GENERAL PROJECT DATA

Research Line: Health. Nutrition. Neurosciences. Physiology of Nutrition and the Central Nervous System. Sleep Physiology. Ethnography.

Project Title: Neuro-Nutrition as Support for Physiological Performance and Cognitive Skills in People with Trisomy 21, Autism Spectrum Disorders, and Attention Deficit Disorder.

Discipline: Neurosciences. Nutrition. Neurobiology. Ethnography. Psychology. Sleep Physiology.

Specialty: Physiology of Nutrition. Biochemistry. Food Allergies and Sensitivities. Ethnography. Sleep Physiology. Neuropsychology. Neurobiology.

Principal Investigator: Dr. Reyes Haro Valencia

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Institutional Alignment and Project Justification

The present project arises from the collaborative efforts of DOMUS Instituto de Autismo A.C., CTDUCA Atención Integral de Personas Down I.A.P., the Instituto Mexicano de Medicina Integral de Sueño, and researchers from the Universidad Nacional Autónoma de México (UNAM). These institutions share the commitment to develop scientific research with social impact, particularly in vulnerable populations with neurodevelopmental conditions.

The initial Neuro-Nutrition project, registered with the National Council of Science and Technology (CONACYT) under the title *"Neuro-Nutrition as Support for Physiological Performance and Cognitive Skills in Individuals with Trisomy 21"* (Project ID: 157118), provided results that exceeded expectations. These findings paved the way to broaden the scope of investigation and extend the benefits of nutritional intervention to other groups, including individuals with Autism Spectrum Disorders and Attention Deficit Disorder, with or without Hyperactivity (ADD/ADHD).

The current study builds on that foundation, seeking not only to confirm previous findings in individuals with Trisomy 21 but also to expand scientific and clinical knowledge in populations with ASD and ADD/ADHD, thereby contributing to improved quality of life, social inclusion, and health outcomes.

SYNTHESIS

Based on an extensive literature review, multiple genetic, immunological, metabolic, physiological, and therapeutic management affinities have been documented among individuals diagnosed with Trisomy 21 (Down Syndrome), Autism Spectrum Disorders (ASD), and Attention Deficit Disorder with or without Hyperactivity (ADD/ADHD). This project aims to help regularize altered metabolic processes and improve cognitive and behavioral skills in these populations through the design of an appropriate diet and the formulation of a specialized Dietary Supplement developed specifically to address the metabolic deficiencies of individuals with these conditions.

By removing harmful elements from the body and providing the appropriate nutrients, it is expected that participants' quality of life will improve both in their immediate social environment and in their sleep performance.

INTRODUCTION

According to data from the Instituto Nacional de Estadística y Geografía (INEGI) and the Secretaría de Salud (SSA), there are currently an estimated 150,000 individuals with Trisomy 21 (Down Syndrome) in Mexico. In relation to the population with Autism Spectrum Disorders (ASD), the Clínica Mexicana de Autismo estimates approximately 45,000 individuals nationwide, with an annual growth rate of 17%. Furthermore, the Programa Específico de Trastorno por Déficit de Atención (SSA Report 2001–2006) estimated 1.5 million children and adolescents with this condition, a number that could potentially double when including adults who continue to be affected.

Although individuals with Autism Spectrum Disorders (ASD) and Down Syndrome continue to be considered vulnerable minority groups in Mexico, the increasing prevalence of Attention Deficit Disorder, with or without Hyperactivity (ADD/ADHD), has made this condition an important focus of public health.

According to the 2010 National Population and Housing Census conducted by the Instituto Nacional de Estadística y Geografía (INEGI), there are 5,739,270 individuals in Mexico living with some form of physical or mental disability. Based on this data, approximately 30% of the disabled population in the country consists of individuals with Autism Spectrum Disorders, Down Syndrome, or Attention Deficit Disorder, with or without Hyperactivity (ADD/ADHD).

Despite awareness of these statistics, limited economic, scientific, and technological resources have been allocated to address the specific needs of these populations. In addition to the social vulnerability resulting from neglect, these groups share physiological and metabolic characteristics that make their clinical management highly specialized and complex.

Another common feature among these three populations is the global reliance on pharmacological treatment models, whose effectiveness is often limited unless combined with behavioral therapies. Stimulants such as methylphenidate and dextroamphetamine are among the most frequently prescribed medications for individuals with Down Syndrome, Autism Spectrum Disorders (ASD), and/or Attention Deficit Disorder with or without Hyperactivity (ADD/ADHD) (Rappley, 2005; Frohlich, Lanphear, & Epstein, 2007; Findling, 2008). These medications act directly on neurotransmitters such as norepinephrine and dopamine, which are closely associated with cognition, anxiety regulation, and satiety.

Some of the reported benefits of these medications include reduced impulsivity and hyperactivity, as well as improved concentration. However, their use has also been associated with adverse effects such as risk of dependency, fluctuations in body weight,

severe appetite disturbances (including anorexia or obesity), impaired growth, gastrointestinal problems, headaches, significant sleep disorders, marked variations in blood pressure (Rappley, 2005; Frohlich, Lanphear, & Epstein, 2007; Findling, 2008; Najib, 2008), and substantial hormonal imbalances.

The potential side effects of these medications often lead patients and their legal guardians (parents or caregivers) to discontinue their use, turning instead to multidisciplinary behavioral therapies. The limited understanding of the full scope of Trisomy 21, Autism Spectrum Disorders (ASD), and Attention Deficit Disorders (ADD/ADHD)—combined with the challenges of neurostimulant treatments and the modest effectiveness of psychological and behavioral interventions—has prompted both researchers and families to explore alternative therapeutic approaches. Increasingly, the scientific community is recognizing nutritional factors as decisive and fundamental in the development and clinical expression of these conditions (Sinn, 2008; Schnoll, 2003).

It is also important to acknowledge that society has prompted a redefinition of disability. Considering disability solely as a personal or individual attribute, detached from its broader social context, has significant implications for international taxonomies and for the standards used to evaluate functional impairments (Ferreira, 2006). For instance, the World Health Organization's International Classification of Impairments, Disabilities, and Handicaps (ICIDH) conceptualizes disability primarily as the consequence of a medical condition—essentially, a "natural" accident.

Research on different forms of disability has demonstrated that the family plays a central role in fostering behavioral and cognitive changes in affected individuals (Ramírez, 2011). Such changes may result from a variety of interventions, ranging from psychological programs to clinical protocols. However, there is a notable lack of quantitative studies specifically evaluating improvements in family quality of life derived from nutritional interventions.

The underlying issue is that, with the growing prevalence of neurodevelopmental disorders, it has become increasingly important to understand and anticipate their progression, as they affect individuals throughout the lifespan. Evidence from studies on these populations—and the challenges they face during the transition to adulthood, when many will outlive their parents and legal guardians—must inform discussions on service provision and public policy planning to ensure a better quality of life.

BACKGROUND – Feasibility of the Proposal

Research Extension

The need to implement this protocol arises from the above-expected results of a 2011 research project supported by the Consejo Nacional de Ciencia y Tecnología (CONACYT) under the PROINOVA program (Project No. 157118), titled *"Neuro-Nutrition as Support for Physiological Performance and Cognitive Skills in Individuals with Trisomy 21."* The theoretical basis of that project was grounded in the physiological similarities observed between individuals with Autism Spectrum Disorders (ASD) and those with Trisomy 21 (Down Syndrome).

Key findings from the previous study that support extending the nutritional intervention to populations with Autism Spectrum Disorders (ASD) and Attention Deficit Disorder (ADD) included: strengthened immune function with fewer parasitic infections; improved absorption of proteins, calcium, phosphorus, and iron, resulting in higher growth rates compared to controls; healthier cholesterol and triglyceride profiles, thereby reducing cardiovascular risk; more efficient digestion and decreased chronic intestinal inflammation; and improved intestinal motility. In addition, participants demonstrated greater concentration, enhanced attention, and more socially adaptive behaviors.

Building on this evidence, and considering that the theoretical framework of the prior project already encompassed individuals with ASD, the present study aims to explicitly include them as a primary target population, alongside individuals with ADD.

Etiology

The precise causes of Autism Spectrum Disorders (ASD), Down Syndrome, and Attention Deficit Disorder (ADD) remain unclear. Current therapeutic approaches are primarily aimed at alleviating symptoms that compromise quality of life, cognitive performance, and social integration. Although their etiology has not been fully established, these conditions are widely recognized as neurodevelopmental disorders that share significant genetic, immunological, metabolic, and gastrointestinal characteristics.

Genetics

Post-mortem brain studies examining genes associated with these disorders have highlighted immunological convergence rather than differences limited to neurodevelopmental genes. Consistently observed findings include immune system depression and elevated oxidative stress, both of which influence the type and severity of the disorder, as well as the degree of intellectual disability (Lintas, Sacco, & Perisco, 2010).

Mineral deficiencies—particularly calcium, magnesium, zinc, iron, and selenium—have also been linked to immune dysfunction.

Another critical factor involves neuronal development and microglial function. Excessive glutamate release and the presence of pro-inflammatory cytokines have been documented in post-mortem brains of individuals with Down Syndrome and ASD, leading to impaired inter-neuronal communication and disruption of long-range cortical–subcortical connections. These disruptions are strongly associated with deficits in cognition, social interaction, and sensory integration (Rubenstein & Merzenich, 2003; Courchesne & Pierce, 2005; Geschwind & Levitt, 2007; Belmonte, 2010).

Metabolism

Immune suppression in individuals with Down Syndrome, Autism Spectrum Disorders (ASD), and Attention Deficit Disorder (ADD) predisposes them to recurrent infections of the gastrointestinal tract, respiratory system, and ears. The use of antibiotics further disrupts the gut microbiota, exacerbating dysbiosis. This imbalance promotes Candida overgrowth, which contributes to the secretion of immunotoxins, intestinal wall damage, and inhibition of immunoglobulin A (IgA), ultimately leading to increased intestinal permeability (*leaky gut*). In Down Syndrome, intestinal sluggishness caused by hypotonia further prolongs exposure to pathogens.

These intestinal alterations impair secretin production, reducing pancreatic and hepatic enzyme release, and thereby hindering nutrient digestion and absorption. The processing of complex proteins such as casein (milk) and gluten (wheat, barley, rye, oats) is disproportionately affected, leaving peptides only partially digested. These altered peptides can cross compromised intestinal and blood–brain barriers, accumulate in the temporal lobes—critical for language and cognition—and exert opioid-like activity. Such effects contribute to mood instability, sensory alterations, sleep disturbances, respiratory depression, reduced attention, antisocial behaviors, and academic underperformance (Shaw, 2008).

Candida also interferes with carbohydrate metabolism by fermenting sugars, leading to three major outcomes:

1. Reduced ATP production from glycolysis/Krebs cycle, depriving specialized cells (e.g., hepatocytes, neurons, pancreatic beta cells) of energy.
2. Production of pentosidines, accelerating oxidative stress and impairing tissue regeneration.

3. Creation of alcoholic byproducts in the intestine, further damaging mucosa, impairing enzymatic activity, and reducing vitamin B synthesis.

Oxidative Stress and Allergies

The fermentative activity of Candida in protein and carbohydrate metabolism, together with oxidative stress, has been associated with degenerative and autoimmune diseases such as Alzheimer's disease, diabetes, fibromyalgia, and multiple sclerosis. Nutritional control and targeted supplementation may significantly reduce these risks in populations with Down Syndrome, Autism Spectrum Disorders (ASD), and Attention Deficit Disorder (ADD).

The functional sensitivity of these groups also predisposes them to allergic or food sensitivity reactions, which may manifest as behavioral, psychological, and cognitive disturbances.

Quality of Life

Scientific research on quality of life (QoL) has expanded considerably worldwide, ranging from Anglo-European contexts (Roy Brown, 2000) to Latin American settings (Verduzco, 2010). Disability is often conceptualized as the functional and social manifestation of an impairment, medically attributed to a natural accident or condition. However, this framework tends to overlook the subjective and socially constructed dimensions of disability (Ferreira, 2006).

Recognizing QoL within disability contexts now requires greater emphasis on social action and inclusion. Understanding the interrelationship between disability and QoL is fundamental to promoting equitable participation and overall well-being.

Sleep Physiology

ASD and Sleep Disorders

Studies have shown that children with Autism Spectrum Disorders (ASD) frequently experience sleep–wake disturbances, particularly irregular circadian rhythms (Gail, 2004). While many findings are derived from parent-reported questionnaires, objective assessments such as actigraphy and polysomnography have confirmed abnormalities in sleep architecture (Allik & Malow, 2006; Goldman & Souders, 2009). Reported prevalence rates of sleep disorders in ASD range from 44% to 83% (Gail, 2004).

Genetic anomalies affecting melatonin synthesis and signaling are considered central to these disturbances. Clinical studies indicate that melatonin administration can improve total sleep time, reduce sleep latency and nighttime awakenings, and enhance daytime behavior, with minimal adverse effects (Richdale, 1995; Wright, 2010; Rossignol, 2011; Leu, 2010).

ADD and Sleep Disorders

In children with suspected Attention Deficit Disorder (ADD), evaluation of sleep is crucial, as sleep disturbances can exacerbate ADD symptoms. Some children initially diagnosed with ADD may in fact present with primary sleep disorders such as sleep apnea or restless legs syndrome (Mindell, 2003). Sleep and attention are bidirectionally linked, sharing common prefrontal cortex mechanisms (Dahl, 1996; Kirov, 2004). The prevalence of sleep disturbances in ADD is higher than in both healthy controls and psychiatric controls (Ball, 1997; Stein & Corkum, 1999).

Experimental studies on sleep deprivation have confirmed that reduced sleep worsens attention and executive performance (Kim, 2011; Prihodova, 2010; Touchette, 2009). Adequate sleep, by contrast, has been associated with better motor skills, reaction times, and REM/N3 sleep architecture (Prehn-Kristensen, 2011). Meta-analyses estimate that up to 70% of children with ADD experience sleep disorders, with consequences for cognitive functioning, school attendance, parental mental health, and family dynamics (Sciberras, 2010; O'Callaghan, Meltzer, & Chiang, 2010).

Behavioral sleep interventions—such as sleep hygiene programs—have shown positive outcomes. When insufficient, melatonin supplementation may be considered, with evidence supporting the effectiveness of combining behavioral and pharmacological approaches (Weiskop, 2005; Hannah & Malow, 2009).

Previous Dietary Supplements

Historical attempts at dietary supplementation for Down Syndrome include:

- **1940s (USA, Dr. Henry Turkel):** A mix of 48 vitamins, minerals, and hormones. No proven long-term benefits were reported (Turkel, 1975).
- **1960s (Germany, Dr. Habound):** A vitamin–hormone–enzyme mix with no confirmed effectiveness (Habound, 1955).
- **1980s (USA, Dr. Ruth Harrell):** A supplement of vitamins, minerals, and thyroid hormone showed preliminary IQ improvements in three Down Syndrome patients

(Harrell, 1981), but results were not replicated. Commercial versions like “Haps Caps” remain unsubstantiated by scientific studies.

- **1990s (USA, Dixie Lawrence Tafoya):** Building on Turkel’s formula, MSB Plus was tested on her adopted daughter with Down Syndrome. Despite anecdotal improvements, it lacked scientific support. The product evolved into MSB V7 (Nutri-Chem Labs) and later NuTriVene-D (International Nutrition), now marketed with modifications but still lacking independent clinical evidence.

For ASD and ADD populations, examples include:

- **Formula One Supplement (Singapore, Autism Recovery Center):** Marketed as detoxifying and calming, but without scientific validation.
- **Kirkman Laboratories (USA):** Offers a broad line of supplements categorized by function (antioxidant, digestive, immune, sleep, cognition/attention, etc.). Despite popularity, no peer-reviewed studies confirm their effectiveness. The company itself notes: *“These nutritional statements have not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”*

JUSTIFICATION

T-2 investigational nutritional formulation (research use only)

The T-2 investigational nutritional formulation, developed within the framework of this research, is a functional food formulated to support the nutritional management of individuals with Trisomy 21 (Down Syndrome), Autism Spectrum Disorders (ASD), and Attention Deficit Disorder (ADD/ADHD). Because of the distinctive characteristics of their immune systems, these individuals are particularly susceptible to intestinal dysbiosis, which disrupts metabolic pathways and exacerbates the biochemical imbalances inherent to these conditions. The T-2 investigational nutritional formulation provides naturally sourced nutrients in bioavailable forms that can be metabolized by dysbiotic intestines to help restore disrupted metabolic processes.

It is important to emphasize that the T-2 investigational nutritional formulation is not a complete food. Rather, it is designed as nutritional support specifically aimed at mitigating intestinal dysbiosis in individuals with the above-mentioned neurodevelopmental disorders. It is not intended as a treatment and does not seek to reduce intellectual disabilities or correct neurological deficits. For these reasons, it cannot be considered a drug or medication.

The T-2 formulation is formulated as a synergistic system, in which its specific ingredients interact to transform into bioactive forms that can be effectively absorbed by an organism compromised by dysbiosis. Its components function as precursors to one another, ensuring bioavailability in individuals with impaired metabolic function. When taken separately, these elements would not achieve the same therapeutic effect as when combined in the precise balance provided by the T-2 formulation.

Qualitative Description of Ingredients

The scientific name of this sugar is *6-O-α-D-glucopyranosyl-D-fructofuranose*, a disaccharide that occurs naturally in honey, sugar cane, beets, and certain fruits, though only in trace amounts. For this reason, it is commercially produced from food-grade sucrose through an enzymatic rearrangement that converts its glycosidic bond from 1,2-fructosyl to 1,6-fructosyl (Lina, Jonker, & Kozianowski, 2002).

While its properties are similar to sucrose, isomaltulose presents several important differences: it has approximately 50% of sucrose's sweetness, a lower melting point, and greater stability under acidic conditions, making it more resistant to microbial fermentation. Isomaltulose is absorbed more slowly than sucrose and is completely hydrolyzed in the small intestine, resulting in lower plasma glucose and insulin peaks. A 1985 study conducted at the University of Tsukuba showed that plasma glucose following isomaltulose ingestion rose gradually over 60 minutes to 110.9 mg/dl and then remained stable for two hours. By contrast, sucrose ingestion produced a rapid peak of 143.3 mg/dl within 30 minutes, followed by a sharp decline. These results were consistent even among individuals with diabetes, supporting isomaltulose as a suitable sweetener for this population (Kawai, Okuda, & Yamashita, 1985).

The complete hydrolysis of isomaltulose in the small intestine has been further demonstrated in urinary excretion studies, confirming that its breakdown products, glucose and fructose, are fully metabolized and absorbed (Menzies, 1974).

Isomaltulose has been extensively studied, with findings demonstrating that its consumption promotes fat oxidation both at rest and during exercise, thereby sparing glycogen reserves and reducing body fat mass without compromising systemic function (König, Theis, Kozianowski & Berg, 2011).

Further studies conducted at the University of Sydney reported that Isomaltulose has a glycemic index of 32, classified as *very low*, and provides sustained energy without abrupt glucose fluctuations. Its hydrolysis in the small intestine occurs four to five times more slowly than that of sucrose, prolonging energy release.

Because of these properties, Isomaltulose is widely used in sports nutrition, diabetic-friendly foods, and as a sucrose substitute. It does not ferment in the gut, thereby avoiding bacterial overgrowth—particularly of *Candida*—and enhances nutrient absorption when consumed in solution.

Whey Protein Concentrate

Proteins are essential nutrients, second only to water in abundance in the human body. They are the fundamental components of muscles, vital organs, blood cells, enzymes, and hormones (Herman, 2009). Structurally, proteins are chains of amino acids; there are 20 in total, 9 of which are essential and must be obtained from the diet.

Animal-based proteins typically provide all essential amino acids in balanced proportions, whereas plant-based proteins require careful combination to achieve adequacy. Protein quality is evaluated through indices such as Biological Value (BV) and the Protein Digestibility Corrected Amino Acid Score (PDCAAS), the latter having been the preferred method of assessment by both the FDA and WHO since 1993.

The primary role of protein is to support tissue repair and maintenance. When consumed in excess, protein can also serve as a precursor for energy production through the Krebs cycle (Meléndez-Hevia, Waddell & Cascante, 1996). Conversely, insufficient intake compromises tissue integrity.

In individuals with Down Syndrome, Autism Spectrum Disorders (ASD), or Attention Deficit Disorder (ADD), metabolic deficiencies—including allergies or sensitivities—may impair the hydrolysis of certain animal proteins (such as casein, albumin, and red meat proteins) as well as plant proteins like gluten (Shaw, 2008).

The whey protein incorporated into the T-2 investigational nutritional formulation provides all essential amino acids with high bioavailability and closely resembles the composition of human breast milk, making it highly efficient and particularly beneficial for individuals with intestinal dysbiosis. As a pure whey protein concentrate, it carries no allergenic risk.

Flaxseed

The use of flaxseed as a functional food dates back centuries, particularly in European bread-making traditions. Modern studies in the United States have confirmed its health benefits. Flaxseed varieties suitable for human consumption include brown and golden,

with an average composition of 41% fat, 20% protein, 28% dietary fiber, 7.7% moisture, and 3.4% ash (Morris, 2007).

Its protein profile is similar to soy but lacks sulfur double bonds that hinder digestion. Flaxseed oil is rich in polyunsaturated essential fatty acids, including alpha-linolenic acid (Omega-3), linoleic acid (Omega-6), and oleic acid (Omega-9). Omega-3 fatty acids are metabolized into EPA and DHA with the assistance of vitamins B3, B6, C, E, and A, along with minerals such as magnesium and zinc. EPA supports the production of anti-inflammatory prostaglandins, while DHA serves as a structural component of the brain, retina, and sperm, and is a precursor to neurotransmitters such as serotonin and acetylcholine. In contrast, Omega-6 metabolism leads to arachidonic acid and pro-inflammatory prostaglandins, which must be balanced by Omega-3 derivatives (Schmidt, 1997).

Western diets often present an Omega-6 to Omega-3 ratio of approximately 20:1, inadequate for optimal EPA and DHA synthesis, and potentially contributing to the prevalence of cardiovascular diseases. Beyond its fatty acids, flaxseed provides soluble and insoluble fiber, which promotes satiety, supports glucose regulation, improves bowel motility, and contributes to lipid reduction (Morris, 2007).

Flaxseed also contains phenolic compounds with antioxidant activity, including phenolic acids, flavonoids, and lignans, which have been studied for their role in cancer prevention (Jacobs & White, 1998; Sonnenberg & Müller, 1993; Kune et al., 1998). Another component, gamma-tocopherol, acts as an antioxidant, supports blood pressure regulation, and may help prevent cardiovascular disease, cancer, and Alzheimer's disease (Chandan, Savita & Sashwati, 2006; Daun & Przybylski, 2000; Morris et al., 2005).

In addition, flaxseed contains vitamins C, B-complex, carotenoids, vitamin E isoforms, and vitamin K, which is essential for blood clotting and bone mineralization (Berkner & Runge). Its mineral profile includes calcium, copper, magnesium, manganese, phosphorus, potassium, sodium, and zinc.

The flaxseed incorporated into the T-2 investigational nutritional formulation is milled golden flaxseed and is sourced from golden flaxseed harvested at peak maturity. Its specialized processing preserves fat micelles and maximizes antioxidant content, particularly lignans, providing 10 mg per gram, equivalent to approximately 30% of the daily antioxidant requirement. Milled golden flaxseed also offers a favorable Omega-6 to Omega-3 ratio (2:3), which supports neurotransmitter production and contributes to overall metabolic balance.

Milk Serum Mineral Complex

Calcium is a vital mineral, with 99% of the body's stores located in bones and teeth. It also plays an essential role in muscle contraction, blood clotting, and nerve transmission. Inadequate calcium intake during childhood and adolescence compromises bone development, as nearly half of total bone mass is formed during these life stages.

The calcium included in the T-2 investigational nutritional formulation is obtained through ultrafiltration of milk serum, a process that preserves its natural nutrient balance. Its composition closely resembles that of human bone. The FDA has recognized several health claims for milk-serum mineral complex, including its role in promoting bone health, supporting postmenopausal women, enhancing calcium absorption, and preventing osteoporosis (Ward, 2007).

Milk-serum mineral complex also demonstrates high solubility in acidic environments, ensuring superior bioavailability. This enhances cellular nutrient uptake and potentiates the absorption of other nutrients present in the T-2 formula.

Short-Chain Fructooligosaccharides (scFOS)

Short-chain fructooligosaccharides (scFOS) are composed of fructose molecules with a terminal glucose unit. They occur naturally in foods such as onions, asparagus, garlic, oats, rye, and artichokes, and are resistant to digestion in the upper gastrointestinal tract. Once they reach the colon, they are fermented by the microbiota and act as prebiotics.

Human studies have demonstrated that scFOS intake can increase bifidobacteria populations up to tenfold, while simultaneously suppressing pathogenic microorganisms such as Clostridia and Candida (Molis et al., 1996; Mitsuoka, Hidaka & Eida, 1987). Their prebiotic role has been formally recognized by both the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) (2001), highlighting their contribution to gut health through selective microbial modulation.

Additional benefits of scFOS include enhanced absorption of calcium, magnesium, and copper (Van Den Heuvel et al., 1999; Tahiri et al., 2001; Ducros et al., 2005).

The scFOS incorporated into the T-2 investigational nutritional formulation is derived from sucrose oligomers through enzymatic processes using non-GMO Aspergillus japonicus.

More than 200 studies have confirmed that scFOS promotes the growth of bifidobacteria and lactobacilli, restores intestinal balance, enhances nutrient absorption, and improves mineral utilization. It has also been shown to support cholesterol and triglyceride reduction, accelerate gastrointestinal transit, and contribute to overall health.

Lactoferrin

Lactoferrin is a globular glycoprotein (peptide) responsible for transporting and delivering iron to cells, thereby regulating the presence of free iron in the bloodstream and in biological secretions. It exists in two forms: holo-lactoferrin (iron-saturated) and apo-lactoferrin (iron-free) (Levay & Viljoen, 1995).

Beyond its role in iron binding and transport, lactoferrin can also associate with other metals such as copper, zinc, manganese, gallium, and vanadium (Davidson & Lönnerdal, 2007). Its affinity for iron is approximately 300 times greater than that of transferrin, another plasma glycoprotein that regulates iron levels in biological fluids. This affinity increases in acidic environments, explaining its interaction with transferrin during inflammatory processes, when tissue pH decreases due to the secretion of lactic acid and other metabolites.

Lactoferrin is a critical component of the immune system owing to its bactericidal, fungicidal, and antiviral properties. It is present on mucosal surfaces and constitutes a major component of several secretions, including bile, saliva, pancreatic fluid, and semen, making it a key element of epithelial defense barriers. Numerous studies have demonstrated its effectiveness in combating intestinal infections caused by *Escherichia coli*.

Its antimicrobial activity is linked to its ability to sequester iron, acting as a natural bacteriostatic agent. In addition, lactoferrin exerts direct microbicidal effects by damaging microbial membranes through cytoplasmosis, thereby impairing permeability and disrupting cellular respiration in pathogens.

Although its fungicidal properties are less extensively studied, lactoferrin is known to combat Candida infections by acting synergistically with leukocytes to inhibit fungal reproduction. Its antiviral activity is primarily achieved by blocking viral attachment to host cells, thereby preventing entry and replication. This effect has been documented against several viruses, including hepatitis, rotavirus, leukemia viruses, and herpes.

Humans receive their highest dose of lactoferrin through colostrum, the first maternal milk produced after childbirth. Human milk contains the greatest concentration of lactoferrin of all mammalian milks, with colostrum containing approximately three times more than mature milk (Nagasawa, Kiyosawa & Kuwahara, 1972). After human milk, cow's milk provides the next richest source.

The lactoferrin included in the T-2 investigational nutritional formulation is sourced from cow's milk. It is extracted from whey using a process that preserves its bioactivity. Documented properties include immune modulation, stimulation of intestinal cell growth,

antimicrobial action, iron transport, inhibition of intestinal dysbiosis, and suppression of fungal overgrowth in the oral and gastrointestinal tract (Ward, 2006).

Pyridoxine Hydrocloride (Vitamin B6)

Vitamin B6, also known as pyridoxine, is one of the eight vitamins in the B-complex group. Collectively, B vitamins are essential for converting carbohydrates into glucose—the body's primary energy source via the Krebs cycle—and are also involved in lipid and protein metabolism.

Specifically, Vitamin B6 plays a central role in brain development and function. It serves as the primary cofactor for the enzymes delta-5-desaturase and delta-6-desaturase, which are required for the breakdown of omega-6 and omega-3 fatty acids into critical neurotransmitters, including serotonin, epinephrine, norepinephrine, dopamine, melatonin, and gamma-aminobutyric acid (GABA). Together with Vitamin B12, it is also indispensable for the production of erythrocytes (red blood cells) and leukocytes (white blood cells), the latter being key components of the immune system.

Vitamin B6 is metabolized primarily in the liver, jejunum, and ileum, exerting much of its activity through the digestive system before being distributed to other tissues. Functionally, it acts as a coenzyme in the synthesis of hemoglobin, histamine, neurotransmitters, and in the metabolism of lipids, glucose, and amino acids.

The T-2 formulation includes pyridoxine hydrochloride (vitamin B6).

Systemic Functioning of the T-2 investigational nutritional formulation

The T-2 investigational nutritional formulation acts on multiple metabolic pathways and biochemical processes, not only through the properties of its individual components but also through their synergistic interactions, which enhance systemic balance across organs and tissues.

Isomaltulose, being enzymatically rather than bacterially hydrolyzed, is not a viable substrate for pathogenic microorganisms such as *Candida*. This property reduces parasitic colonization throughout the gastrointestinal tract and helps prevent nutrient malabsorption. In combination with lactoferrin, which provides antimicrobial protection at entry points such as the oral cavity, the investigational formulation establishes protective conditions from ingestion onward.

The strong glycosidic bond of Isomaltulose ensures sustained energy release, avoiding abrupt glucose spikes and subsequent hypoglycemic crashes. Unlike sucrose, which is rapidly fermented by bacteria, Isomaltulose supports a balanced supply of glucose and glycogen, stabilizes insulin secretion, and reduces anxiety, thereby contributing to improved learning, concentration, emotional regulation, and appetite control.

Its synergy with milled golden flaxseed flaxseed further promotes fat metabolism by encouraging the body to utilize fat reserves when carbohydrate absorption is slowed. Together, Isomaltulose, flaxseed, and scFOS promote the restoration of intestinal balance by stimulating the growth of beneficial bifidobacteria and lactobacilli, improving nutrient absorption, and optimizing osmolarity (170–295 mOsm/L).

Whey protein concentrate whey protein supports the repair of intestinal lesions caused by *Candida* and *Clostridia*. This is particularly relevant given that the small intestine produces up to 95% of the body's serotonin and 50% of its dopamine (Manocha et al., 2012; Gershon, 1999; Mirre, 2012). By restoring intestinal integrity, Whey protein concentrate enhances neurotransmitter production, with synergistic effects amplified by milk-serum mineral complex calcium and flaxseed-derived vitamin K, both of which are essential for bone health and blood coagulation.

Milled golden flaxseed flaxseed provides 1.09 g of dietary fiber per serving, which contributes to improved intestinal motility and helps maintain microbiota balance. Its fatty acid profile ensures the sequential metabolic conversion of oleic acid (omega-9), linoleic acid (omega-6), and alpha-linolenic acid (omega-3) into arachidonic acid, EPA, DHA, and prostaglandins, thereby supporting inflammatory regulation and cerebral blood flow.

Dosage and Administration

Participants will be instructed to take 23 g of the T-2 investigational nutritional formulation, twice daily, dissolved in 250 ml of liquid.

For the study population (Trisomy 21, ASD, and ADD/ADHD), it is recommended that the investigational formulation be prepared with Casein-free beverage, which is casein-free and enriched with probiotic fiber. However, it may also be consumed with other liquids—including cow's milk, plant-based beverages, coffee, tea, water, or natural juice—without altering its properties. The formulation can be taken hot, cold, or warm.

The first daily dose should be consumed upon waking, ideally 30–60 minutes before breakfast. The second dose should be taken in the afternoon, approximately two hours before sleep, regardless of dinner timing.

Ethnography

Studying quality of life (QoL) in families with a member diagnosed with Autism Spectrum Disorders (ASD), Attention Deficit Disorder (ADD/ADHD), or Trisomy 21 (Down Syndrome) is a central aspect of this research. Such analysis makes it possible to assess not only the progress of participants undergoing nutritional intervention but also the broader impact on family dynamics.

In recent years, QoL has gained increasing importance due to the limited opportunities for social, family, and leisure activities, particularly in households managing neurodevelopmental conditions. Evidence from the initial phases of this line of research has demonstrated that nutritional interventions can strengthen specific abilities in individuals with disabilities while also enhancing the overall well-being of their families.

These outcomes justify expanding the scope of investigation from ethnographic exploration to sociological analysis, providing valuable insights into the cognitive and behavioral evolution of participants, as well as the adaptive changes within their families over the course of one year.

Sleep Physiology

This study aims to evaluate a balanced dietary intervention formulated with Isomaltulose, whey protein concentrate, flaxseed, milk-serum mineral complex, scFOS, Luo Han Guo (as a natural sweetener), and lactoferrin. The impact of this intervention on children with Trisomy 21 (Down Syndrome), Autism Spectrum Disorders (ASD), and Attention Deficit Disorder (ADD/ADHD) will be objectively assessed through neurophysiological testing and blood chemistry analyses.

Given that sleep disorders are highly prevalent in these populations and that diet is known to influence symptom expression, this project also seeks to explore the interplay between diet, sleep, and behavior. By addressing this understudied area, the study aims to generate evidence that can inform more comprehensive management strategies for children with neurodevelopmental conditions.

Neuropsychological

Down Syndrome (DS) is the most common genetic cause of intellectual disability (ID), defined as an IQ below 70. Severity is typically classified as mild (IQ 55–70), moderate (IQ 40–54), severe (IQ 25–39), or profound (IQ < 25) (Vaillend et al., 2008). Approximately 30% of moderate to severe cases of intellectual disability are associated with DS (Stoll et al., 1990; Pulsifer, 1996).

Intellectual disability in DS impacts multiple domains, including cognitive development, language acquisition, motor skills, learning, and memory (Brown et al., 1990; 2003; Raz, 1995; Pulsifer, 1996; Hodapp et al., 1999; Chapman et al., 1998; Carlesimo et al., 1997; Clark & Wilson, 2003; Nadel, 2003; Pennington et al., 2003).

Although IQ testing has traditionally been the primary diagnostic tool, current recommendations emphasize the use of comprehensive assessments that incorporate daily living skills, cognitive processes, and emotional functioning, employing tools that are both culturally and linguistically adapted (Rondal, Perera & Spiker, 2011; Edgin et al., 2010).

HYPOTHESIS

Through a biomedical protocol involving dietary intervention and nutritional reinforcement with the T-2 investigational nutritional formulation, formulated for individuals with Down Syndrome (DS), Autism Spectrum Disorders (ASD), and Attention Deficit Disorder (ADD/ADHD), it is anticipated that intestinal dysbiosis, pathogenic burden (bacteria, fungi, yeasts), and oxidative stress will be reduced. This intervention is expected to promote a balanced nutritional state and support the production of key neurotransmitters, thereby contributing to improvements in quality of life, sleep regulation, concentration, cognition, self-regulation, and social interactions.Secondary Hypothesis

Oral administration of T-2 in mice will increase dendritic spines and synapses and improve performance in motor and cognitive tasks.

OBJECTIVES

- Improve compromised metabolic processes inherent to these conditions, as reflected in indicators such as dysbiosis, infections, food sensitivities, malnutrition, thyroid function, and neurotransmitter utilization.
- Strengthen the immune system, reducing allergies, sensitivities, otic and respiratory infections, and gastrointestinal pathogens.

- Reduce oxidative stress, leading to decreased anxiety, improved sleep quality, and enhanced Krebs cycle efficiency.
- Enhance gastrointestinal function and nutrient absorption, assessed through markers such as reflux, cholesterol and triglyceride levels, bowel regularity, stool formation, and improvements in body mass index (BMI).
- Improve quality of life, including stabilization of mood, increased social interactions, and reinforcement of cognitive processes such as attention, adaptability, and concentration.

Secondary Objectives

- Ethnography: Quantify the impact of the nutritional intervention on families of individuals with Trisomy 21, Autism Spectrum Disorders (ASD), and Attention Deficit Disorder (ADD/ADHD), with particular attention to changes in family dynamics across different phases of the study.
- Sleep Physiology: Investigate the relationship between diet and sleep in children with ADD and ASD, evaluating the effectiveness of dietary modification on sleep patterns and expression.

CONTRIBUTION OF THE PROJECT TO ADVANCING KNOWLEDGE IN ITS OWN FIELD AND AREA OF RESEARCH

This project represents the first biomedical protocol in Mexico to investigate neuro-nutrition—defined as dietary intervention combined with nutritional enrichment—in populations with Autism Spectrum Disorders (ASD) and Attention Deficit Disorder (ADD/ADHD), while also expanding upon the findings previously obtained in the first stage of this protocol with individuals with Trisomy 21 (Down Syndrome).

The primary aim is to provide both quantitative and qualitative evidence that disability in individuals with DS, ASD, and ADD extends beyond intellectual impairment into biological domains.

The project further seeks to enhance understanding of the metabolic and physiological characteristics of these populations, thereby informing the design of appropriate therapeutic management strategies.

Finally, it intends to demonstrate that ADD encompasses neurobiological, electrical, and biochemical processes, extending beyond the psychosocial dimensions traditionally emphasized.

METHODOLOGY

Operational Duration

The project will run for a period of 13 months.

Population Description

The estimated total population is 72 individuals between 2 and 35 years of age, divided into three groups based on their neurodevelopmental condition:

- Trisomy 21 (Down Syndrome, DS)
- Autism Spectrum Disorder (ASD)
- Attention Deficit Disorder (ADD)

Each group included between 24 and 27 participants, with more males than females. Ages ranged from 2–33 years for ASD, 2–30 years for DS, and 5–14 years for ADD. Mean ages and BMI values are shown in Table 1.

Participants	ASD (N = 27)	ADD (N = 25)	DS (N = 24)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	2-33 11.51±8.5	5-14 8.8±2.32	2-30 13.7±7.25
Body mass index (kg/m^2)	19.11±3.71	18.41±4.01	21.92±6.27
Men	24	20	14
Women	3	5	10

Table 1. Characteristics of each group

For participants with Autism Spectrum Disorders (ASD), recruitment was conducted at DOMUS Instituto de Autismo A.C., where diagnoses were confirmed using DSM-IV criteria (First et al., 2002). Symptom severity was assessed with the IDEA (Inventario del Espectro Autista-Autism Spectrum Inventory), which evaluates 12 developmental dimensions across four areas and is scored on a scale from 0 to 8. Scores between 70–96 indicate classic Kanner autism, 50–70 correspond to regressive autism, 40–50 reflect high-functioning

autism, and 30–45 indicate Asperger's syndrome (Martos & Morueco, 2007; García-López & Narbona, 2014b). The mean IDEA score for this sample was 63 ± 18 (Table 2).

Diagnostic (DSM-IV)	IDEA (Autism Spectrum Inventory)
ASD N = 27 Pervasive Developmental Disorders (PDD): Autistic Disorder – 74% Pervasive Developmental Disorders, Not Otherwise Specified (PDD-NOS) – 26%	Classic Kanner Autism (70–96) – 40%
	"Regressive Autism" (50–70) – 40%
	High-Functioning Autism (40–50) – 4%
	Asperger's Syndrome (30–45) – 16%

Table 2. Diagnosis and IDEA scores in ASD participants

For participants with Attention Deficit Disorder (ADD/ADHD), recruitment was conducted through schools specializing in this condition. Diagnosis was confirmed using the Conners' Parent Rating Scale – Revised (Long Form), which assesses behavioral and learning difficulties, psychosomatic complaints, impulsivity, hyperactivity, and anxiety (Conners, 1999). The Hyperactivity Index was applied, with scores greater than 16 for boys and 12 for girls aged 6–11 indicating clinically significant hyperactivity (Orjales Villar, 1998) (Table 3).

Check list DSM-IV	Hyperactivity Index Conners Revised Scale	
ADD N = 25	Girls (n=4) with suspected ADD (>12)	50 %
	Boys (n=21) with suspected ADD (>16)	33 %

Table 3. Conners' Scale results for ADD participants

For DS, participants came from "CTDUCA Atención Integral de Personas Down IAP" and "Integración Down IAP." All had karyotype-confirmed diagnoses, with one case of mosaicism.

Population Segregation

Each diagnostic group was further divided into three subgroups:

- Pilot Group: Received 23 g of T-2 twice daily and followed a strict dietary intervention protocol.
- Diet Group: Followed the dietary intervention protocol without supplementation.
- Control Group: Received neither supplementation nor dietary intervention.

The study population (ages 2–35) was further stratified into subgroups A–G (3–30 years) according to developmental stages *(Figure 6: Age distribution)*.

Subgroup	Lower limit	Upper limit
A	3	5
B	6	9
C	10	13
D	14	17
E	18	21
F	22	25
G	26	30

Figure 6. Population distribution by age groups

Clinical Evaluation

Clinical follow-ups included parental reports and physical examinations aimed at detecting allergies, food sensitivities, candidiasis, infections, gastrointestinal disturbances, chronic otitis media, and other recurrent conditions. A 25-item checklist was applied, covering digestive, respiratory, dermatological, and systemic indicators.

Laboratory Studies

Laboratory support included:

- Blood count: red/white series, platelets, sedimentation.
- Blood chemistry: glucose, urea, creatinine, uric acid, lipids, triglycerides.
- C-reactive protein: marker of inflammation.
- Serum homocysteine: marker of fat metabolism and oxidative stress.
- Plasma cortisol: indicator of adrenal activity.
- Thyroid panel: T4, free T4, T3, protein-bound iodine, TSH, total cholesterol.

- Stool analyses: coprological, coproparasitoscopic (3 samples).

Some specialized biochemical analyses were conducted at The Great Plains Laboratory (Kansas, USA), led by Dr. William Shaw, including:

- IgG Food Allergy Panel (93 foods).
- Comprehensive Organic Acid Test (65 metabolites).
- Urinary peptides from gluten and casein.

Anthropometrics

Weight, height, and BMI were measured monthly, compared against WHO growth standards (BMI-for-age) and Mexican NOM references (NOM-008-SSA2-1993; NOM-174-SSA1-1998).

Ethnography

The study adopted a longitudinal approach using the Sherlock model, combining quantitative and qualitative assessments of personal, functional, and social quality of life. Families underwent three structured interviews (baseline, mid-study, final), recorded in audio and video, with statistical and content analysis applied to results.

Neuropsychology

IDEA Inventory (ASD): Applied to establish severity, guide interventions, and assess treatment impact across 12 dimensions.

Down Syndrome: Cognitive assessments emphasized daily life skills, cognitive processes, and emotional capacities. Recommended tests were culturally and linguistically adapted (Rondal, Perera & Spiker, 2011; Edgin et al., 2010). Tools included:

- **Ages 3–6:** BATELLE developmental inventory (Newborg et al., 1998).
- **Ages 6–35:** NEUROPSI Attention and Memory (Ostrosky et al., 2003), Executive Function Battery (Flores et al., 2008, 2011), computerized neuropsychological tasks (Ostrosky et al., 2003), basic emotion recognition tasks, Barthel Index (Cid-Ruzafa & Damián-Moreno, 1997), and BRIEF executive function scale (Goia et al., 2000).

The neuropsychological evaluation was coordinated by Dr. Maura Jazmín Ramírez Flores, with support from trained psychology interns (4–6 students).

ADD: NEUROPSI Attention and Memory (6–85 years), EDAH (for ADHD), and Conners' Scales (long parent version, 80 items) were applied.

Polysomnography and P300

Polysomnographic assessments included recordings of EEG, EOG, EMG, heart rate, respiratory effort, airflow, oxygen saturation, limb movements, and sleep architecture. Data were analyzed according to international standards and compared with control groups using ANOVA.

Measured variables included total sleep time, wake time, sleep efficiency index, distribution of sleep stages, number of awakenings, apnea–hypopnea index, and periodic limb movement index. Additionally, P300 event-related potentials were incorporated as an independent clinical measure.

All studies were conducted at a specialized sleep clinic in Mexico City, and participants received dietary support throughout the study period.

Family Seminars

To support families and disseminate the objectives of the study, a series of educational seminars was organized. Topics addressed included candidiasis, allergies, biomedical protocols, psychological adaptation to disability, family dynamics, and nutritional interventions (e.g., gluten-free diets, food additives, and cooking classes).

The sessions were delivered by Dr. Javier Hernández Covarrubias, Psychologist María Angélica Núñez, and Biochemical Engineer Cecilia Fernández Aguirre.

BENEFITS AND RISKS FOR THE POPULATION

This is considered a minimal-risk study, as supplementation does not pose a health risk and does not involve pharmaceutical compounds.

Risks associated with sample collection, electrophysiological studies, and psychological testing will be managed by the professional staff of the Instituto Mexicano de Medicina Integral de Sueño. In all cases, follow-up will be provided by a multidisciplinary medical

team that includes specialists in Otorhinolaryngology, Psychology, Geriatrics, Dentistry, Pediatrics, Neurology, Psychiatry, Pulmonology, and Internal Medicine.

All participants will receive reports from their clinical assessments, evaluations, and electrophysiological studies, along with specialized counseling. Any conditions requiring medical care will be addressed and followed up by qualified medical professionals.

ASSIGNMENT OF RESPONSIBILITIES: RESEARCH TEAM AND ASSOCIATED ENTITIES

Professional Staff

- Dr. Reyes Haro Valencia – Principal Investigator (CONACYT CVU: 74747)
- Dr. Elizabeth Ibarra Coronado – Sleep Physiology Area Leader (CONACYT CVU: 288056)
- I.Q.I. Edilberto Sánchez – Technical Coordinator (CONACYT CVU: 392429)
- Eng. Miguel Hidalgo Olvera – Legal Representative and Administrative Coordinator (CONACYT CVU: 392684)
- Lic. Mónica Matilde Apodaca Aragón – Project Administrator (CONACYT CVU: 499625)
- I.B. Cecilia Fernández Aguirre – Biomedical Area Leader (CONACYT CVU: 353604)
- Dr. Octavio César García González – Neurobiology Area Leader (CONACYT CVU: 39694)
- Dr. Maura Jazmín Ramírez Flores – Neuropsychological Evaluation for Down Syndrome (CONACYT CVU: 174346)
- Lic. Juana Elvira Portillo Navarro – Neuropsychological Evaluation for ADD (CONACYT CVU: 510484)
- Arturo Ramírez Ramos – Ethnographic Area Leader (CONACYT CVU: 510634)

Institutional Site
Instituto Mexicano de Medicina Integral de Sueño

Associated Entities

- Mexico: Olarte y Akle Bacteriólogos, S.A. de C.V.
- United States: The Great Plains Laboratory, Inc.

- Integración Down, I.A.P.
- Domus Instituto de Autismo

PROGRESS CONTROL PLAN

The project is scheduled to last 13 months, from December 2021 to December 2022, and will be divided into two stages of approximately six months each.

Stage I: Design and Intellectual Property Protection

Duration: First Semester

Objectives:

- Confirm the physiological and metabolic similarities documented in the literature across the study populations and design a unified nutritional intervention scheme.
- Determine expected cerebral modifications resulting from the intervention by standardizing the protocol in neurotypical animal models.

Goals:

- Create a homogeneous information base documenting physiological and metabolic affinities among the target populations.
- Obtain audiovisual records of families highlighting quality of life aspects.
- Establish a specialized dataset on sleep habits of individuals with the studied neurodevelopmental disorders.
- Document neuropsychological and behavioral profiles within family, social, and school contexts.

Activities:

- **Bimonthly 1:** Confirm study populations (Down Syndrome, ASD, ADD).
- Assign dietary subgroups (Pilot, Diet, Control).
- Conduct studies of the T-2 investigational nutritional formulation
- Baseline studies including laboratory tests, clinical reviews, anthropometric measures, ethnographic interviews, neuropsychological tests, full polysomnographic records, and P300 potentials.

- Standardize animal model protocol.
- **Month 1:** Start nutritional intervention (diet implementation).
- **Month 4-6:** Report baseline results, documenting biomedical, dietary, familial, cognitive, behavioral, and sleep-related findings. Conduct behavioral tests in animal models.

Expected Results at the End of Stage I (6 months):

- Statistical report on physiological profiles, allergies, and food sensitivities.
- Statistical report on sleep disorders and comorbidities.
- Repository of family testimonies on quality of life.

Stage II: Scientific Conclusions

Duration: Second Semester

Document and analyze biomedical, neuropsychological, sleep-physiology, and ethnographic outcomes across groups.

Goals:

- Validate or reject the hypothesis of cognitive and behavioral improvements following dietary intervention, contrasting supplemented versus non-supplemented groups.
- Evaluate secondary hypotheses regarding ethnography and sleep physiology.

Activities:

- Conduct follow-up studies (laboratory tests, clinical reviews, anthropometric measures, ethnographic interviews, neuropsychological tests, polysomnography, P300 potentials).
- Report comparative analyses between baseline and follow-up results.
- Document biochemical, immunological, familial, social, and neuropsychological changes, as well as sleep physiology outcomes.

Expected Results and Deliverables at the End of Stage II:

- Technical reports on biochemical, anthropometric, and dietary allergy/sensitivity changes.

- Technical reports on changes in quality of life within families and social circles.
- Technical reports on sleep habit modifications.
- Technical reports on cognitive and behavioral changes.

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APPENDIX “A”: INFORMED CONSENT

ETHICAL CONSIDERATIONS AND/OR INFORMED CONSENT FORM

The principles of this informed consent process are grounded in the ethical foundations of the Declaration of Helsinki, the International Conference on Harmonization (ICH), Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements.

For this study, written informed consent will be obtained prior to the initiation of any procedure or evaluation by the investigator or an authorized delegate, as documented on the Delegation of Responsibilities Sheet.

Legal guardians of participants will be provided with both oral and written information regarding the nature and objectives of the study, as well as the procedures involved, before consent is obtained.

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Protocol Title: Neuro-Nutrition as Support for Physiological Performance and Cognitive Skills in Individuals with Trisomy 21, Autism Spectrum Disorders, and Attention Deficit Disorder.

CONACYT Project Number: _____

Research Team:

- Sleep Physiology Area Lead: Dr. Elizabeth Ibarra Coronado
- Biomedical Area Lead: I.B. Cecilia Fernández Aguirre
- Ethnographic Area Lead: Lic. Arturo Ramírez Ramos

The study will be conducted at the following locations:

- DOMUS Instituto de Autismo
- Integración Down I.A.P.
- Facultad de Psicología – Universidad Nacional Autónoma de México (UNAM)
- Instituto Mexicano de Medicina Integral de Sueño
- Participants' homes

Name of Participant: _____

You and your child are invited to participate in this research study. Before making a decision, you should carefully read and understand each section of this document. This process is known as informed consent. Please feel free to ask any questions at any time to clarify any doubts you may have.

If you agree for your child to take part in the study, you will be asked to sign this consent form.

JUSTIFICATION OF THE STUDY

Improvements in cognitive skills and overall quality of life have been documented in individuals with Down Syndrome (DS), Autism Spectrum Disorders (ASD), and Attention Deficit Disorders (ADD/ADHD) when dietary modifications eliminate gluten and casein and

incorporate nutritional supplements. The objective of this project is to extend these benefits to a broader population with the same conditions.

A maximum of 90 participants will be enrolled, each assigned to one of three groups (two dietary intervention groups and one control group) and monitored over the course of one year.

Progress will be evaluated through a combination of traditional laboratory tests (hematology, blood chemistry, cortisol, homocysteine, C-reactive protein, stool analyses), cognitive and behavioral assessments, polysomnography, event-related potentials (P300), anthropometric measurements, and ethnographic interviews. Additionally, specialized analyses will be performed in the United States, including Organic Acid Profile, IgG Food Allergy and Sensitivity Tests, and Gluten/Casein Peptide Assays.

OBJECTIVE OF THE STUDY

The purpose of this study is to investigate behavioral and cognitive changes in individuals with Autism Spectrum Disorders (ASD), Attention Deficit Disorder (ADD/ADHD), or Down Syndrome (DS) through dietary modification. The intervention specifically involves eliminating harmful dietary components while incorporating nutrients that are typically under-metabolized due to the underlying characteristics of these conditions.

BENEFITS OF THE STUDY

The study aims to expand scientific knowledge on the role of nutrition in cognitive functioning among individuals with these conditions, with the goal of supporting therapeutic management and contributing to the improvement of quality of life.

STUDY PROCEDURES

If you consent for your child to participate, the following procedures will be performed:

- Blood, urine, and stool tests.
- Medical examinations by specialists.
- Cognitive and behavioral assessments.
- Ethnographic interviews and questionnaires.
- Polysomnographic sleep studies to evaluate sleep physiology.

These procedures are non-invasive and will not cause pain.

RISKS ASSOCIATED WITH THE STUDY

No significant risks are expected from the procedures mentioned.

CLARIFICATIONS

- Participation is voluntary.
- All dietary guidelines, supplement intake, and dosage instructions must be followed precisely.
- Parents are required to attend support sessions throughout the research period.
- Declining participation will not result in any negative consequences.
- You may withdraw your child at any time without penalty by informing the research team.
- There will be no cost to you for the tests or procedures required for this study.
- No financial compensation will be provided for participation.
- Confidentiality of personal and medical information will be strictly maintained.
- If participation requirements (dietary compliance, supplement intake) are not met, the research team may ask you to withdraw without prejudice.
- Periodic progress reports will be provided to participating families during the study.

If you agree to participate, you formally commit to complying with the nutritional instructions provided, as these are essential for the accuracy and validity of the study results.

INFORMED CONSENT FORM

I, _____, have read and understood the information above, and my questions have been answered satisfactorily. I understand that study data may be used for scientific purposes. I consent to participate in this research study.

Parent/Guardian Signature: _____ **Date:** _____

Witness: _____ **Date:** _____

Witness: _____ **Date:** _____

Investigator's Statement:
I have explained to Mr./Ms. _____ the nature and purpose of the research, the risks and benefits of participation, and answered questions to the best of my ability. I certify that I am familiar with applicable ethical standards for research involving human participants.

Investigator's Signature: _____ **Date:** _____

CONSENT WITHDRAWAL FORM

Protocol Title: Neuro-Nutrition Phase II as Support for Physiological Performance and Cognitive Skills in Individuals with Trisomy 21, Autism Spectrum Disorders, and Attention Deficit Disorder.

Study Sites
The study will be conducted at the following locations:

- DOMUS Instituto de Autismo
- Facultad de Psicología – Universidad Nacional Autónoma de México (UNAM)
- Instituto Mexicano de Medicina Integral de Sueño
- Participants' homes

Participant's Name: _____

I hereby inform you of my voluntary decision to withdraw from this research protocol for the following reasons:

Upon this withdrawal, no further study information or documents will be provided, and I commit to returning any unused formulation to the principal investigator.

Parent/Guardian Signature: _____ **Date:** _____

Witness: _____ **Date:** _____

Witness: _____ **Date:** _____