Expert consensus on neurodevelopmental outcomes in pregnancy pharmacovigilance studies

Rebecca Bromley ClinPsyD, PhD

Paediatric Neuropsychologist & Senior Research Fellow

On behalf of the Expert Working Group

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant nº 821520

Background

- Neurodevelopmental outcomes are the observable postnatal skills/functioning that represent the efficiency of the developing brain.
- Understanding child neurodevelopment following exposure in utero is important:
  - A higher risk medication may be used without optimal counselling for longer
  - Women/ their doctors may avoid optimal treatment due to concerns regarding a lack of evidence
- However, only 25% of PASS studies include neurodevelopmental outcomes[1]

1 Roque Pereira et al 2022. Drug Safety. 45:333–344.

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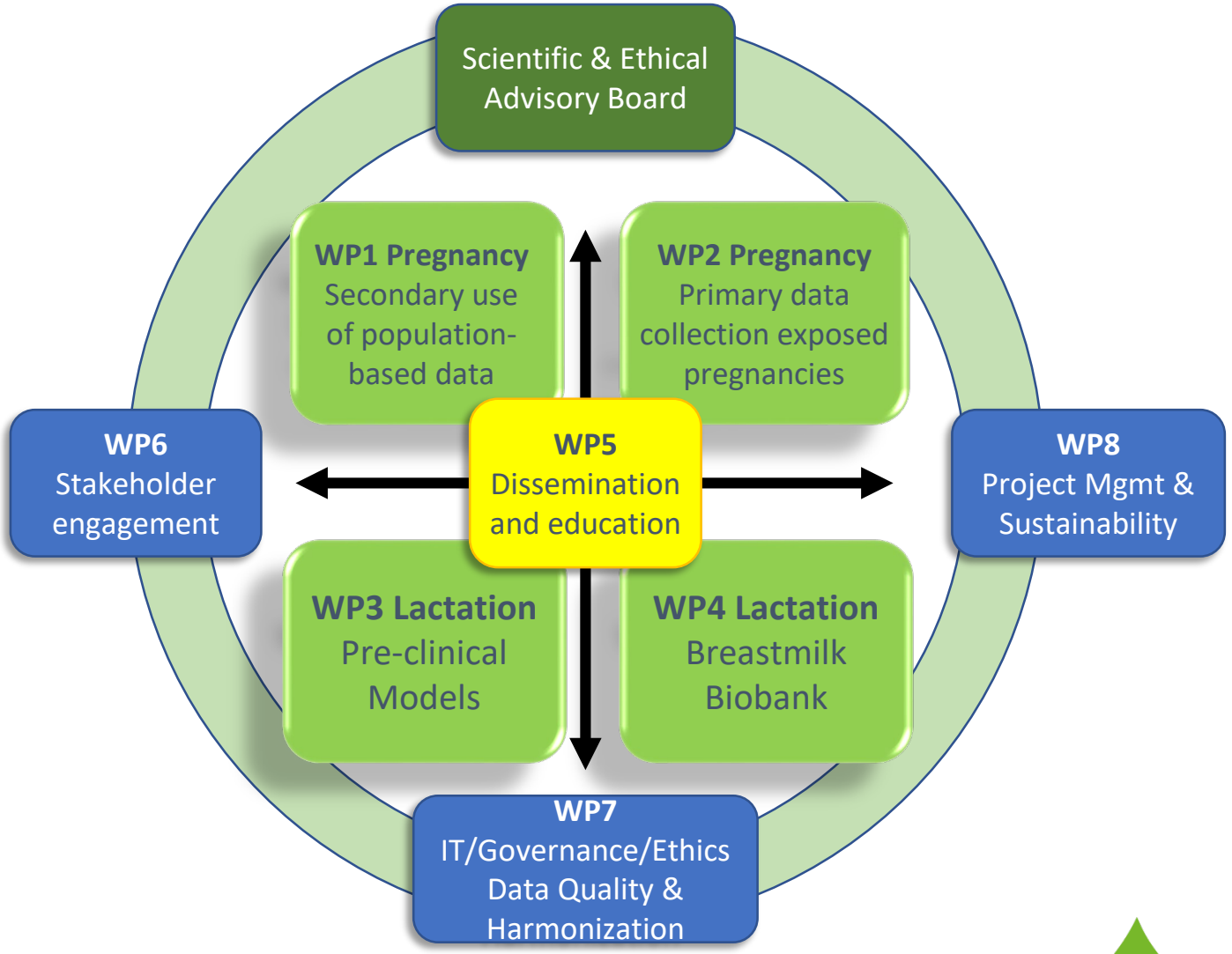
ConcePTION Study



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Overview of our consensus project

WP1 Pregnancy
Secondary use of population-based data

WP2 Pregnancy
Primary data collection exposed pregnancies

Inform longer term outcome work within ConcePTION

Inform wider work in the community; standardised practice, promote inclusion of neurodevelopmental outcomes

Stakeholder input

Delphi method selected

Small organizing group formed

Identified experts

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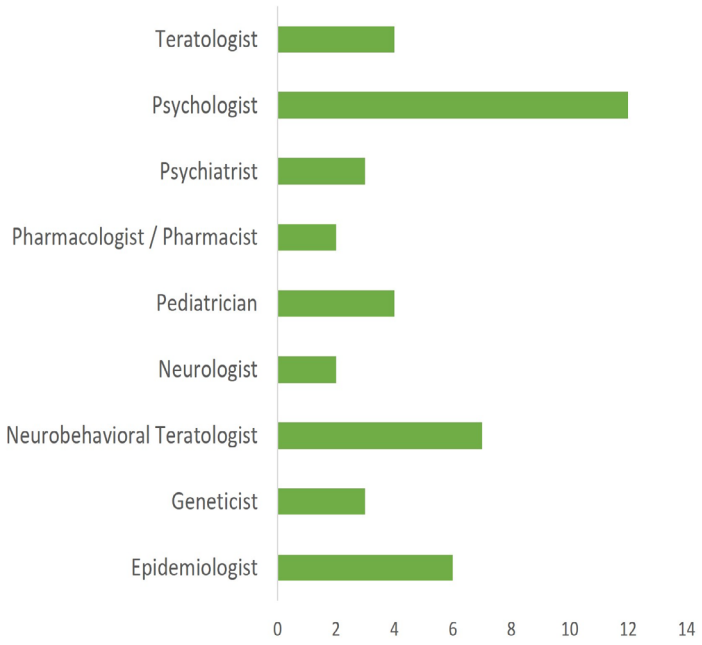
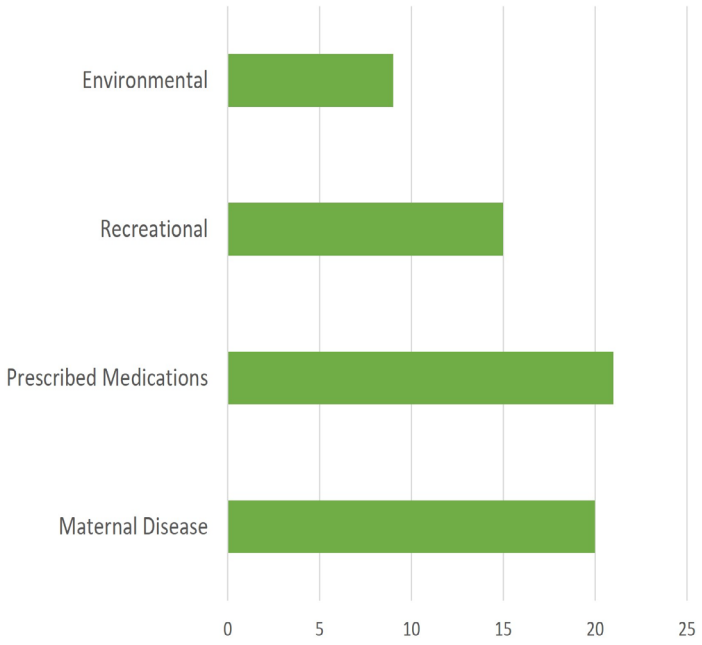
The Experts

a) Participant Professional Background



b) Areas of exposure researched by participants



Note: Participants were able to select multiple responses to describe background and areas of expertise. Some categories represent multiple items collapsed into an over-arching domain.

- Methodological experience
  - Observational cohort studies,
  - Secondary use population dataset studies,
  - Pre-clinical/ animal neurobehavioral teratology studies
- Length of experience
  - Mean years of experience = 22.3 (range: 4-44 years)

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The Experts

Rebecca Bromley, UK
Miriam Bickle Graz, Switzerland
Matthew Bluett-Duncan, UK
Christina Chambers, USA
Per Damkier, Denmark
Kim Dietrich, USA
Helen Dolk, UK
Kimberley Grant, USA
Sarah Mattson, USA
Kim Meador, USA
Hedvig Nordeng, Norway
Tim Oberlander, Canada
Asher Ornoy, Israel
Alexis Revet, France
Jonathan Richardson, UK
Joanne Rovet, USA
Lavinia Schuler-Faccini, Brazil
Erica Smearman, USA
Victoria Simms, UK
Charles Vorhees, USA
Katrina Wide, Sweden
Amanda Wood, Australia
Laura Yates, South Africa
Eivind Ystrom, Norway
T.A Supraja, India
Jane Adams, USA

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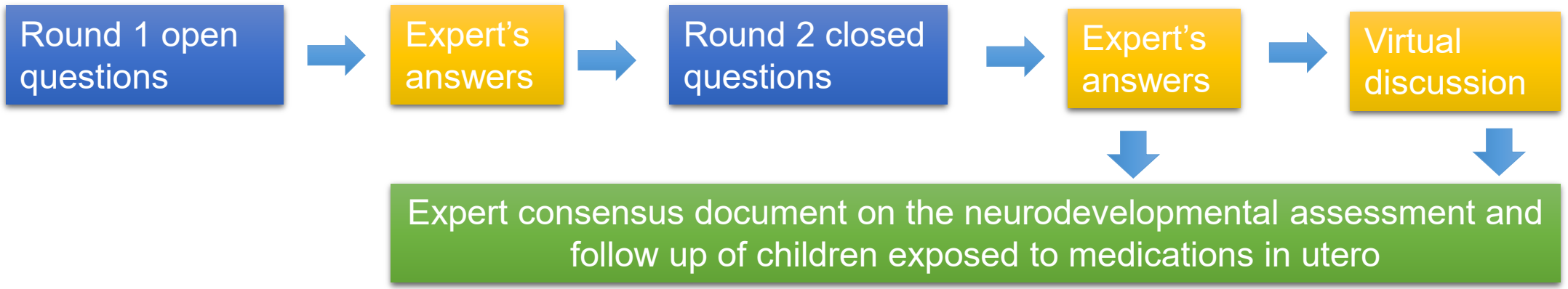
Consensus project overview



Round 1 open questions

Theme: At what point following approval should human neurodevelopmental outcomes be assessed.		
Question 1.	Should child neurodevelopment be investigated routinely for all medications following approval for use in humans?	
	Answer	[Yes/ No]
	F/UP Question	1.1. If yes, please explain why. Are there certain medications that should be prioritized?
	Answer	[Free text]
	F/UP Question	1.2. If no, under what circumstances should child neurodevelopment be investigated?
	Answer	[free text]
Question 2.	Are pre-clinical (animal) study results predictive of human neurodevelopmental outcomes?	
	Answer	Please explain your answer. [Free text]
Theme: Barriers to neurodevelopmental outcome research		
Question 3.	Are there any barriers to researching neurodevelopmental outcomes in children exposed in the womb?	
	Answer	[Yes/ No]
	Answer	If Yes, please describe [Free text]

Theme: core outcome set		
Question 4.	From your experience and the literature which aspects of neurodevelopment can be altered by prenatal exposures (chemical, environmental or medicinal)?	
	Answer	[Free text]
Question 5.	Given the number of brain functions which fall under the term 'neurodevelopment', can a single score or single aspect of neurodevelopment be used to summarize functioning in all other areas?	
	Answer	[Yes/ No]
	F/UP Question	6.1. If yes, please give the name of the outcome you think would provide an overall summary of neurodevelopmental functioning and explain your answer
	Answer	[Free text]
	F/UP Question	6.2 If no, please explain your reasons against having a single outcome to represent functioning across neurodevelopmental functioning
Question 6.	What areas of neurodevelopment would you consider important enough to have needed investigation before any conclusion about risk or safety can be made (e.g. by regulators, prescribers)?	
	Answer	[free text]
Question 7.	What type(s) of investigations into neurodevelopment should be completed before conclusions can be made regarding either risk or safety?	
	Answer	[Free text]

Theme: Optimization of measurement		
Question 8.	What is the optimal way to measure neurodevelopment in a group of children exposed in utero?	
	Answer	[Free text]
Question 9.	We are looking to understand your views on the optimal age of assessment. At what age should the investigation of neurodevelopmental outcomes start?	
	Answer	Please explain your answer: [Free text]
	FU Question	At what age should the investigation of neurodevelopmental outcomes in exposed cohorts end?
	Answer	Please explain your answer: [Free text]
	FU Question	At what interval should longitudinal follow up studies assess neurodevelopment?
	Answer	Please explain your answer: [Free text]
	FU Question	Would the recommended interval of assessment be different for exposures where there were early deviations in developmental trajectories versus those where development was consistent early on to control children?
	Answer	Please explain your answer: [Free text]
Question 10.	There are a large number of variables which positively and negatively influence child neurodevelopmental trajectories. From your experience and the literature, what variables are important to adjust for?	
	Answer	[Free text]
Question 11.	From your experience and the literature, what details about the exposure are important to record and consider?	
	Answer	[Free text]

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Round 1 open questions → Expert's answers

- There was an incredible amount of data provided in the free text round
- Reviewed by core group
- Used to generate Round 2 closed questions

Should child neurodevelopment be investigated routinely for all medications following approval for use in humans? And what are the priorities?

The majority of respondents (77.7%) indicated that child neurodevelopment should be routinely investigated for all medications following approval for use in humans. There was a broad consensus that current system of pharmacovigilance is insufficient and that there is a need for routine screening to identify potential risk, as a minimum, and for the development of a purposeful, comprehensive and long-term approach to assessing neurodevelopmental outcomes. The importance of including routine neurodevelopmental assessment was reflected in observations that the brain is unique in terms of its period of development (and therefore vulnerability), that impairments at this level have persistent and significant effects on individuals, families and wider society, and that while significant, neurodevelopmental alterations are not as readily observable as structural malformations, thereby requiring more purposeful investigation. However, it was acknowledged that a somewhat pragmatic and targeted approach might be required under certain circumstances. Respondents also highlighted a number of factors or medication characteristics which could help to guide investigations to areas which require more focused or intensive study.

Please rate the extent to which you agree or disagree with the importance of each of the following factors in selecting particular medications for routine human research:

- Central Nervous System acting medications.

○ *Strongly disagree*	○ *Disagree*	○ *Neither agree nor disagree*	○ *Agree*	○ *Strongly agree*

- Medications with documented impact on the physical development of the fetus (i.e. malformation, dysmorphic facial features, growth restriction).

○ *Strongly disagree*	○ *Disagree*	○ *Neither agree nor disagree*	○ *Agree*	○ *Strongly agree*

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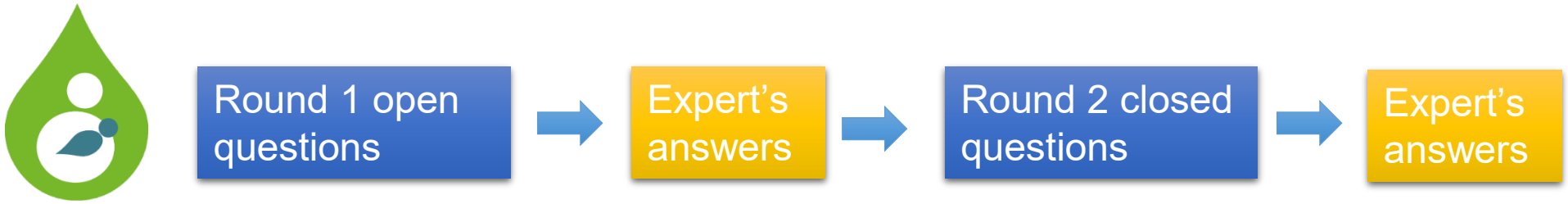

- Generally, there was a large amount of consensus (>4, 80%)
  - Importance
  - Recommendations of when to initiate/ start
  - Range of brain functioning domains should be considered
  - Optimal design
  - Continuation of investigations throughout the period of brain development
  - Barriers

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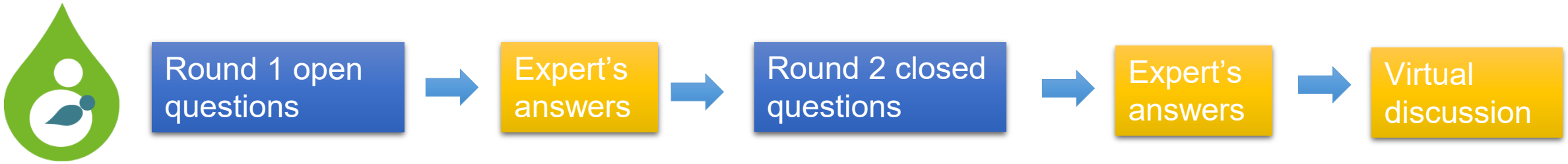

- Given the limit time and the high level of consensus, focused on 5 main topics:

1. Prioritization of medications to investigate
2. Core / central domains for investigation
3. Optimal investigation
4. Confounders and mediator selection
5. Selection of control and comparator groups

- Discussion, additional voting

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Results

11 Recommendations

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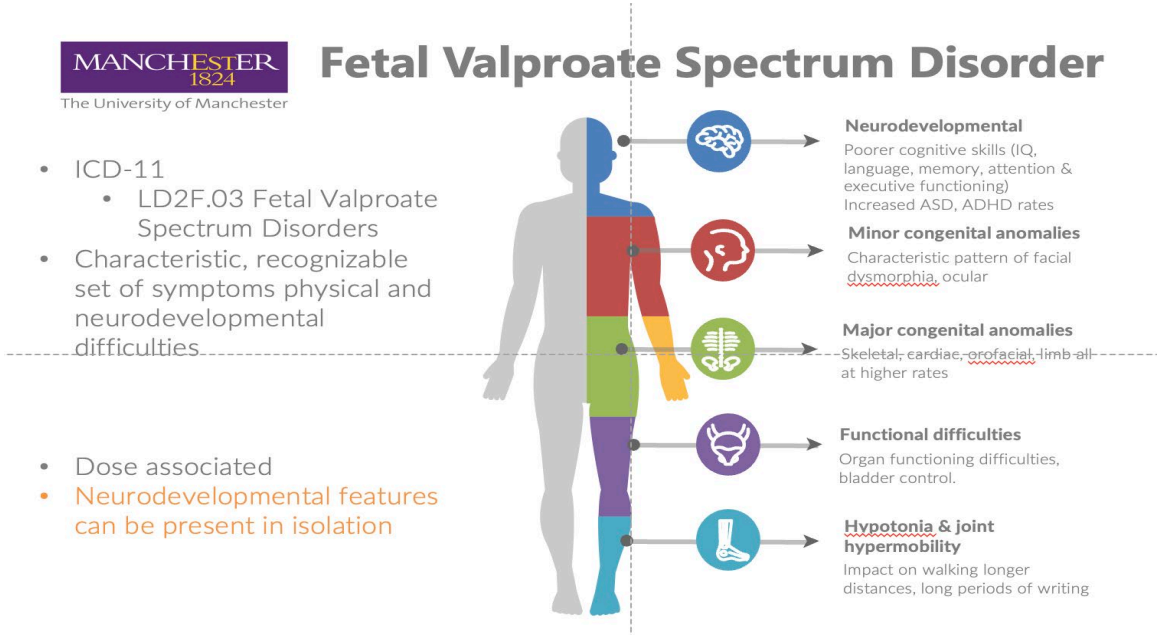
Recommendation 1:

Neurodevelopmental outcomes should be integral to pregnancy pharmacovigilance.



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Recommendation 2:

Neurodevelopmental investigations should automatically be part of the PregPV initiatives for a medication where one or more apply:

- It is mechanistically plausible for the medication to be associated with an increased risk or it belongs to a class of medications where effects have been observed (e.g., central nervous system acting medications).
- There is evidence (preclinical or human data) of a higher risk to physical (e.g., structural anomalies) development.
- There is evidence (preclinical or human data) of a higher risk to brain development.
- The medication is likely to be widely used among women of childbearing potential.

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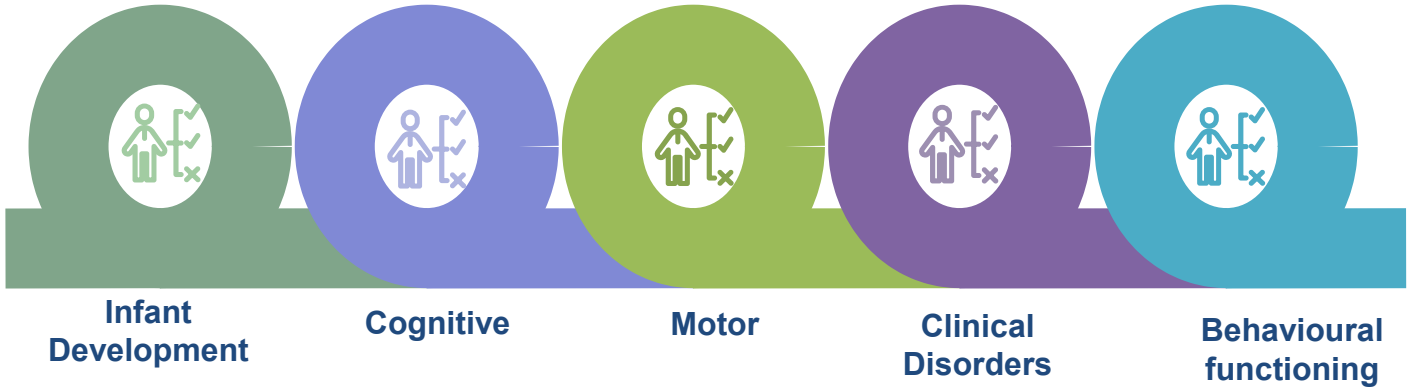
Recommendation 3:

An evidence base must include assessment of these expert agreed neurodevelopmental functions. These include cognitive, motor, behaviour and emotional functioning as well as clinical disorders and educational outcomes.



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Recommendation 4:

Neurodevelopmental outcomes are diverse and require different measurement approaches. Use of a standardized set of direct assessments, by trained assessors blinded to exposure status for the whole cohort receives the highest recommendation in terms of measurement sensitivity.

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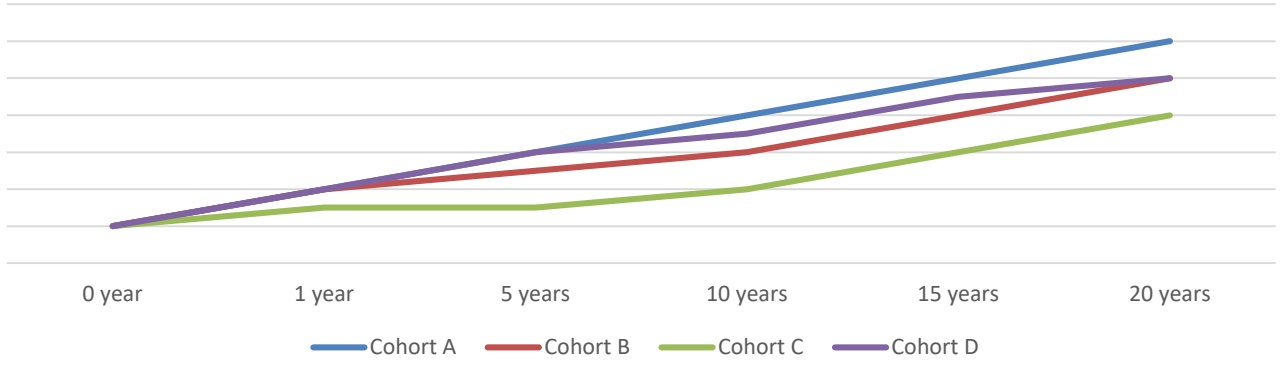
Recommendation 6:

The investigation of neurodevelopmental outcomes should start in infancy with an extended period of investigation into adolescence. Investigation or sampling intervals should be more frequent during periods of rapid development or after signals of early developmental deviations.



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Recommendations 5,7-11:

Exposure variables, aspects of optimal study design, reporting of results, barriers.

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EDITED BY
Helga Zoega,
University of New South Wales, Australia

REVIEWED BY
Jonathan Brett,
University of New South Wales, Australia
Erin Kelty,
University of Western Australia, Australia
Sarah Donald,
University of Otago, New Zealand
Adrienne Chan,
The University of Hong Kong, Hong Kong SAR, China
Wojciech Hanke,
Nofer Institute of Occupational Medicine, Poland

*CORRESPONDENCE

Expert consensus on neurodevelopmental outcomes in pregnancy pharmacovigilance studies

R. L. Bromley[1,2]*, M. Bickle Graz[3], M. Bluett-Duncan[1], C. Chambers[4], P. Damkier[5], K. Dietrich[6], H. Dolk[7], K. Grant[8], S. Mattson[9], K. J. Meador[10], H. Nordeng[11,12], T. F. Oberlander[13], A. Ornoy[14], A. Revet[15,16], J. Richardson[17], J. Rovet[18,19], L. Schuler-Faccini[20], E. Smearman[21], V. Simms[22], C. Vorhees[23], K. Wide[24], A. Wood[25], L. Yates[26,27], E. Ystrom[28,29], T. A. Supraja[30] and J. Adams[31]

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Summary

- Neurodevelopmental outcomes are important.
- Should be routinely included in PASS where indicated.
- Range of core neurodevelopmental outcomes should be investigated.
- Require different but complimentary methodological approaches.
- Need to address barriers to more groups undertaking this work, to reduce the current latency between medication onset and comprehensive knowledge.

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Thank you to the stakeholders, experts and colleagues who inputted into this.

Thank you for listening.

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