INTENSIVE BEHAVIOURAL INTERVENTION FOR THE TREATMENT OF AUTISM SPECTRUM DISORDER IN PRESCHOOL AND SCHOOL AGE CHILDREN:

A SYSTEMATIC REVIEW AND META-ANALYSIS

MIRHAD LONČAR

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School of Epidemiology, Public Health and Preventive Medicine
Faculty of Medicine
University of Ottawa, Ottawa, Ontario, Canada

ABSTRACT

Intensive Behavioural Intervention (IBI) is one of the most widely used treatments for children with an autism spectrum disorder (ASD). While IBI has been recognized as the treatment of choice for very young children with an ASD, its sensible use among school age children is a matter of dispute. The aim of this thesis was to determine the clinical effectiveness of IBI, as compared with no treatment or treatment-as-usual, for the management of cognitive functioning and adaptive skills in preschool and school age children with an ASD, as well as to examine predictors of treatment response. Peer-reviewed, English language publications were identified using MEDLINE, EMBASE, PsychINFO, CINAHL, and ERIC from 1995 to September 1, 2014. Grey literature and reference lists of published papers were also searched for relevant records. Retrieved citations were screened by two independent reviewers, and data extraction was performed by a single reviewer with verification by a second reviewer. The methodological quality and procedural fidelity of included studies was assessed by one reviewer, and a subset of included studies were pooled in a random-effects meta-analysis using the standardized mean difference (SMD) effect size. A total of 24 unique studies were selected for inclusion in this review, comprising a total of 1,816 participants. Findings revealed that IBI improves full-scale IQ (SMD ES = 0.66, 95% CI 0.46 to 0.85, $p<0.00001$; 13 studies) and adaptive skills (SMD ES = 0.57, 95% CI 0.33 to 0.82, $p<0.00001$; 12 studies) in preschool and school age children with an ASD, with seemingly higher clinical benefits in children aged under 4 years at intake. Better outcomes with IBI are predicted by children's relatively younger age, increased cognitive and adaptive ability, as well as a milder severity of symptoms at treatment entry. Results warrant careful interpretation in light of several methodological limitations and inadequate monitoring of procedural fidelity.

ACRONYMS AND ABBREVIATIONS

AB	Adaptive behaviour
ABA	Applied Behavioural Analysis
ACBC-TRP	Achenbach Child Behavior Checklist—Teacher Report Form
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ADOS-LC	ADOS Language and communication domain
ADOS-RSI	ADOS Reciprocal social interaction domain
AP	Academic/educational placement
ASD	Autism Spectrum Disorder
ASQ	Autism Screening Questionnaire
BCBA	Board Certified Behavior Analyst
BSID	Bayley Scales of Infant Development
BSID-II	Bayley Scales of Infant Development - 2nd Ed.
BSID-R	Bayley Scales of Infant Development – Revised
CARS	Childhood Autism Rating Scale
CADTH	Canadian Agency for Drugs and Technologies in Health
CB	Child behaviour
CI	Confidence interval
COG	Cognitive
DAS	Differential Abilities Scale
DBC	Developmental Behavior Checklist
DBS	Developmental Behavioral Scales
DIR	Developmental Individual Difference Relationship
DP-II	Developmental Profile-II
DR	Diagnostic recovery
DSM	Diagnostic and Statistical Manual of Mental Disorders
E-LAP	Early Learning Accomplishment Profile
ELG	Expressive language
EOPVT	Expressive One-Word Picture Vocabulary Test
ESCS	Early Social Communication Scales
FMF	Fine Motor Function
FSQ	Family Satisfaction Questionnaire
Fx	Functioning
GMF	Gross Motor Function
HADS	Hospital Anxiety and Depression Scale
IBI	Intensive Behavioural Intervention
IEP	Individualized education plan
IQ	Intellectual quotient (cognitive/intellectual functioning)
IQ (Non-verbal)	Visual-spatial IQ
JA	Joint attention (non-verbal social communication)
KIPP	Kansas Inventory of Parental Perceptions
Lang	Expressive and receptive language
LAP-D	Learning Accomplishment Profile-Diagnostic
MA	Mental age/ratio IQ
MCYS	Ministry of Child and Youth Services

MD	Difference in means
MDI	Mental Developmental Index
ML	Mirhad Lončar
MPSMT	Merrill-Palmer Scale of Mental Tests
MS	Mastery of skills/Initial skill acquisition
MSEL	Mullen Scales of Early Learning
NCBRF	Nisonger Child Behavior Rating Form (Positive Social Subscale)
PDD	Pervasive Developmental Disorder
PDD-NOS	Pervasive Developmental Disorder – Not Otherwise Specified
PECS	Picture Exchange Communication System
PPVT	Peabody Picture Vocabulary Test (3rd Ed.)
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Psy	Psychopathology/severity of symptoms
PWB	Parental well-being/family satisfaction
PWR	Prewriting
QRS-FSF	Questionnaire on Resources and Stress–Friedrich short form
RCog	Cognitive rate of development
RCT	Randomized controlled trial
RDev	Adaptive date of development/developmental rate
RDLS-III	Reynell Developmental Language Scales–3rd Ed.
RDLS-EL	Reynell Expressive Language
RDLS-LC	Reynell Language Comprehension
RLG	Receptive language
ROPVT	Receptive One-Word Picture Vocabulary Test
SB4	Stanford-Binet Intelligence Scale–4th Ed.
SBH	Social behaviour
SEF	Social emotional functioning
SFC	Self-care
SK	Shazya Karmali
SMD	Standardized mean difference
TAU	Treatment-as-usual
TC	Tammy Clifford
TEACCH	Treatment and Education of Autistic and Related Communication Handicapped Children
UCLA YAP	University of California Los Angeles Young Autism Project
UK	United Kingdom
USA	United States of America
VABS-Composite	Vineland Adaptive Behavior Scales
VABS-C	Vineland Adaptive Behavior Scales - Communication
VABS-DLS	Vineland Adaptive Behavior Scales - Daily Living Skills
VABS-MS	Vineland Adaptive Behavior Scales - Motor Skills
VABS-S	Vineland Adaptive Behavior Scales - Socialization
WIAT	Wechsler Individualized Achievement Test
WPPSI	Wechsler Preschool and Primary Scales of Intelligence

DEDICATION

Abraham Lincoln once said:

"All that I am, all that I hope to be,

I owe to my angel mother;

My hand she guided as I learned to write,

My feet she guided in the ways of right,

My hopes she cherished, like a flame of light, –

God bless her soul, God bless her memory,

My angel mother."

I lovingly dedicate this thesis to my angel mother Nermana, who instilled in me the love for learning. Her words of encouragement and push for tenacity still ring in my ears.

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CHAPTER I: INTRODUCTION & BACKGROUND

1.1 Introduction

1.1.1 Statement of the problem

Throughout the 1950s, it was widely accepted that children who exhibited a peculiar set of neurological signs and symptoms – a range of repetitive and involuntary movements such as spasms, tics, rocking, spinning, or flapping of the hands; balance and coordination problems; difficulties in initiating movements analogous to what has been observed in parkinsonism; a wide array of atypical sensory responses, with heightened or intolerable sensitivity to certain stimuli and (often paradoxically) diminished responsiveness to other stimuli; complex and unusual language difficulties – were the products and reflection of bad parenting, most notably of an alarmingly detached, often uncaring, "refrigerator mother.(1)" This popularized belief consequently led to an entire generation of parents – mothers, particularly – who were riddled with feelings of guilt and self-deprecation related to their child's challenging behaviours, a symptomatic profile which would only a decade later become more aptly recognized as "infantile autism," a biological condition impervious to a maternal lack of affection.(2) With a growing volume of data supporting a biological basis of disease, it was not long before the misleading parental etiology became widely discarded and the autistic subject was brought to light. Although infantile autism is better known today as autism spectrum disorder (ASD), a neurodevelopmental condition characterized by a triad of impairments in social relationships, communication, and play and imaginative activities, its true etiology still remains unknown and there is no cure.(3)

Over the course of the last several decades, and perhaps most markedly in the recent past, epidemiological studies have shown that the prevalence of this perplexing condition is on the rise(4,5). Accordingly, the need for effective intervention approaches for children with an ASD has become increasingly important. This is especially true given the long-term implications of ASD on the quality of life of children and their families,(6–8) as well as the large strain placed on the health care system which may not have the adequate or appropriate resources to support these individuals or their caregivers.(9,10)

Fortunately, efforts in the development and application of interventions for the management of core behavioural deficits related to ASD are ever-increasing.(11,12) Indeed, among a variegated panoply of pharmacologic and non-drug treatments, intensive behavioural intervention (IBI) has emerged as one of the most scientifically documented and empirically validated therapeutic approaches for young children with an ASD.(13) Rooted in the psychological principles of applied behaviour analysis, this therapy is intended to kick-start the learning rate of very young children with an ASD so that they may reach the developmental levels of typically developing peers as they enter the school setting.(14) However, increased demand for this therapy over time, coupled with a delay to diagnosis, has resulted in serious systemic issues regarding its timely access across several jurisdictions. In particular, some children may not be initiating IBI until after they have entered school, an age at which the efficacy of treatment has not been well studied. Consequently, given the large economic burden that is associated with publicly-funded IBI in Canada, and elsewhere,(15–17) the provision of treatment which may be unable to alter the developmental trajectory of its recipients as intended is of great concern. Perhaps of

greater concern, however, are the lasting sequelae endured by those children who are denied access to timely care if it is shown to be effective.

1.1.2 Objectives

The overarching goal of this thesis is to provide a better understanding of the evidence base surrounding the effectiveness of IBI in the treatment of ASD in preschool and school age children, as well as to explore predictors of treatment response with IBI. Findings will be interpreted from a decision-making perspective, taking into consideration the relative role of clinical efficacy, cost-effectiveness, and equity in resource allocation decision-making.

Objective 1

To determine the clinical effectiveness of Intensive Behavioural Intervention (IBI), as compared with no treatment or treatment as usual (TAU), for the management of cognitive functioning and adaptive skills in preschool and school age children with an autism spectrum disorder (ASD).

To address this objective, the following specific research questions will be answered:

1. Among children younger than 6 years of age with an ASD, what is the clinical effectiveness of IBI, as compared with no treatment or TAU, for the management of cognitive functioning and adaptive behaviour?
2. Among children aged 6 years and older with an ASD, what is the clinical effectiveness of IBI, as compared with no treatment or TAU, for the management of cognitive functioning and adaptive behaviour?

Objective 2

To examine predictors of response to IBI treatment in preschool and school age children with an ASD.

To address this objective, the following research question will be answered:

1. Among preschool and school age children with an ASD, what are the predictors of response to IBI therapy?
    a. Is the effectiveness of IBI affected by the frequency, duration, or intensity of the intervention?
    b. Is the effectiveness of IBI affected by the training or experience of the individual providing the therapy?
    c. What characteristics, if any, of the child, modify the effectiveness of IBI?
    d. Are there other factors which may predict treatment response with IBI?

1.1.3 Relevance to research and decision-making

The information generated from this thesis is primarily intended to provide a comprehensive synthesis of the current published literature regarding the clinical effectiveness of IBI in the treatment of ASD among preschool and school age children, as well as to provide a better understanding of the participant and/or intervention characteristics which may be associated with optimal treatment response and ultimately lead to a difference in treatment effect among subgroups of this population. Findings will be interpreted based on the quality and strength of the evidence, as well as its applicability to the Canadian setting, with particular focus on the decision making context of the

province of Ontario, home of the country's largest and most comprehensive IBI program. Finally, consideration for cost-effectiveness and equity implications will allow to contextualize the evidence and, in turn, provide a springboard for policy and decision-makers to make choices regarding any changes to the current reimbursement process of IBI services in Ontario, and elsewhere.

1.1.4 Monograph outline

The present chapter provides a thorough background to the patient population of interest, the studied intervention, and describes the relevant policy context. The second chapter provides a detailed description of the methods used in conducting the systematic review and meta-analysis, including the criteria for considering studies for inclusion, the main outcome measures being assessed, the search methods for identifying studies, as well as a description of the data collection process and statistical analysis. The third chapter presents the results of the review and meta-analysis, as well as an assessment of the methodological quality of included studies. The extent to which procedural fidelity was monitored and reported across the body of evidence is also discussed, as well as findings from studies reporting on predictors of treatment response. Chapter four offers a discussion of the relevance and applicability of the findings, and considers these findings in the context of Canadian clinical practice, highlighting potential equity implications and considerations for cost and cost-effectiveness. The final chapter considers the implications of the findings for clinical practice and offers guidance for future research.

1.2 Background

1.2.1 Autism Spectrum Disorder

Almost three decades ago, American psychologist Kenneth D. Gadow – in reference to what modern-day clinicians recognize as attention deficit hyperactivity disorder (ADHD) – wrote: "In recent years, no other childhood disorder has received as much attention, generated more controversy, or left educators and parents in more confusion about what to do than the condition known as hyperactivity. The vagueness of the term has resulted in an 'epidemic' of cases, causes, and cures.(18)" Though this remark may very well still apply to ADHD, present-day experts in child development would certainly agree that it applies just as well to one of the most prevalent and fastest growing neurodevelopmental disorders among children today: autism.

Commonly referred to as autism spectrum disorder (ASD), this condition encompasses a wide range of developmental and neurological symptoms and behaviours that affects individuals from all walks of life from early childhood years into adulthood.(1,19,20) As hinted at by its name, clinical manifestations of autism fall on a continuum of severity, with some individuals showing mild symptoms and others having a much more severe clinical profile.(20,21) These symptoms often include impaired communication affecting spoken language and nonverbal communication, impaired social skills and diminished capacity to engage in social relationships, perseveration on interests and activities resulting in a narrow range of interests and in repetitive, stereotyped body movements, as well as abnormal responses to sensory stimulation and lack of flexible imaginative skill.(1,21) Therefore, ASD fundamentally impairs a person's ability to communicate and to relate to others. Given the condition's diverse symptomatology, each

affected individual may present with a different combination of symptoms, and each person's symptomatic profile may fluctuate throughout their lifespan.(21) Indeed, the variability in expression of disease is one of ASD's distinguishing features. Some people with an ASD, for instance, may have delayed or absent verbal abilities, whereas others may be highly proficient in spoken or expressive language. Similarly, some may be uncomfortably bothered by sounds, whereas others may well be musical savants. Furthermore, a number of medical (e.g. epilepsy, gastrointestinal problems, sleep disorders, metabolic disease) and psychiatric (e.g. ADHD, obsessive compulsive disorder, intellectual disability) comorbid disorders have been found to co-exist to varying degrees in children with an ASD.(22–26) It is this great heterogeneity which ultimately complicates both the selection of appropriate treatments and treatment response among those living with an ASD.

Since the concept of autism in children was first introduced by Leo Kanner in 1943, the disorder's symptomatic profile has widened dramatically.(27) Undoubtedly, these changes in symptomatology have occurred in parallel with the broadening of the diagnostic criteria and definition of autism. Currently, the most widely accepted definition of ASD is based on the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the American Psychiatric Association. Although the term 'autism' as a childhood medical condition first received its own classification in the third edition of the DSM, close to four decades after Kanner's first description of the autism prototype, it wasn't until the fourth edition of the DSM (DSM-IV-TR) that the description was expanded to incorporate the notion of a continuum of related disorders referred to as pervasive developmental disorders (PDDs), of which 'autistic disorder' was the most severe form.(27–29) Up until recently,

this neurodevelopmental condition was subsumed under the general PDD category alongside four other disorders, namely Asperger's disorder, childhood disintegrative disorder (CDD), Rett syndrome, and PDD-not otherwise specified (PDD-NOS) (30). However, the latest edition of the DSM (DSM-V), released in May 2013, no longer considers autistic disorder, PDD-NOS, CDD, and Asperger's disorder as distinct conditions, but rather collectively defines them as 'Autism Spectrum Disorder,' thus formally recognizing what has been the de-facto term in previous years.(30) Despite a seemingly improved understanding of ASD's clinical manifestations, no known cause of this puzzling disorder has been identified to date.(3,4) In fact, the suspected causes of ASD are perhaps as diverse as the spectrum itself, and presumably reflect a child's genetic endowment and early life environment.(31,32) Due in part to unknown etiology, there are currently no definitive diagnostic tests for autism; therefore, clinicians rely heavily on a detailed developmental history and direct behavioural observation to arrive at the diagnosis.(3,27) For many children, ASD diagnosis usually occurs during the first three years of life and is four times more common in boys than girls (3,33).

Just as ASD's clinical profile has increased over time, so too has its prevalence. In fact, more children are being diagnosed with an ASD each year in the United States than AIDS, cancer, and diabetes combined.(34) According to recent estimates from the Centers for Disease Control and Prevention's (CDC) Autism and Developmental Disabilities Monitoring Network (ADDM), one in 68 children (or 14.7 per 1,000 children) are thought to be affected by this disorder, a number reflecting a 123% increase in reported prevalence since 2002 (one in 150; 6.6 per 1,000).(35) Findings from the National Epidemiologic Database for the Study of Autism in Canada (NEDSAC), which compared data between

2003 and 2010 in Prince Edward Island, southeastern Ontario, and Newfoundland and Labrador, revealed similar trends in prevalent ASD cases, with an estimated 1 in 94 Canadian children affected.(36) Given the rising prevalence estimates, coupled with the fact that autism was thought to be a rare condition as recently as the mid-1990s, it is not surprising that popular opinion is that autism is affecting more and more individuals today than ever before. However, it's important to note that the degree to which ASD is on the rise is a matter of some controversy. Though it cannot be contested that the number of children diagnosed with an ASD has increased over the past decade or so, it is unclear exactly how much of this is a true increase in prevalence and how much is due to a broadening of the clinical definition of ASD, changing diagnostic criteria, different methods used in epidemiological studies, and greater awareness of the condition among parents and professional workers.(37)

Though the underlying reasons for rising prevalence rates remain elusive, the long-term impact of ASD on the quality of life of affected individuals and their caregivers is well recognized. In general, longitudinal studies have consistently demonstrated poor outcomes of individuals with an ASD in adolescence and adulthood, with many adults being socially isolated and unable to lead independent lives.(6,8,38) A high level of dependence on their caregivers or other support services during the adult years is also often coupled with a progressive decline in cognition and communication skills, as well as an increased rate of challenging behaviours.(39,40) Recent data have indicated, however, that prognosis may be more favourable than previously found, with a 10% increase over 20 years in individuals attaining "good" outcomes in adulthood.(38) The impact of broadening diagnostic criteria or better case finding on this apparent increase in good outcomes in

adulthood remains unclear. In general, favourable outcomes are commonly experienced among individuals with higher intellectual ability, and better adaptive functioning and communication skills.(41,42)

1.2.2 Intervention for Children with an ASD

Though uncertainty still shrouds much of autism, a myriad of treatment modalities are currently in place for the management of core symptoms associated with ASD. Pharmacologic interventions for instance, though not indicated for the treatment of ASD itself, are occasionally effective in addressing various associated symptoms.(43) Furthermore, a range of complementary and alternative medicine approaches, such as hyperbaric oxygen therapy and chemical chelation, also exist; however, they generally have little research to support their clinical efficacy.(44) In fact, few medical and nonmedical interventions show strong evidence of substantial benefit for children with an ASD; nonetheless, advances in treatment continue to be made. In particular, there are currently well over 50 different non-pharmacologic therapies targeting various deficits, including pro-social and play-based interventions (e.g. social stories), language and communication-based interventions (e.g. Picture Exchange Communication System (PECS)), sensory and motor interventions (e.g. sensory integration), interventions targeting challenging behaviour (e.g. intrusive behaviour reduction procedures) and those for general skill building (e.g. behavioural teaching), as well as expressive psychotherapies (e.g. music therapy).(11,45) While many of these treatment approaches carry a certain value, none has received as much attention and empirical support as Intensive Behavioural Intervention (IBI), a comprehensive form of early intervention for ASD.(13) Anchored in the principles of applied behaviour analysis (ABA), a scientific approach designed to change behaviour and

measure the resulting change, IBI consists of a highly structured teaching approach for young children with an ASD.(46,47) Treatment is typically administered in a one-to-one format (in the beginning) for 20 to 40 hours per week over approximately two years, and the overarching goal of therapy is to decrease challenging behaviours, to increase social skills and cognitive ability, and to promote development.(47–49) More specifically, IBI is intended to alter children's developmental trajectory and enable them to learn at the level of typically developing children as they transition into the school environment.(50,51)

The pioneering method of IBI was developed by Dr. O. Ivar Lovaas at the University of California, Los Angeles (i.e. the UCLA Young Autism Project), who proposed a very specific method of IBI treatment delivery targeted for very young children with an ASD.(50) While the Lovaas method follows a specified treatment manual,(52) IBI has been administered to children with an ASD in a variety of ways across a number of different settings since it was first introduced. Each IBI program, although different from the Lovaas method, typically consists of a core set of unifying features. These include treatment that begins as early as 3 to 4 years of age, an intensive delivery of therapy (around 20 to 40 hours per week), the use of an individualized and comprehensive approach that targets a wide range of skills, the development of adaptive repertoires using multiple behaviour analytic teaching techniques, a gradual progression of intervention delivery from a one-to-one format to group activities and naturalistic settings, treatment goals which are guided by normal developmental sequences, and the involvement of parents, to varying degrees, as active co-therapists.(53) Despite these commonalities, IBI programming may still vary in terms of the selected treatment intensity, the age at which children start therapy, the focus on specific skills areas as treatment targets, the level of experience and

competence of therapists and/or program supervisors, as well as the setting (e.g. clinic-, community-, school-, or home-based).

A recent overview of meta-analyses on the efficacy of IBI, also sometime referred to as early intensive behavioural intervention (EIBI), reached the conclusion that "the current evidence on the effectiveness of EIBI meets the threshold and criteria for the highest levels of evidence-based treatments" and that "EIBI is the comprehensive treatment model for individuals with ASDs with the greatest amount of empirical support."(13) In spite of these findings, it is important to note that some studies examining the effectiveness of IBI have yielded conflicting results in that not all children with an ASD benefit equally from this intervention. A better understanding of the various factors which may contribute to the different outcomes experienced by children who undergo IBI therapy could potentially aid in refining IBI programming to meet the needs of the population which responds optimally to the goals of treatment, and at the same time, offering alternatives to those children who do not respond to IBI-specific treatment targets.

1.2.3 The Ontario IBI Program

Based on a growing evidence base supporting IBI as an effective therapy option for children with an ASD, the province of Ontario launched a province-wide IBI initiative in the year 2000, the largest and most comprehensive IBI program of its kind worldwide.(47) Funded by the provincial Ministry of Child and Youth Services (MCYS), Ontario's Autism Intervention Program (AIP) is provided free of charge by one of nine regional programs to families residing in both large rural areas and densely-populated urban centres, with services provided in either English or French. The goal of therapy provided at each regional

centre is to increase the developmental trajectory, or rate of learning, of children with an ASD toward the severe end of the spectrum.(14)

When the Ontario IBI program was initially launched, children who were diagnosed with an ASD were admitted following an assessment of eligibility based on consideration of their adaptive functioning, severity of symptoms, and at times, intellectual ability. Once a child met the specific eligibility criteria, which included a diagnosis toward the severe end of the spectrum, he or she would start therapy on an intensive basis (20 to 40 weekly hours) for up to two years, or until they reached their sixth birthday, at which time they would transition into the school system.(47) Therefore, for children who were aged 6 years or older at the time of diagnosis, and ultimately at the time of referral to IBI, funding for treatment would be denied. As a result, a class action lawsuit was filed against the provincial government in 2000, challenging the termination of public funding for IBI at the age of 6 for qualifying individuals, in spite of the program's mandate and the evidence base supporting the use of IBI in very young children prior to enrollment in school.(54) In April 2005, the Superior Court of Ontario ruled in favor of the plaintiffs based on the fact that the age criterion was deemed discriminatory.(54) This effectively directed regional autism programs to accept children into IBI over the age of 6 and after entry in school, albeit unsupported by evidence. This decision was later overturned at the Court of Appeal for Ontario; however, the provincial government did not re-implement the age cut-off criterion.(55) As a result, a number of older children are currently being admitted into the program, and waitlists for treatment have become even lengthier than before.(55) With increasing numbers of children reaching the age of 6 and beyond (at which point IBI is ostensibly less effective) before ever receiving the care they need, discontent among

families seeking IBI services in Ontario is pervasive. Matters are further complicated by the fact that program eligibility criteria restrict IBI services only to those children whose ASD symptoms are clinically judged to be on the severe end of the autism spectrum, with recent estimates showing that about one quarter of children with an ASD diagnosis who apply for IBI are denied treatment because their autism is not considered severe enough.(56) It is therefore not surprising that the equitable provision of IBI services in Ontario is a matter of considerable controversy.

According to a recent evaluation of autism services and supports for children in Ontario conducted by the Office of the Auditor General of Ontario, there were approximately 2,000 children with an ASD receiving IBI services in the 2012/2013 fiscal year (56); yet, close to the same amount of children were also waiting for this government-funded treatment. Transfer payments for provincial ASD services and supports during the same fiscal year totalled approximately $182 million, 64% of which were the result of spending on IBI programming and transition supports for children entering the school system.(56) This number represents a significant increase from an initial investment of $14 million on ASD services and supports in year 2000/01 by the Ministry of Child and Youth Services, and a substantial economic burden on the province's finite resources.

CHAPTER II: METHODS

The preceding chapter provided an overview of the patient population under study and the intervention of interest, including an introduction to the decision-making context upon which this thesis is based.

The following chapter outlines the methodology used in conducting the systematic review of literature and meta-analyses relating to the comparative clinical effectiveness of IBI in preschool and school age children with an ASD, as well as information relating to predictors of treatment response. Detailed information is provided on the criteria which guided the selection of articles for inclusion, the search methods used to identify relevant published evidence, as well as the method of data collection and statistical analysis.

2.1 Objectives

2.1.1 Objective 1

To determine the clinical effectiveness of Intensive Behavioural Intervention (IBI), as compared with no treatment or treatment as usual (TAU), for the management of cognitive functioning and adaptive skills in preschool and school age children with an autism spectrum disorder (ASD).

To address this objective, the following specific research questions will be answered:

1. Among children younger than 6 years of age with an ASD, what is the clinical effectiveness of IBI, as compared with no treatment or TAU, for the management of cognitive functioning and adaptive behaviour?

2. Among children aged 6 years and older with an ASD, what is the clinical effectiveness of IBI, as compared with no treatment or TAU, for the management of cognitive functioning and adaptive behaviour?

2.1.2 Objective 2

To examine predictors of response to IBI treatment in preschool and school age children with an ASD.

To address this objective, the following research question will be answered:

1. Among preschool and school age children with an ASD, what are the predictors of response to IBI therapy?
    a. Is the effectiveness of IBI affected by the frequency, duration, and intensity of the intervention?
    b. Is the effectiveness of IBI affected by the training and/or experience of the individual providing the therapy?
    c. What characteristics, if any, of the child, modify the effectiveness of IBI?
    d. Are there other factors which may predict treatment response with IBI?

2.2 Criteria for considering studies for this review

A number of pre-specified eligibility criteria guided the selection of key studies for inclusion in this review. These criteria were implemented in a successive manner such that a given record was considered as excluded as soon as it met one of the following reasons for exclusion: (1) the study was published prior to year 1995; (2) the study was not a full, published journal article (e.g. conference abstract, thesis or dissertation); (3) the study was

not written in English; (4) the study was a duplicate (this includes multiple reports from the same study); (5) the study was not accessible through electronic databases; (6) the study did not report on original primary research (e.g. review, discussion article, methods paper, critique); (7) the study reported on a single-subject design (SSD) or on multiple non-consecutive case reports; (8) the study participants were aged 18 years or older; (9) the study participants did not have a formal diagnosis of an ASD (including autistic disorder, pervasive developmental disorder (PDD), or similar diagnostic variant) according to the Autism Diagnostic Interview – Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS), the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for autism, or a combination of any of these methods; (10) the experimental treatment of interest (i.e. IBI or similarly-named behaviour analytic therapy) was not described as intensive (i.e. 20 or more hours of intervention per week) nor comprehensive (i.e. addresses several domains or multiple areas of functioning affected by an ASD); (11) the intervention of interest was not administered by a trained professional or qualified therapist, and (12) the study outcomes were not an objective measure of the participant's achievement or treatment response.

The rationale underpinning these exclusion criteria was manifold. First, given that behaviour analytic treatment is clinically relevant and justified only for those individuals with medically recognized deficits in development that are characteristic of autism (or similar diagnostic variant like PDD or PDD-NOS), at-risk patient groups and those with a self-reported or parent-reported ASD were excluded from the review. In keeping with the aims of early behavioural therapy, participants aged older than 18 years were also excluded, even though onset of IBI treatment in children of school-bearing age and adolescents is

considered uncommon, and to some degree unsubstantiated. Participants were not restricted to a specific age window at treatment onset or excluded based on IQ or the presence of comorbid disorders. Second, interventions whose treatment intensity averaged less than 20 hours per week or which were narrowly focused on a single developmental domain like speech or play were excluded from the review because these characteristics reflect deviations from the defining features and principles of Intensive Behavioural Intervention. While the effect of treatment with IBI may be observed at thresholds below 20 hours per week, this cut-off criterion is consistent with several IBI program guidelines and principles of behaviour analysis. Third, studies in which measurement of treatment response relied exclusively on an indirect assessment of a child's achievement, for example via telephone surveys with parents, were excluded because these outcomes were not considered to be objective measures of response to therapy. Fourth, single subject design (SSD) studies or those describing multiple non-consecutive case-reports were also excluded because their focus is on solitary cases rather than groups of individuals, and this would require special statistical manipulation in the estimation of treatment effect. Accordingly, these studies would likely have a disproportionate impact on the intervention effect as they do not adequately describe the target population as a whole. Fifth, studies which evaluated parent-directed or parent-administered behavioural therapy were excluded because parents lack adequate training and experience in delivering ABA-based treatment in a competent manner, and this poses a significant threat to internal and external validity. Finally, any studies that were published prior to year 1995 were excluded because the age of the evidence base would not likely reflect current clinical practice.

Criteria for considering studies for inclusion were carefully selected to meet the requirements for identifying studies for both objectives of this review. While it is common for studies reporting on the clinical efficacy or effectiveness of IBI to also report data relating to predictors of treatment response, not all studies follow this practice. Therefore, the pre-defined eligibility criteria allowed for the inclusion of studies relating to the efficacy/effectiveness of the intervention and/or predictors of treatment response.

2.3 Types of outcome measures

2.3.1 Primary outcomes

Cognitive functioning (as measured by the intellectual quotient or IQ) was selected as the primary outcome measure for this review. IQ adequately reflects the goal and potential benefit of IBI in the study population given that this intervention is designed to jumpstart the learning rate of children so that they may meet the developmental milestones of same-aged peers as they reach the school age. Therefore, IQ was deemed as the most appropriate primary outcome.

2.3.2 Secondary outcomes

The secondary outcome measure of this review was adaptive behaviour (AB). While acquisition of adaptive skills is important in the evaluation of therapeutic change in children with an ASD undergoing behavioural therapy, an improvement in adaptive behaviour does not reflect the primary goal of IBI therapy. As a result, it was assessed as a secondary outcome in this review.

2.4 Search methods for identification of studies

A thorough search of the literature was conducted from both electronic databases and grey literature sources to identify studies for both objectives of this review. Due to time and resource constraints, only full-text English language publications were included in the review. However, no restrictions based on language or study design were placed on the initial search. Details of these search strategies are presented below.

2.4.1 Electronic searches

The following electronic databases were searched for relevant publications between the year 1995 to present (September 1, 2014): MEDLINE including In-Process & Other Non-Indexed Citations, Embase, PsycINFO, CINAHL and ERIC. All databases were searched using the Ovid interface, with the exception of CINAHL and ERIC which were accessed through the EBSCOhost and ProQuest interfaces, respectively. The MEDLINE search strategy was developed using appropriate syntax and a combination of controlled vocabulary and free-text terms. This core strategy was peer reviewed by an information scientist experienced in systematic review searching, using the PRESS standard.(57) The MEDLINE search was subsequently adapted for the other electronic databases. No language or study design limits were applied to any of the searches. The search strategies used are presented in Appendix 1: Search Strategies.

2.4.2 Searching other resources

Grey Literature

Electronic searches were supplemented by a search of various grey literature sources. This search was performed using the Canadian Agency for Drugs and

Technologies in Health (CADTH) Grey Matters checklist (February 2014), an online resource for grey literature searching. To ensure consistency in the searching process, four key search terms were applied systematically across all sources: autism, autism spectrum disorder, applied behavioural analysis, and intensive behavioural intervention. The searched grey literature sources included national and international health technology assessment (HTA) agency websites, clinical practice guidelines, clinical trial registries, as well as the websites of key national and international professional ASD associations or organizations. Any potentially relevant CADTH reports were also included in the grey literature search.

Reference lists

In addition to the grey literature search, reference lists of studies included in this review were hand-searched and verified for reports of other relevant studies in the published or unpublished literature.

2.5 Data collection and statistical analysis

2.5.1 Selection of studies

Two independent reviewers (ML and SK) screened the titles and abstracts of all records identified in the database searches using the computerized screening program ABSTRACKR™ (Tufts Medical Center, Boston, MA), an open-source web-based software.(58) Ineligible studies in this first screening phase were excluded based on population and/or intervention. If it was unclear whether a given study met inclusion criteria for target population or intervention of interest, the full text of the citation was retrieved for further assessment in the second phase of screening. During the second screening phase, full-text articles of relevant citations were retrieved and assessed by the

same two independent reviewers using the pre-defined exclusion criteria. Disagreements were resolved through discussion or through adjudication by a third reviewer (TC).

2.5.2 Data extraction and management

For objective 1 and objective 2, data from the selected review articles were extracted by one reviewer (ML) using a piloted data collection instrument, and a second reviewer (SK) performed a 10% validation of the extracted information. Disagreements were resolved by the two reviewers through discussion, and a third reviewer (TC) was sought for adjudication when consensus could not be reached.

The following data were retrieved and recorded from all included studies: (1) baseline characteristics of participants in the treatment and/or control or comparison group(s), including diagnosis, comorbid conditions, mean pre-intervention chronological age in months, mean pre-intervention IQ, percentage of male participants, and total sample size; (2) intervention characteristics, including experimental treatment delivery model (UCLA model or other general IBI model), treatment intensity (hours per week), treatment duration (months), number and frequency of follow-up assessments, setting of service delivery, primary treatment provider(s), and role of parent(s) in treatment delivery, if any; (3) outcome data on all reported outcome measures, including available pre- and post-test outcome measures (mean and standard deviation) and corresponding measurement tools; (4) data on predictors of treatment response (objective 2), where available, including predictive variables, observed associations, and measure of association values; and (5) general study characteristics, including funding source(s), study objective(s), study design (randomized controlled trial, non-randomized controlled trial, uncontrolled multiple-group comparison, one-group pre/post design), group assignment, as well as participant selection

criteria and recruitment procedures. Key conclusions and limitations of each review article were also documented.

2.5.3 Assessment of methodological quality in included studies

The methodological quality of included studies was evaluated by means of the Downs and Black (1998) checklist for randomized and non-randomized studies of health care interventions.(59) Due to resource constraints, assessment of study quality was conducted by a single reviewer (ML).

This quality checklist was selected primarily because it was deemed flexible enough to be applicable to both one-group pre/post design studies as well as controlled multiple-group comparison studies, whether randomized or not. This tool adopts a component approach to quality assessment and covers five quality domains: reporting (10 items), external validity (3 items), internal validity – bias (7 items), internal validity – confounding (6 items), and power (1 item). A total of 28 points are possible, with higher total scores indicating higher quality studies. To prevent over-representation of checklist domains containing more items (e.g. reporting), each of the tool's five domains was also rated on a scale of 0 to 1 points, resulting in a 5-point total quality range. Following the original author's guidelines, this checklist was adapted specifically to the field of applied behavioural analysis for autism in a previous meta-analysis conducted by Virues-Ortega et al. (2010),(60) which served as the basis for evaluating the quality of studies included in this review. Furthermore, the last item on the checklist (item 27) was simplified to consider whether or not the study authors had reported a power estimation or provided a sample size justification. This modified Downs and Black checklist with new additions and specifications used in this review is presented in Table 7 of Appendix 6.

2.5.4 Assessment of procedural fidelity

Treatment fidelity, also referred to as procedural fidelity or treatment integrity, refers to the degree to which a given intervention has been implemented as planned or intended.(61,62) Evaluating how accurately or faithfully an intervention has been put into practice, whether reproduced from a treatment manual or delivered by way of a theoretical model, is integral for considering behavioural treatment efficacy as it allows for unambiguous interpretation of study findings related to therapeutic change, and in turn, predictors of treatment response.(61,63) Accordingly, procedural fidelity in included studies was examined using the conceptual systems of treatment integrity proposed by Perepletchikova and Kazdin (2005) and Gresham (2005).(61,64) According to Perepletchikova and Kazdin (2005), treatment integrity encompasses three related aspects: treatment adherence, therapist competence, and treatment differentiation.(61) Treatment adherence refers to the extent to which specified therapeutic procedures were delivered as designed across the study sample (e.g. strictly following a treatment manual, or performing all prescribed tasks and activities). Conversely, therapist competence represents the skill level and judgement displayed by the therapist in delivering the intervention, and treatment differentiation relates to whether treatments under study differ from each other along appropriate lines, often defined by a treatment manual (i.e. implementing procedures prescribed for treatment A and avoiding procedures prescribed for treatment B and vice versa). In keeping with this conceptual framework, Gresham (2005) proposed three methods for measuring treatment integrity, which guided this assessment: (1) direct measures, (2) indirect measures, and (3) manualized treatments. Namely, direct measures of treatment integrity included reports of either direct observations of treatment delivery or videotaping/audiotaping of therapy sessions, while indirect measures comprised evidence

of self-reports of treatment implementation or collection of completed therapy checklists after each session to indicate which procedures were or were not delivered as designed or prescribed in a manual. Evidence that delivery of prescribed tasks and avoidance of proscribed procedures was carried out in different interventions of a comparative study, as is often the case for comparisons of manualized treatments against status quo, was considered sufficient to demonstrate treatment differentiation.

2.5.5 Measures of treatment effect

Dichotomous data were not encountered in any of the studies included in this review. This was not surprising given that the outcomes of interest (i.e. cognitive level and adaptive behaviour) are commonly measured on a continuous scale. Had binary outcomes been reported, they would have been analyzed by computing an odds ratio (OR) with a 95% confidence interval (CI) for each outcome.(65)

Analysis of continuous data was based on the assumption that the means and standard deviations reported in the study papers were derived from a normally distributed sample with no evidence of skew.(65) Where outcomes of a similar construct were estimated using different measurement scales or tools, the standardized mean difference (SMD) with the 95% CI was calculated using Hedges *g* with small sample size correction and used as a summary statistic.(66) In instances where a uniform measurement scale is used to ascertain similar outcomes, the difference in means (MD) statistic is generally favoured(65); however, because data from studies of alternate designs (i.e. controlled comparisons and uncontrolled studies) were aggregated within the same meta-analysis, the SMD statistic with the 95% CI was calculated instead using Hedges *g* with small sample size correction and used as summary measure, as suggested by Morris & DeShon

(2002).(67) Although many of the included studies reported change scores from baseline as a measure of treatment effect, these same studies also reported means (and SD) at pre- and post-intervention times. Therefore, means and accompanying SD at baseline and at the last recorded follow-up were extracted from the relevant articles.

2.5.6 Unit of analysis issues

Repeated measures studies

Studies with long follow-up periods may often report measures of outcome at more than one time point within the study time frame. However, combining data from several time points in a standard meta-analysis poses the risk of a unit-of-analysis error.(65) Consequently, in cases where studies selected for inclusion in a meta-analysis documented repeated observations on participants, interim measures were always discarded and pre-test and post-test measures for the longest follow-up period from each study were chosen to assess the effect of treatment on the chosen outcome, even when the last follow-up outcome measure was reported in a separate or subsequent publication. Although this method reduces the potential for a unit-of-analysis error, it may lead to a lack of consistency across studies and result in greater heterogeneity.

Studies with multiple intervention groups

Studies which compared more than one experimental condition but which lacked a control arm were treated with care. In such cases, although both groups implemented similar therapy based on ABA principles, only one intervention group was chosen as the treatment arm, and the other group was treated as a comparison group and dropped from the analysis. The choice of treatment group was based on the intervention characteristics which

more closely aligned with the pre-specified criteria for eligible interventions for this review. It was deemed inappropriate to combine results across two intervention groups since one group often deviated from the requisite intervention characteristics specified as part of the inclusion criteria.

A serious unit-of-analysis problem may also arise when multiple pair-wise comparisons between all possible intervention pairs from studies with a single experimental condition and multiple control arms are included in meta-analysis. In such instances, only one control group was chosen for a single pair-wise comparison, and this choice was based on the control condition which more closely reflected other control or treatment-as-usual (TAU) groups across the included studies.

2.5.7 Dealing with missing data

Missing data and loss to follow-up was examined across all included studies and this assessment was reflected in the analysis of the methodological quality of studies. For studies in which either mean or standard deviation values were missing, or selectively reported at either baseline or treatment discharge, an attempt was made to contact the original investigators of relevant publications to request the missing data. When such attempts were unsuccessful, outcome data for the corresponding article were dropped from the quantitative, but not qualitative, synthesis. Thus, only the available data were analyzed in meta-analysis, and replacement values were not imputed for missing data. The influence of missing data on altering the results of the review is assessed and discussed (see 4.3 Quality of the evidence)

2.5.8 Assessment of heterogeneity

For objective 1, the clinical and methodological heterogeneity across studies was evaluated based on the variability or differences between participants, interventions, and outcomes of relevant studies, as well as their design and conduct or risk of bias. Where studies were considered similar enough to allow pooling of data using meta-analysis, the degree of statistical heterogeneity was assessed by visual inspection of forest plots and by examining the Chi^2 test for heterogeneity (Cochran Q) and the I^2 statistic. Specifically, the presence of statistical heterogeneity was indicated by a Chi^2 statistic greater than the degrees of freedom (df) and a low P-value; due to the low power of the chi-squared test to detect heterogeneity, a P value of 0.10 was used as the level of significance ($P < 0.10$).(65) The percentage of variability that was due to heterogeneity rather than sampling error or chance was quantified by the I^2 statistic, with higher I^2 values representing greater heterogeneity of treatment effects. Moreover, poor overlap between the confidence intervals for each effect estimate on the forest plot suggested that statistical heterogeneity was likely present. Where heterogeneity was found in pooled effect estimates, possible reasons for variability were considered and further investigated through subgroup analyses where data permitted, as described below.

In the event that variability, whether from clinical, methodological, and/or statistical sources, was too high across studies, results would not have been synthesized quantitatively in a meta-analysis, and a narrative synthesis would have instead been provided.

2.5.9 Assessment of reporting biases

The likelihood of reporting biases was assessed qualitatively based on the characteristics of included studies and based on information obtained from published

literature suggesting that there may be relevant unpublished studies. Where sufficient studies (at least 10) were included in a meta-analysis for a specified outcome, funnel plots were constructed to investigate small study effects, which may indicate the presence of publication bias.(68) Funnel plots were not formally tested for asymmetry using statistical methods (e.g. Egger's regression test) due to limitations in the statistical software used; however, visual inspection of funnel plot asymmetry allowed interpretation of the possible effects of publication bias.

2.5.10 Data synthesis

To ensure meaningful conclusions from a statistically-pooled result for objective 1, the decision to meta-analyse data or not was guided by an assessment of the similarity of interventions across the included studies in terms of their participants, treatment intensity and settings, as well as their theoretical basis and use of outcome measures with similar psychometric properties. Where two or more studies with complete pre-test and post-test measures (means and SD) were found, and the studies were considered similar enough based on the aforesaid attributes, a meta-analysis was performed on the results. Controlled comparisons and uncontrolled before-and-after studies were combined in the same meta-analysis following the rationale provided by Morris & DeShon (2002).(67) Due to the possibility of variation in intervention techniques and differences in participant populations, a random-effects model was used for meta-analysis. When quantitative synthesis of data was not possible, a narrative description of the study results was provided. Data synthesis relating to the first objective was conducted using the Review Manager software (RevMan 5.3, The Cochrane Collaboration).

For objective 2, predictive variables which were reported in more than one study were considered for further analysis in order to increase confidence in specific findings. Information relating to these predictors of treatment response was synthesized qualitatively. Consequently, a critical review of isolated variables (i.e. reported by only one study) was deemed unsuitable owing to the limited information available.

2.5.11 Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted to explore potential causes for heterogeneity. When heterogeneity was identified in pooled effect estimates, the impact of children's chronological age (<48 months vs. >48 months), baseline IQ score (≤55 vs. 55.01-69.99 vs. ≥70), IBI treatment model (UCLA model vs. general non-UCLA IBI model), and the study design (controlled comparisons vs. uncontrolled before-and-after studies) was examined in subgroup analyses. These explanatory variables, however, were selected post hoc as a result of insufficient familiarity of the clinical diversity which may impact treatment response during the early stages of the review process. Due to the small number (<10) of relevant studies for some outcome measures, subgroup analyses were deemed inappropriate.

2.5.12 Sensitivity analysis

No sensitivity analyses were conducted as part of any meta-analyses.

CHAPTER III: RESULTS

The previous chapter provided a detailed outline of the methods used in the conduct of this systematic review and meta-analysis.

The current chapter presents the results of the systematic review of literature and meta-analysis relating to the effectiveness of IBI in preschool and school age children with an ASD. A qualitative synthesis of included studies is followed by as assessment of the methodological quality of the evidence and the results of the various meta-analyses. Findings relating to predictors of treatment response are also presented.

3.1 Description of studies

A detailed overview of the characteristics of studies included in this review can be found in Appendix 4, and a detailed summary of findings in Table 5 of Appendix 5.

3.1.1 Results of the search

A total of 6,512 citations were identified through electronic database searching, and an additional 46 records were identified from grey literature sources. Following the removal of duplicate records, the titles and abstracts of 4,648 citations were screened, and 4,474 records were subsequently excluded. A total of 174 articles were assessed in full-text, 149 of which were excluded (κ=0.74), and hand-searching of reference lists of selected review articles identified one additional relevant record. Ultimately, 26 papers describing 24 unique studies were selected for inclusion in the final qualitative synthesis. Pooling of data for meta-analysis was possible for 17 studies which reported complete pre- and post-intervention measures of cognitive level and adaptive skills, and these studies are included

in the quantitative synthesis. Figure 1 outlines the study selection process through a PRISMA flow diagram, including reasons for exclusion of full-text articles.

3.1.2 Characteristics of included studies

Table 1 presents a brief overview of the characteristics of included studies.

Study location, sponsorship and design

There were a total of 24 unique studies included in this review which examined the efficacy or effectiveness of IBI in preschool and school age children with an ASD. Of these, eight were conducted in the United States,(69–77) six were conducted in Canada,(78–83), five in Israel,(84–88) three in the UK,(89–91) and one each in Norway (92,93) and Spain (94). Sources of funding varied considerably between and within the different jurisdictions. Namely, four studies received sponsorship from national funding bodies, including the National Institutes of Health (NIH),(92,93) the Health Foundation UK,(91) as well as independent grants from the National Institute of Mental Health (NIMH).(69,74,90) Two studies conducted in Israel received funding support from the country's Ministry of Education,(84,87) and one Canadian study was funded by the Ministry of Child and Youth Services in the province of Ontario.(78,81) Moreover, there were three university-funded studies, including two Canadian studies which received sponsorship from York University in Toronto,(82,83) and one US study which reported the UCLA Department of Education and Regents Scholar Society as a funding source. Another Canadian study was funded by the Regional Autism Programs of Ontario Network (RAPON), and two studies conducted in Israel were privately sponsored (Mr. Dov Moran).(85,88) The remaining nine studies did not disclose any funding sources.(80,70–73,76,77,86,89,94)

Figure 1. PRISMA flow diagram

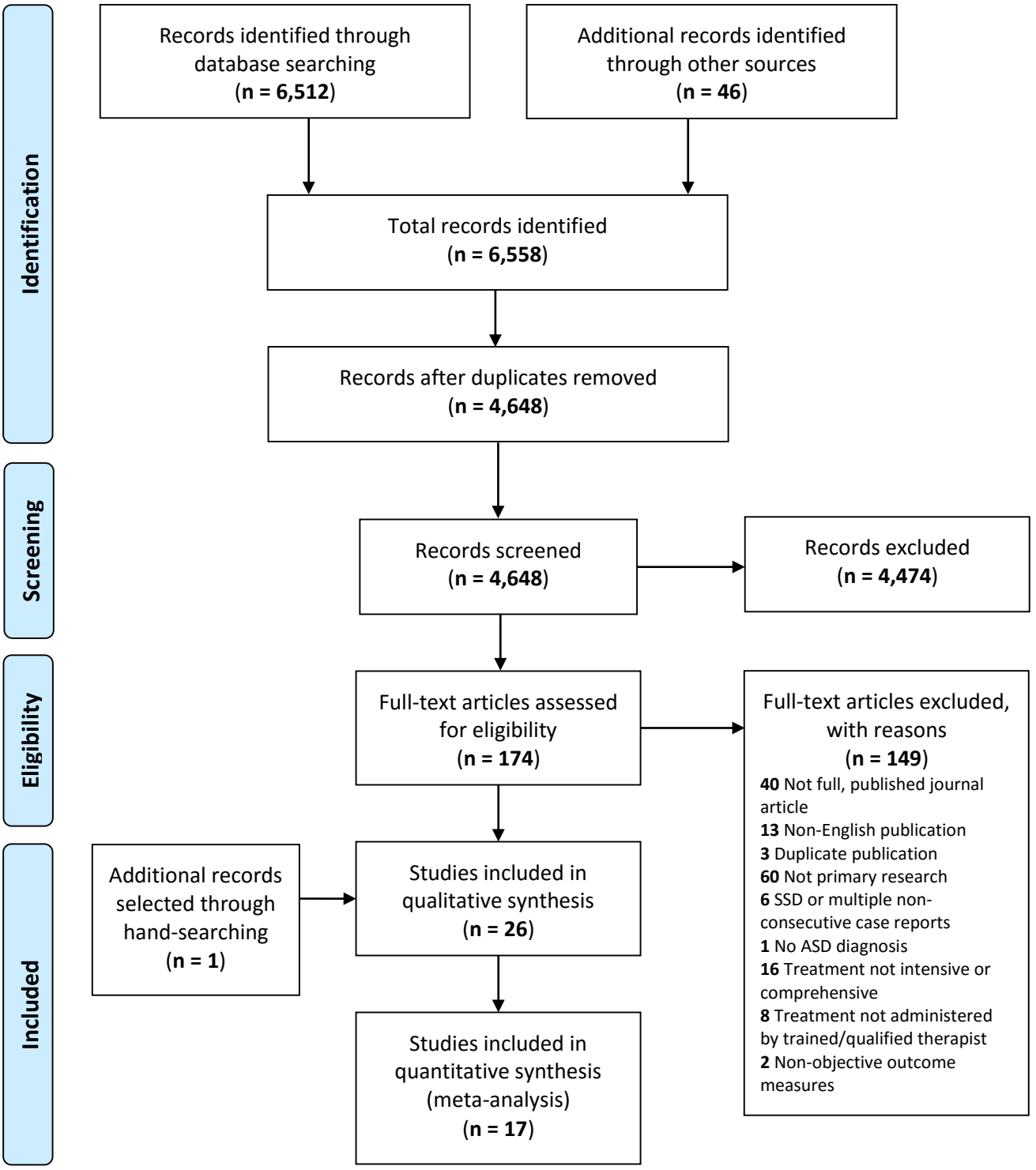


Table 1. Brief overview of characteristics of included studies.

First author, year (Ref. No.)	Country	Sponsorship[i]	Design		Sample size[iv]		Timing of assessment (standardized instrument)	
			Diagnosis[ii]	Type[iii]	EG	CG	IQ	AB
Ben-Itzchak, 2007 (84)	Israel	Ministry of Education	Autism	BA	25	–	Pre/post	NR
Ben-Itzchak, 2009 (85)	Israel	Private support	Autism	BA	68	–	NR	NR
Ben-Itzchak, 2014 (86)	Israel	–	ASD	BA	46	–	Pre/post	Pre/post
Blacklock, 2014 (82)	Canada	York University	Autism/autistic disorder (55%), PDD or ASD (38%), PDD-NOS (7%)	BA	68	–	Pre/post	Pre/post
Cohen, 2006 (69)	USA	NIMH	Autism (83%), PDD-NOS (17%)	NRCT	21	21	Pre/post (partial)	Pre/post (partial)
Eikeseth, 2002, 2007 (92,93)	Norway	NIH	Autism	NRCT	13	12	Pre/post	Pre/post
Eikeseth, 2009 (89)	UK	–	Autism	BA	20	–	Pre/post	Pre/post
Flanagan, 2012 (79)	Canada	RAPON	Autism (50%), PDD-NOS (50%)	NRCT	61	61	Post	Pre/post
Freeman, 2010 (80)	Canada	–	Autistic disorder (61%), PDD-NOS (31%), PDD or ASD (8%)	BA	89	–	Pre/post	Pre/post
Granpeesheh, 2009 (70)	USA	–	Autistic disorder (93%), PDD-NOS (7%)	BA	245	–	NR	NR
Harris, 2000 (71)	USA	–	Autistic disorder	BA	27	–	Pre/post	NR
Hayward, 2009 (90)[v]	UK	NIMH	Autism	UCT	23 21		Pre/post	Pre/post
Howard, 2005, 2014 (72,73)[vi]	USA	–	Autistic disorder, PDD-NOS	NRCT	29	16 16	Pre/post	Pre/post

Table 1. (continued)

First author, year (Ref. No.)	Country	Sponsorship[i]	Design		Sample size[iv]		Timing of assessment (standardized instrument)	
			Diagnosis[ii]	Type[iii]	EG	CG	IQ	AB
Perry, 2008, 2011 (78,81)	Canada	MCYS	Autistic disorder (58%), PDD or ASD (28%), PDD-NOS (14%)	BA	332	–	Pre/post	Pre/post
Perry, 2013a (83)	Canada	York University	Autistic disorder, PDD-NOS, ASD	BA	207	–	Pre	Pre
Perry, 2013b (83)[vii]	Canada	York University	Autistic disorder, PDD-NOS, ASD	UCT	60 60	– –	Pre/post	Pre/post
Remington, 2007 (91)	UK	Health Foundation	Autism	NRCT	23	21	Pre/post	Pre/post
Sallows, 2005 (74)[viii]	USA	NIMH	Autism	UCT	13 10	– –	Pre/post	Pre/post
Smith, 2000 (75)	USA	Department of Education & UCLA Regents	Autism (50%), PDD-NOS (50%)	RCT	15	13	Pre/post	Pre/post
Stoelb, 2004 (76)	USA	–	Autism	BA	19	–	NR	Pre
Virues-Ortega, 2013 (94)	Spain	–	ASD	BA	24	–	Pre/post	NR
Weiss, 1999 (77)	USA	–	Autism (90%), PDD-NOS (10%)	BA	20	–	NR	Pre/post
Zachor, 2007 (87)	Israel	Ministry of Education	Autism, PDD-NOS	NRCT	20	19	Pre	NR
Zachor, 2010 (88)	Israel	Private support	Autism	NRCT	45	33	Pre/post	Pre/post

[i]NIMH: National Institute of Mental Health; NIH: National Institutes of Health; RAPON: Regional Autism Programs of Ontario Network; MCYS: Ministry of Child and Youth Services. [ii]ASD: autism spectrum disorder; PDD: pervasive developmental disorder; PDD-NOS: pervasive developmental disorder – not otherwise specified. [iii]BA: before-and-after study (one-group pre-post design); NRCT: non-randomized controlled trial (multiple-group comparison); UCT: uncontrolled trial (multiple-group comparison); RCT: randomized controlled trial. [iv]EG: experimental/ treatment group; CG: control and/or comparison group. [v]EG1: Clinic-based; EG2: Parent-managed. [vi]CG1: Autism educational programming (AP); CG2: Generic educational programming (GP). [vii]EG1: Younger (2-5 yrs.) group; EG2: Older (6-14 yrs.) group. [viii]EG1: Clinic-directed; EG2: Parent-directed.
Note: "–" signifies not reported or not applicable.

Participant characteristics

There were a total of 1,816 participants across the included studies. Of the participants, 1,604 (88%) received active treatment (IBI), and 212 (12%) received no treatment or treatment as usual (TAU; i.e. special education services, eclectic therapy, etc.). The smallest study in this review had 19 participants,(76) while the largest reported 332 participants.(78,81) The mean chronological age (CA) at intake across all participants spanned 25 months (2.1 years) to about 90 months (7.5 years), with the majority being boys (range 70% to 95%). Studies conducted in Israel reported the youngest participant samples, with a mean CA ranging from 25.1 to 27.7 months at intake.(84–88) Conversely, some of the oldest participants came from two Canadian studies: the mean CA of participants at IBI program entry in studies by Blacklock et al. (2014) and Perry et al. (2013b) was 88.81 months and 89.4 months, respectively.(82,83) Considerable overlap in participant data may exist between these two studies given that the study sample described by Perry et al. (2013b) was fully drawn from the Perry et al. (2008, 2011) and Blacklock (2014) studies. Although there was considerable variability in participants' age at baseline between the selected studies, there were, on average, more studies with participants aged below 48 months (14 studies),(79,69,72–75,77,84–91) as compared with children above 48 months of age at intake (10 studies).(78,80,81,70,71,76,82,83,92–94) In addition, the mean intake CA range among participants receiving UCLA-based IBI (30.2 to 66.31 months) was much narrower than the age range of participants following non-UCLA-based treatment (25.1 to 89.4 months).

Initial level of cognitive functioning was assessed among participants in 19 studies, and the mean pre-treatment IQ standard scores ranged from 36.7 to 76.1 for children in

active treatment groups and from 50.69 to 79.6 for children receiving TAU or no treatment (7 studies). Five studies did not report baseline IQ scores.(79,70,76,77,85) Moreover, three studies specified an IQ inclusion criterion. In Cohen et al. (2006), children with autism had to have a pre-treatment IQ greater than 35, while participants in studies by Eikeseth et al. (2002, 2007) were required to have an IQ greater than 50 at intake. Similarly, Smith et al. (2000) study participants had to have a ratio IQ score between 35 and 75 at treatment entry.

Many participants across studies did not have any comorbid conditions or genetic disorders in addition to their ASD diagnosis. In fact, the presence of such diagnoses was used as an exclusion factor for recruitment in 50% of the included studies.(69,72–75,84,86–93) For instance, Eikeseth et al. (2002, 2007) and Smith et al. (2000) specified the absence of major medical problems other than autism as an inclusion criterion, and Ben-Itzchak et al. (2014) excluded any children with hearing deficiencies and genetic syndromes. Similarly, Remington et al. (2007) restricted participation only to those children who did not have any other chronic or serious medical conditions that might interfere with treatment delivery or that might adversely affect development.

Notwithstanding the narrow inclusion criteria applied in certain studies, participants across all studies had one of the following autism spectrum diagnoses: autism/autistic disorder, autism spectrum disorder (ASD), pervasive developmental disorder – not otherwise specified (PDD-NOS), PDD or ASD. Studies which included participants of varying diagnoses on the autism spectrum commonly specified the distribution of diagnoses within the study sample. Moreover, diagnoses were made by an independent psychologist or qualified clinician based on DSM-IV/DSM-IV-TR, DSM-III-R, or ICD-10 classification, and were confirmed using one or more standardized tools for diagnosis, including the

Autism Diagnostic Interview – Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS), or the Childhood Autism Rating Scale (CARS). Table 2 in Appendix 4 highlights the variability in diagnoses among study participants within and between studies, as well as the difference in choice of diagnostic label used across studies.

Intervention characteristics and delivery format

The instructional model and delivery format of interventions varied measurably across the included studies; yet, the intervention content was generally comparable. Seventeen samples (71%) received IBI based on a general early intervention model, while seven samples (23%) received treatment based on the UCLA Young Autism Project (YAP) model (also referred to as the Lovaas model). Although both instructional models are essentially rooted in the same theoretical principles and science of applied behavioural analysis (ABA), the UCLA YAP model is based wholly on a treatment manual and teachings developed by Dr. O. Ivar Lovaas in the United States.

The intensity of interventions was primarily measured in weekly treatment hours and ranged from an average of 20 to 40 hours per week across the study samples, with 9 of 24 samples (38%) reporting a mean treatment intensity of at least 30 hours per week.(69,72–74,84,85,87,89,90,94) However, information on treatment intensity was not always provided in a clear and consistent manner across studies. For instance, whereas several study authors reported the precise range and mean treatment hours per week received by study participants (as measured during study enrolment), other authors merely reported an estimate of average weekly treatment hours(77,84) or an approximate intensity range,(78,80,81,69,72,73,82,83) and one author reported intensity in terms of mean hours

per month.(70) In addition, several studies noted a reduction in treatment hours for certain age groups,(69,92,93) or a reduced treatment intensity following a specified time period after treatment onset.(74,75)

The mean duration of treatment with IBI varied from 12 months up to 48 months across studies. Six samples (25%) received 12 months of intervention,(76,84,85,87,88,90) while nine study samples (38%) received 24 months of treatment or greater.(79,69,73–75,77,86,91,93) Participants of seven other studies followed a treatment program which lasted variably between 12 and 24 months,(78,80–83,89,94) and two studies did not report this information.(70,71)

Treatment providers across studies usually comprised a team of behaviour therapists of varied qualifications, and often under the supervision of a Board Certified Behaviour Analyst (BCBA), with or without auxiliary aides (speech-language pathologist, occupational therapist, etc.). Therapists providing treatment under the UCLA YAP model were additionally required to complete a mandatory 3- to 4-month training program at the University of California, Los Angeles prior to treatment onset.(69) In addition to a team of trained therapists, three studies included special education teachers in treatment implementation,(86,88,92,93) and another two studies employed parents as active co-therapists.(91,94) Furthermore, although detailed information concerning the role of parents during intervention was not always provided across the included studies (see Table 3 in Appendix 4), parents received some form of training in 17 of 24 (71%) study samples. Training provided to parents was generally focused on skill generalization and maintenance procedures that could be implemented outside of regular treatment hours with the aim to foster the child's skill acquisition and development in the natural environment.

Therapy sessions were provided in a variety of settings including the participant's home or school, a designated treatment centre, or in the community. Namely, 10 of 24 (42%) samples were recipients of community- or centre-based intervention, and another four (17%) and two (8%) study samples received intervention administered at home or at school, respectively. For the remaining eight samples (33%), more than one setting was used to implement therapy.

While there was great variability between studies with respect to the intensity and duration of treatment, as well as the treatment providers and setting, variation in the therapeutic techniques or content of the experimental intervention was less apparent. Since UCLA-based IBI is a manualized treatment, its teaching methods were invariably described as a combination of discrete trial training (DTT), natural environment teaching, and incidental teaching across the relevant study samples.(69,74,75,89,90,92–94) Three UCLA-based studies further specified that contingent aversives, as initially proposed by Lovaas, were not employed as part of the intervention.(69,74,92,93) Studies which did not fully rely on the UCLA YAP treatment manual frequently described similar teaching methods, with reference to ABA as the source of behavioural teaching strategies. For instance, Ben-Itzchak and Zachor (2009), Ben-Itzchak et al. (2014), and Zachor et al. (2007, 2010) quoted the application of DTT, naturalistic, and incidental teaching techniques in addition to several other procedures (shaping for positive reinforcement, successive approximation, systematic prompting and fading procedures, etc.).(85–88) Similarly, Granpeesheh et al. (2009) referred to the use of several structured and unstructured behavioural teaching methods, as well as other strategies for behaviour modification (errorless prompting and least-to-most prompting strategies, reinforcement, extinction, stimulus control,

generalization training, chaining and shaping, etc.).(70) Details of specific instructional techniques were not always directly provided within the study articles; however, reference to IBI program guidelines which explained the key features of the instructional approach was provided in several publications.(78–83)

The concomitant use of other interventions with IBI was generally not employed across the included studies. However, Harris and Handleman (2000) noted that some families sought occupational and/or physical therapy for their child outside of IBI treatment hours,(71) and Remington et al. (2007) mentioned that the Picture Exchange Communication System (PECS) and Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) was used for some children in the experimental group, in addition to speech therapy, dietary restrictions, routine prescription medications, and vitamin injections.(91) Sallows and Graupner (2005) similarly reported that some children within their sample received supplemental intervention before or during the first year of IBI, including private therapies, speech therapy, sensory and auditory integration training, music therapy, and horseback riding.(74) Lastly, the use of supplementary dietary intervention was reported in about 40% of participants in the study by Stoelb et al. (2004).(76) While other studies did not disclose the use of auxiliary treatments prior to or during IBI, families were not prohibited from seeking such treatments.

Control or comparison condition

There were a total of eight controlled multiple-group comparisons across the included studies in this review, one of which applied a randomization procedure.(75) While

all eight studies compared the experimental treatment group with a group not receiving IBI, the nature of the comparison or control conditions varied between study samples. Cohen et al. (2006), for instance, employed a comparison group receiving various non-intensive public school education classes and community services selected by parents, and described the instructional methods used as 'eclectic'.(69) Control group participants in the study by Eikeseth et al. (2002, 2007) similarly received eclectic special education services incorporating elements of TEACCH, sensory-motor therapies, ABA techniques, as well as methods derived from personal experience; additionally, these services were provided at about 20 to 35 hours per week, mirroring the treatment intensity of the study's experimental group.(92,93) In contrast, Remington et al. (2007) control participants received treatment as usual (TAU) whereby parents were not actively seeking behavioural intervention but were instead receiving publicly-funded services offered by their Local Education Authority.(91) Moreover, Smith et al. (2000) employed a parent training control group in which parents applied treatment techniques described in the Lovaas manual with the aim to facilitate their child's skill acquisition. Control group children in studies by Zachor et al. (2007) and Zachor and Ben-Itzchak (2010) followed a community-based eclectic-developmental (ED) program based on the principles derived from several approaches (i.e. mainly from the Developmental, Individual-Difference, Relationship-Based (DIR) model, but also incorporating TEACCH and ABA strategies).(87,88) Unlike other controlled studies identified in this review, Flanagan et al. (2012) was the first to employ wait-list controls, that is participants not yet receiving IBI,(79) and the study by Howard et al. (2005, 2014) was the only one which used two comparison arms, one based on an intensive eclectic approach (autism educational programming), and another consisting of less intensive public

early intervention programs (generic educational programming) provided through local community special education classrooms.(72,73)

Although three additional multiple-group comparisons which addressed the research questions of this review were identified in the literature, these studies were not deemed to be controlled comparisons since all participants received some form of experimental intervention. Sallows and Graupner (2005) and Hayward et al. (2009) both compared two different service coordination models of the same UCLA-based intervention; namely, one group received a clinic-directed IBI program while services provided to the other treatment group were directed or managed by parents, meaning that intensive supervision was provided by program consultants while the tutoring staff or therapists were recruited and managed by parents.(74,90) Conversely, Perry et al. (2013b) conducted a retrospective matched-pairs before-and-after study exploring differences in response to IBI within a younger (2-5 years) and older (6-14 years) age group, both of which received the same government-funded experimental treatment.(83)

Outcomes assessed

Included studies typically considered multiple primary and/or secondary outcomes of interest. Most notably, there were 21 studies which measured change in full-scale IQ,(78–81,69,71–75,82–94) 19 studies which measured adaptive behaviour,(78–81,69,72–77,82,83,85,86,88–93), and 17 studies measured both change in full-scale IQ and adaptive behaviour.(69,72,74,75,78–80,82,83,85,86,88–93) Receptive and/or expressive language ability was the next most commonly measured outcome, as reported by 10 studies. (69,72–76,84,89–92) The rationale for the choice of outcome measures was generally lacking, and

the instruments used frequently varied across and within studies. In addition, the use of standardized instruments or tools in assessing similar constructs was often inconsistent from participant to participant as well as from baseline to follow-up. This was especially true in the assessment of cognitive functioning which often consisted of using several different IQ tests for participants of the same sample from pre- to post-intervention. Table 4 in Appendix 4 details the specific outcome measures and associated instruments used across the included studies.

In addition to the commonly applied standardized measures of assessment, some study authors chose to administer non-validated measures or tools developed specifically for their study sample. For example, Ben-Itzchak and Zachor (2007) administered the developmental-behavioural scales (DBS) to assess several functioning domains such as imitation, verbal and non-verbal communication, play skills, and stereotyped behaviours.(84) Stoelb et al. (2004) similarly developed and applied an EIBI Performance Scale (EPS) to retrospectively measure comparable domains of functioning,(76) and Granpeesheh et al. (2009) and Weiss (1999) measured the number of monthly mastered behavioural objectives and mastery of initial skills, respectively, among study participants using pre-defined mastery criteria.(70,77) Furthermore, there were four studies which identified academic or classroom placement as an outcome measure,(69,71,75,77) despite the highly contested nature of this measure due to concerns that it may reflect factors such as parent advocacy and school policy rather than the child's functioning. Because it can be potentially misleading to draw inferences from the pooled results of such measures or other isolated measures across the included studies, data were not aggregated across these measures in the meta-analysis.

On the whole, outcome measures were assessed immediately following treatment discharge or at multiple time points within the study time frame in the case of repeated measures studies. Long-term outcome data, that is, assessments extending beyond 48 months, were not reported in any of the included studies.

3.1.3 Procedural fidelity

The analysis of procedural fidelity according to the conceptual systems proposed by Perpletchikova and Kazdin (2005) and Gresham (2005) revealed mixed results (refer to Table 4 in Appendix 4). Of the 24 selected review studies, only 14 samples (58%) employed procedures and/or measures to ensure or document treatment integrity.(78,69,73–77,86,88–94) In measuring treatment adherence, 3 of 14 studies used direct measures, 11 studies used indirect measures, and 9 studies used a treatment manual. While studies reporting on the use of a manual to guide treatment implementation provided a reference to the specific manual(s) used, there was no independent verification that manuals were used or not used as intended. Treatment differentiation could only be measured for the eight controlled comparative studies; four of these assessed treatment differentiation using indirect measures while one study used direct measures and three others did not report measures of treatment differentiation. Therapist competence was measured in 13 of 24 studies; eight studies assessed therapist competence using direct measures and five studies used indirect measures. Among the ten studies which did not appear to evaluate the degree to which IBI was implemented as intended,(79,80,70,71,82–85,87) seven were before-and-after studies with no control group, and 6 of 10 studies reported a retrospective design. Indeed, the assessment of treatment integrity was more common among controlled comparative studies than those with no control group, with 75% of controlled studies

employing procedural fidelity measures, as compared with only 50% of studies with an uncontrolled before-and-after design.

3.1.4 Excluded studies

Of those studies for which full-text articles were retrieved, 149 were excluded from this review. Excluded studies comprised 60 papers which were not deemed as original, primary research publications, 40 papers which were not full published journal articles, 13 papers published in a language other than English, eight papers in which treatment was not administered by trained staff or qualified therapists, six papers reporting a single subject design (SSD) or multiple non-consecutive case reports, three duplicate publications, two studies which did not use an objective outcome measure, and one study whose participants did not have an ASD diagnosis. A detailed list of these articles and corresponding reasons for exclusion is presented in Appendix 2.

3.2 Risk of bias in included studies

Methodological quality scores across the 24 included studies, using the modified Downs and Black checklist (Table 7), ranged from 7 to 21 points (mean=15.29, SD=3.42). In other words, included studies attained 25% to 75% of the maximum quality score (28 points). Based on the scoring cut-offs reported in a recent systematic review by Pereira et al. (2015) which assessed study quality on a 28-point scale using a simplified version of the Downs and Black checklist,(95) only two of the included studies in this review were assessed to be of high quality, scoring 20 or more points.(74,92,93) Conversely, 17 studies scored less than 20 points and were considered to have a moderate risk of bias,(78–81,69,71–73,75,76,83,84,86,88–91,94) while five additional studies scored less than 13

points and were deemed to be of poor quality.(70,77,82,85,87) The results of individual items of the quality assessment checklist are presented in Table 8 of Appendix 6.

Assessment of results by methodological quality domains revealed that major concerns across studies were associated with external validity, internal validity (confounding), and statistical power, while the reporting and internal validity (bias) domains contributed to a lesser extent to the overall risk of bias between and within studies. More specifically, only five studies (21%) provided sufficient information on the recruitment of participants to inform the representativeness of the study sample (item 11), three of which further cited the representativeness of subjects who were willing to participate in the study (item 12); the implementation of the intervention was deemed to be representative of that in use in the source population in 67% of the included studies (item 13). Although randomization of participants and concealment of treatment allocation (items 23, 24) were only possible for the eight controlled comparison studies, only one applied randomization procedures and none of the studies concealed intervention assignment from staff. Furthermore, it was generally unclear whether participants had been recruited over the same time period (item 22), and only 13 of 24 studies (54%) used intention-to-treat analysis (item 25). With the exception of one study, none of the included studies performed a power estimation or provided a justification for the number of recruited participants (item 27); as a result, it was difficult to assess whether study samples were sufficiently powered to detect a clinically relevant treatment effect, and the validity of inferences made based on small samples reported across many of the included studies remains questionable. Finally, while most studies fared relatively well on items relating to reporting and internal validity (bias), none of the included studies made an effort to report potential adverse events associated

with the intervention (item 8), and none of the participants across studies were blinded to the intervention they received (item 14). The risk of bias from lack of blinding of study participants, however, was difficult to prevent owing to the nature of the intervention which demands a high frequency and regularity of interaction between participants and study personnel.

In considering each of the five quality domains on a scale of 0 to 1 points such that checklist domains containing more items (e.g. reporting) are not over-represented, the mean quality score across the included studies (of a possible maximum of 5) was 2.1±0.7 (range 0.7 to 3.7). On average, studies tended to score higher in the reporting (0.7 out of 1.0) and internal validity – bias (0.6) domains, as opposed to external validity (0.3), internal validity – confounding (0.4), and power (0.0). If the scoring cut-offs from the 28-point quality assessment scale were to be transformed onto the 5-point scale, 18 of 24 studies (75%) would be rated as low quality, while five (21%) and one (4%) studies, respectively, would be regarded as moderate and high quality studies. This shift toward an apparent reduction in overall quality among included studies as a result of attributing equal importance to each of the quality domains of the modified checklist is likely due to the general lack of reporting of a power estimation across all studies and the considerable weight this domain carries on a 5-point rating scale. The results by domain of the quality assessment checklist are presented in Table 9 of Appendix 6.

3.3 Effects of intervention

3.3.1 Cognitive functioning (IQ)

Cognitive functioning or intelligence (IQ) was measured before and after IBI implementation in 13 of 24 studies (78,71,72,74,75,82,84,86,89–94); results of these

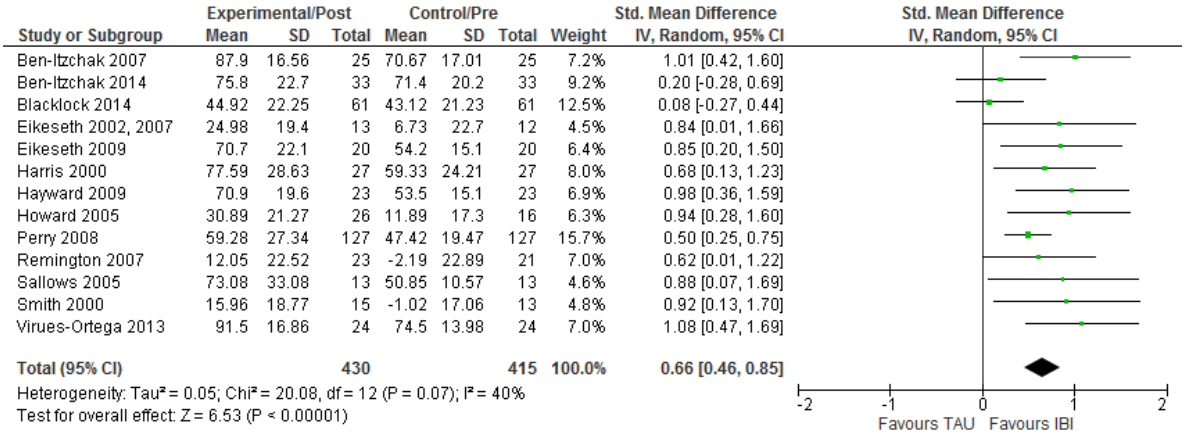
studies were synthesized in a random-effects meta-analysis using the standardized difference in means (SMD) effect size with small sample correction.(66) The eleven studies which were not included in the meta-analysis comprised four studies which reported partial outcome data, that is, either only pre-intervention or only post-intervention IQ scores,(79,69,83,87) two studies which did not report full-scale IQ scores (MSEL subdomain scores only),(85,88) as well as three studies which did not measure change in IQ among the study participants(70,76,77). In addition, two Canadian studies by Freeman and Perry (2010) and Perry et al. (2013b) were also excluded from the meta-analysis due to risk of double-counting of participant data (80,83); namely, participant data for the study by Freeman and Perry (2010) were entirely drawn from a previously published study by Perry et al. (2008),(78) and the study sample reported in Perry et al. (2013b) overlapped with participant data reported in Perry et al. (2008) and Blacklock et al. (2014).(78,82)

The SMD effect size across studies for change in IQ, covering a total of 492 participants, was 0.66 (95% CI 0.46 to 0.85, $p<0.00001$). There was evidence of moderate statistical heterogeneity, as suggested by the I^2 statistic (40%). In addition, the statistically significant Q-statistic ($Q(12)=20.08$, $p=0.07$) indicated that there was definite heterogeneity between the 13 included studies. Accordingly, the influence of heterogeneity on the pooled effect size estimate was further explored through subgroup analysis. Figure 2 shows the effect of IBI on children's IQ for the included studies.

Findings from the subgroup analyses (see Figure 8, Figure 9, Figure 10, Figure 11 in Appendix 7) suggested that the effects of intervention tended to be stronger for UCLA-based IBI programs (UCLA model: ES=0.94, 95% CI 0.65 to 1.22, $p<0.00001$; general IBI model: ES=0.51, 95% CI 0.27 to 0.76, $p<0.0001$), as well as for participants aged less than

48 months (age <48 months: ES=0.74, 95% CI 0.52 to 0.96, p<00001; age >48 months: ES=0.55, 95% CI 0.23 to 0.88, p<0.007), and for participants who had a mean baseline IQ score of 70 or higher (intake IQ≥70: ES=0.74, 95% CI 0.15 to 1.33, p<0.01; intake IQ 55.01 to 69.99: ES=0.69, 95% CI 0.32 to 1.05, p<0.0002; intake IQ ≤55: ES=0.64, 95% CI 0.35 to 0.92, p<0.0001). In addition, intervention effects tended to be higher among controlled comparisons (ES=0.81, 95% CI 0.46 to 1.16, p<0.00001), as compared with before-and-after uncontrolled studies (ES=0.62, 95% CI 0.38 to 0.87, p<0.00001).

Figure 2. Forest plot of comparison: IBI vs TAU, outcome: 1.1 IQ



Visual inspection of the funnel plot of the standard error as a function of the effect size (SMD) of each study revealed substantial asymmetry (see Figure 7 in Appendix 7), suggesting the potential for the presence of publication bias. Given that the majority of smaller studies clustered to the right of the mean, it appears as though smaller studies tended to report larger effects of treatment on children's cognitive functioning; however, small study effects must be interpreted with caution in the absence of an objective measure of publication bias.

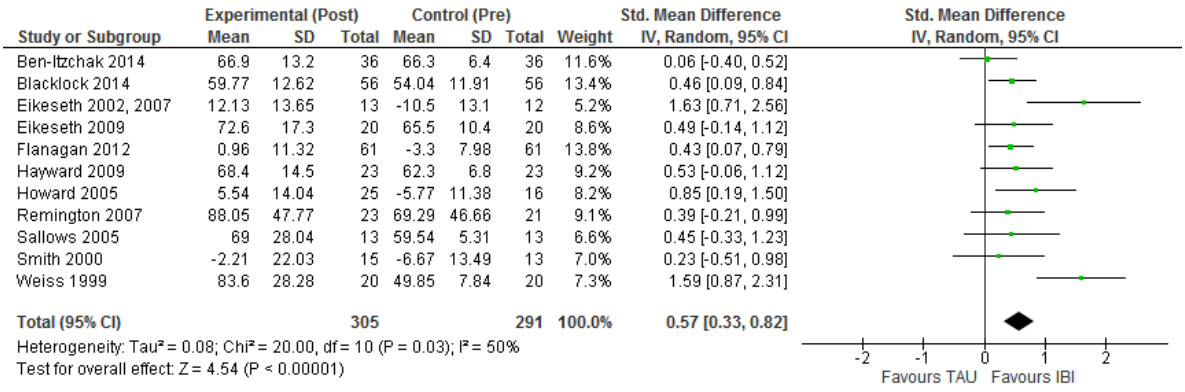
3.3.2 Adaptive behaviour

Twelve of 24 selected review studies measured adaptive skills before and after intervention using the Vineland Adaptive Behaviour Scales (VABS) (79,72,74,75,77,82,86,88–93); results of these studies were combined in a random-effects meta-analysis using the SMD effect size with small sample correction.(66) Study results were pooled separately for the adaptive behaviour composite measure (11 studies) and each of the VABS subdomains (8 studies). The twelve studies whose data were not aggregated across this effectiveness measure comprised three studies reporting partial outcome data (i.e. some or no post-intervention adaptive scores),(69,76,83) and six studies did not measure adaptive functioning among study participants or report data in a meaningful way (70,71,84,85,87,94). Three studies conducted in Canada (Freeman and Perry, 2010; Perry et al. (2008); Perry et al. (2013b)) were excluded due to risk of double-counting participant data resulting from overlap between study samples: participant data reported in Freeman and Perry (2010) and Perry et al. (2008) overlapped with the controlled study by Flanagan et al. (2012),(79) and the study sample reported in Perry et al. (2013b) overlapped with participant data reported in studies by Blacklock et al. (2014) and Perry et al. (2008). Furthermore, one non-randomized trial by Zachor and Ben-Itzchak (2010) only reported VABS subdomain scores without a composite measure of adaptive skills; as a result, it was excluded from the meta-analysis assessing change in the adaptive behaviour composite, but its data were used when examining the pooled effects of intervention on each of the VABS subdomains. Conversely, Flanagan et al. (2012) only reported pre- and post-intervention standard scores for the adaptive behaviour composite; thus, it was excluded from meta-analyses of the three VABS subdomains.

VABS Adaptive Behaviour Composite

The SMD effect size across studies for change in adaptive behaviour composite, covering a total of 428 participants, was 0.57 (95% CI 0.33 to 0.82, p<0.00001). There was evidence of moderate statistical heterogeneity, as suggested by the I^2 statistic (50%). In addition, the statistically significant Q-statistic (Q(10)=20.00, p=0.03) indicated that there was definite heterogeneity between the 11 included studies. Accordingly, the influence of heterogeneity on the pooled effect size estimate was further explored through subgroup analysis. Figure 3 shows the effect of IBI on children's adaptive behaviour composite score for the included studies.

Figure 3. Forest plot of comparison: IBI vs TAU, outcome: 1.2 VABS Composite



Findings from the subgroup analyses suggested that the effects of intervention tended to be slightly stronger for UCLA-based IBI programs (UCLA model: ES=0.60, 95% CI 0.21 to 1.00, p<0.003; general IBI model: ES=0.56, 95% CI 0.22 to 0.90, p<0.001), and much stronger for participants 48 months of age and older (age >48 months: ES=0.97, 95% CI -0.17 to 2.11, p<0.09; age <48 months: ES=0.52, 95% CI 0.26 to 0.78, p<0.0001), as well as for participants who had a mean baseline IQ score between 55 and 70 (intake

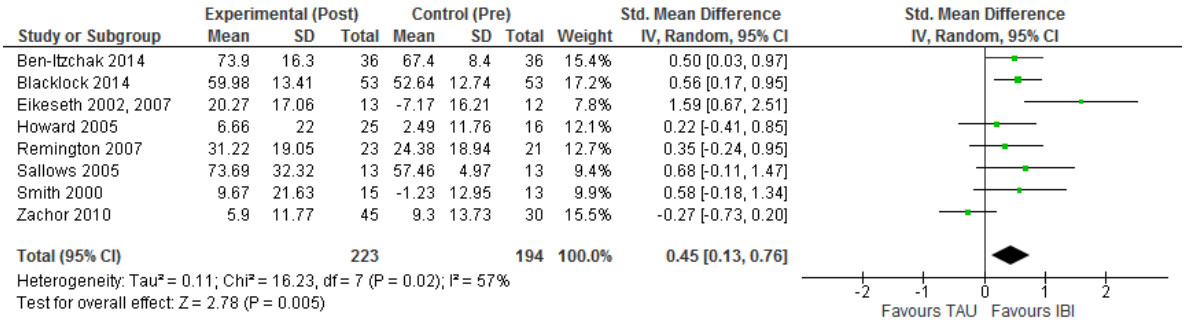
IQ≥70: ES=0.06, 95% CI -0.40 to 0.52, p<0.81; intake IQ 55.01 to 69.99: ES=0.96, 95% CI -0.26 to 2.17, p<0.12; intake IQ ≤55: ES=0.50, 95% CI 0.27 to 0.74, p<0.0001). However, findings from the subgroup analyses which favoured older age and a moderately low IQ were not statistically significant. Moreover, intervention effects tended to be somewhat higher among controlled studies (ES=0.61, 95% CI 0.24 to 0.99, p<0.001), as compared with before-and-after uncontrolled studies (ES=0.55, 95% CI 0.19 to 0.91, p<0.003).

The funnel plot of the standard error as a function of the SMD effect size of each study was noticeably asymmetric (see Figure 12 in Appendix 7), with several smaller studies clustering to the right of the mean. Although publication bias may be present based on visual impression, an objective measure of small study effects is required to confirm the validity of this inference.

VABS Communication

The SMD effect size across studies for change in daily communication skills, measured using the VABS communication domain and covering a total of 315 participants, was 0.45 (95% CI 0.13 to 0.76, p<0.005). Although there was evidence of substantial statistical heterogeneity between the eight studies, as indicated by the I^2 statistic (57%) and the statistically significant Q-statistic (Q(7)=16.23, p=0.02), the small number of studies included in the meta-analysis precluded any further investigation of the influence of heterogeneity on the pooled effect size estimate. Figure 4 shows the effect of IBI on participant's communication skills for the included studies.

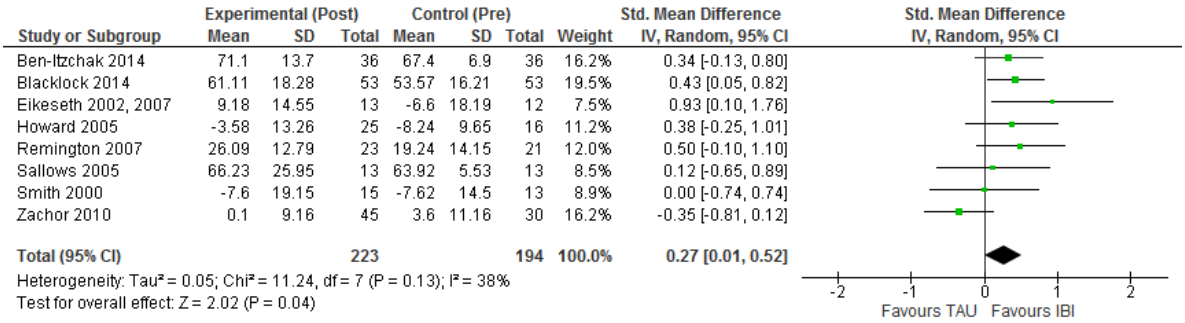
Figure 4. Forest plot of comparison: IBI vs TAU, outcome: 1.3 VABS Communication



VABS Daily Living Skills

The SMD effect size across studies for change in daily living skills, measured using the VABS daily living skills domain and covering a total of 315 participants, was 0.27 (95% CI 0.01 to 0.52, p<0.04). Although there was evidence of possible statistical heterogeneity between the eight included studies, as indicated by the I^2 statistic (38%) and the Q-statistic (Q(7)=11.24, p=0.13), the small number of studies included in the meta-analysis did not allow for any further exploration of the influence of heterogeneity on the pooled effect size estimate. Figure 5 shows the effect of IBI on participant's daily living skills for the included studies.

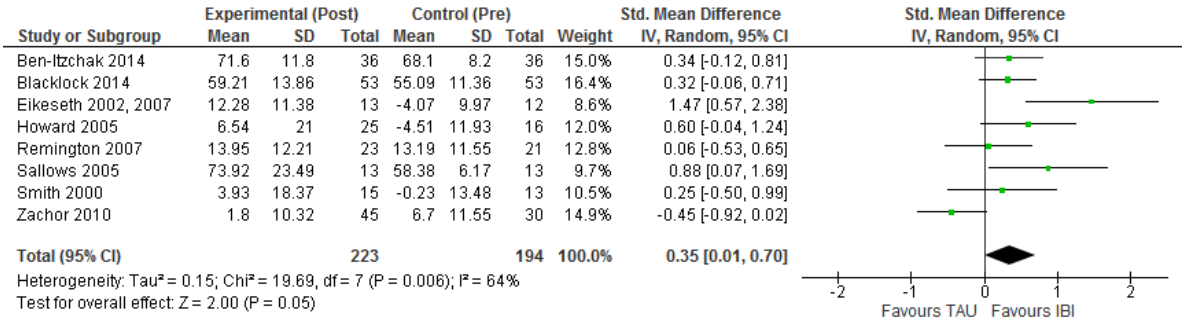
Figure 5. Forest plot of comparison: IBI vs TAU, outcome: 1.4 VABS Daily Living Skills



VABS Socialization

The SMD effect size across studies for change in socialization skills, measured using the VABS socialization domain and covering a total of 315 participants, was 0.35 (95% CI 0.01 to 0.70, p<0.05). Although there was evidence of substantial statistical heterogeneity between the eight included studies, as indicated by the I^2 statistic (64%) and the statistically significant Q-statistic (Q(7)=19.69, p=0.006), the small sample of studies included in the meta-analysis prevented further investigation of the influence of heterogeneity on the pooled effect size estimate. Figure 6 shows the effect of IBI on participant's communication skills for the included studies.

Figure 6. Forest plot of comparison: IBI vs TAU, outcome: 1.5 VABS Socialization



3.3.3 Intervention effects among studies excluded from meta-analysis

A total of 11 of 24 studies selected for inclusion in this review were not synthesized quantitatively in a meta-analysis estimating the effects of treatment with IBI on cognitive functioning or IQ. These studies were excluded for various reasons, including the reporting of partial outcome data which did not permit the calculation of a standardized mean difference effect size,(79,69,83,87) the absence of participant IQ assessment (3 studies) or the lack of reporting of full-scale IQ scores,(70,76,77,85,88) as well as overlap of participant data between studies.(80,83)

Of the eight studies which measured therapeutic progress using IQ, four were non-randomized controlled comparisons while the remainder did not have a control group. Findings related to change in IQ following IBI treatment reported in these studies were generally consistent with the magnitude and direction of the previously reported pooled effect estimate for cognitive functioning. Namely, Cohen et al. (2006) reported a 25-point mean increase in IQ score among participants in the experimental group, as compared with an increase of only 14 points in the control group over a 36-month follow-up period. A significant difference in IQ scores of about 19 points was observed between the treatment and control group in the study by Flanagan et al. (2012) after about 28 months of treatment, with results favouring the IBI group over the wait-list controls. Moreover, Freeman and Perry (2010) noted an increase in about 11 IQ points among a subset of their study sample (n=20) which had complete information on participants' cognitive levels at intake and discharge, and Perry et al. (2013b) observed that younger participants (2-5 years) made average gains of about 17 IQ points at treatment exit, as compared to a mere 2-point improvement in mean IQ scores among the older group aged 6-14 years; both studies followed children's progress in an IBI program over a mean course of about 20 months. In contrast to studies showing a positive effect of IBI on the cognition of preschool-aged children, there was one controlled comparison by Zachor and Ben-Itzchak's (2010) which did not observe a significant change in cognitive abilities between the treatment and control groups following 12 months of school-based IBI therapy. Finally, the effect of IBI on cognitive functioning was unclear in studies by Ben-Itzchak and Zachor (2009), Perry et al. (2013a), and Zachor et al. (2007) given that change in IQ from intake to the last follow-up was not explicitly measured; rather, IQ was treated as an independent or predictive variable in these analyses.

Similarly to the meta-analysis which measured the effect of IBI on the cognitive performance of children with ASD, there were 12 of 24 selected review studies which did not contribute any data to the pooled effect estimates regarding adaptive behaviour composite or associated VABS domains. Reasons for exclusion comprised the reporting of partial outcome data which precluded the estimation of the SMD statistic, (69,76,83) the absence of a full assessment of adaptive functioning or the lack of meaningful reporting of data relating to participants' overall adaptive skills, (70,71,84,85,87,94) as well as overlap of participant data between study samples. (78,80,83)

Of the six studies which measured therapeutic change between and within participants using the Vineland Adaptive Behaviour Scales, only two studies were controlled comparisons while the rest did not have a control group. Findings relating to a functional change in adaptive skills following IBI were mixed across these studies; yet, results generally followed the direction of the previously reported pooled treatment effect size for the VABS composite and weighted mean effect sizes for the associated subdomains. More specifically, Cohen et al. (2006) noted an average increase of 9 points in VABS composite scores among the IBI treatment group, while participants in the comparison group experienced a 4-point decline following three years of treatment; significant and similar differences were also observed in each of the constituent scales with the exception of VABS socialization where a non-significant trend was observed. Moreover, Perry et al. (2008) found that while children who received IBI for a mean duration of about 18 months improved significantly on all domains of adaptive functioning (n=274), large gains were noted only in the VABS Age Equivalent scores, while differences in VABS standard scores, which are corrected for age, were generally quite

small and only statistically significant for the VABS Communication and Socialization subdomains. A similar trend was observed within a smaller sample of participants (n=81) in the study by Freeman and Perry (2011) whereby improvement in adaptive functioning was only significant in VABS Age Equivalent scores, as compared with standard scores which remained fairly stable; this finding is perhaps not surprising given that participant data for this analysis was drawn entirely from the Perry et al. (2008) study. Another uncontrolled trial by Perry et al. (2013b) which examined treatment response of a matched sample of younger (2-5 years) versus older (6-14 years) children during a course of 20 months of IBI revealed that adaptive gains were more modest and were similar across groups (VABS composite standard score increased by 5 points and by 4 points in the younger and older group, respectively); age-equivalent scores at treatment exit were not reported. Finally, the influence of IBI treatment on adaptive functioning was unclear in studies by Perry et al. (2013a) and Stoelb et al. (2004) given that adaptive gains were not explicitly measured at admission to IBI and following treatment discharge; rather, these studies treated measures of adaptive behaviour as independent or predictive variables within the analysis.

3.3.4 Adverse events

No adverse events or deterioration on primary or secondary outcome measures were reported as a result of treatment in any study.

3.4 Predictors of treatment response

A wide range of variables which appear to be related to varied outcomes across study participants were examined statistically across 16 of 24 (67%) studies included in this review,(79,81,70,71,74–76,82–86,89,90,92–94) while the remaining eight studies (33%)

did not explore any active ingredients of effective treatment.(80,69,72,73,83,87,88,91) A total of five predictor variables were examined statistically across two or more studies; the five predictors included cognitive functioning as measured by IQ (11 studies), children's chronological age at treatment onset (11 studies), adaptive functioning (7 studies), severity of symptoms or psychopathology (4 studies), and treatment duration (2 studies). Table 6 of Appendix 5 presents a summary of findings for each of the 16 studies reporting on predictors of treatment response, detailing the specific predictor variables examined, the observed associations, and whether or not findings were statistically significant. What follows is a synthesis of the results by predictor variable.

Cognitive functioning (IQ). A total of 11 of 24 (46%) studies statistically examined IQ as a predictor of treatment response.(81,71,74,75,82–86,90,92,93) Of these, nine studies found significant associations between IQ at intake and various outcome measures. Harris and Handleman (2000), for instance, found that children who had higher IQ scores at admission to IBI were more likely to be placed in regular education classes at follow-up, as opposed to special education ($r=0.655$, $p<0.005$).(71) A significant association was also present between higher IQ at discharge and regular classroom placement at follow-up ($r=0.779$, $p<0.005$), although this relationship seems somewhat intuitive. Blacklock et al. (2014) observed a strong linear relationship between full-scale IQ at baseline and all follow-up outcome variables, including full-scale IQ ($r=0.65$, $p<0.01$; $n=63$), mental age ($r=0.64$, $p<0.01$; $n=63$), cognitive rate of development ($r=0.49$, $p<0.01$; $n=61$), adaptive behaviour standard scores ($r=0.66$, $p<0.01$; $n=49$), adaptive behaviour age equivalent scores ($r=0.70$, $p<0.01$; $n=64$), and adaptive rate of development ($r=0.31$, $p<0.01$; $n=49$).(82) Similar relationships were also observed within two prospective uncontrolled multiple-group

comparisons by Hayward et al. (2009) and Sallows and Graupner (2005). While Hayward et al. (2009) found that baseline cognition was significantly correlated with follow-up IQ ($r=0.66$, $p<0.01$), visual-spatial or non-verbal IQ ($r=0.60$, $p<0.01$), and the composite measure of adaptive behaviour ($r=0.57$, $p<0.01$), the authors also observed that correlations between intake IQ and treatment gains (change scores) on all measures were non-significant.(90) Sallows and Graupner (2005) further assessed the predictive power of IQ at one year after IBI onset with three outcome variables (full-scale IQ, language, and social skills) following three years of treatment and observed a significant positive relationship between IQ after one year of IBI and full-scale IQ scores at the three-year treatment mark ($r=0.75$, $p<0.01$).(74) It was unclear, however, whether the predictive modeling among these uncontrolled trials was conducted using data from either the clinic-based or parent-managed/parent-directed treatment group alone, or if correlations represented the relationship between pre-treatment variables and outcomes for all study participants, irrespective of group assignment. Furthermore, there were three studies which used various analysis of variance methods to investigate the predictive utility of intellectual functioning on treatment response.(84–86) Namely, Ben-Itzchak and Zachor (2007) found that children belonging to a higher cognitive ability group ($IQ \geq 70$) showed greater progress in receptive and expressive language, play skills, and non-verbal communication skills, as compared with children in a low IQ (<70) group.(84) The same authors also found a significant negative correlation between IQ and the ADOS reciprocal-social interaction measure ($r=-0.606$, $p<0.01$), which suggested that higher IQ scores were more likely to result in fewer deficits in social interaction skills. Ben-Itzchak et al. (2014) similarly examined differences in treatment response among children belonging to high ($DQ \geq 70$) and low ($DQ<70$) cognitive ability groups and found that while improvement in autism severity between the

two groups was not affected by baseline cognition, significant increases in the communication, socialization, and daily living domains of adaptive functioning were noted only in the higher cognitive ability group, whereas standard scores remained unchanged among children with lower cognitive function. These authors also found that children with lower cognitive functioning experienced gains in fine-motor and receptive language MSEL subdomains, while decreases in standard scores on the same measures were observed in the higher cognition group. Another study by Ben-Itzchak and Zachor (2009) compared outcomes of children whose diagnostic classification (severity) remained the same after treatment (i.e. unchanged group) with those of children who improved their diagnosis post intervention (i.e. improved group); findings revealed only one significant trend: the improved group had significantly better non-verbal and verbal scores on the MSEL standardized measure as compared with the unchanged group. Furthermore, regression modeling techniques were applied within two of the 11 studies which statistically examined IQ as a predictor variable. Specifically, Perry et al. (2011) carried out a stepwise linear regression for eight primary dependent variables at follow-up and found that baseline IQ accounted for 53% of the variance in IQ at treatment discharge (Step 1 of regression) and that baseline IQ accounted for a significant but small amount of incremental variance for adaptive behaviour (ΔR^2=0.053, p<0.001) and disease severity (ΔR^2=0.074, p<0.001), beyond that associated with the initial value of IQ.(81) These authors also showed that there were significant and strong correlations between initial IQ and all outcome variables, including full-scale IQ (r=0.73, p<0.01), adaptive behaviour composite (r=0.67, p<0.01), and severity of symptoms (r=-0.42, p<0.01). Similarly, Perry et al. (2013a) carried out a hierarchical multiple regression on data from 207 children enrolled in the Ontario IBI program and found that baseline IQ, controlling for treatment duration, accounted for 59%

of the variance in IQ at follow-up ($p<0.001$) and that initial IQ accounted for a significant and substantial proportion of variance in adaptive behaviour standard scores at follow-up ($\Delta R^2=0.44$, $p<0.001$).(83) Initial IQ did not however predict the magnitude in IQ gains (i.e. change in IQ from baseline to follow-up), and while children with higher skill levels before treatment tended to have higher skill levels after treatment, those who were higher functioning cognitively were not the ones who necessarily made the largest IQ gains. Finally, there were only two controlled comparison studies which assessed the predictive value of IQ on treatment response. Eikeseth et al. (2007) found that intake IQ was strongly and significantly associated with follow-up IQ ($r=0.60$, $p<0.05$) and adaptive behaviour scores, except the socialization subdomain score on the VABS measure (AB composite: $r=0.58$, $p<0.05$); similar correlations were found in the previous 2002 publication by the same authors.(92,93) Although children with higher intake IQ were more likely to score higher on follow-up outcome measures, the authors found that they did not tend to make larger gains in IQ, language or adaptive scores. Conversely, Smith et al. (2000) did not find baseline IQ to be reliably associated with full-scale IQ at follow-up and reported that IQ was not significantly correlated with any other measured outcome variable.

On the whole, there is some evidence that higher baseline cognition may be associated with better outcomes following treatment with IBI. However, there were only three studies which statistically examined the relationship between baseline IQ scores and IQ treatment gains (i.e. change in IQ from baseline to follow-up), while most other studies explored the predictive utility of baseline IQ on post-treatment scores. Of those studies which attempted to quantify the association between intake IQ and treatment gains (or

change scores at IBI discharge), findings were either non-significant or revealed that initial IQ did not reliably predict the magnitude of IQ gains at follow-up.

Child Age. Eleven of the 24 (46%) included studies statistically examined child age at intake as a predictor of treatment response.(79,81,70,71,76,82,83,85,90,92–94) Of these studies, five reported children's baseline chronological age as a significant predictor of treatment outcome, while another six did not find a significant relationship between initial age and various outcome measures. Studies which reported significant results consistently identified younger age at entry to IBI as predictive of optimal treatment response.(81,70,71,83,94) In particular, Perry et al. (2011) found that age at entry was significantly negatively correlated with IQ ($r=-0.39$, $p<0.01$) and the adaptive behaviour composite measure ($r=-0.43$, $p<0.01$) at treatment exit, suggesting that children who started IBI younger tended to score higher at discharge on cognitive and adaptive assessments. The authors also found that younger age at entry was correlated with milder autism severity at exit ($r=0.18$, $p<0.01$), and findings from a stepwise linear regression analysis revealed that age accounted for a significant, but very small amount of unique variance for IQ ($\Delta R^2=0.063$, $p<0.001$) and autism severity ($\Delta R^2=0.015$, $p<0.05$), but made no contribution to the adaptive behaviour composite score at follow-up. Moreover, findings from a hierarchical multiple regression analysis by Perry et al. (2013a) conducted using data from 207 children aged two to 14 years (mean=5.33, SD=2.01) demonstrated that young age at admission into IBI resulted in higher cognitive (but not adaptive) functioning at the end of treatment, even after controlling for treatment duration and the child's initial cognitive level ($\Delta R^2_{IQ\ at\ T2}=0.05$, $p<0.001$; $\Delta R^2_{total}=0.064$, $p<0.001$). In this study, age at IBI entry was also the only predictor that was related to change in IQ, that is, cognitive gains during

intervention. Granpeesheh et al. (2009) further demonstrated that there was a significant linear relationship between the examined predictor variables (age and treatment intensity) and the number of mastered behavioural objectives among children in three age groups spanning two to 12 years; however, results of this study warrant careful interpretation given the limitations associated with using mastered behavioural objectives as a measure of therapeutic progress. Additionally, Harris and Handleman (2000) found that children who were younger at admission to IBI were more likely to be placed in a regular education setting at follow-up, as opposed to special education, than were children who were older at intake ($r=0.658$, $p<0.005$); they also found that younger children had higher IQ scores at discharge than those who entered at an older age ($r=-0.401$, $p<0.025$). Although these findings are significant and lend support for early intervention, the validity of academic placement as an outcome measure has been highly criticized and the true magnitude of the relationship between initial age and discharge IQ is uncertain given the relatively young age of the study sample (mean=49 months, range=31-65 months). The final analysis which reported significant results regarding the predictive value of chronological age in estimating response to treatment was conducted by Virues-Ortega et al. (2013) by way of multilevel regression modeling; specifically, the authors found that age was the second most efficient predictor in a two-predictor model (keeping intervention time as the first factor) in terms of improving fit of the regression models for measures of gross motor function, receptive language, self-care, and social behaviour.

In contrast to the aforementioned findings, there were five studies, including two controlled comparisons by Eikeseth et al. (2002, 2007) and Flanagan et al. (2012), which did not find an association between the age at which children started treatment and outcome

or amount of change in scores (79,76,82,85,92,93); however, these results were not statistically significant. This is particularly striking for the study by Blacklock et al. (2014) which found weak linear relationships between age at entry with outcomes at treatment discharge among participants aged six to 14 years (88.81±21.94 months). Based on a scatterplot analysis by the same authors, it is possible that there may be a curvilinear relationship between child's age at intake and treatment outcomes at follow-up given that more variable outcomes were noted for the relatively younger children within the sample, as compared with older children (>8 years) which had uniformly low and less variable outcomes.

On the whole, the evidence suggests that younger age at intake, particularly preschool age, may be associated with better outcomes following treatment with IBI. Certain factors, however, limit the interpretability of the results, including the paucity of significant associations found among controlled comparison studies.

Adaptive behaviour. A total of seven of 24 (29%) studies included in this review statistically examined adaptive functioning at intake, measured using the VABS standardized assessment, as a predictor of treatment response.(79,81,74,82,85,90,92,93) Four of these studies found that adaptive functioning at treatment onset was a reliable predictor of effective treatment, while three studies did not report statistically significant results. Studies which reported significant results commonly suggested that higher initial adaptive skills were associated with positive therapeutic progress.(79,81,82,90) Specifically, Perry et al. (2011) found that initial Vineland adaptive behaviour composite (ABC) scores were significantly and highly correlated with full-scale IQ at follow-up ($r=0.72$, $p<0.01$), as well as follow-up VABS composite scores ($r=0.77$, $p<0.01$); baseline

ABC scores were also significantly negatively correlated with severity of symptoms at treatment exit ($r=-0.51$, $p<0.01$). Results of a stepwise linear regression by the same authors further revealed that initial ABC scores accounted for significant incremental variance in IQ ($\Delta R^2=0.059$, $p<0.001$) and autism severity ($\Delta R^2=0.118$, $p<0.001$) at follow-up, beyond that associated with the initial ABC value. Blacklock et al. (2014) observed similar associations between intake adaptive skills and several measured outcomes within a sample of school-age participants (mean age=88.81 months, range=70-163 months): VABS ABC standard scores at intake were highly and significantly associated full-scale IQ ($r=0.91$, $p<0.01$, $n=61$), mental age ($r=0.84$, $p<0.01$; $n=61$), cognitive rate of development ($r=0.32$, $p<0.05$; $n=61$), ABC standard scores ($r=0.75$, $p<0.01$; $n=45$), ABC age equivalent scores ($r=0.75$, $p<0.01$; $n=60$), and adaptive rate of development ($r=0.71$, $p<0.01$; $n=46$) at follow-up. Furthermore, results of a hierarchical multiple regression analysis from a wait-list controlled comparison study by Flanagan et al. (2012) showed that higher initial adaptive skills, controlling for duration and initial age, contributed a large amount of variance across groups ($\Delta R^2=0.262$, $p<0.001$). Finally, Hayward et al. (2009) also found that baseline adaptive skills were significantly correlated with all outcome measures (full-scale IQ at follow-up: $r=0.56$, $p<0.01$; non-verbal IQ at follow-up: $r=0.41$, $p<0.01$; ABC at follow-up: $r=0.53$, $p<0.01$); however, the authors found that correlations between intake ABC scores and treatment gains (change scores at follow-up) were non-significant.

While the aforementioned analyses suggest that children with higher baseline adaptive functioning may respond in a more favourable manner to IBI, as compared with children with relatively lower adaptive skills at intake, three additional studies by Ben-Itzchak and Zachor (2009), Eikeseth et al. (2007), and Sallows and Graupner (2005) found

that pre-treatment adaptive behaviour was not reliably associated with outcome or amount of change in outcome measures (74,85,93); however, results of these analyses were not statistically significant.

Although current evidence suggests that higher pre-treatment adaptive functioning may be predictive of better outcomes following treatment with IBI, data on this topic are limited. Additional predictive analyses are needed, especially from controlled studies, to make reliable inferences regarding the impact of pre-treatment adaptive skills on treatment response.

Severity of symptoms. There were only four of 24 (17%) included studies which statistically examined disease severity as a predictor of treatment response,(79,81,84,90) of which only two found statistically significant results. Namely, Perry et al. (2011) found modest negative correlations between initial autism severity scores (CARS) and discharge full-scale IQ ($r=-0.43$, $p<0.01$) and ABC standard scores ($r=-0.34$, $p<0.01$), as well as a positive correlation with CARS scores at treatment exit ($r=0.52$, $p<0.01$). This finding effectively lends support for a milder initial autism severity as a predictor of better outcomes with IBI. However, a stepwise linear regression analysis by the same authors indicated that pre-treatment autism severity did not account for any variance in outcome measures other than post-treatment IQ scores ($\Delta R^2=0.038$, $p<0.001$). Perry et al. (2011) also found that when initial IQ, age at IBI entry, and initial adaptive skill level were controlled in a hierarchical multiple regression analysis, initial severity of symptoms (CARS) contributed an additional 2.0% of variance to predictions in follow-up IQ, while a considerable amount of variance ($\Delta R^2=0.637$, p=NR) can be predicted based on the combination of all four predictive variables. Similarly to Perry et al. (2011), findings from a

hierarchical multiple regression analysis by Flanagan et al. (2012) found that when controlling for treatment duration, initial age and adaptive skill level, milder initial autism severity appeared to contribute an additional 1% of variance to predictions in follow-up IQ (ΔR^2=0.013, p<0.092). Therefore, regression analyses suggest that initial autism severity may not be a meaningful predictor of treatment response when variables such as intake age and baseline adaptive functioning are controlled.

In contrast to the observed relationships in the previous two studies, Ben-Itzchak and Zachor (2007) found that pre-treatment autism severity in communication and in reciprocal-social interaction domains did not impact the gain in IQ scores among participants, and Harris and Handleman (2000) did not find a significant correlation between severity of symptoms (CARS) and participants' classroom placement at follow-up.

On the whole, the evidence base relating to the predictive utility of autism severity is limited. Although two of the four studies which examined the impact of initial autism severity levels on treatment outcomes support the presence of a milder symptomatic profile as predictive of better outcomes following IBI, additional data are required, particularly from controlled comparisons, to draw reliable conclusions about the true impact of baseline disease severity on treatment response.

Treatment duration. Three of 24 (13%) included studies statistically examined the duration of IBI treatment as a predictor of treatment outcome.(79,83,94) Namely, Flanagan et al. (2012) conducted a hierarchical multiple regression analysis using data from their matched-pairs comparison of 122 participants, 61 of which received IBI for at least 12 months (mean duration of 28 months). They found that while treatment duration initially contributed

significantly to predictions, it did not remain a significant predictor after controlling for group membership and other intervention variables. Another hierarchical multiple regression analysis conducted by Perry et al. (2013a) among an older group of participants (mean age=5.33±2.01 years, range=2.08 to 14.50 years) that received IBI treatment for an average of 20 months (range 10-55) revealed that longer treatment duration was associated with slower rates of cognitive and adaptive development between intake and program discharge. The authors also found that the duration of IBI was not significantly associated with other measured outcomes, suggesting that children who were in the IBI program longer were not necessarily showing better outcomes on full-scale IQ, adaptive behaviour composite, or change in IQ at treatment exit. Finally, Virues-Ortega et al. (2013) conducted a series of multilevel regression models using different sets of predictors in order to select models which would maximize goodness-of-fit for a given outcome when compared to an unconditional baseline model, and they found that intervention duration had a positive impact on the model's fit, but to a lesser extent than total intervention time (weekly hours multiplied by total weeks of treatment) in all eight measured outcomes. Although methodological contributions of this study were clear, the clinical or practical implications of the findings relating to the predictive utility of treatment duration remain unclear.

To date, there are few studies that have identified a clear statistical association between treatment duration and therapeutic progress following IBI treatment. Consequently, it is premature to conclude that a specific treatment duration may adversely affect IBI treatment response.

CHAPTER IV: DISCUSSION

4.1 Summary of main results

Effects of intervention

A total of 24 unique studies which compared the effects of IBI to TAU or no treatment in preschool and school age children with an ASD were identified. Sixteen studies used an uncontrolled before-and-after design, while eight were controlled comparison studies, one of which used a RCT design. Meta-analyses were conducted using a random-effects model on thirteen and twelve studies, respectively, for full-scale IQ and adaptive behaviour composite; data from eight studies were additionally aggregated for each of the VABS adaptive behaviour domains. On the whole, findings revealed that IBI improves full-scale IQ (SMD ES = 0.66, $p<0.00001$) and adaptive skills (SMD ES = 0.57, $p<0.00001$) for this population; moderate SMD effect sizes were also found in communication skills (SMD ES = 0.45, $p<0.005$), daily living skills (SMD ES = 0.27, $p<0.04$), and socialization (SMD ES = 0.35, $p<0.05$). Results of subgroup analyses performed on the IQ and VABS ABC standardized measures further revealed that the effect of treatment may differ between preschool and school age children, across different pre-treatment cognitive levels, and based on the format of treatment delivery. Namely, the effect of IBI on both of these measures tended to be stronger for preschool aged participants (<48 months at intake), for participants without significant cognitive impairment at treatment intake (i.e. intake IQ >55), and for those following a UCLA-based IBI program. Controlled trials also tended to show higher treatment effects in comparison with uncontrolled studies on both measures; however, the reasons underpinning this

difference in treatment effect remain elusive and may be due to limitations in the statistical techniques used.

Due to reliance on only a portion of selected review studies for meta-analysis, most of which comprised uncontrolled studies, as well as the overall moderate rating given to the body of evidence, results should be interpreted with caution. Additional data, especially from controlled comparison studies, could very well change the estimate of treatment effect and the confidence placed on its precision. Moreover, the amount of benefit that the observed treatment gains may contribute to the quality of life of children and their families over a longer term is an issue that merits further investigation and follow-up.

Predictors of treatment response

Sixteen of 24 studies included in this review statistically examined predictors of treatment response. A total of five variables which appear to predict optimal response or better outcomes with IBI were examined across two or more studies: cognitive level at treatment intake, intake chronological age, pre-treatment adaptive functioning and severity of symptoms, as well as treatment duration. Overall, results of predictive modeling across studies demonstrated that better outcomes with IBI were largely experienced by children who were relatively younger at treatment onset, those who had higher baseline levels of cognitive and adaptive functioning, as well as children who had a milder severity of symptoms at intake; the predictive utility of treatment duration revealed mixed results. However, these findings warrant careful interpretation given the variability and lack of justification regarding the choice of dependent variables used (and ultimately, agreement on that which constitutes better or 'best outcome' or optimal response), uncertainty

surrounding the appropriateness of some statistical approaches, and perhaps most importantly, the dominance of uncontrolled studies which limit the interpretation of variables associated with change in the treated group as actual predictors of treatment response (as not all of the observed change can be attributed to the effect of IBI).

4.2 Overall completeness and applicability of evidence

Several factors impact the completeness and applicability of findings of this review and meta-analysis. First, while the pooled estimates of the intervention effect suggest that IBI results in improved cognition and adaptive skills among children with an ASD, and that the magnitude of effects may be more pronounced in preschool aged children as opposed to children who have enrolled in school, these findings are based on an evidence base which is largely composed of uncontrolled before-and-after studies. The lack of a control makes it difficult to attribute any observed improvement in intellectual or adaptive functioning to the effect of IBI therapy alone since the design of the study does not allow control for the effect of maturation or the natural course of a child's development. In other words, improved functioning following IBI may, in part, be due to a natural progression in development or learning that occurs as a child ages or matures over the course of follow-up, and not necessarily wholly attributable to the success of behavioural therapy. For this reason, studies which lack a control group often tend to overestimate the true intervention effects. Reliance on published evidence which is composed, in large part, of repeated measures studies with no control group (or uncontrolled multiple-group comparisons) limits the internal validity of that body of evidence and, in turn, makes it difficult to generalize findings about to the strength of IBI to contexts outside of the study setting. Second, the lack of a standardized control group among controlled comparisons may also limit the

generalizability of results, especially where TAU conditions varied widely in the application of intervention techniques. Specifically, while all controlled studies compared the treatment group with a group not receiving IBI, some control conditions incorporated elements of ABA as part of a multi-method eclectic approach and/or provided services at a similar intensity to the IBI group, while other TAU groups comprised children whose caregivers were not actively seeking behavioural services or consisted of wait-list participants not yet receiving publicly-funded IBI programming. Third, randomization to group assignment was not implemented across the majority of controlled studies (with the exception of one RCT), which raises serious internal validity concerns (i.e. lack of equivalent groups). Fourth, the intervention effects estimated through meta-analysis may not be generalizable to children with significant cognitive impairments (e.g. intellectual disability) or those with comorbid conditions given that participants with these attributes were typically absent from the study samples of included studies. In fact, a number of studies specified the presence of severe medical conditions other than ASD or genetic disorders and/or a low pre-treatment IQ score (e.g. IQ<50) as exclusion criteria during participant recruitment. Similarly, there were several studies which specified a very narrow age range as part of the participant eligibility criteria (e.g. intake CA >24<42 months) prior to enrolment in an IBI program. Nevertheless, there were several recent community-based studies conducted within a Canadian setting which examined the effect of IBI across a broad age range of participants, and which did not exclude participants on the basis of comorbid disorders or a relatively lower cognitive ability. Despite the inclusion of more heterogeneous samples within the recent published literature, the ability to generalize the magnitude of effect IBI has on individuals with an ASD who concurrently suffer from another medical disorder or whose intellectual ability is significantly diminished, across a

variety of settings, remains limited. Therefore, while the current published evidence suggests that differential treatment effects may exist among preschool and school aged children with an ASD, additional research using rigorous methods, standardized control groups, random assignment of group membership, and heterogeneous samples of participants including a broad age range may be needed before generalizations regarding the effect of IBI in this population (and sub-populations) can be made with confidence.

The applicability of findings relating to predictors of treatment response is also limited by several factors. While younger age, increased cognitive and adaptive ability, as well as a milder symptomatic profile appear to be related to better outcomes following treatment with IBI, data which have allowed to statistically examine these relationships are limited, and the majority of predictive variables have been identified from datasets of uncontrolled studies using, at times, potentially inappropriate statistical methods. Yoder and Compton (2004) have suggested that few studies appropriately identify predictors of treatment response, and point out that research which predicts the presence or amount of change on a given outcome among the experimental group of an uncontrolled study is merely examining predictors of growth within that sample, rather than predictors of treatment response.(96) The authors further explain that a treatment response is typically only a small portion of the total observed growth within a sample, and that predictors of treatment response refers to "correlates of change due exclusively to the treatment.(96)" As a result, variables associated with change in the treated groups of uncontrolled studies in this review may not necessarily reflect actual predictors of treatment response as not all of the change or growth observed among participants can be exclusively attributed to the effect of IBI. Moreover, the paucity of significant associations stemming from the

predictive modeling results of controlled comparison studies is also of potential concern. Non-significant findings among school aged samples are particularly troubling; yet, it seems plausible that, given a large enough sample, admission into IBI after reaching school age may not be reliably associated with optimal treatment response, and that IBI might not be equally effective across child and adolescent groups. Such inferences, however, are currently unsupported by the published literature relating to predictors of treatment outcome. Finally, there were several inconsistencies in the choice of dependent variables across predictive modeling studies, suggesting that there is a general lack of agreement regarding the operational definition of a 'best outcome' or optimal treatment response, and that a definition of 'responders' and 'non-responders' to treatment is often independent of the treatment goals. In light of these limitations, findings warrant careful interpretation, and additional data, especially from experimental studies with a control group, may help to determine and to draw reliable conclusions regarding the true impact of relevant participant and intervention characteristics on response to IBI.

On the whole, although the available evidence supports the use of IBI among children with an ASD, and while it appears to suggest that preschool age children respond better to treatment than school age populations, the variability in interventions including the duration and intensity, differences in the intervention content and delivery, as well as the variability in participant characteristics and the experimental design of studies, means that these important questions cannot yet be answered will full confidence. Indeed, certain factors need to be considered when making any generalisations about the body of evidence. Nonetheless, this review provides a basis for concluding that IBI does appear, on average,

to lead to positive changes in cognition and adaptive skills among preschool and school age children with an ASD.

4.3 Quality of the evidence

This review considered 24 unique studies, representing 1,816 children with an ASD. Of these young participants, 1,156 (63.7%) were aged, on average, above 48 months at intake, while the remainder comprised much younger, preschool aged children. Additionally, there were only three samples across the included studies where the youngest participant was aged above 4 years at baseline. In the meta-analyses, data from a maximum of 492 children (Analysis 1.1: IQ) were statistically combined, with 62 (Analysis 1.1: IQ) to a maximum of 123 children (Analysis 1.2: VABS ABC) making up the control conditions. In addition, estimates from 81 and 240 participants with a mean intake age above 48 months were combined in meta-analysis for full-scale IQ and VABS AB composite, respectively. Therefore, while a considerable portion of the total number of participants across the included studies had, on average, attained school age (>48 months), only a fraction of the estimates regarding outcomes experienced by these participants was available for pooling in the quantitative synthesis.

The quality of the evidence, as rated by the modified Downs and Black (1998) checklist, is affected by a number of factors, with the majority of studies receiving a low or moderate rating. This rating mostly reflects concerns with the external validity, internal validity (confounding), and statistical power domains of the quality assessment tool. Of particular concern is the use of non-randomized trials, retrospective study design, small samples of participants, incomplete outcome data, inadequate adjustment for confounding

in the analyses, and perhaps most markedly, the dominance of uncontrolled, repeated measures studies. Furthermore, intervention providers and the children's parents were aware of, and in some cases selected, the treatment status, which effectively increases the risk of performance bias; however, this risk is difficult to mitigate given the nature of the intervention. While blinding of parents or treatment staff was not possible, about 50% of included studies successfully blinded those measuring the main outcomes of the intervention; nevertheless, the risk of detection bias remains high. Additionally, because data from studies which reported partial outcome measures were not aggregated in meta-analysis, these missing data have the potential to bias the findings of the meta-analyses; however, based on the results reported in the individual reports of relevant studies, missing data are unlikely to influence the direction of the observed effect. Given the various threats to both internal and external validity, results should be interpreted cautiously. Finally, the risk of publication bias cannot be ruled out.

The quality of the evidence in this review is also reflected in the extent to which procedural fidelity was measured across the included studies. Namely, while more than half of the studies included in this review contained elements to maintain treatment integrity, indirect measures were on average more common than direct measures in assessing treatment adherence and therapist competence. In using indirect measures of assessment, it becomes difficult to gauge definite levels of treatment integrity across and within studies since these measures can underrepresent or overemphasize true fidelity levels. Conversely, direct assessment methods may generate a more accurate portrayal of treatment integrity since direct measures may be less susceptible to bias and distortions in self-interest. With the exception of one study which reported direct measures of treatment adherence, therapist

competence, and treatment differentiation, many of the selected review studies did not appear to measure therapy implementation at a level sufficient enough to draw definitive conclusions about the quality and similarity of treatment across participants or within a participant across therapists. Previous studies examining IBI implementation have found that some therapists and parents experienced difficulty achieving high levels of treatment integrity,(97,98) and it is well documented that questionable fidelity can limit research conclusions in behavioural research.(99–101) Therefore, inferences regarding the impact of treatment integrity levels on therapeutic change observed in studies included in this review should be made with caution, and future studies should endeavour to measure procedural fidelity directly across participants, therapists, and conditions. Once acceptable levels of treatment integrity have been achieved, analyses relating to the impact of different levels of integrity may allow to determine the levels of precision necessary for IBI to be optimally effective.

4.4 Potential biases in the review process

While bias may exist in the methods used across included studies in a review, it can also be introduced in the methods used during the systematic review process, commonly referred to as metabias.(102) There are three general types of metabias that may occur during the course of the review process: selection bias, information bias, and bias in the analysis. First, the risk of selection bias in the review process is high where unpublished studies tend to have different results than published studies (publication bias), where there is selective reporting of relevant outcomes, and where studies which are easier to find have different results from those that are more difficult to find (ascertainment bias). In this review, the likelihood that all relevant studies have been identified is relatively high owing

to the comprehensive and systematic search of the evidence across several electronic databases as well as the grey literature. Nevertheless, it is still possible that some relevant studies may have been missed. Similarly, the presence of publication bias cannot be ruled out. Second, concerns regarding the introduction of information bias in the review process relate to the accuracy of quality assessment, as well as the accuracy and completeness of the data abstraction that is done from the individual studies included in the review. In addition, the outcome of a systematic review, and meta-analysis where applicable, may be affected if study findings are known to the reviewer when study inclusion/exclusion criteria are defined or data are abstracted (inclusion bias). While the screening of electronic citations and full-text articles in this review was conducted using two independent reviewers, data abstraction was carried out through single data abstraction and verification by a second reviewer, as opposed to independent double data abstraction. In addition, only one reviewer performed the methodological quality assessment of included studies, as well as the assessment of procedural fidelity. As a result, information bias was not fully prevented during the course of the review; yet, the impact that this bias may have had on study findings is likely not significant. Moreover, given that study findings were unknown to the reviewer at the outset of the review process, the risk of inclusion bias is low. Finally, metabias may also be introduced in the analysis of a systematic review and meta-analysis through the choice of statistical methods used and the investigation of heterogeneity. Indeed, the decision to include non-randomized studies and statistically combine controlled and uncontrolled studies may have introduced some bias in the analysis of this systematic review and meta-analysis, even though the aggregation of data from studies of different designs was justified. Finally, the post hoc selection of subgroup analysis for exploring heterogeneity may also be a potential source of metabias in this review. On the whole,

while the presence of metabias in this review and meta-analysis is likely, standards for minimizing meta-bias have also been implemented, including a thorough search for relevant studies, the prevention of errors in data abstraction using verification by a second reviewer, as well as the consideration for the impact of the used methods of analysis.

4.5 Agreements and disagreements with other studies or reviews

This review and meta-analysis is the first to consider the effectiveness of IBI in both preschool and school age children with an ASD, and it is the first to incorporate published Canadian evidence.

Over the course of the last five years, however, six different systematic reviews with meta-analysis have been published,(60,103–107) all of which endeavoured to examine the clinical effectiveness of IBI (or ABA-based early intervention programs) in children with an ASD. Nevertheless, several factors distinguish each of the published reviews from one another, as well as from the current review and meta-analysis. First, the numbers of studies and the amount of participant data which have been previously synthesized, both qualitatively and quantitatively, have varied considerably. Virues-Ortega et al. (2010) published the largest review,(60) consisting of 22 studies (n=503), while the smallest review was published by Spreckley & Boyd (2009),(105) with four selected review articles (n=76). Second, although comparative effectiveness research relating to IBI has certainly increased over the years, and while it seems plausible that variation in the amount of data synthesized across reviews is attributable (at least in part) to a growing evidence base, the large variation in study inclusion criteria across the published reviews appears to be a more likely cause for the observed differences. For instance, most of the previous review authors

chose to focus on a much more restricted age range and include only preschool aged children. In addition, different definitions of IBI, or a narrower focus on only UCLA-based IBI studies, have also likely contributed to the differences in which studies were included in each of the previous reviews. Third, the decision to combine controlled and uncontrolled studies has also varied in previous studies, as well as the methods used for meta-analysis. Namely, four of the previous reviews have statistically combined controlled comparisons with pre/post one-group design studies,(60,104–106) while two review authors chose to only select controlled designs for inclusion in their quantitative synthesis.(103,107) Effect size calculations also varied across reviews between the use of the standardized mean difference (SMD) in four studies,(60,103,105,106) the standardized mean change (SMC) metric in one study,(104) and another study estimated effect size using the difference in means (MD).(107) Furthermore, analyses in one review were based on individual raw data gathered from selected study authors,(103) rather than group averages reported in original papers, and a fixed-effect meta-analysis was used in two previous reviews,(103,105) while three others used a random-effects model(60,104,107); one study did not report the approach used for data synthesis.(106) Finally, the authors of one review did not assess the methodological quality of included studies,(103) and only one review formally assessed procedural fidelity across the selected review articles.(104)

Despite the differences identified between previously published reviews with meta-analysis and this systematic review and meta-analysis, the results of this review are consistent with the majority of previously published studies. Specifically, five of the previously published meta-analyses demonstrated that IBI is an effective intervention for improving cognitive and adaptive outcomes in children with an ASD,(60,103,104,106,107)

while one review did not show positive effects in favour of IBI for IQ or adaptive behaviour.(105) However, while the authors of the latter review concluded that applied behaviour intervention (ABI) did not result in significant improvement in cognitive, language, or adaptive skills in comparison with standard care, their meta-analysis was based on only three studies, and suffered from a major methodological limitation (i.e. misinterpretation of a comparison group in one study), which effectively influenced the results of their meta-analysis.(105) On the whole, findings from this review and meta-analysis are in line with the direction of effects (albeit not necessarily magnitude of effects) found in previous quantitative syntheses. The quality of the evidence, however, still remains as a major concern.

4.6 Consideration for cost and cost-effectiveness

The importance of economic evaluation of health care interventions in informing resource allocation decision making has been well recognized.(108–110) While findings from clinical comparative effectiveness research can inform decisions regarding the use of drugs and other health care interventions or programs, the increasing availability of novel and costly health care interventions over time within a climate of constrained resources has led to a growing need to prioritize and ration health care resources. As a result, consideration for the budget impact of health care interventions, as well as their cost-effectiveness, has become increasingly important across many decision-making contexts and jurisdictions.

Cost-effectiveness of the Ontario IBI program: The need for an economic evaluation

Since the launch of the Ontario IBI program almost 15 years ago, funding for autism services in Ontario, particularly for IBI, has markedly increased over the years.(56) However, an assessment of the budget impact and cost-effectiveness of IBI in pre-school and school age children is not yet available in the public domain.

To date, one economic evaluation of the Ontario IBI program has been published which examined the cost-effectiveness of expanding this program to all children with an ASD in Ontario. Published in 2006 by Motiwala et al., this study specifically sought to examine the costs and consequences of expanding the Ontario IBI program from the reimbursement strategy at the time of the study (i.e. coverage provided to about one third of all ASD-affected children under the age of six with a severe diagnosis) to all children aged two to five in Ontario.(15) Comparators included (1) status quo provision, (2) expansion of IBI services, and (3) no intervention. Data on resource use and costs was obtained from the provincial government and comprised information on the hours and costs of IBI and the cost associated with educational and respite services. Treatment efficacy data were derived from the published literature and evaluated in terms of patients' levels of functioning (or rates of normalization) at the completion of a three-year IBI program: normal, semi-dependant, and very dependant functioning. Namely, it was assumed that the number of individuals attaining normal functioning was 25% for the *No Intervention* group, 26.9% for *Status Quo*, and 30% for the *Expansion* cohort. The distribution of individuals in a semi-dependant state was 25%, 34.3%, and 50%, respectively, for the *No Intervention*, *Status Quo*, and *Expansion* groups, while individuals whose level of functioning was assumed to be very dependent for those same groups was distributed at 50%, 38.9%, and 20%. Thus,

the authors assumed that expansion of IBI services would result in a higher proportions of individuals attaining normal or semi-dependent functioning, and a lower proportion of very dependent individuals, as compared with no intervention or status quo. Disease progression was modeled over the course of the "productive lifetime" (until the age of 65), and individuals' functional classification was assumed to remain constant over this time frame. Because caregiving costs typically increase for all individuals after the age of 65, and would therefore be more difficult to attribute to the effects of ASD alone, the authors did not model the costs and benefits associated with IBI beyond this upper age limit. The final outcome of the analysis was expressed in terms of incremental cost savings and gains in dependency-free life years (DFLY), which would permit understanding of the extent to which children are able to live on their own once they reach adulthood (i.e. free from the care of a family member or other support services). Motiwala et al. reasoned that this outcome best reflected the cognitive, social, communication, behavioural, and functional outcomes of this population. The perspective adopted in the analysis was that of the provincial government payer, with costs presented in 2003 Canadian dollars. Base-case findings revealed that the expansion of the IBI program at the time of the study resulted in total savings of over $45.1 million dollars. Furthermore, the incremental savings per child over his or her lifetime as a result of expanding IBI from *Status Quo* (n=485) to all children under six years who were eligible for IBI (n=1,309) was $34,479, with the majority of savings arising from a decreased proportion of individuals in a very dependent state, and therefore decreased spending on support services in adulthood (ages 18-65). Furthermore, the incremental improvement in DFLYs per child was 2.8 years. In comparison with no treatment, the number of dependency-free life years gained was 4.5 years per person. Therefore, the authors concluded that expanding IBI services to all eligible children

resulted in lower overall costs of care and increased health benefits (i.e. increase in overall dependency-free life years). Results, however, were sensitive to assumptions relating to the discount rate and IBI efficacy data.

Overall, though this study appears to be well-designed, several factors may limit the utility of study findings in aiding decision-making. First, treatment efficacy data were derived from selected studies in the published literature which are of questionable quality, and it is unclear how functional classification following IBI discharge was ascertained. This is a significant limitation of the economic analysis, especially in light of more recent studies which have measured treatment effectiveness using several standardized outcome measures, such as IQ and adaptive behaviour. Second, the authors assumed that individuals' functional classification following treatment discharge, and by association IBI efficacy, remained constant over the modeled population's lifetime (or until age 65); yet, this relationship has not been demonstrated in the published literature. Third, the target population comprised only preschool aged children, and the model assumed that all children started IBI treatment at the age of two for a period of three years; however, with delays to diagnosis and increased numbers of school aged children receiving IBI, children may not start treatment until a much later age, and treatment duration is unlikely to last three years (which impacts treatment cost, and potentially estimates of treatment efficacy). Reliance on these assumptions therefore limits the applicability of this study. Finally, the age of the study does not reflect current clinical evidence or cost data. As a result, this study is of poor applicability to the current decision making context.

Another cost-effectiveness analysis was recently published by Penner et al. (2015) regarding ASD services in Ontario.(111) This economic evaluation built on the previous

analysis by Motiwala et al. (2006) and accounted for some of the limitations of that study. Most notably, IQ was used as a surrogate marker in the analysis, linking intervention gains (change in IQ from baseline) with future levels of dependence. However, the primary aim of this analysis was to examine the costs and benefits (measured in DFLYs) associated with the provision of two pre-diagnosis interventions for ASD (i.e. intensive Early Start Denver Model (ESDM-I) and parent-delivered ESDM (ESDM-PD)) with the Ontario IBI program (Status Quo). Accordingly, the target population of interest comprised toddlers aged 15 to 36 months with "undifferentiated developmental concerns," that is, very young children who have not yet received an ASD diagnosis. Given the choice of comparators and target population in this analysis, the applicability of any findings in facilitating decision making within the current policy context is limited. Besides, though novel ways to overcome some of the modeling challenges outlined in the study by Motiwala et al. (2006) were proposed by Penner et al. (2015), methodological limitations still persist. In particular, the use of effectiveness data which is based on single, and in some cases uncontrolled, experimental studies, as well as reliance on a single longitudinal cohort study with small sample size to derive transition probabilities related to functional independence of children with an ASD in adulthood, is of great concern.

Despite previous efforts, the need for an economic evaluation of the Ontario IBI program which takes into consideration the differential effectiveness of treatment between preschool and school age children with an ASD, as signalled by the results of this systematic review and meta-analysis, remains a priority. The complexity of this task, however, cannot be underestimated. Indeed, previous attempts in quantifying the cost-effectiveness of IBI bring to light several barriers to conducting economic evaluations in

pediatric populations. Whether these barriers can be overcome is a question for further study.

Barriers to conducting economic evaluations in child health

The peculiarity of child health poses several challenges to the economic evaluation of interventions designed specifically for children. Namely, the pediatric population consists of many groups from the perinatal period to adolescence, each of which is characterized by a different set of physiological characteristics that influences response to treatment, maturity, and development. Indeed, differences between child and adult health must be acknowledged. In comparison to adults, children are different in terms of their developmental vulnerability (disease expression and response to treatment may vary along the trajectory of development) and their changing dependency relationships which influence both their ability to seek and utilize health resources as well as their ability to report their physical and emotional well-being. In addition, children have unique patterns of health resource use (adults often serve as gatekeepers to accessing health care, and care is provided in a variety of settings) and unique patters of morbidity and mortality (incidence of disease is generally lower in children as compared with adults).(112)

Specific challenges in the conduct of economic evaluations of child health interventions are mainly related to issues in costing, defining health-related outcomes, measurement of preference-based utility measures, and issues in the analysis.(112) First, measuring costs in child health often extends beyond the health system to include home, school, and community resources, impacting resources use and relevant costs as the setting of care delivery and age changes. Parent and other caregiver productivity costs may also

need to be considered since caring for a child affected by a given ailment can often be accompanied by parents' absenteeism from work or a change in work status (e.g. presenteeism – the ability to continue work, but at much lower productivity). Data on parent productivity losses, however, are not always readily available. Costing is further complicated by the need to account for future child productivity costs given that morbidity during childhood may reduce future work productivity and absorb more resources and special services in adulthood. Moreover, in adopting lifelong time horizons, costing by stage of development may be required, although data are not always available and there is uncertainty associated with prediction. This is particularly true for modeling ASD, where the availability of good data on costs associated with different developmental levels of ASD across the life course is currently lacking. Second, while several reviews of child health outcomes are available, defining health-related outcomes can be challenging. This is largely due to the interwoven nature of child health with social determinants of health and well-being, the physical environment, biologic and genetic determinants, and behavioural responses. In addition, natural changes during phases of development are difficult to measure. In the case of ASD, for instance, modeling disease progression in adults based on small changes in childhood can be very difficult, and is often accompanied by a great deal of uncertainty. Third, preferences for health states or utilities, a critical component of many economic evaluations, are extremely challenging to measure in children. In fact, there are no good instruments for preschool aged children. As a result, parents are often used as proxies or proxy reporters of children's functional status along different clinical dimensions. However, while parents may be good proxies for observable symptoms, they may not be reliable reporters for more subjective outcomes (e.g. mood and emotion). Finally, several issues may be encountered in the modeling of child health interventions.

This particularly relates to challenges in constructing lifetime models and issues surrounding valid data over the length of the time horizon. Reliance on multiple assumptions in the modeling exercise can significantly impact the reliability and applicability of results.

In brief, care must be taken when undertaking economic evaluation in pediatric populations. Indeed, rationing of health care resources is an endeavour where choices inevitably need to be made. For each choice that is made, however, there is an opportunity cost associated with it – that is, something else must be given up. Placing a value on the opportunity that is sacrificed, or the benefit forgone as a result of not employing the best alternative use of an intervention, can be challenging without knowing whether something is worth the cost. Therefore, to make choices about how best to ration a finite number of health care resources, like services for children with an ASD for example, costs of interventions are weighed against their benefits. Where an intervention, in comparison to an alternative, (1) does what the alternative does but costs less, (2) costs the same as the alternative but does better, or (3) costs less and does better than the alternative, it will be judged as a good option (or economically attractive). Conversely, where an intervention is available at a reduced total cost and reduced clinical benefit or at an increased total cost with an improvement in clinical benefits, in comparison to an alternative, cost-effectiveness will need to be considered. Economic evaluation, therefore, provides a measure of "value for money," and allows for a systematic way to compare two or more health interventions. In the context of interventions for children with an ASD, economic evaluations must be policy relevant and respond to the needs of health care providers making decision for individual patients as well as the needs of decision-makers which allocate budgets. By

choosing to fund interventions that are judged to be "cost-effective," provision of health services should be become more efficient, and health benefits should increase within the affected population. Nevertheless, consideration must be given to potential gaps in the methods used, especially with respect to the availability and validity of outcome measures, the ability to model cost and outcomes over the lifetime time horizon, as well as the integration of family preferences.

4.7 Equity implications of research findings

Evidence-informed decision making can often be met with important equity implications for a given patient population, especially when patients' health needs are situated in an environment of constrained resources.(113) Access to and coverage of IBI programming for children with an ASD in Ontario is no exception to this quandary.

Based on the findings of this review which suggest that IBI may be more efficacious in young pre-schoolers than children who are enrolled in school, and that relatively younger age at entry to IBI predicts better outcome, it could reasonably be argued that funding for this costly treatment should only be provided to those who have not yet reached the school age. Reasoning for this decision would be justified purely on grounds of "best evidence," keeping in mind that uncertainty surrounding the results cannot be ruled out. However, by making the choice to restrict coverage to only a subpopulation of children affected by ASD (e.g. children under six years), without providing an alternative option to those who are ineligible for coverage based on "best evidence," the school aged population unavoidably becomes vulnerable to disadvantage. This unequal distribution of publicly-funded (albeit limited) resources could, in turn, be deemed as "unnecessary, avoidable, unfair, and

unjust," and therefore inequitable,(114) in spite of an evidence-informed approach to resource allocation. Indeed, proponents of equitable provision of health care resources and distributive justice would agree that all children with an ASD and for whom treatment is indicated should be able to access IBI, irrespective of age. Yet, where demand for therapy exceeds the supply, choices on how to best distribute the limited resources is less clear. Whether "best evidence" alone can be used to inform policy changes regarding IBI within this resource-constrained context and enforce controlled access by those who are more likely to accrue a larger clinical benefit from timely intervention is a question that warrants serious consideration. Finally, in light of the findings in this review which suggest that children with relatively milder forms of ASD tend to do better with IBI, as compared with children with more severe forms of disease, decision-makers will also need to consider whether the severity of illness argument (which currently disqualifies all children who are not on the severe end of the autism spectrum from accessing IBI) still applies to the current decision making context.

CHAPTER V: CONCLUSIONS

5.1 Implications for practice

Overall, the objectives of this review sought to answer some important questions of direct relevance to parents, professionals, and policy makers. In particular, the findings of this review and meta-analysis have a number of implications for practice. First, there is considerable evidence that IBI is an effective treatment for preschool and school age children diagnosed with an ASD, with moderately large gains in both intellectual functioning (IQ) and adaptive skills. Findings of positive clinical benefit with IBI in this review are in agreement with previously published comparative effectiveness research; however, this review was the first to incorporate Canadian evidence of IBI efficacy and the first to consider school aged populations of children with an ASD who were treated with this intervention. The results of the meta-analyses conducted as part of this review suggest that some school age children may also benefit from IBI; however the intensive treatment appears to be more effective in increasing their adaptive skills as compared with cognition, which did not seem to improve to the same degree. The inverse relationship was observed in preschool children, whereby the effects of IBI on cognitive ability were much larger than those observed in adaptive functioning. Furthermore, findings related to predictors of treatment response revealed that younger age, increased cognitive and adaptive ability, as well as a milder severity of symptoms at admission to IBI appear to be related to better outcomes at IBI completion. However, this review and meta-analysis is not devoid of limitations. Namely, a number of included studies had small sample sizes, many were conducted without a control group, and procedural integrity was generally not well monitored. Nonetheless, results remain very relevant to the Canadian decision making context, and particularly striking in light of current clinical practice in the province of

Ontario where a considerable proportion of children receiving publicly-funded IBI have reached the school age at treatment entry. Whether an age cut-off criterion should be re-implemented within this jurisdiction is a question that warrants serious consideration on the part of decision-makers dealing with limited resources, who need to be mindful of the limitations associated with this body of evidence. Additionally, in light of the findings which suggest that a milder symptomatic profile may lead to a better improvement with IBI, decision-makers should also consider the appropriateness of the current eligibility criteria for entry into the Ontario IBI program. While decisions relating to changes in the current coverage of IBI should be evidence-informed, these decisions also have inherent equity implications which need to be carefully weighed against the budget impact and cost-effectiveness of a potentially restrictive funding strategy.

5.2 Implications for research

While the present review and meta-analysis does add to the growing evidence base regarding the effectiveness of IBI in children with an ASD, and though it attempts to elucidate the differential effectiveness that may exist between preschool and school age recipients of this intervention, the quality of the evidence is of great concern. In fact, many of the included studies had similar methodological flaws, and these shortcomings, if avoided, could improve the quality of the of the available evidence – and in turn, the confidence placed in the pooled estimates of treatment effect, as well as the findings relating to predictors of therapeutic progress. First, the need for studies with larger samples of participants cannot be ignored. Larger samples will help to increase power of study results, and allow for more rigorous exploration of predictors of outcome. Second, future studies should strive to conduct controlled comparisons with appropriate randomization

procedures, when possible, in order minimize threats to their internal validity and control for factors outside of the treatment which may be contributing to an improved clinical profile among participants. While it is not always ethical to not provide treatment, especially in the case of children affected by an ASD, novel attempts to overcome this limitation in the design of experimental studies have been previously explored with the use of wait-list controls, for instance, and future studies should endeavour to adopt similar methods. Where wait-list controls are not available, a standardized control group receiving eclectic intervention at a similar intensity to IBI could be utilized. Third, prospective follow-up should be favoured over retrospective file review, which might, to some extent, help reduce the amount of partial or incomplete outcome data common to retrospective studies. Fourth, the variable blinding of outcome assessors could be remediated in future studies by enforcing blinding of those measuring participant outcomes, especially given that blinding of participants is not possible due to the nature of the intervention. Fifth, greater consistency in the types and numbers of outcome measures used across studies is urgently needed, and measured outcomes should be both objective and tailored to reflect the mandate or goal of IBI. Sixth, there is a great need to include more heterogeneous study samples in future research on IBI efficacy, with the inclusion of a broad age range of participants, those with comorbid conditions and below average cognitive skill. This will hopefully provide a more accurate portrayal of characteristics of children in everyday clinical practice and increase the generalizability of findings. Finally, procedural fidelity should be monitored and measured during treatment provision, and reported in the final research publications. Improvements in the design and conduct of future IBI efficacy studies will ultimately lead to an even better understanding of the effects of IBI treatment, and provide better insight into the variables that predict treatment response.

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APPENDICES

Appendix 1: Search Strategies

Ovid MEDLINE (R)

1 Behavior Therapy/
2 "Early Intervention (Education)"/
3 intensive behavio?ral intervention.tw.
4 (intens* adj3 (interven* or therap* or treat* or program*)).tw.
5 (applied behavio* analy* or ABA).tw.
6 Lovaas*.tw.
7 or/1-6
8 exp Child Development Disorders, Pervasive/
9 (autis* adj3 disorder*).tw.
10 autism.tw.
11 (Kanner* adj syndrome*).tw.
12 (pervasive devel* adj3 (NOS or specified)).tw.
13 or/8-12
14 7 and 13
15 limit 14 to yr="1995 -Current"

EMBASE (Ovid)

1 Behavior Therapy/
2 Early childhood intervention/
3 intensive behavio?ral intervention.tw.
4 (intens* adj3 (interven* or therap* or treat* or program*)).tw.
5 (applied behavio* analy* or ABA).tw.
6 Lovaas*.tw.
7 or/1-6
8 exp autism/
9 (autis* adj3 disorder*).tw.
10 autism.tw.
11 (Kanner* adj syndrome*).tw.
12 (pervasive devel* adj3 (NOS or specified)).tw.
13 or/8-12
14 7 and 13
15 limit 14 to yr="1995 -Current"

PsycINFO (Ovid)

1 Behavior Therapy/
2 Early intervention/
3 intensive behavio?ral intervention.tw.
4 (intens* adj3 (interven* or therap* or treat* or program*)).tw.
5 (applied behavio* analy* or ABA).tw.
6 Lovaas*.tw.
7 or/1-6
8 exp autism/
9 (autis* adj3 disorder*).tw.
10 autism.tw.
11 (Kanner* adj syndrome*).tw.
12 (pervasive devel* adj3 (NOS or specified)).tw.
13 or/8-12
14 7 and 13
15 limit 14 to yr="1995 -Current"

CINAHL Plus (EBSCOhost)

S1 (MH "Early Childhood Intervention") OR (MH "Early Intervention")
S2 (MH "Behavior Therapy") OR (MH "Behavior Modification")
S3 (TI intensive behavioral intervention or AB intensive behavioral intervention) OR (TI intensive behavioural intervention or AB intensive behavioural intervention)
S4 (TI intens* N3 interven* or AB intens* N3 interven*) OR (TI intens* N3 therap* or AB intens* N3 therap*) OR (TI intens* N3 treat* or AB intens* N3 treat*) OR (TI intens* N3 program* or AB intens* N3 program*)
S5 “applied behavio* analy*" or “ABA”
S6 “lovaas*"
S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8 (MH "Autistic Disorder")
S9 TI autis* N1 disorder* or AB autis* N1 disorder*
S10 TI autis* N1 spectrum N1 disorder* or AB autis* N1 spectrum N1 disorder*
S11 TI autism or AB autism
S12 TI Kanner* N1 syndrome or AB Kanner* N1 syndrome
S13 TI pervasive N1 development* N1 disorder N1 "not otherwise specified" or AB pervasive N1 development* N1 disorder N1 "not otherwise specified"

S14 TI pervasive N1 development* N1 disorder N1 NOS or AB pervasive N1 development* N1 disorder N1 NOS
S15 (MH "Asperger Syndrome")
S16 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
S17 S7 AND S16
S18 Limiters - Published Date: 19950101-20141231
S19 S17 AND S18

ERIC Dialog Datastar

ALL(behavio* therapy OR behavio* modification OR early intervention OR intensive behavio* intervention OR early intensive behavio* intervention OR (intens* NEAR/3 (interven* OR therap* OR treat* OR program*)) OR applied behavio* analy* OR Lovaas*) AND ALL (autism OR (autis* NEAR/1 disorder*) OR (autis* NEAR/1 spectrum NEAR/1 disorder*) OR Kanner* syndrome* OR asperger* syndrome OR (pervasive NEAR/1 development* NEAR/1 disorder* NEAR/1 "not otherwise specified") OR (pervasive NEAR/1 development* NEAR/1 disorder* NEAR/1 NOS)) AND YR(>=1995)

Appendix 2: List of Excluded Studies

Reference	Reason for exclusion
Akshoomoff NA, Stahmer A. Early Intervention Programs and Policies for Children with Autistic Spectrum Disorders. In: Fitzgerald HE, Zucker RA, Freeark K, editors. The Crisis in Youth Mental Health: Childhood disorders. Praeger; 2006. p. 109–31.	Not full, published journal article
Ames C. Book review: Social and Communication Development in Autism Spectrum Disorders: Early Identification, Diagnosis and Intervention by Tony Charman and Wendy Stone (eds). Autism. 2007;11(4):389–90.	Not full, published journal article
Arikawa H. The Japanese Association of Special Education NII-Electronic Library Service. Japanese J Spec Educ. 2009;47(4):265–75.	Non-English publication
Arnold CL. A longitudinal re-evaluation of home-based behavioral treatment for children with pervasive developmental disorders. 2002.	Not full, published journal article
Azarbehi AC. The effectiveness of early intervention programs for children with autism: A one-year follow-up study of Intensive Behavioural Intervention versus preschool integration. 2009.	Not full, published journal article
Baghdadli A, Assouline B, Sonié S, Pernon E, Darrou C, Michelon C, et al. Developmental trajectories of adaptive behaviors from early childhood to adolescence in a cohort of 152 children with autism spectrum disorders. J Autism Dev Disord. 2012;42(7):1314–25.	Treatment not intensive or comprehensive
Beglinger LJ. An information processing test and social subtyping questionnaire as predictors of intensive behavioral treatment outcome in children with autism. 2002.	Not full, published journal article
Ben Itzchak E, Zachor DA. Who benefits from early intervention in autism spectrum disorders? Res Autism Spectr Disord. 2011;5(1):345–50.	Treatment not intensive or comprehensive
Berry LN. Early treatments associated with optimal outcome in children with autism spectrum disorders. 2009.	Not full, published journal article
Blue Cross Blue Shield Association. Special Report: Early Intensive Behavioral Intervention Based on Applied Behavior Analysis among Children with Autism Spectrum Disorders [Internet]. Technology Evaluation Center Assessment Program. 2009 [cited 2014 May 22]. Available from: http://www.bcbs.com/blueresources/tec/press/special-report-early.html	Not full, published journal article
Bono M a., Daley T, Sigman M. Relations among joint attention, amount of intervention and language gain in autism. J Autism Dev Disord. 2004;34(5):495–505.	Treatment not intensive or comprehensive
Butter EM, Mulick JA, Metz B. Eight case reports of learning recovery in children with pervasive developmental disorders after early intervention. Behav Interv. 2006;21(4):227–43.	SSD or multiple non-consecutive case reports
Cann P. Timely intervention. Nurs Stand. 2000;14(32):20.	Not primary research
Carr JE, Firth AM. The verbal behavior approach to early and intensive behavioral intervention for autism: A call for additional empirical support. J Early Intensive Behav Interv. 2005;2(1):18–27.	Not primary research
Clark J. Merit mentalization enhanced remediation: An integrated treatment a comprehensive intervention for children with autism. 2011.	Not full, published journal article
Coucouvanis J. Behavioral intervention for children with autism. J Child Adolesc Psychiatr Nurs. 1992;10(1):37–44.	Not primary research
Darrou C, Pry R, Pernon E, Michelon C, Aussilloux C, Baghdadli A. Outcome of young children with autism: does the amount of intervention influence developmental trajectories? Autism. 2010;14(6):663–77.	Treatment not intensive or comprehensive
Dawson G. Early intensive behavioral intervention appears beneficial for young children with autism spectrum disorders. J Pediatr. United States: Mosby, Inc.; 2013;162(5):1080–1.	Not primary research

Dawson G. Review: more RCTs on early intensive behavioural intervention for young children with autism spectrum disorders needed. Evid Based Ment Heal. England: Department of Psychiatry, University of North Carolina, Autism Speaks, Chapel Hill, North Carolina, USA.; 2013;16(2):45.	Not primary research
Dawson G, Burner K. Behavioral interventions in children and adolescents with autism spectrum disorder : a review of recent findings. Curr Opin Pediatr. 2011;23(6):616–20.	Not primary research
Dawson G, Jones EJH, Merkle K, Venema K, Lowy R, Faja S, et al. Early behavioral intervention is associated with normalized brain activity in young children with autism. J Am Acad Child Adolesc Psychiatry. Elsevier Inc.; 2012;51(11):1150–9.	Treatment not intensive or comprehensive
Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. Pediatrics. Am Acad Pediatrics; 2010;125(1):e17–23.	Treatment not intensive or comprehensive
Dawson M, Gernsbacher MA. Effectiveness of intensive autism programmes. Lancet. 2010;375(9716):722–3.	Not primary research
De La Osa D. An applied behavior analysis after-school program to treat autistic children and educate their parents. 2002.	Not full, published journal article
De Rivera C. The use of intensive behavioural intervention for children with autism. J Dev Disabil. 2008;14(2):1–15.	Not primary research
Dionne C, Paquet A, Rousseau M. Programmes d'intervention précoce pour les enfants ayant un trouble envahissant du développement et des retards de développement. Approch Neuropsychol des apprentissages chez l'enfant. PDG Communication; 2011;(115):466–72.	Non-English publication
Douglas L. An Evaluation of the Effectiveness of Early Intervention on Autistic Children. 1999.	Not full, published journal article
Eapen V, Črnčec R, Walter A. Clinical outcomes of an early intervention program for preschool children with Autism Spectrum Disorder in a community group setting. BMC Pediatr. 2013;13(1):1–9.	Treatment not intensive or comprehensive
Eikeseth S. Intensive behavioural intervention for children with autism. A reply to prior. J Paediatr Child Health. 2005;41(7):391–2.	Not full, published journal article
Eikeseth S, Klintwall L, Jahr E, Karlsson P. Outcome for children with autism receiving early and intensive behavioral intervention in mainstream preschool and kindergarten settings. Res Autism Spectr Disord. 2012;6(2):829–35.	Treatment not administered by trained/qualified therapist
Eldevik S, Hastings RP, Hughes JC, Jahr E, Eikeseth S, Cross S. Meta-analysis of Early Intensive Behavioral Intervention for children with autism. J Clin Child Adolesc Psychol. 2009;38(3):439–50.	Not primary research
Eldevik S, Hastings RP, Hughes JC, Jahr E, Eikeseth S, Cross S. Using participant data to extend the evidence base for intensive behavioral intervention for children with autism. Am J Intellect Dev Disabil. 2010;115(5):381–405.	Not primary research
Eldevik S, Hastings RP, Jahr E, Hughes JC. Outcomes of behavioral intervention for children with autism in mainstream pre-school settings. J Autism Dev Disord. 2012;42(2):210–20.	Treatment not intensive or comprehensive
Eriksson MA, Westerlund J, Hedvall A, Amark P, Gillberg C, Fernell E. Medical conditions affect the outcome of early intervention in preschool children with autism spectrum disorders. Eur Child Adolesc Psychiatry. 2013;22(1):23–33.	Treatment not administered by trained/qualified therapist
Farrell P, Trigonaki N, Webster D. An exploratory evaluation of two early intervention programmes for young children with autism. Educ child Psychol. 2005;22(4):29–40.	Not primary research
Fava L, Strauss K, Valeri G, D'Elia L, Arima S, Vicari S. The effectiveness of a cross-setting complementary staff- and parent-mediated early intensive behavioral intervention for young children with ASD. Res Autism Spectr Disord. 2011;5(4):1479–92.	Treatment not administered by trained/qualified therapist
Fernell E, Eriksson MA, Gillberg C. Early diagnosis of autism and impact on prognosis: a narrative review. Clin Epidemiol. 2013;5(1):33–43.	Not primary research

Fernell E, Hedvall A, Westerlund J, Hoglund Carlsson L, Eriksson M, Barnevik Olsson M, et al. Early intervention in 208 Swedish preschoolers with autism spectrum disorder. A prospective naturalistic study. Res Dev Disabil. 2011;32(6):2092–101.	Treatment not administered by trained/qualified therapist
Finch L, Raffaele C. Developing expert practice Intensive behavioural intervention for children with autism: a review of the evidence. Occup Ther Now. 2003;5(4):20–3.	Not full, published journal article
Flanagan HE. The impact of community-based intensive behavioural intervention. 2009.	Not full, published journal article
Foxx RM. Applied behavior analysis treatment of autism: the state of the art. Child Adolesc Psychiatr Clin N Am. 2008;17(4):821–34.	Not primary research
Freitag CM. Empirically based early intervention programs for children with autistic disorders-a selective literature review. Zeitschrift fur Kinder-und Jugendpsychiatrie und Psychother. 2010;38(4):247–56.	Non-English publication
Gabriels RL, Ivers BJ, Hill DE, Agnew J a., McNeill J. Stability of adaptive behaviors in middle-school children with autism spectrum disorders. Res Autism Spectr Disord. 2007;1(4):291–303.	Treatment not intensive or comprehensive
Goods KS, Ishijima E, Chang YC, Kasari C. Preschool based JASPER intervention in minimally verbal children with autism: Pilot RCT. J Autism Dev Disord. 2013;43(5):1050–6.	Treatment not intensive or comprehensive
Gould E, Dixon DR, Najdowski AC, Smith MN, Tarbox J. A review of assessments for determining the content of early intensive behavioral intervention programs for autism spectrum disorders. Res Autism Spectr Disord [Internet]. Elsevier Ltd; 2011;5(3):990–1002. Available from: http://dx.doi.org/10.1016/j.rasd.2011.01.012	Not primary research
Granpeesheh D, Kenzer A, Tarbox J. FC05-06 - Comparison of two-year outcomes for children with autism receiving high versus low-intensity behavioral intervention. Eur Psychiatry. 2011;26(Suppl1):1839.	Not full, published journal article
Granpeesheh D, Tarbox J, Dixon DR, Carr E, Herbert M. Retrospective analysis of clinical records in 38 cases of recovery from autism. Ann Clin Psychiatry. 2009;21(4):195–204.	Not primary research
Granpeesheh D. Applied behavior analytic interventions for children with autism: a description and review of treatment research. Ann Clin Psychiatry. 2009;21(3):162–73.	SSD or multiple non-consecutive case reports
Green G. Early behavioral intervention for autism: What does research tell us? In: Maurice C, Green G, Luce SC, editors. Behavioral Intervention for Young Children With Autism: A Manual for Parents and Professionals. Pro-Ed.; 1996. p. 29–44.	Not full, published journal article
Green G. On valid inferences: Comments on Weiss. Behav Interv. 1999;14(1):23–7.	Not primary research
Harris SL, Weiss MJ. Right from the Start: Behavioral Intervention for Young Children with Autism. Woodbine House; 2007.	Not primary research
Harris SL, Delmolino L. Applied Behavior Analysis : Its application in the treatment of autism and related disorders in young children. Infants Young Child. 2002;14(3):11–7.	Not full, published journal article
Herpertz-Dahlmann B, Konrad K, Freitag C. Autismus heute. Frühförderung Interdiszip. 2009;29(1):3–12.	Non-English publication
Horner CH. Influences of combined intervention therapies on learning, achievement, and behavior ratings for children diagnosed with autism spectrum disorders. 2009.	Not full, published journal article
Horner RH, Carr EG, Strain PS, Todd a W, Reed HK. Problem behavior interventions for young children with autism: A research synthesis. J Autism Dev Disord. 2002;32(5):423–46.	Not primary research
Hourmanesh N. Early comprehensive interventions for children with autism: A meta-analysis. 2006.	Not full, published journal article
Howlin P. The effectiveness of interventions for children with autism. J neural Transm. 2005;(s69):101–19.	Not primary research
Howlin P, Magiati I, Charman T. Systematic review of early intensive behavioral interventions for children with autism. Am J Intellect Dev Disabil. 2009;114(1):23–41.	Not primary research

Hutchison-Harris J. Does first year treatment intensity predict outcome in young autistic children receiving Lovaas ABA intervention? 2003.	Not full, published journal article
Jones JT. Applied Behavior Analysis as a treatment for autism: A comprehensive literature review. 2007.	Not full, published journal article
Kelley E, Naigles L, Fein D. An in-depth examination of optimal outcome children with a history of autism spectrum disorders. Res Autism Spectr Disord. 2010;4(3):526–38.	Treatment not intensive or comprehensive
Kerr KP, Mulhern F, McDowell C. Applied Behaviour Analysis. It Works, It's Positive; Now What's the Problem? Early Child Dev Care. 2000;163(1):125–31.	Not primary research
Klintwall L, Eikeseth S. Number and controllability of reinforcers as predictors of individual outcome for children with autism receiving early and intensive behavioral intervention: A preliminary study. Res Autism Spectr Disord. 2012;6(1):493–9.	Treatment not administered by trained/qualified therapist
Klintwall L, Gillberg C, Fernell E, Bo S. The efficacy of intensive behavioral intervention for children with autism: a matter of allegiance? J Autism Dev Disord. 2012;42(1):139–40.	Treatment not administered by trained/qualified therapist
Kodak T, Grow LL. Behavioral treatment of autism. In: Fisher WW, Piazza CC, Roane HS, editors. Handbook of Applied Behavioural Analysis. New York: The Guilford Press; 2011. p. 402–16.	Not full, published journal article
Koegel R. O. Ivar lovaas (1927-2010). Am Psychol. 2011;66(3):227–8.	Not primary research
Koegel RL, Kern L, Camarata SM. Definitions of empirically supported treatment. J Autism Dev Disord. 2010;40(4):516–7.	Not full, published journal article
Kotsopoulos S. OP04 A model of continuous intervention for children with autism spectrum disorder (ASD). Child Adolesc Ment Health. 2011;16(s1):3.	Not full, published journal article
Kovshoff H, Hastings RP, Remington B. Two-year outcomes for children with autism after the cessation of early intensive behavioral intervention. Behav Modif. 2011;35(5):427–50.	Duplicate publication
Kuhn LD. Evaluation of a public school group-based applied behavioral analysis program for elementary students with autism. 2010.	Not full, published journal article
Kuppens S, Onghena P. Sequential meta-analysis to determine the sufficiency of cumulative knowledge: The case of early intensive behavioral intervention for children with autism spectrum disorders. Res Autism Spectr Disord. 2012;6(1):168–76.	Not primary research
Leaf RB, Taubman MT, McEachin JJ, Leaf JB, Tsuji KH. A Program Description of a Community-Based Intensive Behavioral Intervention Program for Individuals with Autism Spectrum Disorders. Educ Treat Child. 2011;34(2):259–85.	SSD or multiple non-consecutive case reports
Leblanc L, Mcintosh J. The use of Applied Behavioral Analysis in teaching children with autism. Int J Spec Educ. 2005;20(1):13–34.	SSD or multiple non-consecutive case reports
Lovaas OI, Buch G. Intensive behavioral intervention with young children with autism. In: Singh NN, editor. Prevention and Treatment of Severe Behavior Problems: Models and Methods in Developmental Disabilities. Brooks/Cole Publishing; 1997. p. 61–86.	Not full, published journal article
Luiselli JK. Behavior support of people with intellectual and developmental disabilities: Contemporary research applications: Introduction to the special issue. J Dev Phys Disabil. 2009;21(6):441–2.	Not primary research
Lund SK. Discrete trial instruction in early intensive behavioral intervention. In: Boutot AE, Tincani M, editors. Autism Encyclopedia: The Complete Guide to Autism Spectrum Disorders. Austin, Texas: Prufrock Press Inc.; 2009. p. 201–7.	Not full, published journal article
Magiati I, Tay XW, Howlin P. Early comprehensive behaviorally based interventions for children with autism spectrum disorders: a summary of findings from recent reviews and meta-analyses. Neuropsychiatry (London). 2012;2(6):543–70.	Treatment not administered by trained/qualified therapist

Magiati I, Charman T, Howlin P. A two-year prospective follow-up study of community-based early intensive behavioural intervention and specialist nursery provision for children with autism spectrum disorders. J Child Psychol Psychiatry. 2007;48(8):803–13.	Treatment not administered by trained/qualified therapist
Magiati I, Moss J, Charman T, Howlin P. Patterns of change in children with Autism Spectrum Disorders who received community based comprehensive interventions in their pre-school years: A seven year follow-up study. Res Autism Spectr Disord. 2011;5(3):1016–27.	Not primary research
Maglione MA, Gans D, Das L, Timbie J, Kasari C, Network HAIRB (AIR-B. Nonmedical interventions for children with ASD: Recommended guidelines and further research needs. Pediatrics. 2012;130(Suppl 2):S169–78.	Not primary research
Makrygianni MK, Reed P. A meta-analytic review of the effectiveness of behavioural early intervention programs for children with Autistic Spectrum Disorders. Res Autism Spectr Disord. Elsevier Ltd; 2010 Oct;4(4):577–93.	Not primary research
Mandell DS, Levy SE, Schultz RT. Department of error: Effectiveness of intensive autism programmes - author's reply. Lancet. 2011;378(9805):1778.	Duplicate publication
Matson JL, Benavidez D a., Compton LS, Paclawskyj T, Baglio C. Behavioral treatment of autistic persons: A review of research from 1980 to the present. Res Dev Disabil. 1996;17(6):433–65.	Not primary research
Matson JL, Goldin RL. Early Intensive Behavioral Interventions: Selecting behaviors for treatment and assessing treatment effectiveness. Res Autism Spectr Disord. 2014;8(2):138–42.	Not primary research
Matson JL, Konst MJ. What is the evidence for long term effects of early autism interventions? Res Autism Spectr Disord. 2013;7(3):475–9.	Not primary research
Matson JL, Rieske RD. Are outcome measures for early intensive treatment of autism improving? Res Autism Spectr Disord. 2014;8(3):178–85.	Not primary research
Matson JL, Smith KRM. Current status of intensive behavioral interventions for young children with autism and PDD-NOS. Res Autism Spectr Disord. 2008;2(1):60–74.	Not primary research
Mercier C, Cusson N. Le traitement précoce de l'autisme: L'intensité de l'intervention seule en cause? Rev québécoise Psychol. 2005;26(3):13–28.	Non-English publication
Morris EK. A case study in the misrepresentation of applied behavior analysis in autism: the Gernsbacher lectures. Behav Anal. 2009;32(1):205–40.	Not primary research
Mrug S, Hodgens JB. Behavioral Summer Treatment Program improves social and behavioral functioning of four children with Asperger's disorder`. Clin Case Stud. 2008;7(3):171–90.	No ASD diagnosis
Muratori F, Narzisi A, Tancredi R. Interventi precoci nell'autismo: una review [Early interventions for autism: A review]. G Di Neuropsichiatr Dell'età Evol. 2010;30(2):136–48.	Non-English publication
Nakajima Y. Social Life and Institutional Care of Severely Autistic Adolescents. Japanese J Child Adolesc Psychiatry. 1996;37(1):12–8.	Non-English publication
O'Connor AB, Healy O. Long-term post-intensive behavioral intervention outcomes for five children with Autism Spectrum Disorder. Res Autism Spectr Disord. 2010;4(4):594–604.	SSD or multiple non-consecutive case reports
Ogiwara H, Takahashi O. Developmental Changes in Autistic Toddlers who Received Very Early Intervention. Japanese J Child Adolesc Psychiatry. 2003;44(3):305–20.	Non-English publication
Olszyk RK. Changes in symptomatology and functioning of preschoolers with autism in the context of the DIR model. 2005.	Not full, published journal article
Ospina MB, Seida JK, Clark B, Karkhaneh M, Hartling L, Tjosvold L, et al. Behavioural and developmental interventions for autism spectrum disorder: a clinical systematic review. PLoS One. 2008;3(11):1–32.	Not primary research
Pellecchia M. Predictors of outcome for children with autism receiving a behavioral intervention. 2013.	Not full, published journal article
Pérez-González LA, Williams G. Comprehensive program for teaching skills to children with autism. Psicothema. 2005;17(2):233–44.	Non-English publication

Petermann F, Petermann U. Intensivtherapie. Kindheit und Entwicklung. Hogrefe & Huber; 2012;21(2):77–80.	Non-English publication
Peters-Scheffer N, Didden R, Korzilius H, Sturmey P. A meta-analytic study on the effectiveness of comprehensive ABA-based early intervention programs for children with Autism Spectrum Disorders. Res Autism Spectr Disord. 2011;5(1):60–9.	Not primary research
Poustka L, Rothermel B, Banaschewski T, Kamp-Becker I. Intensive verhaltenstherapeutische Interventionsprogramme bei Autismus-Spektrum-Störungen. Kindheit und Entwicklung. Hogrefe & Huber; 2012;21(2):81–9.	Non-English publication
Prichard EA. Short-term follow-up of of children with autism who have received intensive behavioural intervention. 2011.	Not full, published journal article
Prior M. Editorial comment. J Paediatr Child Health. 2004;40(9-10):506–7.	Not primary research
Reichow B. Overview of meta-analyses on early intensive behavioral intervention for young children with autism spectrum disorders. J Autism Dev Disord. 2012;42(4):512–20.	Not primary research
Reichow B, Barton EE, Boyd B a, Hume K. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database Syst Rev. 2012;(10):1–60.	Not primary research
Reichow B, Wolery M. Comprehensive synthesis of early intensive behavioral interventions for young children with autism based on the UCLA young autism project model. J Autism Dev Disord. 2009;39(1):23–41.	Not primary research
Reitzel J, Summers J, Lorv B, Szatmari P, Zwaigenbaum L, Georgiades S, et al. Pilot randomized controlled trial of a Functional Behavior Skills Training program for young children with Autism Spectrum Disorder who have significant early learning skill impairments and their families. Res Autism Spectr Disord. Elsevier Ltd; 2013;7(11):1418–32.	Treatment not intensive or comprehensive
Rhea P. Sally J. Rogers and Geraldine Dawson: Review of Early Start Denver Model for Young Children with Autism: Promoting Language, Learning and Engagement. J Autism Dev Disord. 2011;41(7):978–80.	Not full, published journal article
Ringdahl JE, Kopelman T, Falcomata TS. Applied behavior analysis and its application to autism and autism related disorders. In: Matson JL, editor. Applied Behavior Analysis for Cihldren with Autism Spectrum Disorders. New York: Springer Science+Business Media; 2009. p. 15–32.	Not full, published journal article
Rivers J, Nye C. The conclusion that ABI has inconclusive effects for children with autism may stem from the fact that there are few high quality studies. Evid Based Commun Assess Interv. 2010;4(2):62–4.	Not primary research
Romanczyk RG. Comments on Weiss. Behav Interv. 1999;14(1):35–6.	Not primary research
Roussel B, Zimmermann C, Duldulao P, Ahmed T. IBI Training: Predictors of Outcome in the Area of Language Acquisition in Children with Autism Spectrum Disorder. J Dev Disabil. 2010;16(3):78–80.	Non-objective outcome measure
Sénéchal C, Forget J, Giroux N. Les programmes de type Lovaas et la réadaptation en autisme infantile. / Lovaas-type programs and readaptation in autistic children. Rev Psychoéducation. 2003;32(1):123–48.	Non-English publication
Shade-Monuteaux DM. An innovative approach for children with autism spectrum disorders: A preliminary outcome evaluation. 2003.	Not full, published journal article
Shapiro T, Hertzig M. Applied behavioral analysis: astonishing results? J Am Acad Child Adolesc Psychiatry. 1995;34(10):1255–6.	Not full, published journal article
Sharma P, Heywood A, Rajkumar D. IBI training: Social and play skills upon entry as predictors of outcome in children with autism spectrum disorder. J Dev Disabil. 2010;	Non-objective outcome measure
Shattuck PT, Grosse SD. Issues related to the diagnosis and treatment of autism spectrum disorders. Ment Retard Dev Disabil Res Rev. 2007;13(2):129–35.	Not primary research
Shea V. A perspective on the research literature related to early intensive behavioral intervention (Lovaas) for young children with autism. Commun Disord Q. 2005;26(2):102–11.	Duplicate publication

Shea V. A perspective on the research literature related to early intensive behavioral intervention (Lovaas) for young children with autism. Autism. 2004;8(4):349–67.	Not primary research
Shi P, Yu Q, Guo S-Q, Li Y. Applied behavioral analysis treatment for autism. J Clin Rehabil Tissue Eng Res. 2007;11(52):10489–91.	Non-English publication
Siegel B. Autistic Learning Disabilities and Individualizing Treatment for Autistic Spectrum Disorders. Infants Young Child. 1999;12(2):27–36.	Not primary research
Simpson RL. Early Intervention with Children with Autism: The Search for Best Practices. J Assoc Pers with Sev Handicap. 1999;24(3):218–21.	Not primary research
Smith IM, Koegel RL, Koegel LK, Openden DA, Fossum KL, Bryson SE. Effectiveness of a novel community-based early intervention model for children with autistic spectrum disorder. Am J Intellect Dev Disabil. 2010;115(6):504–23.	Treatment not intensive or comprehensive
Smith T, Lovaas OI. Intensive and early behavioral intervention with autism: the UCLA Young Autism Project. Infants Young Child. 1998;10(3):67–78.	SSD or multiple non-consecutive case reports
Smith T, Eikeseth S, Klevstrand M, Lovaas OI. Intensive behavioral treatment for preschoolers with severe mental retardation and pervasive developmental disorder. Am J Ment Retard. 1997;102(3):238–49.	Not full, published journal article
Smith T. Early and Intensive Behavioral Intervention in Autism. In: Weisz JR, Kazdin AE, editors. Evidence-Based Psychotherapies for Children and Adolescents. Second Edi. New York; 2010. p. 312–26.	Not primary research
Smith T, Eikeseth S, Sallows GO, Graupner TD. Efficacy of applied behavior analysis in autism. J Pediatr. 2009;155(1):151–2.	Not full, published journal article
Smith T, Groen AD, Wynn JW. ERRATA. Am J Ment Retard. 2001;106(3):208.	Not full, published journal article
Soltanifar A, Hojati M, Mashhadi A, Reebye P. P01-353 A comparative efficacy of Holistic Multidimensional Treatment Model (HMTM) and Applied Behavioral Analysis (ABA) in the treatment of children with Autism Spectrum Disorder (ASD). Eur Psychiatry. 2011;26(s1):355.	Not full, published journal article
Spreckley M, Boyd R. Efficacy of applied behavioral intervention in preschool children with autism for improving cognitive, language, and adaptive behavior: a systematic review and meta-analysis. J Pediatr. 2009;154(3):338–44.	Not primary research
Strain PS, Schwartz I. Positive behavior support and early intervention for young children with autism: Case studies on the efficacy of proactive treatment of problem behavior. In: Sailor W, Dunlap G, Sugai G, Horner R, editors. Handbook of Positive Behavior Support. Springer Science+Business Media; 2009. p. 107–23.	Not full, published journal article
Strauss K, Mancini F, Fava L, SPC Group. Parent inclusion in early intensive behavior interventions for young children with ASD: a synthesis of meta-analyses from 2009 to 2011. Res Dev Disabil. 2013;34(9):2967–85.	Not primary research
Technology Assessment Reports. Autism and Lovaas treatment: a systematic review of effectiveness evidence. Int J Technol Assesment Heal Care. 2001;17(2):252.	Not primary research
Tonge BJ, Bull K, Brereton A, Wilson R. A review of evidence-based early intervention for behavioural problems in children with autism spectrum disorder: the core components of effective programs, child-focused interventions and comprehensive treatment models. Curr Opin Psychiatry. 2014;27(2):158–65.	Not primary research
Tsakiris EA. Treatment Effectiveness in Preschool Autism: A Look at Affective Variables. 2009.	Not full, published journal article
Valenti M, Cerbo R, Masedu F, De Caris M, Sorge G. Intensive intervention for children and adolescents with autism in a community setting in Italy: a single-group longitudinal study. Child Adolesc Psychiatry Ment Health. 2010;4(1):1–9.	Treatment not intensive or comprehensive
Van Dyke EM. Autistic disorder: early interventions can improve outcomes. JAAPA Off J Am Acad Physician Assist. 2009;22(7):18–9.	Not primary research
Van Kraayenoord C. Revisiting the key lessons learned from inclusive education: Continuing the research agenda. Int J Disabil Dev Educ. 2007;54(2):145–9.	Not primary research

Velazquez R, Nye C. Systematic review offers cautious support for positive effects from ABA-based early intervention programs for children with autism spectrum disorder. Evid Based Commun Assess Interv. 2011;5(2):70–3.	Not primary research
Virués-Ortega J. Applied behavior analytic intervention for autism in early childhood: Meta-analysis, meta-regression and dose-response meta-analysis of multiple outcomes. Clin Psychol Rev. 2010;30(4):387–99.	Not primary research
Vivanti G, Dissanayake C, Zierhut C, Rogers SJ, Team VA. Brief report: predictors of outcomes in the early start Denver model delivered in a group setting. J Autism Dev Disord. 2013;43(7):1717–24.	Treatment not intensive or comprehensive
Warren Z, McPheeters ML, Sathe N, Foss-Feig JH, Glasser A, Veenstra-VanderWeele J. A systematic review of early intensive intervention for autism spectrum disorders. Pediatrics. 2011;127(5):e1303–11.	Not primary research
Webster A, Feiler A, Webster V. Early Intensive Family Intervention and Evidence of Effectiveness: Lessons from the South West Autism Programme. Early Child Dev Care. 2003;173(4):383–98.	Treatment not intensive or comprehensive
Weinmann S, Schwarzbach C, Begemann M, Roll S, Vauth C, Willich SN, et al. Behavioural and skill-based early interventions in children with autism spectrum disorders. GMS Health Technol Assess. 2009;5:1–10.	Not primary research
Weyandt A. The effectiveness of specialized applied behavior analysis (ABA) on daily living skills for individuals with autism and related disorders ages 8 to 19. 2010.	Not full, published journal article
Wheeler JJ, Baggett B a., Fox J, Blevins L. Treatment Integrity: A Review of Intervention Studies Conducted With Children With Autism. Focus Autism Other Dev Disabl. 2006;21(1):45–54.	Not primary research
Yang Y, Christensen M. Autism: an introduction to behavioural therapy models used for autism and nursing the person with autism in the primary care setting. Singapore Nurs J. 2012;39(3):18–24.	Not primary research
Yoder PJ. Although there is variability in response to early intensive behavioral intervention (EIBI), EIBI tends to facilitate IQ in children with autism. Evid Based Commun Assess Interv. 2010;4(1):14–7.	Not primary research
New guidance on autism. Lancet. 2007;370(9599):1590.	Not primary research

Appendix 3: List of Included Studies

Ref No.	Reference	Category of Publication
(85)	Ben Itzchak E, Zachor D a. Change in autism classification with early intervention: Predictors and outcomes. Res Autism Spectr Disord. 2009;3(4):967–76.	Unique study
(86)	Ben-Itzchak E, Watson LR, Zachor D a. Cognitive Ability is Associated with Different Outcome Trajectories in Autism Spectrum Disorders. J Autism Dev Disord. 2014;44(9):2221–9.	Unique study
(84)	Ben-Itzchak E, Zachor D a. The effects of intellectual functioning and autism severity on outcome of early behavioral intervention for children with autism. Res Dev Disabil. 2007;28(3):287–303.	Unique study
(82)	Blacklock K, Perry A, Geier JD. Examining the Effectiveness of Intensive Behavioural Intervention in Children with Autism Aged 6 and Older. J Dev Disabil. 2014;20(1):37–49.	Unique study
(69)	Cohen H, Amerine-Dickens M, Smith T. Early intensive behavioral treatment: replication of the UCLA model in a community setting. J Dev Behav Pediatr. 2006;27(2 Suppl):S145–55.	Unique study
(89)	Eikeseth S, Hayward D, Gale C, Gitlesen J-P, Eldevik S. Intensity of supervision and outcome for preschool aged children receiving early and intensive behavioral interventions: A preliminary study. Res Autism Spectr Disord. 2009 Jan;3(1):67–73.	Unique study
(92)	Eikeseth S, Smith T, Jahr E, Eldevik S. Intensive behavioral treatment at school for 4- to 7-year-old children with autism. A 1-year comparison controlled study. Behav Modif. 2002;26(1):49–68.	Publications based on same study
(93)	Eikeseth S, Smith T, Jahr E, Eldevik S. Outcome for children with autism who began intensive behavioral treatment between ages 4 and 7: a comparison controlled study. Behav Modif. 2007;31(3):264–78.	
(79)	Flanagan HE, Perry A, Freeman NL. Effectiveness of large-scale community-based Intensive Behavioral Intervention: A waitlist comparison study exploring outcomes and predictors. Res Autism Spectr Disord. 2012;6(2):673–82.	Unique study
(80)	Freeman N, Perry A. Outcomes of Intensive Behavioural Intervention in the Toronto Preschool Autism Service. J Dev Disabil. 2010;16(2):17–32.	Unique study
(70)	Granpeesheh D, Dixon DR, Tarbox J, Kaplan AM, Wilke AE. The effects of age and treatment intensity on behavioral intervention outcomes for children with autism spectrum disorders. Res Autism Spectr Disord. 2009;3(4):1014–22.	Unique study
(71)	Harris SL, Handleman JS. Age and IQ at intake as predictors of placement for young children with autism: a four- to six-year follow-up. J Autism Dev Disord. 2000;30(2):137–42.	Unique study
(90)	Hayward D, Eikeseth S, Gale C, Morgan S. Assessing progress during treatment for young children with autism receiving intensive behavioural interventions. Autism. 2009;13(6):613–33.	Unique study

(72)	Howard JS, Sparkman CR, Cohen HG, Green G, Stanislaw H. A comparison of intensive behavior analytic and eclectic treatments for young children with autism. Res Dev Disabil. 2005;26(4):359–83.	Publications based on same study
(73)	Howard JS, Stanislaw H, Green G, Sparkman CR, Cohen HG. Comparison of behavior analytic and eclectic early interventions for young children with autism after three years. Res Dev Disabil. 2014;35(12):3326–44.	
(83)	Perry A, Blacklock K, Dunn Geier J. The relative importance of age and IQ as predictors of outcomes in Intensive Behavioral Intervention. Res Autism Spectr Disord. 2013;7(9):1142–50.	Two unique studies within one publication: S1: Perry (2013a) S2: Perry (2013b)
(78)	Perry A, Cummings A, Dunn Geier J, Freeman NL, Hughes S, LaRose L, et al. Effectiveness of Intensive Behavioral Intervention in a large, community-based program. Res Autism Spectr Disord. 2008;2(4):621–42.	Publications based on same study
(81)	Perry A, Cummings A, Geier JD, Freeman NL, Hughes S, Managhan T, et al. Predictors of outcome for children receiving intensive behavioral intervention in a large, community-based program. Res Autism Spectr Disord. 2011;5(1):592–603.	
(91)	Remington B, Hastings RP, Kovshoff H, degli Espinosa F, Jahr E, Brown T, et al. Early intensive behavioral intervention: outcomes for children with autism and their parents after two years. Am J Ment Retard. 2007;112(6):418–38.	Unique study
(74)	Sallows GO, Graupner TD. Intensive Behavioral Treatment for Children With Autism : Four-Year Outcome and Predictors. Am J Ment Retard. 2005;110(6):417–38.	Unique study
(75)	Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. Am J Ment Retard. 2000;105(4):269–85.	Unique study
(76)	Stoelb M, Yarnal R, Miles J, Takahashi TN, Farmer JE, Mccathren RB. Predicting Responsiveness to Treatment of Children with Autism: A Retrospective Study of the Importance of Physical Dysmorphology. Focus Autism Other Dev Disabl. 2004;19(2):66–77.	Unique study
(94)	Virues-Ortega J, Rodríguez V, Yu CT. Prediction of treatment outcomes and longitudinal analysis in children with autism undergoing intensive behavioral intervention. Int J Clin Heal Psychol. 2013;13(2):91–100.	Unique study
(77)	Weiss MJ. Differential rates of skill acquisition and outcomes of early intensive behavioral intervention for autism. Behav Interv. 1999;14(1):3–22.	Unique study
(88)	Zachor DA., Ben Itzchak E. Treatment approach, autism severity and intervention outcomes in young children. Res Autism Spectr Disord. 2010;4(3):425–32.	Unique study
(87)	Zachor DA., Ben-Itzchak E, Rabinovich A-L, Lahat E. Change in autism core symptoms with intervention. Res Autism Spectr Disord. 2007;1(4):304–17.	Unique study

Appendix 4: Characteristics of Included Studies

Table 2. Study, sponsorship and design characteristics of included studies

First author, year (Ref. No.)	Country	Sponsorship[i]	Design			
			Diagnosis[ii]	Label[iii]	Type[iv]	Assignment
Ben-Itzchak, 2007 (84)	Israel	Ministry of Education	Autism	ADI-R, ADOS, DSM-IV	BA	–
Ben-Itzchak, 2009 (85)	Israel	Private support	Autism	ADI-R, ADOS, DSM-IV	BA	–
Ben-Itzchak, 2014 (86)	Israel	–	ASD	ADI-R, ADOS, DSM-IV	BA	–
Blacklock, 2014 (82)	Canada	York University	Autism/autistic disorder (55%), PDD or ASD (38%), PDD-NOS (7%)	CARS, DSM-IV	BA	–
Cohen, 2006 (69)	USA	NIMH	Autism (83%), PDD-NOS (17%)	ADI-R, DSM-IV	NRCT	Parent preference
Eikeseth, 2002, 2007 (92,93)	Norway	NIH	Autism	ADI-R, ICD-10	NRCT	Therapist availability
Eikeseth, 2009 (89)	UK	–	Autism	ADI-R	BA	–
Flanagan, 2012 (79)	Canada	RAPON	Autism (50%), PDD-NOS (50%)	CARS	NRCT	Treatment availability
Freeman, 2010 (80)	Canada	–	Autistic disorder (61%), PDD-NOS (31%), PDD or ASD (8%)	CARS, DSM-IV	BA	–
Granpeesheh, 2009 (70)	USA	–	Autistic disorder (93%), PDD-NOS (7%)	–	BA	–
Harris, 2000 (71)	USA	–	Autistic disorder	CARS, DSM-III-R	BA	–
Hayward, 2009 (90)	UK	NIMH	Autism	ADI-R	UCT	Geographic location
Howard, 2005, 2014 (72,73)	USA	–	Autistic disorder, PDD-NOS	DSM-IV	NRCT	Parent preference

Table 2. (continued)

First author, year (Ref. No.)	Country	Sponsorship[i]	Design			
			Diagnosis[ii]	Label[iii]	Type[iv]	Assignment
Perry, 2008, 2011 (78,81)	Canada	MCYS	Autistic disorder (58%), PDD or ASD (28%), PDD-NOS (14%)	CARS, DSM-IV	BA	–
Perry, 2013a (83)	Canada	York University	Autistic disorder, PDD-NOS, ASD	–	BA	–
Perry, 2013b (83)	Canada	York University	Autistic disorder, PDD-NOS, ASD	–	UCT	Age (younger vs. older)
Remington, 2007 (91)	UK	Health Foundation	Autism	ADI-R	NRCT	Parent preference
Sallows, 2005 (74)	USA	NIMH	Autism	ADI-R, DSM-IV	UCT	Random assignment
Smith, 2000 (75)	USA	Department of Education & UCLA Regents	Autism (50%), PDD-NOS (50%)	–	RCT	Random assignment
Stoelb, 2004 (76)	USA	–	Autism	DSM-IV	BA	–
Virues-Ortega, 2013 (94)	Spain	–	ASD	ADI-R, ADOS-G, DSM-IV-TR	BA	–
Weiss, 1999 (77)	USA	–	Autism (90%), PDD-NOS (10%)	DSM-IV	BA	–
Zachor, 2007 (87)	Israel	Ministry of Education	Autism, PDD-NOS	ADI, DSM-IV	NRCT	Geographic location
Zachor, 2010 (88)	Israel	Private support	Autism	ADI-R, ADOS	NRCT	Geographic location

[i]NIMH: National Institute of Mental Health; NIH: National Institutes of Health; RAPON: Regional Autism Programs of Ontario Network; MCYS: Ministry of Child and Youth Services. [ii]ASD: autism spectrum disorder; PDD: pervasive developmental disorder; PDD-NOS: pervasive developmental disorder – not otherwise specified. [iii]ADI-R: Autism Diagnostic Interview – Revised; ADOS: Autism Diagnostic Observation Schedule; DSM: Diagnostic and Statistical Manual of Mental Disorders; CARS: Childhood Autism Rating Scale; ICD: International Classification of Diseases. [iv]BA: before-and-after study (one-group pre-post design); NRCT: non-randomized controlled trial (multiple-group comparison); UCT: uncontrolled trial (multiple-group comparison); RCT: randomized controlled trial.
Note: "–" signifies not reported or not applicable.

Table 3. Study, sample and treatment characteristics of included studies

First author, year (Ref. No.)	Sample size[i]		Mean CA[vi]	Treatment					
	EG	CG	(mos)	Model[vii]	Intensity (h/w)	Duration (mos)	Setting	Provider	Parent training
Ben-Itzchak, 2007 (84)	25	–	26.6	IBI	≥35	12	Centre	Therapists	Training
Ben-Itzchak, 2009 (85)	68	–	25.4	IBI	35	12	Centre	Therapists	Training
Ben-Itzchak, 2014 (86)	46	–	25.5	IBI	20	24	Centre	Therapists, Teachers	Training
Blacklock, 2014 (82)	68	–	88.81	IBI	20-40†	19.46	Centre	Therapists	–
Cohen, 2006 (69)	21	21	30.2	UCLA	<3 yrs.: 20-30 >3 yrs.: 35-40	36	Community	Therapists	Training
Eikeseth, 2002, 2007 (92,93)	13	12	66.31	UCLA	<6 yrs.: 28 >6 yrs.: 18	31.4	School	Therapists, Teachers	Training
Eikeseth, 2009 (89)	20	–	34.9	UCLA	34.2	14	Home	Therapists	Training
Flanagan, 2012 (79)	61	61	42.93	IBI	25.81	27.84	Multiple	Therapists	Training
Freeman, 2010 (80)	89	–	53.64	IBI	20-40†	19.39	Centre	Therapists	–
Granpeesheh, 2009 (70)	245	–	73.92	IBI	76.65‡	–	Centre	Therapists	Training
Harris, 2000 (71)	27	–	49.0	IBI	27.5	–	Multiple	Therapists	Training
Hayward, 2009 (90)[ii]	23	–	35.7	UCLA	37.4	12	Multiple	Therapists	Training
	21	–	34.4	UCLA	34.2	12	Multiple	Therapists	–
Howard, 2005, 2014 (72,73)[iii]	29	16	30.86	IBI	35-40	36	Multiple	Therapists	Training
		16							
Perry, 2008, 2011 (78,81)	332	–	53.56	IBI	20-40†	18.43	Multiple	Therapists	Training
Perry, 2013a (83)	207	–	63.96	IBI	20-40†	20.16	Centre	Therapists	–
Perry, 2013b (83)[iv]	60	–	51.12	IBI	20-40†	20.53	Centre	Therapists	–
	60	–	89.4	IBI	20-40†	20.2	Centre	Therapists	–

Table 3. (continued)

First author, year (Ref. No.)	Sample size[i]		Mean CA[vi]	Treatment					
	EG	CG	(mos)	Model[vii]	Intensity (h/w)	Duration (mos)	Setting	Provider	Parent training
Remington, 2007 (91)	23	21	35.7	IBI	25.6	24	Home	Therapists, Parents	No training
Sallows, 2005 (74)[v]	13	–	33.23	UCLA	Y1: 38.6 Y2: 36.55	48	Multiple	Therapists	Training
	10	–	34.20	UCLA	Y1: 31.67 Y2: 30.88	48	Multiple	Therapists	Training
Smith, 2000 (75)	15	13	36.07	UCLA	Y1: 24.52 Y2/3: reduced	33.44	Multiple	Therapists	Training
Stoelb, 2004 (76)	19	–	56	IBI	22.79	12	Multiple	Therapists	Training
Virues-Ortega, 2013 (94)	24	–	50.5	UCLA	31.87	21.87	Home	Therapists, Parents	Training
Weiss, 1999 (77)	20	–	41.5	IBI	~40	24	Home	Therapists	–
Zachor, 2007 (87)	20	19	27.7	IBI	35	12	Centre	Therapists	–
Zachor, 2010 (88)	45	33	25.1	IBI	20	12	School	Therapists, Teachers	Training

[i]EG: experimental/treatment group; CG: control and/or comparison group. [ii]EG1: Clinic-based, EG2: Parent-managed. [iii]CG1: Autism educational programming (AP), CG2: Generic educational programming (GP). [iv]EG1: Younger (2-5 yrs.) group, EG2: Older (6-14 yrs.) group. [v]EG1: Clinic-directed, EG2: Parent-directed. [vi]Mean chronological age of behavioural treatment group at intake. [vii]IBI: General IBI model rooted in principles of applied behavioural analysis (ABA); UCLA: University of California, Los Angeles model (Lovaas treatment manual).
[†]Assumed intensity range; actual treatment intensity not explicitly stated. [‡]Hours per month, as reported in original article.
Note: "–" signifies not reported or not applicable.

Table 4. Study, treatment fidelity and outcome characteristics of included studies

First author, year (Ref. No.)	Treatment fidelity			Outcomes measured† (instrument)‡	Repeated measures (≥2 follow-up assessments)	Timing of assessment (standardized instruments)	
	Adherence	Competence	Differentiation			Cognitive	Adaptive
Ben-Itzchak, 2007 (84)	NR	NR	N/A (one-group study)	Imitation (DBS) Lang (DBS) Play skills (DBS) JA (DBS) Stereotyped behaviours (DBS) IQ composite (BSID-II, SB4)	No	Pre/post	NR
Ben-Itzchak, 2009 (85)	NR	NR	N/A (one-group study)	DR (ADOS algorithm) IQ composite (MSEL) AB composite (VABS)	No	NR	NR
Ben-Itzchak, 2014 (86)	Indirect measures, treatment manual.	Indirect measures	N/A (one-group study)	IQ composite (MSEL) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) AB-M (VABS) Psy (ADOS)	Yes	Pre/post	Pre/post
Blacklock, 2014 (82)	NR	NR	N/A (one-group study)	IQ composite (MSEL, WISC-IV, WPPSI-III, SB4/5) MA (n/a) RCog (n/a) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) RDev (n/a)	No	Pre/post	Pre/post

Table 4. (continued)

First author, year (Ref. No.)	Treatment fidelity			Outcomes measured† (instrument)‡	Repeated measures (≥2 follow-up assessments)	Timing of assessment (standardized instruments)	
	Adherence	Competence	Differentiation			Cognitive	Adaptive
Cohen, 2006 (69)	Indirect measures, treatment manual.	Direct measures	Indirect measures	IQ composite (BSID-R, WPPSI-R) Non-verbal IQ (MPSMT) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) Lang (RDLS) AP (n/a)	Yes	Pre/post (partial)	Pre/post (partial)
Eikeseth, 2002 (92)	Indirect measures, treatment manual.	Direct measures	Indirect measures	IQ composite (WPPSI-R, WISC-R, BSID-R) Non-verbal IQ (MPSMT) Lang (RDLS, WPPSI-R, WISC-R) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) AB-M (VABS)	No	Pre/post	Pre/post
Eikeseth, 2007 (93)	Indirect measures, treatment manual.	Direct measures	Indirect measures	IQ composite (WPPSI-R, WISC-R, BSID-R) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) AB-M (VABS) SEF (ACBC-TRF)	Yes	Pre/post	Pre/post

Table 4. (continued)

First author, year (Ref. No.)	Treatment fidelity			Outcomes measured† (instrument)‡	Repeated measures (≥2 follow-up assessments)	Timing of assessment (standardized instruments)	
	Adherence	Competence	Differentiation			Cognitive	Adaptive
Eikeseth, 2009 (89)	Indirect measures, treatment manual.	Direct measures	N/A (one-group study)	IQ composite (WPPSI-R, BSID-R) Non-verbal IQ (MPSMT) Lang (RDLS) AB composite (VABS)	No	Pre/post	Pre/post
Flanagan, 2012 (79)	NR	NR	NR	IQ composite (MSEL, WPPSI-III, SB4) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) Psy (CARS)	No	Post	Pre/post
Freeman, 2010 (80)	NR	NR	N/A (one-group only)	IQ composite (MSEL, BSID-II, WPPSI-III, SB4) MA (n/a) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) AB-M (VABS) Psy (CARS) RDev (n/a)	No	Pre/post	Pre/post
Granpeesheh, 2009 (70)	NR	NR	N/A (one-group study)	MS (n/a)	Yes	NR	NR
Harris, 2000 (71)	NR	NR	N/A (one-group study)	AP (n/a) IQ composite (SB4)	No	Pre/post	NR

Table 4. (continued)

First author, year (Ref. No.)	Treatment fidelity			Outcomes measured† (instrument)‡	Repeated measures (≥2 follow-up assessments)	Timing of assessment (standardized instruments)	
	Adherence	Competence	Differentiation			Cognitive	Adaptive
Hayward, 2009 (90)	Indirect measures, treatment manual.	Direct measures	N/A (no control group)	IQ composite (BSID-R, WPPSI-R) Non-verbal IQ (MPSMT) Lang (RDLS) AB composite (VABS)	No	Pre/post	Pre/post
Howard, 2005 (72)	NR	NR	NR	IQ composite (BSID-II, WPPSI-R, DP-II, SB4, DAS, DAYC, PEP-R) Non-verbal IQ (MPSMT, Leiter-R) Lang (RDLS, Rosetti, REEL-2, PLS-3, PPVT-III, EVT, DP-II, SICD-R, ROPVT, EOPVT) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) AB-M (VABS)	No	Pre/post	Pre/post
Howard, 2014 (73)	Direct	Direct	Indirect	IQ composite (WPPSI-III/-R, WISC-III/-IV, SB4/5, DAS, SIT-R, WJ-III) Non-verbal IQ (MPSMT) Lang (RDLS, ROPVT, EOPVT, PPVT, EVT, SICD-R) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) AB-M (VABS)	Yes	Pre/post	Pre/post
Perry, 2008, 2011 (78,81)	Indirect measures, treatment manual	Direct measures	N/A (one-group study)	IQ composite (MSEL, BSID-II, WPPSI-III/-R, SB4) MA (n/a) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) AB-M (VABS) Psy (CARS) RDev (n/a)	No	Pre/post	Pre/post

Table 4. (continued)

First author, year (Ref. No.)	Treatment fidelity			Outcomes measured† (instrument)‡	Repeated measures (≥2 follow-up assessments)	Timing of assessment (standardized instruments)	
	Adherence	Competence	Differentiation			Cognitive	Adaptive
Perry, 2013a (83)	NR	NR	N/A (one-group study)	IQ composite (various, unspecified) Non-verbal IQ (MA, in years) AB composite (VABS) RCog (n/a) RDev (n/a)	No	Pre	Pre
Perry, 2013b (83)	NR	NR	NR	IQ composite (various, unspecified) AB composite (VABS) RCog (n/a) RDev (n/a)	No	Pre/post	Pre/post
Remington, 2007 (91)	Indirect measures	Indirect measures	Indirect measures	IQ composite (BSID, SB4) MA (n/a) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) AB-M (VABS) JA (ESCS) Lang (RDLS) CB (NCBRF, DBC) PWB (HADS)	Yes	Pre/post	Pre/post
Sallows, 2005 (74)	Indirect measures, treatment manual.	Direct measures	N/A (no control group)	IQ composite (BSID-II, WPPSI-R, WISC-III) Non-verbal IQ (MPSMT, Leiter-R) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) Lang (RDLS, CELF-III) SEF (ACBC-TRF) MS (ELM)	Yes	Pre/post	Pre/post

Table 4. (continued)

First author, year (Ref. No.)	Treatment fidelity			Outcomes measured† (instrument)‡	Repeated measures (≥2 follow-up assessments)	Timing of assessment (standardized instruments)	
	Adherence	Competence	Differentiation			Cognitive	Adaptive
Smith, 2000 (75)	Indirect measures, treatment manual.	Indirect measures	NR	IQ composite (BSID, SB4) Non-verbal IQ (MPSMT) Lang (RDLS) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) SEF (ACBC, ACBC-TRF) PWB (FSQ) AP (WIAT)	No	Pre/post	Pre/post
Stoelb, 2004 (76)	Direct measures	Indirect measures	N/A (one-group study)	AB composite (VABS) Psy (CARS) Fx (EPS) Lang (n/a)	Yes	NR	Pre
Virues-Ortega, 2013 (94)	Indirect measures, treatment manual	NR	N/A (one-group study)	IQ composite (WPPSI-III, BSID, MPSMT) GMF (E-LAP, LAP-D) FMF (E-LAP, LAP-D) PWR (E-LAP, LAP-D) COG (E-LAP, LAP-D) RLG (E-LAP, LAP-D) ELG (E-LAP, LAP-D) SFC (E-LAP, LAP-D) SBH (E-LAP, LAP-D)	Yes	Pre/post	NR
Weiss, 1999 (77)	Indirect measures	Indirect measures	N/A (one-group study)	AB composite (VABS) Psy (CARS) MS (n/a) AP (n/a)	No	NR	Pre/post

Table 4. (continued)

First author, year (Ref. No.)	Treatment fidelity			Outcomes measured† (instrument)‡	Repeated measures (≥2 follow-up assessments)	Timing of assessment (standardized instruments)	
	Adherence	Competence	Differentiation			Cognitive	Adaptive
Zachor, 2007 (87)	NR	NR	Indirect measures	IQ composite (BSID-II, SB4) Psy (ADOS-LC, ADOS-RSI) DR (ADOS algorithm)	No	Pre	NR
Zachor, 2010 (88)	Direct measures	Direct measures	Direct measures	IQ composite (MSEL subdomains) AB composite (VABS) AB-Com (VABS) AB-DLS (VABS) AB-Soc (VABS) AB-M (VABS Psy (ADOS algorithm)	No	Pre/post	Pre/post

†AB: adaptive behaviour, AB-Com: AB communication subdomain, AB-DLS: AB daily living skills subdomain, AB-M: AB motor skills subdomain, AB-Soc: AB socialization subdomain, AP: adacemic/educational placement, CB: child behaviour, COG: cognitive, DR: diagnostic revovery, ELG: expressive language, FMF: fine motor function, GMF: gross motor function, IQ (Non-verbal): visual-spatial IQ, IQ: intellectual quotient, JA: joint attention, Lang: language, MA: mental age/ratio IQ, MS: mastery of skills or behavioural objectives/initial skill acquisition , Psy: Severity of symptoms/psychopathology, PWB: Parental well-being/family satisfaction, PWR: prewriting, RCog: Cognitive rate of development, RDev: Developmental rate/Adaptive rate of development, RLG: receptive language, SBH: social behaviour, SEF: social emotional functioning, SFC: self-care.

‡ACBC: Achenbach Child Behavior Checklist, ACBC-TRP: ACBC Teacher Report Form, ADOS: Autism Diagnostic Observation Schedule, ADOS-G: Autism Diagnostic Observation Schedule-Generic, ADOS-LC: ADOS language and communication domain, ADOS-RSI: ADOS reciprocal social interaction domain, BSID: Bayley Scales of Infant Development, BSID-II: Bayley Scales of Infant Development (2nd Ed.), BSID-R: Bayley Scales of Infant Development - Revised, CARS: Childhood Autism Rating Scale, CELF-III: Clinical Evaluation of Language Fundamentals (3rd Ed.), DAS: Differential Abilities Scale, DAYC: Developmental Assessment of Young Children, DBC: Developmental behavior checklist (parent report version), DBS: Developmental-behavioral scales, DP-II: Developmental Profile-II, E-LAP: Early Learning Accomplishment Profile, ELM: Early Learning Measure (UCLA), EOPVT: Expressive One-Word Picture Vocabulary Test, EPS: EIBI Performance Scale, ESCS: Early Social Communication Scales, EVT: Expressive vocabulary test, FSQ: Family Satisfaction Questionnaire, HADS: Hospital Anxiety and Depression Scale, LAP-D: Learning Accomplishment Profile-Diagnostic, Leiter-R: Leiter International Performance Scale-Revised, MPSMT: Merrill-Palmer Scale of Mental Tests, MSEL: Mullen Scales of Early Learning, NCBRF: Nisonger Child Behavior Rating Form (positive social subscale), PEP-R: Psychoeducational Profile-Revised, PLS-3: Preschool Language Scale-3, PPVT: Peabody Picture Vocabulary Test (3rd Ed.), RDLS: Reynell Developmental Language Scales, REEL-2: Receptive-Expressive Emergent Language Scales-Revised, ROPVT: Receptive One-Word Picture Vocabulary Test, Rosetti: Rosetti Infant-Toddler Language Scale, SB4/5: Stanford-Binet Intelligence Scale (4th/5th Ed.), SB4: Stanford-Binet Intelligence Scale (4th Ed.), SICD-R: Sequenced Inventory of Communication Development-Revised Edition, SIT-R: Slosson Intelligence Test-Revised, VABS: Vineland Adaptive Behaviour Scales, WIAT: Wechsler Individualized Achievement Test, WISC-III: Wechsler Intelligence Scales for Children (3rd. Ed.), WISC-IV:Wechsler Intelligence Scales for Children (4th Ed.), WISC-R: Wechsler Intelligence Scales for Children-Revised, WJ-III: Woodcock-Johnson Tests of Cognitive Abilities-III, WPPSI: Wechsler Preschool and Primary Scale of Intelligence, WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence (3rd Ed.), WPPSI-R: Wechsler Preschool and Primary Scale of Intelligence-Revised.

Appendix 5: Summary of Findings Tables

Table 5. Summary of findings from included studies

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Ben-Itzchak, 2007** (84) *Country:* **Israel** *Study design:* **Prospective one-group pre/post design** *Number of centres:* NR *Funding source:* Ministry of Education in Israel *Quality:* **Moderate**	*Sample size (n):* **25** *Male (%):* 92.00 *Sample attrition:* None *Inclusion criteria for study entry:* • Free of any comorbidities and genetic disorders. • ADI or ADOS scores above cut-off points for autism in all observed domains. Baseline participant characteristics *Age in months, mean±SD (range):* 26.6 (20-32) *IQ at intake, mean±SD (range):* 70.67±17.01	***EG:*** Centre-based ABA program delivered at ≥35 weekly hours. *Other interventions used:* None described *Provider(s):* Skilled behaviour therapist under the supervision of a trained behaviour analyst *Parental role:* Parents learned how to use behavioural methods to apply at home for generalization and maintenance purposes and worked with program supervisor in establishing developmental goals in the natural environment.	*Primary outcome(s):* • Six developmental-behavioural domains: imitation, receptive language, expressive language, play skills, nonverbal communication skills, and stereotypes behaviours • Full-scale IQ *Secondary outcome(s):* None described *Length of follow-up:* 12 months	• Significant change was observed in all six developmental-behavioural domains, and IQ scores increased by an average of 17.3 points from baseline to follow-up. • Children with higher initial cognitive levels and children with fewer measured early social interaction deficits showed better acquisition of developmental skills (especially noted in receptive language, expressive language and play skills). • The gain in IQ scores in this study is acquired regardless of pre-treatment autism severity in communication and in reciprocal social-interaction domains.	• No control group • Small sample size • Developmental-behavioural scales (DBS) is not a validated outcome measure (even though content validity was approved by two assessors).
First author, year (Ref.): **Ben-Itzchak, 2009** (85) *Country:* **Israel** *Study design:* **Prospective one-group pre/post design** *Number of centres:* NR *Funding source:* Private support (Mr. Dov Moran) *Quality:* **Low**	*Sample size (n):* **68** *Male (%): 91.18* *Sample attrition:* Missing outcome data reported on some children (2-7 approx.) at follow-up. *Inclusion criteria for study entry:* • Diagnosis of autism disorder in accordance with the DSM-IV, ADI-R, and ADOS. Baseline participant characteristics *Age (months), mean±SD (range):* 25.4±4.0 (18-35) *IQ at intake, mean±SD (range):* NR	***EG:*** Centre-based autism-specific preschool program based on behavioural principles delivered at about 35 weekly hours; its curriculum included discrete trial training (DTT), naturalistic, and incidental teaching techniques. *Other interventions used:* None described *Provider(s):* Skilled behaviour therapist under the supervision of a trained behaviour analyst *Parental role:* Parent training was offered to address problem behaviours.	*Primary outcome(s):* • Full-scale IQ • Adaptive behaviour • Diagnostic recovery *Secondary outcome(s):* None described. *Length of follow-up:* 12 months	• Participants' diagnostic classification (based on ADOS algorithm) remained very stable after one year of intervention (i.e. 19% moved from autism to the less severe ASD classification and only 3% no longer met criteria for ASD). • Verbal abilities at the time of diagnosis were significantly better in participants whose diagnostic severity improved form baseline to follow up, as compared with participants whose disease severity remained unchanged. • Pre-intervention child factors, including the child's age, level of adaptive skills, and environmental factors such as parents' age or level of education, were not related to the change in autism categorical classification at post-intervention time.	• No control group • Relatively small sample size • Only 40 out of 68 participants received therapy based exclusively on ABA teaching principles. The remaining 28 participants received eclectic treatment, a combination of several teaching approaches.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Ben-Itzchak, 2014 (**86) *Country:* **Israel** *Study design:* **Retrospective one-group pre/post design** (retrospective file review) *Number of centres:* Four centre-based facilities, but most participants (n=33) came from one site. *Funding source:* Private support (Mr. Dov Moran) *Quality:* **Moderate**	*Sample size (n):* **46** *Male (%):* 84.78 *Sample attrition:* Considerable amount of missing data on VABS and MSEL measures at follow-up assessments. *Inclusion criteria for study entry:* • Diagnosis of ASD • Received centre-based IBI for at least 2 years • Presence of baseline cognitive ability scores • Absence of hearing deficiencies and genetic syndromes Baseline participant characteristics *Age (months), mean±SD (range):* 25.5±3.95 (17-33) *IQ at intake, mean±SD (range):* 71.4±20.2 (n=33)	***EG:*** Centre-based ABA program provided at about 20 hours per week. Teaching techniques comprised discrete trial training, incidental teaching, shaping for positive reinforcement, successive approximation, systematic prompting and fading procedures, discrimination learning, task analysis and functional assessment and reinforcement procedures according to several treatment manuals. *Other interventions used:* None described. *Provider(s):* Trained therapists (team of 3 per child), under the supervision of a Board Certified Behaviour Analyst (BCBA), speech-language pathologist, occupational therapist, special education preschool teachers. *Parental role:* Parents received weekly instructions for home treatment from the behaviour analyst who supervised the child's program.	*Primary outcome(s):* • Full-scale IQ • Adaptive behaviour • Severity of symptoms *Secondary outcome(s):* None described. *Length of follow-up:* 24 months. Assessments occurred at baseline (T1) and after the first (T2) and second (T3) year of intervention.	• A significant increase in cognitive abilities (MSEL composite score) was noted only for the low cognitive abilities group (IQ<70) after the second year of intervention. Significant gains in the MSEL expressive language subdomain standard score were found for all participants and only after the first year of intervention. • An increase in overall adaptive skills was only found during the second year of intervention. • A significant increase in adaptive skills was observed in standard scores for the communication, daily living skills and socialization VABS subdomains; yet, improvements in these subdomains were only noted as significant for the higher cognitive ability group (IQ≥70), while standard scores remained unchanged for the IQ<70 group. • A gradual significant decrease in autism severity was observed after 2 years of intervention, with no difference based on cognitive group (i.e. IQ<70 versus IQ≥70). • Baseline cognitive level was not found to be a significant moderator of change in autism symptom severity; however, having a higher baseline cognitive level seemed to enable acquisition of adaptive skills, as compared with the lack of marked progress observed in children with baseline cognitive impairment.	• No control group. • Small sample size. • Considerable amount of missing data (22-30%) on VABS and MSEL outcome measures at follow-up assessments. • Potential for some unaccounted variability in intervention across the different treatment settings, even though authors claim that all study subjects received the same intervention approach and were supervised by the same team. • Exclusion of participants based on presence of comorbid conditions. • Questionable methods used for examining moderators of outcome.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Blacklock, 2014** (82) *Country:* **Canada** *Study design:* **Retrospective one-group pre/post design** (retrospective file review) *Number of centres:* Nine regional IBI program centres providing government-funded services. *Funding source:* York University Faculty of Health Small Research Grant *Quality:* **Low**	*Sample size (n):* **68** *Male (%):* **82.35** *Sample attrition:* Some missing outcome data at follow-up. *Inclusion criteria for study entry:* • Received 10 or more months of IBI treatment through the Ontario Autism Intervention Program (AIP) • Began therapy at 6 years or older • Baseline assessment occurred within 4 months of starting IBI Baseline participant characteristics *Age (months), mean±SD (range):* 88.81±21.94 (70.0-163.0) *IQ at intake, mean±SD (range):* 43.26±21.09 (<20.0-104.0; n=63)	***EG:*** Large, community-based, publicly-funded IBI program delivered at 20 to 40 hours per week. *Other interventions used:* None described. *Provider(s):* Trained instructor-therapists *Parental role:* NR	*Primary outcome(s):* • Full-scale IQ • Adaptive behaviour *Secondary outcome(s):* • Mental age • Cognitive rate of development • Adaptive rate of development (developmental rate) *Length of follow-up:* Mean program duration of about 19 months (range: 10-69 months, n=56)	• Participants as a group did not show statistically significant gains in IQ, cognitive rate of development, adaptive behaviour standard scores or age equivalent scores from program entry to discharge. • Some children (<10%) showed clinically significant gains in their cognitive (increase in IQ score by 15 points) and adaptive functioning (learned new skills), and a few (3%) displayed clinically significant losses on these measures. Gains tended to be made more commonly in adaptive functioning, and to a lesser extent in cognitive level. • There were strong correlations of initial cognitive and adaptive scores, but not initial age, with all variables at follow-up. • A curvilinear relationship was observed between the child's age and outcome measures: relatively younger children (age 6-7 at program entry) had highly variable outcomes but children over 8 years at intake tended to be less variable and showed consistently poor outcomes.	• No control group. • Inconsistency in collected data (i.e. collected from many different sites, which often had different practices). • No control or influence over measures used for assessment, nor the timing of the assessments (due to retrospective nature of study). • Measures used have several limitations (i.e. VABS has parents' biases and large standard error, ratio IQ used at times (since a standardized score was not available for low performance) which isn't as good as full-scale IQ, psychometric limitations of age-equivalent scores - not corrected for age, and may not mean the same thing at different ages). • Different standardized assessments sometimes used at different time points. • No knowledge of whether children received any other intervention prior to or during IBI. • No specific measure of treatment intensity/duration and no measure of quality/fidelity. • Outcome assessors were not blind to children's participation in IBI, nor were they independent of the organization providing IBI. • No exclusion of participants based on presence of comorbid disorders. • Of the 332 children in the Perry et al. (2008) study, there were 20 children who met the inclusion criteria for the current study and were included.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Cohen, 2006** (69) *Country:* **United States** *Study design:* **Non-randomized prospective controlled multiple-group comparison** (matched-pairs comparison) *Number of centres:* NR *Funding source:* National Institute of Mental Health *Quality:* **Moderate**	*Sample size (n):* **42** EG (n): 21 CG (n): 21 *Male (%):* 83.33 *Sample attrition:* Five dropouts (in addition to the 42 participants) excluded from the analyses (3 participants in EG and 2 in CG), and a few participants has missing data at one or more follow-up assessments. *Inclusion criteria for study entry:* • Diagnosis of autism or PDD-NOS confirmed by ADI-R • Pre-treatment IQ>35 • Intake age<48 months and between 18-42 months at diagnosis • No severe medical limitation or illness that would preclude partaking in intensive weekly therapy • Residence within 60 km of treatment agency • No more than 400 hours of behavioural intervention prior to intake • Parent's agreement to actively partake in parent training and generalization and to have an adult present during home intervention hours Baseline participant characteristics *Age (months), mean±SD (range):* EG: 30.2±5.8 CG: 33.2±3.7 *IQ at intake, mean±SD (range):* EG: 61.6±16.4 CG: 59.4±14.7	***EG:*** Community-based early intensive behavioural treatment (EIBT) based on the UCLA instructional model and consisting of three components: (i) in-home 1:1 instruction delivered at 20-30 weekly hours for children below 3 years, and 35-40 weekly hours for children above 3 years, (ii) peer play training, and (iii) regular education classroom inclusion. No aversive interventions were used throughout the study. ***CG:*** Various public school education classes and community services selected by parents. *Other interventions used:* None described. *Provider(s):* Trained therapists (mandatory completion of 3-4 month internship at UCLA) and tutors (main providers of direct services recruited from the community). Site director was a BCBA. *Parental role:* Parents were encouraged to be involved in all levels of intervention (to foster the child's acquisition and generalization skills), and they were asked to be active participants in their child's intervention, although there was no requirement for parents to provide any direct intervention hours.	*Primary outcome(s):* • Full-scale IQ *Secondary outcome(s):* • Non-verbal IQ (visual-spatial skills) • Adaptive behaviour • Language • Academic/classroom placement *Length of follow-up:* 36 months (47 weeks per year). Assessments occurred at baseline (T1) and after the first (T2), second (T3), and third (T4) year of intervention.	• There was a significant difference between groups on cognitive functioning at program discharge: the mean IQ score increased by 25 points in the EG, as compared with 14 points in the CG. • In addition to IQ, the EG made significantly greater gains in receptive language and adaptive functioning as compared with control. • Seventeen of 21 EG children were included into regular education classroom settings, as compared with one of 21 children in the control group (despite IQ gains).	• Small sample size • Non-random assignment (as a result of community program that is mandated to provide treatment to parents and children with ASD who are free to accept a plan or not). • Pre-existing group differences (diagnosis, family education, etc.) may have biased the results, even after statistically controlling for family variables.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Eikeseth, 2002, 2007** (92,93) *Country:* **Norway** *Study design:* **Non-randomized prospective controlled multiple-group comparison** *Number of centres:* Several potential sites within two counties in Norway (number unspecified) *Funding source:* National Institutes of Health *Quality:* **High**	*Sample size (n):* **25** EG (n): 13 CG (n): 12 *Male (%):* 76.0 *Sample attrition:* There were two dropouts in addition to the 25 participants. *Inclusion criteria for study entry:* • Diagnosis of childhood autism (ICD-10) via ADI-R and independent psychologist • Intake age >4<7 years • Deviation IQ>50 at intake or ratio IQ>50 • Absence of major medical conditions other than autism Baseline participant characteristics *Age (months), mean±SD (range):* EG: 66.31±11.31 CG: 65.00±10.95 *IQ at intake, mean±SD (range):* EG: 61.92±11.31 CG: 65.17±14.97	***EG:*** IBI based on Lovaas manual and associated videotapes (UCLA teaching model) delivered at 20-35 weekly hours, with the modification that contingent aversives were not employed. Treatment intensity was reduced to about 5-20 hours per week after participants enrolled in school (≥6 years) ***CG:*** Intensive, eclectic special education services delivered at 20-35 weekly hours, but with less supervision than EG. Treatment incorporated elements of TEACCH, sensory-motor therapies, ABA, as well as methods derived from personal experience. *Other interventions used:* None described. *Provider(s):* Trained therapists (special education teachers) and one or more aides, as well as student instructors and paraprofessionals. *Parental role:* Parents worked alongside therapists for the first 3 months for a minimum of 4 hours per week, and then applied generalization and maintenance procedures.	*Primary outcome(s):* • Full-scale IQ • Adaptive behaviour *Secondary outcome(s):* • Non-verbal IQ (visual-spatial skills) • Language • Social-emotional functioning (SEF) domains *Length of follow-up:* Originally 12 months, then extended to about 31 months in follow-up study. Assessments occurred at baseline (T1), after the first year (T2), and last follow-up (T3).	• IBI treated children showed greater gains on cognitive functioning and adaptive skills with intervention, as compared with children in the CG: average gain of 25 IQ points and 12 points on adaptive functioning (as measured by VABS) at last EG follow-up (after >2 years of intervention). • EG also showed less severe aberrant behaviour and fewer social problems at follow-up compared to control. • Seven of 13 children in the EG (54%) who scored within the range of mental retardation at intake scored within the average range (IQ≥85) on both IQ and visual-spatial IQ at follow-up, as compared with two of 12 children in CG (17%). • None of the demographic variables (e.g. age at intake) or pre-treatment test scores (e.g. IQ) predicted individual differences in response to treatment in the EG.	• Non-random assignment to groups (based on geographical location). • Small sample size. • Inclusion criteria restricted full heterogeneity in sample population (e.g. only those with IQ≥ 50 included), and resulted in participants that may have been higher functioning at intake than is usual for children with ASD. • CG may have functioned at a more advanced level then the EG at intake. • No direct quality control measures of treatment.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Eikeseth, 2009** (89) *Country:* **United Kingdom** *Study design:* **Retrospective one-group pre/post design** *(retrospective file review)* *Number of centres:* NR *Funding source:* NR *Quality:* **Moderate**	*Sample size (n):* **20** *Male (%):* 70.0 *Sample attrition:* NR *Inclusion criteria for study entry:* • Diagnosis of autism according to the ICD-10 criteria • Intake CA >24<42 months • Absence of other severe medical conditions, as certified by a medical practitioner • Residence outside of the catchment area for clinic-based services Baseline participant characteristics *Age (months), mean±SD (range):* 34.9±5.7 (28-42) *IQ at intake, mean±SD (range):* 54.2±15.1 (17-83)	***EG:*** UK Young Autism Project (YAP) home-based therapy delivered at an average of 34 weekly hours (the British replication site for the UCLA international multi-site YAP). *Other interventions used:* None described. *Provider(s):* At least two trained therapists and one program consultant per child. *Parental role:* Parents were offered a half-day course on ABA principles, followed by several days of hands-on training for the purpose of implementing generalization and maintenance procedures.	*Primary outcome(s):* • Full-scale IQ • Non-verbal IQ (visual-spatial skills) • Language • Adaptive behaviour *Secondary outcome(s):* None described. *Length of follow-up:* Mean program duration of about 14 months.	• Intensity of supervision was significantly associated with change in IQ score between intake and program discharge. • Change in IQ score was significantly correlated with baseline visual-spatial IQ, while all other correlations were non-significant.	• Preliminary/exploratory study with low sample size. • No control group. • The study is correlational in nature. • Data from the parent-managed treatment group of the study by Hayward et al (2000) are used.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Flanagan, 2012** (79) *Country:* **Canada** *Study design:* **Non-randomized retrospective controlled multiple-group comparison** (matched-pairs comparison) *Number of centres:* Single centre (Toronto Partnership for Autism Services: the largest of 9 publicly-funded regional IBI programs in Ontario) *Funding source:* Regional Autism Programs of Ontario Network (RAPON) *Quality:* **Moderate**	*Sample size (n):* **122** EG (n): 61 CG (n): 61 *Male (%):* 85.25 *Sample attrition:* None. *Inclusion criteria for study entry:* • Receiving IBI or on waitlist for at least 12 months • Complete information available on adaptive functioning, autism severity, and cognitive skills, with all measures at the same time point and within 3 months of one another • Received <10 weekly hours of IBI from private agencies if on waitlist • Received IBI for 80% of the interval between intake and exit assessment Baseline participant characteristics *Age (months), mean±SD (range):* EG: 42.93±11.53 CG: 42.79±10.51 *IQ at intake, mean±SD (range):* EG: NR CG: NR	***EG:*** Large-scale community IBI program rooted in ABA teaching principles (Toronto Partnership for Autism Services or TPAS) delivered at 20-35 hours per week. ***CG:*** Wait-list participants not yet receiving IBI therapy. Most children attended school (small specialized classrooms for children with developmental disabilities, typical classrooms with or without educational assistant support) for an average of about 18 hours per week. Some children received auxiliary services, such as low intensity behavioural intervention (<10 hours per week), speech-language pathology services, occupational therapy and/or behavioural consultation. *Other interventions used:* None described. *Provider(s):* Trained instructor-therapists. *Parental role:* Parents were encouraged to attend training and meet regularly with treatment staff.	*Primary outcome(s):* • Full-scale IQ • Adaptive behaviour • Severity of symptoms *Secondary outcome(s):* None described. *Length of follow-up:* Mean program duration of about 28 months.	• Although groups did not differ significantly at intake, the EG had milder autism severity, higher adaptive functioning and higher cognitive skills at discharge. The effect size of group differences was medium for autism severity and adaptive functioning, and large for cognitive skills (19-point difference in IQ scores at exit, with results favouring the IBI group). • At the last follow-up assessment, 18% of children in the IBI group has IQ estimates in the average range (>85), as compared with 3.3% in the Waitlist group. • Initial age was found to be an important predictor of better outcomes in IBI relative to a comparison group. • Children with higher initial adaptive skills are more likely to experience good outcomes with IBI, although these children may also benefit the most from other interventions. • Autism severity may not play a meaningful predictor role when age and adaptive skill level are controlled. • Duration was not a significant predictor of outcome.	• Clinicians carrying out assessments knew whether children had received IBI or not (i.e. independent assessors not employed). • Formal measures of treatment quality and fidelity were not available or reported. • Duration between test periods differed significantly between groups. • Information about cognitive functioning was not available at intake (i.e. unable to determine pre-treatment differences in cognitive skills between groups). • Non-random assignment to groups. • Some of the children in the EG were also included in previous studies exploring the impact of the Ontario IBI program (16% were included in Freeman (2010); 27% were included in Perry (2008, 2011))

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Freeman, 2010** (80) *Country:* **Canada** *Study design:* **Retrospective one-group pre/post design** *Number of centres:* Single centre (Toronto Partnership for Autism Services: the largest of 9 publicly-funded regional IBI programs in Ontario) *Funding source:* NR *Quality:* **Moderate**	*Sample size (n):* **89** *Male (%):* 82.02 *Sample attrition:* Incomplete outcome data at follow-up for full-scale IQ score (n=20) and AB composite (n=81) measures. *Inclusion criteria for study entry:* No specific criteria described. Baseline participant characteristics *Age (months), mean±SD (range):* 53.64±13.12 (20-83) *IQ at intake, mean±SD (range):* 36.65±14.83 (15-77)	***EG:*** Large, community-based, publicly-funded IBI program delivered at 20 to 40 hours per week. *Other interventions used:* None described. *Provider(s):* Trained instructor-therapists. *Parental role:* NR	*Primary outcome(s):* • Severity of symptoms • Full-scale IQ • Adaptive behaviour • Adaptive rate of development (developmental rate) *Secondary outcome(s):* None described. *Length of follow-up:* Mean program duration of about 19 months (range: 5-47 months)	• Children showed statistically significant reductions in autism symptom severity (based on change in CARS scores) • Significant improvements in cognitive level (increase in IQ of about 11 points) were observed among children who had complete information on cognitive functioning (n=20), with nine children making clinically significant gains (increase in IQ by 15 or more points). • Children gained significantly in developmental skills in all areas of adaptive behaviour; however, only age equivalent scores increased, while standard scores, which are corrected for age, remained stable. • Children's rate of development during IBI was found to be approximately double their initial rate (prior to IBI). • Average functioning was achieved by 11% of children in the sample (defined as scoring in the non-autism range based on severity and having cognitive and/or adaptive standard scores in the low average range at discharge). • Children who began IBI before age 4 scored significantly better at program discharge on the CARS, VABS, and full-scale IQ estimate scores than those that started treatment after age 4. • Children who received 2 or more years of IBI scored significantly better at program discharge on all outcome variable than those children who had shorter program durations (< 2 years).	• No control/comparison group of similar children who received no treatment or a different treatment. • No measure of treatment fidelity. • Outcome measures are limited and do not tap all possible changes of interest (e.g. problem behaviour), have imperfect reliability and validity, and were not always available for all children. • Outcome assessors (at intake and discharge) were not blind to the children's participation in IBI, nor were they independent of the organization providing treatment.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Granpeesheh, 2009** (70) *Country:* **United States** *Study design:* **Retrospective one-group pre/post design** *Number of centres:* Six centres in across six US states, including west coast, east coast, and middle region. *Funding source:* NR *Quality:* **Low**	*Sample size (n):* **245** *Male (%):* NR *Sample attrition:* NR *Inclusion criteria for study entry:* • Intake age >16 months and <12 years • Received an average of 20 or more hours per month for the duration of the study • Mastery of at least one skill item per month • Not in first month of treatment or has received treatment for more than 4 years Baseline participant characteristics *Age (years), mean±SD (range):* 6.16±2.33 *IQ at intake, mean±SD (range):* NR	***EG:*** Community-based IBI services individualized for each child to address all areas of functioning in which he/she displayed skill deficits and delivered at about 20 to 169 hours per month. Treatment involved both structured (discrete trial training) and unstructured (natural environment training) behavioural teaching strategies, verbal behaviour-oriented language intervention, use of both errorless prompting strategies and least-to-most prompting, use of behavioural principles to design and implement teaching (reinforcement, extinction, stimulus control, generalization training, chaining and shaping), and a function-based approach to assessing and treating challenging behaviours. *Other interventions used:* None described. *Provider(s):* Trained therapists (limited details provided). *Parental role:* Inclusion of parents in all treatment decisions and regular parent training.	*Primary outcome(s):* • Mastery of behavioural objectives (i.e. achievement of 80% correct or higher on an objective for two consecutive therapy sessions; if the child met this criterion, then the objective was scored as "mastered") *Secondary outcome(s):* None described. *Length of follow-up:* NR; Assessments occurred at baseline and once per month for four months.	• An increase in treatment hours and decrease in participant age was associated with the greatest number of mastered behavioural objectives. • The youngest group (2–5 years) showed the greatest response to treatment at low levels of intensity and similar level of gains as the middle age group (5–7 years) at high levels of intensity. • The middle age group (5–7 years) showed a similar increasing trend, like the youngest group, such that there was no point of diminishing-returns from increased treatment hours (i.e. for children under 7 years, there was not a point at which participants began to burn out from treatment). • Children in the highest age group (7–12 years) did not show a significant relationship between treatment hours and the number of behavioral objectives mastered (i.e. efficacy of intervention decreases as the age of the child increases). • Behavioural intervention produces more efficient skill acquisition per unit time in younger children, as compared with older children, thereby underscoring the need for early intervention.	• No control/comparison group. • Use of mastered behavioural objectives as a measure of therapeutic progress is inherently flawed (e.g. different objectives are of different difficulty to master); yet, authors argue that it seems likely that, given a large enough sample size, measurement errors should be evenly distributed across the participants such that the crude measure will be a relatively valid proxy of overall treatment progress. • No formal inter-observer agreement was collected on outcome data. • Participants were unable to be assigned to differing levels of treatment hours (due to non-random assignment and uncontrolled nature of study). • Some participants received treatment at well below 20 hours per week, although the average of all participants was around 20 weekly hours. • Variation in treatment delivery across different centres across the US is possible.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Harris, 2000** (71) *Country:* **United States** *Study design:* **Prospective one-group pre/post design** *Number of centres:* Single centre (Douglas Developmental Disabilities Center) *Funding source:* NR *Quality:* **Moderate**	*Sample size (n):* **27** *Male (%):* 85.19 *Sample attrition:* NR *Inclusion criteria for study entry:* • Complete data on age at admission and discharge, pre and post IQ data, and CARS scores at admission Baseline participant characteristics *Age (months), mean±SD (range):* 49 (31-65) *IQ at intake, mean±SD (range):* 59.33 (35-109)	***EG:*** Intensive centre-based educational instruction (developmentally sequenced and rooted in ABA teaching methods) delivered at an average of 27.5 weekly hours. Children typically begin in a 1:1 setting and then ultimately progressed to an integrated classroom. *Other interventions used:* Some families elected to receive occupational and/or physical therapy outside of school hours. *Provider(s):* Professional therapist in conjunction with a speech therapist and undergraduate assistant. *Parental role:* Each family was expected to provide an additional 10-15 weekly hours of home-based instruction. Generalization and maintenance procedures for material learned in school and/or self-help and life independence skills were also applied.	*Primary outcome(s):* • Academic/classroom placement • Full-scale IQ *Secondary outcome(s):* None described. *Length of follow-up:* Participants followed-up 4 to 6 years after they left the preschool.	• Children's age at intake was significantly associated with educational placement, such that children who started treatment before 4 years were, as a group, more likely to be in regular education settings at follow-up than children who started treatment after 4 years. • Children who had higher IQs at admission were more likely to be in regular education classes at follow-up. Among children with IQ scores of 59 or more at intake, 10 were included in regular classes and 3 were in special education programs, as compared with the 14 children with intake IQs of 52 or less which were placed mainly in special education classes (one child went to a regular education class). • Younger children had higher IQ scores at discharge than those who started treatment at an older age. • Those children who went into special education settings showed measurable gains in IQ from pre- to post-treatment (i.e. mean increase in about 13 IQ points from intake to discharge). By contract, the group of children that went on to regular classes showed a 26-point mean gain in IQ scores.	• Small sample size. • No control/comparison group. • Impact of treatment density remains unclear. • It is possible that not all potentially intercorrelated variables have been controlled.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Hayward, 2009** (90) *Country:* **United Kingdom** *Study design:* **Prospective uncontrolled multiple-group comparison** *Number of centres:* Several potential sites within UK YAP catchment area (number unspecified) *Funding source:* National Institute of Mental Health (NIMH) *Quality:* **Moderate**	*Sample size (n):* **44** EG1 (n): 23 EG2 (n): 21 *Male (%):* 77.27 *Sample attrition:* NR *Inclusion criteria for study entry:* • Diagnosis of autism according to ICD-10 criteria • Intake age >24<42 months • Absence of other severe medical conditions Baseline participant characteristics *Age (months), mean±SD (range):* EG1: 35.7±6.2 EG2: 34.4±5.7 *IQ at intake, mean±SD (range):* EG1: 53.5±15.1 EG2: 54.1±15.1	***EG1:*** Clinic-based program based on UCLA YAP model delivered at an average of 37.4 weekly hours. Teaching methods included discrete trial training (DTT), natural environment teaching, and incidental teaching. ***EG2:*** Parent-managed program delivered at an average of 34.2 weekly hours. Intensive supervision was provided by program consultants, while tutoring staff (therapists) were recruited and managed by parents. *Other interventions used:* None described. *Provider(s):* Tutors, senior tutors, and program consultants. *Parental role:* Parents in both groups were given a half-day course on ABA principles followed by several days of hands-on training from senior tutors and program consultants.	*Primary outcome(s):* • Adaptive behaviour • Full-scale IQ • Non-verbal IQ (visual-spatial skills) • Language *Secondary outcome(s):* None described. *Length of follow-up:* 12 months.	• Participants in both treatment groups improved significantly on all outcome measures between intake and follow-up, and there were no significant differences between the two groups on any of the follow-up measures. • Mean IQ increased by 16 points between intake and follow-up, with 89% of children showing an increase in IQ score, and 50% showing gains of 15 IQ points or more. • VABS composite standard scores increased by 6.4 points between intake and follow-up. • Data suggest that the best predictor of outcome was visual-spatial IQ as it predicted follow-up IQ, visual-spatial IQ, language comprehension, expressive language and adaptive behaviour, as well as changes in IQ and adaptive behaviour. Baseline IQ predicted outcome on all these variables, but not changes in scores as a result of treatment. • Age at intake predicted neither treatment outcome nor gains in treatment.	• Lack of an alternative treatment or a no-treatment control group. • Non-random assignment to groups (based on geographical location). • Small sample size: study was potentially underpowered to predict which participants would benefit most from IBI. • Because of the non-significant group differences, data for both groups were treated as one data set (for the purpose of all analyses). • Five participants did not achieve basal on the visual-spatial IQ test at intake and analysis excluded these lowest-functioning participants. • Treatment density is a composite of total hours spent in 1:1 tutored sessions, parent sessions, shadowed time in school, team meetings and/or workshops.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Howard, 2005, 2014** (72,73) *Country:* **United States** *Study design:* **Non-randomized retrospective controlled multiple-group comparison** *Number of centres:* Several regional centres in California (number unspecified) *Funding source:* NR *Quality:* **Moderate**	*Sample size (n):* **61** EG (n): 25 CG1 (n): 16 CG2 (n): 16 *Male (%):* 88.52 *Sample attrition:* Some missing outcome data across follow-up assessments and unequal groups at pre- and post- measurements. *Inclusion criteria for study entry:* • Diagnosis of autistic disorder or PDD-NOS under DSM-IV criteria • Age at diagnosis and treatment onset before 48 months of age • English as primary spoken language at home • No other significant medical conditions • No prior treatment for more than 100 hours Baseline participant characteristics *Age (months), mean±SD (range):* EG: 30.86±5.16 CG1: 37.44±5.68 CG2: 34.56±6.53 *IQ at intake, mean±SD (range):* EG: 58.54±18.15 CG1: 53.69±13.50 CG2: 59.88±14.85	***EG:*** Early intensive behaviour analytic treatment (IBT) delivered at 23-30 weekly hours for children below 3 years and at 35-40 hours for those above 3 years of age. Initial treatment targets focused on foundational repertoires (e.g. attending, imitating vocal and motor sequences, following spoken directions, receptive and expressive labeling, initiating requests, tolerating change, etc.). Treatment targets duding Years 2 and 3 generally focused on advanced cognitive, social, play, self-care, academic, and communication skills. More complex interactions involving peers and siblings generally occurred during Years 2 and 3 than in Year 1 ***CG1:*** Autism educational programming (AP) consisting of intensive eclectic intervention delivered at 25-30 hours per week in public education classrooms with supervision. ***CG2:*** Generic educational programming (GP) consisting of non-intensive public early intervention programs delivered at 15-17 hours per week through local community special education classrooms. *Other interventions used:* None described. *Provider(s):* Trained team of 4-5 instructional assistants (behaviour technicians) with supervision by highly skilled clinical staff who worked under the direction of a BCBA. *Parental role:* Parents helped support treatment outside of formal treatment hours to varying degrees. Training focused on teaching instruction-following, promoting spontaneous language, re-directing non-functional repetitive behaviour, managing interfering behaviours and building skills (toileting, dressing, independent play, etc.).	*Primary outcome(s):* • Full-scale IQ • Adaptive behaviour • Language *Secondary outcome(s):* • Non-verbal IQ (visual-spatial skills) *Length of follow-up:* Originally 14 months, then extended to about 36 months in follow-up study. Assessments occurred at baseline (T1), and at approximately 14 months (T2), 27 months (T3), and 38 months (T4).	• The EG performed significantly better on all measures than either comparison group after three years of treatment. • Largest gains typically occurred in the first year of treatment and in EG children only. • Benefits of IBT which were incurred after one year of treatment were sustained throughout years 2 and 3. • Outcomes at years 2 and 3 were worse for children in either comparison group than for children receiving IBT, while outcome between comparison groups did not differ significantly. • At final assessment, children who received IBT were more than twice more likely to score in the normal range on measures of cognitive, language, and adaptive functioning than were children who received either form of eclectic intervention (CG1 or CG2). • IQ, language, and adaptive behaviour test scores increased significantly (by at least 1 SD) from baseline to follow-up in children who received IBT, as compared with those in the two other groups. Neither eclectic treatment (CG1 or CG 2) was more likely than the other to produce a favourable outcome. • Though the majority of positive and largest treatment effects were experienced in the first year of treatment with IBT (which may lead to question the benefit of extending the treatment beyond the first year), those children with scores below the normal range were able to attain normal functioning range scores with additional years of intervention (unlike children in the eclectic treatment groups, who did not make substantial gains after year 1).	• Relatively small sample size. • Non-random assignment (based on parental preference and education team decisions) • EG children were on average younger than children in either comparison group. • Examiners who conducted assessments were not blind to participants' group assignment. • Treatment integrity was not measured or reported in the first publication (2005). • Potential cross-over effects in comparator groups (some children switched between the comparison treatments during Years 2 and 3), and intervention in years 2 and/or 3 was not available for a few CG children.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Perry, 2008, 2011** (78,81) *Country:* **Canada** *Study design:* **Retrospective one-group pre/post design** *Number of centres:* Nine regional IBI program centres providing government-funded services *Funding source:* Ministry of Children and Youth Services (MCYS) *Quality:* **Moderate**	*Sample size (n):* **332** *Male (%):* 83.13 *Sample attrition:* Considerable amount of missing data at follow-up assessment, especially for intellectual functioning. *Inclusion criteria for study entry:* • Complete information available on at least one outcome measure at both baseline and follow-up assessment. Baseline participant characteristics *Age (months), mean±SD (range):* 53.56±12.60 (20-86) *IQ at intake, mean±SD (range):* 45.50±19.24 (11-96); n=151	***EG:*** Large, community-based, publicly-funded IBI program delivered at 20 to 40 hours per week. *Other interventions used:* None described. *Provider(s):* Trained instructor-therapists and senior therapists. *Parental role:* Parents were encouraged to participate in goal setting and to promote generalization.	*Primary outcome(s):* • Full-scale IQ • Adaptive behaviour • Severity of symptoms *Secondary outcome(s):* • Mental age • Adaptive rate of development (developmental rate) *Length of follow-up:* Mean program duration of about 18 months (range 4-47).	• Children improved significantly across all measures from program entry to discharge, but there was substantial heterogeneity. • Cognitive functioning showed a clinically significant increase (IQ gains by 15 or more points) in 39% of children (n=127). • Adaptive behavior age equivalents increased substantially in all areas, but standard scores changed only modestly (higher for socialization and communication subdomains but lower for daily living skills). • Participants demonstrated significantly milder autistic symptomatology at program discharge. • Children's rate of development during IBI was roughly double what it had been at baseline (prior to IBI). • Children were classified into seven categories of progress/outcome (n=296). The majority of children (75%) showed some benefit or improvement during the time they received IBI and 11% achieved average functioning. • A subgroup of children who were more similar to children from model programs (younger with milder developmental delays) had similar outcomes to those reported in other efficacy studies. • A non-linear relationship was found between initial age and measured outcomes: Children starting treatment before 4 years scored higher on all outcome measures than children who were 4 years or older at program entry, and children who achieved best outcomes were considerably younger at entry (42 months versus 53 months) than all other outcome groups.	• No control or comparison group of similar children who received no treatment or a different treatment. • No measure of treatment quantity (intensity/duration), or treatment fidelity. • Available outcome measures (although standard and appropriate for this population) are limited, and have imperfect reliability and validity. • It is unknown whether children's gains post discharge were maintained or generalized (or stabilized or even declined). • Outcome assessors at intake and discharge were not blind to the children's participation in IBI, nor independent from the organization providing IBI. • Measurement of developmental rate is based on questionable assumptions (i.e. child's development prior to IBI and during IBI is assumed to have been linear, and the pre- and post- data points are sufficient to derive a slope).

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Perry, 2013a** (83) *Country:* **Canada** *Study design:* **Retrospective one-group pre/post design** *Number of centres:* Nine regional IBI program centres providing government-funded services *Funding source:* York University *Quality:* **Moderate**	*Sample size (n):* **207** *Male (%):* 80.68 *Sample attrition:* None. *Inclusion criteria for study entry:* • All children with a documented initial IQ score. Baseline participant characteristics *Age (years), mean±SD (range):* 5.33±2.01 (2.08-14.50) *IQ at intake, mean±SD (range):* 43.20±20.52 (10-104)	***EG:*** Large, community-based, publicly-funded IBI program delivered at 20 to 40 hours per week. *Other interventions used:* None described. *Provider(s):* Trained instructor-therapists. *Parental role:* NR.	*Primary outcome(s):* • Full-scale IQ • Mental age • Adaptive behaviour • Cognitive rate of development • Adaptive rate of development *Secondary outcome(s):* None described. *Length of follow-up:* Mean program duration of about 20 months (range 10-55).	• Longer duration of IBI was associated with slower rates of development between intake and discharge, and children who were in the program longer were not showing better outcomes on IQ, ABC or change in IQ. • Children with higher skill levels before treatment tended to have higher skill levels after treatment, but children who were higher functioning cognitively at intake were not the ones who necessarily made large IQ gains. • The younger the child was at entry into IBI, the higher their cognitive (but not their adaptive) functioning was after treatment, even after controlling for treatment duration and the children's initial cognitive level. • Age at entry was the only predictor that was related to change in IQ. • Children who entered the program with very low IQ scores (IQ<30) showed uniformly poor outcomes, regardless of age.	• No control group (i.e. predictors of outcomes at discharge may be predictors regardless of treatment). • Outcome measures are imperfect, which may impact on their reliability and validity. • Missing data on some scores. • No precise information on intensity of treatment (although program guidelines require a minimum of 20 hours per week). • Inclusion criterion excluded many children in the younger group • Outcome assessors were not independent nor blind to the child's participation in IBI. • There were younger children than older ones in the sample and the older children tended to be somewhat lower functioning at entry. • Data are drawn from two previously completed studies: Perry at al. (2008, 2011) and Blacklock et al. (2014)
First author, year (Ref.): **Perry, 2013b** (83) *Country:* **Canada** *Study design:* **Retrospective uncontrolled multiple-group comparison** (matched pairs) *Number of centres:* Nine regional IBI program centres providing government-funded services *Funding source:* York University *Quality:* **Moderate**	*Sample size (n):* **120** EG1 (n): 60 EG2 (n): 60 *Male (%):* NR *Sample attrition:* None. *Inclusion criteria for study entry:* • All children with a documented initial IQ score. Baseline participant characteristics *Age (years), mean±SD (range):* EG1: 4.26±1.09 (2.08-5.92) EG2: 7.45±1.87 (6.00-13.58) *IQ at intake, mean±SD (range):* EG1: 40.92±20.68 (11-98) EG2: 40.93±21.12 (10-104)	***EG1:*** Younger age group (2-5 years) ***EG2:*** Older age group (6-14 years) Both groups received the same treatment (large, community-based, publicly-funded IBI program delivered at 20-40 hours per week. *Other interventions used:* None described. *Provider(s):* Trained instructor-therapists. *Parental role:* NR	*Primary outcome(s):* • Full-scale IQ • Mental age • Adaptive behaviour • Cognitive rate of development • Adaptive rate of development *Secondary outcome(s):* None described. *Length of follow-up:* Mean program duration of about 20 months (range 10-42).	• Younger children (2-5 years) made an average of 17 IQ points, while older children (6-14 years) made average gains of only 2 IQ points. • The younger group's rate of cognitive development increased during IBI whereas the older group's remained essentially unchanged. • Very large IQ gains (>30 points) only occurred in younger children. Children aged >8 years and children with low initial IQs (<30), regardless of age, showed uniformly low IQs at program discharge. • Adaptive gains were more modest and were similar across groups (with similar effect sizes in both groups). • Young children gained more rapidly than older children for both cognitive and adaptive development, although this difference was much more pronounced for cognitive rate of development.	• No control group. • Outcome measures are imperfect, which may impact on their reliability and validity. • No precise information on intensity of treatment (although program guidelines require a minimum of 20 hours per week). • Details surrounding the nature of the participants' IBI program was lacking (i.e. it is possible that the curriculum for older children might have been somewhat different). • Outcome assessors were not independent nor blind to the child's participation in IBI. • Study sample was formed by yoke-matching older participants (on the basis of initial IQ) with younger children from Perry et al. (2013a) study.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Remington, 2007** (91) *Country:* **United Kingdom** *Study design:* **Non-randomized prospective controlled multiple-group comparison** *Number of centres:* Several potential sites (exact number unspecified). *Funding source:* Health Foundation UK *Quality:* **Moderate**	*Sample size (n):* **44** EG (n): 23 CG (n): 21 *Male (%):* NR *Sample attrition:* Some missing data on one or more outcome measures at follow-up. *Inclusion criteria for study entry:* • Diagnosis of autism based on ADI-R • Intake age ≥30≤42 months • Free of any other chronic or serious medical condition that might interfere with intervention delivery or that might adversely affect development • Currently living in family home Baseline participant characteristics *Age (months), mean±SD (range):* EG: 35.7±4.0 CG: 38.4±4.4 *IQ at intake, mean±SD (range):* EG: 61.43±16.43 CG: 62.33±16.64	***EG:*** Home-based early intensive behavioural intervention delivered at 18-34 hours per week. Although delivered by a range of service providers, all interventions shared the 10 common features characterizing research-based interventions identified by Green et al. (2002). ***CG:*** Treatment as usual (TAU), whereby parents were not actively seeking behavioral intervention and were instead receiving publicly-funded standard provision offered by their Local Education Authority. *Other interventions used:* PECS & TEACCH for some EG children. Some participants received speech therapy at baseline and follow-up assessments, and dietary restrictions as well as routine prescription medications and vitamin injections were also commonly reported. *Provider(s):* Trained therapists (3-5) and parents. *Parental role:* NR.	*Primary outcome(s):* • Full-scale IQ *Secondary outcome(s):* • Adaptive behaviour • Language • Mental age • Joint attention • Child behaviour • Parental well-being/family satisfaction *Length of follow-up:* 24 months. Assessments occurred at baseline (T1), after the first year (T2), and last follow-up (T3).	• The EG showed significantly greater increases in mental age, intellectual functioning, language functioning, adaptive functioning, and positive social behaviours as compared with control. The 24-month effect size for IQ (based on Cohen's d statistic) was 0.77, indicating a relatively large difference between the groups. • Six children in the EG (26%) achieved a statistically reliable improvement from baseline to the last follow-up, as compared with only three children (14%) in the CG (three CG children also regressed reliably). • Five of the six EG children who achieved reliable change also achieved clinically significant change, and all three children in the CG achieving reliable improvement also achieved clinically significant change. • There was no evidence of differentially increased stress or additional mental health problems in parents of the EG participants as compared with control.	• Small sample size. • Non-random assignment of participants to groups (based on parent preference). • Some pre-existing group differences may have been unobserved. • Range of treatment providers did not allow for uniform/coherent treatment delivery and treatment integrity. • Staff turnover was common and replacement tutors often difficult to obtain and slow to train (tutor shortages have a direct impact on treatment fidelity).

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Sallows, 2005** (74) *Country:* **United States** *Study design:* **Prospective uncontrolled multiple-group comparison** (matched-pairs) *Number of centres:* Three *Funding source:* National Institute of Mental Health *Quality:* **High**	*Sample size (n):* **23** EG1 (n): 13 EG2 (n): 10 *Male (%):* 82.61 *Sample attrition:* NR *Inclusion criteria for study entry:* • Intake age >24<42 months • Ratio estimate (MA/CA of the MDI of ≥35) • Neurologically within "normal" limits" (children with abnormal EEGs or controlled seizures were accepted) as determined by a pediatric neurologist • Diagnosis of autism by an independent child psychiatrist Baseline participant characteristics *Age (months), mean±SD (range):* EG1: 35.00±4.86 EG2: 37.10±5.36 *IQ at intake, mean±SD (range):* EG1: 50.85±10.57 EG2: 52.10±8.98	***EG1:*** Clinic-directed IBI program delivered at an average of 36-38 weekly hours. ***EG2:*** Parent-directed IBI program delivered at an average of 31-32 weekly hours, with 6 hours per month of in-home supervision from a senior therapist and consultation every 2 months by the senior author or clinic supervisor. Both groups received IBI based on the treatment procedure and curriculum described by Lovaas (UCLA model), with the exception that no aversives were used. *Other interventions used:* Some received supplemental treatment prior to or during the first year of intervention (e.g. special education, preschool, private therapies beyond what was offered in school, speech, sensory integration, auditory integration training, music therapy, and horseback riding) *Provider(s):* Therapists (trained for 30 hours) with supervision by senior therapists. *Parental role:* Parents in both groups were encouraged to extend the impact of treatment by practicing newly learned material with their child throughout the day.	*Primary outcome(s):* • Full-scale IQ • Non-verbal IQ (visual-spatial skills) • Adaptive behaviour • Language • Social-emotional functioning (SEF) *Secondary outcome(s):* None described. *Length of follow-up:* 48 months. Assessments occurred at baseline (T1) and every 12 months for four years (T2-T4).	• There was an average 25-point increase in full-scale IQ among all participants. • Eleven of 23 children (48%) achieved full-scale IQ scores in the average range, as well as increases in language and adaptive skills (i.e. rapid learners). • Parent-directed children did about as well as clinic-directed children, although they received much less supervision. • The strongest pre-treatment predictors of outcome were imitation, language, daily living skills, and socialization. Rapid acquisition of new material as measured by the Early Learning Measure, first year IQ, and change in IQ after one year were also strong predictors. A model with 91% accuracy was derived for predicting whether a child in the present sample would be a rapid or moderate learner.	• No control group (i.e. positive findings among rapid learners may be due to either treatment or maturation). • Small sample size. • Use of multiple different tests at pre/post assessments: observed increases in IQ may have reflected the use of different tests instead of treatment effects and many tests on such a small sample increase the likelihood of spurious findings.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Smith, 2000** (75) *Country:* **United States** *Study design:* **Randomized controlled trial** (matched-pairs comparison) *Number of centres:* NR. *Funding source:* Department of Education & UCLA Regents *Quality:* **Moderate**	*Sample size (n):* **28** EG (n): 15 CG (n): 13 *Male (%):* 82.14 *Sample attrition:* *Inclusion criteria for study entry:* • Intake age >18<42 months • Residence within 1 hour of treatment centre • IQ ratio score between 35 and 75 • Diagnosis of ASD or PDD-NOS • Absence of major medical problems (other than autism or mental retardation) Baseline participant characteristics *Age (months), mean±SD (range):* EG: 36.07±6.00 CG: 35.77±5.37 *IQ at intake, mean±SD (range):* EG: 50.53±11.18 CG: 50.69±13.88	***EG:*** Home-based IBI program based on UCLA YAP model (Lovaas manualized treatment) delivered at an average of 25 weekly hours in the first year of treatment, with reduced weekly hours in years 2 and 3. ***CG:*** Parent training group, whereby parents taught to use treatment approaches described in the Lovaas manual and were supervised in using these approaches to help their child acquire skills. Treatment incorporates one hour per week of supervision by primary author, and additional supervision as needed. *Other interventions used:* None reported. *Provider(s):* Student therapists (team of 4-6) under close supervision. *Parental role:* Each primary caregiver was asked to conduct five weekly hours of treatment in the EG.	*Primary outcome(s):* • Full-scale IQ • Non-verbal IQ (visual-spatial skills) • Adaptive behaviour • Language • Social emotional functioning (SEF) domains • Parental well-being/family satisfaction • Academic/classroom placement *Secondary outcome(s):* None described. *Length of follow-up:* Mean program duration of 33 months (range 18-63). Assessments occurred at baseline (T1) and at between ages 7-8 (T2).	• Intensively treated (EG) children outperformed children in the CG at follow-up on measures of intelligence (IQ), visual-spatial ability, language, and academic achievement. As a group, EG children also had less restrictive school placements. • IBI children did not differ from children in the parent training group (CG) on standardized tests of behaviour problems and adaptive functioning at follow-up. • Within each group, PDD-NOS children benefited at least as much from IBI as did children with autism. • Parents in both groups held highly positive views about the services their children received. • Intake data were generally poor predictors of follow-up scores.	• Small sample size. • Lack of a standardized diagnostic instrument.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Stoelb, 2004** (76) *Country:* **United States** *Study design:* **Retrospective one-group pre/post design** *Number of centres:* Two academic medical centres *Funding source:* NR *Quality:* **Moderate**	*Sample size (n):* **19** *Male (%):* 73.68 *Sample attrition:* Some missing data at follow-up. *Inclusion criteria for study entry:* • Diagnosis of autism according to DSM-IV • Completion of a medical/neurological/genetic evaluation • Participation in an EIBI program for at least one year. Baseline participant characteristics *Age (months), mean±SD (range):* 56 (26-122) *IQ at intake, mean±SD (range):* NR	***EG:*** Centre-based IBI program modeled after published descriptions of other early intensive behavioural programs and delivered at 12-36 weekly hours. Individualized intervention programs employed the use of discrete trial technology, and behavioral acceleration and deceleration techniques. *Other interventions used:* Use of supplementary dietary intervention in about 40% of participants. *Provider(s):* Team of 2-6 therapy implementers, overseen by 1 of 3 behavioural consultants. *Parental role:* Efforts were made to include parents in all aspects of treatment, and they were encouraged to participate in intervention delivery as implementers. Some were involved in treatment delivery and treatment decisions, while others opted out of parental involvement.	*Primary outcome(s):* • Adaptive behaviour • Severity of symptoms • Functioning • Language *Secondary outcome(s):* None reported *Length of follow-up:* 12 months. Assessments occurred at baseline (T1), after 6 months (T2), and after one year of treatment (T3).	• Physical dysmorphology was strongly correlated with outcome following both 6 and 12 months of treatment. • Nondysmorphic participants who were linguistic at treatment onset tended to make more progress if they did not have a regressive form of autism and if they began treatment at younger ages. • A wide variety of other variable failed to effectively predict outcome: gender, head circumference, MRI results, history of seizures, pre-treatment functioning, autism subtype, history of sleep difficulties, family history, SES, parental participation in treatment, treatment intensity, and the use of dietary interventions.	• No control group. • Small sample size. • The EPS is not a validated measure for evaluating outcomes with IBI, and it was used retrospectively (rather than prospectively).

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Virues-Ortega, 2013** (94) *Country:* **Spain** *Study design:* **Prospective one-group pre/post design** *Number of centres:* Single centre in Barcelona, Spain (Fundación Planeta Imaginario IBI program) *Funding source:* NR *Quality:* **Moderate**	*Sample size (n):* **24** *Male (%):* 87.50 *Sample attrition:* None. *Inclusion criteria for study entry:* None described. There were no exclusions based on age or pre-intervention functioning. Baseline participant characteristics *Age (months), mean±SD (range):* 50.5±28.3 *IQ at intake, mean±SD (range):* 74.50±13.98	***EG:*** Home-based IBI program based on the UCLA YAP model affiliated with the Lovaas institute and delivered at about 15 to 47 weekly hours. *Other interventions used:* None described. *Provider(s):* Trained tutors, supervised by licensed psychologists. *Parental role:* Parents were active co-therapists during intervention.	*Primary outcome(s):* • Full-scale IQ • Early Learning Accomplishment Profile (E-LAP) domains • Learning Accomplishment Developmental Profile-II (LAP-D) domains *Secondary outcome(s):* None reported. *Length of follow-up:* Mean program duration of about 22 months (range 5.33-58.57). Assessments occurred at baseline (T1) and every six months until discharge (T2-T4).	• Increased intervention time, younger age at intervention onset, and higher pre-intervention functioning might be associated with greater gains on outcome measures for IBI programs of up to four years in duration. • Individuals starting intervention at a lower level in a given outcome were more likely to follow an asymptotical growth as opposed to individuals that initiated treatment with a higher level of performance. • Multilevel regression analyses revealed that total intervention duration in hours (weekly hours multiplied by weeks of intervention) was the single predictor with the highest contribution to the model fit for all outcomes when compared with unconditional models (i.e. both intensity and duration, as represented by total intervention time, remained important factors of intervention gains regardless of pre-intervention functioning or age).	• No control group • Small sample size • E-LAP & LAP-D results are difficult to interpret.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Weiss, 1999** (77) *Country:* **United States** *Study design:* **Prospective one-group pre/post design** *Number of centres:* Single centre (Center for Applier Psychology at Rutgers University) *Funding source:* NR *Quality:* **Low**	*Sample size (n):* **20** *Male (%):* 95.0 *Sample attrition:* NR *Inclusion criteria for study entry:* None described. Baseline participant characteristics *Age (months), mean±SD (range):* 41.5 (20-65) *IQ at intake, mean±SD (range):* NR	***EG:*** Home-based intensive behaviour analytic intervention delivered at about 40 hours per week. *Other interventions used:* None described. *Provider(s):* Trained instructors/therapists. *Parental role:* NR	*Primary outcome(s):* • Adaptive behaviour • Severity of symptoms • Mastery of skills • Academic/classroom placement *Secondary outcome(s):* None described. *Length of follow-up:* 24 months.	• Initial learning rates of children with autism were somewhat related to later learning and status after two years (i.e. children who initially learned quickly continued to demonstrate rapid acquisition rates) • Initial learning rates were also positively correlated with the child's adaptive skills and severity of symptoms at discharge. • All children who struggled with initial skill acquisition continued to struggle with it, exhibited higher degrees autistic behaviour and lower adaptive skills at discharge.	• No control group or group receiving a different level of treatment. • Small sample size. • Some problems with measures selected for outcome (e.g. while the CARS may be potentially quite useful for diagnostic screening, it's not an instrument which discriminates effectively between autism and other disorders, and it's not based on current criteria for diagnosis; both CARS and VABS rely on parental report). • Potential selection bias in selection of participants (i.e. children receiving services may be from higher SES families and those who are very involved with/advocate for their children). • Full-scale IQ is not measured (data would strengthen the study if present). • Other factors may be confounded with learning rate (variability in responsiveness to reinforcement, variability in skill levels of teams). • The author did not collect precise data on the number of hours of therapy/instruction each child received per week (families were advised to provide 40 weekly hours). • CARS scores at pre- and post-IBI were completed by parents, while it is typically used as a standardized behaviour observation measure.

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Zachor, 2007** (87) *Country:* **Israel** *Study design:* **Non-randomized prospective controlled multiple-group comparison** *Number of centres:* Two centres in two different counties. *Funding source:* Ministry of Education *Quality:* **Low**	*Sample size (n):* **39** EG (n): 20 CG (n): 19 *Male (%):* 94.87 *Sample attrition:* Missing outcome data for 3 participants at follow-up. *Inclusion criteria for study entry:* • Age <36 months • Absence of identified medical abnormalities (e.g. seizures, hearing deficiencies) Baseline participant characteristics *Age (months), mean±SD (range):* EG: 27.7 (22-34) CG: 28.8 (23-33) *IQ at intake, mean±SD (range):* EG: 76.1±15.2 CG: 79.6±17.0	***EG:*** Centre-based IBI program based on ABA principles and delivered at about 35 weekly hours, incorporating discrete trial training, naturalistic, and incidental teaching techniques. ***CG:*** Eclectic-developmental (ED) program based on the principles derived from several approaches, mainly from the developmentally oriented philosophy and the DIR model, but also strategies driven from TEACCH and ABA. *Other interventions used:* None described. *Provider(s):* Skilled behaviour therapist, supervised by trained behaviour analyst. *Parental role:* NR.	*Primary outcome(s):* • Severity of symptoms • Diagnostic recovery *Secondary outcome(s):* None described. *Length of follow-up:* 12 months.	• After 1 year of intervention, both the EG and CG showed improvement in reciprocal social interaction (based on ADOS scores), though advancement in this domain is more pronounced in the EG. • EG showed significant progress in language and communication, as compared with CG. • Children with higher IQ scores at intake had better language and communication and reciprocal social skills before and after the intervention; yet, children with higher IQ scores at intake did not improve significantly more than children with lower intake IQ scores. • EG children improved more than children in the CG, regardless of their baseline IQ level. • Diagnostic recovery (change from autism/ASD to off-spectrum) occurred in 20% of the EG sample, and none of the CG members.	• Non-random assignment to groups (based on geographical location). • Small sample size. • No formal measures or reporting of treatment integrity. • Focus of analysis is on demonstrating improvement in core autistic features (reciprocal-social interaction) rather than learning rate (IQ), which deviates from the goal of IBI therapy. • Cognitive functioning (IQ) is only assessed at pre-intervention time, and IQ is treated as an independent variable in the analysis (rather than an outcome measure).

Table 5. (continued)

Study Description	Participants	Intervention/Comparison	Outcomes	Main Findings	Comments
First author, year (Ref.): **Zachor, 2010** (88) *Country:* **Israel** *Study design:* **Non-randomized retrospective controlled multiple-group comparison** *Number of centres:* Seven centre-based autism-specific early intervention community-based preschools (four of which used ABA teaching principles) *Funding source:* Private support (Mr. Dov Moran) *Quality:* Moderate	*Sample size (n):* **78** EG (n): 45 CG (n): 33 *Male (%):* 91.03 *Sample attrition:* Some missing data at follow-up and discordant pre- and post- intervention sample sizes. *Inclusion criteria for study entry:* • Clinical diagnosis of autism based on DSM-IV criteria and cut-off points on the ADI-R • Absence of additional major medical diagnoses • Complete post-intervention assessments Baseline participant characteristics *Age (months), mean±SD (range):* EG: 25.1±3.9 (17-35) CG: 26.0±4.6 (15-33) *IQ at intake, mean±SD (range):* EG: 72.2±19.2 (49-135) CG: 73.3±22.2 (49-132)	Treatment arms ***EG:*** School-based IBI program rooted in ABA teaching principles delivered at about 20 weekly hours and consisting of individualized goals and objectives to increase language, play, social, emotional, academic, and daily living skills, and to reduce inappropriate behaviours. Behavioural analytic techniques used included: discrete trial training, incidental teaching, shaping for positive reinforcement, successive approximation, systematic prompting, fading procedures, discrimination learning, task analysis and functional assessment and reinforcement procedures according to several treatment manuals. ***CG:*** Community-based eclectic program incorporating several intervention approaches (i.e. developmental, DIR, TEACCH). *Other interventions used:* None described. *Provider(s):* Program supervisors (BCBA), trained therapists (team of 3 per child), speech language specialists, occupational therapists, and special education preschool teachers. *Parental role:* Parents received weekly instructions for home treatment from the behaviour analyst who supervised the child's program. CG parents participated one full day per week in the child's preschool, learned how therapists work with the child, practiced intervention, and received individual and group training.	*Primary outcome(s):* • Full-scale IQ • Adaptive behaviour • Severity of symptoms *Secondary outcome(s):* None described. *Length of follow-up:* 12 months.	• Both intervention groups improved significantly, and there were no significant group differences over time on any of the outcomes measures (change in autism diagnostic classification, cognitive abilities, or adaptive skills). • Diagnostic stability was very high at discharge, as 91% of children remained with a classification of autism, with both groups showing similar stability and change of autism symptoms. • CG children with less severe autism symptoms had better outcome in adaptive communication and socialization skills than EG children with similar autism severity, while no such association was found for cognitive functioning.	• Non-random assignment (based on place of residence). • The CG had a greater parental involvement component than the EG (more child centered).

Table 6. Predictors of treatment response and observed associations in included studies

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Ben-Itzchak, 2007 (84)	IQ	(1) HIQ group showed greater progress in receptive language, expressive language, play skills, and nonverbal communication skills, as compared with LIQ group. (2) Significant negative correlation was found between the ADOS reciprocal-social interaction and IQ (i.e. higher IQ scores correlated with fewer deficits in social interaction skills).	(1) one-way MANCOVA on DBS domains (2) Pearson correlation	Yes	(1) $F(6,11)=3.30$, $p<0.05$, $\eta^2=0.643$ (2) $r = -0.606$; $p < 0.01$	Median IQ = 70, <70=LIQ, >71=HIQ HS = high social; LS = low social; HC = high communication; LC = low communication. **Variables associated with change in the treated group may not necessarily reflect actual predictors of outcome as not all of the observed change can be attributed to the effect of behavioural treatment.**
	Psy	HS group showed greater progress in receptive and expressive language, as compared with LS group. No significant effect was observed for the HC and LC groups.	Two one-way MANCOVA tests on all DBS domains	No	NR	
Ben-Itzchak, 2009 (85)	Age	No significant differences between the unchanged and improved groups were noted in child's age, adaptive skills, or parental measures. A trend was only noted in cognitive abilities; specifically, the improved group had significantly better non-verbal and verbal scores (receptive language domain), as compared with the unchanged group.	2 X 2 MANOVA (2 groups x 2 times) with repeated measures	No	NS	Unchanged group (n=53): Children whose diagnostic classification (severity) remained the same after treatment. Improved group (n=15): Children who improved their diagnosis post intervention (i.e. ASD or Off Spectrum vs. Autism) **Variables associated with change in unchanged and improved group may not necessarily reflect actual predictors of outcome as not all of the observed change can be attributed to treatment.** This study therefore examined predictors of growth rather than predictors of treatment response.
	IQ			Yes (receptive language)	NR	
	AB			No	NS	
	Parental factors (education level)			No	NS	

Table 6. (continued)

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Ben-Itzchak, 2014 (86)	IQ	(1) The high (DQ≥70) and low (DQ<70) cognitive ability groups did not differ significantly in their decrease in autism severity (i.e. improvement in autism severity is not affected by baseline cognition) (2) Significant increases in the communication, socialization, and daily living sub-domains were noted only in the higher cognitive ability group, while standard scores remained unchanged for the lower cognitive ability group. (3) Gains in the fine-motor and receptive language MSEL subdomain scores were noted only in the group with lower cognition, with decreases in standard scores observed for the higher cognitive group.	Three separate 3 X 2 MANOVAs with repeated measures on time	No (except for select VABS and MSEL subdomain scores)	Unclear.	Unclear whether statistical methods used were suitable for identifying predictors of treatment response. **Variables associated with change in the treated group may not necessarily reflect actual predictors of outcome as not all of the observed change can be attributed to the effect of behavioural treatment.**
Blacklock, 2014 (82)	IQ	Strong linear relationships were observed between full-scale IQ at baseline and all follow-up (T2) outcome variables.	Pearson correlation	Yes	FS IQ at T2: r=0.65 (p<0.01, n=63) MA at T2: r=0.64 (p<0.01, n=63) RCog: r=0.49 (p<0.01, n=61), ABC SS at T2: r=0.66 (p<0.01, n=49) ABC AE at T2: r=0.70 (p<0.01, n=64) RDev: r=0.31 (p<0.05, n=49)	**Variables associated with change in the treated group may not necessarily reflect actual predictors of response to IBI as not all of the observed change can be attributed to the effect of behavioural treatment (due to study design limitation).**
	AB composite (ABC)	AB composite standard scores at intake were significantly and highly correlated with all six outcome variables.	Pearson correlation	Yes	FS IQ at T2: r=0.91 (p<0.01, n=61) MA at T2: r=0.84 (p<0.01, n=61) RCog: r=0.32 (p<0.05, n=61) ABC SS at T2: r=0.75 (p<0.01, n=45) ABC AE at T2: r=0.75 (p<0.01, n=60) RDev: r=0.71 (p<0.01, n=46)	
	Age	Correlations for age at entry with outcomes at T2 showed weak linear relationships (i.e. age at program entry was not reliably associated with outcome). There is a possible curvilinear relationship between child's age at entry and treatment outcomes at follow-up (as per scatterplot analysis): more variable outcomes were noted for the relatively younger children within the sample, as compared with older children (>8 years) which had uniformly low and less variable scores.	Pearson correlation	No	FS IQ at T2: r=-0.14 (NS, n=64) MA at T2: r=0.25 (p<0.05, n=64) RCog: r=-0.12 (NS, n=61) ABC SS at T2: r=-0.26 (NS, n=50) ABC AE at T2: r=0.24 (NS, n=65) RDev: r=0.18 (NS, n=49)	

Table 6. (continued)

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Eikeseth, 2002 (92)	Age	Age at which children started treatment was not reliably associated with outcome or amount of change in scores.	Unprotected Pearson correlations	No	NS	Correlations were conducted separately for the behavioural and eclectic treatment groups. Multiple regression analysis with a dummy-coded treatment variable might have allowed for more rigorous predictive modeling.
	IQ	Intake IQ was strongly associated with follow-up IQ and language. Correlations on all other measures were non-significant.	Unprotected Pearson correlations	No (except IQ, Lang, and ΔLang)	IQ at T2: r=0.82 (p<0.01) Lang at T2: r=0.89 (p<0.001) ΔLang: r=0.59 (p<0.05)	
	Non-verbal IQ	Performance (non-verbal) IQ at baseline was not reliably associated with outcome. A significant correlation was only noted between non-verbal IQ at intake and follow-up change in non-verbal IQ scores.	Unprotected Pearson correlations	No (except ΔIQ, non-verbal)	ΔIQ (non-verbal): r=-0.84 (p<0.01)	
	AB	Adaptive skills at intake were not reliably associated with outcome. Correlations between intake adaptive behaviour scores and treatment gains were only significant for change in performance IQ.	Unprotected Pearson correlations	No (except ΔIQ, non-verbal)	ΔIQ (non-verbal): r=-0.60 (p<0.05)	
Eikeseth, 2007 (93)	Age	Age at which children started treatment was not reliably associated with outcome or amount of change in scores.	Unprotected Pearson correlations	No	NS	Correlations were conducted separately for the behavioural and eclectic treatment groups. Multiple regression analysis with a dummy-coded treatment variable might have allowed for more rigorous predictive modeling.
	IQ	Intake IQ was significantly correlated only with follow-up IQ and AB scores (except VABS socialization subdomain score);i.e., children with higher intake IQ tended to score higher on follow-up measures but did not tend to make larger gains in IQ, language and adaptive scores.	Unprotected Pearson correlations	Yes	IQ at T2: r=0.60 (p<0.05) AB composite at T2: r=0.58 (p<0.05) AB-Com at T2: r=0.56 (p<0.05) AB-DLS at T2: r=0.60 (p<0.05)	
	AB	Intake adaptive skills were not reliably associated with outcome or amount of change in scores.	Unprotected Pearson correlations	No	NS	
Eikeseth, 2009 (89)	Intensity of supervision	A significant correlation was noted between intensity of supervision and change in IQ scores between intake and follow-up.	Unprotected Pearson correlations Linear regression	No (except ΔIQ)	ΔIQ: r=0.45, p<0.05	Participant data taken from parent-managed treatment arm of Hayward et al (2009) study. Mean intensity of supervision per child per month was 5.2 h, and ranged from 2.9 to 7.8 h.

Table 6. (continued)

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Flanagan, 2012 (79)	Duration of IBI	Although treatment duration contributed significantly to predictions when it was initially entered into the model, it did not remain a significant predictor after information about group membership and intervention variables was added.	Hierarchical multiple regression	Yes	ΔR^2=0.100, p<0.001	n=142 (EG: 79, CG: 63) Step 1 of regression: duration of treatment was added in order to control for any effect it may have on outcome. Step 2: Role of initial age was examined controlling for duration. Step 3: Role of initial adaptive skills (age and duration controlled). Step 4: Autism severity was added to the model, controlling for previous variables. Step 5: Group membership was added to the model. Step 6: Interaction variables were added to the model.
	Age	Although initial age contributed significantly to predictions when it was initially entered into the model, it did not remain a significant predictor after information about group membership and intervention variables was added.	Hierarchical multiple regression	No	ΔR^2=0.024, p=0.055	
	AB	Controlling for duration and initial age, higher initial adaptive skills contributed a large amount of variance across groups.	Hierarchical multiple regression	Yes	ΔR^2=0.262, p<0.001	
	Psy	When duration, initial age and initial adaptive skill level were controlled, there was a trend towards milder initial autism severity contributing additional variance to predictions.	Hierarchical multiple regression	Yes	ΔR^2=0.013, p=0.092	
Granpeesheh, 2009 (70)	Treatment intensity + Age	(1) There was a significant linear relationship between the predictor variables (age+treatment intensity) and the number of mastered behavioural objectives. This relationship accounted for about 14.7% of the observed variance in monthly mastered behavioural objectives. (2) For age group 1 (2-5.15 yrs) and group 2 (5.15-7.14 yrs), there was a quadratic relationship between the number of treatment hours and monthly mastered behavioural objectives, which accounted for 11% and 21% of the observed variance in outcomes among the participants, respectively. Group 3 (7.14-12 yrs) did not show a significant relationship of any kind between treatment hours and outcome.	(1) Linear regression (2) Linear regression for each age group	Yes (except age group 3)	Group 1: F(2,79)=4.715, p<0.05, R^2=0.11, p=NR Group 2: F(2,78)=10.487, p<0.001, R^2=0.21, p=NR Group 3: NS	**Variables associated with change in the treated group may not necessarily reflect actual predictors of treatment response as not all of the observed change can be attributed to the effect of behavioural treatment.**

Table 6. (continued)

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Harris, 2000 (71)	IQ at intake	Children who had higher IQ at admission were more likely to be in regular education classes at follow-up.	Pearson product-moment correlation	Yes	r(25)=0.655, p<0.005	**Variables associated with change in the treated group may not necessarily reflect actual predictors of treatment response as not all of the observed change can be attributed to the effect of behavioural treatment.**
	IQ at discharge	Children who had higher IQ at discharge were more likely to be placed in regular education classroom at follow-up.	Pearson product-moment correlation	Yes	r(25)=0.779, p<0.005	
	Psy	Severity of autism (as measured by the CARS) was not significantly correlated to academic placement at follow-up.	Pearson product-moment correlation	No	NS	
	Age	(1) Children who were younger at admission were more likely to be in regular education settings at follow-up than were children who were older at intake. (2) Younger children had higher IQs at discharge than those who entered at an older age.	Pearson product-moment correlation	Yes	(1) r(25) = 0.658, p<0.005 (2) r(25)= -0.401, p<0.025	
Hayward, 2009 (90)	Age	Age at which children started treatment was not reliably associated with outcome or amount of change in scores.	Unprotected Pearson correlation	No	NS	It is unclear whether predictive modeling was carried out using data from the intensive clinic-based group, or if correlations represent the relationship between pre-treatment variables and outcomes for all participants. Due to non-significant group differences at follow-up, data for the clinic-based and parent-managed groups were treated as one data set. As a result, this same data set may have been used for the analysis of predictive variables. **Variables associated with change in the treated groups (clinic-based and parent-managed) may not necessarily reflect actual predictors of outcome as not all of the observed change can be attributed to the effect of behavioural treatment.**
	IQ	Intake IQ was significantly correlated with follow-up IQ, visual-spatial IQ, and AB; however, correlations between intake IQ and treatment gains (change scores) on all measures were non-significant.	Unprotected Pearson correlation	Yes	IQ at T2: r=0.66 (p<0.01) IQ (non-verbal) at T2: r=0.60 (p<0.01) AB composite at T2: r=0.57 (p<0.01)	
	Non-verbal IQ	Intake visual-spatial (non-verbal) IQ was significantly correlated with all measures at follow-up, as well as with changes in full-scale IQ and AB composite scores.	Unprotected Pearson correlation	Yes	IQ at T2: r=0.77 (p<0.01) ΔIQ: r=0.38 (p<0.05) IQ (non-verbal) at T2: r=0.70 (p<0.01) ABC at T2: r=0.62 (p<0.01) ΔABC: r=0.64 (p<0.01)	
	AB composite (ABC)	Intake adaptive skills were significantly correlated with all measures at follow-up; however, correlations between intake adaptive skills and treatment gains (change scores) on all measures at follow-up were non-significant.	Unprotected Pearson correlation	Yes	IQ at T2: r=0.56 (p<0.01) IQ (non-verbal) at T2: r=0.41 (p<0.01) ABC at T2: r=0.53 (p<0.01)	

Table 6. (continued)

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Perry, 2011 (81)	Age	(1) Children who started IBI younger tended to score higher at discharge on adaptive and cognitive variables (i.e. AB and IQ were significantly negatively correlated with age at entry). Younger age at entry was also correlated with milder autism severity at exit. (2) Age accounted for a significant, but very small, amount of unique variance for IQ and autism severity, but made no unique contribution to AB-composite at T2.	(1) Correlation (2) Stepwise linear regression	Yes	(1) IQ: r = -0.39, p<0.01 AB composite: r = -0.43, p<0.01 Psy (CARS): r=0.18, p<0.01 (2) IQ estimate: R^2=0.063, p<0.001 Psy(CARS): R^2=0.015, p<0.05	Regressions were computed for 8 primary dependent variables at T2. Step 1: T1 score of the same variable was entered (as a way of controlling for it) and report R^2 for the initial step. Step 2: Predictor variable was entered in Step 2 to determine whether it accounted for any additional variance. R^2 Step 2 change scores are reported as measures of association. **Variables associated with change in the treated group may not necessarily reflect actual predictors of outcome as not all of the observed change can be attributed to the effect of behavioural treatment.** This analysis more closely reflect an investigation of predictors of growth rather than predictors of outcome.
	IQ	(1) There were significant and strong correlations with initial IQ on all outcome variables. (2) Initial IQ accounted for a significant but small amount of incremental variance for AB and autism severity (beyond that associated with the initial value of IQ). IQ at intake accounted for 53% of the variance in T2 IQ (Step 1 of regression).	(1) Correlation (2) Stepwise linear regression	Yes	(1) IQ: r = 0.73, p<0.01 AB composite: r = 0.67, p<0.01 Psy(CARS): r = -0.42, p<0.01 (2) AB composite: ΔR^2=0.053, p<0.001 Psy(CARS): ΔR^2=0.074, p<0.001	
	AB	(1) Initial Vineland AB composite scores were significantly and quite highly correlated with all outcome variables. (2) Initial AB composite scores accounted for significant incremental variance (beyond that associated with the initial AB-composite value) in IQ and autism severity.	(1) Correlation (2) Stepwise linear regression	Yes	(1) IQ: r = 0.72, p<0.01 AB composite: r = 0.77, p<0.01 Psy(CARS): r = -0.51, p<0.01 (2) IQ estimate: ΔR^2=0.059, p<0.001 Psy(CARS): ΔR^2=0.118, p<0.001	
	Psy	(1) Correlation with initial severity scores (CARD) indicated modest negative correlations with all outcome variables. (2) Regression analyses showed that, in general, initial autism severity did not contribute to the prediction of outcome variables, with the exception of IQ at T2. (3) When initial IQ, age at entry, and initial adaptive skill level were controlled, autism severity (CARS) contributed an additional 2.0% of variance to predictions. A considerable amount of variance (64%) in outcome IQ can be predicted based on the combination of all four predictive variables.	(1) Correlation (2) Stepwise linear regression (3) Hierarchical multiple regression	Yes	(1) IQ: r = -0.43, p<0.01 AB composite: r = -0.34, p<0.01 Psy(CARS): r = 0.52, p<0.01 (2) IQ estimate: ΔR^2=0.038, p<0.001 (3) R^2=0.637, p=NR	

Table 6. (continued)

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Perry, 2013a (83)	Age	Controlling for duration and initial IQ, age accounted for a significant but small, amount of incremental variance for IQ at T2, but made no unique contribution to AB-composite standard scores at T2. Regression analysis further showed that young age at entry into IBI resulted in higher cognitive (but not adaptive) functioning at the end of treatment, even after controlling for treatment duration and the child's initial cognitive level. Age at entry was the only predictor that that was related to change in IQ (i.e. cognitive gains during intervention)	Hierarchical multiple regression	Yes	IQ at T2: $\Delta R^2=0.05$, $p<0.001$, Total $R^2=0.64$, $p<0.001$ ABC SS at T2: NS	Step 1 of regression: duration of treatment was added in order to control for any effect it may have on outcome; Step 2: initial IQ was added; Step 3: age at start of treatment was added **Variables associated with change in this single combined group study may not necessarily reflect actual predictors of outcome as not all of the observed change can be attributed to the effect of behavioural treatment.**
	IQ	Controlling for duration, initial IQ accounted for 59% of the variance in IQ at T2, and age at entry to IBI an additional 5%, for a total of 64% explained variance (total R^2). Initial IQ did not however predict the magnitude of IQ gains (change in IQ). Initial IQ accounted for a significant and substantial proportion of variance in AB standard scores at T2 (44%), and age at entry added nothing, for a total of 46% of explained variance. Regression analysis further demonstrated that children with higher skill levels before treatment tended to have higher skills levels after treatment, but children who were higher functioning cognitively were not the ones who necessarily made the largest IQ gains.	Hierarchical multiple regression	Yes	IQ at T2: $\Delta R^2=0.59$, $p<0.001$, Total $R^2=0.64$, $p<0.001$ ABC SS at T2: $\Delta R^2=0.44$, $p<0.001$, Total $R^2=0.46$, $p<0.001$	
	Duration of IBI	Longer duration of IBI was associated with slower rates of development between the two assessments. Treatment duration was not significantly associated with other outcomes, suggesting that children who were in the program longer were perhaps not showing better outcomes on IQ at T2, AB, or change in IQ.	Hierarchical multiple regression	Yes (RCog & RDev) No (IQ at T2, ΔIQ, & ABC SS at T2)	RCog: $\beta=-0.23$ ($p<0.01$) RDev: $\beta=-0.24$ ($p<0.001$)	

Table 6. (continued)

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Sallows, 2005 (74)	IQ at Y1	IQ at one year was positively and significantly correlated with full-scale IQ at the three-year treatment mark.	Correlation	Yes	r=0.75, p<0.01	Correlations and regression analyses between pre-treatment variables and three outcome variables (full-scale IQ, language, and social skills) at three years post treatment were examined in this study. However, results of any significant associations between AB composite score, IQ at one year and full-scale IQ at follow-up are presented here. Other pre-treatment variables included: language, Early Learning Measure (ELM) subdomains, VABS subdomains, non-verbal IQ, ratio IQ, and ADI-R scores.
	AB composite	AB composite scores at pre-treatment were not reliably associated with full-scale IQ at three years.	Correlation	No	NS	
	IQ, imitation, language, social relatedness, severity of symptoms	Post-treatment IQ was best predicted by this subset of variables, with 70% of variation in post-treatment IQ explained by this subset.	Linear and logistic regression (best subset approach)	NR	Unclear (70% variance reported in text with correlation value of 0.83)	
Smith, 2000 (75)	IQ	IQ at treatment onset was not reliably associated with full-scale IQ at follow-up. IQ did not significantly correlate with any other outcome variable.	Unprotected Pearson correlation	No	NS	
	Other pre-treatment variables	Other intake measures included: Non-verbal IQ, Lang, AB, SEF, PWB, and AP. There were 3 statistically significant correlations: (1) Intake non-verbal IQ with follow-up non-verbal IQ, (2) intake language with follow-up language, and (3) intake language with follow-up adaptive skills.	Unprotected Pearson correlation	No (except for non-verbal IQ and language)	(1) r=0.43, p=NR (2) r=0.36, p=NR (3) r=0.48, p=NR	

Table 6. (continued)

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Stoelb, 2004 (76)	Pre-treatment functioning	None	Stepwise linear regression	No	NS	The nature of this study does not permit identification of predictors of treatment response; at best, these factors can be considered to be predictors of growth. Outcome measurement was performed retrospectively using a criterion-referenced scale developed for the study (EIBI Performance Scale). Results should be interpreted with caution. An attempt was made to identify predictor variables that were significantly correlated with change among 9 children who were considered linguistic at treatment onset using the Wilcoxon rank rums test. Although the authors conclude that participants who were linguistic at treatment onset tended to make more progress is they began treatment at younger ages, age can only be viewed as a predictor of growth, rather than a predictor of outcome as a result of the study design limitation as well as the applied statistical modeling.
	Age at treatment onset	(1) None (2) Participants who were younger (and had a histories that did not include regression) tended to have higher EPS change scores.	(1) Stepwise linear regression (2) Mann-Whitney (Wilcoxon rank sums) test	(1) No (2) Yes	(1) NS (2) NR, p=0.0081	
	Treatment intensity	None	Stepwise linear regression	No	NS	
	Family involvement	None	Stepwise linear regression	No	NS	
	Dysmorphic features + History of regressive symptoms	Physical dysmorphology and history of regressive symptoms were strongly correlated with outcome (change in EPS scores) following both 6 months and 12 months of treatment. These variables accounted for 58% and 67% of the variance in outcome at 6 and 12 months, respectively.	Stepwise linear regression	Yes	At 6 mos: r^2=0.5835, p=0.009 At 12 mos: r^2=0.6722, p=0.0001	
	Other	None; investigated factors included: MRI results, head circumference, history of seizures, presence of sleep problems, gender, autism classification (essential or complex), family addiction history, family income group, use of supplementary dietary intervention.	Stepwise linear regression	No	NS	

Table 6. (continued)

First author, year (Ref. No.)	Predictive variable(s)	Observed association	Statistical methods	Significant association	Measure of association	Comments
Virues-Ortega, 2013 (94)	Intervention duration	Positive impact in the model's fit, but to a lesser extent than total intervention time in all eight outcomes.	Multilevel regression model : One-predictor model	NR	Various goodness-of-fit (AIC, BIC) parameters per outcome measure	A series of multilevel models were estimated using different sets of predictors in order to select models that would maximize goodness-of-fit for a given outcome (change in E-LAP and LAP-D scores) when compared with an unconditional baseline model (model with no predictors). **Variables associated with change in the treated group (intervention time, age at intervention onset, and pre-intervention functioning) may not necessarily reflect actual predictors of outcome as not all of the observed change can be attributed to the effect of behavioural treatment.**
	Total intervention time	Total intervention time had the highest favorable impact on goodness-of-fit for all E-LAP and LAP-D outcomes.	Multilevel regression model : One-predictor model	Yes	Various goodness-of-fit (AIC, BIC) parameters per outcome measure	
	Age	Two-predictor model: Age was the second most efficient predictor (keeping intervention time as first factor) in terms of improving fit of the regression models for gross motor function, receptive language, self-care, and social behavior.	Multilevel regression model : One-predictor and two-predictor model	Yes	Various goodness-of-fit (AIC, BIC) parameters per outcome measure	
	Gender	Positive impact in the model's fit	Multilevel regression model : Two-predictor model	NR	Various goodness-of-fit (AIC, BIC) parameters per outcome measure	
	Pre-intervention level	Pre-intervention level was the second most efficient predictor for regression models using fine motor function, prewriting, cognitive, and expressive language.	Multilevel regression model : Two-predictor model	Yes	Various goodness-of-fit (AIC, BIC) parameters per outcome measure	

Appendix 6: Risk of Bias in Included Studies

QUALITY ASSESSMENT: Downs & Black (1998) Checklist

Assessment of the methodological quality of included studies was performed by means of the Downs and Black (1998) checklist for randomized and non-randomized studies of heath care interventions.(59)

Following the original author's guidelines, this checklist was adapted specifically to the field of applied behavioural analysis for autism in a previous meta-analysis conducted by Virues-Ortega et al. (2010),(60) which served as the basis for evaluating the quality of studies included in this review.

Items on randomization (items 23 and 24) were considered non-applicable for single group studies with pre/post design, and overall scores for those studies were prorated accordingly. In addition, the last item on the checklist (item 27) was simplified to consider whether or not the study authors had reported a power estimation or provided a sample size justification.

The following table lists the quality criteria of the Downs and Black checklist, with modifications specified in italics:

Table 7. Criteria of the adapted Downs and Black checklist.

Domain	Item	Quality Criteria	Scoring[†]
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?	A
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered no.	A
	3	Are the characteristics of the patients included in the study clearly described? In cohort, *within subject studies* and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given. *(Inclusion criteria or at least one other relevant feature apart from sex and age).*	A
	4	Are the interventions of interest clearly described? Treatments and placebo/*control* (where relevant) that are to be compared should be clearly described.	A
	5	Are the distributions of principal confounders in each group of subjects *or treatment condition* to be compared clearly described? *At least one of the following are described apart from sex and age: past and concurrent interventions, intervention intensity (hours per week), diagnoses, severity of existing illness, intellectual quotient at pretest, treatment fidelity indexes, other relevant confounder. If only sex and/or age are described, answer 1.*	B
	6	Are the main findings of the study clearly described? Simple outcome data should be reported for all major findings so that the reader can check the major analyses and conclusions *(provide means or data from all participants).* (This question does not cover statistical tests, which are considered below).	A
	7	Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.	A
	8	Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events *or at least to prevent them on the basis of specific exclusion and inclusion criteria.*	A
	9	Have the characteristics of patients lost to follow-up been described? This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion *(-10%).* This should be answered 'no' where a study does not report the number of patients lost to follow-up. *Question should be answered 'no' in retrospective studies.*	A
	10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	A
External validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients were selected, the question should be answered as unable to determine.	C
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	C
	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend. *For interventions that took place at the participants' home question should be answered yes.*	C
Internal validity (bias)	14	Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	C
	15	Was an attempt made to blind those measuring the main outcomes of the intervention? *In cases were outcome variables were collected through self-administered questionnaires answer should be answered yes. Question should be answer yes if those measuring the main outcomes were whether blind to group status or were independent of treatment delivery.*	C

	16	If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes. *Question should be answered 'no' for retrospective studies were cases were not admitted consecutively or were selected in anyway. Note: data dredging is the inappropriate (sometimes deliberately so) search for 'statistically significant' relationships in large quantities of data in spite of previous hypothesis.*	C
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control *and within-subjects* studies, is the time period between the intervention and outcome the same for cases and controls? Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.	C
	18	Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	C
	19	Was compliance with the intervention/s reliable? Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes. *In no measure for treatment fidelity assurance were taken, question should be answered no.*	C
	20	Were the main outcome measures used accurate (valid and reliable)? For studies where the outcome measures are clearly described, the question should be answered yes *(e.g., systematic behavioral observation with inter-rater reliability information)*. For studies which refer to other work or that demonstrate the outcome measures are accurate *(e.g., validated psychometric tests)*, the question should be answered as yes.	C
Internal validity (confounding)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies), *or all participants within-subjects designs*, recruited from the same population? For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case control studies where there is no information concerning the source of patients included in the study.	C
	22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) *or participants in within-subjects studies* recruited over the same period of time? For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	C
	23	Were study subjects randomized to intervention groups? Studies that state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.	C
	24	Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non-randomized *controlled* studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	C
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.	C
	26	Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes. *(<10%). For retrospective studies question should be answered 'no.'*	C
Power	27	*Was a power estimation performed and reported with sufficient numbers recruited?*	A

[†]Scoring instructions: A: Yes (1 point), No (0 points); B: Yes (2 points), Partially (1 point), No (0 points); C: Yes (1 point), Unable to determine (0 points), No (0 points)

Table 8. Quality assessment of included studies according to Downs and Black checklist (results by item).

	Reporting										External validity			Internal validity–bias							Internal validity–confounding						Power
First author, year (Ref.)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14†**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23†**	**24†**	**25**	**26**	**27**
Ben-Itzchak, 2007 (84)	1	1	1	1	2	1	1	0	1	1	0	0	0	0	1	0	1	1	0	1	0	0	–	–	0	1	0
Ben-Itzchak, 2009 (85)	0	1	0	0	0	1	1	0	1	0	0	0	0	0	0	0	1	1	0	1	1	0	–	–	0	0	0
Ben-Itzchak, 2014 (86)	1	1	1	1	2	1	1	0	0	1	0	0	0	0	1	0	1	1	1	1	0	0	–	–	0	0	0
Blacklock, 2014 (82)	1	1	1	1	2	1	1	0	0	1	0	0	1	0	0	0	0	1	0	1	1	0	–	–	0	0	0
Cohen, 2006 (69)	1	1	1	1	2	1	1	0	1	1	0	0	1	0	1	1	1	1	1	1	0	0	0	0	1	1	0
Eikeseth, 2002, 2007 (92,93)	1	1	1	1	2	1	1	0	1	0	0	0	1	0	1	1	1	1	1	1	1	1	0	0	1	1	0
Eikeseth, 2009 (89)	1	1	1	1	1	1	1	0	1	0	0	0	1	0	1	0	1	1	1	1	0	0	–	–	0	1	0
Flanagan, 2012 (79)	1	1	1	1	2	1	1	0	0	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	1	0	0
Freeman, 2010 (80)	1	1	1	1	2	1	1	0	0	1	1	0	1	0	0	1	0	1	0	1	1	0	–	–	0	0	0
Granpeesheh, 2009 (70)	1	1	1	1	2	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	–	–	0	0	0
Harris, 2000 (71)	1	1	1	1	2	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	–	–	0	1	0
Hayward, 2009 (90)	1	1	1	1	1	1	1	0	1	0	0	0	1	0	1	0	1	1	1	1	0	0	–	–	0	1	0
Howard, 2005, 2014 (72,73)	1	1	1	1	2	1	1	0	0	0	0	0	0	0	1	1	1	1	1	1	0	1	0	0	1	1	0
Perry, 2008, 2011 (78,81)	1	1	1	1	2	1	1	0	0	1	1	1	1	0	0	0	1	1	0	1	1	1	–	–	1	0	0

Table 8. (continued)

	Reporting										External validity			Internal validity–bias							Internal validity–confounding						Power
First author, year (Ref.)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14†**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23†**	**24†**	**25**	**26**	**27**
Perry, 2013a (83)	1	1	1	1	2	1	1	0	0	1	0	0	1	0	0	0	1	1	0	1	1	0	–	–	1	0	0
Perry, 2013b (83)	1	1	1	1	2	1	1	0	0	1	0	0	1	0	0	0	1	1	0	1	1	0	–	–	1	0	0
Remington, 2007 (91)	1	1	1	1	2	1	1	0	0	1	0	0	1	0	1	1	1	1	0	1	0	0	0	0	1	0	0
Sallows, 2005 (74)	1	1	1	1	2	1	1	0	1	0	1	1	1	0	0	1	1	1	1	1	1	1	–	–	1	1	0
Smith, 2000 (75)	1	1	1	1	2	1	1	0	1	0	0	0	1	0	1	0	0	1	1	1	1	1	1	0	1	1	0
Stoelb, 2004 (76)	1	1	1	1	2	1	0	0	0	1	0	0	0	0	0	1	1	1	1	1	1	0	–	–	1	0	0
Virues-Ortega, 2013 (94)	1	1	1	1	2	0	0	0	0	0	1	0	1	0	1	1	1	1	0	1	1	1	–	–	1	0	1
Weiss, 1999 (77)	1	1	0	1	1	1	0	0	0	1	0	0	1	0	0	1	0	1	0	1	1	0	–	–	0	0	0
Zachor, 2007 (87)	1	1	1	1	2	1	1	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	0	0	0	0	0
Zachor, 2010 (88)	1	1	1	1	2	1	1	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	1	0	0
% of maximum score	96	100	92	96	90	92	79	0	38	50	21	13	67	0	50	54	75	100	42	96	58	33	4	0	54	38	4

Note: 0 or 1 point for all items, except item 5 (0–2 points).
†Items 23 and 24 were only applicable to controlled comparison studies.

Table 9. Quality assessment of included studies according to the Downs and Black checklist (results by domain).

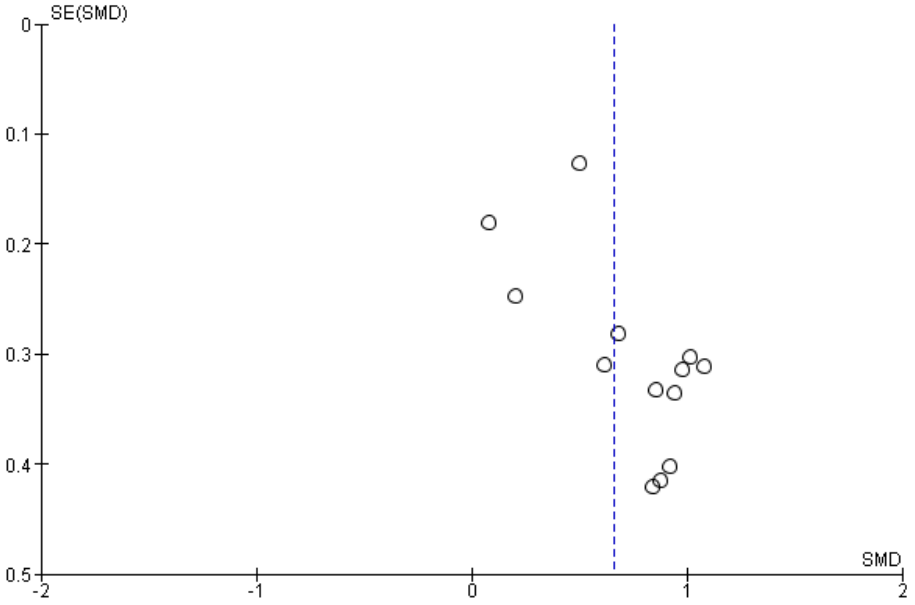
First author, year (Ref.)	Reporting /11 (/1.0)	External Validity /3 (/1.0)	Bias /7 (/1.0)	Confounding /6 (/1.0)	Power /1 (/1.0)	Total /28 (/5.0)
Ben-Itzchak, 2007 (84)	10 (0.9)	0 (0.0)	4 (0.6)	1 (0.3)	0 (0.0)	15 (1.7)
Ben-Itzchak, 2009 (85)	4 (0.4)	0 (0.0)	3 (0.4)	1 (0.3)	0 (0.0)	8 (1.0)
Ben-Itzchak, 2014 (86)	9 (0.8)	0 (0.0)	5 (0.7)	0 (0.0)	0 (0.0)	14 (1.5)
Blacklock, 2014 (82)	9 (0.8)	1 (0.3)	2 (0.3)	1 (0.3)	0 (0.0)	13 (1.7)
Cohen, 2006 (69)	10 (0.9)	1 (0.3)	6 (0.9)	2 (0.3)	0 (0.0)	19 (2.4)
Eikeseth, 2002, 2007 (92,93)	9 (0.8)	1 (0.3)	6 (0.9)	4 (0.7)	0 (0.0)	20 (2.7)
Eikeseth, 2009 (89)	8 (0.7)	1 (0.3)	5 (0.7)	1 (0.3)	0 (0.0)	15 (2.0)
Flanagan, 2012 (79)	9 (0.8)	3 (1.0)	4 (0.6)	3 (0.5)	0 (0.0)	19 (2.9)
Freeman, 2010 (80)	9 (0.8)	2 (0.7)	3 (0.4)	1 (0.3)	0 (0.0)	15 (2.2)
Granpeesheh, 2009 (70)	6 (0.5)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	7 (0.7)
Harris, 2000 (71)	8 (0.7)	1 (0.3)	4 (0.6)	3 (0.8)	0 (0.0)	16 (2.4)
Hayward, 2009 (90)	8 (0.7)	1 (0.3)	5 (0.7)	1 (0.3)	0 (0.0)	15 (2.0)
Howard, 2005, 2014 (72,73)	8 (0.7)	0 (0.0)	6 (0.9)	3 (0.5)	0 (0.0)	17 (2.1)
Perry, 2008, 2011 (78,81)	9 (0.8)	3 (1.0)	3 (0.4)	3 (0.8)	0 (0.0)	18 (3.0)
Perry, 2013a (83)	9 (0.8)	1 (0.3)	3 (0.4)	2 (0.5)	0 (0.0)	15 (2.1)
Perry, 2013b (83)	9 (0.8)	1 (0.3)	3 (0.4)	2 (0.5)	0 (0.0)	15 (2.1)
Remington, 2007 (91)	9 (0.8)	1 (0.3)	5 (0.7)	1 (0.2)	0 (0.0)	16 (2.0)
Sallows, 2005 (74)	9 (0.8)	3 (1.0)	5 (0.7)	4 (1.0)	0 (0.0)	21 (3.5)
Smith, 2000 (75)	9 (0.8)	1 (0.3)	4 (0.6)	5 (0.8)	0 (0.0)	19 (2.6)
Stoelb, 2004 (76)	8 (0.7)	0 (0.0)	5 (0.7)	2 (0.5)	0 (0.0)	15 (1.9)
Virues-Ortega, 2013 (94)	6 (0.5)	2 (0.7)	5 (0.7)	3 (0.8)	1 (1.0)	17 (3.7)
Weiss, 1999 (77)	6 (0.5)	1 (0.3)	3 (0.4)	1 (0.3)	0 (0.0)	11 (1.6)
Zachor, 2007 (87)	8 (0.7)	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)	12 (1.3)
Zachor, 2010 (88)	8 (0.7)	0 (0.0)	6 (0.9)	1 (0.2)	0 (0.0)	15 (1.8)

Note: Score and proportion of the maximum achievable score by domain. Total expressed in raw scores and proportion of maximum achievable score across all domains.

Appendix 7: Data and Analysis

Primary analysis: IQ

Figure 7. Funnel plot of comparison: IBI vs TAU, outcome: 1.1 IQ



Subgroup analyses: IQ

Figure 8. Forest plot of comparison: IBI vs TAU, outcome: 1.1 IQ, subgroup: *Intake Age*

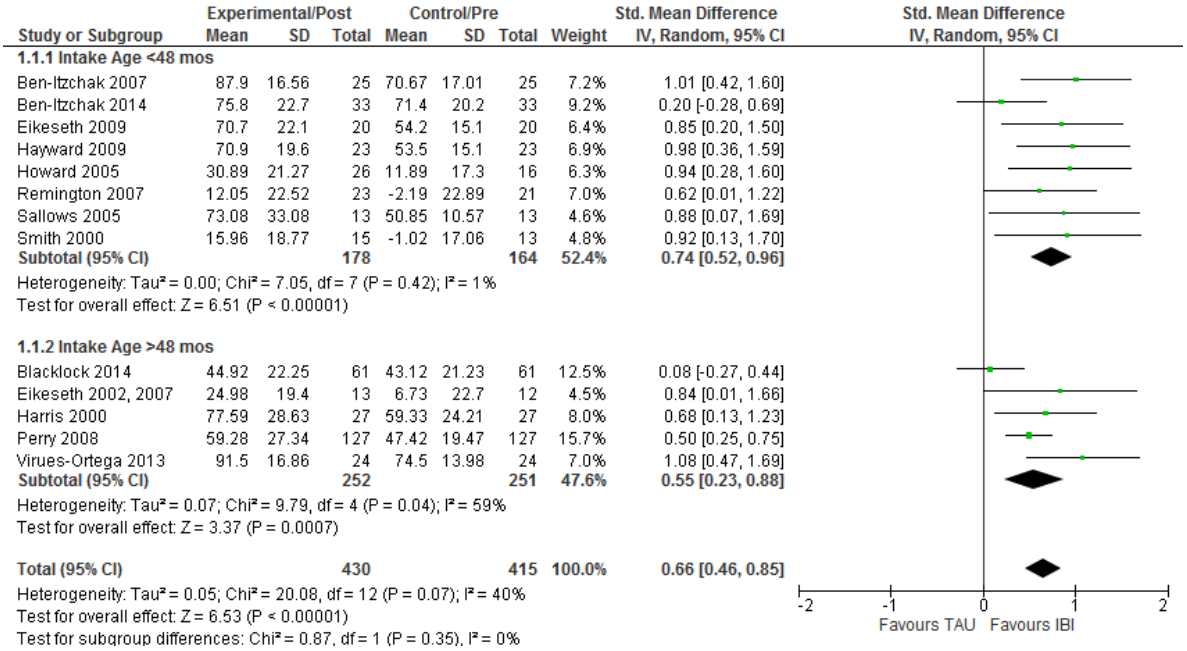


Figure 9. Forest plot of comparison: IBI vs TAU, outcome: 1.1 IQ, subgroup: *Intake IQ*

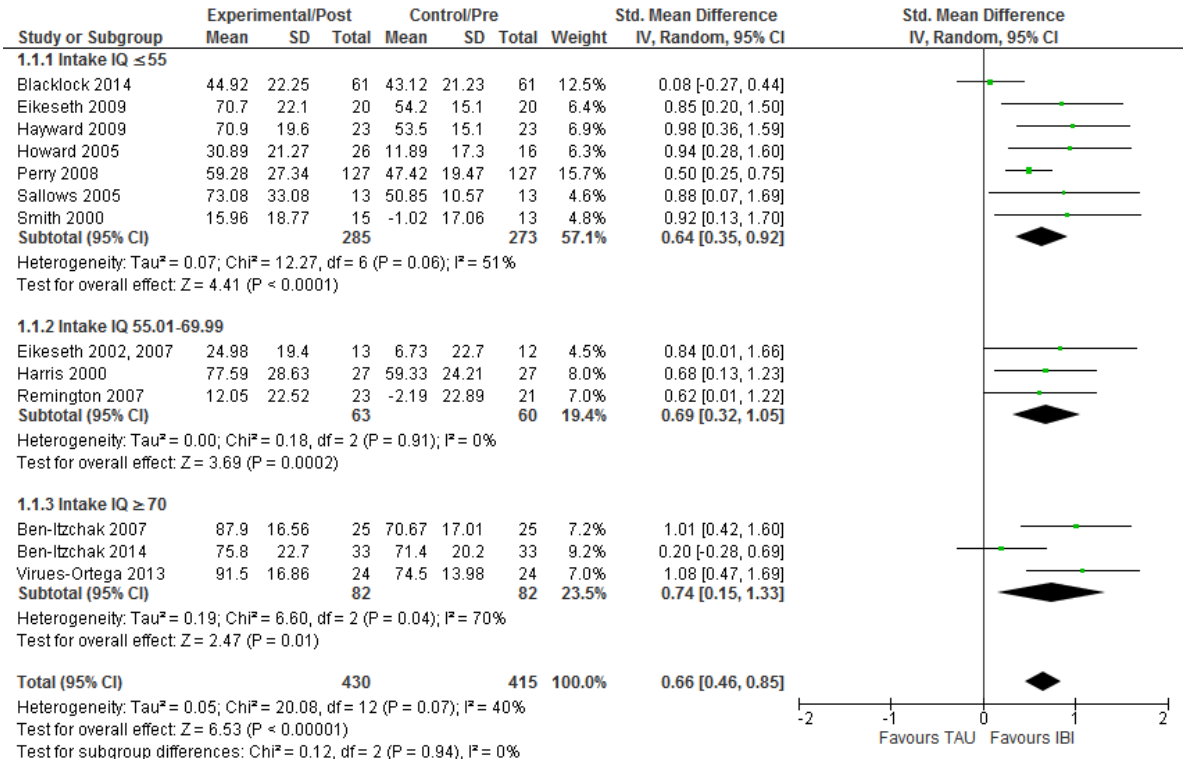


Figure 10. Forest plot of comparison: IBI vs TAU, outcome: 1.1 IQ, subgroup: *Treatment model*

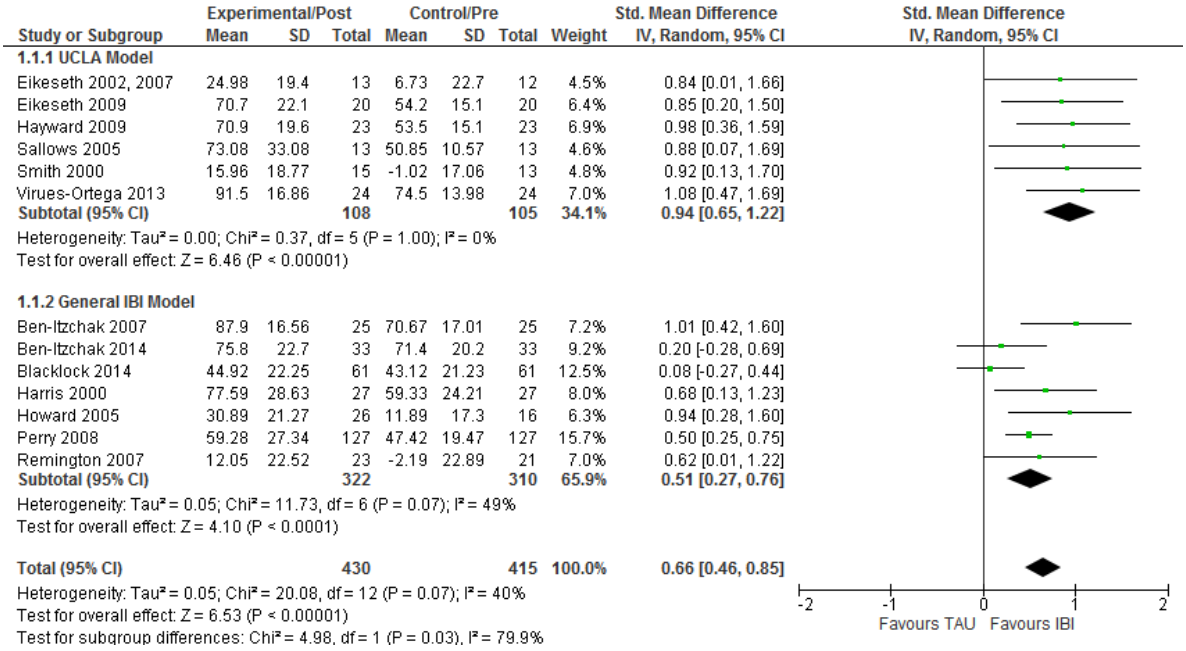
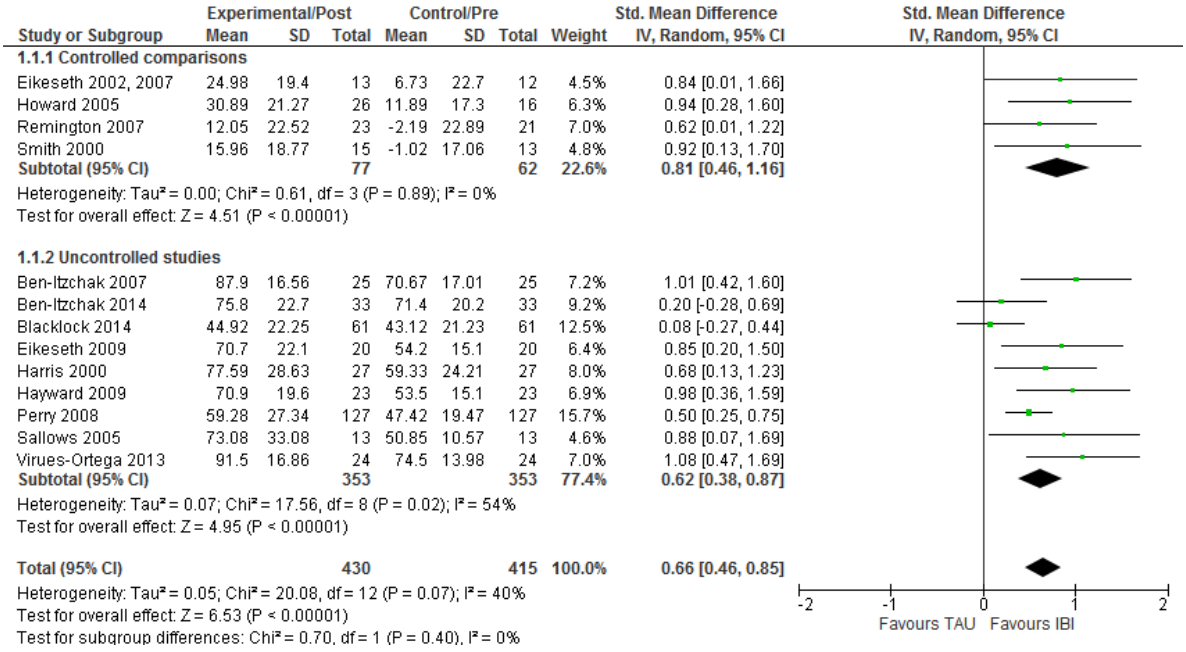
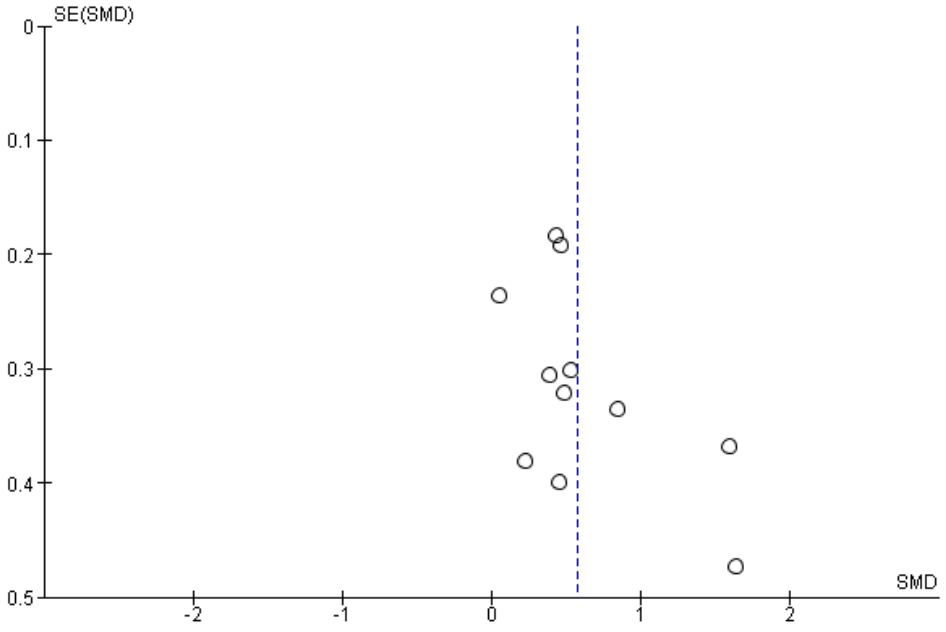


Figure 11. Forest plot of comparison: IBI vs TAU, outcome: 1.1 IQ, subgroup: *Study design*



Primary analysis: VABS Adaptive Behaviour Composite

Figure 12. Funnel plot of comparison: IBI vs TAU, outcome: 1.2 VABS Composite



Subgroup analyses: VABS Adaptive Behaviour Composite

Figure 13. Forest plot of comparison: IBI vs TAU, outcome: 1.2 VABS Composite, subgroup: *Intake Age*

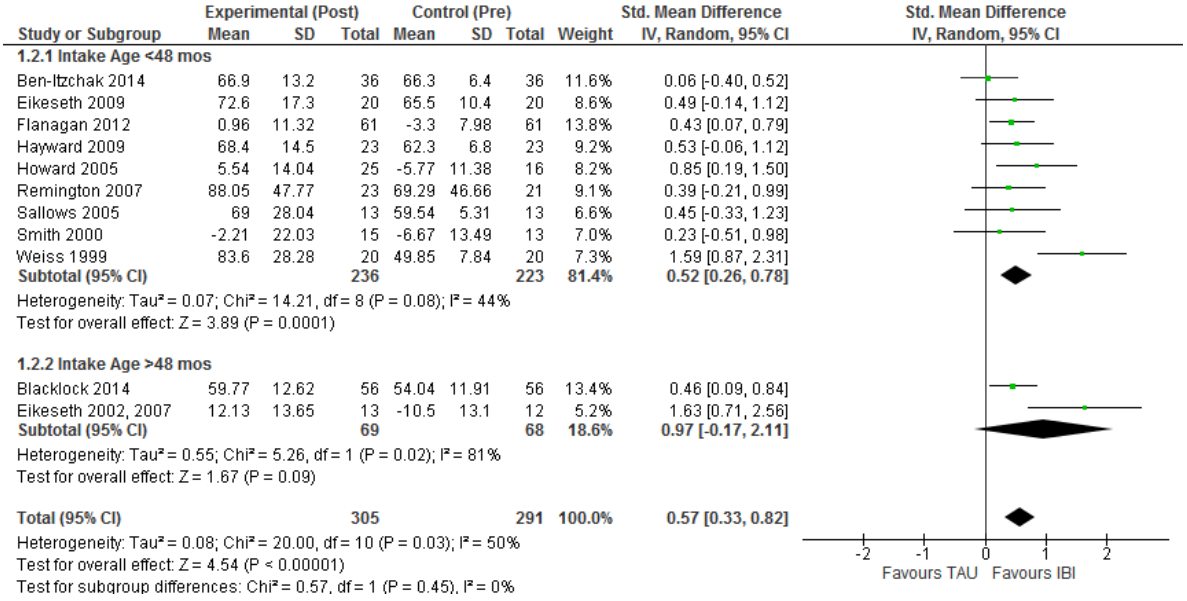


Figure 14. Forest plot of comparison: IBI vs TAU, outcome: 1.2 VABS Composite, subgroup: *Intake IQ*

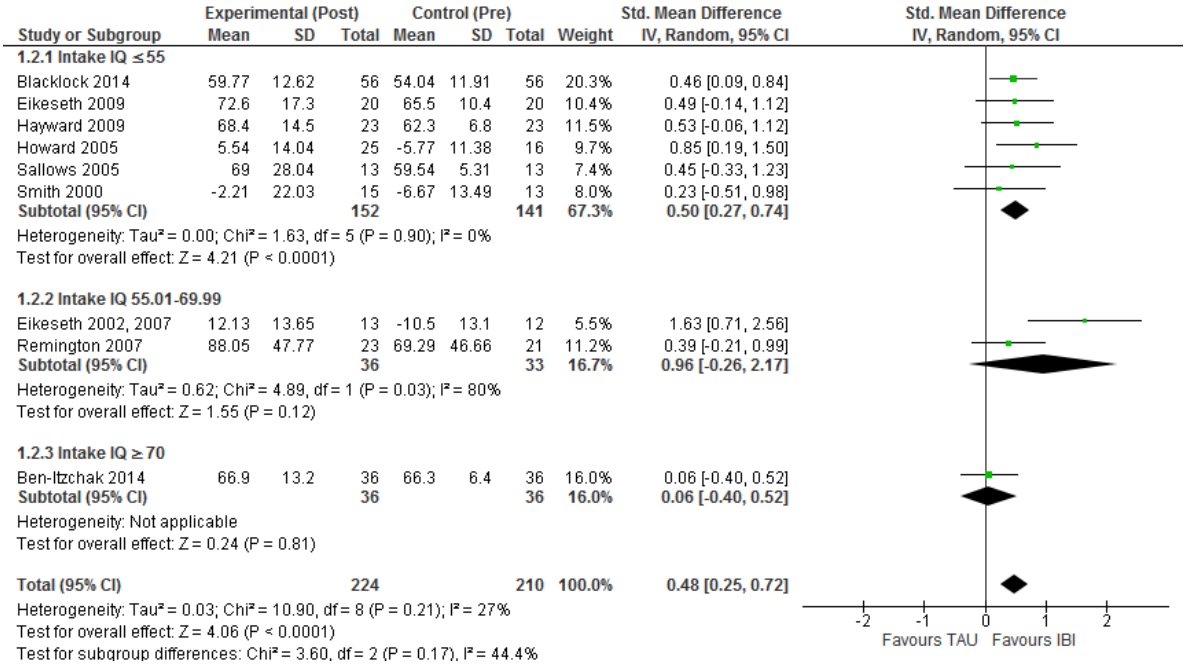


Figure 15. Forest plot of comparison: IBI vs TAU, outcome: 1.2 VABS Composite, subgroup: *Treatment model*

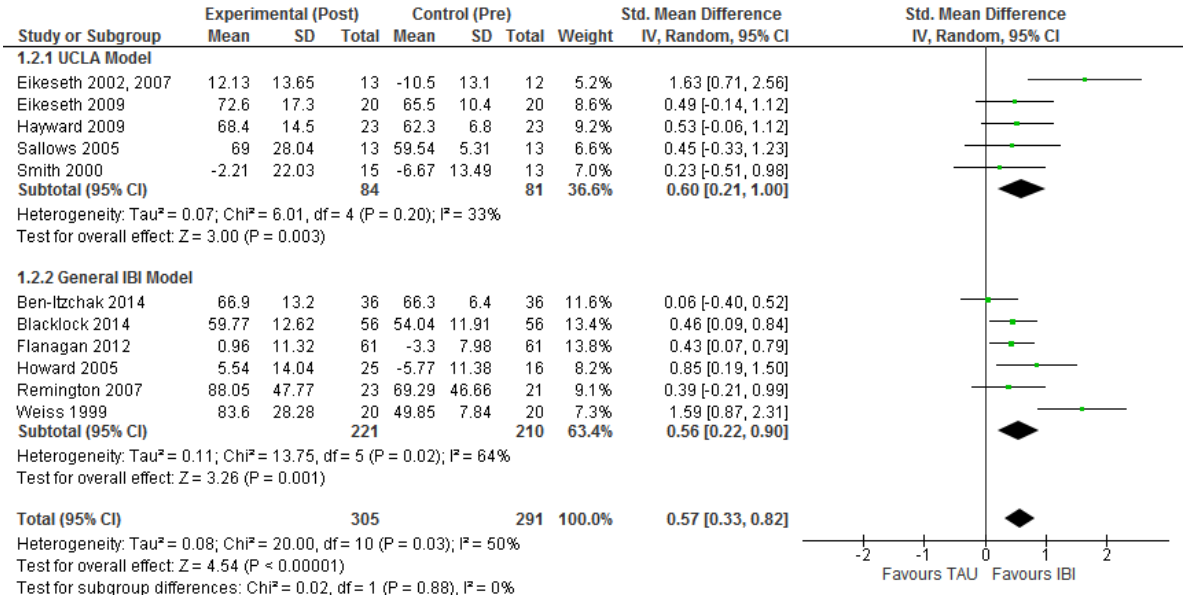


Figure 16. Forest plot of comparison: IBI vs TAU, outcome: 1.2 VABS Composite, subgroup: *Study design*