AHRC
APPLIED HEALTH RESEARCH CENTRE

MONITORING VISIT REPORT

Protocol Title	A randomized placebo-controlled trial of arbaclofen vs. placebo in the treatment of children and adolescents with ASD		
Sponsor	Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital		
Protocol Name	ARBA Study		
Study Drug Name	Arbaclofen		
Site Name, Site #	Holland Bloorview Kids Rehabilitation Hospital		
Site Investigator Name	Dr. Evdokia Anagnostou		
Site Activation Date	March 15, 2019	**Site Address**	Holland Bloorview Kids Rehabilitation Hospital 150 Kilgour Road, Toronto ON, M4G 1R8
Date of Last Monitoring Visit	July 16-19, 2019		
Monitoring Visit Date	December 4th -5th and 12th 2019		
Location of Source Documents	☒ **Research Chart** ☐ **Medical Records**		
Type of Monitoring Visit	☒ **IMV** ☐ **Close-Out** ☐ **Other: _____**		

SUMMARY OF MONITORING VISIT:

Monitoring Activities: This monitoring visit was part two of first Interim Monitoring Visit (IMV) from July 16-19, 2019. IMV1-Part 2 was completed on December 4-5, and 12, 2019. This part of the visit was conducted per study monitoring plan to ensure that Site Data Verification (SDV) was completed. Pending items from previous monitoring visit were reviewed off-site prior to this visit to ensure that the site has addressed all the pending items. To conclude the monitoring visit, the pharmacy review was completed on December 12, 2019 (all pending items were addressed).

Participant charts were available for the audit visit as requested in the audit letter provided on November 19, 2019. The monitors utilized the up-to-date records present in in the online "medidata RAVE" Protocol Monitor module. The entered data were compared with the source documents in the research charts. Assessments and procedures performed were reviewed against the protocol schedule to ensure protocol compliance. Participant-signed informed consents were reviewed to: 1) verify the current REB approved version of the informed consent was utilized, 2) document that each participant has signed and dated the informed consent prior to the conduct of any research procedures and 3) ensure original informed consent documents were properly filed.

Overall Impression: The monitor completed reviewing the ICF and SDV for the following participants; **105-0055, 105-0440, 105-0583, 105-0697, 105-0868.** Participant ID **105-0697** was randomly selected for in depth review per study monitoring plan. The participants' files were well maintained and data entry was overall accurate. Minor issues were

identified and can be found in page 2. Site staff remain accommodating and a pleasure to work with. The organization and cooperation of the site staff was greatly appreciated by the monitors.

Exit Interview Comments: The monitor visit results were conveyed to Dr. Anagnostou and study staff. The monitor discussed the process of monitoring according to monitoring plan. All observations/deficiencies at the time of the IMV were discussed.

Subjects reviewed this visit: For details see pages 3, 7-12

URGENT ISSUES	**Were any issues that require urgent action observed at this visit?** ☒ Yes (*Describe*) A. The sponsor/ARHC coordinating center issued a NTF dated on August 8th, 2019 to remove Tanner staging from the physical exam at screening visit. This was not approved by REB. As result of this NTF, Tanner staging was not completed for few participants. The sponsor is advised to notify the REB regarding this incident, and to submit a memo/amend the protocol if necessary. The study team is also advised to submit a protocol deviation for all participants who didn't have their tanner staging completed at screening visit. B. Please ensure to provide adequate source documents to support each eligibility criterion (when applicable), medical history, and concomitant medications or provide further clarification or guidance on how these information will be collected. C. The site is required to provide a clear documentation to confirm that the capacity to consent was completed for each participant by a qualified clinician before continuing with consenting. The site is also reminded that the capacity assessment is ongoing process per study REB application. ☐ None to Report at this visit

Persons Present at Monitoring Visit	Name	Position/Title/Organization
	Abdalla Abdussamad	Research Education and Compliance Specialist
	Dr. Evdokia Anagnostou	Principle Investigator /Sponsor
	Lisa Genore	Study Coordinator

ENROLMENT STATUS	
Total Number of Subjects Screened	**36**
Total Number of Subjects Consented	**14**
Total Number of Pre-Randomization Failure	**1**
Total Number of Subjects Randomized	**13**
Total Number of Subjects Completed Study	**6**
Total Number of Subjects Ongoing	**7**
Total Number of Subjects Withdrawn from Study	**0**

Describe Recruitment Plan and Current Recruitment Activities: This was not addressed in this monitoring visit

Is recruitment rate adequate?

☐ Yes
☐ No (Please note reason(s) and site action plan.)

INFORMED CONSENT

Was Informed Consent reviewed at this visit?

☒ Yes
☐ No – Reason_____
☐ N/A – All ICFS previously reviewed.

Most Recently REB-Approved ICF Version and Version Date:

Subject Number	ICF Version Date	Correct ICF Version?
105-0055	ICF V7.0 29/04/2019 (27/8/2019)	☒ Yes ☐ No
105-0440	ICF V7.0 29/04/2019 (24/06/2019) ICF V6.0 21/02/2019 (08/04/2019) Assent Form V4.0 21/02/2019 (08/04/2019)	☒ Yes ☐ No
105-0583	ICF V7.0 29/04/2019 (17/07/2019) Assent Form V4.0 21/02/2019 (17/07/2019)	☒ Yes ☐ No
105-0697	ICF V7.0 29/04/2019 (18/06/2019) ICF V6.0 21/02/2019 (03/04/2019) Assent Form V.4 0 21/02/2019 (03/04/2019)	☒ Yes ☐ No
105-0868	ICF V7.0 29/04/2019 (12/09/2019) Assent Form V4.0 21/02/2019 (12/09/2019)	☒ Yes ☐ No

1	Was written Informed Consent obtained for every subject reviewed at this visit, per GCP and applicable site SOPs?	☒ Yes ☐ No	☐ Action Required

2	Was Consent obtained for all subjects prior to their participation in the study?	☒ Yes ☐ No	☐ Action Required
3	Was the Informed Consent process properly documented in source?	☐ Yes ☒ No	☒ Action Required Please address the identified deficiencies noted under the Urgent issues on page 2 of this report
4	Were there any deviations, deficiencies, discrepancies noted in the ICFs reviewed?	☐ Yes ☒ No	☐ Action Required
SITE STAFF/FACILITIES			
5	Did Principal Investigator meet with Monitor at this site visit?	☒ Yes ☐ No	☐ Action Required
6	Have there been any changes to the site staff?	☐ Yes ☐ No ☒ NA	☐ Action Required
7	Have there been any changes to the site facilities or equipment?	☐ Yes ☐ No ☒ NA	☐ Action Required
8	Are study equipment calibration/maintenance logs available and up to date?	☐ Yes ☐ No ☒ N/A	☐ Action Required
9	Is the Principal Investigator maintaining study oversight?	☒ Yes ☐ No	☐ Action Required
10	Are trial-related activities being conducted as indicated on the site signature page and responsibility log?	☒ Yes ☐ No	☐ Action Required
11	Has site been audited or contacted by a regulatory authority since the last visit?	☐ Yes ☒ No	☐ Action Required
12	Were all significant issues discussed with appropriate site study staff?	☒ Yes ☐ No	☐ Action Required
13	Does the site require any additional resources?	☐ Yes ☒ No	☐ Action Required
INVESTIGATOR SITE FILE / MONITORING ACTIVITIES			
14	Was the Monitoring Log signed?	☐ Yes ☒ No	☒ Action Required Please ensure to have a monitoring log available for the monitor to sign off for each IMV.
15	Was the Screening Log found to be complete?	☐ Yes ☐ No ☒ NA	☐ Action Required
16	Were the other applicable study enrollment logs complete?	☐ Yes ☐ No	☐ Action Required

		☒ N/A	
17	Was Investigator Site File (ISF) found to be up-to-date at this visit?	☐ Yes ☐ No ☒ NA	☐ Action Required
RESEARCH ETHICS BOARD			
18	Is study REB approval current?	☒ Yes ☐ No	**Date of REB Approval:** January 17, 2019 **Date of Next Annual Re-Approval:** November 18, 2020 ☐ Action Required
19	Has current version of the protocol been approved by the REB?	☒ Yes ☐ No	**Version Number:** 6.0 **Date:** January 29, 2019 ☐ Action Required
20	Has current ICF been approved by the REB?	☒ Yes ☐ No	**Version Number:** 7.0 **Date:** April 29, 2019 **Version Number:** Assent Form V4.0 **Date:** February 21, 2019 ☐ Action Required
21	Has all other study information provided to subject been approved by the REB?	☒ Yes ☐ No	☐ Action Required
22	Have all advertisements been approved by the REB?	☒ Yes ☐ No	☐ Action Required
23	Has the current Investigator's Brochure/Product Monograph been approved/acknowledged by the REB?	☐ Yes ☐ No ☒ NA (This was not reviewed at this visit)	**Version Number:** **Date:** ☐ Action Required
SAFETY			
24	Were any SAEs observed at this site visit?	☐ Yes ☒ No ☐ NA	☐ Action Required
25	Has site recorded all AEs/SAEs per protocol / study requirements?	☐ Yes ☐ No ☒ NA	☐ Action Required
26	Have all SAEs been assessed and signed off by the PI or Co-I?	☐ Yes ☐ No ☒ NA	☐ Action Required
27	Have all safety reports been submitted to the REB?	☐ Yes ☐ No ☒ NA	☐ Action Required
28	Have all safety reports been acknowledged by the REB (per REB	☐ Yes ☐ No	☐ Action Required

	Guidelines)?	☒ NA	
29	Have all site SAEs been submitted to the REB?	☐ Yes ☐ No ☒ NA	☐ Action Required
30	Have all site SAEs been reported to Sponsor?	☐ Yes ☐ No ☒ NA	☐ Action Required
31	Has any new information been detected, documented or submitted to the appropriate safety group/sponsor for previously reported AEs/SAEs?	☐ Yes ☐ No ☒ NA	☐ Action Required
COMPLIANCE			
32	Were PI and site staff overall compliant with procedures required by the current REB approved protocol?	☒ Yes ☐ No	☒ Action Required Please address the identified deficiencies noted under the Urgent issues on page 2 of this report.
33	Have all Protocol Deviations been reported to the REB per guidelines?	☐ Yes ☒ No	☒ Action Required Please address the identified deficiencies noted under the Urgent issues on page 2 of this report.
34	Has the site recorded all protocol deviations appropriately in source	☐ Yes ☒ No	☒ Action Required Please address the identified deficiencies noted under the Urgent issues on page 2 of this report.
STUDY INVESTIGATIONAL PRODUCT			
35	Was Study Drug accountability found to be complete and accurate at this site visit? (Includes Records of Receipt, dispensing, malfunctions)	☒ Yes ☐ No ☐ N/C ☐ N/A	☐ Action Required
36	Was used and/or expired Study Device destroyed on site per site SOPs or returned to Sponsor?	☐ Yes ☐ No ☐ N/C ☒ N/A	☐ Action Required
37	Does site have adequate supplies of study device with valid expiry date?	☒ Yes ☐ No ☐ N/C	☐ Action Required
38	Was study drug storage found to be acceptable?	☒ Yes ☐ No ☐ N/C	☐ Action Required
39	Was IP administered per protocol and accurately	☐ Yes ☐ No	☐ Action Required

	recorded in documentation?	☐ N/C ☒ N/A	
STUDY SUPPLIES/VENDORS			
40	Does site have adequate study supplies (other than study device)?	☒ Yes ☐ No ☐ N/C	☐ Action Required
SOURCE DOCUMENT VERIFICATION (SDV) AND SOURCE DOCUMENT REVIEW (SDR)			
41	Did all randomized subjects meet the Eligibility Requirements?	☒ Yes ☐ No	☒ Action Required The site is advised to include source documents to support eligibility when applicable
42	Were all subject visits entered into the CRFs within required timeline per the Monitoring Plan and/or study requirements?	☒ Yes ☐ No	☐ Action Required
43	Was source document/CRF review completed as required per the current Monitoring Plan?	☒ Yes ☐ No	☐ Action Required
44	Has the location of site source changed since the last visit?	☐ Yes ☐ No ☒ NA	☐ Action Required
45	Source is adequate, complete, legible, method of correction is compliant, attributable, contemporaneous?	☒ Yes ☐ No	☒ Action Required In few occasions the CRF (source documents) did not meet the GDP (Good Documentation Practice) e.g. errors were not corrected properly. The study staff is advised to follow GDP.
46	In general, were the eCRFs completed correctly?	☒ Yes ☐ No	☐ Action Required

eCRFS AND SUBJECTS CHART REVIEW

Subject Identifier	Items reviewed	Comments	Action Required
105-0055	**Screening:** ICF/Assent, Eligibility, Medical History, Other relevant medical history, Psychiatric co-morbidities, Clinical Lab Tests, Pregnancy Test, CGI-S (Global), Vital Signs, Weight and Height, Physical Exam., Tanner Stage. **Randomization:** Randomization **Baseline (Week 0):** Vineland-3-ABC and Domain Score Summary,	**ICF:** although the site has confirmed that the capacity to consent protocol assessment was completed, the monitor was not able to verify this. There was no documentation of this process to review/verify. **Eligibility, medical history, concomitant medication documentation:** source documents	**ICF:** The site is required to provide a clear documentation to confirm that the capacity to consent was completed for each participant by a qualified clinician before continuing with consenting. The site is also reminded that the capacity assessment is ongoing process per study REB application.

	Vineland-3-Subbdomain Score Summary, C-SSRS, CGI-S (Global), ESS-CHAD, Vital Signs. **Week 2:** CGI-I (Global), ESS-CHAD, Vital Signs, C-SSRS. **Week 4:** C-SSRS, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs. **Week 6:** CGI-I (Global), ESS-CHAD, Vital Signs, C-SSRS. **Week 8:** C-SSRS, Clinical Lab Tests, Pregnancy Test, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs. **Study Drug:** Study Drug Dispensing, Study Drug Administration. **Adverse Events/SAEs:** Adverse Events, Serious Adverse Event Report.	were incomplete or insufficient to support all of eligibility criteria and medical history. **Physical exam:** tanner staging: This evaluation was not completed at screening visit as per REB approved protocol.	**Eligibility, medical history, concomitant medication documentation**: Please ensure that there is a source document to support each inclusion and exclusion criterion, when applicable**.** **Physical exam:** Please submit a protocol deviation. Moving forward, please ensure to complete all component of physical exam required for each study visit.
100-0440	**Screening:** ICF/Assent, Eligibility, Medical History, Other relevant medical history, Psychiatric co-morbidities, Clinical Lab Tests, Pregnancy Test, CGI-S (Global), Vital Signs, Weight and Height, Physical Exam., Tanner Stage. **Randomization**: Randomization **Baseline (Week 0):** Vineland-3-ABC and Domain Score Summary, Vineland-3-Subbdomain Score Summary, C-SSRS, CGI-S (Global), ESS-CHAD, Vital Signs. **Week 2:** CGI-I (Global), ESS-CHAD, Vital Signs, C-SSRS. **Week 4:** C-SSRS, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs.	**ICF:** although the site has confirmed that the capacity to consent protocol assessment was completed, the monitor was not able to verify this. There was no documentation of this process to review/verify. **Eligibility, medical history, concomitant medication documentation:** source documents were incomplete or insufficient to support all of eligibility criteria and medical history.	**ICF:** The site is required to provide a clear documentation to confirm that the capacity to consent was completed for each participant by a qualified clinician before continuing with consenting. The site is also reminded that the capacity assessment is ongoing process per study REB application. **Eligibility documentation**: Please ensure that there is a source document to support each inclusion and exclusion criterion, when applicable**.**

	Week 6: CGI-I (Global), ESS-CHAD, Vital Signs, C-SSRS. **Week 8:** C-SSRS, Clinical Lab Tests, Pregnancy Test, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs. **Week 12:** C-SSRS, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs. **Week 16:** Vineland-3-ABC and Domain Score Summary, Vineland-3-Subbdomain Score Summary, C-SSRS, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs, Height/Weight, Clinical Lab Tests. **Week 18:** CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs, C-SSRS. **Study Drug**: Study Drug Dispensing, Study Drug Administration. **Adverse Events/SAEs:** Adverse Events, Serious Adverse Event Report.		
105-0583	**Screening:** ICF/Assent, Eligibility, Medical History, Other relevant medical history, Psychiatric co-morbidities, Clinical Lab Tests, Pregnancy Test, CGI-S (Global), Vital Signs, Weight and Height, Physical Exam., Tanner Stage. **Randomization:** Randomization **Baseline (Week 0):** Vineland-3-ABC and Domain Score Summary, Vineland-3-Subbdomain Score Summary, C-SSRS, CGI-S (Global), ESS-CHAD, Vital Signs. **Week 2:** CGI-I (Global), ESS-CHAD,	**ICF:** although the site has confirmed that the capacity to consent protocol assessment was completed, the monitor was not able to verify this. There was no documentation of this process to review/verify. **Eligibility, medical history, concomitant medication documentation:** source documents were incomplete or insufficient to support all of eligibility criteria. For example; exclusion criterion 3 (H/O epilepsy), and medical history.	**ICF:** The site is required to provide a clear documentation to confirm that the capacity to consent was completed for each participant by a qualified clinician before continuing with consenting. The site is also reminded that the capacity assessment is ongoing process per study REB application. **Eligibility, medical history, concomitant medication documentation**: Please ensure that there is a source document to support each inclusion and exclusion criterion, and medical

	Vital Signs, C-SSRS. **Week 4:** C-SSRS, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs. **Week 6:** CGI-I (Global), ESS-CHAD, Vital Signs, C-SSRS. **Week 8:** C-SSRS, Clinical Lab Tests, Pregnancy Test, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs. **Week 12:** C-SSRS, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs. **Week 16:** Vineland-3-ABC and Domain Score Summary, Vineland-3-Subbdomain Score Summary, C-SSRS, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs, Height/Weight, Clinical Lab Tests. **Study Drug:** Study Drug Dispensing, Study Drug Administration. **Adverse Events/SAEs:** Adverse Events, Serious Adverse Event Report.		history, when applicable**.**
105-0697 (In depth review)	**Screening:** ICF/Assent, Eligibility, Medical History, Other relevant medical history, Psychiatric co-morbidities, Clinical Lab Tests, Exploratory Lab Tests, Pregnancy Test, CGI-S (Global), ADOS-2, Vital Signs, Weight and Height, Physical Exam., Tanner Stage. **Randomization:** Randomization **Baseline (Week 0):** Vineland-3-ABC and Domain Score Summary, Vineland-3-Subbdomain Score Summary, C-SSRS, CGI-S (Global), ESS-CHAD, ABC (Questions 1-58), SEQ (Questions 1-105), DCDQ,	**ICF:** although the site has confirmed that the capacity to consent protocol assessment was completed, the monitor was not able to verify this. There was no documentation of this process to review/verify. **Eligibility, medical history, concomitant medication documentation:** source documents were incomplete or insufficient to support all of eligibility criteria, concomitant medication (e.g. non-pharmacologic behavioral intervention), and medical history.	**ICF:** The site is required to provide a clear documentation to confirm that the capacity to consent was completed for each participant by a qualified clinician before continuing with consenting. The site is also reminded that the capacity assessment is ongoing process per study REB application. **Eligibility, medical history, concomitant medication documentation**: Please ensure that there is a source document to support each inclusion and

	PedsQL, AIM, Vital Signs. **Week 2:** CGI-I (Global), ESS-CHAD, Vital Signs, C-SSRS. **Week 4:** C-SSRS, CGI-S (Global), CGI-I (Global), ESS-CHAD, ABC (Questions 1-58), PedsQL, AIM, SEQ (Questions 1-105), Vital Signs. **Week 6:** CGI-I (Global), ESS-CHAD, Vital Signs, C-SSRS. **Week 8:** C-SSRS, Clinical Lab Tests, Pregnancy Test, CGI-S (Global), CGI-I (Global), ESS-CHAD, ABC (Questions 1-58), PedsQL, AIM, SEQ (Questions 1-105), Vital Signs. **Week 12:** SEQ (Questions 1-105), ABC (Questions 31-58), PedsQL, AIM. **Week 16:** ABC (Questions 1-58), Exploratory Lab Tests, SEQ (Questions 1-105), DCDQ, PedsQL, AIM **Study Drug:** Study Drug Dispensing, Study Drug Administration. **Adverse Events/SAEs:** Adverse Events, Serious Adverse Event Report. **Concomitant Intervention and Medications:** Concomitant (Non-Pharmacologic Interventions), Concomitant Medications.	**ADOS-2:** the ADOS-2 available for review was an uncertified photocopy of the original source document (ADOS-2 was completed on 24/10/2017). **CGI-I (Global) and CGI-S (Global):** in multiple occasions the rate of improvement has been changed (CGI-I: week 4, week 8, week 12, week 16), sometimes after few weeks of assessment (CGI-S: week 12, CGI-I: week 12, week 16). **C-SSRS:** although C-SSRS CRFs were completed per study protocol, however, the monitor was not able to verify if this assessment was completed by a qualified research staff (no initials or staff signature)	exclusion criterion, when applicable**.** **ADOS-2:** Please ensure to provide the original document, if this deemed not possible the study team is advised to include a certified copy of the original ADOS-2 (per PM this was addressed in MOP V.3). **CGI-I (Global) and CGI-S (Global):** Although the study team has confirmed that the correction was part of quality control process and staff training. The study team is advised to add NTF to explain these changes and to provide more details. **C-SSRS:** please ensure that C-SSRS is completed by a qualified staff who was delegated to perform this task. The form should be signed, dated and completed.
105-0868	**Screening:** ICF/Assent, Eligibility, Medical History, Other relevant medical history, Psychiatric co-morbidities, Clinical Lab Tests, Pregnancy Test, CGI-S (Global), Vital Signs, Weight and Height, Physical Exam., Tanner Stage.	**ICF:** although the site has confirmed that the capacity to consent protocol assessment was completed, the monitor was not able to verify this. There was no documentation of this process to review/verify.	**ICF:** The site is required to provide a clear documentation to confirm that the capacity to consent was completed for each participant by a qualified clinician before continuing with consenting. The site is also reminded that the capacity

	Randomization: Randomization **Baseline (Week 0):** Vineland-3-ABC and Domain Score Summary, Vineland-3-Subbdomain Score Summary, C-SSRS, CGI-S (Global), ESS-CHAD, Vital Signs. **Week 2:** CGI-I (Global), ESS-CHAD, Vital Signs, C-SSRS. **Week 4:** C-SSRS, CGI-S (Global), CGI-I (Global), ESS-CHAD, Vital Signs. **Study Drug:** Study Drug Dispensing, Study Drug Administration. **Adverse Events/SAEs:** Adverse Events, Serious Adverse Event Report.	**Eligibility documentation:** source documents were incomplete or insufficient to support all of eligibility criteria and medical history. **Physical exam**: Tanner staging wasn't done at screening (Tanner staging was completed at baseline visit instead).	assessment is ongoing process per study REB application. **Eligibility, medical history, concomitant medication documentation**: Please ensure that there is a source document to support each inclusion and exclusion criterion, when applicable. **Physical exam:** Please submit a protocol deviation. Moving forward, please ensure to complete all component of physical exam required for each study visit.

REPORT ATTACHMENTS
Follow Up Letter dated 21/01/2020
Site Action Items Log

REQUIRED SIGNATURES				
	Print Name	**Title/Position**	**Signature**	**Date**
Monitor **Author of Monitoring Report**	**Abdalla Abdussamad**	**Research Compliance & Education Specialist**	Abdalla Abdussamad Digitally signed by Abdalla Abdussamad Date: 2020.02.14 09:13:07 -05'00'	
Research Manager, **Signature Confirms Report has been Reviewed**	**Karima Noordin**	**Project Manager**	Karima Noordin I have reviewed this document 2020.02.14 08:51:01 -05'00'	
Sponsor **Signature acknowledges Report has been Received**	**Evdokia Anagnostou**	**Sponsor-Study Principle Investigator**		