Supplement to the preprint "Most clinical trials involving American children that violated FDAAA legal reporting requirements had not published outcomes in the scientific literature"

CORRESPONDENCE WITH CLINICAL TRIAL SPONSORS

(1) Responses received from sponsors

Advocate Health Care NCT02975999

In response to your enquiry, please note that the investigator has updated the clinicaltrials.gov record as withdrawn because the larger study was not able to be conducted. He does not intend to post any results and unfortunately the study findings were not able to be published due to the small size.

> *Note: We believe that Advocate Health Care is legally obliged to make public the results of the pilot phase of this trial during which 10 patients were apparently recruited. We contacted the PRS support team of ClinicalTrials.gov for clarification; PRS support declined to comment on the trial's legal status.*

Carillion Clinic NCT03364218

Due to COVID-19, the recruitment period has been extended for this study through July 2023. We are compliant with federal regulations.

> *Note: We removed this trial from our list. However, Carillion Clinic has yet to update its registry record to reflect the new estimated primary completion date.*

Conneticut Eye Consultants NCT02544529

The study associated with this NCT number did not receive funding through the NIH and was never initiated. In the meantime, [PI name redacted] became ill and has passed away.

> *Note: We retained this trial on our list as its registry entry continues to state that the trial's status is "unknown". Trials not funded by NIH can also be subject to FDAAA reporting requirements.*

Emalex Biosciences NCT02102698

The results of clinical trial NCT02102698 were published in the journal *Movement Disorders* and the article is available on PubMed.
Psyadon Pharmaceuticals was the sponsor of clinical trial NCT02102698. Our company, Emalex Biosciences, acquired Psyadon and its assets in August 2018 with the expectation that Psyadon fulfilled the reporting requirements for all of its clinical trials.
We appreciate the opportunity to respond to your inquiry and will investigate to determine how Emalex can submit results for a Psyadon-sponsored study on clinicaltrials.gov.

> *Note: This sponsor was contacted by accident; our first search had located the journal article.*

Fresh Tracks Therapeutics NCT03785587

Fresh Tracks is no longer the sponsor or owner of that cited study.

> *Note: Sponsorship for NCT03785587 was reassigned to Botanix Pharmaceuticals on 19 December 2022, and results were submitted to the registry on 22 December 2022.*

Gillette Children's Specialty Healthcare NCT03107546

As a result of your inquiry we uncovered a mistake in the data reported on the CT.gov site relative to this trial. While the last participant was enrolled at the end of 2020, the primary outcome includes 24-month post-operative follow-up which will be completed at the end of 2022. The results of the study will then be published by the end of 2023 as required. We have reached out to CT.gov requesting that the dates be corrected and expect that update to be complete shortly.

> *Note: The registry has since been updated. The trial's primary completion date is now listed as 31 December 2022. Therefore, this trial is not yet legally required to make its results public and was removed from our list.*

Hennepin County Medical Center, Minneapolis NCT03762317

The study Principal Investigator has submitted the results information to Clinicaltrials.gov and per the website instructions, the updated study record will post to the public site after they have completed their review. The study record was not linked with our institutional account in the Clinicaltrials.gov system so we were not aware the record needed updating. Thank you for bringing this to our attention.

> *Note: Results were submitted to the registry on 21 November 2022.*

Mayne Pharma International NCT03992261

We feel there has been an error here around this study as we thought the study results had been made public. The person responsible for the trial is no longer with the company and so we are looking into this now. If we do however find we are required to list, we will do so in a timely manner.

> *Note: results were submitted to the registry on 20 December 2022.*

Mednax Center for Research, Education, Quality and Safety NCT01708707 & NCT02534077

The studies you cited are completed, as indicated on clincialtrials.gov. However, results were not published due to inadequate sample size (n=29) in the case of NCT01708707, and the fact that the U.S. Food and Drug Administration approved Omegaven in 2018 based on data collected from Boston Children's Hospital, Texas Children's Hospital and UCLA Medical Center and a low sample size (n=14) in the case of NCT02534077.

Nemours Children's Health NCT01619488

Thank you for reaching out to Nemours Children's Health. We appreciate your work on this topic. I have reached out to the folks involved in clinical trial NCT01619488 and would like to share with you the results that have been published. Please see below for the links to the abstracts and attached for

the full text since they are behind a paywall.

Journal: Surgery for Obesity and Related Diseases
27th Annual Meeting of the ASBMS Plenary Session
Vol 6. Issue 3, Supplement, S18, May 1, 2010
Short-term changes in metabolic syndrome risk factors following gastric band surgery: https://doi.org/10.1016/j.soard.2010.03.054

Journal: Surgery for Obesity and Related Diseases
27th Annual Meeting of the ASBMS Plenary Session
Vol. 6., Issue 3, Supplement, S62-63, May 1, 2010
Cardiovascular and muscular fitness in morbidly obese adolescents after gastric band surgery: https://doi.org/10.1016/j.soard.2010.03.149

Journal: Surgery for Obesity and Related Diseases
Vol. 13., Issue 10, Supplement, S77, October 1, 2017
Visit Adherence in the First Two Years Following Adolescent Bariatric Surgery: https://doi.org/10.1016/j.soard.2017.09.168

Journal: Surgery for Obesity and Related Diseases
Vol. 13., Issue 1, P58-64, January 1, 2017
Psychological contributors to noncompletion of an adolescent preoperative bariatric surgery program:
https://doi.org/10.1016/j.soard.2016.08.020

> *Note: None of the publications listed above report any of the primary or secondary outcomes listed for clinical trial NCT01619488 on ClinicalTrials.gov.*

Ovid Therapeutics NCT04106557

Thank you for reaching out about our NEPTUNE trial in Angelman syndrome (Identifier NCT04106557). Transparent and timely communications about our trial results are important to Ovid Therapeutics and the patient and physician communities who we seek to serve.
In June 2022, we were notified that the NEPTUNE trial results were in review with ClinicalTrials.gov, following our uploading of them. However, the data was apparently never posted, nor did we receive notice of any issues. So, we were unaware of the fact that they were not available, until you kindly brought it our attention. Since receiving your note, we re-submitted the results to the ClinicalTrials.gov system again on November 15th. The portal has accepted the submission, which can be found here:
https://clinicaltrials.gov/ct2/show/results/NCT04106557?term=NCT04106557&draw=2&rank=1
Importantly, ClinicalTrials.gov is only one forum through which we have shared the findings of our failed trial. While the findings were heartbreaking to us and the families who participated in our research, we feel it is important that the clinical research and patient community were fully informed. Therefore, in addition to the ClinicalTrials.gov posting, our efforts to transparently communicate the findings have included the following activities:
December 2020 – Announced the drug failure within 24 hours of becoming aware of the results:
https://www.globenewswire.com/news-release/2020/12/01/2137913/0/en/Ovid-Therapeutics-Announces-Phase-3-NEPTUNE-Clinical-Trial-of-OV101-for-the-Treatment-of-Angelman-Syndrome-Did-Not-Meet-Primary-Endpoint.html
November 2021 - Presented the data at the leading industry research conference in Angelman syndrome called, the Angelman Syndrome Biomarker and Outcome Measure (ABOM). This

presentation was by the request of physicians so that they could better understand the data from our trial and what could be inferred from the results.
May 2022 – In a desire to help the Angelman syndrome community further utilize our data from NEPTUNE to advance research and understanding of the condition, Ovid agreed to provide our de-identified baseline data from the trial to the Linking Angelman and Dup15q Data for Expanded Research (LADDER) database. We were the first company to make this form of data contribution to the community and we hope it further fuels insight into the condition.
https://www.angelman.org/ladder-database-ovid-dataset/
https://globalgenes.org/2022/11/18/how-a-drug-setback-became-a-patient-communitys-gain/?fbclid=IwAR21WW99t7P38WN1Ls97skEq6OYIKOjbduIccLNbenLaDncyyBs5Qp__D-o
Finally, we are in the midst of preparing a journal submission on the placebo effect and findings seen with gaboxadol on our NEPTUNE trial. We do not yet have a confirmed publication date, though we would be happy to share it with you when it is available.

Note: Results were submitted to the registry on 15 November 2022.

Rhodes Pharmaceuticals NCT02683265

Thank you for your inquiry regarding clinical trial NCT02683265. We have made the results public in the following locations:

Poster:
- Childress AC, Foehl HC, Kollins SH, Kupper RJ, Newcorn JH, Adjei AL. Safety of extended-release methylphenidate in preschool children with ADHD. Presented at the American Academy of Child & Adolescent Psychiatry 66th Annual Meeting, October 14–19, 2019, Chicago, IL.

Manuscript:
- Childress AC, Kollins SH, Foehl HC, Newcorn JH, Mattingly G, Kupper RJ, Adjei AL. Randomized, double-blind, placebo-controlled, flexible-dose titration study of methylphenidate hydrochloride extended-release capsules (MPH-MLR, Aptensio XR®) in preschool children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2020;30(2):58-68.

Further, we are actively engaged in fulfilling our regulatory obligation to report the results of the referenced trial on ClinicalTrials.gov, and have been working with reviewers to finalize that process. We anticipate the results will be published on the site by the end of the year.

Because the activity in regard to posting on clinicaltrials.gov is well underway, and because we have made the results of NCT02683265 public in the other forums noted above in service of transparency with the scientific community, this clinical trial should not be included in your report. We respectfully ask that you remove it.

Note: Results were submitted to the registry on 12 December 2022. Our first search had not detected the journal article flagged by the sponsor.

University of Nebraska NCT03374982

Please note that the principal investigator on the below-referenced clinical trial is no longer with the University. However, the University is taking active measures to contact and coordinate with the principal investigator to address and/or take any necessary action on the below-referenced trial.

Wayne State University NCT02524249 & NCT04149808

Thank you for alerting us about the two clinical trials that were not updated on clinicaltrials.gov. One of the studies was never started and the other was terminated prior to completion. We have contacted both principal investigators – one of whom is no longer with the university – and they have both committed to submitting pertinent information to the website as soon as they can.

> *Note: NCT02524249 is marked as terminated after enrolling 110 patients ("actual" enrolment) on the registry, and is legally required to report results there. We retained NCT04149808 on our list because the registry lists its status as "unknown"; as of 28 December 2022 the registry entry has not been updated to state that the trial never started.*

(2) Contact email template

- Template of email sent to trial sponsors on 15 November 2022
- Reminder email sent on 08 December 2022

Media enquiry – RSVP by 22 November – your clinical trial NCT[number] is violating U.S. law

Dear Sir/Madam,

Your clinical trial NCT[number] has failed to make its results public in violation of U.S. law. In addition, we have been unable to find an article in a peer-reviewed medical journal describing the trial's results.

TranspariMED, a global campaign to improve medical research, is currently preparing a report on clinical trials involving American children that have never made their results public. The report will highlight the harms to patients and waste of resources caused by companies and institutions that fail to make clinical trial results public. We will share the report with the media. Past media coverage here: https://www.transparimed.org/about

We plan to include your trial in our report. Therefore, we would like to give you the right to respond.

(1) If your trial has made its results public and we overlooked them, please send us a hyperlink to the results so we can remove your trial from our list if appropriate.

(2) If you believe that you are not obliged to make the results of this trial public, please explain why, and we will remove the trial from the list if appropriate.

(3) If you accept that your trial should have made its results public but has so far failed to do so, please provide a short statement summarising your relevant policies and future plans.

Your response will be included in full in an annex to the report.

(You can find some useful background information further below.)

Please respond by Tuesday 22 November 2022.

Thank you for your time, I look forward to hearing from you,

Till Bruckner, PhD
TranspariMED
www.TranspariMED.org

BACKGROUND

The FDA Amendments Act, Section 801, requires the sponsors of certain completed or terminated clinical trials subject to the law to upload their tabular summary results to ClinicalTrials.gov within 12 months of the trial's primary completion date. (The sponsor is the company or institution running the trial, *not* the party that funded the trial.) By law, the FDA can impose a fine of over $13,000 for every day a trial result is overdue in violation of the law. The law equally applies to sponsors regardless of whether they are commercial or non-commercial, or are based in a foreign country.

The World Medical Association's Declaration of Helsinki requires all clinical trial results to be made public. Any failure to make a clinical trial result public is therefore a violation of global medical research ethics. However, the Declaration of Helsinki is not legally binding.

You can find more information on your trial by searching Google for NCT[number]. In particular, you should review the official ClinicalTrials.gov record for your trial, which is used to determine whether or not your trial violates U.S. law. You can email the support team at ClinicalTrials.gov for further information or support regarding your trial: register@clinicaltrials.gov

You can search the FDAAA Trials Tracker for additional, non-paediatric trials of yours that may be in violation of the law: https://fdaaa.trialstracker.net/rankings/

The TranspariMED website lists useful resources for sponsors that wish to improve their clinical trial reporting: http://www.transparimed.org/resources

[EMAIL MESSAGE ENDS]