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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 85281

REPORT DATE: September 2018

TYPE OF REPORT: Annual Report

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

STANDARD FORM (SF) 298:

REPORT DOCUMENTATION PAGE

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1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
Sept 2018	Annual	Sept 1 2017 to Aug 31, 2018

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
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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)

ARIZONA STATE UNIVERSITY
JANIE MORALES-CASTRO
660 S MILL AVE STE 312
TEMPE AZ 85281-3670

8. PERFORMING ORGANIZATION REPORT NUMBER

2018 Annual Report

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

U.S. Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5014

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** USAMRMC
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U	UU	17	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

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:** Provide a brief list of keywords (limit to 20 words).

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

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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.

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	**PCH**
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	21%	
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	
Review applications	11-24	35%	
Consent interested applicants	12-24	25%	
Collect baseline questionnaires, collect and review medical history	12-24	21%	
Validate ASD diagnosis with ADOS	12-24	21%	
Milestone: Complete recruitment	24	21%	
Begin Clinical Trial	13-25	21%	
Safety Monitoring Committee meets quarterly (once treatment starts)	13-36	Sept 2017; Aug 2018	
Milestone: Complete Part 1 of clinical trial (randomized, double-blind, placebo-controlled study)	27	21%	
Milestone: Complete Part 2 of clinical trial (extension of treatment)	30	15%	

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.

1) **Major Activities:**
   - Responding to the HRPO questions about the protocol and receiving HRPO approval.
   - Training the staff
   - Advertising and recruiting participants
   - Beginning two groups of study participants

2) **Specific Objectives:**
   - Approval of study protocol by HRPO
   - Recruit study participants, and enroll them in the treatment study

3) **Significant Results/Key Outcomes**
   - Applications– we have received 164 applications. 64 were accepted, 30 denied, and 70 pending review/additional information
   - Informed consent interviews were conducted for 19 participants, and 14 have signed informed consent so far.
   - Enrolled Group 1, consisting of 5 ASD participants, and they successfully completed part 1 of the study, and are most of the way through part 2 (finishing Sept 22 2018)
   - Enrolled Group 2, consisting of 4 ASD participants, and they started part 1 on July 21, and will complete part 1 in mid-October
   - Have begun enrolling Group 3, which we hope will reach about 10-12 participants, and we expect to start in mid-November
   - Held second meeting of our Data Safety Monitoring Board (DSMB), who reviewed the safety data, adverse events, and methods to prevent adverse events

4) **Other Achievements**
   - We developed online versions of our PGIA and GSSQA questionnaires

5) **Goals Not Yet Met**
   - ASU: Enrollment is behind schedule since we started advertising later than expected, but it is progressing.
   - Phoenix Children's Hospital (PCH): Study progress has been stopped while we wait for approval from DoD of the transfer of funds to PCH (the original site was Un. of Arkansas, but the PI for that site move to PCH). The request was made in April 2018, and as of Sept 2018 we do not have approval. No concerns have been raised, so we hope to have approval very soon.

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.

The Study Coordinator for the ASU site (Devon Coleman) has completed training for The Association of Clinical Research Professionals (ACRP) Clinical Research Coordinator Certification, and will take the exam in late September 2017. This has helped to better prepare her for her role as study coordinator for this study.

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.

Nothing to Report yet.

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

For the ASU site, we plan to continue recruiting and enrolling subjects. We have just hired a 2nd study coordinator (starting Oct 2018) to help increase the rate of progress.

For the PCH site, we hope to receive funding from DoD so that this site can start recruiting.

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).

Nothing to Report Yet

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.

Nothing to Report Yet

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.*

Nothing to Report Yet

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.*

Nothing to Report Yet

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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.

There have not been any major changes in approach.

We have made two minor changes:

1) We modified the medication instructions to clarify them
2) On the day of fasting and bowel cleanse we now allow a light breakfast, to decrease risk of an adverse event

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.

There were several significant problems with the software app that ACES developed for us for collection of autism and GI data. So, we had to replace that with an online survey we created.

Our study coordinator has found that the study is more time-intensive than expected. So, we have hired a 2nd study coordinator to assist, and she will start in October 2018.

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 delay in starting recruiting means that we spent significantly less at both sites in year 2 than expected.

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

We had an unexpected Adverse Event involving temporary loss of consciousness, probably a fainting episode due to poor hydration, which occurred several days after the bowel cleanse. We have modified the medication instructions to emphasize the importance of fluid intake during and after the bowel cleanse.

We had one significant dosing deviation, in which the study participant took the vancomycin and full-spectrum microbiota in the wrong order. To prevent this in future we have changed our procedures to only provide 1 medication at a time.

These events were reported to our IRB and DSMB, and the changes described above were approved by them.

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:** 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).*

Nothing to Report Yet.

  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).*

Nothing to Report Yet.

  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.*

Nothing to Report Yet.

- **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.

Nothing to Report Yet.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to Report Yet.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. 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.

Nothing to Report Yet.

- **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:
  - *data or databases;*

- *biospecimen collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report.

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."

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 (2 months) and this DoD grant (3 weeks)**

Name:	**Devon Dale**
Project Role:	**Study Coordinator**
Research Identifier:	
Nearest person month worked:	**7 months**
Contribution to Project:	**Study coordination**
Funding Support:	**this DoD grant**

Name:	**Elena Pollard**
Project Role:	**Autism Evaluator and Study Coordinator**

Research Identifier:
Nearest person month worked: **2 months**
Contribution to Project: **Autism evaluations and assistance with study coordination**
Funding Support: **this DoD grant**

Name: **Richard Frye**
Project Role: **Co-Principal Investigator**
Research Identifier: **0000-0003-4442-2937**
Nearest person month worked: **1.2 month**
Contribution to Project: **Assisted with IND and IRB documents**
Funding Support: **this DoD grant**

Name: **Gurjot Kaur**
Project Role: **Study Coordinator**
Research Identifier:
Nearest person month worked: **4.0 months**
Contribution to Project: **Preparing for study coordination**
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?
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.

No major changes.

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.*

Organization Name: Crestovo/Finch
Location of Organization: Cambridge, MA
Partner's contribution to the project: development of Full Spectrum Microbiota, and supply of it for this project.

Organization Name: ACES Health, Inc.
Location of Organization: Atlanta, GA
Partner's contribution to the project: development of an "App" for smart phones for data entry by participants

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating 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.

No Appendices