AWARD NUMBER: Wi1XWH-16-1-0492

TITLE: Treating Gastrointestinal and Autism Symptoms in Adults with Autism Using Microbiota Transfer Therapy (MTT)

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RECIPIENT: Arizona State University, Tempe, AZ

REPORT DATE: December 2022

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
December 2022	Final	01Sep2016-31Aug2022

4. TITLE AND SUBTITLE

Treating Gastrointestinal and Autism Symptoms in Adults with Autism Using Microbiota Transfer Therapy (MTT)

5a. CONTRACT NUMBER
W81XWH-16-1-0492

5b. GRANT NUMBER
W81XWH-16-1-0492

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

James B. Adams

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

2022 Annual Report

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

US Army Medical Research and Development
Command Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release – distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Purpose: The purpose of this study is to determine the safety and efficacy of Microbiota Transfer Therapy for adults with autism and chronic gastrointestinal problems.
Scope: The scope of the project is a randomized, double-blind, placebo-controlled trial of MTT for 84 adults with autism. The trial also includes an extension, partial cross-over, and long-term follow-up (6, 12, and 18 months). It includes extensive evaluation of autism-related and gastrointestinal symptoms, evaluation of microbiome composition, and blood safety tests. It includes 84 neurotypical controls (half with GI symptoms, half without) for comparison of baseline microbiota (no treatment for the neurotypical group).
Major findings: none to report yet

15. SUBJECT TERMS

Autism; gastrointestinal problems; constipation; diarrhea; microbiota transplant; fecal transplant

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	10	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

The purpose of this research is to investigate the use of a new treatment, Microbiota Transfer Therapy (MTT) for the treatment of adults with both autism and chronic gastrointestinal problems. The scope of the research involves a Phase 2 clinical trial to determine the safety and efficacy of MTT, and to investigate how to optimize the therapy to maximize benefit while minimizing risk.

2. KEYWORDS:

Autism; gastrointestinal problems; constipation; diarrhea; microbiota transplant; fecal transplant

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The original specific aims of the project are:

1) Conduct a multi-site, randomized, double-blind, placebo-controlled trial of MTT in 84 adults with ASD who also have gastrointestinal problems. Evaluate the efficacy of MTT in adults with ASD, including gastrointestinal symptoms and autism-related symptoms.
2) Evaluate the effect of MTT on gastrointestinal microbiota and biomarkers of GI health.
3) Compare the GI microbiota of adults with ASD vs. neurotypical controls, matched for age and gender, half of whom have similar GI symptoms
4) Validate the GSRS for adults with autism.

The original milestones and target dates for year 1 and 2, and the actual completion dates or % of completion, are shown below:

Milestone	**Original Target Date**	**Actual Completion Date or % Completed**	**Actual Completion Date or % Completed**
		ASU (ASD/NT)	**PCH (ASD/NT)**
Subtask 1: Submit study plans to FDA and IRBs for approval	Sept 2016-May-2017	Sept 2016-Aug 2017	same
Submit modification of IND to FDA	Sept 2016	March 2017	same
Respond to FDA	Oct 2016	March-April 2017	same
Milestone Achieved: FDA approval of IND	Dec 2016	April 2016	same
Submit to IRB and USAMRMC ORP HRPO	Jan 2017	May 2017 (IRB) and Aug 2017 (HRPO)	Jan 17, 2018 (IRB) and April 27, 2018 (HRPO)
Review feedback from IRBs and USAMRMC ORP HRPO	Feb 2017	May 2017-Aug 2017	Jan 17, 2018 (IRB) and May 10, 2018 (HRPO)
Final submission to IRBs and USAMRMC ORP HRPO	March 2017	Aug 2017 (IRB); Oct 2017 to HRPO	Feb 14, 2018 (IRB) and May 11, 2018 (HRPO)

Milestone Achieved: IRB and HRPO approval	March 2017	Dec 2017	Feb 20, 2018 (IRB) and May 24, 2018 (HRPO)
		ASU	PCH
Subtask 2: Conduct clinical trial	June 2017 to Sept 2019		
Coordinate logistics at both study sites	9	Jan 2018	May 2018
Train study staff in approved protocol	9	Sept 2017	May 2018
Meeting with clinical trial monitor and research monitor	9	Sept 2017	May 2018
Milestone Achieved: Research staff trained	9	Sept 2017	May 2018
Advertise for participants	10-23	Jan 2018	Jan 2018
Review applications	11-24	Sept 2021	Sept 2021
Consent interested applicants	12-24	Sept 2021	Sept 2021
Collect baseline questionnaires, collect and review medical history	12-24	Sept 2021	Sept 2021
Validate ASD diagnosis with ADOS	12-24	Oct 2021	Oct 2021
Milestone: Complete recruitment	24	Oct 2021	Oct 2021
Begin Clinical Trial	13-25	Oct 2021	Oct 2021
Safety Monitoring Committee meets quarterly (once treatment starts)	13-36	Sept 2017 to July 2022	same
Milestone: Complete Part 1 of clinical trial (randomized, double-blind, placebo-controlled study)	27	100%	100%
Milestone: Complete Part 2 of clinical trial (extension of treatment)	30	100%	100%

What was accomplished under these goals?

1) **Major Activities:**
   Completed treatment of all ASD participants.
   Continuing long-term evaluations of participants.
   Continued recruiting TD participants.

2) **Specific Objectives:**
   - Treat current participants, and continue long-term monitoring of them

3) **Significant Results/Key Outcomes**
   ASU: Completed 29 ASD participants through the treatment period of the study (29 enrolled, 26 completed part 2)

   Consented – 31 typically-developing controls (23 completed, 8 planning to attend clinic)

   PCH: Completed 27 ASD participants through the treatment period of the study (27 enrolled, 25 completed part 2)

4) Other Achievements

- Continued meetings with our DSMB

5) Goals Not Yet Met

Our enrollment target of 84 ASD participants was reduced, due to financial costs and time-delays due to COVID and due to the drug manufacturer (Finch) being unable to supply all the drug so we had to change drug suppliers.

What opportunities for training and professional development has the project provided?
Nothing to Report

How were the results disseminated to communities of interest?
Nothing to Report yet. We will be submitting a detailed annual report to the FDA, and will then work on writing and publishing scientific articles on the study results.

What do you plan to do during the next reporting period to accomplish the goals?
Our DoD funding has ended, so this is our final report. However, we have received donations from hundreds of autism families that will allow us to continue the long-term follow-up of the study participants.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
The preliminary results of the analysis of the unblinded data suggest that the treatment was more effective than placebo at improving autism symptoms. The results appear to be strong enough to justify either a Phase 2 or Phase 3 study to get closer to drug approval.

What was the impact on other disciplines?
The preliminary results suggest that this treatment is effective in reducing ASD symptoms, so it may also be effective at treating other related conditions.

What was the impact on technology transfer?
We are sharing our results with Finch Therapeutics, who has licensed our patents on MTT for autism, and are hoping they will fund a follow-on Phase 2 or Phase 3 trial.

What was the impact on society beyond science and technology?
The preliminary results suggest that this treatment could be the first FDA-approved medication for improving the core symptoms of autism.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
There have been 3 major changes due to SARS-CoV-2/COVID-19.

Microbiota Testing for SARS-CoV-2: The FDA has added a requirement that the microbiome donor or their stool samples need to be tested for SARS-CoV-2. So, the previous batch (batch 3) we had set aside for ASU cohort 4 could not be used at the present time. We worked with one company, CosmosID, which developed a validated test for SARS-CoV-2 in stool, and the FDA approved the test for use in our study. CosmosID tested batch 3,4, and 5 and found them to be negative for SARS-CoV-2. The FDA authorized us to use Batch 3.

Microbiota Supply. Production of new microbiota capsules at the Un. of Minnesota was halted in March 2020 when the university closed all research facilities. They restarted production in July, but the halt caused some delay in restarting. New batches became available in Dec 2020.

Temporary changes to study protocol due to Coronavirus/COVID-19:

Due the disruption of travel and other activities due to the COVID-19 virus, we propose the following temporary changes be made to the study protocol on an "as-needed" basis as determined by the PI's and the study physician.

For participants who are travelling long-distance to participate in the study, the following changes will be made to the study protocol for the end of Part 1 and Part 2. These changes are being made to increase the safety of the participants. There will be no change to the baseline protocol at the start of Part 1.

1) Physical Exam: The study physician will conduct a telehealth visit with the participant instead of an in-person visit. If there is a health concern the study physician may also request an in-person evaluation, either by themselves or by the participant's PCP. In the latter case the study physician will either talk to the PCP or review a report by them after the in-person exam.

2) Blood draw: The blood draw can be done by a local laboratory (with a preference for LabCorp if available). The blood draw will include our standard safety tests (comprehensive metabolic panel and complete blood count with differential). In addition, if possible, the lab will also draw the extra blood samples for additional tests, and those samples will be shipped to ASU on dry ice.

3) CARS: The CARS evaluation can be done by Zoom or equivalent, so that the evaluator can speak with the participant and their evaluator and observe them, but if that is not possible then phone interviews will be allowed. As per our standard practice, the same CARS evaluator will be used for all CARS evaluations of a participant if at all possible.

4) Leiter: It is not possible to conduct the Leiter evaluation long-distance, so this evaluation will not be conducted at those visits.

5) There may be some delays in scheduling different evaluations and sample collections, so the schedule of events may change somewhat, but the treatment duration for each medication will remain unchanged.

These changes to the protocol were added to the consent form (approved by DoD in April 2020) and all participants in treatment were informed of the changes and reconsented with the new, approved form.

Actual or anticipated problems or delays and actions or plans to resolve them
The major problems were the COVID-19 issues discussed above.

Changes that had a significant impact on expenditures
The delays in enrolling participants due to COVID19 substantially increased our study costs, primarily for the study coordinator salaries.
Due to these expenses we reduced the total enrollment in the study.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
As described above, we made some changes in our study protocol due to COVID-19.

Significant changes in use or care of vertebrate animals.
Not applicable.

Significant changes in use of biohazards and/or select agents
No changes to report.

6. PRODUCTS:

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

  Journal publications.
  Nothing to report yet.

  Books or other non-periodical, one-time publications.
  Nothing to report yet.

  Other publications, conference papers, and presentations.
  Nothing to report yet.

- **Website(s) or other Internet site(s)**
  Nothing to report yet.

- **Technologies or techniques**
  Nothing to report yet.

- **Inventions, patent applications, and/or licenses**
  Nothing to report yet.

- **Other Products**
  Nothing to report yet.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	**James B. Adams**
Project Role:	**Principal Investigator**
Research Identifier:	
Nearest person month worked:	**3 months**
Contribution to Project:	**Primary author of IND and IRB documents; oversight of study**
Funding Support:	**ASU and personal time**

Name:	**Austin Cronen**
Project Role:	**Study Coordinator**
Research Identifier:	
Nearest person month worked:	**9 months**
Contribution to Project:	**Study coordination**
Funding Support:	**this DoD grant and/or gift funds**

Name:	**Pompa Bhatterjee**
Project Role:	**Study Coordinator**
Research Identifier:	
Nearest person month worked:	**3 months**
Contribution to Project:	**Study coordination**
Funding Support:	**this DoD grant and/or gift funds**

Name: Jasmine Kirby
Project Role: Study Coordinator
Research Identifier:
Nearest person month worked: 1 month
Contribution to Project: Study coordination
Funding Support: this DoD grant and/or gift funds

Name: Elena Pollard
Project Role: Autism Evaluator and Study Coordinator
Research Identifier:
Nearest person month worked: 1 month
Contribution to Project: Autism evaluations
Funding Support: this DoD grant and/or gift funds

Name: Julie Ingram
Project Role: Autism Evaluator and Study Coordinator
Research Identifier:
Nearest person month worked: 1 month
Contribution to Project: Autism evaluations
Funding Support: this DoD grant and/or gift funds

Name: Brielle Evans
Project Role: Study Coordinator
Research Identifier:
Nearest person month worked: 7 months
Contribution to Project: recruitment and enrollment of typically-developing adult controls
Funding Support: this DoD grant

Name: Rosa Krajmalnik-Brown
Project Role: co-PI
Research Identifier:
Nearest person month worked: 1 months
Contribution to Project: advice on study design; will supervise microbiome analysis next year
Funding Support: this DoD grant

Name: Richard Frye
Project Role: Co-Principal Investigator
Research Identifier: 0000-0003-4442-2937
Nearest person month worked: 1 month
Contribution to Project: Oversaw PCH site
Funding Support: this DoD grant

Name: Amanda Jensen
Project Role: Study Coordinator
Research Identifier:
Nearest person month worked: 8 months
Contribution to Project: Recruiting subjects, conducting study visits
Funding Support: this DoD grant

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
No major changes.

What other organizations were involved as partners?
Organization Name: University of Minnesota
Location of Organization: Minneapolis, MN
Partner's contribution to the project: development of Full Spectrum Microbiota, and supply of it for this project.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

Transition Plan:
We will complete the long-term follow-up with separate gift funds. We will submit the results to the FDA, and discuss with them the next steps required for eventual FDA approval. We will also publish the results of this study.