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Canadian Critical Care Trials Group

Network of Canadian Emergency Researchers

Use of activated CHARcoal in Poisoned Patients (CHARPP Program)

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Canadian Association of Poison Control Centres
Association canadienne des centres antipoison

www.ccctg.ca

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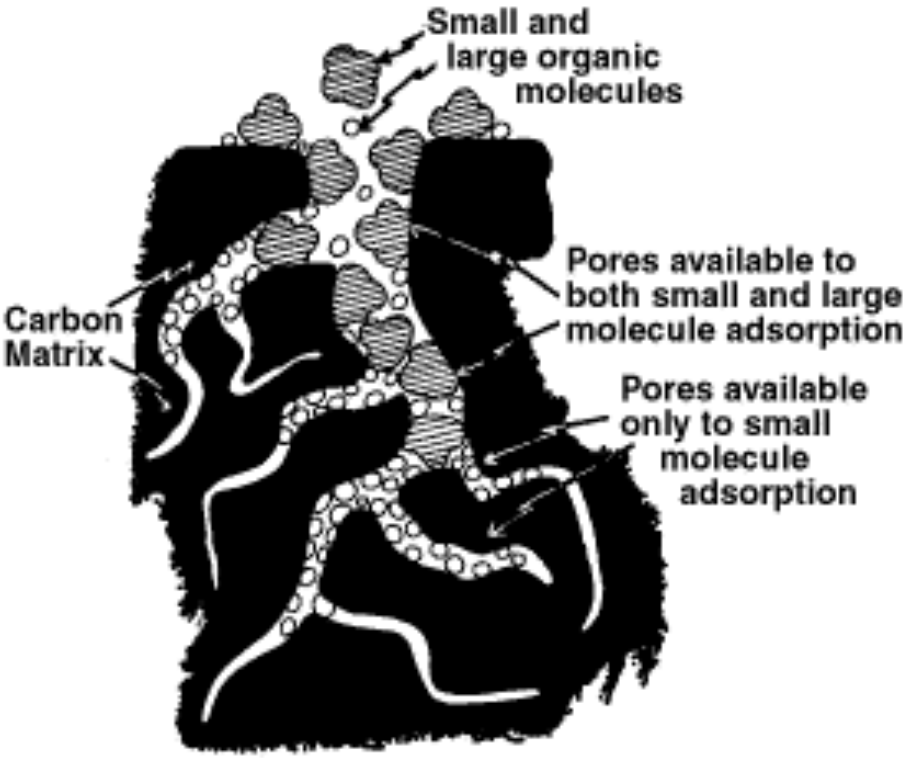
Background

- In 2010
  - 5 516 Canadians died from poisonings
  - 88 922 patients consulted in the ED and 24 024 were admitted in a Canadian hospital because of poisonings
  - 4,2 billions CAD were spent in health care because of poisonings

- Activated charcoal is one of the most frequent intervention recommended by Canadian poison centres and used by acute care physicians in poisoned patients

Background

- 57,888 poisoned patients treated with activated charcoal in the United States in 2012
- As per the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT): *«There are no satisfactorily designed clinical studies assessing benefit (…)»*
- International organisations not able to develop recommendations



1 lb of activated carbon has 200 miles of pores and fissures, and offer the adsorbing surface area of 4 million ft2.

The Problem

- Unknown benefit
- Potential for a clinical impact
- No optimal designed trial assessing benefit
- No good alternatives
- Well-known adverse events
- Distasteful
- Frequent intervention

The Question

In acutely poisoned patients, what are the benefits and the risks associated with the use of activated charcoal in poisoned patients?

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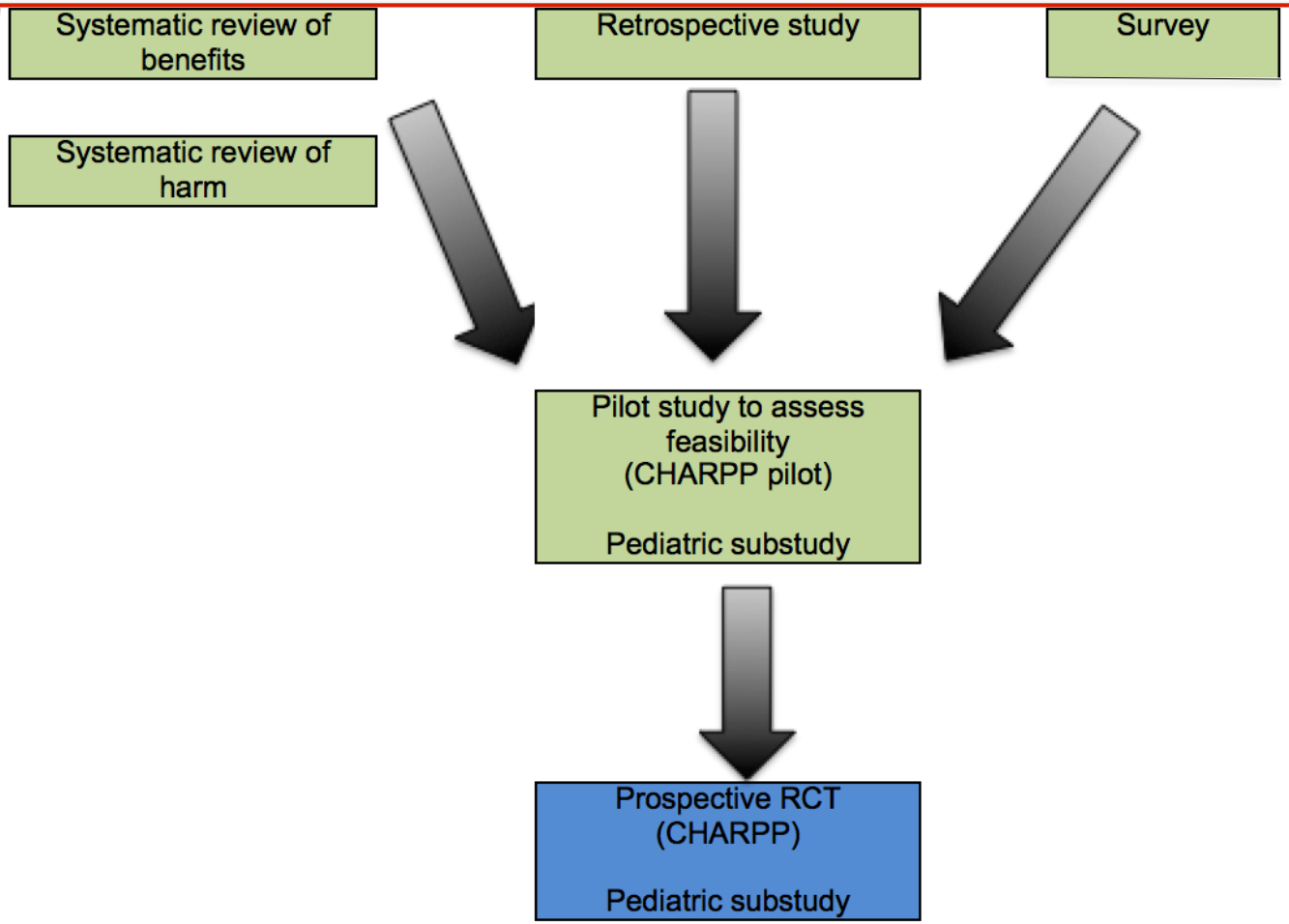

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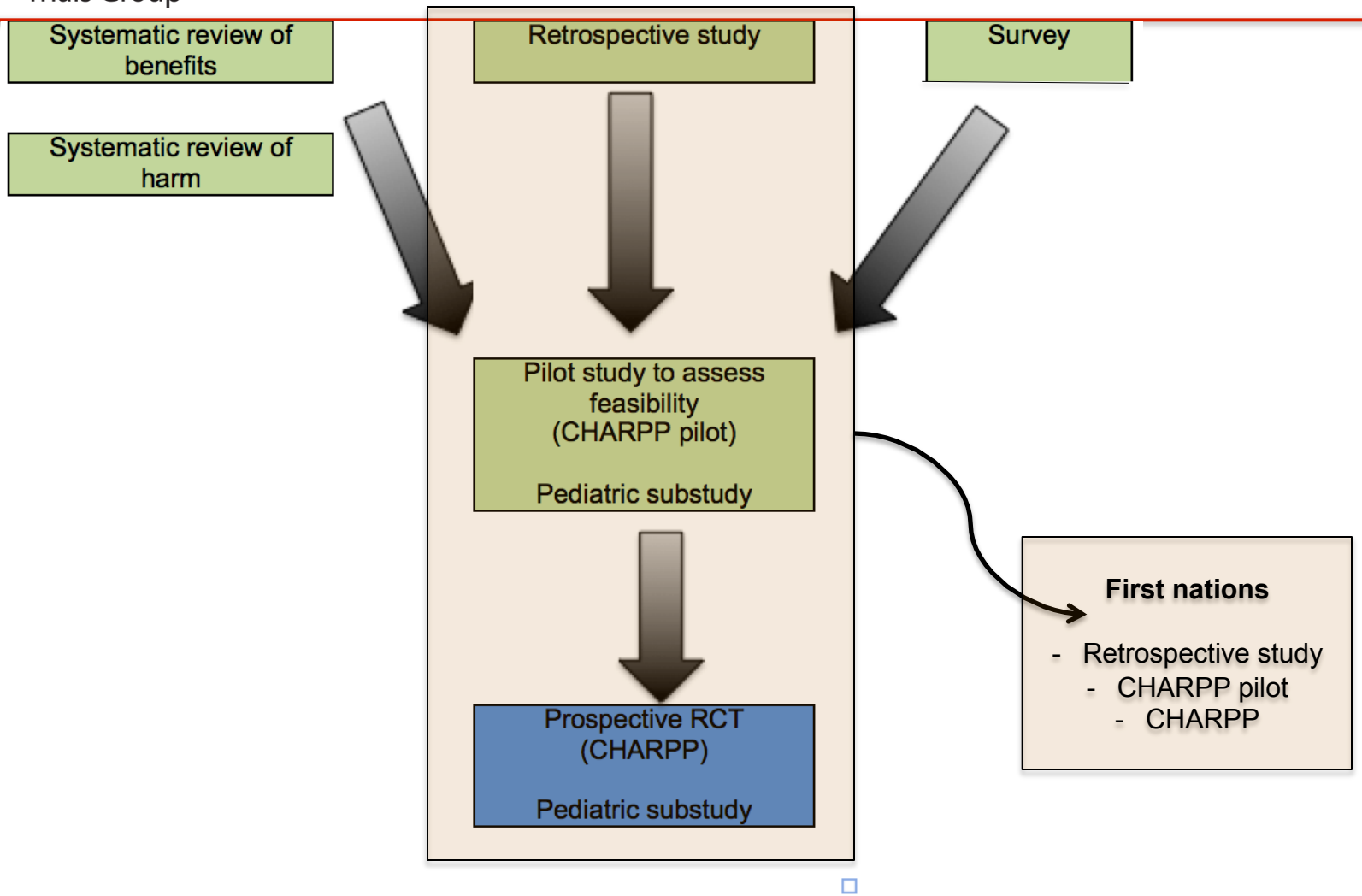

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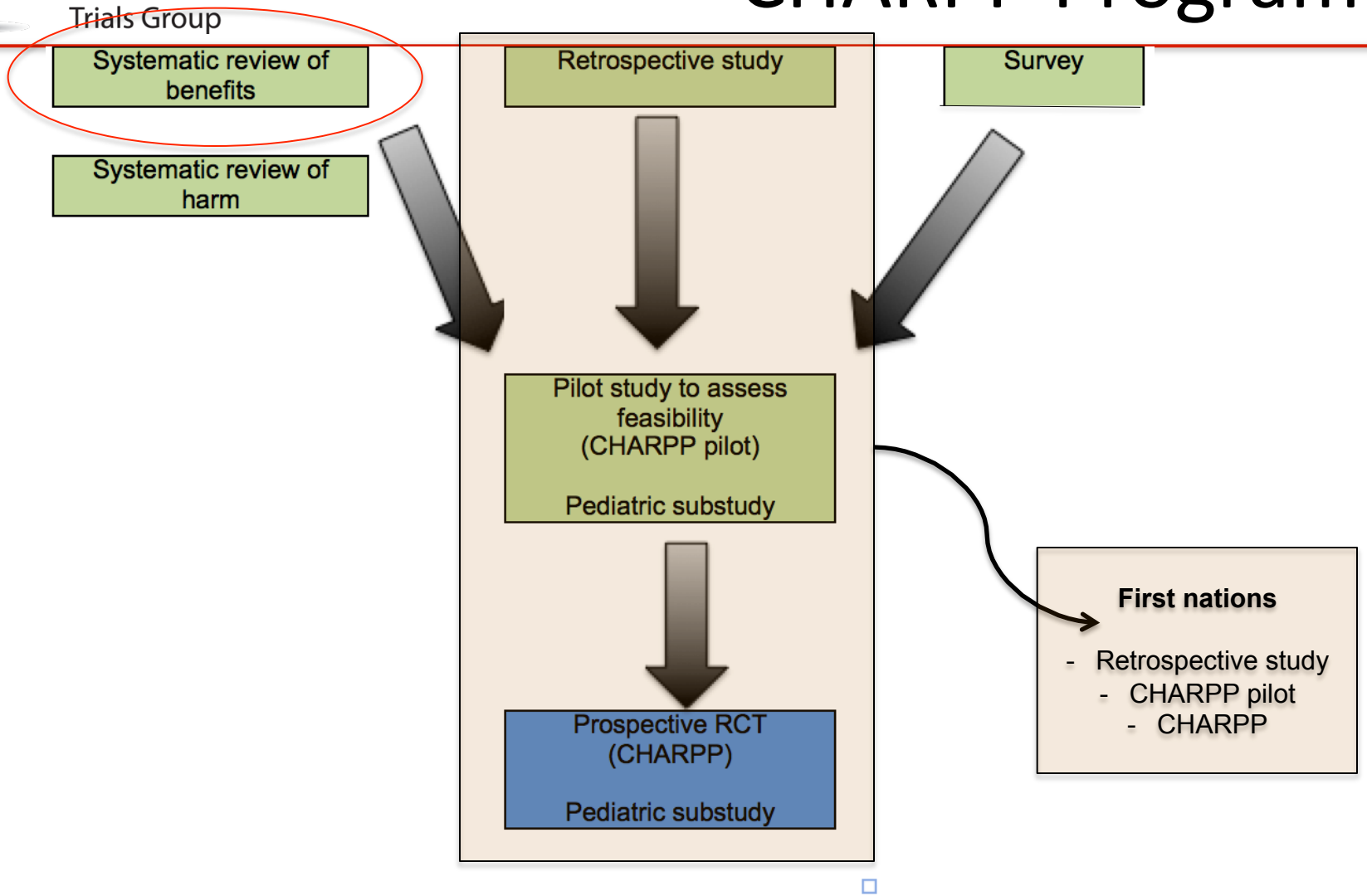

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Systematic review - Benefits

- **P**: Adults or children who ingested a potentially toxic dose of a poison
- **I**: Activated charcoal
- **C**: No decontamination or any other type of decontamination
- **O**:
  - Primary: mortality
  - Secondary: length of stay in hospitals or intensive care units, incidence or severity of toxicity, functional outcomes
- **S**: Randomized trials or quasi-randomized trials

Systematic review - Benefits

- **Methods:**
  - Search strategy:

    OVID Medline, Embase, Web of Science, Scopus, Cochrane Library, Conferences abstracts in toxicology

  - Studies selection and data abstraction by two independent reviewers (third if needed)
  - Risk of bias in individual studies assessed with the Cochrane risk of bias tool and the overall quality of evidence using the GRADE approach

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Systematic review - Benefits

- **Preliminary results**
  - 13 330 records identified through database searching
  - 11 087 records after duplicates removed
  - 810 full-text articles are currently assessed for eligibility
  - 3 studies included so far…

Systematic review

- Eddleston et al. (2008)
  - Open-label study conducted in Sri Lanka
  - Patients randomized in 3 groups: 1) no activated charcoal, 2) 50g, 3) 50g Q4h X 6 doses
  - Primary outcome: mortality
  - 4 629 patients (311 deaths) – **85% pesticides poisoning**
  - No difference, but other methods of decontamination used

Systematic review

- Cooper et al. (2005)
  - Open-label study conducted in Australia
  - Patients randomized in 2 groups: 50g of activated charcoal vs no activated charcoal
  - Primary outcome: length of stay
  - 327 patients – (**more than ¼ intoxicated with acetaminophen**)
  - No difference

Systematic review

- Merigian et al. (2002)
  - Study conducted in an American hospital (Memphis Regional Medical Center)
  - **Quasi-random allocation** based on the day of the week
  - Outcomes: length of stay, clinical deterioration, incidence of complications
  - 1 479 patients
  - No difference in terms of clinical deterioration, but more vomitting and longer length of stay in the group of patients who received activated charcoal

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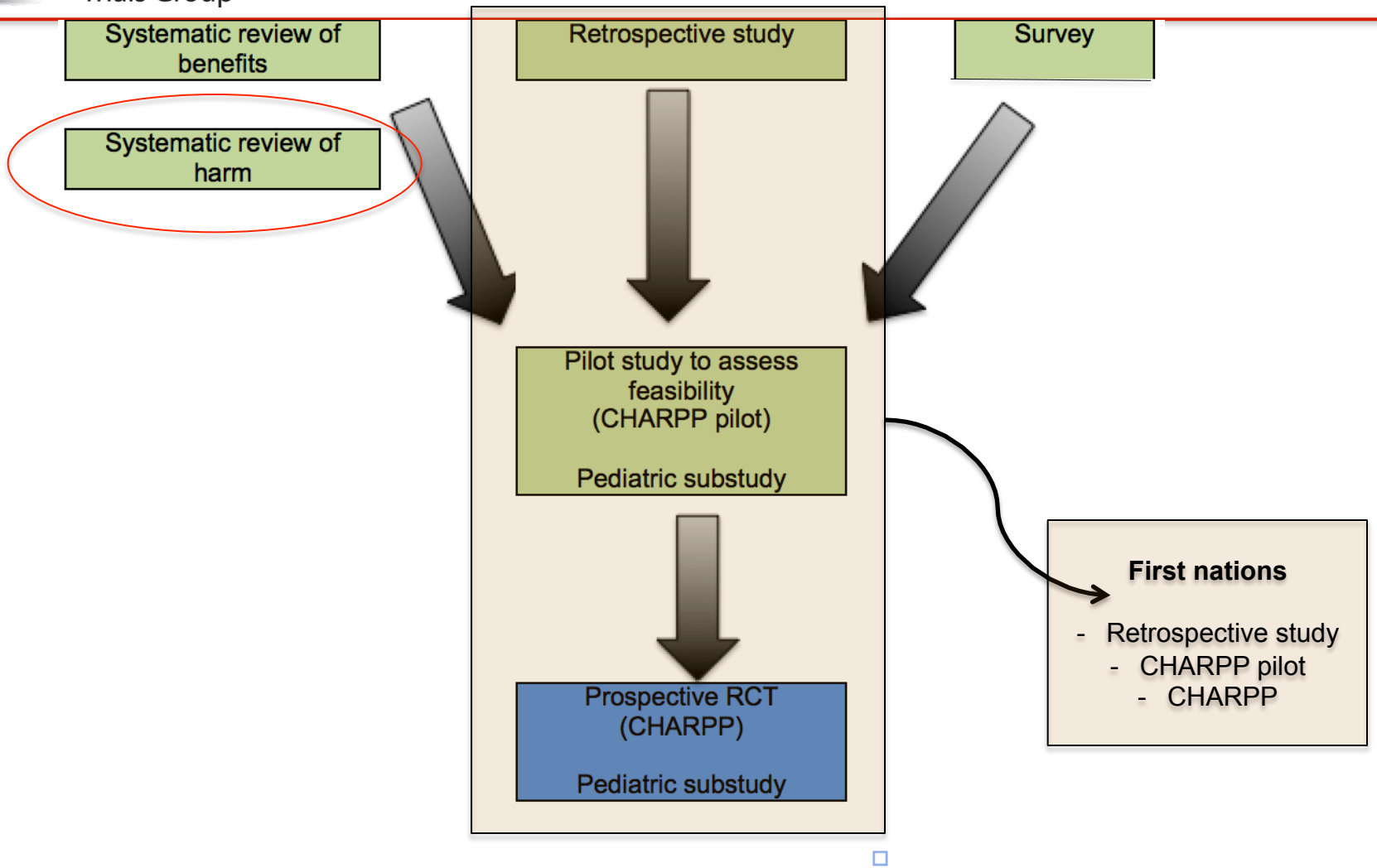

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Systematic review - Harm

- **P**: Adults or children who ingested a potentially toxic dose of a poison
- **I**: Activated charcoal
- **C**: No decontamination or any other type of decontamination
- **O**: Incidence of adverse effects
- **S**: Any type of studies

Systematic review - Harm

- **Methods:**
  - Search strategy:

    OVID Medline, Embase, Web of Science, Scopus, Cochrane Library, Conferences abstracts in toxicology

  - Studies selection and data abstraction by two independent reviewers (third if needed)
  - Risk of bias in individual studies assessed with tools developed for each type of study and the overall quality of evidence using the GRADE approach

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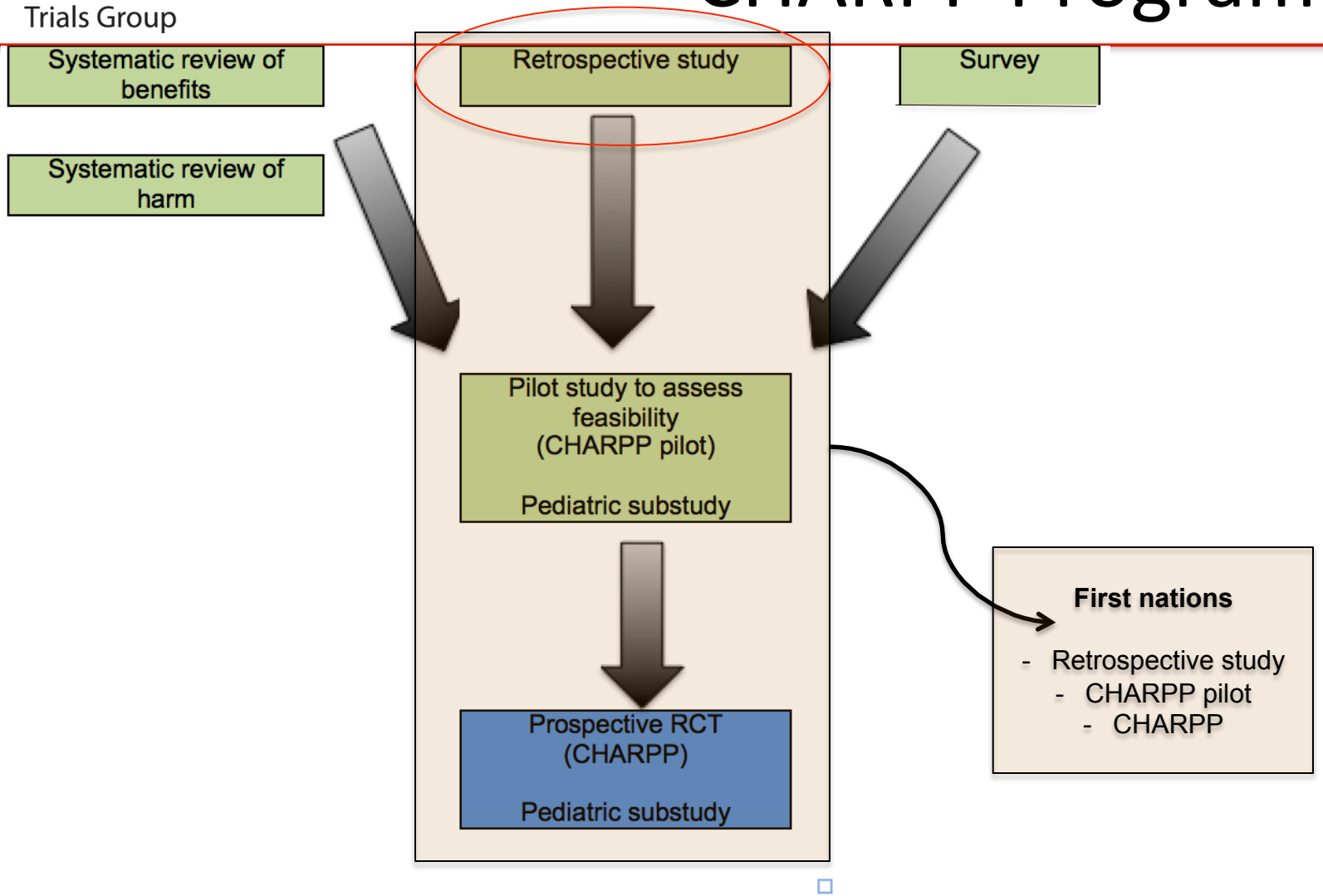

Retrospective study

- **Objectives:**
  - Document the incidence of poisoning cases involving a substance that can be adsorbed by activated charcoal
  - Describe the cases' characteristics
  - Describe the intervention characteristics
  - Describe the outcomes
  - Document the proportion of call to the poison control centre
- **Study sites:**
  - Canadian poison centres + representative tertiary centres (at least 1 pediatric centre and 3 first nations primary care facilities by Canadian poison centre)

Retrospective study

- **Study participants:**
  - Adults or children who present within 12h after the ingestion of a potentially toxic dose of a poison that can be adsorbed by activated charcoal
  - Exclusion criteria:
    - Ingestion of a substance not adsorbed by activated charcoal (iron, lithium, toxic alcohols, etc)
    - Unprotected airway
    - GI perforation or risk of perforation (i.e.: ingestion of a corrosive)
    - Need for a medicine given orally

Retrospective study

- **Outcome measures:**
  - Primary: progression of toxicity measured by the "Poison Severity Score" (PSS)

Severity Grades

NONE (0):	No symptoms or signs related to poisoning
MINOR (1):	Mild, transient and spontaneously resolving symptoms
MODERATE (2):	Pronounced or prolonged symptoms
SEVERE (3):	Severe or life-threatening symptoms
FATAL (4):	Death

[1] Persson H, Sjöberg G, Haines J, Pronczuk de Garbino J. Poisoning Severity Score: Grading of acute poisoning. J Toxicology - Clinical Toxicology (1998) 36:205-13.

  - Secondary: mortality, length of stay in the intensive care unit and hospital, functional outcomes (back to baseline or not at discharge)
  - Incidence and severity of adverse events (at least possible based on the Naranjo probability scale)

Retrospective study

- **Sampling and data collection:**
  - 300 adults based on an incidence of patients reaching a PSS of 3 or 4 of 15% (confidence interval [11-19])
  - Patients randomly selected among each participatory centre (6 centres, 50 patients per centre)
  - Data collected by a person blinded to the study objectives on a form approved by a group of experts
  - 10% of the charts will be verified by another person to evaluate the reliability of data collection and to calculate interobserver agreement with the PSS

Retrospective study

- **Descriptive analysis:**
  - Incidence of poisoning cases involving a substance that can be adsorbed by activated charcoal
  - Cases' characteristics (age, sexe, comorbidities, medication, substance, state at arrival)
  - Intervention characteristics (time of administration, dose regimen, co-interventions)
  - Incidence of adverse events
  - Outcomes (PSS, mortality, etc)
  - Proportion of call to the poison control centre

Retrospective study

- **Sensitivity analysis:**
  - All poisonings except acetaminophen poisonings
  - All poisonings except cases who received more than one dose of activated charcoal
  - Worst and best case scenarios with missing data
- **Funding:**
  - 25 000$ by CHU de Québec
  - In kinds from Canadian poison control Centers
  - Applications to professional associations in toxicology, emergency medicine, critical care

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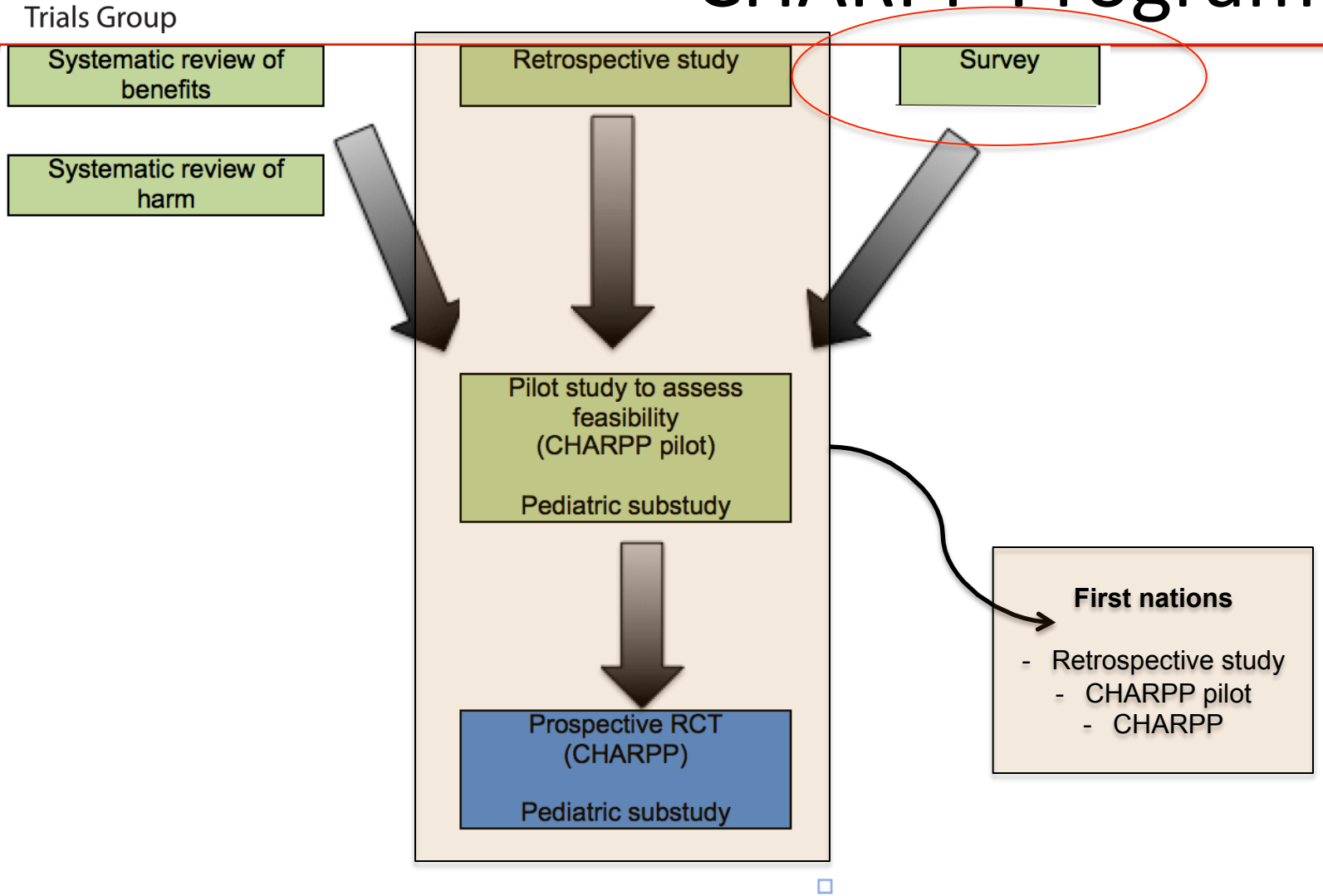

Survey

- **Objectives:**
  - Explore the opinions of key stakeholders in regard to indications and contraindications

- **Study participants:**
  - Members of the Canadian Critical Care Society, the Canadian Association of Emergency Physicians, the Canadian Association of Poison Centers and poison centre nurses

Survey

- **Methods:**
  - Item generation based on the literature by a group of experts including a member of each association
  - Item reduction
  - Pre-tested and pilot-tested by 2 French speaking and 2 English speaking representatives of each association
  - Validity assessed by one scientist of each association
  - Link sent to members of the participating associations (two reminders) and letter sent to non-respondents

Survey

- **Methods:**
  - Analysis:
    - Median
    - Disagreement index
      - Interpercentile range / interpercentile range adjusted for symetry
      - Clinical equipoise = disagreement index of more than 1

- **Funding:**
  - In kinds from Canadian poison control Centers
  - 10 000$ by CHU de Québec

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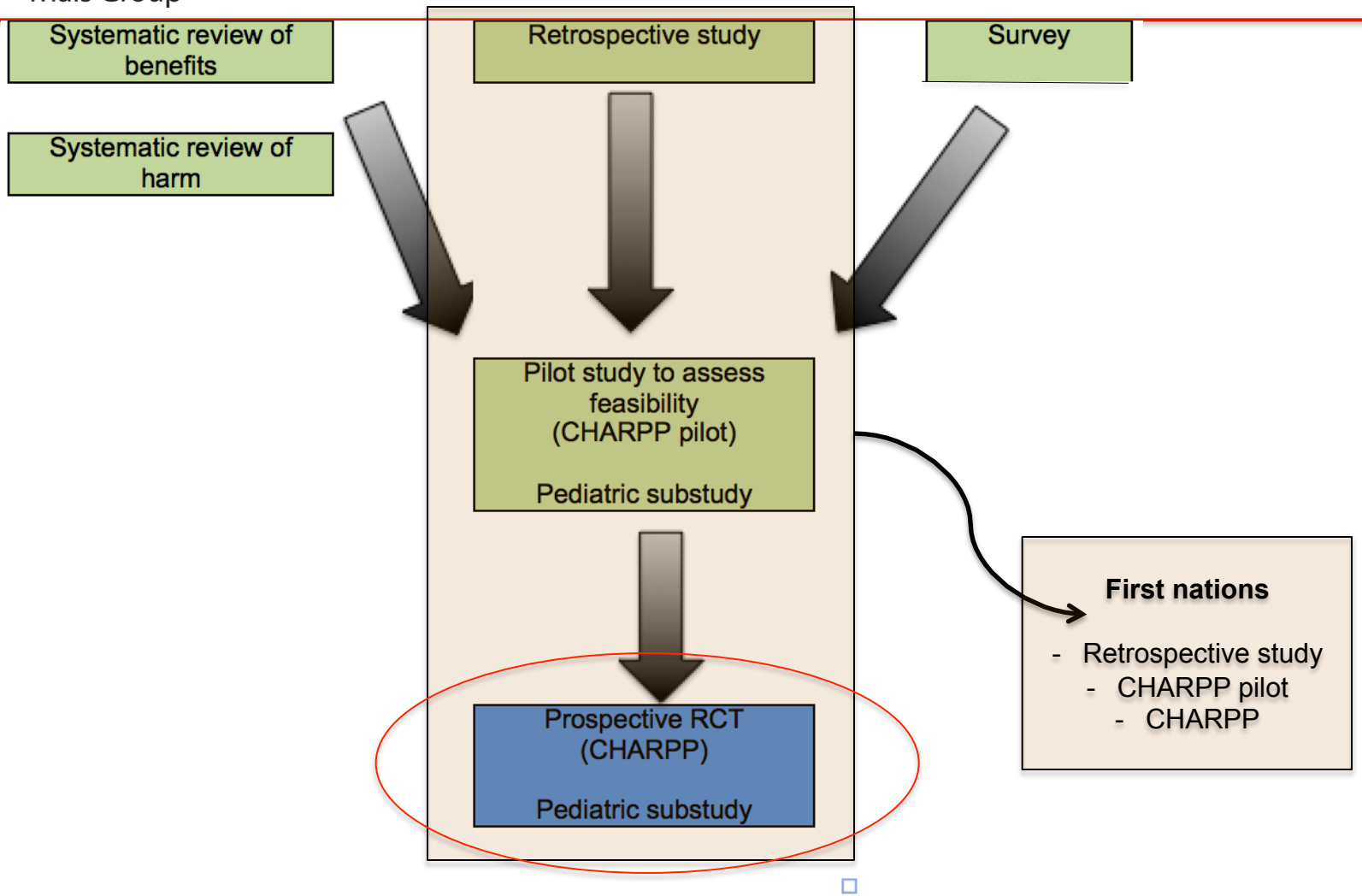

Large scale RCT

- **Objectives:**
  - Evaluate the effect of the use of activated charcoal in poisoning on clinically significant outcomes
  - Evaluate the adverse events associated with its use

- **Outcome measures:**
  - Primary: progression of toxicity measured by the "Poison Severity Score" (PSS)
  - Secondary: mortality, length of stay in the intensive care unit and hospital, functional outcomes (back to baseline at discharge or not)
  - Adverse events (i.e. vomiting, pneumonia, acute respiratory distress syndrome, etc.)

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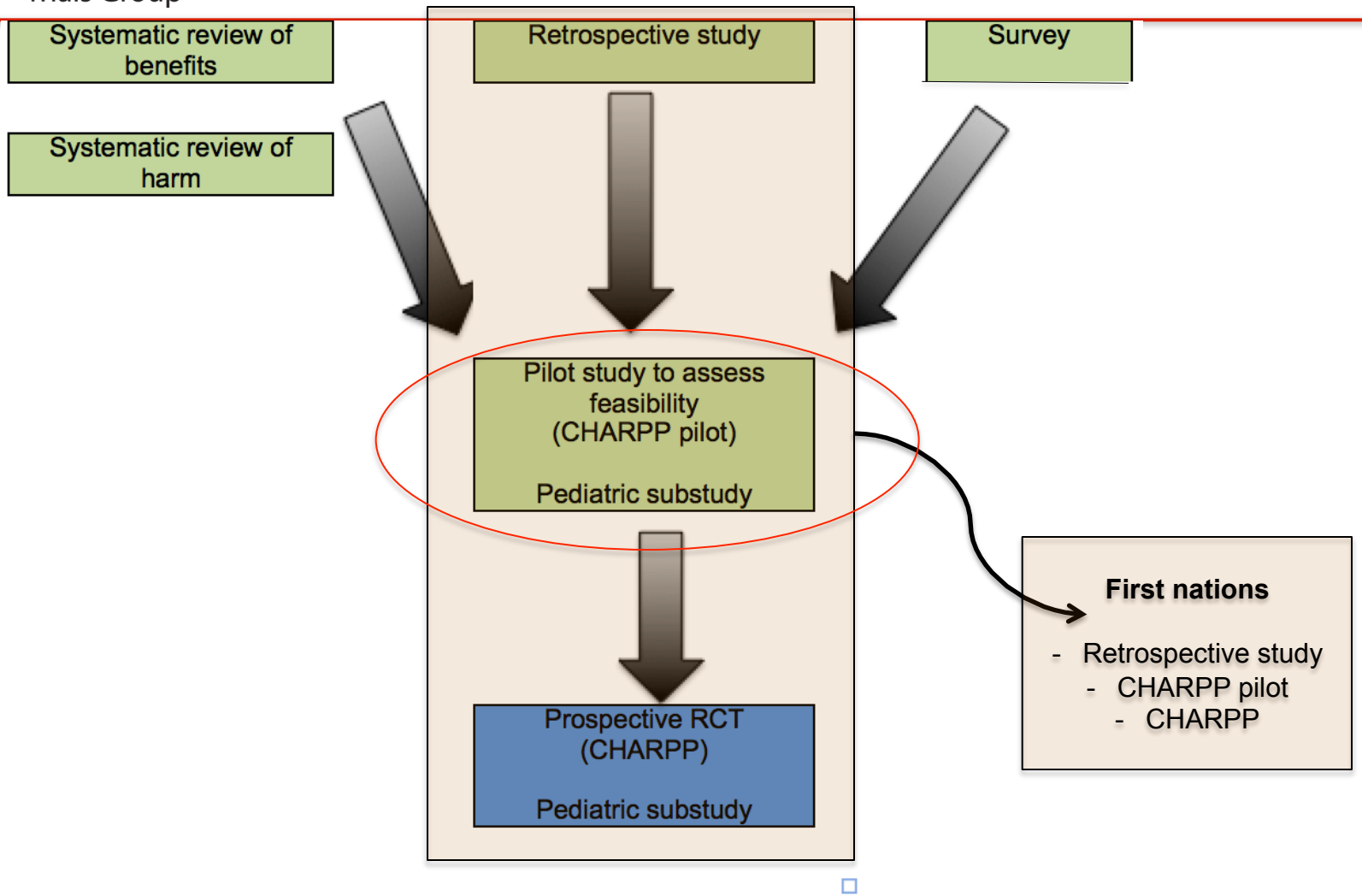

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Centre Antipoison du Québec 1 800 463-5060
Canadian Association of Poison Control Centres
Association canadienne des centres antipoison
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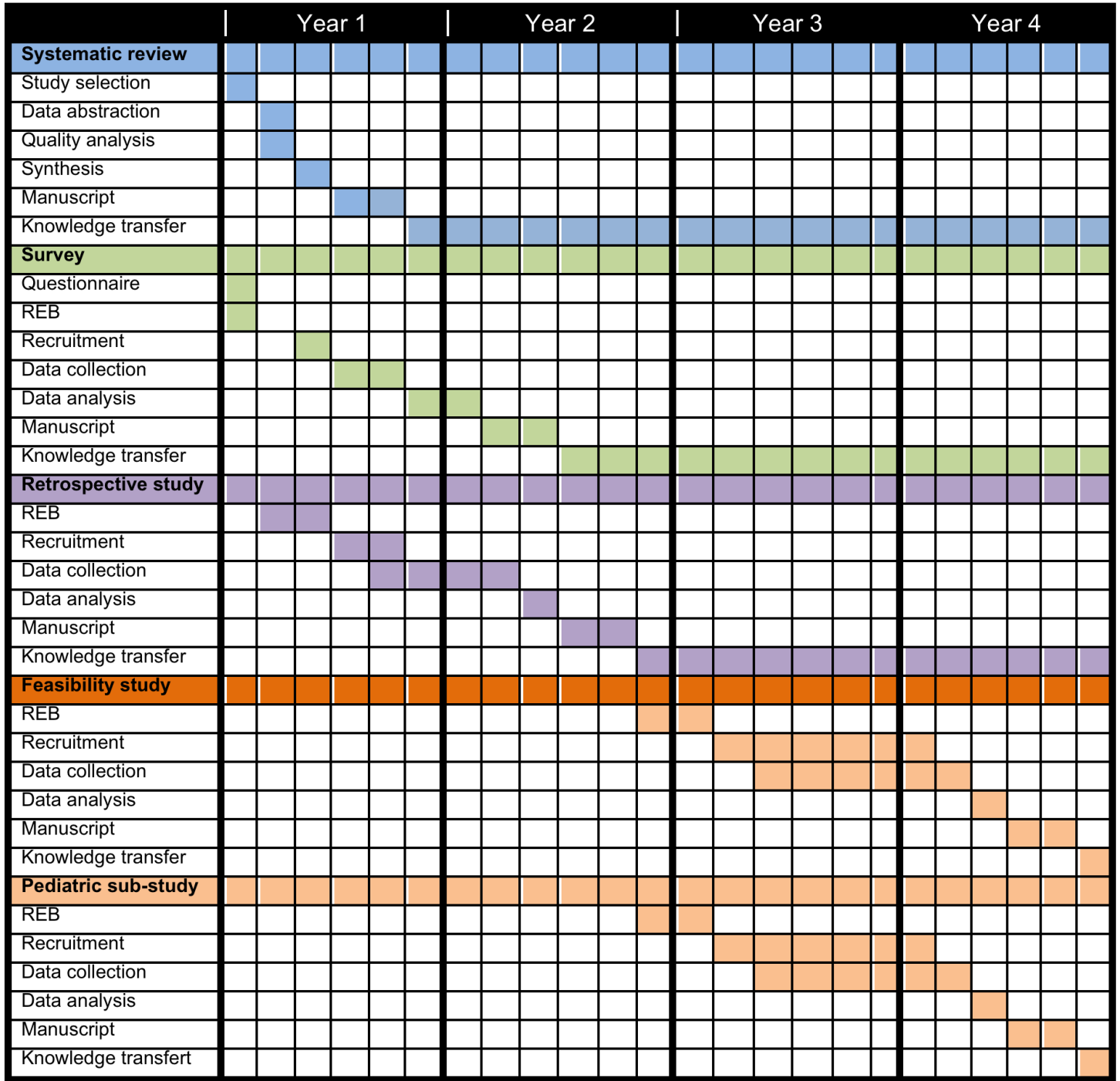
Pilot study

- **Objectives:**
  - Feasibility of conducting a large scale trial
- **Study sites:**
  - Canadian poison centres + representative tertiary centres
  - Canadian poison centres + representative first nations primary care facilities
- **Study participants:**
  - Adults (or children) who ingested a potentially toxic dose of a poison that can be adsorbed by activated charcoal and who consult in a Canadian hospital

Pilot study

- **Outcome measures:**
  - Recruitment rate
  - Proportion of consent
  - Adherence to study protocol
  - Data collection
  - Proportion of participants lost to follow-up


Year 1
Year 2
Year 3
Year 4
Systematic review
Study selection
Data abstraction
Quality analysis
Synthesis
Manuscript
Knowledge transfer
Survey
Questionnaire
REB
Recruitment
Data collection
Data analysis
Manuscript
Knowledge transfer
Retrospective study
REB
Recruitment
Data collection
Data analysis
Manuscript
Knowledge transfer
Feasibility study
REB
Recruitment
Data collection
Data analysis
Manuscript
Knowledge transfer
Pediatric sub-study
REB
Recruitment
Data collection
Data analysis
Manuscript
Knowledge transfert

Impact

- CHARPP will inform future health policies and recommendations
- It is a great opportunity to collaborate with the Canadian Critical Care Trials Group and the Canadian Association of Poison Centres

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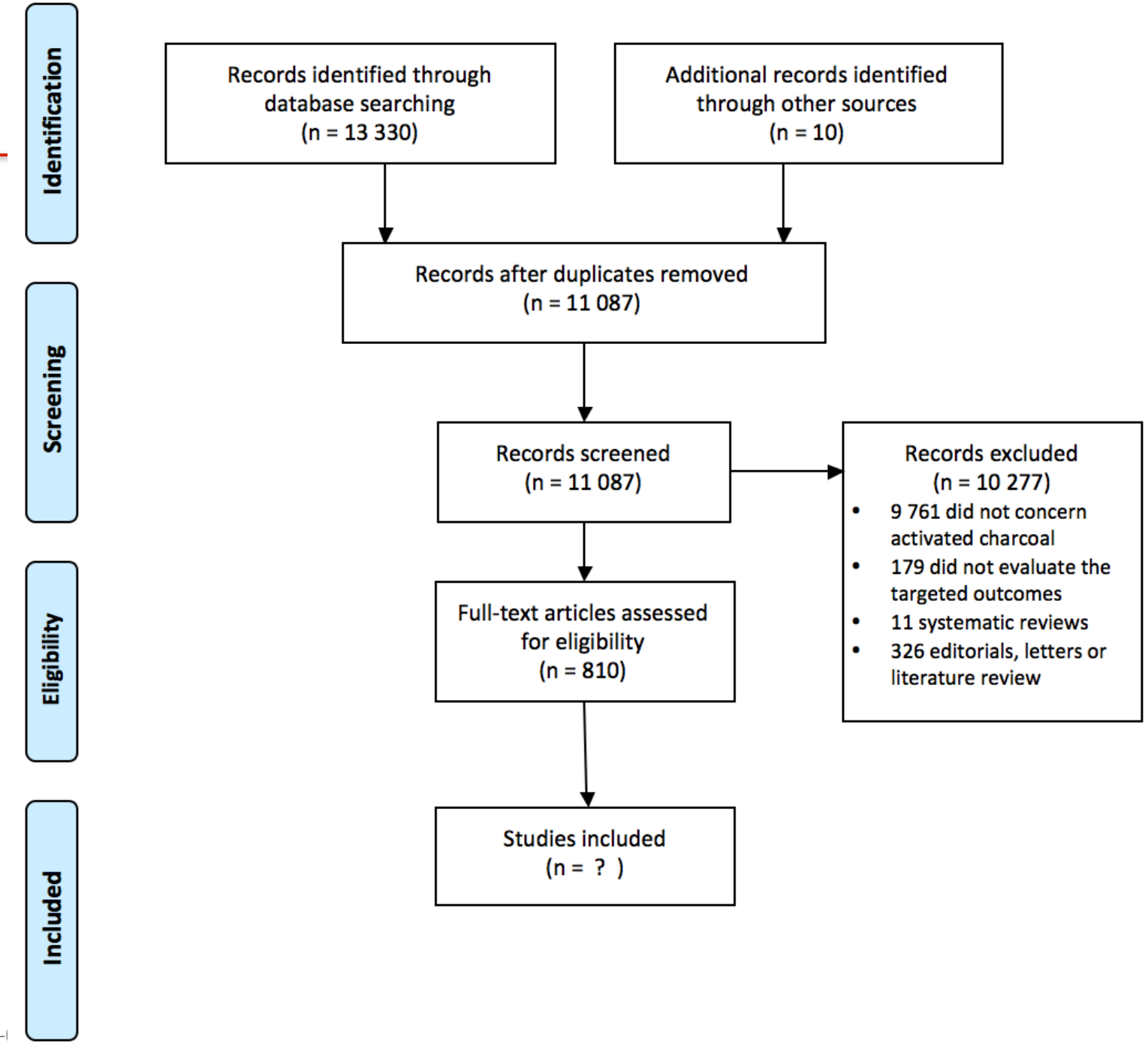
QUESTIONS FOR NCER

- Do you agree to collaborate to this research program?
- Who would like to be listed as a research collaborator (methodology input at this stage)?
- Does CAEP agree to participate to the survey?

Thank You


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 13 330)
Additional records identified through other sources (n = 10)
Records after duplicates removed (n = 11 087)
Records screened (n = 11 087)
Records excluded (n = 10 277)
• 9 761 did not concern activated charcoal
• 179 did not evaluate the targeted outcomes
• 11 systematic reviews
• 326 editorials, letters or literature review
Full-text articles assessed for eligibility (n = 810)
Studies included (n = ?)

POISONING SEVERITY SCORE (PSS)
IPCS/EAPCCT

Severity Grades

NONE (0): No symptoms or signs related to poisoning
MINOR (1): Mild, transient and spontaneously resolving symptoms
MODERATE (2): Pronounced or prolonged symptoms
SEVERE (3): Severe or life-threatening symptoms
FATAL (4): Death

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
	0	1	2	3	4
	No symptoms or signs	Mild, transient and spontaneously resolving symptoms or signs	Pronounced or prolonged symptoms or signs	Severe or life-threatening symptoms or signs	Death
GI-tract		• Vomiting, diarrhoea, pain • Irritation, 1st degree burns, minimal ulcerations in the mouth • Endoscopy: erythema, oedema	• Pronounced or prolonged vomiting, diarrhoea, pain, ileus • 1st degree burns of critical localization or 2nd and 3rd degree burns in restricted areas • Dysphagia • Endoscopy: ulcerative transmucosal lesions	• Massive haemorrhage, perforation • More widespread 2nd and 3rd degree burns • Severe dysphagia • Endoscopy: ulcerative transmural lesions, circumferential lesions, perforation	
Respiratory system		• Irritation, coughing, breathlessness, mild dyspnoea, mild bronchospasm • Chest X-ray: abnormal with minor or no symptoms	• Prolonged coughing, bronchospasm, dyspnoea, stridor, hypoxemia requiring extra oxygen • Chest X-ray: abnormal with moderate symptoms	• Manifest respiratory insufficiency (due to e.g. severe bronchospasm, airway obstruction, glottal oedema, pulmonary oedema, ARDS, pneumonitis, pneumonia, pneumothorax) • Chest X-ray: abnormal with severe symptoms	
Nervous system		• Drowsiness, vertigo, tinnitus, ataxia • Restlessness	• Unconsciousness with appropriate response to pain • Brief apnoea, bradypnoea • Confusion, agitation, hallucinations, delirium • Infrequent, generalized or local seizures	• Deep coma with inappropriate response to pain or unresponsive to pain • Respiratory depression with insufficiency • Extreme agitation • Frequent, generalized seizures, status epilepticus, opisthotonus	

Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			TOTAL SCORE:	

Modified from: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-245.

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Systematic review - Benefits

- **Methods:**
  - Qualitative synthesis to summarize evidence for all studies
  - Random effect models (Relative risks)

Systematic review - Harm

- **Methods:**
  - Risk of bias in individual studies assessed with:
    - STROBE and Thomas tool for observational studies
    - Institute of Health Economics tool for quality of case series and quality reporting
    - ARRIVE and NRCNA for animal studies
  - Qualitative synthesis to summarize evidence for all studies.