Neurodevelopmental outcomes in children and adults with Fetal Valproate Spectrum Disorder: a contribution from the ConcePTION project

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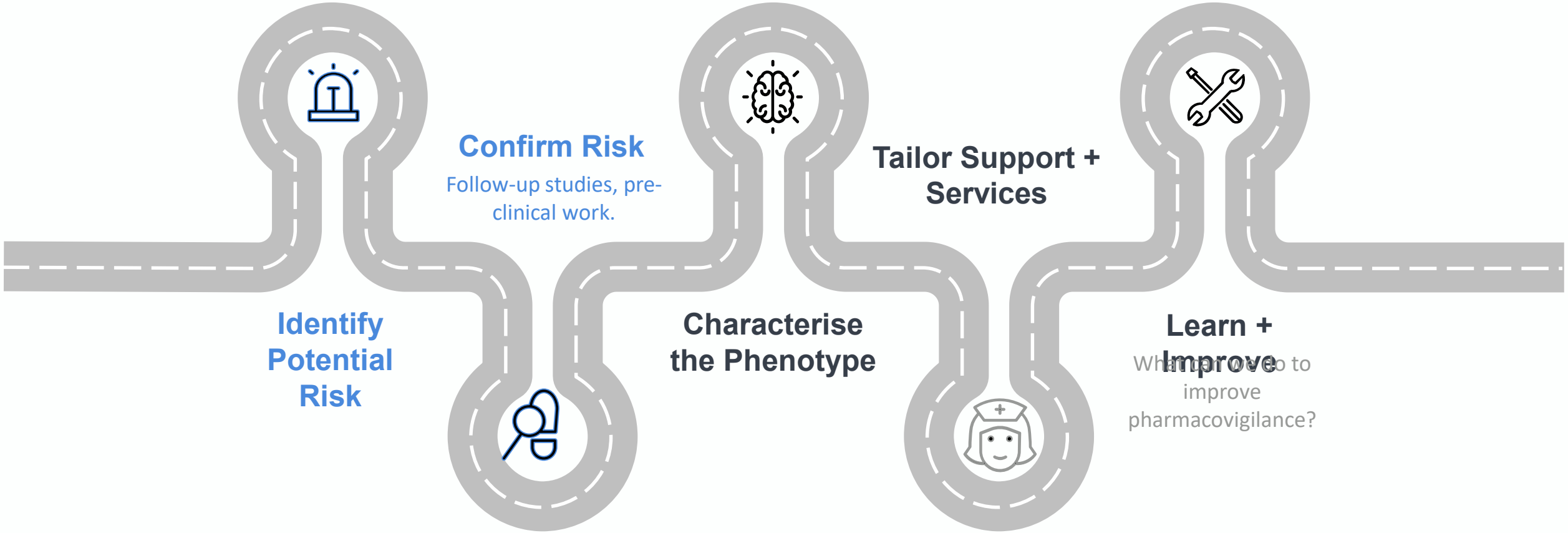
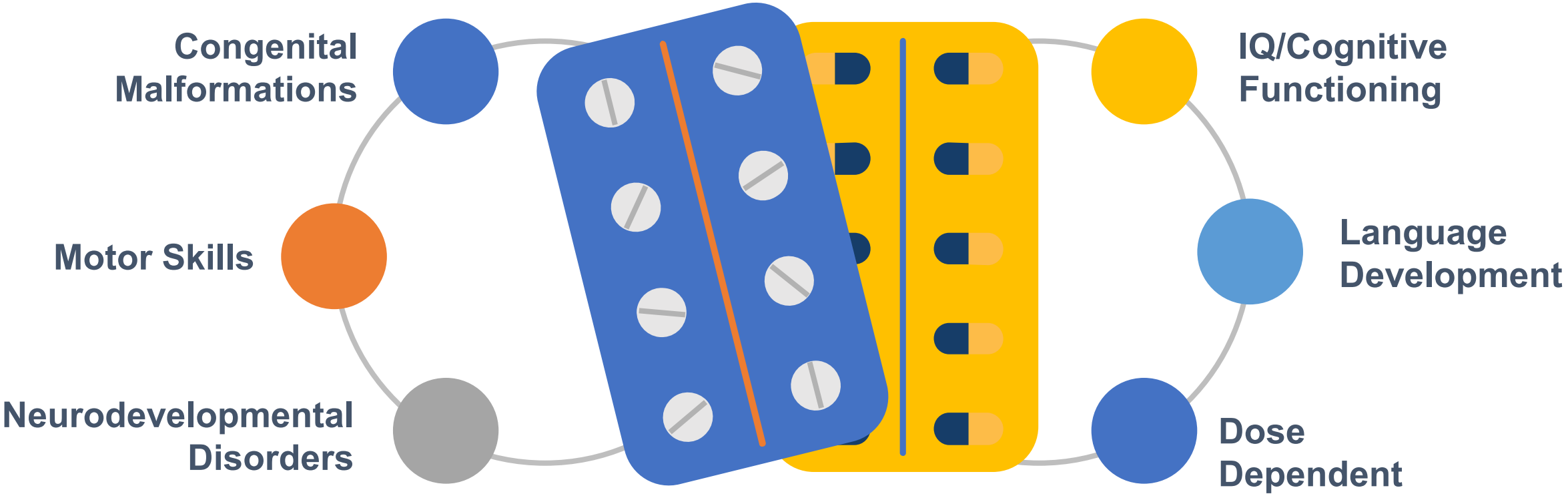
Teratology Roadmap



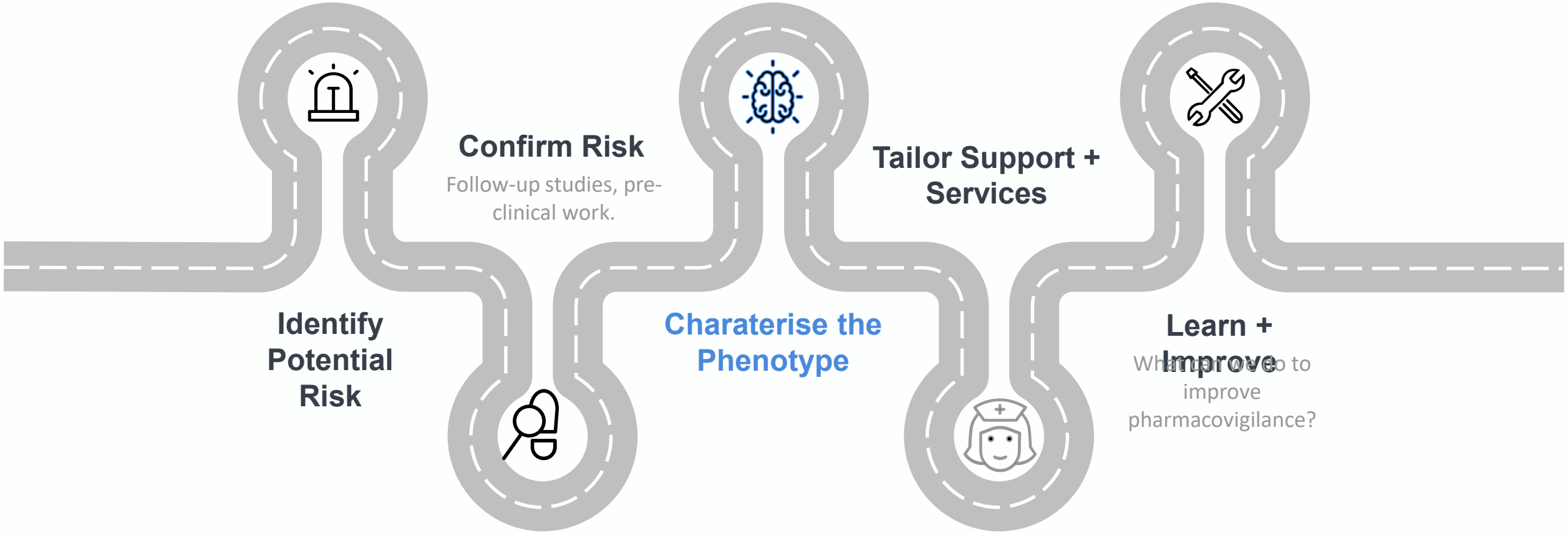
Identifying Risk: Valproate



Increased risk of altered neuronal development and ASD-like phenotypes confirmed via pre-clinical studies of VPA exposure in absence of epilepsy.

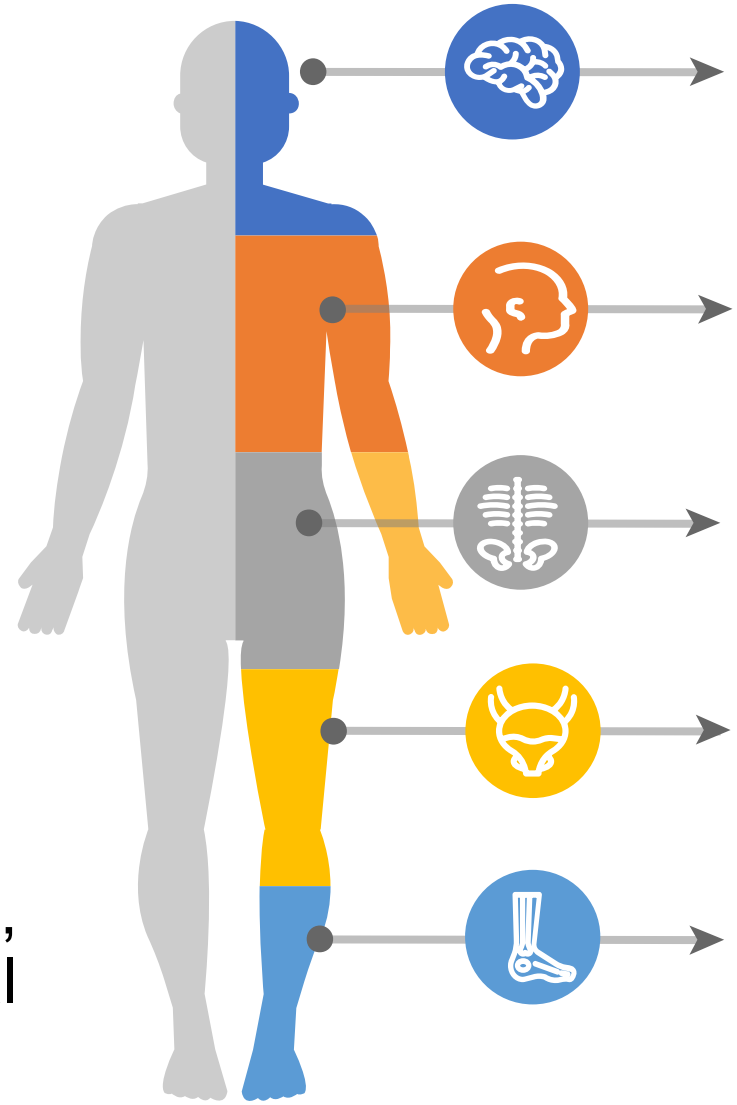
Weston et al., 2016; Clayton-Smith et al., 2019; Bjork et al., 2022; Bromley et al., 2010, 2016; Baker et al., 2015; Meador et al., 2013, 2021; Christensen et al., 2019; Veiby et al., 2013; Huber-Mollema et al., 2020; Shallcross et al., 2011, 2014)

Teratology Roadmap



Fetal Valproate Spectrum Disorder (FVSD)

- ICD-11: LD2F.03
- Diagnosis of exclusion
- Not all exposed are affected or diagnosed.
- Recognisable pattern of physical and neurodevelopmental effects.
- Neurodevelopmental (ND) effects can be present in isolation.
- But, presence of physical features, heightens the neurodevelopmental risk



Neurodevelopmental
Poorer cognitive skills (IQ, language, memory, attention & executive functioning)
Increased ASD, ADHD rates

Minor congenital anomalies
Characteristic pattern of facial dysmorphia, ocular

Major congenital anomalies
Skeletal, cardiac, orofacial, limb all at higher rates

Functional difficulties
Organ functioning difficulties, bladder control.

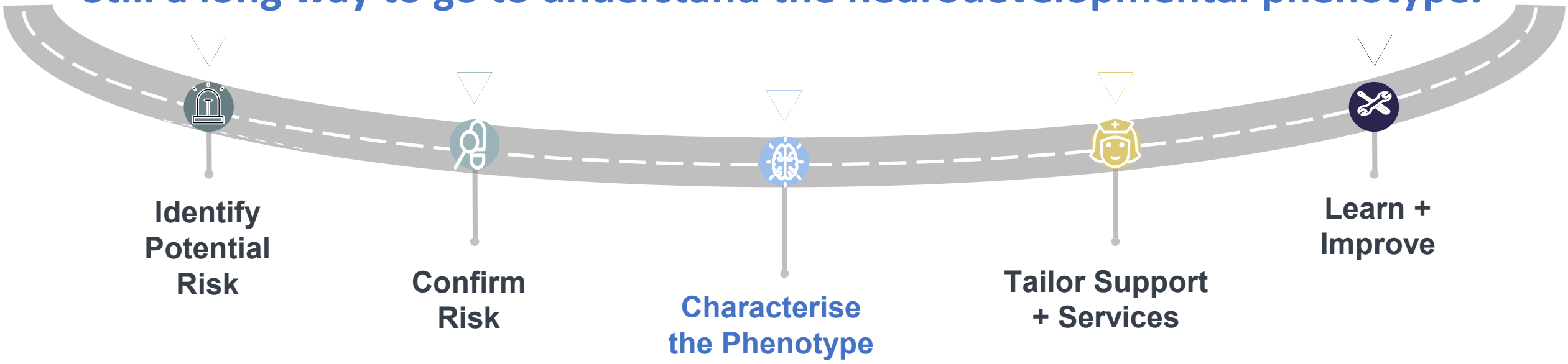
Hypotonia & joint hypermobility
Impact on walking longer distances, long periods of writing

Clayton-Smith et al 2019, Orphanet Journal of Rare Diseases, Bromley et al 2019 Neurotoxicology and Teratology

Understanding the FVSD Phenotype

- Limited research focusing exclusively on those with formal diagnosis of FVSD
- Focus has been on younger aged children.
- Extrapolation from VPA-exposed and childhood data has limitations.

Still a long way to go to understand the neurodevelopmental phenotype.



FVSD Phenotype Study

Neurodevelopmental outcomes in children and adults with Fetal Valproate Spectrum Disorder: a contribution from the ConcePTION project. **Bluett-Duncan M.,** Astill D., Charbak R., Clayton-Smith J., Cole S., Cook P. A., Cozens J., Keely K., Morris J., Mukherjee R., Murphy E., Turnpenny P., Williams J., Wood A. G., Yates L. M., Bromley R. L. **Neurotoxicology and Teratology.** *Under Review.*

Research Aims:

- To delineate the neurodevelopmental phenotype of older children and young adults with FVSD.
- To assess sensitivity of Q'aire set in a known neurobehavioural teratogen.

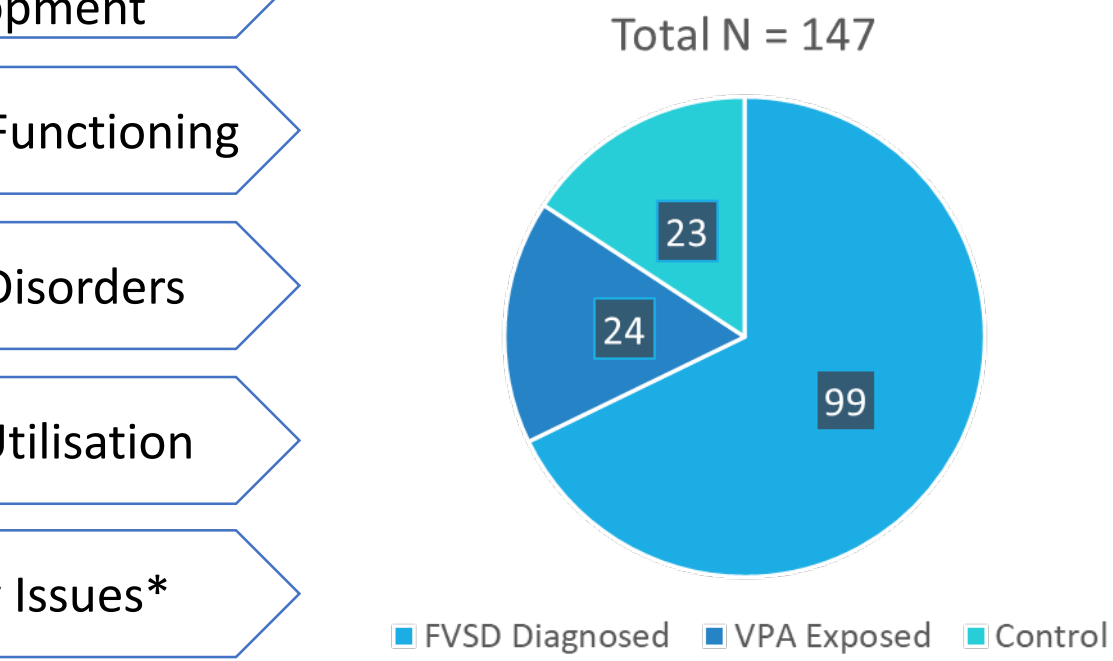
Study Design

- Co-designed in collaboration with PPI (family groups/charities) and clinical/academic experts.
- Cross-sectional, questionnaire-based study relying on parental reports of development.
- Opportunistic sampling via family groups/social media.

FVSD Phenotype Study

- Cognitive Development
- Academic Functioning
- Clinical Disorders
- Service Utilisation
- Sensory Issues*
- Psychosocial
- Physical Health

Groups: FVSD Diagnosed, VPA Exposed, Non-Exposed

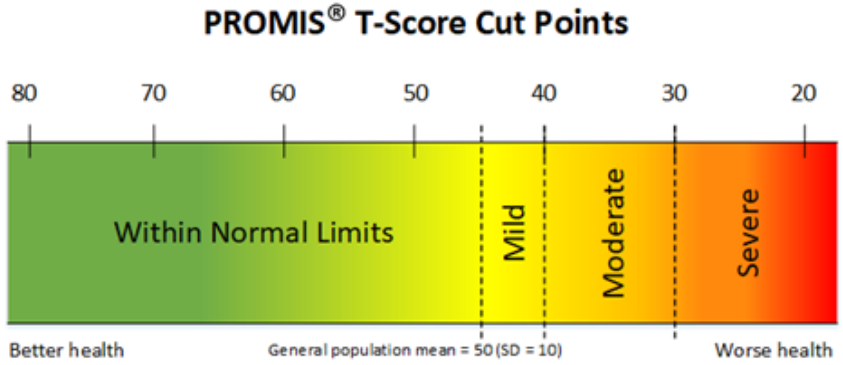


Age (Years)	N	%
<10	16	11.0%
10-19	70	48.3%
20-29	51	35.2%
30-39	8	5.5%

Mean Dose = 1470mg/d
Monotherapy = 75.8%
Polytherapy = 24.2%

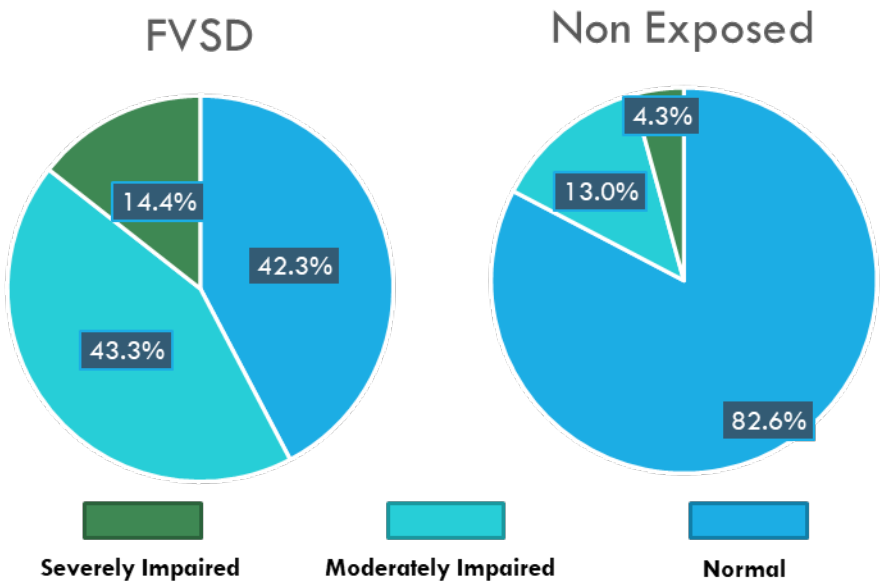
Mean Age = 18.1 years
Range = 7 – 37 years

COGNITIVE DEVELOPMENT



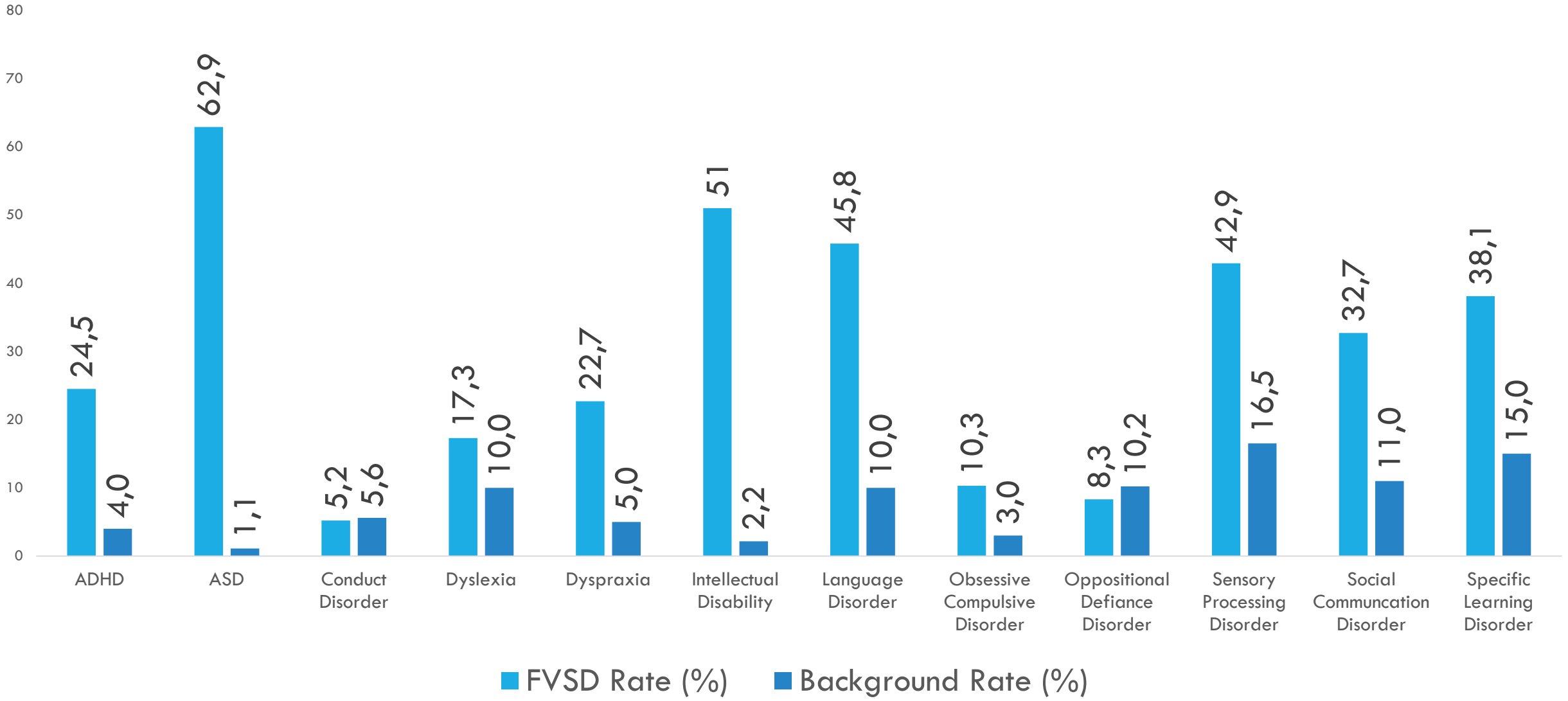
Mean score for individuals with FVSD diagnosis was 38.5, in the **moderately impaired** range.

Only **42.4%** of individuals with FVSD scored within the **"normal"** range.



77.6% of individuals with FVSD received **formal educational support**.

Clinical Disorders



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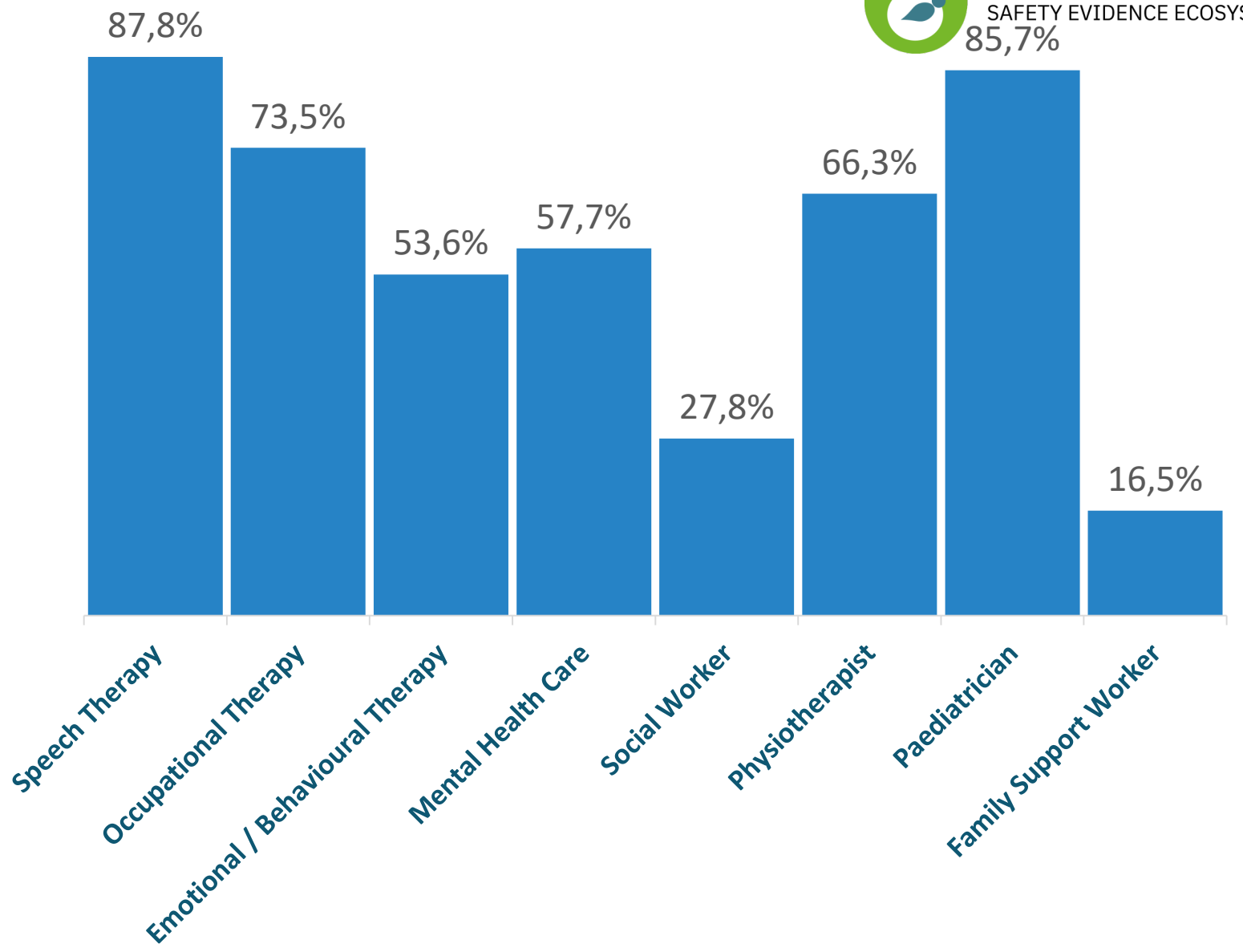
conceptION
SAFETY EVIDENCE ECOSYSTEM

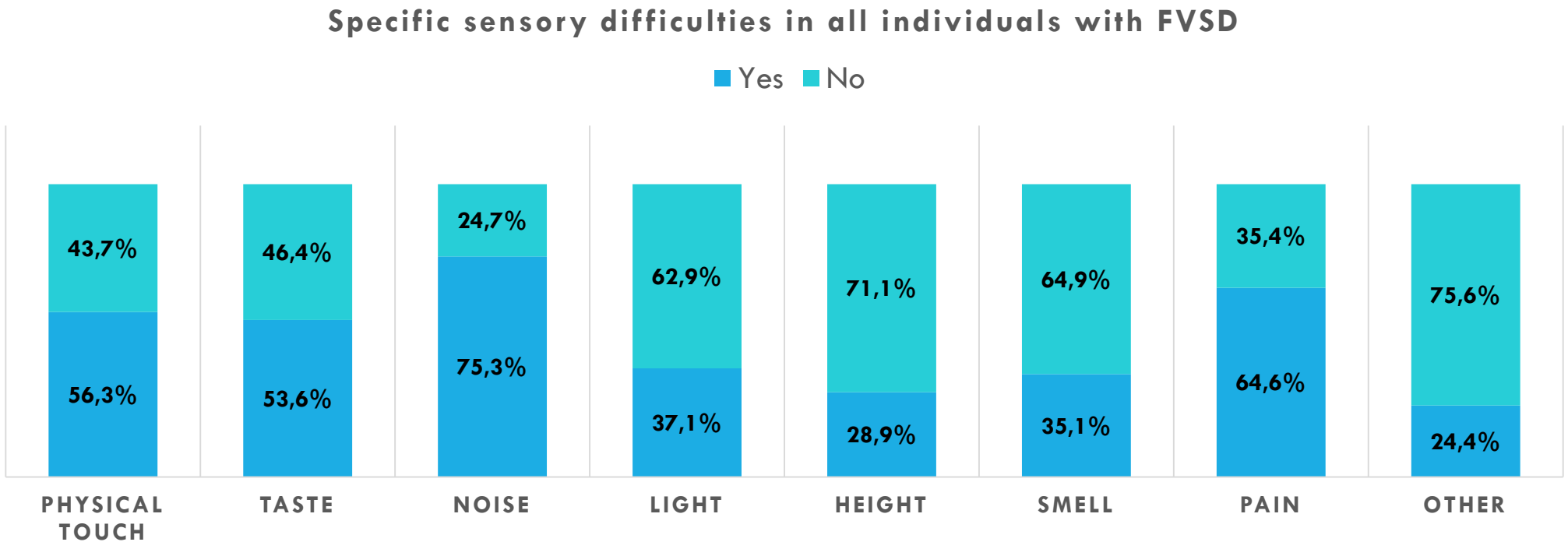
Service Utilisation



Sensory Difficulties

80.6% of individuals with FVSD were reported to have **significant sensory difficulties**.

33.0% = Oversensitive only
6.2% = Under sensitive only
40.2% = Both

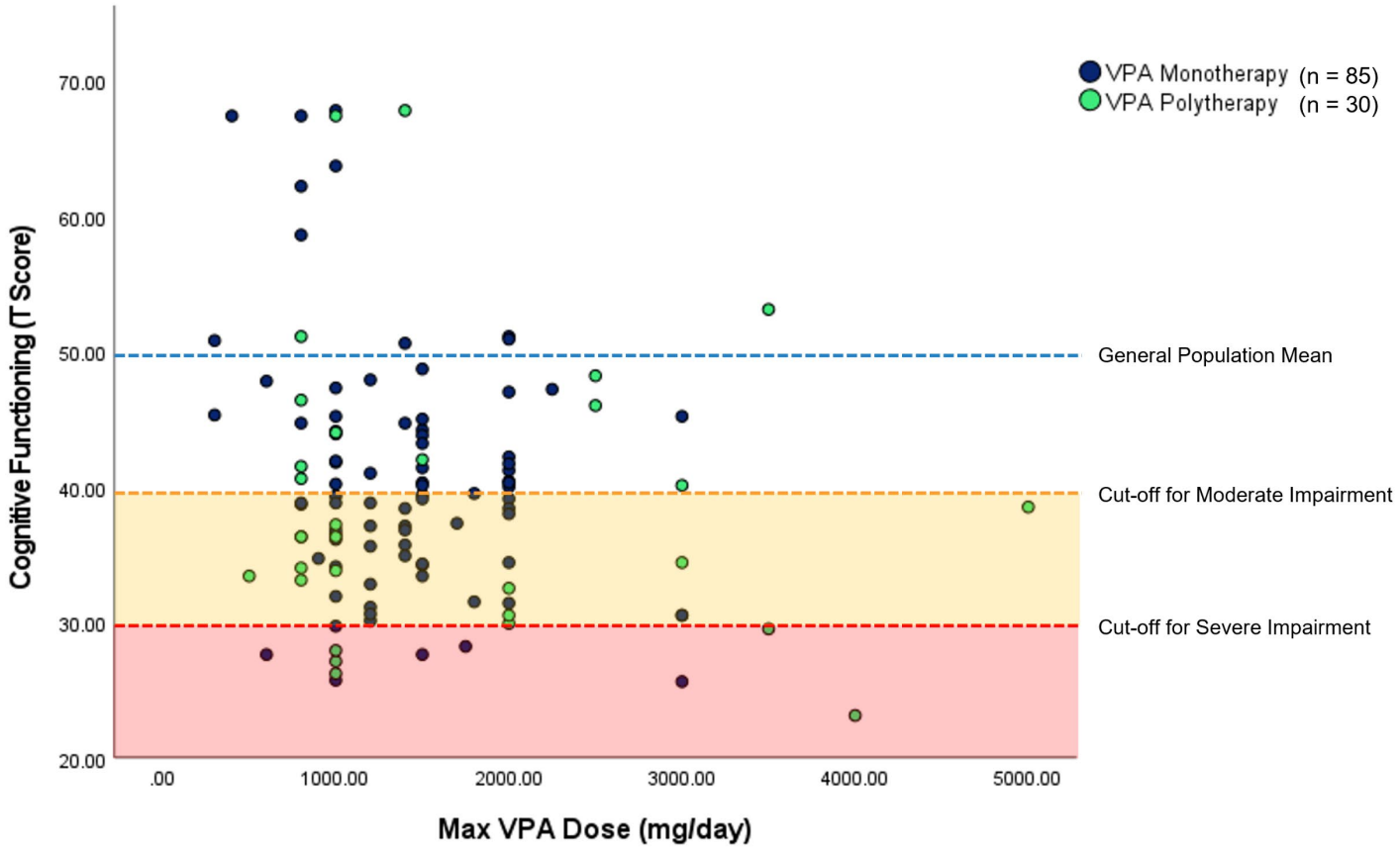


Dose Dependent Effects

- We generally see expected dose effects in children with FVSD.
- But what happens when we have a sample with a **uniformly high dose**?
- We found no statistically significant associations.

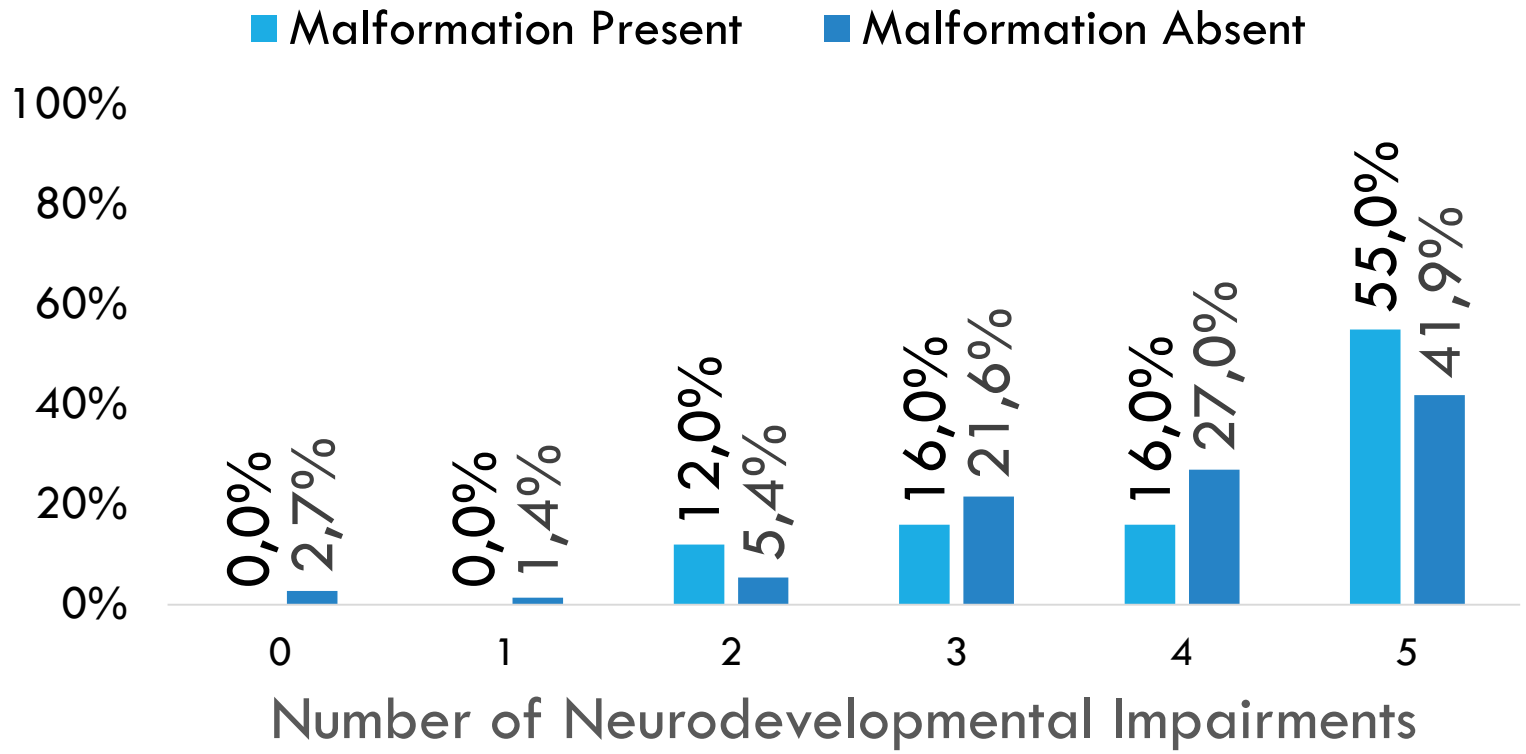
Why might that be the case?

- Lack of variation in dose.
- Majority below the mean score.
- Above a certain threshold the impact of dose may start to plateau.



Physical vs Neurodevelopmental Risk

Can we determine neurodevelopmental risk based on presence or absence of CAs?



Neurodevelopmental impairment appears to be common in children and young adults with FVSD regardless of whether they have any reported congenital anomalies.

Strengths & Limitations

Limitations

- Could not confirm FVSD diagnostic status.
- Parent-report open to bias.
- Opportunistic sampling may bias toward more severe presentations.
- Small control group limited comparisons, but not a risk study.

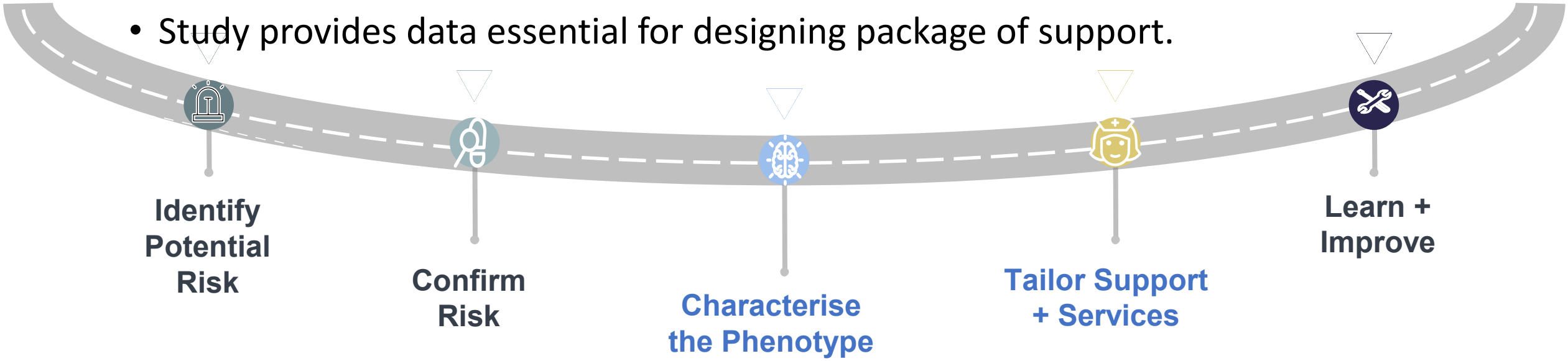
Strengths

- First study to explore wide range of neurodevelopmental outcomes in this group.
- Largest cohort of individuals with FVSD.
- Study was co-designed with families and experts by experience.

Clinical Implications

Understanding the phenotype & improving services

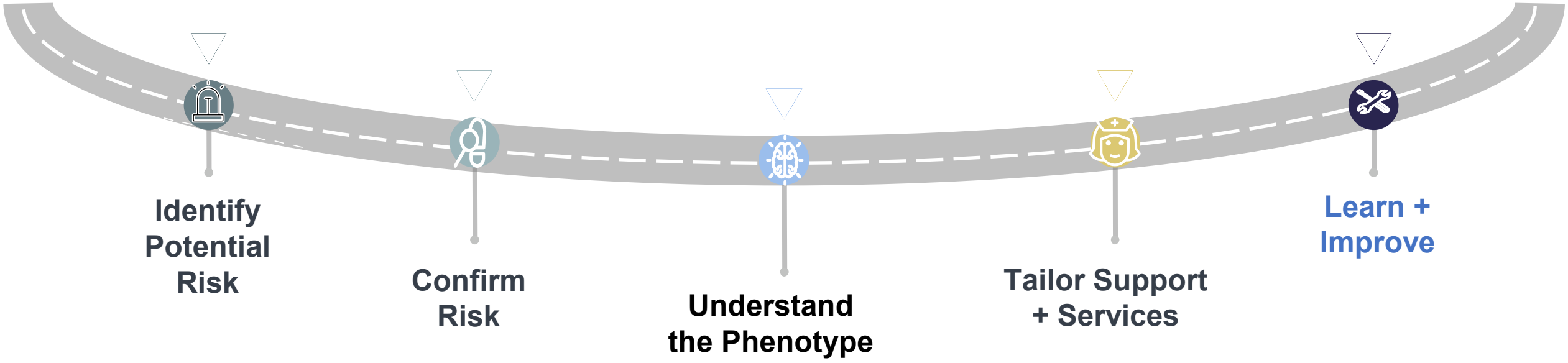
- Older individuals with FVSD continue to experience a range of difficulties
- Further clinical studies required to confirm pattern of impairment.
- Wide range of difficulties, clinical disorders & services demonstrates variety of specialist services required to support individuals as they get older.
- Study provides data essential for designing package of support.



Implications for Pharmacovigilance

What can we learn for the future?

- Substantial neurodevelopmental impairment present without physical symptoms.
- Cannot rule out neurodevelopmental effects at birth.
- Systematic & routine long-term follow-up of potential teratogens essential.



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- Jo Cozens, OACS
- Karen Keely, OACS Ireland
- Jacki Morris, FACS NZ
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- Professor Penny Cook, Professor of Public Health
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