Adaptation of Risk of Bias Assessment for Environmental Exposures: The IRIS Experience

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Outline

- Overview of IRIS evaluation methods for epidemiology studies
- Experience with protocol development
- Lessons learned and future plans
- Panel discussion

Study Evaluation: Purpose

Study evaluation process should:

- appropriately distinguish among studies
  - reliability and validity of methods and results
  - specificity (false positives) and sensitivity (false negatives)
- assure that same criteria used to evaluate all studies
- provide means to document decisions (for benefit of people working on the assessment, for benefit of external peer review panel, for the benefit of the public)

Study Evaluation – Epidemiology

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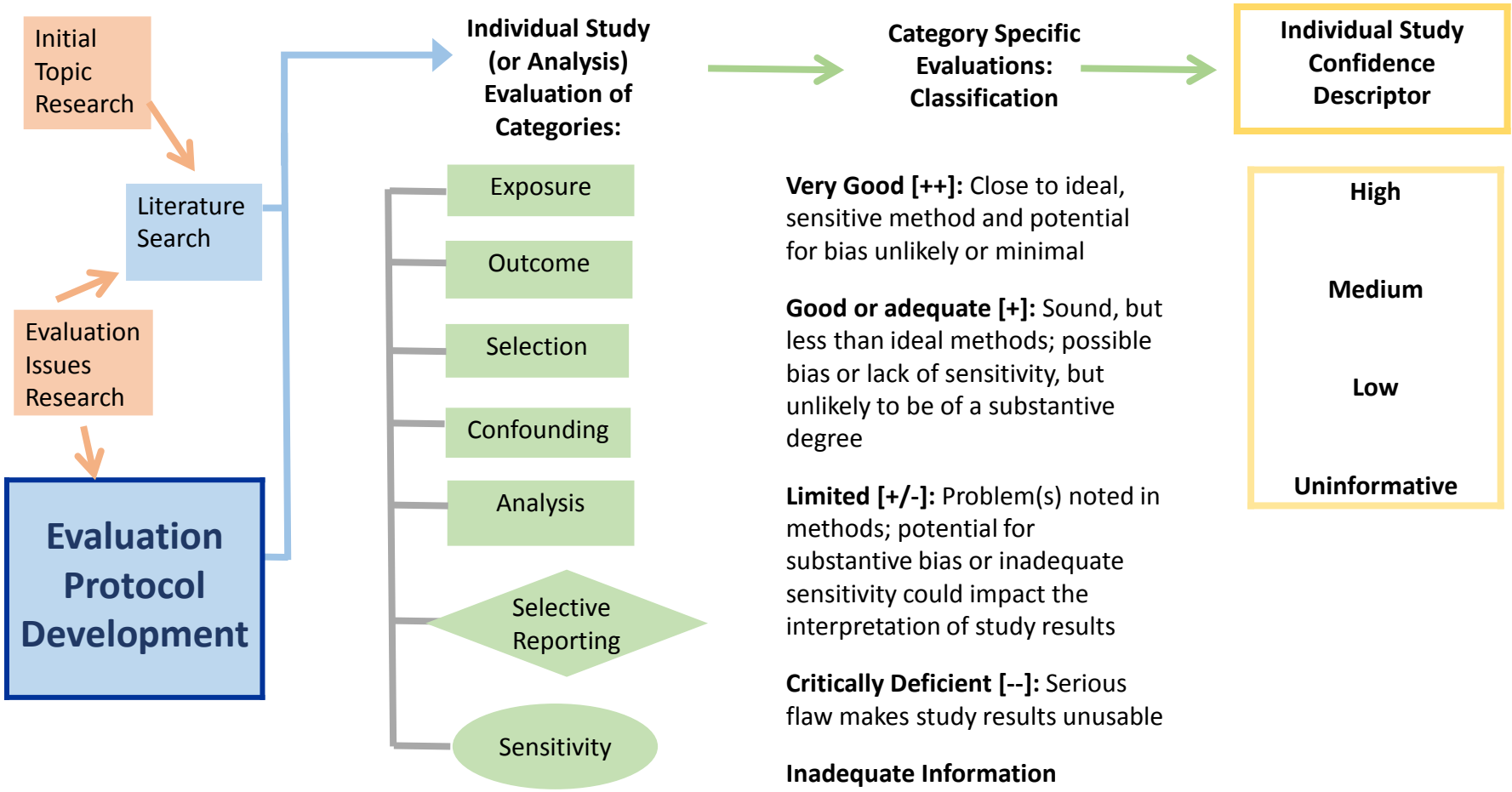
- Draws upon Cochrane ROBINS-I tool:
  - Begin with background research, review of issues in the studies
  - Develop evaluation protocol specifying criteria for classification of specific features; draw upon subject-matter expertise as needed
  - Emphasis on discerning a bias that would be expected to produce a substantive change in the effect estimate; expected direction and magnitude of bias/limitation explicitly considered and incorporated into evaluation, when possible
  - Overall judgment about confidence in study (or specific analysis)

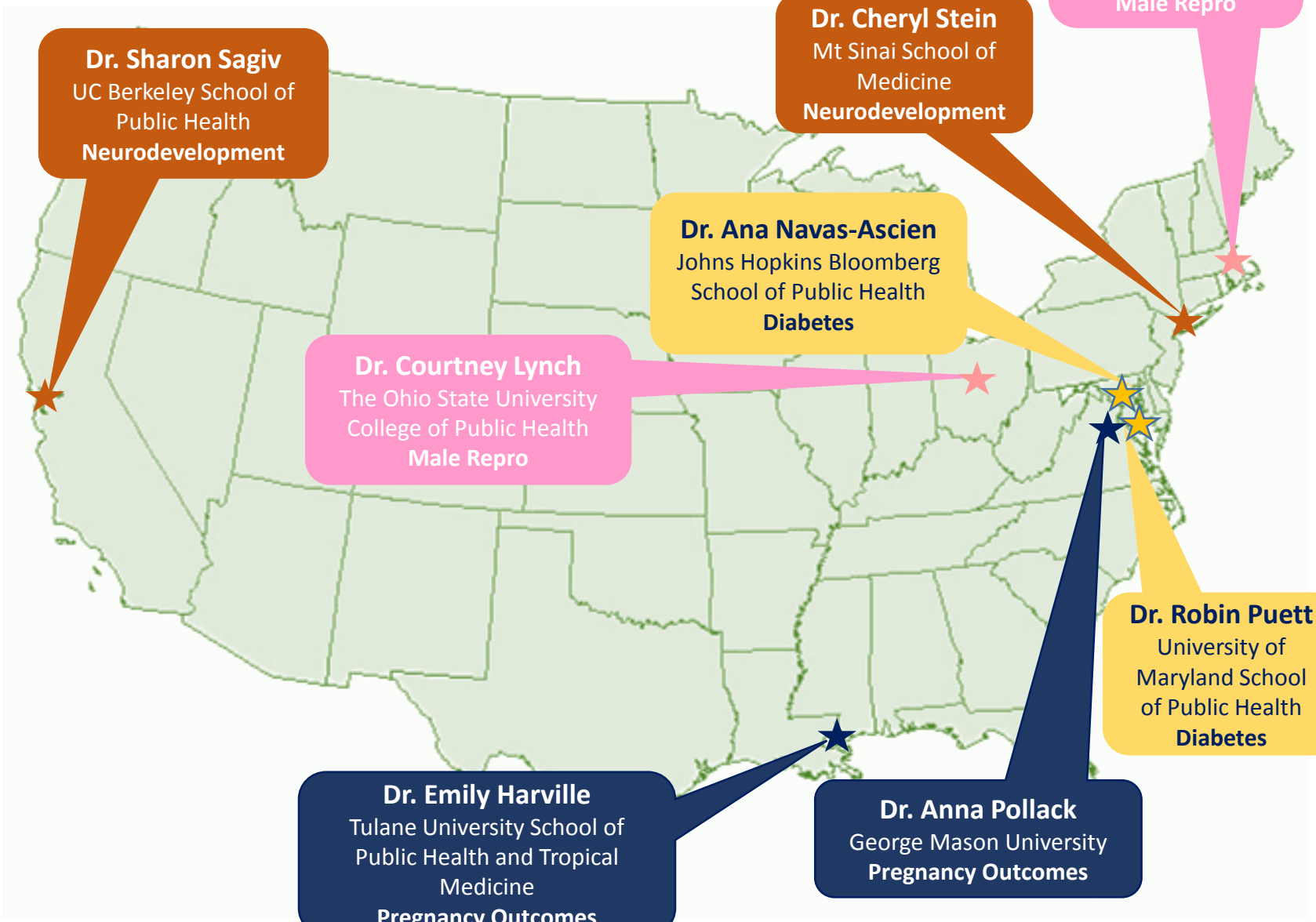
Overview of Epidemiology Study Evaluation



Protocol Development

- 4 teams working on evaluation protocols for 8 outcomes:
  - Diabetes and related measures of hyperglycemia and insulin
  - Pregnancy outcomes
    - preterm birth
    - spontaneous abortion
  - Male reproductive outcomes
    - pubertal development
    - reproductive hormones
    - sperm parameters
    - time to pregnancy/fecundability
  - Neurodevelopment
- Sets of studies drawn primarily from phthalates literature
- Epidemiologists experienced in area of research (but not involved in phthalates studies)

Epidemiology Protocol Teams



Process and Progress

- Background material
  - ROBINS-I handbook
  - Description of IRIS procedures for epidemiology evaluation
  - 6-10 example articles

- Series of phone meetings
  - What is “ideal” study with respect to…outcome ascertainment, participant selection, confounding, analysis?
  - What would be a “critical deficiency” with respect to….
  - How would you classify levels in between those “top” and “bottom” levels?

- Phase 1 testing completed or in progress

Protocol Development (example sets of studies)	Phase 1 testing (use by developers)	Phase 2 testing (use by people not involved in development)

Lessons

- The terminology of the “classification levels” – number of levels, words and meaning of words – was difficult to standardize (across categories; across outcomes)
- The different levels of complexity of the outcomes (e.g., diabetes versus neurodevelopment) was a strong determinant of the difficulty of the protocol development process
- Similarities in the way each group discussed confounding and analysis domains were noted; these “generic” similarities may be useful as a starting point for the development of future protocols
- Need diversity in the set of studies you are working with to foster identification of all issues in the protocol development process

The Future

- Study evaluation protocols will become part of the preliminary materials released after Problem Formulation, before Toxicological Review draft development
- A protocol for a given outcome in one assessment is a good starting point for protocol use in another assessment
- The development of study evaluation protocols for outcomes other than the 8 discussed here will be easier now that we have examples; e.g. we can draw from confounding and analysis components (similarities)

Protocol Panel Questions

- What were the most difficult aspects of developing a study evaluation protocol, with respect to consideration of epidemiology methods?

- How optimistic or pessimistic are you that the development of this type of protocol will result in a well thought out, well-conducted evaluation of a set of studies?

- How can the protocol development process be more efficient and useful? How can the process be improved? Was there a specific impediment (logistical, or pertaining to methodological issues) that was “rate limiting”?