Protocol: Screening and Treatment for Developmental Delay in Early Childhood

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Section I. Purpose and Background

A 2001 Statistics Canada report stated that developmental delay is the most common disability in children aged 0 to 4 years in Canada, with 1.1% experiencing developmental delay.[1] More recent surveys suggest that 1% to 3% of children are affected with global developmental delay and 5-10% have a delay in a single domain.[2,3] Developmental delay is a delay in any one of the four developmental domains, whereas global developmental delay in early childhood is defined as a significant delay (ie: ≥25% or 1.5-2 standard deviations discrepancy from age-expected milestones) in two or more of the four main developmental domains: 1. gross and fine motor skills, 2. speech and language, 3. social and personal and activities of daily living, and 4. performance and cognition.[2,4] Children with global developmental delay often develop learning, behavioural, or emotional problems and may be at higher risk for other health problems.[5] It has been reported that developmental delay in some children can be improved with early identification and early intervention.[2,5,6] Interventions can include parenting programs, early learning centres, speech and language programs, and physical or occupational therapy.[7,8] Interventions may influence school readiness, which in turn could increase rate of high school graduation, which in turn could increase employability.[9,10] Finally, lower IQ is associated with higher all-cause mortality – raising the hypothesis that interventions which increase IQ may also lead to reduced mortality in adulthood.[11]

In Canada, Ontario has implemented an enhanced 18 month well-baby visit, which includes using the Nipissing District Developmental Screen (NDDS) to screen for global developmental delays.[5,12] The implementation of an enhanced well-baby visit has been supported by the Canadian Paediatric Society (CPS).[8]

Screening for developmental delay was identified by family physicians as a topic of interest, especially because there is a perceived lack of resources available for interventions directed at management of developmental delay. Such interventions could be either initiated or monitored at the level of primary care. In addition, timely access to consultation for children identified with possible development delay remains an ongoing challenge for family physicians.

This protocol will be used to develop a systematic review to support recommendations on screening for developmental delay in children aged 1 to 4 years in a primary care setting, as infants younger than 1 year are unlikely to be assessed for developmental delay.

Section II. Previous CTFPHC Recommendations

In 1990, the Canadian Task Force on Preventive Health Care (CTFPHC) recommended using the Preschool Development Questionnaire or other tests to assess development at 2, 4, 6, and 9 months and 2 and 3 years of age (C recommendation) during routine visits for vaccination.[13] The CTFPHC updated their review on well-baby care in 1994 and found fair evidence to assess developmental milestones at each well-baby visit in the guideline on Well-Baby Care in the First 2 Years of Life (B recommendation).[14] This recommendation was based on evidence that an enriched environment may improve developmental delay that is due to lack of stimulation. The 1994 CTFPHC recommendation on Preschool

Screening for Developmental Problems[15] recommended against the use of the Denver Developmental Screening Test[16] in asymptomatic preschool children. There was insufficient evidence for other screening tools. No other Canadian national screening guidelines were identified on screening for developmental delay.

Section III. Scan of Changes in Clinical Practice since Previous Recommendation

Since the publication of the CTFPHC guidance in 1994, other guidance has been published by other organizations.

Canadian organizations

In 2005, an Expert Panel on the 18-Month Well Baby Visit recommended that Ontario provide an enhanced 18-month well baby visit including a developmental review and evaluation using NDDS and the Rourke Baby Record (a health supervision guide).[5] A fee code was introduced in 2009 in Ontario following the Expert Panel report, and although this has increased the uptake of screening, a follow-up report states that uptake of the recommendation is not ideal with 38.2% of eligible children receiving screening in 2010.[17] A 2011 Canadian national scan indicated that most provinces are interested in 18-month monitoring and some provinces (Alberta, Manitoba, Nova Scotia, Saskatchewan) are undertaking or have completed pilot programs of screening.

The Canadian Paediatric Society (CPS) issued a position statement in 2011 supporting an enhanced 18-month well-baby visit.[8] The CPS suggests that the 18-month well baby visit is the optimal time to assess development as it is a crucial time in development (when issues such as child care, behaviour management, nutrition, and sleep are prominent) and may be the last scheduled visit for immunizations with the primary care provider before children begin school. The CPS recommends strengthening the early childhood development system by having physicians incorporate a health supervision guide (such as the Rourke Baby Record) and a developmental screening tool (such as NDDS[12], Ages and Stages Questionnaire [ASQ][18] or Parents' Evaluation of Developmental Status [PEDS][19]). The CPS also recommends that practitioners screen for parental morbidities (such as mental health problems or illnesses), promote early literacy activities, and provide information about resources in the community for early childhood development.

Guidelines from international organizations

In 2006, the United States Preventive Services Task Force (USPSTF) assessed screening for speech and language delay in preschool children and found insufficient evidence for the use of screening instruments in children up to 5 years of age to detect speech and language delay in primary care.[20] The USPSTF is currently updating the evidence review for this guideline.[21]

The merits of screening for autism have been examined by The Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Health and Care Excellence (NICE). SIGN recommended against population screening for autism spectrum disorders (ASD) in 2007.[22] SIGN states that as part of child health surveillance, health professionals can be aware of early signs of ASD and may use M-CHAT

(modified checklist for autism in toddlers)[23] to identify children who may be at risk for autism, while some expert panels such as the American Academy of Pediatrics (AAP) recommends that all children receive autism-specific screening at 18 and 24 months of age. In 2011, NICE recommended that practitioners should take parents' concerns into account when assessing the possibility of developmental delay, and to consider the possibility of autism if there are concerns about development or behaviour.[24] The USPSTF is currently finalizing a research plan for a guideline on screening for ASD in children between the ages of 12 and 36 months.[25] Further details on the guidelines produced by other organizations are reported in Appendix I.

The American Academy for Pediatrics (AAP) recommends screening for developmental delay using a standardized tool at 9, 18 and 24 or 30 months of age[26] and screening for autism at 18 months and 24 months.[27] Rates of referral to early intervention following failed screening were assessed following a pilot program based on the AAP recommendations, and results showed that these rates varied (from 48% to 78%) and did not meet the recommendation that every child who fails developmental delay screening be referred for early intervention. The screening test that was used differed across the various centres involved in the pilot project, and included PEDS, ASQ-II, and Denver.[28]

Section IV. Review Approach

This review will be conducted by the Evidence Review and Synthesis Centre (ERSC) at McMaster University, which will conduct a systematic literature search to address the effectiveness of screening for developmental delay and the test characteristics of commonly used screening tests. The screening tests include general tests that are used to assess developmental delay as well as tests for a single domain. This will be a staged review, and stage I will include the identification of studies that address screening effectiveness in children 1 to 4 years who are not suspected of having developmental delay or at risk.

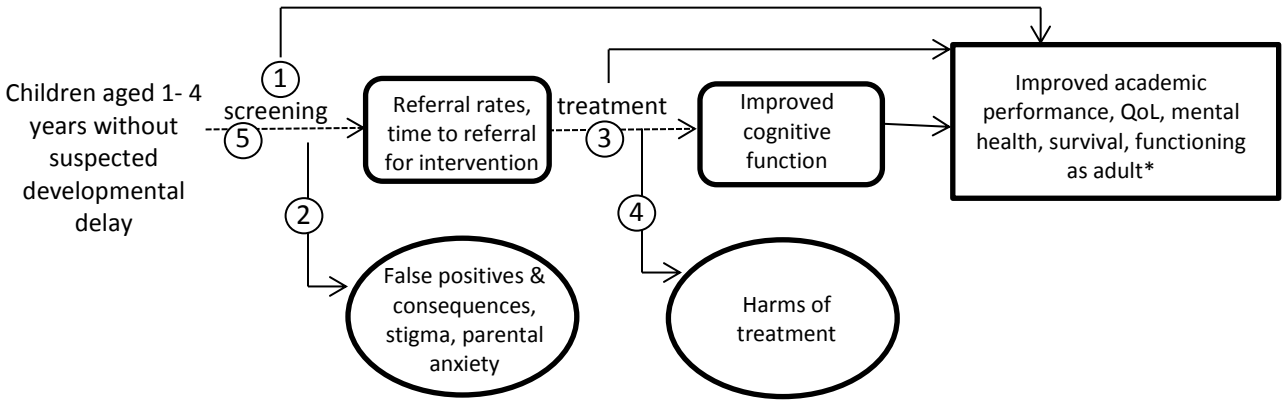
If no good-quality evidence to evaluate screening for developmental delay is identified in stage I, then stage II will be initiated. Stage II will include a search for systematic reviews (or RCTs if no systematic reviews are identified) that address treatment effectiveness, and this indirect evidence may be used to inform a screening recommendation.

Stage III will be conducted if evidence about benefit of screening is identified in the prior stages. This stage will involve a search for the test characteristics of validated screening tests or tests in use that assess developmental delay in the same population.

Identifying studies for possible inclusion and exclusion will be done independently by two reviewers. At the title and abstract level, any citation that is selected for inclusion by either reviewer will move to full text review. At that level any disagreement will be discussed between reviewers and a third party will be involved to help reach consensus, as necessary. Risk of bias will be assessed using the Cochrane risk of bias framework (key questions 1 – 4) or QUADAS II (Quality of Diagnostic Accuracy Studies; key question 5) with decisions made by one reviewer and a second reviewer verifying those decisions. Disagreements will be resolved through consensus between the two reviewers. In the case of disagreements that cannot be resolved, a third party will be asked to arbitrate. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to assess the strength and the

quality of evidence using GRADEPro software. Individual study quality will be assessed for risk of bias due to limitations in design, indirectness, inconsistency of findings, imprecision, publication bias and other potential bias. Meta-analysis will be conducted where appropriate. The evidence review and recommendation statement will be peer-reviewed by individual reviewers as well as relevant organizations.

Analytic Framework and Key Questions



Key Questions

Stage I:

1. What is the effectiveness of screening children aged 1 to 4 years without suspected developmental delay to improve outcomes*?
    a. What is the optimal interval for screening for developmental delay?
2. What is the incidence of harms of screening children aged 1 to 4 years without suspected developmental delay?

Stage II:

3. What is the effectiveness of treatment for children diagnosed with developmental delay to improve outcomes?
4. What are the harms of treatment for children diagnosed with developmental delay?

Stage III:

5. What is the sensitivity, specificity, positive and negative predictive values, and likelihood ratios of the various screening tests to assess developmental delay in children aged 1 to 4 years who are not already suspected of having developmental delay?

Contextual Questions

1. What is the cost-effectiveness and feasibility of screening for developmental delay in preschool children aged 1 to 4 years?

* functioning as an adult includes outcomes such as employment, criminality, independence

2. What are parent or primary caregiver values and preferences for screening for developmental delay in preschool children aged 1 to 4 years?
3. What is the evidence for a higher burden of disease, a differential treatment response, differential performance of screening for developmental delay, or barriers to implementation of screening for developmental delay in subgroups? Subgroups include: Aboriginal population, rural or remote populations, low socioeconomic status, drug or alcohol dependency, or other ethnic populations.

Literature Search

There are four separate search strategies, the first (Stage I) focuses on screening of developmental delays in children. This search will aim to identify RCTs or controlled cohort studies examining the effectiveness of screening for developmental delay. Observational study designs will be included for the harms question. The second search (Stage II) focuses on treatment for developmental delays. This search will include systematic reviews and RCTs. The Stage III search will focus on identifying the sensitivity, specificity, positive and negative predictive values, and likelihood ratios of the various screening tests to assess developmental delay. This search will include RCTs, controlled cohort studies, and observational studies. The fourth search focuses on the contextual questions, a search of selected databases for the last 5 years. All four search strategies combine subject heading and text word terms for developmental delays and screening adapted to be appropriate for each database. The fourth search will be a grey literature search of websites to find relevant Canadian statistics. As well, reference lists of all relevant systematic reviews and included studies will be searched.

Analysis Plan

KQ1: Benefits of screening for developmental delay
The data will be analyzed for any screening (that meets inclusion criteria) with the eight outcomes of interest. Eight GRADE tables will potentially be provided for any screen and the outcomes of interest. Extracted data will be analyzed in a metaanalysis when appropriate. In order to complete GRADE, all studies will be assessed for risk of bias (RoB) using the Cochrane RoB tool, directness, precision, consistency and publication bias.

KQ1a: Optimal screening interval
Eight GRADE tables wil potentially be provided with multiple rows of analysis. The actual number of rows cannot be determined until it is know how data are presented in the studies (how many different intervals are assessed).

KQ2: Harms of screening for developmental delay
The data will be analyzed for any screening with the four outcomes of interest. Four GRADE tables will potentially be provided; one for each of the identified harms of interest. Extracted data will be analyzed in a metaanalysis when appropriate. In order to complete GRADE, all studies will be assessed for risk of bias directness, precision, consistency and publication bias. RoB tools: Cochrane Risk of Bias tool for RCTs, Newcastle Ottawa Scale for controlled observational studies, and since there is no tool to assess RoB in non-controlled observational studies these will be Very Low quality for the RoB domain.

The overall analysis will combine studies which report on benefits or harms of screening for general developmental delay with those studies which report on benefits or harms of screening only for delay in specific domains. This analysis will address whether *any eligible form* of screening influences the

outcomes of interest. A separate analysis will be performed based on screening interval to evaluate the optimal interval for screening for developmental delay.

For continuous outcomes such as time to referral, and changes in referral rates, where outcome is reported using the same outcome measure across studies, the DerSimonian and Laird random effects models with inverse variance method will be utilized to generate the summary measures of effect in the form of mean difference (MD) between screening and control arms.

For continuous outcomes such as cognitive function, academic performance, and quality of life etc., where the outcome is assesed using potentially different outcome measures or scales across studies, it is necessary to standardize the results of the studies before comparing them across studies or combining them in a quantitative synthesis. Therefore, we will utilize the DerSimonian and Laird random effects models with inverse variance method to generate the summary measures of effect in the form of standardized mean difference (SMD) between screening and control arm for each outcome. The WG will choose one commonly used tool for each outcome and the SMD will be reverted to mean difference for that one test.

For binary outcomes such as survival, we will utilize the number of events; proportion or percentage data to generate the summary measures of effect in the form of risk ratio (RR) using utilize the DerSimonian and Laird random effects models with inverse variance method.
For Harms of screening outcomes, the false positive rates for screening across studies will pooled using the DerSimonian and Laird random effects models with inverse variance method to generate the summary measures of effect; while the continuous harms such as parental anxiety and stigma etc will be meta-analyzed using mean difference (MD) or standardized mean difference (SMD) approach.

The Cochran's Q (α=0.10) and I^2 statistic will be employed to quantify the statistical heterogeneity between studies, where $p<0.05$ indicates a high level of statistical heterogenity between studies. Sensitivity analyses will be performed on study risk of bias to evaluate statistical stability and effect on statistical heterogeneity.

Appendix II reports the outcomes and summary measure of effect that will be included in the systematic review.

For benefits and harms of treatment (key questions 3 and 4), a review of reviews will be done. A search for systematic reviews on treatment for developmental delay published in the past 5 years will be conducted. Results from systematic reivews that receive high scores (10 or 11/11) on AMSTAR will be reported narratively.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for this review are detailed in Table 1. Outcomes for the screening stage of this review will focus on referrals to early intervention and detection of children with developmental delay, as well as the longer term outcomes such as academic performance and cognitive function. Screening is limited to screening using a general tool such as the NDDS in the primary care setting, excluding screening in daycare or school settings. Children with existing conditions that may be associated with developmental delay will be excluded.

Trials of treatment for developmental delay assess improvements in test scores on various scales measuring cognitive functioning, such as Bayley and Wechsler Intelligence Scale for Children (WISC), which may then be linked to outcomes such as academic performance, quality of life, and survival. Outcomes such as speech and language are not specified as an outcome of interest but will be captured as a component of academic performance and quality of life. Longer term outcomes such as those measured in adolescence or adulthood include employment, criminality, and independence. Treatment of conditions such as attention deficient hyperactivity disorder (ADHD) and conduct disorders are excluded as these are conditions usually identified in school age children. Treatment of hearing and vision problems are also excluded as these are usually detected through specific screening programs. In addition, children with vision or hearing problems will be excluded as these children are generally identified through specific hearing and vision screening tests.

Table 1: Inclusion and exclusion criteria

	INCLUSION	**EXCLUSION**
Patient population	*Screening*: Children aged 1 to 4 years not at high risk (high risk = prematurity; low birth weight; other disorders that may be associated with developmental delays) *Treatment*: children beginning intervention for developmental delay between the ages of 1-6 years Developmental delay = delay in one or more of the domains (gross and fine motor skills; speech and language; social, personal, and activities of daily living; performance and cognition)	*Screening*: Children born prematurely (gestational age less than 37 completed weeks at birth) or with low birth weight (birth weight less than 2,500 g); children with other known disorders that may be associated with or affect development; screening children over the age of 4 years; case finding in children in whom developmental delay is suspected or at high risk for developmental delay; screening for hearing or vision problems (as these are usually identified through specific hearing and vision screening tests) *Treatment*: Children beginning intervention after age 6 years; children with conduct disorders, ADHD (as these disorders are associated with children of school age); children with hearing and vision problems (as these are usually identified through specific hearing and vision screening tests)
Intervention	*Screening*: Any tests, tool, or questionnaire used to screen for developmental delay; including tools for specific domains and tools for general developmental delay *Treatment*: any intervention for developmental delay using behavioral, pharmacological, or psychological interventions	*Screening*: specific tools to identify a delay in a specific aspect of a single domain *Treatment*: interventions initiated over the age of 6 years
Comparator	*Screening*: no screening *Treatment*: no intervention	
Outcome	*Screening*: clinically relevant changes in **referral rates for early intervention**; **time**	

	to referral to early intervention; clinically relevant changes in: **cognitive function** (as measured by the WISC, Bayley, or other validated tests), **academic performance** (measures of academic performance include test scores, grades, grade point average, academic attainment [completion of high school, post-secondary education]), **incidence of mental health conditions** (as defined by DSM-IV: anxiety, depression, oppositional defiant disorder, OCD; can include symptoms of these conditions if a formal diagnosis not made), **overall quality of life, survival, functionality as an adult** (including employment, criminality, and independence) *Screening harms*: **false positives and consequences** (e.g. inappropriate program placement, inappropriate resource use), **parental anxiety**, **stigma** (labeling) *Treatment*: **cognitive function** (as measured by the WISC, Bayley, the Child Behavior Checklist, or other validated tests), **academic performance** (measures of academic performance include test scores, grades, grade point average, academic attainment [completion of high school, post-secondary education]), **incidence of mental health conditions** (as defined by DSM-IV: anxiety, depression, oppositional defiant disorder, OCD; can include symptoms of these conditions if a formal diagnosis not made), overall quality of life, survival, functionality as an adult (including employment, criminality, and independence) *Treatment harms:* any harm associated with treatment for developmental delay	
Setting	Primary care, public health clinics	Screening in school settings, daycare settings, or specialist settings
Study	*Screening*: RCTs, controlled cohort studies,	Uncontrolled observational studies

design	observational studies for harms *Treatment*: systematic reviews, RCTs	

Section V. Planned Schedule and Timeline

- Draft protocol: September 2013
- Final protocol: November 2013
- Draft evidence review: June 2014
- Final evidence review: October 2014
- Draft recommendation statement: October 2014
- Published recommendation statement: April 2015

The literature search will be updated six weeks prior to publication to ensure that the recommendations include all relevant data. In addition, authors of key studies will be contacted to determine if they are planning to release new data from their trials in the immediate future.

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APPENDIX I: Guidelines from other guideline developers

Guideline Group	Guideline Title and questions	Level of Evidence	Evidence Synthesis	Search Strategy	Recommendations
USPSTF, 2006[20]	Screening for speech and language delay in preschool children Questions: Does screening for speech and language delay result in improved speech and language as well as improved other non-speech and language outcomes? Do screening evaluations in the primary care setting accurately identify children for diagnostic evaluation and interventions? (a. does identification of risk factors improve screening? B. what are screening techniques and how do they differ by age? C. what is the accuracy of screening techniques and how does it vary by age? D. what are the optimal ages and frequency for screening?) What are the adverse effects of screening? What is the role of enhanced surveillance by primary care clinicians? Do interventions for speech and language delay improve speech and language outcomes, or other non-speech and language outcomes? Does improvement in speech and language outcomes lead to improved additional outcomes? What are the adverse effects of interventions?	RCTs were considered for examining the effectiveness of interventions	SR	Medline, PsycINFO, and CINAHL databases (1966-November 19, 2004	The USPSTF concludes that the evidence is insufficient to recommend for or against routine use of brief, formal screening instruments in primary care to detect speech and language delay in children up to 5 years of age.
SIGN, 2007[22]	Assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders	RCTs, observational, diagnostic	SR	Medline, Embase, Cinahl,	Population screening for ASD is not recommended. (Level C) As part of the core program of

Guideline Group	Guideline Title and questions	Level of Evidence	Evidence Synthesis	Search Strategy	Recommendations
	25 research questions were asked, including methods for screening for ASD. The majority of questions were for diagnosis and treatment.	studies		PsychINFO, Cochrane Library; 1196-2006	child health surveillance, healthcare professionals can contribute to the early identification of children requiring further assessment for ASD, and other developmental disorders: clinical assessment should incorporate a high level of vigilance for features suggestive of ASD, in the domains of social interaction and play, speech and language development and behavior. CHAT or M-CHAT can be used in young children to identify clinical features indicative of an increased risk of ASD but should not be used to rule out ASD.
NICE, 2011[24]	Autism diagnosis in children and young people: Recognition, referral and diagnosis of children and young people on the autism spectrum Questions: what are the signs and symptoms that should prompt a healthcare professional or other professional in any context to think of autism? (b) When should a child or young person be referred for diagnostic assessment? Also asked questions about referral and diagnosis.	Controlled Observational	SR with GRADE	Medline 1950-2009; Cochrane; DARE; EMBASE; Cinahl; PsychINFO; EBM Reviews - Health Technology Assessment; EBM Reviews - NHS Economic Evaluation Database;	Consider the possibility of autism if there are concerns about development or behaviour, but be aware that there may be other explanations for individual signs and symptoms. Always take parents' or carers' concerns (and if appropriate the child's or young person's concerns) about behaviour or development seriously, even if these are not shared by others.

APPENDIX II: GRADE tables combining ANY screen (that meet inclusion criteria) for Developmental Delay

Outcome	Type	Summary measure of Effect
Change in referral rate	Binary	Risk Ratio
Time to referral	Continuous	Mean Difference
Cognitive Function (assessed using various different scales / measures)	Continuous	Standardized Mean Difference
Academic performance (assessed using various different scales / measures)	Continuous	Standardized Mean Difference
Incidence of any mental health outcome	Binary	Risk Ratio
Quality of Life (assessed using various different scales / measures)	Continuous	Standardized Mean Difference
Survival (Based on number of events / proportion)	Binary	Risk ratio
Functionality as an adult (assessed using various different scales / measures)	Continuous	Standardized Mean Difference
Optimal Screening Interval	Binary or Continuous	SMD or MD or RR (depending on type of data); for up to 10 outcomes
Harms – False positives	Proportion / percentage	Pooled Effect size
Harms – Parental Anxiety (assessed using various different scales / measures)	Continuous	Standardized Mean Difference
Harms - Consequences of false positives	Continuous or Binary	SMD or MD or RR (depending on type of data)
Harms – Stigma/ labelling (assessed using various different scales / measures)	Continuous or Binary	SMD or MD or RR (depending on type of data)

MD = mean difference; SMD = standardized mean difference; RR = risk ratio