Form 3.1

Informed Consent of Parents of a Minor for Participation in a Medical Trial



This form is written in the masculine form for convenience only and is intended for both sexes.

Your child is being invited to participate in a medical research study.

A medical study is an investigational process involving a treatment, procedure, or intervention that is not yet established as standard medical care in Israel, or whose safety and/or effectiveness have not yet been fully established. Therefore, there is uncertainty regarding its safety and effectiveness.

This form explains the study to which your child has been invited. We ask that you read the information carefully and discuss it with anyone you wish, including family members, friends, physicians, or other healthcare professionals who are not directly involved in the study.

Additional information regarding the study and answers to any questions may be obtained from the study physician or his representatives.

Before deciding whether your child will participate, it is important that you understand the potential risks and benefits of participation so that you can make an informed decision. This process is called **informed consent**. As parents, you are responsible for providing consent on behalf of your child.

Your child's participation in this study is entirely voluntary. You may choose not to allow your child to participate and not to sign this consent form. You may also withdraw your child from the study at any time without providing a reason.

Your decision not to participate, or to withdraw from the study, will not adversely affect your child's current or future medical care. Alternative treatment options available to your child will be explained to you.

If you decide to allow your child to participate, you will be asked to sign this consent form. You will receive a signed copy for your records, and the original will be retained at the medical institution.

Your child will receive an explanation of the study from the study physician or his representatives in your presence.

Informed Consent of Parents of a Minor for Participation in a Medical Trial



Minor's First Name:	**Minor's Last Name:**
ID Number:	
Address:	
Date of Birth:	

1. Information About the Study [0038-26-SZMC]

Study Title: The Effect of Folinic Acid Treatment on Behavioral Problems and Communication Deficits in Children with Autism: A Controlled Study

1.1 Investigator

Prof. Adi Aran has received approval to conduct this study from the Institutional Helsinki Committee and from the Director of Shaare Zedek Medical Center, in accordance with the Public Health Regulations (Medical Experiments in Human Subjects), 1980.

Study Objective

The purpose of this study is to determine whether treatment with folinic acid can improve behavioral difficulties and communication deficits in children with autism more effectively than placebo treatment.

1.2 Study Treatment

Children with autism often exhibit communication deficits, restricted and repetitive behaviors, and significant behavioral difficulties.

Currently, there are no approved pharmacological treatments for the core symptoms of autism (communication deficits and restricted/repetitive behaviors), and medications used for behavioral difficulties are often only partially effective and may be associated with significant side effects.



In this study we will evaluate **folinic acid**, a treatment commonly prescribed in Israel for children with autism.

The study treatment will be administered in addition to any behavioral, pharmacological, or dietary treatment the child is already receiving at study entry.

Folinic acid is a derivative of folate (vitamin B9), which plays an important role in brain function.

The medication is approved by the U.S. Food and Drug Administration (FDA) for treatment of children with cerebral folate deficiency. However, it is also widely used in children with autism who have not been formally diagnosed with such deficiency.

The rationale for treatment is the hypothesis that many children with autism have relatively low folate levels within the brain due to antibodies that interfere with folate transport.

Treatment in this study will be administered at a dose of:

2 mg/kg/day (maximum 50 mg/day), divided into two equal daily doses.

This dosage has been used in previous studies.

Some participants will receive a lower dose of:

1 mg/kg/day

which is still considered a relatively high dose and may provide similar benefits with fewer side effects. This hypothesis will be evaluated in the present study.

The study duration is approximately **four months**.

During the first two months, participants will receive either:

- Folinic acid, or
- Placebo

Approximately half of the participants will receive active treatment and half placebo.

Treatment assignment will be determined by randomization.



Neither the investigators nor the participants will know whether active treatment or placebo is being administered until the study is completed.

Folinic acid will be supplied as an oral solution.

Treatment initiation will be gradual. The dose will be increased over five days until the target dose is reached.

After completion of the first treatment period of **9 weeks**, all participants will receive folinic acid for an additional **8 weeks**.

Participants will be randomly assigned to receive one of two concentrations:

- 1 mg/kg/day
- 2 mg/kg/day

(Maximum 50 mg/day, divided into two equal daily doses.)

The assigned dose will be determined by randomization.

Neither participants nor study personnel will know which dose has been assigned until study completion.

1.3 Study Methods

This is a multicenter study conducted in Israel involving approximately **150 children aged 3–6 years** diagnosed with autism spectrum disorder and exhibiting behavioral difficulties of at least moderate severity.

Participants will first undergo screening to determine eligibility.

A child may participate only if all the following criteria are met:

a. Age 3–6 years.

b. Diagnosis of Autism Spectrum Disorder according to DSM-5 criteria, supported by ADOS-2 and CARS-2 assessments.



c. Presence of behavioral difficulties as assessed by the ABC-I questionnaire.

d. Overall symptom severity rated as moderate or greater by the Principal Investigator.

e. Body weight between 11.45 kg and 27 kg.

All participants will receive one of the following treatments during the first 9-week treatment period:

A. Folinic acid at a dose of **1 mg/kg twice daily** (maximum 25 mg per dose)

B. Placebo, which appears identical to the folinic acid preparation but contains no active ingredient.

Assignment to treatment will be determined by randomization.

Neither the investigators nor the participants will know whether active treatment or placebo is being administered until completion of the study.

Participants who complete the first 9-week treatment period and undergo all required assessments at the beginning and end of that period will continue to **Phase B** of the study.

During Phase B, all participants will receive folinic acid for an additional two months at one of two dosages:

- 1 mg/kg/day
- 2 mg/kg/day

(Maximum 50 mg/day)

Dose assignment during Phase B will also be determined by randomization.

Participants will undergo additional assessments at the end of this treatment period.



Study Visits

During the entire study period (17 weeks), participants will attend four assessment visits:

1. Screening Visit

Evaluation of eligibility for participation.

Duration:

- Approximately 1.5 hours for completion of questionnaires.
- Approximately 15 minutes with study personnel.

2. Baseline Visit

Conducted at the start of the randomized controlled phase.

Duration:

- Approximately 2 hours.
- Approximately 1.5 hours devoted to questionnaires.

3. Week 9 Visit

Conducted approximately two months after study initiation (end of the first treatment period).

Duration:

- Approximately 2 hours.
- Approximately 1.5 hours devoted to questionnaires.

4. End-of-Study Visit

Conducted approximately four months after study initiation (end of the second treatment period).

Duration:

- Approximately 2 hours.
- Approximately 1 hour devoted to questionnaires.

In addition, telephone follow-up assessments will take place:



- Between the second and third visits (midway through the first treatment period).
- Six months after completion of the study.

Questionnaire completion during these telephone contacts will require approximately 30 minutes.

The same parent should complete the questionnaires throughout the study whenever possible.

Because the study is funded through a donation, available funding is insufficient to compensate parents for the time required for participation.

Blood Samples

At the second and third study visits (baseline and Week 9), a blood sample of approximately **15 mL (about 3 teaspoons)** will be collected.

The following tests will be performed:

Safety Assessments

- Complete blood count (CBC)
- Liver enzyme testing

Biomarkers Potentially Associated With Treatment Response

- Homocysteine
- Folate
- Vitamin B12
- Oxidized/reduced glutathione ratio
- Folate receptor alpha autoantibodies
- Transcriptomic analyses
- Proteomic analyses



Stool Samples

At the second and third study visits (baseline and Week 9), a stool sample will be collected for microbiome analysis (assessment of intestinal bacterial composition).

Optional Maternal Blood Sample

In addition to samples obtained from the participant, the biological mother will be asked to provide an optional blood sample of approximately **5 mL (one teaspoon)** for testing of antibodies against the folate receptor in maternal blood.

This assessment is optional. Participation in the study is possible even if the mother declines this blood test.

The sample will only be collected if the mother signs the specific consent form included later in this document.

Storage and Confidentiality of Study Materials

Questionnaires and study visits are conducted solely for research purposes and are not part of routine clinical care.

All study information will be stored in coded form in a locked cabinet or in secure databases protected by two levels of password security.

Biological samples will be stored in coded form (without identifying information) in a dedicated research freezer.

The code linking participant identity to the study participant number will be maintained in a locked safe located in a secured room whenever not in active use.

1.4 Responsibilities of Parents of a Participating Minor

The participant may not take part in any other clinical trial involving investigational products during participation in this study.

If the participant requires any medical treatment during the study period, including:

- Prescription medications
- Over-the-counter treatments
- Alternative therapies
- Nutritional supplements



The parents should consult the study physician before initiation of such treatment.

Parents should also discuss with the study physician any decision to discontinue participation before study completion and any recommended follow-up procedures.

1.5 Known Risks and Expected Discomforts

The treatment used in this study has previously been evaluated in approximately 300 children with autism and has been administered outside research settings to many thousands of children.

In controlled clinical trials, adverse events were not reported more frequently than in placebo-treated participants.

However, side effects occasionally reported in routine clinical use include:

- Difficulty falling asleep
- Frequent nighttime awakenings
- Decreased appetite
- Increased appetite
- Hyperactivity
- Irritability

In addition, there may be risks that are currently unknown or cannot be predicted.

1.6 Potential Benefits

During the first phase of the study, approximately half of the participants will receive folinic acid treatment.

During the second phase, all participants will receive folinic acid at one of the study dosages.

The treatment may improve behavioral problems and core symptoms of autism.

However, there is no guarantee that any individual participant will benefit from participation.



1.7 Alternative Treatments

Current standard treatment for severe behavioral difficulties in individuals with Autism Spectrum Disorder typically includes:

- Behavioral interventions
- Antipsychotic medications
- Antiepileptic medications used for behavioral regulation

There are currently no approved pharmacological treatments for the core symptoms of autism, although behavioral interventions are available.

The investigator will explain the risks and benefits of available treatment alternatives for your child.

1.8 Circumstances Under Which Participation May Be Discontinued

Participation in the study may be discontinued under any of the following circumstances:

Safety Concerns

The Principal Investigator determines that continuation of treatment may place the participant or others at risk, for example:

- Improper use of the study medication
- Unexpected adverse effects

Regulatory Decision

Participation may be terminated by:

- The Ministry of Health
- The Institutional Helsinki Committee

Use of Prohibited Medications

Participation will be discontinued if the participant receives medications that interfere with folate metabolism.



Examples include:

Methotrexate

- Used for malignancies, autoimmune diseases, and psoriasis.

Trimethoprim and **Pyrimethamine**

- Antifolate medications used for bacterial and protozoal infections.

1.9 Cost of Participation

Participation in this study is provided **at no cost to participants or their families**.

2. Information About Biological Samples

The samples collected during this study will be used solely for the purposes of this research study.

The samples collected during the study include:

Safety Assessments

- Complete blood count (CBC)
- Liver enzyme testing

Biomarkers Potentially Associated with Treatment Response

- Homocysteine
- Folate
- Vitamin B12
- Oxidized/reduced glutathione ratio
- Antibodies against the cerebral folate receptor
- Transcriptomic analyses
- Proteomic analyses



Microbiome Assessment

- Stool sample for characterization of the intestinal microbiome (gut bacterial profile)

The samples will be stored in coded form (identified only by study numbers on sample tubes) in the Principal Investigator's research freezer.

Samples will be retained for **15 years after completion of the study**.

Samples may be transferred to research laboratories in Israel and/or abroad in coded form.

Any future use of data or biological samples collected during this study for purposes not described in the present protocol will require additional consent from participants.

Agreement or refusal regarding future use will not affect participation in the present study.

3. General Information

For any problem related to the study, you may contact the investigator at any time, 24 hours a day, at: **Telephone:** provided in the signed informed consent form.

In the event of any medical problem, injury, or other health-related event occurring during the study period, you must notify the study team immediately so that your child may receive appropriate medical care and so that you may receive information regarding your rights in this regard.

Medical Care for Adverse Events

In the event that side effects occur as a result of the study treatment, the participant will receive the optimal available medical treatment for the condition that develops, according to the participant's preferences and within the State of Israel.

Responsibility for coordinating such treatment rests with the Principal Investigator.

Communication With the Treating Physician

The investigator will inform your child's community physician about participation in the study for purposes of awareness and medical follow-up.

If clinically significant medical findings are identified during the study that were previously unknown, this information will also be communicated to the community physician.



New Information

Any new information that may affect your willingness to allow your child to participate or continue participation in the study will be communicated to you as soon as possible.

Questionnaires

As part of the study, you may be asked to complete questionnaires.

You may choose not to answer any specific question or questions within a questionnaire.

Sponsor Information

The sponsor of the study, **Dr. Adi Aran**, also serves as the Principal Investigator.

The sponsor will provide the study medication free of charge throughout the duration of the study.

Insurance Coverage

The sponsor and the medical institution have arranged insurance coverage in the event of injury resulting from participation in the study.

Intellectual Property

Results generated during this study may have scientific or commercial value and may contribute to:

- Patents
- Drug development
- Medical products
- Other healthcare technologies

Participants will have no ownership rights or financial claims relating to patents, products, medications, or technologies developed as a result of this study.



Clinical Trial Registration

A description of this clinical study appears on the Israeli Ministry of Health clinical trials website: **MyTrials**

The website will not contain information that could identify your child.

You may search for information regarding this study on the website at any time.

4. Privacy and Confidentiality of Information

4.1 Collection of Personal and Medical Information

The study in which you have been invited to enroll your child involves collection of personal and medical information.

This information will be maintained within the participant's medical record.

The healthcare team responsible for your child is obligated to maintain medical confidentiality.

You are entitled to access information contained in your child's medical record in accordance with the Patient Rights Law.

If you are aware that information in the medical record is inaccurate or incomplete, you should notify the healthcare team.

4.2 Information Maintained in the Medical Record

The medical record may include information such as:

- Results of medical examinations
- Administration of medications
- Use of devices or implants
- Experimental treatments or procedures
- Other relevant medical information



4.3 Transfer of Information to External Parties

By consenting to your child's participation in this study, you also consent to transfer of medical and personal information collected during the study to external parties responsible for data processing and analysis.

Information transferred outside the institution will be coded.

The transferred information will not contain:

- First name
- Last name
- National identification number
- Home address
- Any other direct governmental identifier

As a general principle, coded information is still considered potentially identifiable information.

The link between the study code and your child's identifying information will be securely maintained by the Principal Investigator in Israel.

In certain circumstances, decoding may be performed by the investigator when necessary.

4.4 Data Retention

The coded study information will be retained by the sponsor for the period required by law, namely at least **15 years after completion of the study**.

The following results, which have clear clinical significance, will be disclosed to you:

- Complete blood count (CBC)
- Liver enzyme tests

These tests are performed primarily for monitoring treatment safety.



The following research biomarker results will **not** routinely be disclosed:

- Homocysteine
- Folate
- Vitamin B12
- Oxidized/reduced glutathione ratio
- Antibodies against the cerebral folate receptor
- Transcriptomic analyses
- Proteomic analyses
- Stool microbiome analyses

These assessments are investigational in nature and are not currently considered clinically validated for routine medical decision-making.

4.5 Access to Medical Records

Access to study records for purposes of verification and auditing may be granted only to authorized individuals, including:

- Authorized representatives of the sponsor
- Members of the Institutional Helsinki Committee
- Institutional quality assurance personnel
- Inspectors of health authorities

Such access will occur only through the investigator and in accordance with applicable laws and regulations regarding confidentiality and privacy.

4.6 Publications

Your child's identifying information will not appear in any scientific publication, presentation, report, or other disclosure arising from this study.



5. Withdrawal From the Medical Study

You have the right to withdraw your child from the study at any stage by notifying the Principal Investigator or a designated study representative.

You are not required to explain the reason for withdrawal.

The investigator may continue to use only those coded samples and coded data that were collected prior to the date of withdrawal, as permitted by applicable law.

After withdrawal, no additional information will be collected regarding your child.

However, if medically significant information concerning your child or your family is discovered after withdrawal, the study team may contact you.

You have the right to decline receipt of such information.

6. Documentation of Consent

Under the Israeli Legal Capacity and Guardianship Law, 1962, both parents are responsible for providing consent on behalf of a minor participant.

Parent Declaration

By signing below, I declare that:

- I have read the contents of this document.
- The study has been explained to me.
- I understand the information provided.
- I voluntarily agree that my child may participate in this study.

Parent 1

Name (First and Last): _____ Signature: _____ Date: _____

Parent 2

Name (First and Last): _____ Signature: _____ Date: _____



Investigator Declaration

By signing below, I declare that:

- I have explained this study orally to the parents of the minor participant in accordance with the information contained in this consent form.
- In my opinion, the parents understood the information provided.
- The parents were given sufficient time to read and consider the consent form.
- The parents voluntarily agreed to enroll their child in the study.

In addition, I declare that:

- I explained the study to the minor participant in the presence of the parents.
- The minor participant expressed willingness to participate in the study.

Name (First and Last): _____ Signature: _____ Date: _____

Institution Stamp with License Number: _____

Independent Witness Declaration

I, the undersigned, was present throughout the explanation of the study.

I confirm that:

- The contents of this document were explained orally in my presence to the parents and their child.
- I was satisfied that they understood the explanation.
- I heard them provide oral agreement for participation in the study.

Name (First and Last): _____ Signature: _____ Date: _____



Note

The independent witness section is required only when:

- The parents are unable to read the informed consent document (for example, due to visual impairment or illiteracy), or
- Participation occurs under circumstances of medical urgency as defined by law.

The independent witness must be present throughout the explanation of the study.

Additional Optional Consent (1)

The study sponsor wishes to test antibodies against the folate receptor in the blood of the participant's biological mother.

This request is based on preliminary research suggesting a possible relationship between such antibodies and response to folinic acid treatment.

Refusal to participate in this optional component will **not** prevent participation in the main study.

Optional Maternal Blood Sample Consent

I agree to provide a blood sample (approximately 5 mL, one teaspoon) for testing of antibodies against the folate receptor in my blood.

Name (First and Last): _____ Signature: _____ Date: _____



Additional Optional Consent (2)

The study sponsor requests permission to make additional use of data and/or biological samples collected as part of this study for future research.

Such future use is **not part of the current study protocol**.

Refusal to provide this additional consent will **not** affect participation in the present study.

8. Biological Samples – Future Use Outside the Current Study

8.1 Collection of Samples

As described in Section 2 of this consent form, blood and stool samples will be collected during the study.

8.2 Storage of Samples

The samples will be stored in coded form in a secured research freezer for a period of **15 years**.

At the end of this period, the samples will be destroyed in accordance with applicable regulations.

8.3 Permission for Future Research Use

We request your permission to use any remaining samples after completion of the present study for future autism-related research.

Any future research use will require prior approval by an appropriately authorized Ethics Committee (Helsinki Committee) and will be conducted in accordance with applicable laws and regulations.

9. Use of Study Information for Future Research

9.1 Information Collected During This Study

As part of this study, information regarding your child will be collected through clinical evaluations and questionnaires as described in Section 1.3 of this consent form.

9.2 Storage of Information

The information collected during the study will be maintained in coded form without direct personal identifiers.



The coded information will be retained for **15 years after completion of the study** and will then be destroyed.

9.3 Permission for Future Research Use of Data

We request your permission to use the coded information collected during this study for future autism-related research.

Any such future research will require approval by an authorized Ethics Committee and will be conducted in accordance with applicable laws and regulations.

Authorization for Future Use of Samples and Data

By signing below, you agree that the coded data and/or biological samples collected during this study may be used in future autism research studies that receive all legally required approvals.

You may withdraw this authorization at any time by notifying the Principal Investigator or a designated study representative.

You are not required to provide a reason for withdrawal of this authorization.

Parent Declaration Regarding Future Research Use

By signing below, I declare that:

- I have read Sections 8 and 9 of this document.
- The meaning and implications of these sections have been explained to me.
- I understand the information provided.
- I agree to the future use of coded samples and coded data for autism research studies approved in accordance with applicable laws and regulations.

Parent 1

Name (First and Last): _____ Signature: _____ Date: _____

Parent 2

Name (First and Last): _____ Signature: _____ Date: _____



Investigator Declaration Regarding Future Use of Samples and Data

By signing below, I declare that:

- I explained the contents and implications of Sections 8 and 9 to the parents of the minor participant.
- In my opinion, the parents understood the information provided.
- They were given sufficient time to review the information.
- They voluntarily agreed to the future use of coded samples and coded data as described above.

Name (First and Last): _____ Signature: _____ Date: _____

Institution Stamp with License Number: _____

Independent Witness Declaration Regarding Future Use of Samples and Data

I, the undersigned, was present throughout the explanation of the study and the explanation of Sections 8 and 9 concerning future use of samples and data.

I confirm that:

- The contents of this document were explained orally in my presence to the parents and their child.
- I was satisfied that they understood the explanation.
- I heard them provide oral agreement to the future use of coded samples and coded data as described above.

Name (First and Last): _____ Signature: _____ Date: _____



Note

This section is required only when:

- The parents are unable to read the informed consent document (for example, because of visual impairment or illiteracy), or
- Participation occurs under circumstances of medical urgency as defined by law.

The independent witness must be present throughout the explanation process.