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TITLE: Early Treatment of Language Impairment in Young Children with Autism Spectrum Disorder with Leucovorin Calcium

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Phoenix Children's Hospital
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13. SUPPLEMENTARY NOTES

14. ABSTRACT Autism Spectrum Disorder (ASD) has an enormous impact on individuals, families and society, yet there is no FDA approved treatment that addresses underlying ASD pathophysiology and/or core deficits. However, a growing body of evidence indicates that leucovorin, a form of folate (vit B9) that bypasses physiological blocks in folate metabolism found in ASD, can significantly improve verbal communication as well as other symptoms associated with ASD. Our recent double blind placebo controlled (DBPC) trial published in **Molecular Psychiatry**, found that leucovorin significantly improved verbal communication in children with ASD with a medium-to-large effect size especially in the subset positive for the folate receptor autoantibody (FRAA+). However, the effect on social communication measures was mixed. We hypothesize that leucovorin could have a definitive positive impact on social communication if treatment is initiated beginning around 2-3 years of age, when neuroplasticity is greater and social communication is being established. We will also study the neuronal mechanisms underlying leucovorin's improvement in social communication / language. We propose a multisite 12-week DBPC trial with 12-week open-label extension of leucovorin in 2½-5 year old children with ASD who are FRAA+. Our primary outcome will be the Brief Observation of Social Communication Change, a sensitive, validated, direct assessment of change in social communication developed by C. Lord at the Center for Autism and the Developing Brain. We will also measure changes in neuronal activation and connectivity using non-invasive neuroimaging: magnetoencephalography and near infra-red spectroscopy. If leucovorin can be shown to improve the core deficit of social communication in ASD, the potential *positive impact* will be significant, laying the groundwork for a 'precision medicine' approach in which FRAA screening identifies children likely to benefit from leucovorin treatment.neuronal activation and connectivity using non-invasive neuroimaging: magnetoencephalography and near infra-red spectroscopy. If leucovorin can be shown to improve the core deficit of social

15. SUBJECT TERMS
Autism Spectrum Disorder; leucovorin; social communication; verbal communication.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION:

Autism Spectrum Disorder (ASD) has an enormous impact on individuals, families and society, yet there is no FDA approved treatment that addresses underlying ASD pathophysiology and/or core deficits. However, a growing body of evidence indicates that leucovorin, a form of folate (vit B9) that bypasses physiological blocks in folate metabolism found in ASD, can significantly improve verbal communication as well as other symptoms associated with ASD. Our recent double-blind placebo controlled (DBPC) trial published in **Molecular Psychiatry**, found that leucovorin significantly improved verbal communication in children with ASD with a medium-to-large effect size especially in the subset positive for the folate receptor autoantibody (FRAA+). However, the effect on social communication measures was mixed. We hypothesize that leucovorin could have a definitive positive impact on social communication if treatment is initiated beginning around 2-3 years of age, when neuroplasticity is greater and social communication is being established. We will also study the neuronal mechanisms underlying leucovorin's improvement in social communication / language. We propose a multisite 12-week DBPC trial with 12-week open-label extension of leucovorin in 2½-5-year-old children with ASD who are FRAA+. Our primary outcome will be the Brief Observation of Social Communication Change, a sensitive, validated, direct assessment of change in social communication developed by C. Lord at the Center for Autism and the Developing Brain. We will also measure changes in neuronal activation and connectivity using non-invasive neuroimaging: magnetoencephalography and near infra-red spectroscopy. If leucovorin can be shown to improve the core deficit of social communication in ASD, the potential *positive impact* will be significant, laying the groundwork for a 'precision medicine' approach in which FRAA screening identifies children likely to benefit from leucovorin treatment.

2. KEYWORDS:

Autism Spectrum Disorder; leucovorin; social communication; verbal communication.

3. ACCOMPLISHMENTS:

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: Major Task 1: Subtask 1:

1. Develop data sharing agreements (DSAs) between SUNY and SARRC -- On Going
2. Prepare REDCap Database System - On Going
3. Refine eligibility criteria, exclusion criteria, screening protocol – Complete
4. Request use of Investigational New Drug (IND) application filed for L-Leucovorin – Complete
5. Finalize consent form & human subjects protocol – Complete
6. Coordinate with Sites for IRB protocol submission – Reliance Agreement - Complete
7. Submit Protocol to IRB – Complete
8. Submit IND to FDA -- Complete

Specific Aim 1: Major Task 1: Subtask 2:

1. Acquire psychological testing materials and set up outcome procedures – On Going
2. Train psychometrician/testers to research level of reliability – On Going

Specific Aim 1: Major Task 2: Coordinate Clinic Trial:

1. Advertise and recruit potential participants – On Hold – Awaiting Transfer
2. Screen Participants– On Hold – Awaiting Transfer
3. Evaluate Psychometrician Rated Measures: – On Hold – Awaiting Transfer
4. Monitor fidelity of Psychometrician Measures– On Hold – Awaiting Transfer
5. Evaluate Clinical Rated Measures: – On Hold – Awaiting Transfer
6. Track and Score Behavioral Questionnaires– On Hold – Awaiting Transfer
7. Distribute Treatment– On Hold – Awaiting Transfer
8. Check Compliance– On Hold – Awaiting Transfer
9. Enter Data in Database– On Hold – Awaiting Transfer

Specific Aim 1: Major Task 3: Analyze Data and Complete Report

1. Check Research Files for Completeness -- On Hold – Awaiting Transfer
2. Check Database for Entry Errors-- On Hold – Awaiting Transfer
3. Assemble Final Recruitment Reports -- Pending: Requires Complete Clinical Trial Data Collection
4. Analyze Clinical Trial Data—Ongoing – Interim Analysis Directed by the DSMB
5. Write and Submit Study Findings-- Pending: Requires Complete Clinical Trial Data Collection

Specific Aim 2: Major Task 1: Prepare for Clinical Trial

1. Develop material transfer agreements (MTAs) between SUNY and SARRC - Ongoing
2. Prepare Laboratories for Sample Processing – On Hold – Awaiting Transfer

Specific Aim 2: Major Task 2: Biomarkers for Clinical Trials

1. Obtain and Process Samples for Biomarkers– On Hold – Awaiting Transfer
2. Process Samples for Biomarkers– On Hold – Awaiting Transfer
3. Enter Data in Database– On Hold – Awaiting Transfer

Specific Aim 2: Major Task 3: Analyze Data and Complete Report

1. Check Research Files for Completeness-- On Hold – Awaiting Transfer
2. Check Database for Entry Errors-- On Hold – Awaiting Transfer
3. Analyze Biomarker Trial Data-- Ongoing – Interim Analysis Directed by the DSMB
4. Write and Submit Study Findings-- Pending: Requires Completed Clinical Trial Data Collection

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

We were enrolling at a good pace until the lead organization (PCH) decided to discontinue employment of the PI and its involvement in the study. As such, the PI and Sponsor has transferred the IND to Rossignol Medical Center and the IRB to WCG. At this time, it is believed best to transfer the IND to SARRC, the new main site. This request has been submitted to the FDA.

During the reporting period, the PI/Sponsor has been working diligently to transfer all study materials from PCH to the new site. The parties are in the process of preparing and appropriately transferring the materials to the PI/Sponsor, including source documentation, study site level materials and biological samples. PCH has supplied the FDA correspondence and main IND documents, the protocols and some case report forms and subject facing material. A copy of the RedCap database has been supplied in Excel form so it can be recreated at the SUNY site. The creation of this new RedCap database is ongoing. The DSMB has recommended an interim analysis of the data and a new statistician has been engaged to perform the analysis.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

We are regularly involved in both training and professional development. When the trial is recruiting patients, we have regular training session as a group on the outcome measures usually several times per week, with those with knowledge of the outcome measure providing the training and those not proficient with the instruments undergoing professional development. This is occurring in several settings including in-person at each site and across sites through Zoom meetings.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

We have recently published an article pertaining to our work.

1. Frye, R.E. Rossignol, D.A., Scahill, L., McDougle, C.J., Huberman, H., Quadros, E.V. Treatment of Folate Metabolism Abnormalities in Autism Spectrum Disorder. Seminars in Pediatric Neurology, 2020 Oct;35:100835. doi: 10.1016/j.spen.2020.100835. Epub 2020 Jun 25. PMID: 32892962; PMCID: PMC7477301.
2. Rossignol DA, Frye RE. Cerebral Folate Deficiency, Folate Receptor Alpha Autoantibodies and Leucovorin (Folinic Acid) Treatment in Autism Spectrum Disorders: A Systematic Review and Meta-Analysis. J Pers Med. 2021 Nov 3;11(11):1141. doi: 10.3390/jpm11111141. Erratum in: J Pers Med. 2022 Apr 29;12(5): PMID: 34834493; PMCID: PMC8622150.
3. Frye RE, Lane A, Worner A, Werner BA, McCarty PJ, Scheck AC, Collins HL, Adelman SJ, Quadros EV, Rossignol DA. The Soluble Folate Receptor in Autism Spectrum Disorder: Relation to Autism Severity and Leucovorin Treatment. J Pers Med. 2022 Dec 8;12(12):2033. doi: 10.3390/jpm12122033. PMID: 36556254; PMCID: PMC9786140.
4. Almekkawi AK, AlJardali MW, Daadaa HM, Lane AL, Worner AR, Karim MA, Scheck AC, Frye RE. Folate Pathway Gene Single Nucleotide Polymorphisms and Neural Tube Defects: A Systematic Review and Meta-Analysis. J Pers Med. 2022 Sep 29;12(10):1609. doi: 10.3390/jpm12101609. PMID: 36294748; PMCID: PMC9605131.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

1. Interim Data Analysis
2. Start up new Phoenix site at SARRC.
3. Restart enrollment of participants in the trial at SUNY.
4. Monitor and verify study records.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, *successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

This project will provide a better understanding of the treatment and underlying biology associated with ASD

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

This project will provide a better understanding of the treatment and underlying biology associated with nervous system development and other neurodevelopmental disorders besides ASD.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

None

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Improving the lives of children with ASD will no doubt have a broad positive effect on society as the cost and resource currently required to care for such children is significant.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

1. We are moving the lead site to a new site in Phoenix due to PCH no longer wishing to employ the PI or be involved with the study
2. We are working with PCH to obtain all data and copies of files from the PCH site

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

1. PCH no longer wishing to employ the PI or be involved with the study, so the main site needed to be transferred
2. PCH has not provided full access to all study records / data / samples to the PI/Sponsor, so the PI/Sponsor is working with PCH to locate and transfer the information / samples.
3. Monitoring of the study has been delayed, so a new monitoring plan and timeline will be established as soon as the transfer is complete.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

The commercial IRB, WCG is an added expense.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

None

Significant changes in use or care of vertebrate animals

None

Significant changes in use of biohazards and/or select agents

None

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

1. Frye, R.E. Rossignol, D.A., Scahill, L., McDougle, C.J., Huberman, H., Quadros, E.V. Treatment of Folate Metabolism Abnormalities in Autism Spectrum Disorder. Seminars in Pediatric Neurology, 2020 Oct;35:100835. doi: 10.1016/j.spen.2020.100835. Epub 2020 Jun 25. PMID: 32892962; PMCID: PMC7477301.
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4. Almekkawi AK, AlJardali MW, Daadaa HM, Lane AL, Worner AR, Karim MA, Scheck AC, Frye RE. Folate Pathway Gene Single Nucleotide Polymorphisms and Neural Tube Defects: A Systematic Review and Meta-Analysis. J Pers Med. 2022 Sep 29;12(10):1609. doi: 10.3390/jpm12101609. PMID: 36294748; PMCID: PMC9605131.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

None

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

None

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

None

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  None

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

  None

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

  None

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Richard Frye, MD, PhD
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): 0000-0003-4442-2937
Nearest person month worked: 1.8
Contribution to Project: Dr. Frye is a Professor of Child Health at the University of Arizona College of Medicine and Chief of Neurodevelopmental Disorders and Director of the Autism and Fragile X Programs at the Barrow Neurological Institute at Phoenix Children's Hospital. Dr. Frye is a Child Neurologist with fellowship training in both Behavioral Neurology and Psychology. He has become a national leader in the medical evaluation and treatment of children with neurodevelopmental disorders, particularly children with autism spectrum disorder (ASD) and published multiple papers on abnormalities in folate metabolism and mitochondrial function as well as seizure treatment in children with ASD, including recent papers in Molecular Psychiatry. As Principal Investigator, Dr. Frye will oversee the project progress from startup to data analysis. Dr. Frye will be responsible for assuring the success, startup, and organization of the project, obtaining regulatory approval, facilitating and overseeing recruitment and retention of participants, monitoring of the ongoing trial, assuring timely and accurate follow-up with families, data analysis and interpretation, and writing publications and reports. He will act as the treating clinician in this study.

Name: Sallie McLees
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 1.2
Contribution to Project: Planned overall project, worked w team refining, developing and piloting baseline / outcome measures and procedures.

Name: Harris Huberman
Project role: Site Co-PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.5
Contribution to project: Planned overall project, worked w team refining, developing and piloting baseline / outcome measures and procedures.

Name: Edward Quadros
Project role: Site Co-PI
Researcher Identifier (e.g. ORCID ID):
Start date: 3/1/19
Nearest person month worked: 0.2
Contribution to project: Planned overall project and laboratory procedures, conducted initial lab assays for initial subjects

Name: Daniel Mishan
Project role: Co-Investigator
Start date: 2/14/20
Nearest person month worked: 1.2
Contribution to project: Participated in overall project planning, helped with regulatory and IRB aspects of project, conducted recruitment screening, baseline / outcome measures and procedures for enrolled subjects and laboratory processing of subject samples

Name: Cara Gomberg
Project role: Psych testing – grad student
Start date: 2/14/20
Nearest person month worked: 1.8
Contribution to project: Conducted outcome measures including VABS with enrolled subjects

Name: Maria Gabriela Mantilla-Garcia
Project role: Research Support Specialist
Start date: 1/2/22
Nearest person month worked: 1.2
Contribution to project: Participated in overall project planning, conducted recruitment screening, baseline / outcome measures and procedures for enrolled subjects and laboratory processing of subject samples

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

None

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.