease
NCT04886284	https://clinicaltrials.gov/study/NCT04886284	Combination Cefazolin with Ertapenem for Methicillin-susceptible Staphylococcus Aureus Bacteremia (CERT)	RECRUITING	2025	60	Communicable disease
NCT05137119 - Australia	https://www.clinicaltrials.gov/study/NCT05137119	Staphylococcus Aureus Network Adaptive Platform Trial (SNAP)	RECRUITING	2028	8000	Communicable disease
NCT05137119 - Montreal	https://www.clinicaltrials.gov/study/NCT05137119	Staphylococcus Aureus Network Adaptive Platform Trial (SNAP)	RECRUITING	2028	8000	Communicable disease
NCT06637332	https://clinicaltrials.gov/study/NCT06637332	Daptomycin Vs. Vancomycin for the Treatment of Methicillin Resistant S. Aureus Bacteremia (DAPTO-SNAP)	RECRUITING	2027	300	Communicable disease
NCT01730170	https://clinicaltrials.gov/study/NCT01730170	Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) (MONEAD)	COMPLETED	2022	565	NCDs
NCT04615624	https://clinicaltrials.gov/study/NCT04615624	Furosemide vs. Placebo for Severe Antepartum Hypertension	COMPLETED	2022	65	NCDs
NCT06157684	https://clinicaltrials.gov/study/NCT06157684	Timing of Ambulation and Infant Birth Weight in Gestational Diabetes	RECRUITING	2024	90	NCDs
NCT04492566	https://clinicaltrials.gov/study/NCT04492566	Automated Insulin Delivery in Pregnant Patients With Type 1 Diabetes With Extension Into Outpatient at Home	COMPLETED	2022	10	NCDs
NCT04021602	https://clinicaltrials.gov/study/NCT04021602	Diabetes Prevention Program Feasibility Study of Breastfeeding	COMPLETED	2021	35	NCDs

Thematic Coding

Legend

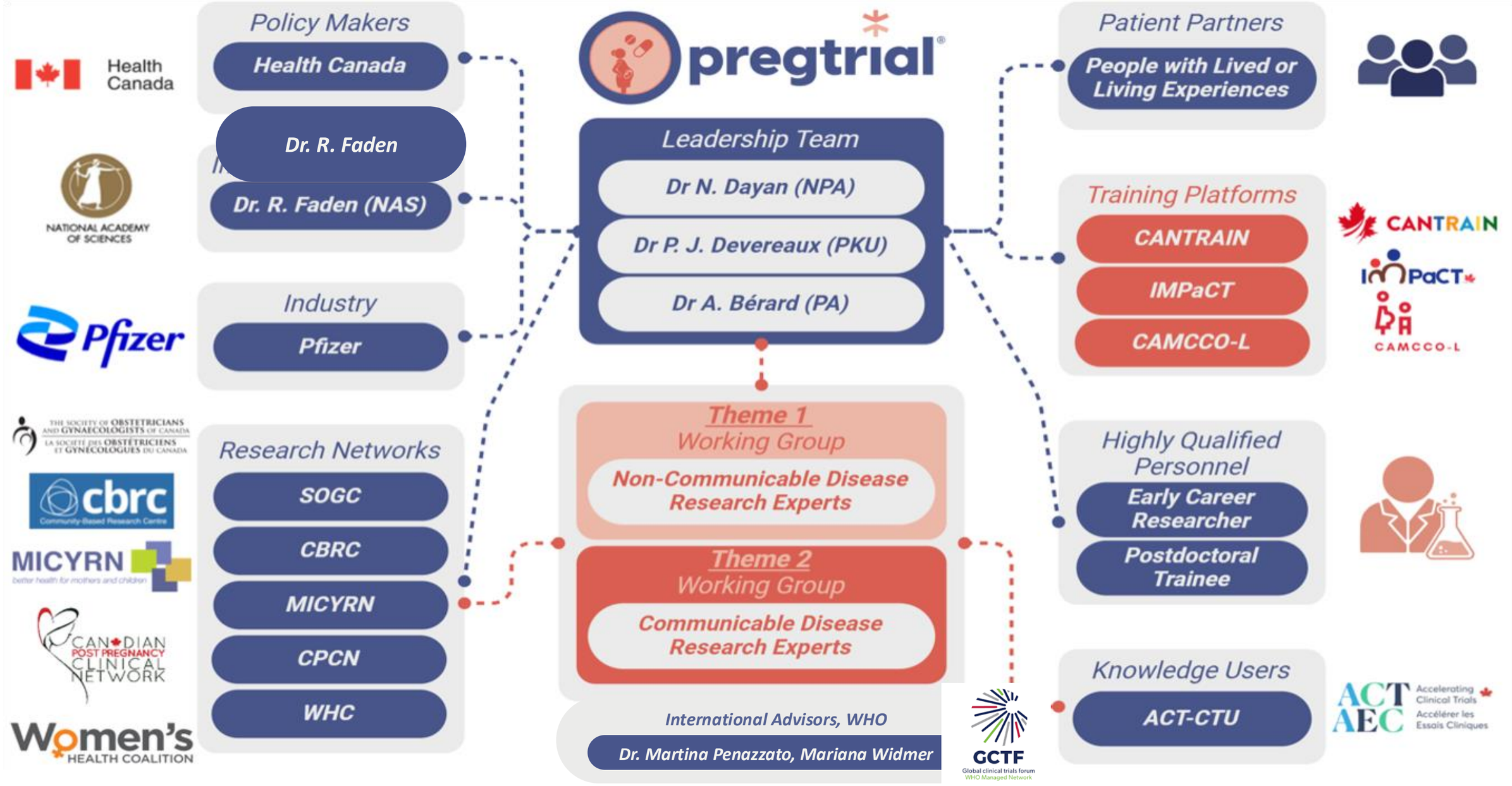
- **G** = general
- **P** = pregnancy-specific
- **L** = lactating individuals-specific
- **PL** = impact on both P/L participants
- **R** = participants who are women of reproductive age

Sub-theme code	Legend	Examples of subtheme explanation
G-WITHDRAW	Explanation around withdrawal process and if there is the possibility of a follow-up necessary after withdrawal	
G-FUTURE	Explanation of any future use of data or specimens collected from the P/LP and their infants	
G-PRIVACY	How maternal and infant records, or their linked records will be shared or protected	
P-INCL	Rationale for inclusion of pregnant people in the CT	
P-RISKFRAME	Specific benefits and risks to pregnancy/fetus health	
P-FETALSHORT	Short-term risk to the fetus	Does the CT require more prenatal visits? Are drug classes mentioned?
P-FETALLONG	Long-term risk to the fetus and infant	Does the CT require additional visits (follow-up) postpartum?
P-BIRTHPLAN	Explanation to how the birth plan and delivery will be affected the day of the birth due to the participation in the CT	Additional monitoring, tests/procedures, specific hospital required for birth, etc.
L-INCL	Rationale for inclusion of lactating people in the CT	
L-RISKFRAME	Specific benefits and risks to lactation/infant/child health	
L-INFANTRISK	Information about how breastfeeding can affect the infant's health	
L-MGMTPLAN	How participation in the CT will affect breastfeeding times, procedures, patterns	
PL-FOLLOWUP	Postpartum and child follow-up after the main study timeline	How frequently the mom/baby will be followed in postpartum period for beneficial and/or adverse effects due to study's intervention? What is the data collection required?
PL-DECISION	Shared decision-making and support with family and friends to partake in the CT	
PL-COMPENSATION	How much compensation, if any, will be given as well as specific considerations for P/LP and their infants	Childcare, transportation
R-CONTINUE	Explanation to how there will be continuation during pregnancy if starting off as non-pregnant for women of reproductive age, and re-consent procedures	

Summary

1. Including P/LP in clinical trials is a matter of equity and safety
2. There are issues specific to this population that require expertise and coordinated action
3. Implementation is complex & layered

Thank you & Acknowledgements



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www.pregtrial.ca

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