

**AWARD NUMBER:** W81XWH-16-1-0492

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

**PRINCIPAL INVESTIGATOR:** James B. Adams

**RECIPIENT:** Arizona State University, Tempe, AZ

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**TYPE OF REPORT:** Annual Report

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# REPORT DOCUMENTATION PAGE

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<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  ARIZONA STATE UNIVERSITY JANIE MORALES-CASTRO 660 S MILL AVE STE 312 TEMPE AZ 85281-3670				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>  2021 Annual Report	
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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> 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					
<b>15. SUBJECT TERMS</b> Autism; gastrointestinal problems; constipation; diarrhea; microbiota transplant; fecal transplant					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>  UU	<b>18. NUMBER OF PAGES</b>  11	<b>19a. NAME OF RESPONSIBLE PERSON</b> James B. Adams
<b>a. REPORT</b> U	<b>b. ABSTRACT</b> U	<b>c. THIS PAGE</b> U			<b>19b. TELEPHONE NUMBER (include area code)</b> 480 965 3316

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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)
<b>Subtask 1:</b> 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
<i>Milestone Achieved: FDA approval of IND</i>	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)

Milestone	Original Target Date	Actual Completion Date or % Completed	Actual Completion Date or % Completed
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)
<i>Milestone Achieved: IRB and HRPO approval</i>	March 2017	Dec 2017	Feb 20, 2018 (IRB) and May 24, 2018 (HRPO)
		ASU	PCH
<b>Subtask 2:</b> 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
<i>Milestone Achieved: Research staff trained</i>	9	Sept 2017	May 2018
Advertise for participants	10-23	Jan 2018	Jan 2018
Review applications	11-24	71% / 36%	62% / 26%
Consent interested applicants	12-24	71% / 36%	62% / 26%
Collect baseline questionnaires, collect and review medical history	12-24	71% / 7%	62% / 26%
Validate ASD diagnosis with ADOS	12-24	71% / n/a	62% / n/a
<i>Milestone: Complete recruitment</i>	24	71% / 7%	62% / 26%
Begin Clinical Trial	13-25	71% / 7%	52% / n/a
Safety Monitoring Committee meets quarterly (once treatment starts)	13-36	Sept 2017; Feb 2018; Sept 2018; Dec 2018; Feb 2019; May 2019; Oct 2019; April 2020; Sept 2020	same
<i>Milestone: Complete Part 1 of clinical trial (randomized, double-blind, placebo-controlled study)</i>	27	57% / n/a	29% / n/a
<i>Milestone: Complete Part 2 of clinical trial (extension of treatment)</i>	30	55% / n/a	29% / n/a

### What was accomplished under these goals?

#### 1) Major Activities:

- ASU: Completed 23 participants through the treatment period of the study
- PCH: Completed 12 participants through the treatment period of the study
- Update IND protocol due to COVID-19

## 2) Specific Objectives:

- Treat current participants, and continue long-term monitoring of them
- Update IND protocol due to COVID-19

## 3) Significant Results/Key Outcomes

### ASU Site:

#### ASD Participants

972 applications

- 30 consented and attended first clinic (Cohorts 1, 2, 3, and 4)
  - 7 disqualified or withdrawn
    - 1 disqualified due to anemia prior to treatment
    - 1 disqualified due to need for dental surgery prior to treatment
    - 2 disqualified because recent change in medication prior to treatment
    - 1 withdrawn due to dosing error by participant
    - 1 withdrawn due to AE (fainting)
    - 1 withdrew themselves prior to clinic 2 due to lack of interest
  - 23 participants finished Part 2, 9 of which are in follow up
- 7 are consented for Cohort 5, including 4 participants that were disqualified from a previous cohort.
- 2 consented but transferred to PCH to do the study due to family's preference
- 301 denied/Screen Failed/No longer interested/ No response
- 685 have not been processed yet

#### Neurotypical Participants:

694 applications received

- 182 processed
  - 21 processing
  - 15 consented
  - 35 waitlisted (female)
  - 102 Screen Fail
- 511 need to be processed (some have already been processed by PCH)
- 3 completed the study

### PCH Site:

#### ASD Participants:

- 26 consented into study
  - 12 completed treatment period
  - 10 participants in treatment
  - 4 waiting to start study
- 3 participants lost to follow up or withdrawn
- 49 denied/screen failed/no longer interested/no response

#### Neurotypical Participants:

- 760 applications received from ASU
  - 11 completed the study
  - 583 ineligible
  - 130 eligible but not age or gender matched
  - 42 no response

#### **4) Other Achievements**

- Continued meetings with our DSMB
- Updated protocol due to COVID-19

#### **5) Goals Not Yet Met**

ASU:

We are working to start Cohort 5, which currently has 7 participants in pre-screening stages. We also plan to finish recruiting neurotypical participants.

We will then conduct the microbiome measurements and analyze that data and all the other data.

Phoenix Children's Hospital (PCH): We need to finish recruiting for ASD and NT participants, and getting them started and through the study.

#### **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.

#### **What do you plan to do during the next reporting period to accomplish the goals?**

For the ASU site, we plan to start treatment of another 7 participants, and follow them. We will also recruit more TD participants. We will conduct the microbiome analyses once we have all the samples, and we will then analyze all the data.

For the PCH site, we have completed enrollment and at this time 4 participants are waiting to enter baseline.

Note that due to large extra costs and delays due to COVID-19, we anticipate only enrolling 55-60 ASD and 55-60 TD participants, instead of the 84 of each we originally planned. We believe that will be enough to achieve most of our goals of evaluating safety and efficacy of this novel treatment.

#### **4. IMPACT:**

##### **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to Report Yet

##### **What was the impact on other disciplines?**

Nothing to Report Yet

##### **What was the impact on technology transfer?**

Nothing to Report Yet

##### **What was the impact on society beyond science and technology?**

Nothing to Report Yet

## 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, and we are awaiting approval from the FDA for use of those batches

**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. However, we now have more microbiota capsules and have been using them to treat participants.

## **Changes that had a significant impact on expenditures**

The delays in enrolling participants due to COVID19 have substantially increased our study costs, primarily for the study coordinator salaries.

Due to these expenses we only anticipate having the funding to complete approximately 55-60 participants in this study, and then we will analyze the results.

## **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:** Devon Coleman  
**Project Role:** Study Coordinator  
**Research Identifier:**  
**Nearest person month worked:** 9 months  
**Contribution to Project:** Study coordination  
**Funding Support:** this DoD grant and gift funds

**Name:** Jasmine Kirby  
**Project Role:** Study Coordinator  
**Research Identifier:**  
**Nearest person month worked:** 3 months  
**Contribution to Project:** Study coordination  
**Funding Support:** 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 and assistance with study coordination  
**Funding Support:** this DoD grant

**Name:** Julie Ingram  
**Project Role:** Autism Evaluator and Study Coordinator  
**Research Identifier:**  
**Nearest person month worked:** 1 month  
**Contribution to Project:** Autism evaluations and assistance with study coordination  
**Funding Support:** this DoD grant

**Name:** Ian Altobelli  
**Project Role:** Biosample collection and storage  
**Research Identifier:**  
**Nearest person month worked:** 1 month  
**Contribution to Project:** collected samples from participants  
**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 months  
**Contribution to Project:** Assisted with IND and IRB documents  
**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

**Name:** Mohammed Karim  
**Project Role:** Study Coordinator  
**Research Identifier:**  
**Nearest person month worked:** 2 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:**

No Appendices