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Return of participant-level clinical trial results to participants: Pilot of a simplified centralized approach

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Abstract

Objectives: Public access databases achieve dissemination of clinical trial design and aggregated results. However, return of participant-level data is rarely done. A key barrier includes the proprietary ownership of data by the sponsor. Additionally, investigators may not have access to centralized data, and per ICH Good Clinical Practice, must maintain the confidentiality of participants. This study piloted an approach to return both individual and aggregate clinical trial data to parents of children participating in a series of open-label clinical trials. **Setting and Design:** A small biotech company obtained central ethics approval (Western IRB, non-exempt). The study was advertised via parent advocacy groups. Parents of trial participants were offered the option to contact an employee (coordinator) within the company, requesting return of their child's study results. Ethics approval covered participation in 6 countries. **Interventions**: Contact initiated by the parent enabled the coordinator to obtain informed consent (and separate GDPR consent), with phone translation when needed. Using date of birth and study site location provided by the parent, the data manager reported the participant number to the coordinator. The coordinator retrieved and compiled data, along with an aggregate summary, which was mailed via a password protected and encrypted memory device to the parent. Pre-and post-return surveys were sent to consented parents (n=19; 40% of 48 total trial participants) and investigators. **Results:** Pre-return surveys indicated a request for as much data as offered, in all formats offered. Post-return survey showed high satisfaction with the process and data returned. Survey of the physician site investigators (n=10; 100% participation of investigators) voiced general satisfaction with the process, with some reservations. **Conclusions:** This pilot study demonstrates an innovative, simple, and labor conservative approach to return of participant-level and aggregate data to participants in studies.

Strengths and limitations of this study

- The study demonstrates a simple and cost-effective approach to participant-level data return by a small company.
- The study provides insight into the preferences of parents and physicians surrounding return of participant-level data.
- A limitation of our approach is the effectiveness of indirect outreach to the parents of participating children via patient advocacy groups. We do not know if those that did not participate did so because they did not hear of the study (e.g. ineffective outreach to them), or if they did not wish to participate.

Introduction

Health authorities, academic societies, and patient advocacy groups are increasingly focused on increasing transparency of clinical trial design and conduct, as well as data sharing and data stewardship. This is reflected in the United States 21st Century Cures legislation which supports the National Institutes of Health data sharing mandates [1,2], and is further exemplified by recent European Union Clinical Trial Regulations, which note key initiatives of improving information-sharing and increasing transparency of information related to clinical trials (https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation). Access to participant-level data enables alternative approaches to data analysis, including meta-analyses and modeling to facilitate drug development (e.g. predictive clinical disease progression models, clinical trial simulation tools) [3]. Data siloes, driven by economic and academic incentives, have the potential to undermine development of treatments for rare diseases [4]. Studies demonstrate that most clinical trial participants view data sharing positively, despite some concerns related to confidentiality and data security, awareness about access and control, and potential harms resulting from these risks [5,6].

Clinical trial data disclosure or sharing may take several forms, including the posting of aggregate results on a public or private website, sharing of de-identified data with a 3rd party (for research or other purposes), or return of an individual's personal health data back to them (**Figure 1; Panel A**). Some data collected during a clinical trial are monitored in order to assess a person's well-being during the trial, or response to therapy (e.g. weight, height, clinical chemistries); some of these data could duplicate data found in their medical record or be used by their physician during their clinical care. Other data collected during a trial may be less relevant to their healthcare (e.g. biomarkers and changes in outcome measures that were selected to measure the effect of a drug); often these data are not regularly assessed during the care of a patient. Sometimes these data are not accessible to their physician during the trial

due to use of a central laboratory or a non-CLIA approved laboratory, and even if they are, may not be easily interpreted by the physician because they are exploratory, or intended to assess the pharmacodynamics of a drug. Participants (or parents) may misunderstand that biospecimens are being collected for research purposes only, and not for their direct care.

With the emergence of the General Data Protection Regulations (GDPR) in Europe, there is an acknowledgement that individuals have a fundamental right to ownership of their own personal health data, including data collected during a clinical trial (**Figure 1; Panel B**) [7]. Efforts are underway to enable individual ownership of personal health data through secure 'data lockers', and *FAIR* consensus foundational principles have evolved to create a construct for such data return, ownership, and sharing (Findability, Accessibility, Interoperability, Reusability) [8]. Patient advocacy groups have begun to focus on mechanisms to encourage and implement *FAIR* data lockers for their stakeholders [9]. We hypothesized that the driving principle for a clinical trial participant may be 'a right to know and understand' their personal clinical trial results, and not as much a 'right to own' their clinical trial data. Additionally, while "machine operability" is an imperative for data sharing under GDPR, a recent study of clinical trial participants demonstrated a preference for receiving data by mail and not via a website [10].

We sought to understand parent/caregiver and physician views on return of their child's individual personal health data at the end of an open-label clinical trial. We also sought to develop a cost-effective process for returning clinical trial data directly to participant families, while viewing it as an opportunity to be transparent about how these data were similar or different from data obtained by their physician during clinical care. In 2019, ReveraGen received an Administrative Supplement for Research on Bioethical Issues award from NINDS, a supplement to an existing NIH clinical trial grant. This supplemental project was entitled "Establishing a Cost-effective Return of Results to Parents of Boys in VISION-DMD Clinical

Trials"; the goal of this study was to pilot a centralized approach for return of participant-level data to families participating in clinical trials of vamorolone. Here we discuss this pilot process using data from a series of small open-label trials, and present findings from parental and physician surveys, intended to inform application of this process to other studies.

Methods

Patient population and trial design.

This study was focused on participants in two vamorolone trials, VBP15-002 (4 weeks dose-ranging study) [11], and VBP15-003 (24-week extension study) [12]. These two trials were sequential open-label trials, with 48 DMD participants, age 4 to <7 years at study entry. VBP15-002 was a multiple-ascending dose study over a 24-fold range of vamorolone doses (0.25 mg/kg/day to 6.0 mg/kg/day), recruited 12 participants in each of 4 dose groups, and was a 4-week safety and pharmacokinetics study (2 weeks on drug, 2 weeks washout). All participants were then enrolled into a 24-week dose-finding study at the same doses (VBP15-003), with motor outcomes at baseline, 12-weeks, and 24-weeks treatment, and laboratory outcomes (safety labs, exploratory biomarkers). In this report we focused on test results reported back to patient families. These included the motor outcomes Time to Stand from Supine velocity (in event/sec), Six-minute Walk Test (in meters walked), Time to Run/Walk 10 meters (in meters/sec), Time to Climb 4 Stairs (in event/sec), and NorthStar Ambulatory Assessment (total score). Blood laboratory tests (safety biomarkers) assessed in a central laboratory included creatine kinase, osteocalcin, P1NP (N-terminal propeptide of type 1 collagen), CTX1 (C-terminal telopeptide of type I collagen), morning cortisol, fasting insulin and glucose, and glutamate dehydrogenase. Exploratory blood pharmacodynamic protein biomarkers, tested at Somalogic, were CD23, MDC/CCL22, IL22BP, lymphotoxin a1b2, IGFBP2, MMP12.

Patient and Public Involvement Statement

The concept of this study evolved from discussions with parents of patients and advocates at disease-focused conferences. Multiple patient advocacy group leaders, physicians and parents of children with DMD were consulted about the concept of this project, and were asked to comment upon and contribute to the design of the data return and questionnaire content.

Ethics approval and consent of participants.

A single central ethics approval (IRB) was received by the Sponsor (ReveraGen BioPharma, Rockville, MD, USA) for this study through Western IRB (WIRB), as 'expedited review, no continuing review required'. The approval included advertisement of the study via patient advocacy groups in countries in which enrollment had taken place (USA, Canada, United Kingdom, Sweden, Israel, Australia), and the ability to consent the participant via telephone with use of a telephone interpreter if requested by the parent (**Figure 2; Panel A**). The advertisements included the contact information of a single coordinator employed by the Sponsor; a strict firewall was established where the coordinator shared no identifying information with any other employee of the Sponsor or others.

Once a trial participant family (parent) contacted the coordinator and requested participation in the return of results study, the coordinator then explained the study and conducted the informed consent process by teleconference. The informed consent was sent via Adobe Acrobat Sign for signature (**Supplemental File 1**). For patients in European countries, a separate GDPR consent was also completed, and signed via Adobe sign. (**Supplemental File 2**). Only those who signed informed consent participated in the return of results study (**Figure 2; Panel A**). Following completion of informed consent, the coordinator collected the following information from the family and stored it in a password-protected, cloud-based file: parent's name, home address, parent's email address, child's study site, child's date of birth. The child's study site

and date of birth were provided to the data manager, who identified the study subject number. The data were extracted from the electronic data capture system using only the subject number, and then were presented in a standardized format and converted to a pdf file.

Return of clinical trial results to families was done by sending (by mail) an encrypted and password-protected USB memory device. The memory device used SanDisk Secure Access software (128 bit AES encryption to create a password-protected folder—SanDiskSecureAccess Vault—on the flash drive). Locked files were moved into the SanDiskSecureAccess Vault and only accessed with a password sent separately via email to the family.

Surveys

Three surveys, two for parents, and one for their physicians, were developed, and feedback sought on draft content of surveys from parents, stake-holder foundations, and physicians prior to finalization and dissemination.

The first parental survey was administered after signing of consent to partici8ate in the study, but before results were returned (**Supplemental File 3**). This parental survey was designed to instruct parents on the types of data available from clinical trials (motor outcome, clinical laboratory, exploratory biomarkers), and ask what type of data they were interested in receiving (aggregate, patient-level), and in what data format for data return. The second parental survey was administered after the return of results, to gauge parental satisfaction with the materials received (**Supplemental File 4**).

A third survey was developed to administer to the clinical trial site physicians caring for the patient and patient family that had consented to participate in the return of results (**Supplemental File 5**). The purpose of this survey was to assess the opinions of the physicians regarding the return of patient-level clinical and laboratory data directly from the Sponsor to the parents.

Data statement. All data is provided as supplemental files.

Results

Parental attitudes and desires regarding clinical trial return of results. Of the 48 patient families participating in the VBP15-002/003 clinical trial of vamorolone, 19 (40%) responded to advertisements via stakeholder foundations. We also developed an informational sheet that could be handed out at the clinical trial sites during patient family follow up visits, but clinical trial sites were uncomfortable handing out this informational sheet without their own institutional ethics approval.

The full results of the survey of 19 parents prior to return of results are provided (**Supplemental File 6**). We queried whether aggregate or individual participant level data were important to parents, and the majority (90%) felt that access to both types of data was 'very important'. We then asked if data should be best presented in tabular, or graphical form. Most parents (97%) indicated that receipt of data in both formats was preferred. We then queried what biomarkers were important to report back to parents, giving examples of safety labs (cortisol, insulin, glucose), bone turnover biomarkers (osteocalcin, P1NP, CTX1), and exploratory efficacy biomarkers. The majority of parents responded that they would like all data reported to them.

For the questions "What do you expect you would do with the information returned that summarizes results for all boys in the trial?", most responses acknowledged that the return of data would be for informational purposes only. For "What do you expect you would do with information return on your son's individual results?", most again responded that it would be for informational uses only, although four (of 18) mentioned the possibility of discussing the data with their physician.

Return of results.

Both aggregate and individual (participant-level) were returned to patient parents on a password protected USB memory device sent via the mail. An example report is provided (**Supplemental File 7**). The report included a 2-page educational introduction to aid interpretation of the report. This included definitions of efficacy and safety outcomes, the concept of aggregated data for interpretation of drug efficacy and safety, distinctions between data generated in a research study vs. clinical care. For educational purposes, the report also elaborated on challenges facing Sponsors in terms of return of data, including confidentiality firewalls and risk for parent/patient over-interpretation of research data regarding clinical care. The following 15 pages provided the trial participants individual clinical trial data (motor outcomes, quantitative muscle testing, anthropomorphic data, and laboratory data), as well as his data superimposed on aggregated data, both as tabular and graphical form for key clinic visits (Baseline, 12 weeks, 24 weeks treatment). The graphical form of data presentation showed each individual in the specific vamorolone dose group (n=12), with their child's data color coded within this group (**Figure 2; Panel B**).

Parent follow-up survey.

Of the 19 families to whom the pre-return survey was completed and results were returned, 12 of these completed the post-return survey (63%). The complete responses are provided (**Supplemental File 8**). The majority of the families were "very satisfied" with both the return of data approach (10/12; 83%), and method of return of data on a password-protected USB memory device (8/12; 67%) (**Figure 3**). One family expressed dissatisfaction with both of these queries (1/12; 8%), but did not provide reasons for their dissatisfaction.

When asked if they felt that the return of results was important to them, all (12/12) replied that it was 'very important' (7/12; 58%) or 'important' (5/12; 42%). When given an open-field query for why they felt the data return was important, 10 responded (see **Table 1**). The responses

primarily oriented about the importance of knowledge about the trial and being informed about the child's health.

Table 1: Responses of parents of participating children in the clinical trial when asked why they thought that data return was important to them, and their physicians regarding their degree of support of Sponsor direct return of data to families.

Parents of trial participants: Why is trial data return important to them?	
Personal knowledge	
To be informed	
It is a great benefit to be able to see how my son may have responded during the Clinical Trial in all of these areas recorded, In Hopes to see some good benefit from the medication.	
We took a big risk in being in the trial. Want to know if it works and how my son paired with the other boys	
It's nice to see how things are going and not be in the dark	
All data to do with how my son is managing the condition/meds is important	
We would like further understanding about how the trial was going, and what difference it's made to our child as well as the rest of the children	
To understand the clinical help VBP15 provided	
We would like further understanding about how the trial was going, and what difference it's made to our child as well as the rest of the children	
To see actual data of improvement and/ or progression is important. Data helps you to understand if treatment works or not.	
Just to see how our son is doing. We are hopeful he is doing better because if the drug and seeing the results gives us more hope.	
Physician concerns of a Sponsor returning participant-level data to directly to trial participants.	
Supportive	*after trial is finished, data should be shared*
	No comments
Supportive with reservations about timing of delivery	*I agree, but it needs to be done in a thoughtful manner, properly contextualized..At the end of the trial, all data should be returned to families. However, on a week by week basis during the trial, I don't favor providing results to individual families*

Supportive, with reservations about delivery outside of the healthcare or investigative team and interpretation of data	*What's meant by 'clinical trial data'? I don't think getting e.g. ECG, echo or MRI data is very useful and even some of the functional or strength measurements don't mean much to a family. It's a nice option for a family to see clinical trial data, but it would probably be more meaningful to provide them through a healthcare professional, either a doctor or a physiotherapist.*
	Has to go through PI, SI and/or site staff
	Not to disagree with this objective, but to raise the concern that the PI/treating physician for the participant could be blind-sided by the parent contacting the office and requesting an urgent discussion with the physician over an abnormal lab result. How to educate parents on labs/biomarkers/tests that are predicted to be abnormal (due to having DMD)? The poster does not go into this in any detail.
	Interpreting the data and put the individual data in the context of the study results and of a progressive disease might not be easy for all families and can create some false judgement and/or anxiety. It creates some "inequality" as proactive and well informed families are more likely to ask for the data

Most parents indicated that it was important to see their child's data in comparison to others in the trial (11/12; 92%) and provided free text justifications that were concordant with increased information exchange is preferred over more narrow information regarding their child. Parents were queried regarding the amount of data provided, and the majority (11/12; 92%) responded that it was "about the right amount of information", and 1 parent reporting that it was too little information.

Parents were asked if they would have preferred their child's data returned to them via their physician, rather than the Sponsor (ReveraGen). Most (8/12; 67%) responded "I'm neutral; either way would be fine"; some responded that they would strongly prefer to receive their child's data from the Sponsor and not their physician (3/12; 25%), and a single parent stated that they mostly agree with their preference for receiving the data from their physician, but not strongly (8%).

The parents were queried as to whether they had shared the returned data with others. Half of respondents had shared data with family members, 42% with health care providers, 17% with friends, and 8% with teachers; 42% responded that they had not shared the data with anyone. When asked if they would participate in such a return of results study again, all responded affirmatively (12/12).

Survey of clinical trial site physicians.

Of the 10 physicians that we asked to complete the survey (e.g. those physicians following the 19 patients), all 10 responded. The trial had 12 sites in 6 countries, so this represented 83% of physicians and sites. The complete responses are provided (**Supplemental File 9**). The physicians were unanimous in their opinion that parents put a great deal of importance on receiving both individual and aggregated trial data, and all physicians affirmed that families should receive this data if requested by the family (**Figure 4**). We asked, “Do you agree with the concept of a Sponsor returning individual clinical trial data directly to trial participants?”, most (8/10) were supportive of this, but 5 of these 8 expressed some reservations (“Yes, but it depends on the circumstances”); 1 was not sure, and 1 responded “no”. When asked to elaborate on any concerns of a Sponsor returning participant-level data directly to families, responses are shown (**Table 1**).

Discussion

We carried out a centralized return of both participant-level and aggregated clinical trial data to parents of children in an open-label dose-ranging study of vamorolone. Key to our approach was the efficient navigation of human subjects oversight, where we received a single centralized ethical approval for patients worldwide to contact the Sponsor to request the clinical trial data on their child. Our method of alerting patient families of this return of results project was through stakeholder foundations in the 6 countries in which the clinical trial was being conducted (US, UK, Canada, Israel, Australia, and Sweden). As the parents were contacting the Sponsor directly to request information on their own child, the ethical committee felt that it was adequate to remotely consent parents (with a translator if needed), and that the study was "expedited with no requirement for continuing review," much as other survey-type research projects.

The more typical alternative approach of returning clinical trial data to participants is through collaborating clinical trial sites via their health care providers. This would require (in our case) local clinical site ethics approval (12 sites in 6 countries), as well as contracts between the Sponsor and each site to carry out the return of results. Our approach of implementing direct contact between the parents contacting the Sponsor greatly simplified the otherwise complex challenge of returning patient-level clinical trial data to clinical trial participants. Critical to our approach is that the parents initiate contact with the Sponsor, not the Sponsor with parents. Also central to our approach is a 'data/information firewall' within the Sponsor, where only a single employee had direct contact with families, and no de-identifying information was relayed to any other employee of the Sponsor. Additionally, an interpreter in the parents' native language was always made available, and consent forms were translated to the parents' native language.

A clear limitation of our approach is the effectiveness of outreach (advertisement) to the parents of participating children. We had a 40% participation rate (19/48). We do not know if the 60% that did not participate was because they did not hear of the study (e.g. ineffective outreach to them), or if they did not wish to participate. Our ethics approval included an 'informational flyer' that was meant to be distributed to clinical trial sites and provided to patient families, but sites were uncomfortable with distributing this flyer without their own institutional ethics approval. If other Sponsors wish to take our centralized approach, we advise that the informational flyer for direct Sponsor return of data be provided to sites for distribution to trial participants at initial contracting and ethics review and be handed to patients at initial enrollment in the clinical trial, and/or exit from the trial.

We queried the attitudes of participating parents both before the return of results, to learn what type of information they felt was important, and how they would like this data to be provided to them. In general, parents expressed a strong desire for as much information as possible, in all formats offered (individual, aggregate; tabular, graphical). 15In returning the data to participants' parents, we instructed that this was clinical research data and not generally relevant to the clinical care of their child, and we provided tutorials on motor outcome measures, and interpretation of clinical laboratory and exploratory biomarker data. Participant families who participated in the return of results directly by the Sponsor expressed overall satisfaction with all aspects, including the process, the amount of information received, the graphical and tabular presentation, the presentation of both individual and aggregate data, and the manner in which it was received (password protected and encrypted USB memory stick mailed directly to the family). We note that our approach included two factor authentication (direct mail, separate password communication), which is important to maintain privacy and confidentiality.

Our finding that most parents would prefer to obtain the data from the Sponsor or were indifferent to whether they obtained data from the Sponsor of their physician, supports our

approach to providing individual-level data. All participants felt that return of data was quite important to them, and parents showed a variable degree of sharing of information with family, friends, teachers and their physicians. Physician respondents unanimously acknowledged the importance that families place on return of clinical trial data. Some had reservations about return of results without involving clinicians or the clinical site investigators; these concerns will need to be further explored and addressed in future return of results approaches.

For parents of children with Duchenne muscular dystrophy, participation in clinical research is a balance of hope and expectations. Parents of children with DMD report a feeling of investment in the trial [13]. In one study, at the termination of a trial in DMD, parents wished for more communication from the sponsor. Some parents felt that when the trial ended, the partnership between the parent and sponsor "broke down" and that the sponsor no longer valued them [14]. Parents describe the significant burdens that participation in clinical trials places on their families [15].

In keeping with the ethical principles of beneficence and autonomy, return of data demonstrates respect for participants' ownership of their health data, encourages family engagement, and fosters increased trust of researchers by patients who are clinical trial participants and their families. Operationally, there is a disconnect, as the clinical trial site personnel and physician have direct contact and responsibility for care for the patient, but typically do not have access to all of the patient's data. Direct industry-patient interaction for returning individual results after trial completion, without the study site/physician interface, has not been common historically due to potential for perceived loss of patient confidentiality, concerns about results interpretation and the potential for clinical follow up for actionable findings if clinicians are not involved, and possible conflict of interest. However, our approach demonstrates that this can be achieved by having an internal coordinator who is not involved in the study conduct, keeps records confidential, and is under a "firewall" of confidentiality when it

comes to the study. Another approach could be to use a 3rd party vendor, though this would increase costs and complexity. Sponsors may perceive the return of results to trial participants as a risk to the participant and the trial, or at least as a distraction to the Sponsor, adding additional time and cost to the drug development process. We have demonstrated that this can be a relatively straightforward process that is not costly and can be done after study completion, and public disclosure of trial data.

Not all clinical trial data is relevant to a patient's medical care, and indeed may not add value or be acceptable to add to the participant's electronic medical health record. While clinical trial data is personal health data, it likely has different value to a clinical trial participant compared to their own electronic medical health record. The National Academies of Science (NAS), Engineering, and Medicine convened a committee that published "Returning Individual Research Results to Participants: Guidance for a New Research Paradigm", a process-oriented approach to return of results that considers value to the participants, feasibility of return, and quality of research results [16]. The NAS committee formulated 6 principles to help guide deliberations and development of recommendations presented in their report. One principle was that the potential value of returning individual research results must be carefully considered along with the trade-offs for research participants, investigators, research institutions, and society. According to the committee, "value" should consider the perspective of the participant (or parent) and might entail clinical utility or personal utility, as well as personal meaning. Thus, *the value of a result is not necessarily tied to its use, as viewed solely through the eyes of the clinician or sponsor.* DMD parents and advocacy groups in the US and European Union clearly indicate that they value provision of individual and aggregate clinical trial results to the study participant.

Recent reviews of efforts to return clinical trial data to participants have found that these are relatively rare and typically only include summarized or aggregate results (not personal

participant-level data). Bruhn et al. (2021) studied identified clinical trials in a period from January 2008 to August 2019 and identified 33 studies involving 12,700 participants that explored returning results to trial participants, and found that aggregate data was returned, without evaluation of what information trial participants wished to receive [17]. Of the 33 studies reviewed, only 2 returned individual data to the participant, and for both of these only 'unblinding' was reported to the participant (not participant-level clinical and laboratory data). Also, the authors noted that there was a general lack of "actively including patients or the public as partners in the development of the dissemination of results". The authors noted that a weakness of their study was relying on literature reports, and this likely underestimated dissemination efforts. Shroter et al. (2019) took an approach of surveying authors of published clinical trials to ascertain efforts to return clinical trial results to clinical trial participants [18,19]. Questionnaires were emailed to 19,321 authors, and analyzed 1,818 responses of authors that had enrolled individual patients. Of these, 498 (27%) had disseminated results to trial participants, but most were aggregate data (academic reports, lay reports). Of the 164 (33%) reporting that individualized data was returned, the type of individualized data was not specified. Raza et al. (2019) queried the UK's research permissions system for Phase III trials for a 6-year period (2012 to 2017 inclusive), and found that of the 1404 Phase III trials studied, 88% reported the intention to disseminate results to trial participants [20]. However, only ten of the End of Study reports cited dissemination activities, and 6 of these were through a lay summary or letter.

In conclusion, there is a strong desire for clinical trial participants to receive patient-level and aggregate returns of clinical trial data to them. Their treating physicians, and stake holder foundations all uniformly acknowledge the importance of return of results to trial participants. Despite this need, it is largely unmet due to fundamental barriers (pragmatic, financial, organizational, confidentiality, ethics). We have piloted a simplified return of results process that

removes most barriers, and we found that trial participants (parents of children in a trial) were highly satisfied with this novel process, and their treating physicians were also generally satisfied while expressing some reservations.

Authors' contribution statement: EPH contributed substantially to concept and study design and drafted the manuscript. SG contributed substantially to study design, data acquisition and interpretation, and reviewed the manuscript critically. WT contributed substantially to data interpretation and presentation and reviewed the manuscript critically. HP contributed substantially to concept and study design and reviewed the manuscript critically. PC contributed substantially to concept and study design and reviewed the manuscript critically. UD contributed substantially to data interpretation and presentation and reviewed the manuscript critically. LSC contributed substantially to concept and study design, data acquisition and interpretation and drafting of the manuscript.

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to provide expert insight into study design and interpretation of results. Dr. Hoffman and Ms. Gaglianoni are employees of ReveraGen BioPharma. Drs. Hoffman and Conklin are stock holders in ReveraGen BioPharma. Dr. Clemens holds NIH, FDA and foundation grants on vamorolone clinical trials with ReveraGen BioPharma.

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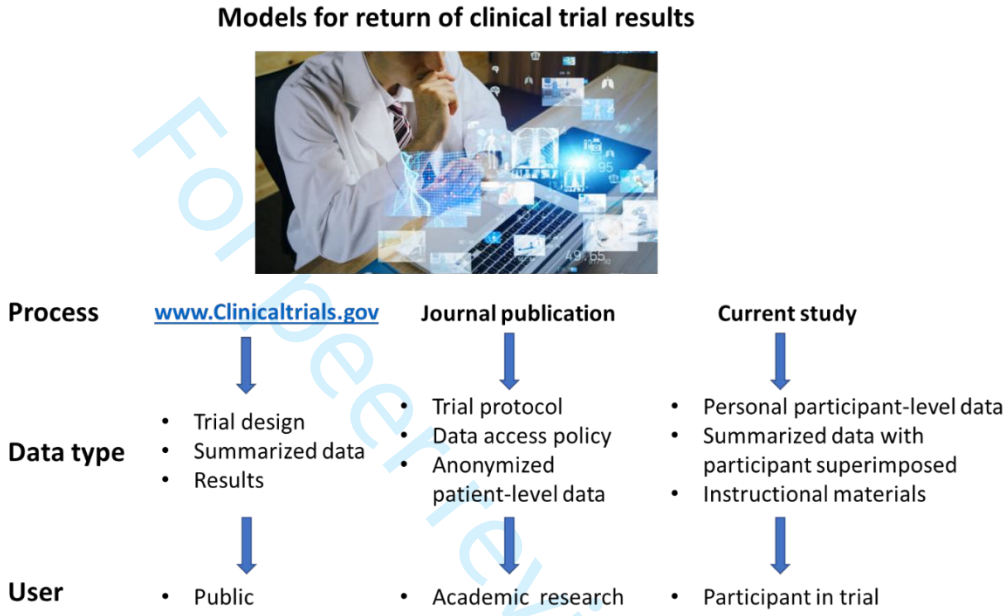
Figures

Figure 1. Models or return of clinical trial results and return of patient-level data. Panel A: Models of return of clinical trial results. Panel B: Models for return of participant level data.

Panel A.



Panel B.

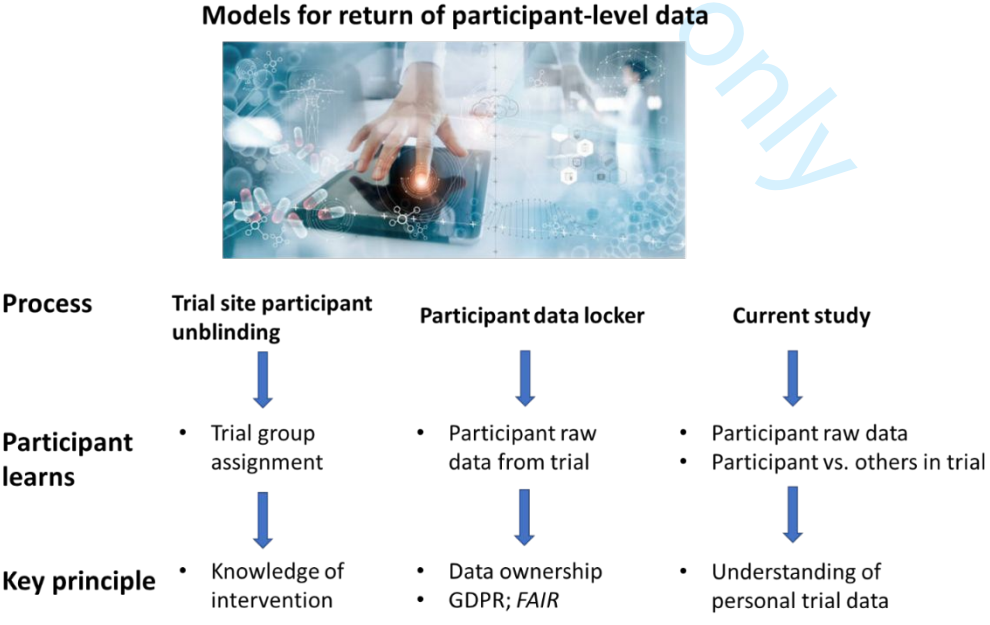
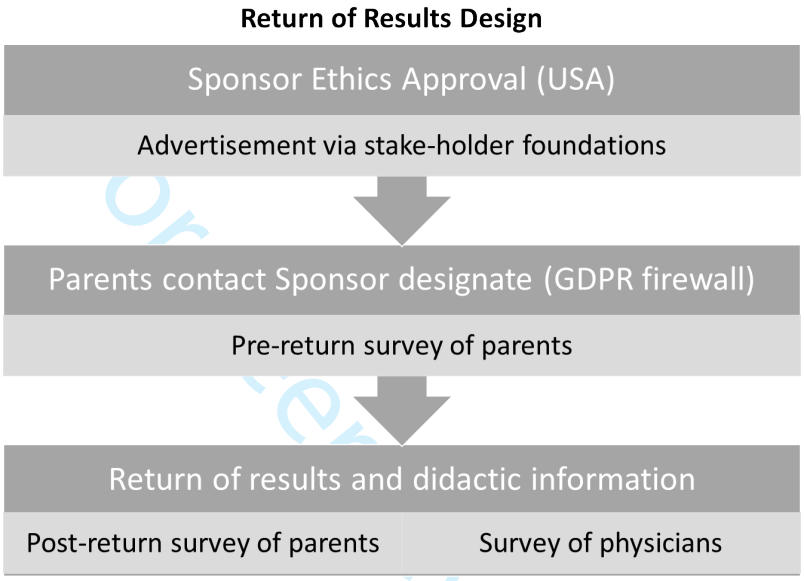


Figure 2. Return of Results Design. Panel A: Overall study design of Sponsor direct return of participant-level and aggregate data to clinical trial participants. Panel B: Example of graphical return of participant-level data, showing the participant's data relative to other participants in the same treatment group.

Panel A.



Panel B.

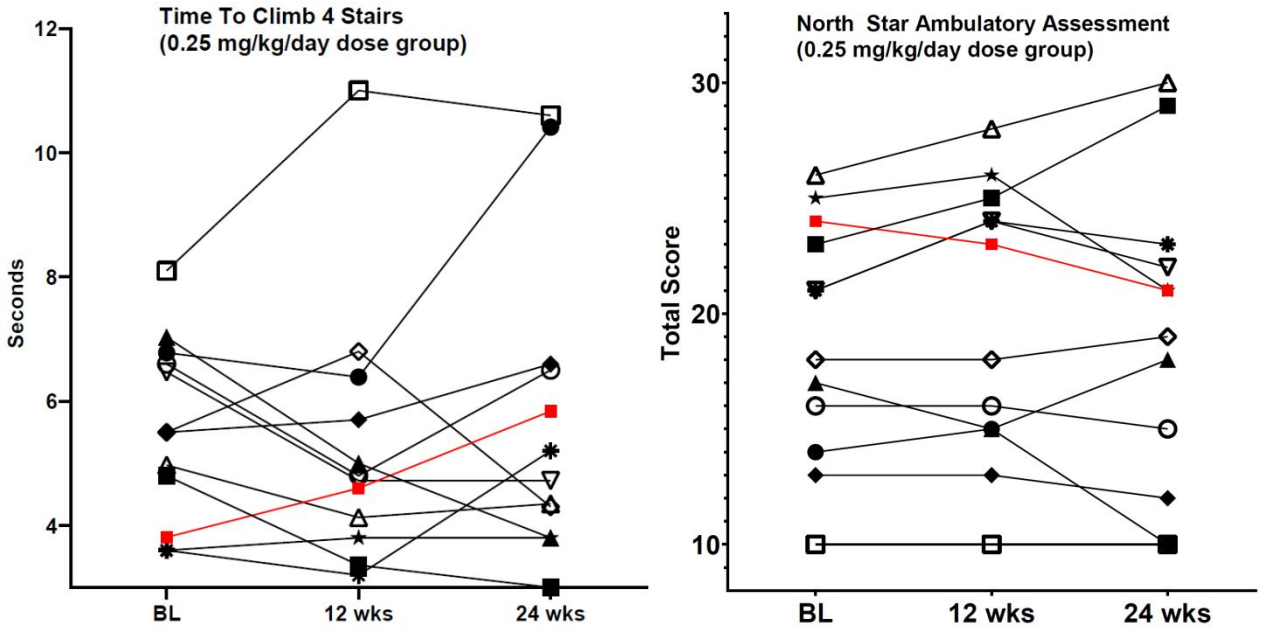


Figure 3. Post-return of results parental satisfaction. Inner pie: Parental satisfaction with return of data approach utilized by the Sponsor. Outer donut: Parental satisfaction with delivery of the data by mailed, encrypted memory stick.

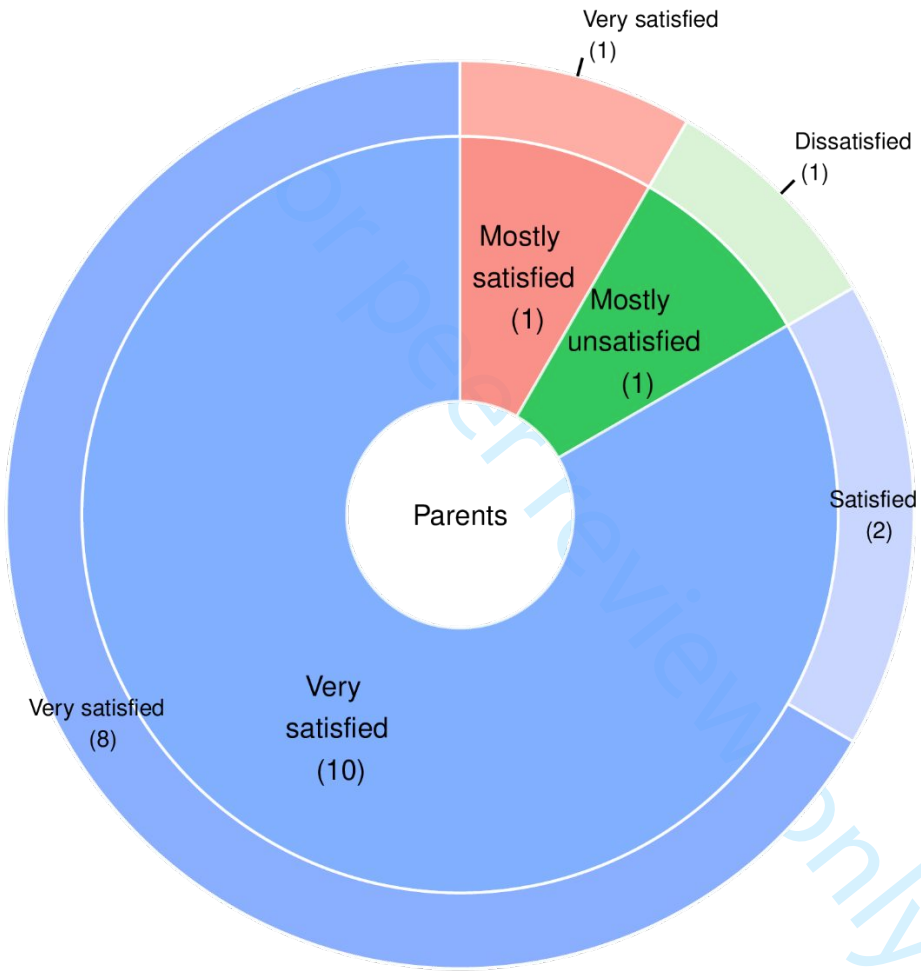
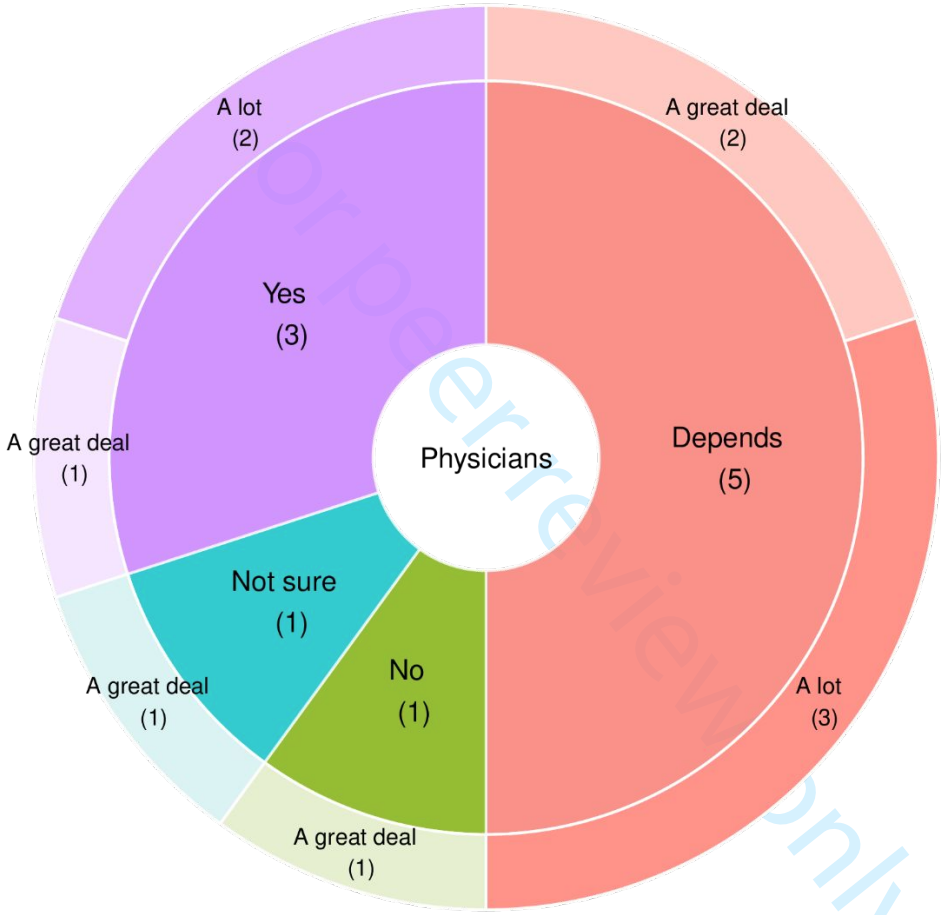


Figure 4. Physician attitudes towards returning clinical trial data to participating families.

Inner pie: Physician agreement with concept of Sponsor returning individual data directly to participants. Outer donut: Physician perception of importance families place on receiving individual trial results.



Supplemental Files:

Supplemental File 1: Consent/Parental Permission and HIPAA authorization to Participate in a Study

Supplemental File 2: Consent For The Processing Of Personal Data From The European Union To Facilitate Return Of Results Per Protocol

Supplemental File 3: Parental Survey Prior to Data Return

Supplemental File 4: Parental Follow-up Survey Post Data Return

Supplemental File 5: Physician Survey

Supplemental File 6: Results of Pre-Return Parental Survey

Supplemental File 7: Example report of data return to patient parents

Supplemental File 8: Results of Post-Return Parental Survey

Supplemental File 9: Results of Physician Survey

Place Barcode Label Here

IRB APPROVED
Oct 09, 2019

Consent/Parental Permission and HIPAA authorization to Participate in a Study

Title: Establishing a Cost-effective Return of Results to Parents of Boys in VISION-DMD Clinical Trials

Protocol No.: VBP15-ROR
WIRB® Protocol #20192458

Principal Investigator:
Laurie Conklin, MD
155 Gibbs St
Suite 433
Rockille, Maryland 20850
United States

Sponsor: ReveraGen BioPharma

Study is funded by: National Institutes of Neurological Diseases and Stroke (National Institutes of Health)

Study-Related Phone Number(s): 240-672-0295
646-283-1074 (24 Hours)

You are being asked to be in a research study.

Introduction

Return of data to parents/caregivers of participants in clinical trials demonstrates respect for participants' ownership of their health data. However, disclosure of an individual's research results raises many ethical and logistical challenges. There are many questions regarding the perceived and real usefulness of the information, how the data is communicated, the impact of return of results on the well-being of parents and participants, feelings toward the research experience, and subsequent research participation. In a clinical trial with many recruitment sites and patients, the burden on physicians/coordinators may be a concern, and there are challenges regarding re-identification of data, and the need to reconsent if consent for sharing was not part of original consent. Challenges associated with randomized trials include the timing and approach to sharing individual level data. There are

additional regulatory and legal challenges associated with return of research results across international boundaries. To inform this project, we have held discussions with leaders of DMD foundations; all strongly endorsed the value of providing a DMD child's clinical trial data to their parents/guardians

This form is designed to tell you things you need to think about before you decide if you want to participate in this study. **It is entirely your choice. If you decide to participate in the study, you may change your mind at any time.** The decision to participate in this study will not affect any aspect of your son's participation in vamorolone clinical trials. The decision to participate will not cause you to lose any medical benefits you have. If you decide not to take part in this study, your doctor will continue to take care of your son.

Before making your decision:

- Please carefully read this form or have it read to you
- Please ask questions about anything that is not clear

Feel free to take your time thinking about whether you would like your son to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. You are free to refuse to join this research or join now and decide to withdraw later. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled. By signing this form you will not give up any legal rights.

What is the purpose of this study?

The purpose of this study is to evaluate the process of informing patients about re-consent for returning results to the families of trial participants. We will get feedback from stakeholders (parents/guardians, physicians, advocates/foundations), and this information will help to improve the process and design the most ethical and efficient system possible. This system is designed to protect the privacy of trial participants and maintain the integrity of the clinical trial.

As part of the study, the sponsor (ReveraGen BioPharma) will return individual and aggregate research results to the parents/guardians of clinical trial participants.

What will I be asked to do?

You will be asked to complete a survey pre-data return. This will be an anonymous survey—your identity and your child's identity will not be linked to your responses. Responses will be compiled and analyzed together with other people's responses.

Next you will be mailed an encrypted USB drive with your child's data and a summary of the data from all who participated in the trial. You will also be provided with the password to access this drive via email. If you would prefer a paper copy, please let the study coordinator know. After you receive your child's data and a summary of data from all who participated in the trial, you will receive another survey. Again, your identity and your child's identity will not be linked to your responses. Responses will be compiled and analyzed together with other people's responses.

Your physician (the clinical trial investigator at your site) will be notified when you enroll in the study, and he/she will be asked to complete a survey after the data has been returned to you. This will provide information from the perspective of the physician.

You will be asked to directly contact the coordinator at ReveraGen by phone or email if you have questions. This is to maintain confidentiality.

If you have questions about the data and how it relates to your child's health, please discuss with your physician.

What are the possible risks of participating in the study?

Risk of loss of confidentiality:
Your son will only be identified by a study site and date of birth, to protect his confidentiality. At ReveraGen, only a single coordinator will know your identity and communicate with you directly.

Although many precautions are being taken (only identifying your data by your child's birthdate/study site), use of a dedicated coordinator who will be the only one at ReveraGen who knows your identity, there is a risk of loss of confidentiality.

There is a risk of the USB drive being lost. The information on it will be encrypted, and only date of birth/study site will be on the drive with the data (no other identifying information).

Receiving your child's data could lead to distress or confusion. It could raise additional questions. Some questions may be answered by our coordinator. Questions about how this information may or may not impact your child's health. We encourage you to discuss these questions with your physicians.

What are the potential benefits of participating in this study?

A potential benefit of participating in this study is the receipt of your child's data and a summary of compiled results from others in the trial. This research may also help guide our approach to providing data to future subjects in clinical trials.

Will I be compensated for my time and effort?

You will not be offered compensation for participating in this study.

The are no costs associated with participating in the study.

What are my other options?

You have the option not to participate in this study.

How will my confidentiality be maintained?

- A single coordinator at our company will be the only one to know your identity. She will be contacted by you, and will store your child's name, date of birth, address, your email address, and study site (as provided by you) in a password-protected file stored on a cloud-based server.
- The coordinator will request your child's data using only the site location and date of birth as identifiers.

The following entities may review the study records and medical records (including your son's identifying information in rare cases) to make sure that the study is carried out correctly and that we are following the law and protecting the children in the study: US Food and Drug Administration, the study's Coordinating Centers, the study sponsor ReveraGen BioPharma and its representatives, the National Institutes of Health (NIH), and the Institutional Review Board or ethics board overseeing the study activities at Western IRB.

Data obtained from this study may be presented, or published or shared with other investigators interested in DMD. However, nothing shared will contain information that can identify your son.

Contact Information

Contact Suzanne Gaglianone at 609-206-0939 or suzanne.gaglianone@reveragen.com

- if you have any questions about the study

Contact Laurie Conklin at 240-672-0295, 646-283-1074 (24 Hours) or laurie.conklin@reveragen.com

- if you have questions/concerns/complaints about the conduct of the study or if you feel you or your son have been harmed by participating in this research.

Contact the Western IRB at (800) 562-4789

- if you have questions about your son's rights as a treatment recipient.
- if you have questions, concerns or complaints
- If you would like to provide feedback

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Participation in this research requires us to access your son's medical record.

What information may be used and given to others?

The study doctor will get your son's personal and medical information. For example:

- Past and present medical records
- Research records

Who may use and give out information about you?

The study doctor and the study staff.

Who might get this information?

The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information may be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- The institution where the research is being done
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to make sure that the research was done right.

What if I decide not to give permission to use and give out my son's health information?

Then you and your son will not be able to be in this research study.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically.

You may withdraw or take away your permission to use and disclose your son's health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

IRB APPROVED
Oct 09, 2019

When you withdraw your permission, no new health information identifying your son will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

VOLUNTARY CONSENT:
The above information has been explained to me and all of my current questions have been answered.

I understand that I am encouraged to ask questions at any time, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

_____
Child's Name (Print)

_____
Parent or Guardian's Name (Print)

_____
Relationship to Subject (Child)

_____ _____
Parent or Guardian's Signature Date

CERTIFICATION OF INFORMED CONSENT:
I certify that I have explained the nature and purpose of this screening to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____
Printed Name of Person Obtaining Consent

_____
Role in Research Study

_____
Signature of Person Obtaining Consent

_____
Date

ReveraGen BioPharma

CONSENT FOR THE PROCESSING OF PERSONAL DATA FROM THE EUROPEAN UNION TO FACILITATE RETURN OF RESULTS PER PROTOCOL VBP15-ROR/WIRB PROTOCOL 20192458

1. Pursuant to the European Union General Data Protection Regulation ("EU GDPR"), Reveragen BioPharma ("Reveragen"), in its capacity as a data controller and/or processor under the EU GDPR, must obtain your explicit, affirmative, and informed consent before it can collect or process any personal data.

2. Per protocol, return of data will be facilitated through Reveragen's coordinator. Personal information including your child's date of birth, study site, your home address, and phone number will need to be provided to the coordinator.

3. You have the right to withdraw your consent to the processing of your above personal data at any time. However, refusal of consent may make it impossible for Reveragen to carry out the activity of returning data. **If you would like to withdraw consent, please contact the Study Coordinator, Suzanne Gaglianone at suzanne.gaglianone@reveragen.com or 1-609-206-0939**.

4. Reveragen is committed to ensuring the security of your information.

Having read this notice (items 1-4), I, _____, the

[Print Full Name Here]

undersigned, hereby:

☐ **give consent** ☐ **does not give consent**

for the use of the following personal data (of my child and/or myself) for the sole purpose of facilitating the process described in item 2 above.

Son's date of birth : _____

Mailing Address: _____

Phone Number: _____

Signature: _____

Date [Month/Day/Year]: _____

ReveraGen BioPharma

Return of Results parent follow-up survey

Post Data-Return Survey

Thank you for participating in the 'return of patient data' study.

Now that you have received information on your son and the results of the vamorolone clinical trial, we would appreciate your feedback on this process, and how important or useful this information was to you.

1. Please answer the following questions.

How important was it to you to receive your child's individual clinical trial results?

- ◯ Not important
- ◯ Somewhat important
- ◯ Important
- ◯ Very important

2. If it was important to you to receive your son's data, why was this important to you? You may skip this question if it does not apply.

3. How important was it to you to receive a summary of the results from other children in the trial?

- ◯ The most important priority
- ◯ A top priority, but not the most important
- ◯ Not very important
- ◯ Not important at all

4. If it was important to you to receive a summary of data from other trial participants, can you tell us why? You may skip this question if it does not apply.

5. How satisfied were you with the delivery of data on an encrypted USB drive by mail?

- ◯ Very satisfied
- ◯ Satisfied
- ◯ Somewhat satisfied
- ◯ Neither satisfied nor dissatisfied
- ◯ Somewhat dissatisfied
- ◯ Dissatisfied
- ◯ Very dissatisfied

6. The amount of information provided was

- ◯ Much too little information
- ◯ Too little information
- ◯ About the right amount of information
- ◯ Too much information
- ◯ Far too much information

7. Were you satisfied with return of data to you directly by ReveraGen?

- ◯ Not at all satisfied
- ◯ Mostly unsatisfied
- ◯ Neither satisfied nor unsatisfied
- ◯ Mostly satisfied
- ◯ Very satisfied

8. I would have preferred my child's individual data to be returned by my physician instead of by ReveraGen.

- ◯ I strongly agree with this statement. I would have preferred that my physician returned my son's research data.
- ◯ I mostly agree with this statement.
- ◯ I'm neutral- either way would be fine.
- ◯ I mostly disagree with this statement.
- ◯ I completely disagree with this statement. I would prefer to receive my son's data directly from the company.

9. I had unanswered questions after receiving the data.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

10. Who have you told anyone about the results you received from the ReveraGen? (Choose all that apply)

- ☐ No one
- ☐ Family members
- ☐ Health care providers
- ☐ Other (please specify)
- ☐ Teachers
- ☐ Friends

11. Are there other people that you intend to tell about the results you received from ReveraGen? (Choose all that apply)

- ☐ No one
- ☐ Family members
- ☐ Health care providers
- ☐ Other (please specify)
- ☐ Teachers
- ☐ Friends

12. I regret having made the decision to participate in this data return study

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

13. If I had to it again, I would participate in this data return study.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

14. If you regret the decision to receive your son's data or felt that the choice did you harm, can you tell us why? You may skip this question if it does not apply.

15. Do you have any additional concerns, comments, or questions for ReveraGen? You may skip this question if it does not apply to you.

Thank you for participating in the survey!

Best wishes to you and your family.
From the ReveraGen team

ReveraGen BioPharma

Return of Results parent follow-up survey

Post Data-Return Survey

Thank you for participating in the 'return of patient data' study.

Now that you have received information on your son and the results of the vamorolone clinical trial, we would appreciate your feedback on this process, and how important or useful this information was to you.

1. Please answer the following questions.

How important was it to you to receive your child's individual clinical trial results?

- ◯ Not important
- ◯ Somewhat important
- ◯ Important
- ◯ Very important

2. If it was important to you to receive your son's data, why was this important to you? You may skip this question if it does not apply.

3. How important was it to you to receive a summary of the results from other children in the trial?

- ◯ The most important priority
- ◯ A top priority, but not the most important
- ◯ Not very important
- ◯ Not important at all

4. If it was important to you to receive a summary of data from other trial participants, can you tell us why? You may skip this question if it does not apply.

5. How satisfied were you with the delivery of data on an encrypted USB drive by mail?

- ◯ Very satisfied
- ◯ Satisfied
- ◯ Somewhat satisfied
- ◯ Neither satisfied nor dissatisfied
- ◯ Somewhat dissatisfied
- ◯ Dissatisfied
- ◯ Very dissatisfied

6. The amount of information provided was

- ◯ Much too little information
- ◯ Too little information
- ◯ About the right amount of information
- ◯ Too much information
- ◯ Far too much information

7. Were you satisfied with return of data to you directly by ReveraGen?

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- ◯ Very satisfied

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- ◯ I strongly agree with this statement. I would have preferred that my physician returned my son's research data.
- ◯ I mostly agree with this statement.
- ◯ I'm neutral- either way would be fine.
- ◯ I mostly disagree with this statement.
- ◯ I completely disagree with this statement. I would prefer to receive my son's data directly from the company.

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- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

10. Who have you told anyone about the results you received from the ReveraGen? (Choose all that apply)

- ☐ No one
- ☐ Family members
- ☐ Health care providers
- ☐ Other (please specify)
- ☐ Teachers
- ☐ Friends

11. Are there other people that you intend to tell about the results you received from ReveraGen? (Choose all that apply)

- ☐ No one
- ☐ Family members
- ☐ Health care providers
- ☐ Other (please specify)
- ☐ Teachers
- ☐ Friends

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- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

13. If I had to it again, I would participate in this data return study.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

14. If you regret the decision to receive your son's data or felt that the choice did you harm, can you tell us why? You may skip this question if it does not apply.

15. Do you have any additional concerns, comments, or questions for ReveraGen? You may skip this question if it does not apply to you.

Thank you for participating in the survey!

Best wishes to you and your family.
From the ReveraGen team

Return of Results Site Physician Survey

1. ReveraGen received a Bioethics supplement from the NIH to study a process of returning individual clinical trial data to patient families. We are returning data to study participants after the database is locked, the clinical study report written, and top-line results announced.

One of the vamorolone clinical trial participants recently requested their data.

We want to understand this issue from a physician perspective- thank you for completing this anonymous survey and answering the following questions.

How much importance do you believe families place on receiving their son's individual clinical trial results?

- ◯ A great deal
- ◯ A little
- ◯ A lot
- ◯ None at all
- ◯ A moderate amount

2. How much importance do you believe families place on receiving their aggregate clinical trial results?

- ◯ A great deal
- ◯ A little
- ◯ A lot
- ◯ None at all
- ◯ A moderate amount

3. Do you think a parent/guardian should receive their child's individual clinical trial data if the parent requests it?

- ◯ Yes
- ◯ No

4. Do you agree with the concept of a Sponsor returning individual clinical trial data directly to trial participants?

- [ ] Yes
- [ ] No
- [ ] I'm not sure
- [ ] Yes, but it depends on the circumstances

5. If you don't agree with the concept of a company returning clinical trial data to participants, can you list your concerns?

6. Are you aware of additional questions/comments/concerns from parents/guardians directed to you/your team following return of their data from ReveraGen?

- ◯ Yes
- ◯ No

7. If your team received questions/concerns from parents/guardians about the returned data, can you elaborate on what types of questions/concerns they had?
This question may be skipped if it does not apply.

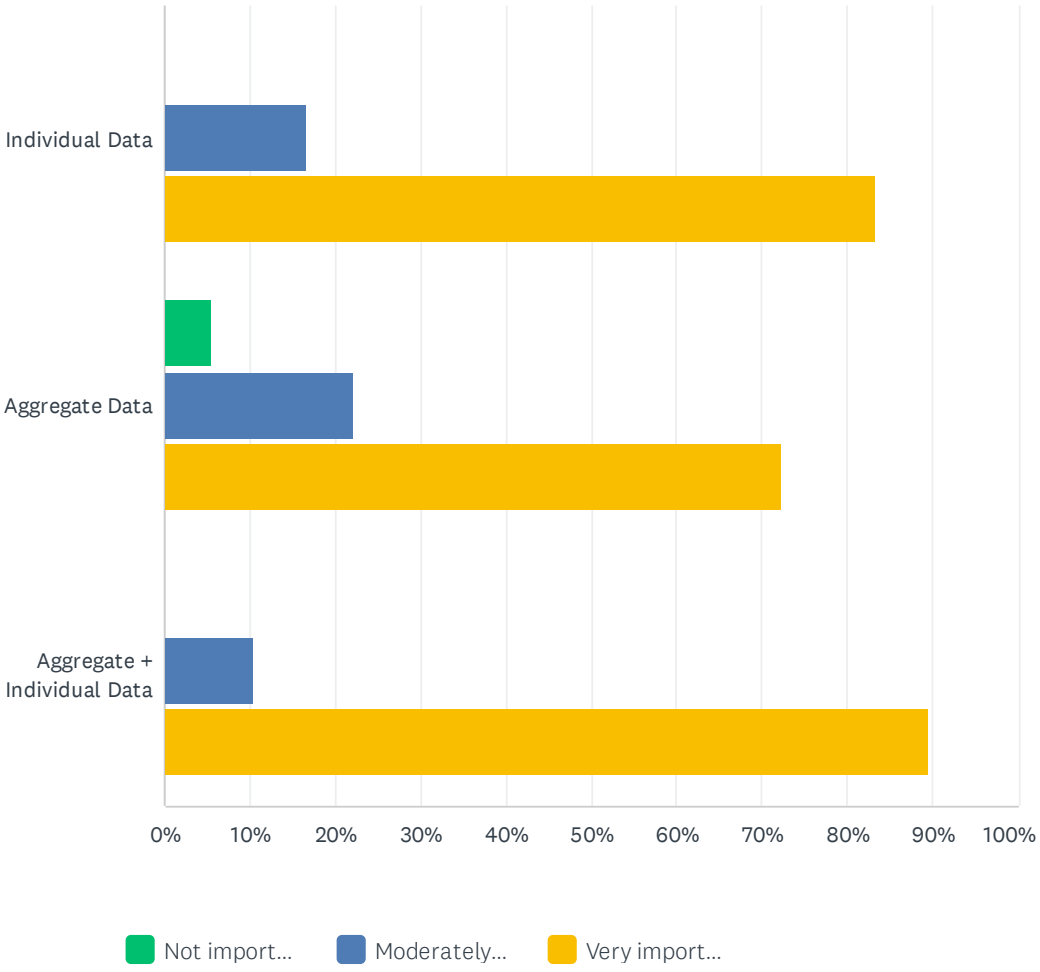
8. Do you have any feedback for ReveraGen on this process?
This question may be skipped.

Thank you for completing our survey!

With best wishes from the ReveraGen team

Q1 1. There are different types of clinical trial data that can be returned:· individual (only your child's data, and no one else's) · aggregate (general findings across trial participants, without specific reference to your son)· aggregate + individual (comparing your son to others, in the form of aggregate data, in the same trial)How important are each of these for you to receive?

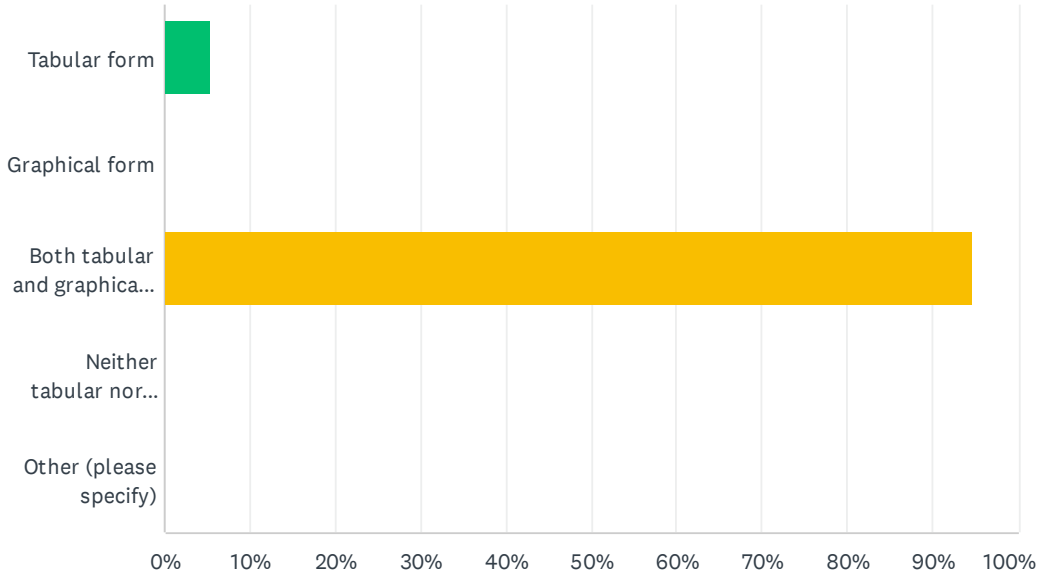
Answered: 19 Skipped: 0



	NOT IMPORTANT	MODERATELY IMPORTANT	VERY IMPORTANT	TOTAL
Individual Data	0.00% 0	16.67% 3	83.33% 15	18
Aggregate Data	5.56% 1	22.22% 4	72.22% 13	18
Aggregate + Individual Data	0.00% 0	10.53% 2	89.47% 17	19

Q2 There are different ways that data from clinical trials can be returned to you: · Tabular. These are numbers in a table. An example is shown below.· Graphical. These show graphs over time. An example is shown below. Of these types, which would you prefer?

Answered: 19 Skipped: 0

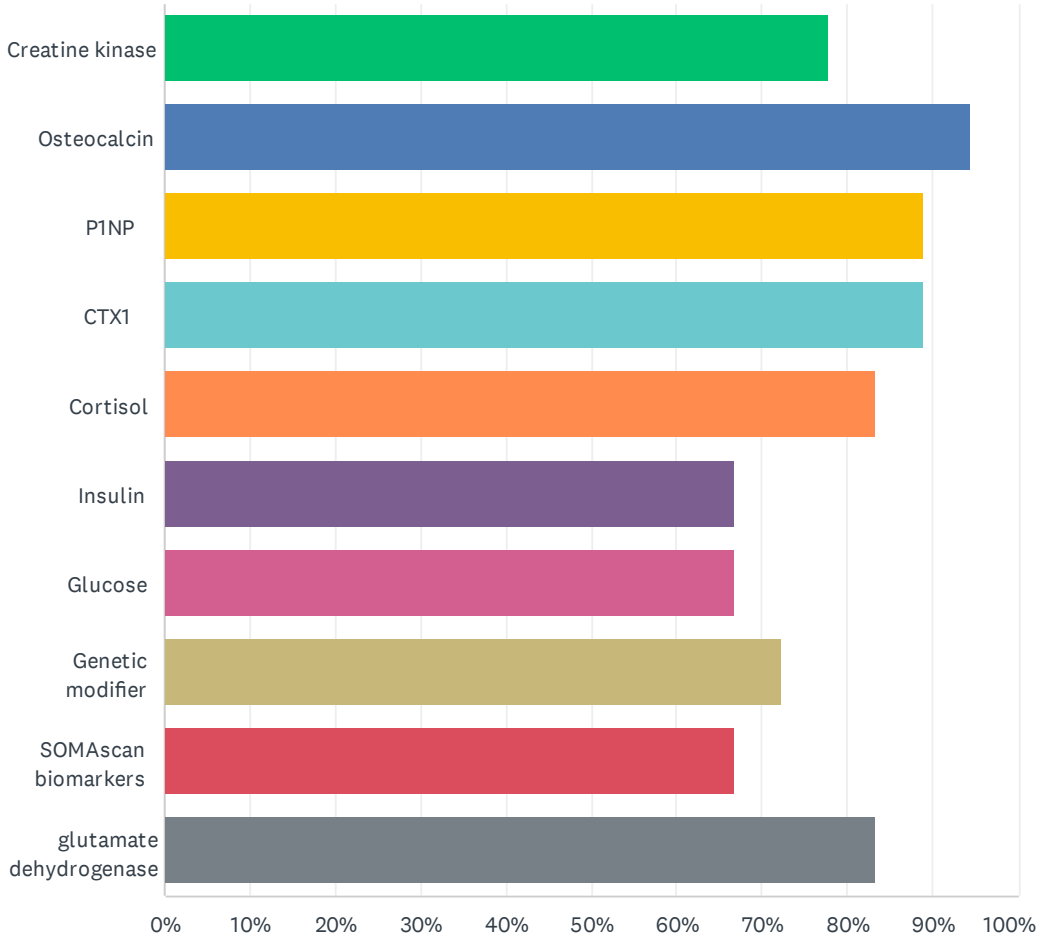


ANSWER CHOICES	RESPONSES	
Tabular form	5.26%	1
Graphical form	0.00%	0
Both tabular and graphical form	94.74%	18
Neither tabular nor graphical form	0.00%	0
Other (please specify)	0.00%	0
TOTAL		19

Q3 Your son generally contributes to 3 types of data collected in a clinical trial:· Clinical efficacy. These are measures of the benefit of the drug. In DMD these are typically measured by timed function tests. An example is the 6-minute walk test.· Clinical safety. These are measures of side effects or other health concerns. An example is stunting of growth.· Laboratory measures. These are often blood tests, typically called "biomarkers". An example is blood sugar.In the vamorolone trials, many different efficacy, safety and laboratory measures were collected and studied.Efficacy and safety information are relatively easy to understand. However, it is important to recognize that the clinical trial information returned to you may not directly impact the clinical care of your child.For laboratory measures, biomarkers may be difficult to interpret and may not be useful to your doctor in your son's medical care. For example, in some cases, we don't know what the "normal" levels of a particular biomarker are in boys with DMD. In some cases the test itself may not be studied well enough to interpret the result in a clinically useful way.A table of biomarkers used in the vamorolone trials is shown below, with a notation of the limitations of the test in the fourth column. As a result of these, and other limitations, none of these tests are recommended for routine use in the care of boys with DMD. However, they are done within the trial to answer a specific question about vamorolone treatment, or for a research purpose (to potentially develop better biomarkers). The term "exploratory biomarker" means that some information is known about the biomarker, but more information needs to be collected before it can be really useful to a physician, or a researcher, or a regulator. Which of the following biomarkers do you feel are important for you to receive, knowing the limitations of the testing (as shown in table above)?

Answered: 18 Skipped: 1

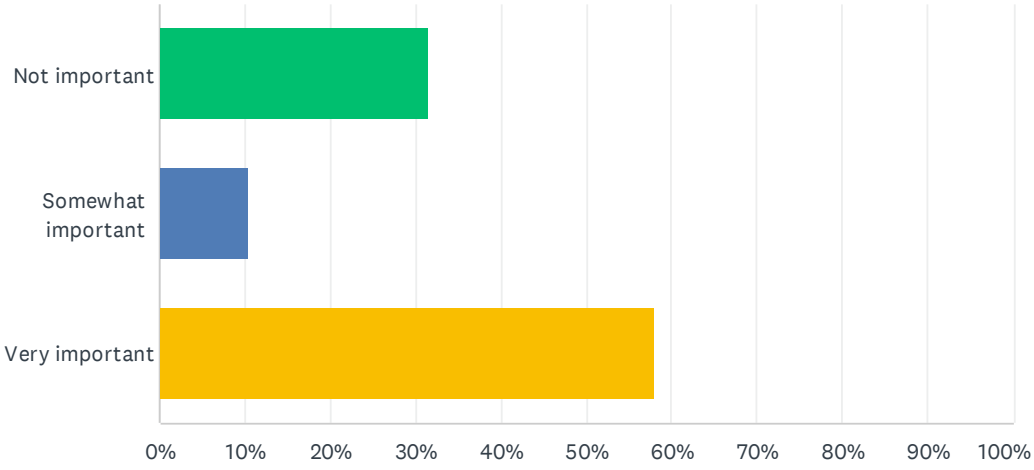
Return of results parent survey



ANSWER CHOICES	RESPONSES	
Creatine kinase	77.78%	14
Osteocalcin	94.44%	17
P1NP	88.89%	16
CTX1	88.89%	16
Cortisol	83.33%	15
Insulin	66.67%	12
Glucose	66.67%	12
Genetic modifier	72.22%	13
SOMAscan biomarkers	66.67%	12
glutamate dehydrogenase	83.33%	15
Total Respondents: 18		

Q4 “Blinding” is a procedure in which you and your son are unaware of which treatment arm you have been assigned to. A clinical trial is often double-blind – this means the doctor, study staff, drug company, and participant all don’t know who is receiving placebo, who is receiving study drug, and at what dose. This is done so that the effects of the drug can be assessed without unconscious bias of the doctor or participant or study staff. If this information is revealed during the study or while the study data are being analyzed, it could lead to bias. How important would it be for you to know what arm your son was in?

Answered: 19 Skipped: 0



ANSWER CHOICES	RESPONSES	
Not important	31.58%	6
Somewhat important	10.53%	2
Very important	57.89%	11
TOTAL		19

Q5 If it is important, why is it important to you?If it is not important, why is it not important to you?

Answered: 14 Skipped: 5

#	RESPONSES	DATE
1	To see if the dose has had an impact on safety and efficacy and discuss with the doctor.	5/27/2021 7:31 AM
2	wasn't important as all of the kids got the vamorolune if I recall correctly (each got at different dosage), and right after everybody got the same dosage.	5/13/2021 6:09 AM
3	This trial was not blind. None of the boys received placebo, and we knew the dose of the Vamorolone our son was getting, all along the trial.	5/7/2021 6:02 PM
4	To know any side effects to look for.	4/28/2021 4:37 PM
5	I would want to know if he was getting the drug to gauge his deterioration to children on other drugs vs no drugs etc.	4/7/2021 1:19 AM
6	We weren't in a blind	9/10/2020 2:34 AM
7	While it cannot change the outcome or results, knowing what arm can validate personal observations. Put to rest many "what-if" questions and scenarios.	8/23/2020 7:04 PM
8	I believe this is the only true way to understand the efficiency of the drug.	8/19/2020 6:32 AM
9	We received Vamorolone from the beginning.	8/18/2020 5:42 PM
10	To know whether or not he was given the medication, or a placebo.	8/18/2020 12:42 PM
11	We would like to know so that we can also gauge any benefits or differences. It is very frustrating not knowing given trials can be for long periods of time	8/10/2020 3:33 PM
12	If my son is in the placebo arm, that means that he'll get the drug eventually in the second leg of the trial. But he'll get the drug later than what he needs, and that is critical.	7/5/2020 1:37 PM
13	I just want to know everything I possibly can.	7/1/2020 2:40 PM
14	It's important because this drug could have effected his body. We want to know what was or wasn't effected	1/20/2020 9:06 AM

Q6 What do you expect you would do with information returned that summarizes results for all boys in the trial?

Answered: 18 Skipped: 1

#	RESPONSES	DATE
1	I may not have use for the information right now but in the future if Vamorolone becomes available I can use it to decide if we want to continue	5/27/2021 7:31 AM
2	Will try to see if it works for everybody as a whole, and if not, why it would work for some and not others. I would also also like to see the different effects, if such occur, between dosages.	5/13/2021 6:09 AM
3	I would be happy to know that the trial was successful, and that we had the right decision to join this trial.	5/7/2021 6:02 PM
4	Study it, keep it with medical folder.	4/28/2021 4:37 PM
5	Look it over	4/8/2021 9:48 AM
6	Consider things we may need to do to help our son stay healthy and active. Give me an idea how boys are doing as a whole.	4/7/2021 1:19 AM
7	Compare them to our sons results	12/5/2020 12:52 AM
8	Read and be more informed	9/10/2020 2:34 AM
9	Review and compare how our son aligned with others and stand of care.	8/23/2020 7:04 PM
10	Helps us be more informed and gives us an understanding of what impact the drug is having on an individual level.	8/19/2020 7:32 AM
11	Read it thoroughly to help me understand the efficiency of the drug.	8/19/2020 6:32 AM
12	Comparisons with other steroids treatment.	8/18/2020 5:42 PM
13	For my own knowledge, to get a better understanding of how effective Vamorolone is/was across the board, not only in my son.	8/18/2020 12:42 PM
14	It will help to make a future choice when the medication is approved and available.	8/17/2020 6:04 PM
15	Nothing - we'd just use to bench mark against our son for our own knowledge/piece of mind	8/10/2020 3:33 PM
16	Try to get my younger son enrolled in the next cohorts based on the results of the older one's trials.	7/5/2020 1:37 PM
17	File away in my personal file cabinet after reviewing them.	7/1/2020 2:40 PM
18	Google terms so we understand what terms mean	1/20/2020 9:06 AM

Q7 What do you expect you would do with information returned on your son's individual results?

Answered: 18 Skipped: 1

#	RESPONSES	DATE
1	I will have the information so we can discuss with the doctor if we may want to increase or decrease the dose. I hope to see information that makes me think we were lucky to be in the trial	5/27/2021 7:31 AM
2	For my son I the drug seemed to have worked. I would look at it to see if there were effects I'm not aware of, and to better understand as much as I can his current medical status for the results. Perhaps I'll show the individual results to our doctor to consult, if I'll need to.	5/13/2021 6:09 AM
3	I would read it carefully, and maybe will share it with my son (not sure). and maybe it would be helpful for future trials or approved drugs.	5/7/2021 6:02 PM
4	Same	4/28/2021 4:37 PM
5	To go over it	4/8/2021 9:48 AM
6	Compare his results	4/7/2021 1:19 AM
7	Share them with his doctor	12/5/2020 12:52 AM
8	Read and be more informed	9/10/2020 2:34 AM
9	The data would potentially influence our decision to stay on Vamorolone long term. Also, the results of biomarkers that are not standard may lead us to pursue further intervention with our son's primary medical team.	8/23/2020 7:04 PM
10	Not sure yet. Possibly talk with my son's neuro-muscular consultant about them and the GP.	8/19/2020 7:32 AM
11	Read it thoroughly to see how well my son is doing on the drug in comparison to others.	8/19/2020 6:32 AM
12	Discuss continued use or consider alternative treatments or trials if results are not as expected.	8/18/2020 5:42 PM
13	Be able to make more informed decisions on further participation in clinical trials.	8/18/2020 12:42 PM
14	Understand the effect of the medication on my son's progression based on data.	8/17/2020 6:04 PM
15	Nothing, we'd just use to satiate our own knowledge of his situation which if positive would give us hope and a positive mental mindset	8/10/2020 3:33 PM
16	Correlate to his ambulation. Cause we are seeing a drastic drop in his ambulation since he was moved to Prednisone in March 2020.	7/5/2020 1:37 PM
17	File away in my personal file cabinet after reviewing them.	7/1/2020 2:40 PM
18	Look to see how he compares to the other kids	1/20/2020 9:06 AM

Q8 Is there anything else that you would like ReveraGen to know?

Answered: 16 Skipped: 3

#	RESPONSES	DATE
1	I would like to know if Vamorolone is shown to be helpful, will we be able to continue to get the Vamorolone until it can be approved by public health insurance in Israel	5/27/2021 7:31 AM
2	I have to sons with Duchenne, currently both on Vamorolone. I hope this data may possibly help me better understand why it would seem to work for one and not for the other.	5/13/2021 6:09 AM
3	Even though we don't know the final results, we feel it did good for our son, and hopefully we be available soon for all boys with DMD, and even for other medical conditions, the requires the use of steroids.	5/7/2021 6:02 PM
4	Love the Vamorolone!	4/28/2021 4:37 PM
5	No	4/8/2021 9:48 AM
6	We are happy with the trial and all the work that goes into it! We are hoping it won't cost more than we can afford. That is our biggest fear because we are very positive about Vamorolone.	4/7/2021 1:19 AM
7	We might use this data to decide if we are to continue	9/10/2020 2:34 AM
8	Thank you for pursing the opportunity to release data to families!	8/23/2020 7:04 PM
9	no	8/19/2020 7:32 AM
10	No.	8/18/2020 5:42 PM
11	Thank you for releasing the data; it's much appreciated, especially for those of us who understand how to read and interpret data.	8/18/2020 12:42 PM
12	Estimated time of approval and if it is going to be a good substitute for current steroids regime	8/17/2020 6:04 PM
13	No	8/10/2020 3:33 PM
14	I have absolutely no doubt that Vamorolone helped my older one and was tolerated really well. I am hoping it gets approved in early 2021, so that I can switch both my kids on it. Please keep up your excellent work.	7/5/2020 1:37 PM
15	We are so grateful we were selected to participate in this trial.	7/1/2020 2:40 PM
16	This information is important. I'd like a call to discuss what it is I am looking at	1/20/2020 9:06 AM

Thank you for consenting to participate in a study about the process of returning clinical trial data to patient families. If you have questions about any of the information provided, please reach out to Suzanne Gaglianone at suzanne.gaglianone@reveragen.com.

We are very grateful to your child and to your family for participating in a vamorolone clinical trial, and also for participating in this current data return study.

We look forward to your feedback on a follow-up survey after your son's clinical trial data is returned to you.

As you requested, we are providing individual and aggregate data to you in this report.

Your son participated in VBP15-002 and VBP15-003, trials which have both been completed.

Your son's dose group was 0.25 mg/kg/day.

There are generally 3 types of data on your son that are collected in a clinical trial:

- **Clinical efficacy**. These are measures of the benefit of the drug. In DMD these are typically measured by timed function tests. An example is 6-minute walk test.
- **Clinical safety**. These are measures of side effects or other health concerns. An example is stunting of growth.
- **Laboratory measures**. These are typically blood tests, typically called "biomarkers". An example is blood sugar.

In the vamorolone trials, many different efficacy, safety and laboratory measures were studied.

Efficacy and safety information are relatively easy to understand. However, it is important that this clinical trial information may not have direct impact on the clinical care of your child.

Although we are giving you individual data, these tests are not being done in the trial to measure your son's individual abilities, or how the drug worked or didn't work *in your son.* In order to answer questions about how the drug is working, your son's test results are part of a whole program of multiple studies. Your son's test results are being analyzed as part of a cohort of patients, according to a pre-designed study plan.

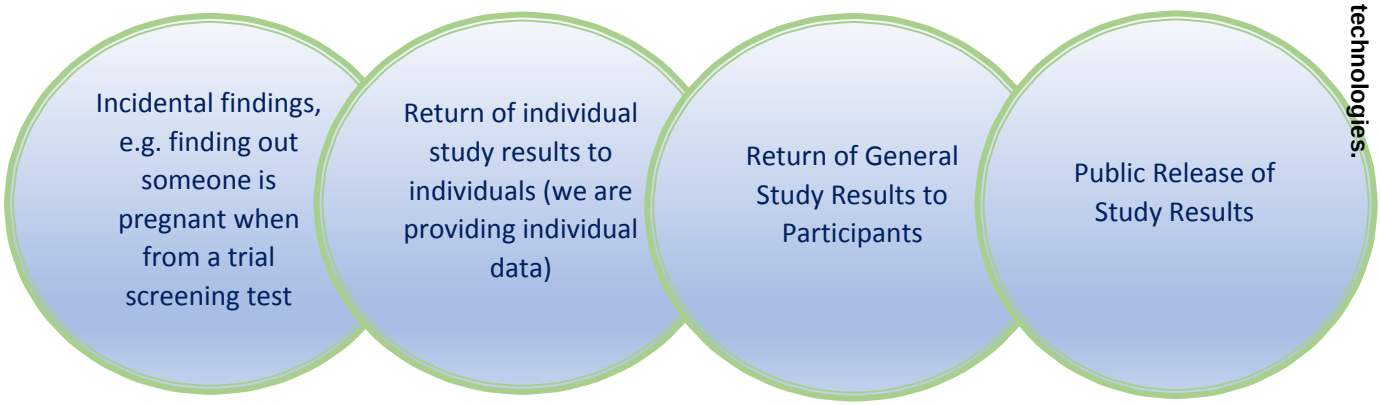
Your doctor doesn't have access to these data and may not be able to interpret them easily. To find out more information about how your son is doing clinically, it is best not to rely on these data, but to speak to your doctors and nurses! Your doctors and nurses know your son as an individual. They know how to take care of children with DMD, and they have a very important

relationship with your son and your family. At ReveraGen, there are researchers and pediatricians who care about helping kids with DMD. But we are not experts in taking care of children with DMD, and we're not supposed to know your son as an individual. Research is different from clinical care- they're both important, but they're kept separate *on purpose*. Your doctor's primary goal is to take the best care of your son and your family that he or she possibly can. As a drug company, we are going through the careful steps that are necessary to see if vamorolone is safe and effective in boys with DMD. If it is safe and effective, we will do our best to make it available to help patients.

So now that this has been stated, we will explain why drug companies don't usually give out their data.

There are different types of data, including incidental findings, individual study results, general study results, and public release of data. Incidental findings that are critical to the patient's health need to be reported to their physician. After a study is complete, often a company needs to publicly release data if there are investors in the company (to avoid getting into legal troubles). Sometimes scientific groups have rules about publishing a manuscript or giving a presentation at a scientific meeting before data is released. Also, it's important for companies not to "promote" their drug to patients or physicians before it's approved by the regulatory agencies to be marketed for a specific group of patients. The regulatory agencies approve drugs after they review all the data and determine that the drug is safe and effective. ReveraGen (and the regulatory agencies) don't know if vamorolone is safe and effective while the trials are still ongoing and before the data is all analyzed. If individual or general study results get released too early, people might misinterpret the data and be either too hopeful or too critical about the drug. Sometimes trial data can be misleading if it isn't presented or interpreted in the right way. And sometimes a drug may look very promising in early trials, but then not work in a placebo-controlled trials.

Many of these tests aren't very important or helpful to your doctor when he or she is assessing the progress of your son. So the doctor may not want to provide the results because they are difficult to interpret out of context from the study, and may not helpful for the care of your son. Giving these results might worry parents or cause them false hope or worry. Many of these results are more important to help researchers assess vamorolone.



Here is your son's Individual Data:

Functional outcome measures before and after treatment with vamorolone

	6-minute walk test	Time to Stand from the Floor test		10-meter run/walk		Climb 4 stairs		North Star Ambulatory Assessment
	Distance in meters	In seconds	In velocity (rises/ second)	In seconds	In velocity (meters/ second)	In seconds	In velocity (tasks/ second)	Score
Baseline 30Jun2016	387	7.59	.132	6.37	1.57	3.81	.262	24
12 weeks 17Oct2016	367	Unable to do the test	.000	7.57	1.32	4.6	.217	23
24 weeks 17Jan2017	321	Unable to do the test	.000	8.12	1.23	5.84	.171	21

Here is a table showing the aggregate (rounded average) data for the boys in your son's dose group (0.25 mg/kg/day):

	6-minute walk test	Time to Stand from the Floor test	10-meter run/walk	Climb 4 stairs	North Star Ambulatory Assessment
Visit	Distance in meters rounded up to nearest 10	Average seconds rounded up to nearest 0.1	Average seconds rounded up to nearest 0.1	Average seconds rounded up to nearest 0.1	Average rounded up to nearest 1
Baseline	320	6.1	6.5	5.6	19
12 weeks	310	6.9	6.8	5.3	20
24 weeks	300	7.3	6.8	5.8	19

Here is a table of your son's Quantitative Muscle Testing results before and after treatment with vamorolone:

	Elbow extension (pounds)	Elbow flexion (pounds)	Knee extension (pounds)	Knee flexion (pounds)
Baseline	N/A	N/A	N/A	N/A

30Jun2016				
12 weeks 17Oct2016	5.98 8.50	9.97 9.86	18.66 18.55	9.76 9.86
24 weeks 17Jan2017	5.65 5.52	9.24 8.66	10.66 12.31	11.74 12.24

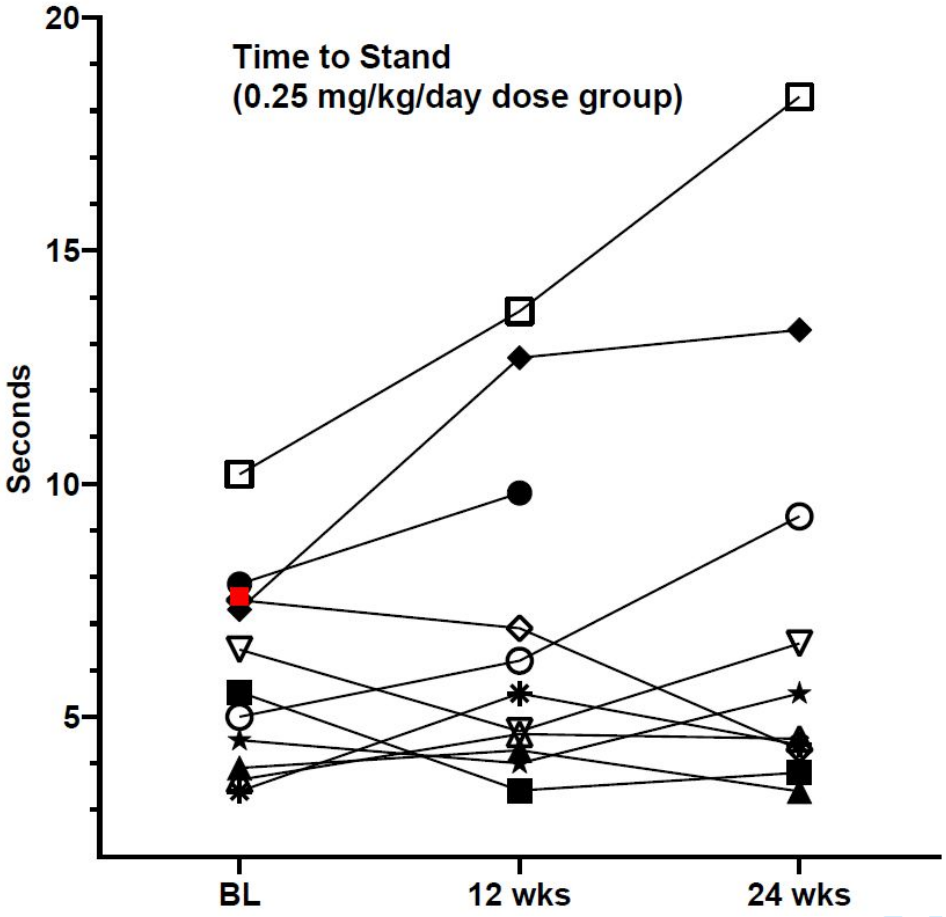
*N/A= data is missing

Here is a table showing the aggregate (rounded average) data for the boys in your son's dose group (0.25 mg/kg/day):

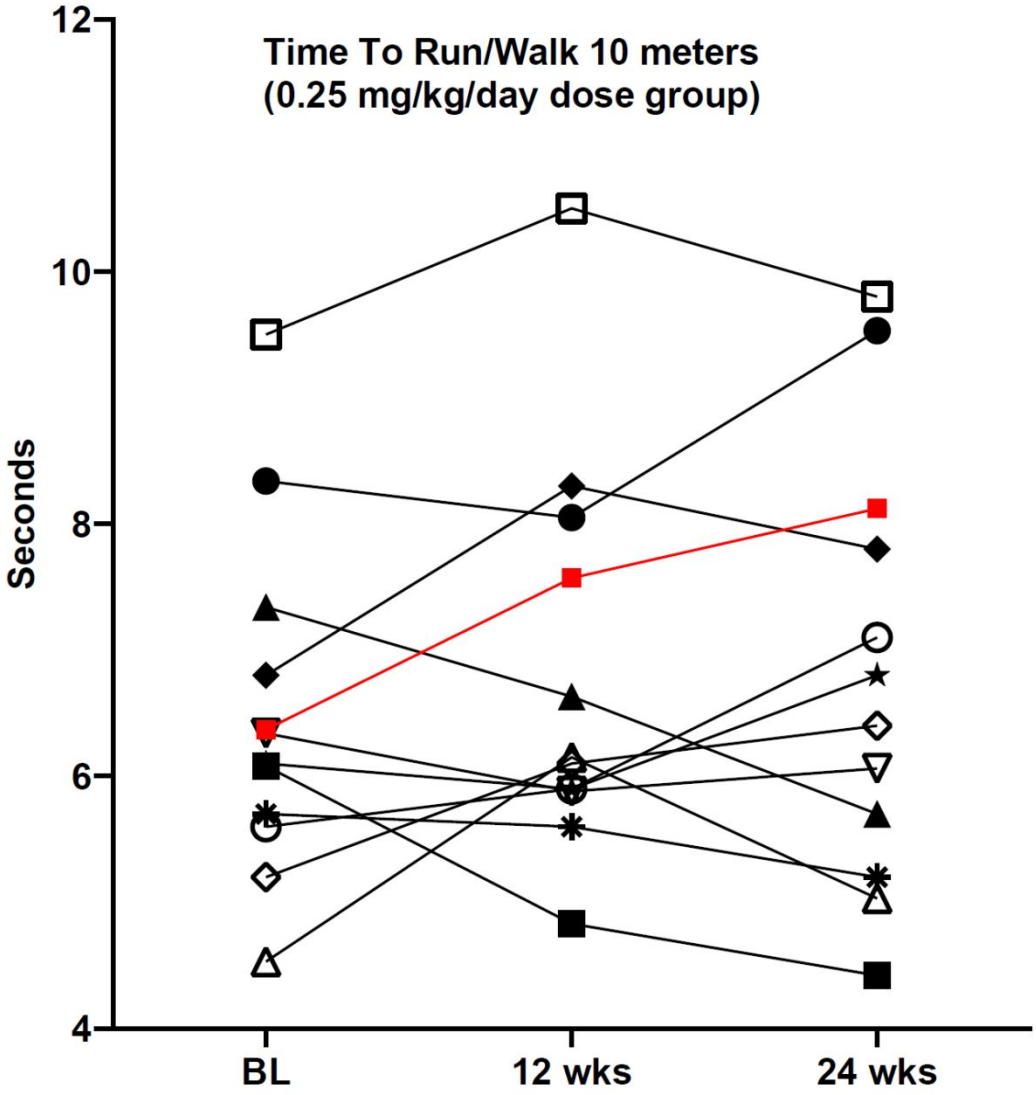
	Elbow extension (pounds)	**Elbow flexion (pounds)**	**Knee extension (pounds)**	**Knee flexion (pounds)**
Baseline	5.2	6.0	10.87	6.961
12 weeks	5.4	6.6	11.82	7.827
24 weeks	6.2	6.1	10.95	8.263

	Weight (kg)	Height (cm)	Body Mass index (BMI) (kg/m^2)
Baseline 30Jun2016	26.2	118	19
24 weeks 17Jan2017	29.6	122.1	19.9

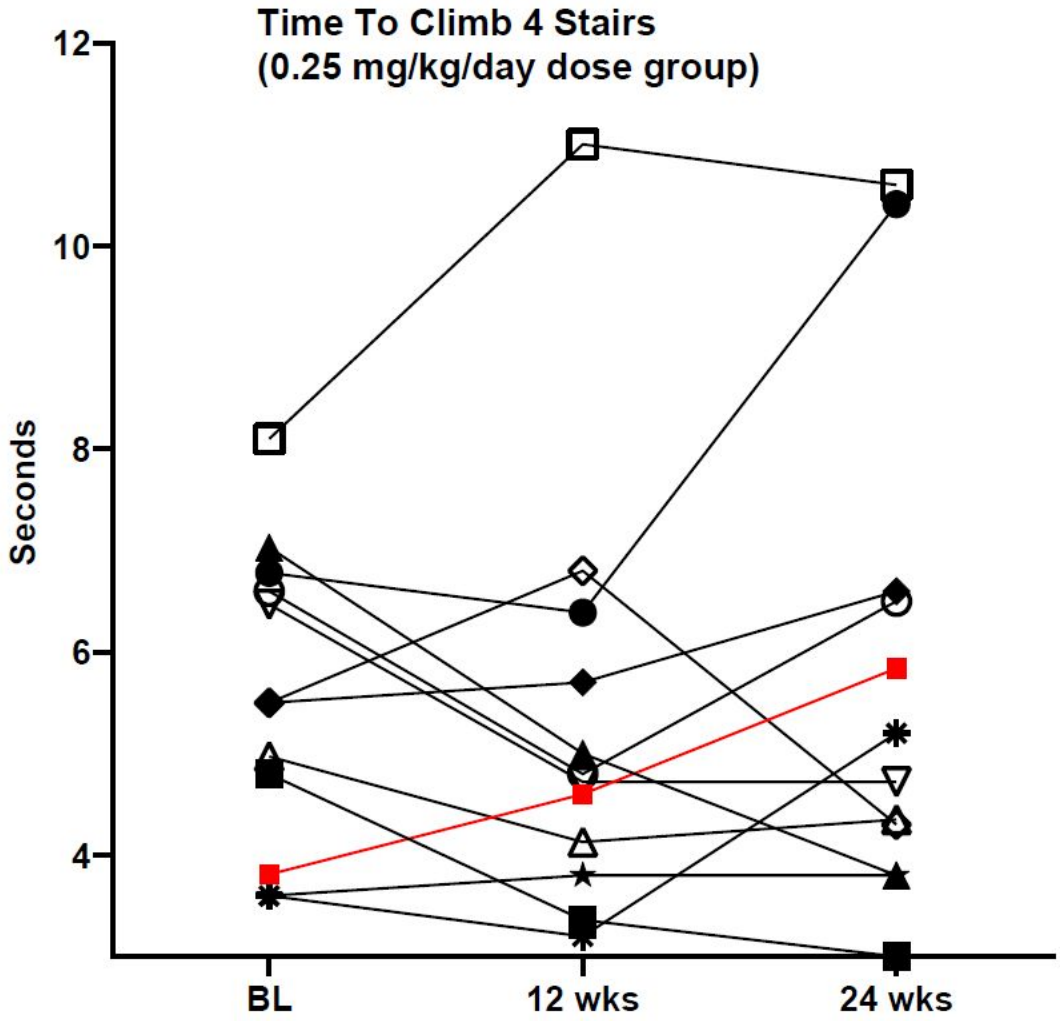
Time to Stand from the floor test, measured in seconds.
Your son's results are noted by the red square. Only one square can be seen because it was reported that your son was unable to do the test at 12 and 24 weeks.



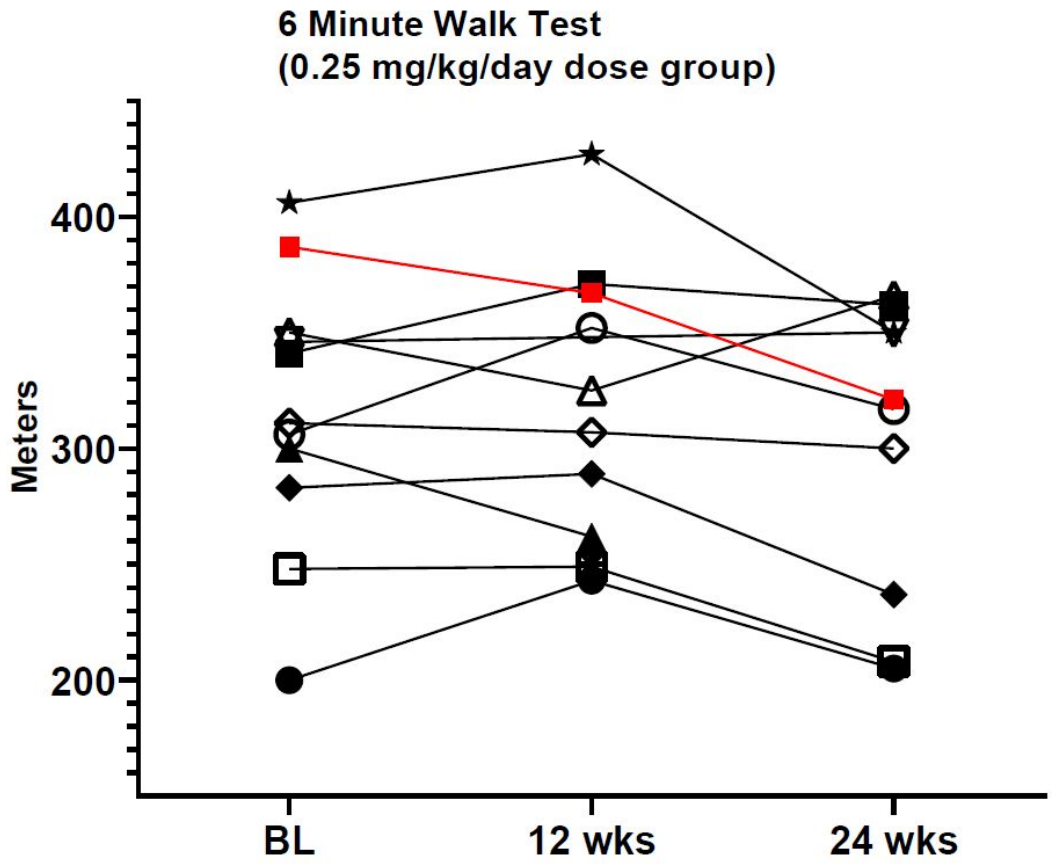
Time to Run/Walk 10 meters test, measured in seconds.
Your son's results are noted by the red square.



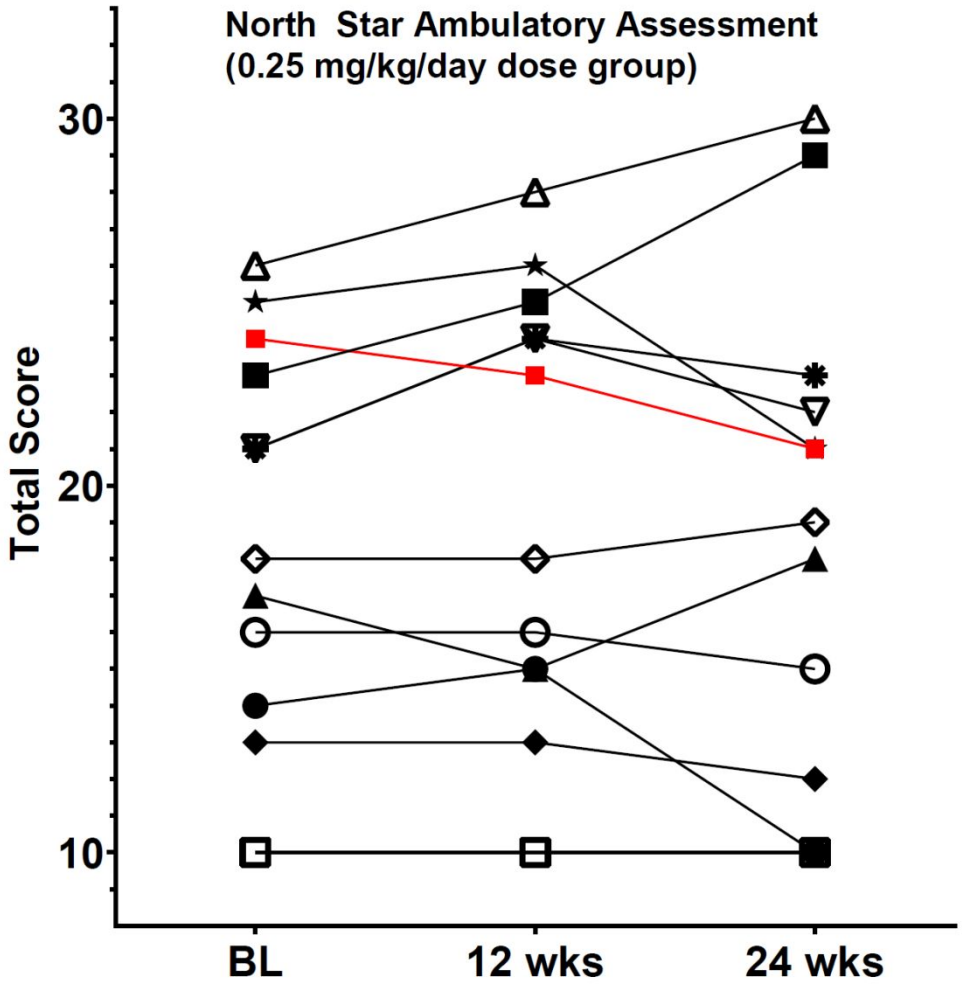
Time to Climb 4 Stairs Test, measured in seconds.
Your son's results are noted by the red square.



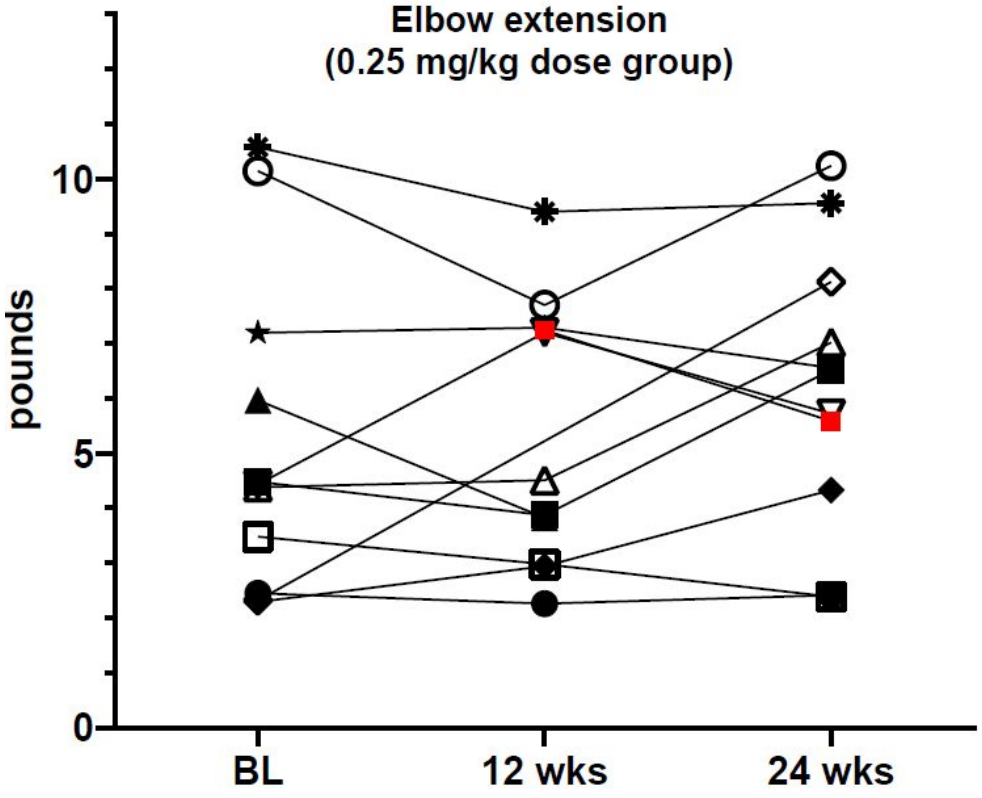
6 Minute Walk Test, measured in meters.
Your son's results are noted by the red square.

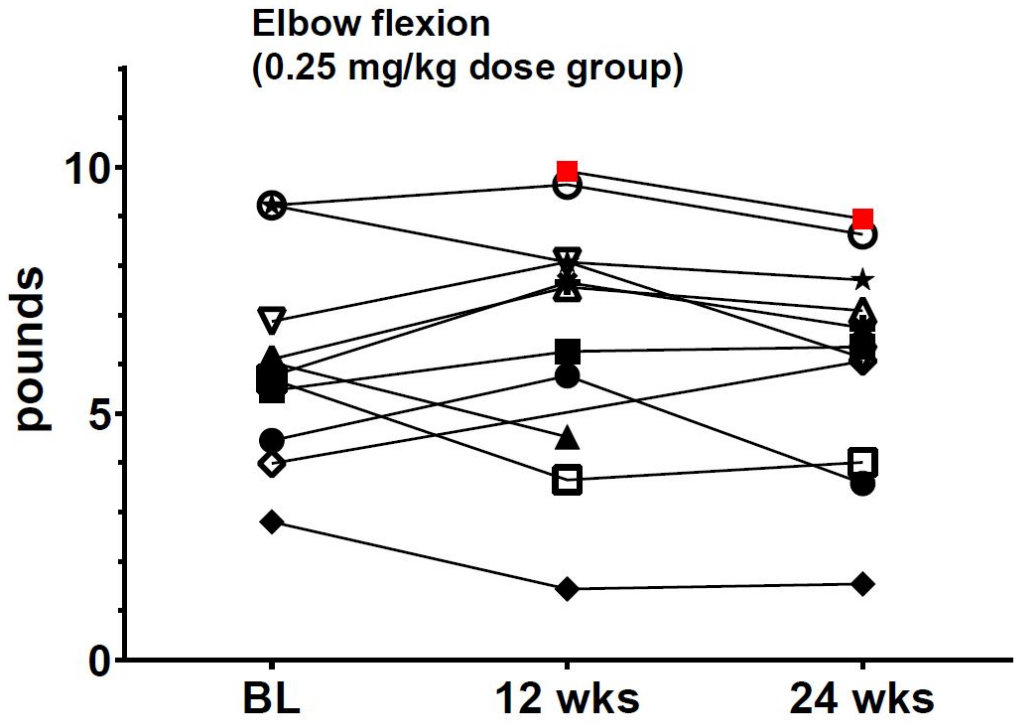


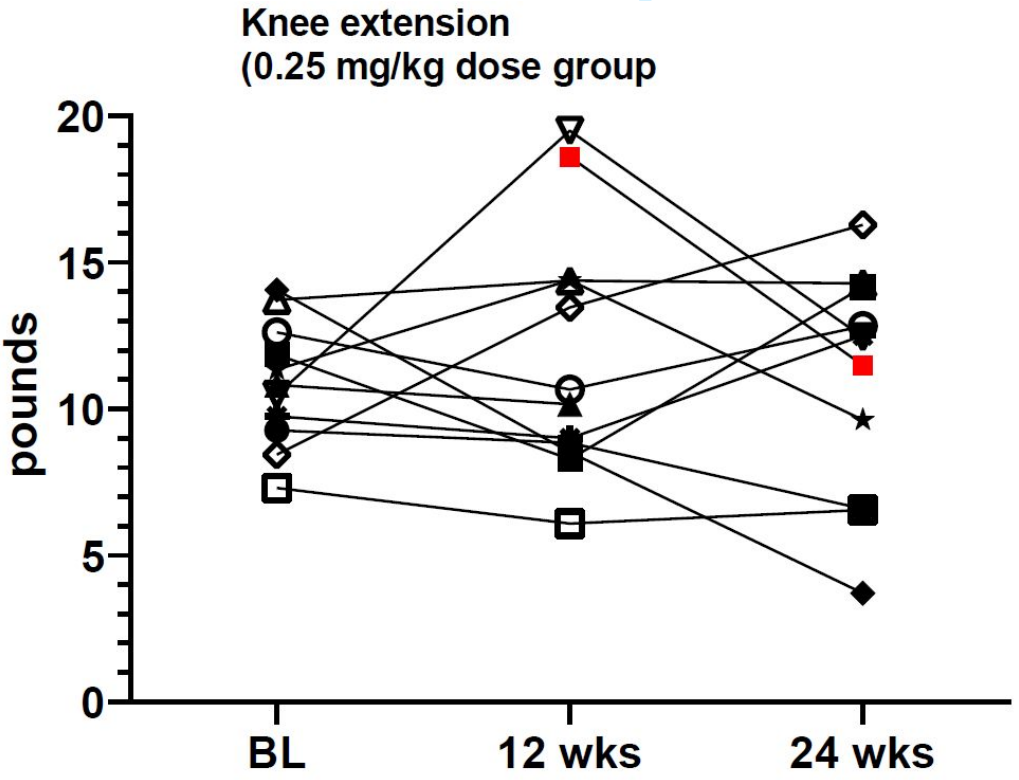
North Start Ambulatory Assessment score.
Your son's results are noted by the red square.

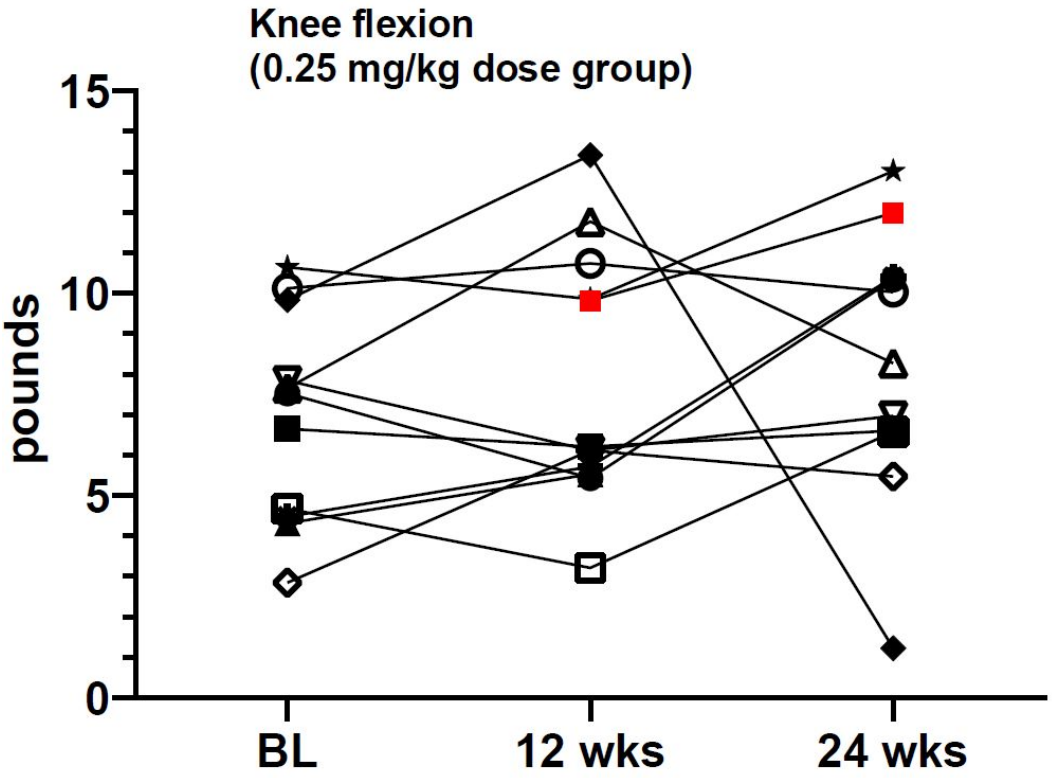


Quantitative Muscle Testing (elbow extension, elbow flexion, knee extension, knee flexion)
Your son's results are noted by the red square.









Biomarkers

For laboratory measures, biomarkers may be difficult to interpret and may not be useful to your doctor in your son's medical care. For example, in some cases, we don't know what the "normal" levels are in boys with DMD. In some cases, the test itself may not be studied well enough to interpret it in a clinically useful way.

A table of biomarkers used in the vamorolone trials is shown below, with a notation of the limitations of the test in the fourth column. As a result of these, and other limitations, none of these tests are recommended for routine use in the care of children with Duchenne muscular dystrophy. However, they are done within the trial to answer a specific question about vamorolone treatment, or for a research purpose (to potentially develop better biomarkers).

Blood test	What is the test measuring?	Why is ReveraGen testing this?	Some limitations of the test	Does your doctor typically order this test in the clinic?
Creatine kinase	Leakiness of muscle	To determine if vamorolone may change	Often quite variable from day-to-day in a person.	Often used as a diagnostic screening test.

		leakiness in DMD muscle.		
Osteocalcin, P1NP (N-terminal propeptide of type 1 collagen)	Bone formation	Part of evaluation of vamorolone's effect on bone (along with x-rays, growth monitoring, keeping track of bone fractures)	Varies depending on a person's age. Can be impacted by a drug, or by DMD itself, or by lack of growth for some other reason. Interpreted along with other bone biomarkers, x-rays, and growth (not by itself).	No
CTX 1 (C-terminal telopeptide of type I collagen)	Bone loss	Part of evaluation of vamorolone's effect on bone (along with x-rays, growth monitoring, keeping track of bone fractures)	Varies depending on a person's age. Can be impacted by a drug, or by DMD itself, or by lack of growth for some other reason. Interpreted along with bone formation biomarkers, x-rays, and growth (not by itself).	No
Cortisol	Adrenal suppression	Part of evaluation of effects of vamorolone on the adrenal glands (along with an additional ACTH stimulation test in VBP15-004, monitoring for symptoms associated with adrenal suppression).	Varies depending on time of day that blood was drawn. Test doesn't tell how well the adrenals will respond to stress or illness.	Not usually- a child on chronic corticosteroids will likely have a low morning cortisol. All children who become seriously ill, or need surgery while taking steroids should be given "stress dose steroids". As we don't know about the effects of vamorolone on the adrenal glands yet, we ask parents/physicians to take this same precaution for children in vamorolone trials.
Fasting insulin/glucose	Low blood sugar,	Part of the evaluation of	Varies depending on whether child is	Sometimes.

	insulin resistance	effects of vamorolone on insulin resistance	fasting or not. Not a challenge test (like an oral glucose tolerance test). Not diagnostic of diabetes.	
Genetic modifiers	Differences in specific DNA sequences in your child.	To determine if certain genetic differences may affect the way a child responds to vamorolone (both efficacy and safety)	This will be done for research purposes. We are not certain when this data will become available.	No. There isn't yet enough known about genetic modifiers to make them useful in the clinic.
Glutamate dehydrogenase	Liver toxicity	To determine the effects of vamorolone on the liver.	This test is still experimental in patients with Duchenne muscular dystrophy.	No.

Here are your son's biomarker results. These tests have been done for research purposes only- to see how treatment with vamorolone affects these blood tests.

	Osteocalcin (bone formation)	P1NP (bone formation)	CTX1 (bone resorption)
Baseline 30Jun2016	52.6	1024	906
24 weeks 17Jan2017	54.4	1031	1455

	Result At Baseline	Result at Week 24-29	Low-High Range
Cortisol (mcg/dL)	4.4	3.2	2-17
Hemoglobin A1C (%)	4.9	4.9	4-6
Glucose (mg/dL)	79	87	60-99
Insulin	4.5	7.7	n/a
Glutamate dehydrogenase	4.8	5.5	0-<7
Creatine kinase (U/L)	42458	24246	18-158

ReveraGen not have genetic modifier data yet- these tests have not yet been run.

ReveraGen conducted a research study to evaluate how "exploratory" blood biomarkers change from before to after treatment with vamorolone for 2 weeks. We chose to look at inflammatory proteins in the blood that have been shown to change quickly after treatment with corticosteroids (in patients with different diseases, including DMD). These data are reported in "Relative Fluorescence Units", abbreviated RFU, which is how the test measures the protein level. A dose-responsive change was seen in 6 of the biomarkers. Your son's results are here at baseline and 2 weeks, followed by the aggregate data from the study, which showed Your son is in the 0.25 mg/kg dose group. It's important to remember that these biomarkers are not adequate to show efficacy of vamorolone in boys with DMD, but changes in these proteins may be an indication of vamorolone's anti-inflammatory activity in the body.

This is an example of test that is only done for research purposes. They haven't been tested well enough to use them in the clinic and aren't available for your doctors to run. It is not possible for us or your doctors to use these tests to explain anything about your son's medical condition or progress.

The results of your son's exploratory biomarker testing are shown here.

Note that are focusing on the 6 biomarkers that importantly showed a dose response to vamorolone in the study (on average, bigger changes were seen in kids who were taking higher doses).

Protein	Baseline RFU	2 Week RFU	Change from Baseline
CD23	7530.2	7221	- 309.1
MDC/CCL22	2604.2	2649.3	+ 45.1
IL22 BP	5192.7	4618.9	-573.8
Lymphotoxin a1b2	466.4	517.3	+50.9
IGFBP2	405.4	352.5	-52.9
MMP12	6421.9	6081	-340

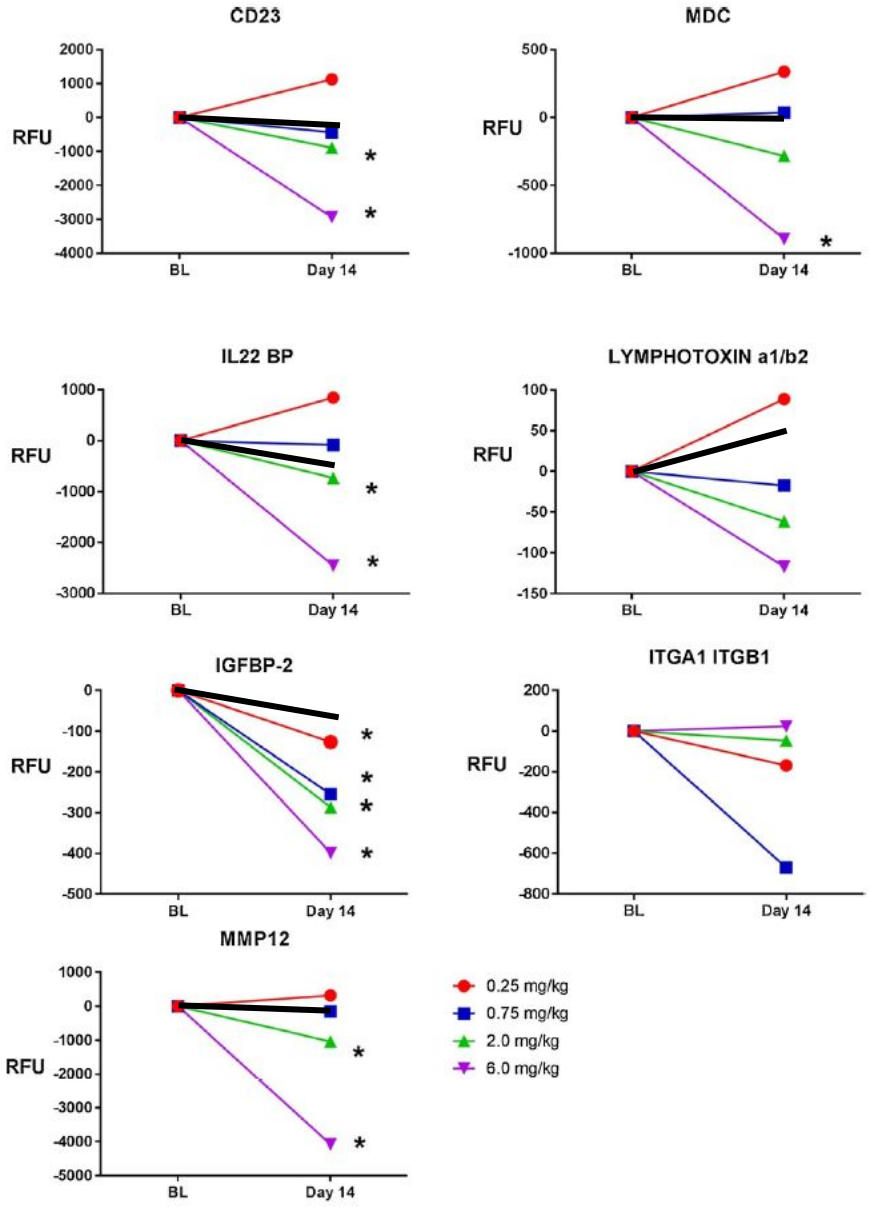
RFU= relative fluorescence units; MDC = macrophage derived chemokine (aka CCL22); IL22 BP = Interleukin 22 binding protein; IGFBP2= insulin growth factor binding protein 2; MMP12 = matrix metalloproteinase 12

The average results from the boys in the 0.25 mg/kg/day dose group (your son's dose group) are shown here for these same biomarkers:

Protein	Average Baseline RFU for 0.25 mg/kg/dose group	Average 2 Week RFU for 0.25 mg/kg/dose group	Average Change from Baseline for 0.25 mg/kg/dose group
CD23	8824	9951	+ 1127
MDC	2458	2796	+ 338
IL22 BP	6261	7110	+ 849
Lymphotoxin a1b2	471.0	559.9	+ 89
IGFBP 2	6261	7110	+ 849
MMP12	3421	3746	+ 324

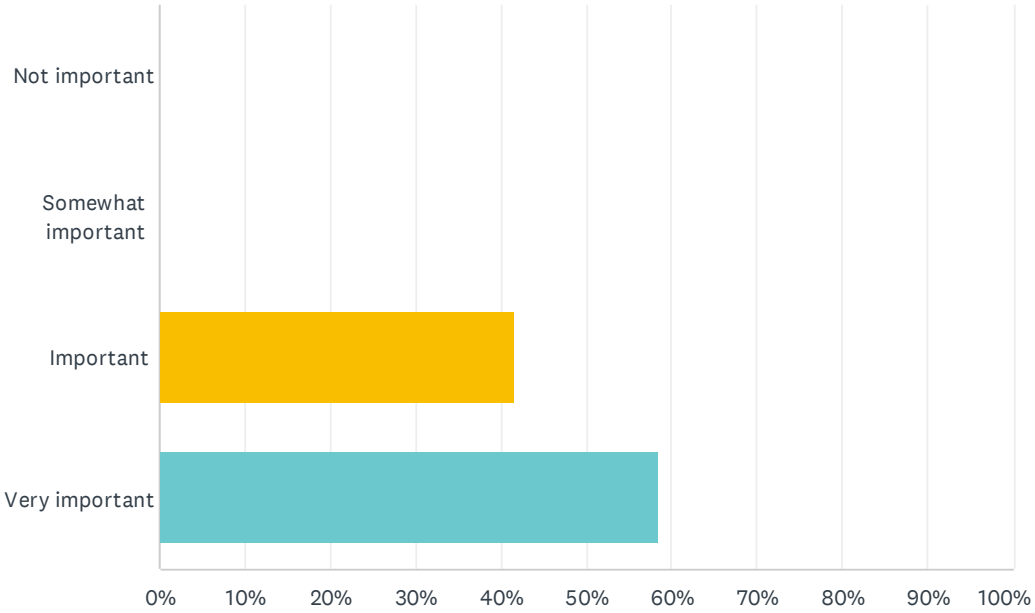
RFU= relative fluorescence units

Here these same data are shown above in graphical form. Each line shows the *average* change in RFU from baseline (red line = 0.25 mg/kg/day dose group; blue line 0.75 mg/kg/day dose group; green line 2.0 mg/kg/day dose group; purple line 6.0 mg/kg/day dose group). The 0.25 mg/kg/day dose group is your son's dose group. A black line represents an approximation of your son's data.



Q1 Please answer the following questions.How important was it to you to receive your child's individual clinical trial results?

Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Not important	0.00%	0
Somewhat important	0.00%	0
Important	41.67%	5
Very important	58.33%	7
TOTAL		12

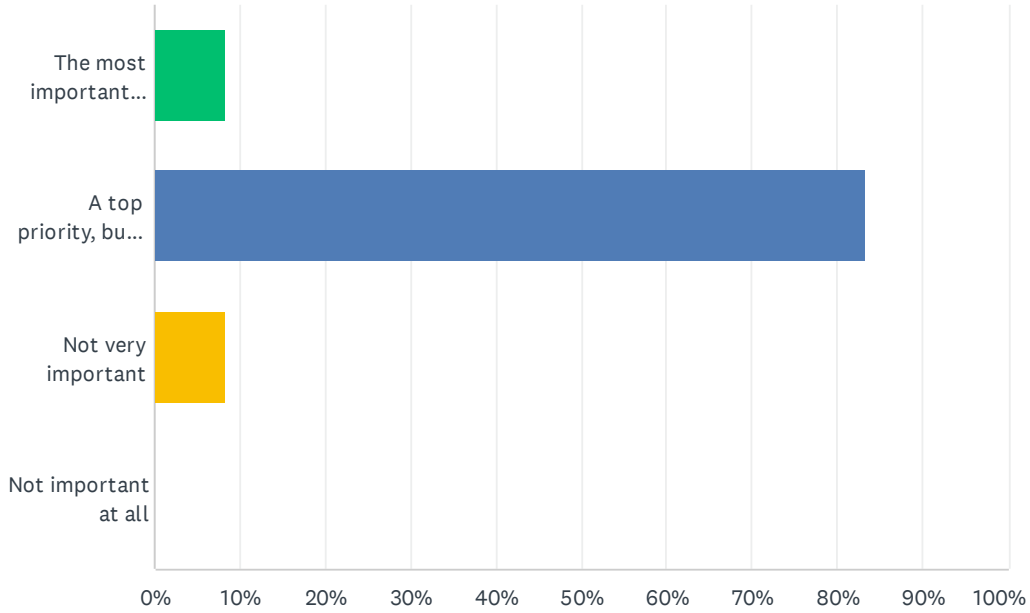
Q2 If it was important to you to receive your son's data, why was this important to you? You may skip this question if it does not apply.

Answered: 10 Skipped: 2

#	RESPONSES	DATE
1	Personal knowledge	6/29/2021 4:56 PM
2	To be informed	6/25/2021 12:31 PM
3	It is a great benefit to be able to see how my son may have responded during the Clinical Trail in all of these areas recorded, In Hopes to see some good benefit from the medication.	6/22/2021 8:49 PM
4	We took a big risk in being in the trial. Want to know if it works and how my son paired with the other boys	6/22/2021 4:29 PM
5	It’s nice to see how things are going and not be in the dark	6/22/2021 3:53 PM
6	All data to do with how my son is managing the condition/meds is important.	6/22/2021 3:14 PM
7	To understand the clinical help VBP15 provided	6/17/2021 10:34 PM
8	We would like further understanding about how the trial was going, and what difference it's made to our child as well as the rest of the children	6/9/2021 5:23 AM
9	To see actual data of improvement and/ or progression is important. Data helps you to understand if treatment works or not.	6/4/2021 11:58 AM
10	Just to see how our son is doing. We are hopeful he is doing better because if the drug and seeing the results gives us more hope.	6/3/2021 3:29 PM

Q3 How important was it to you to receive a summary of the results from other children in the trial?

Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
The most important priority	8.33%	1
A top priority, but not the most important	83.33%	10
Not very important	8.33%	1
Not important at all	0.00%	0
TOTAL		12

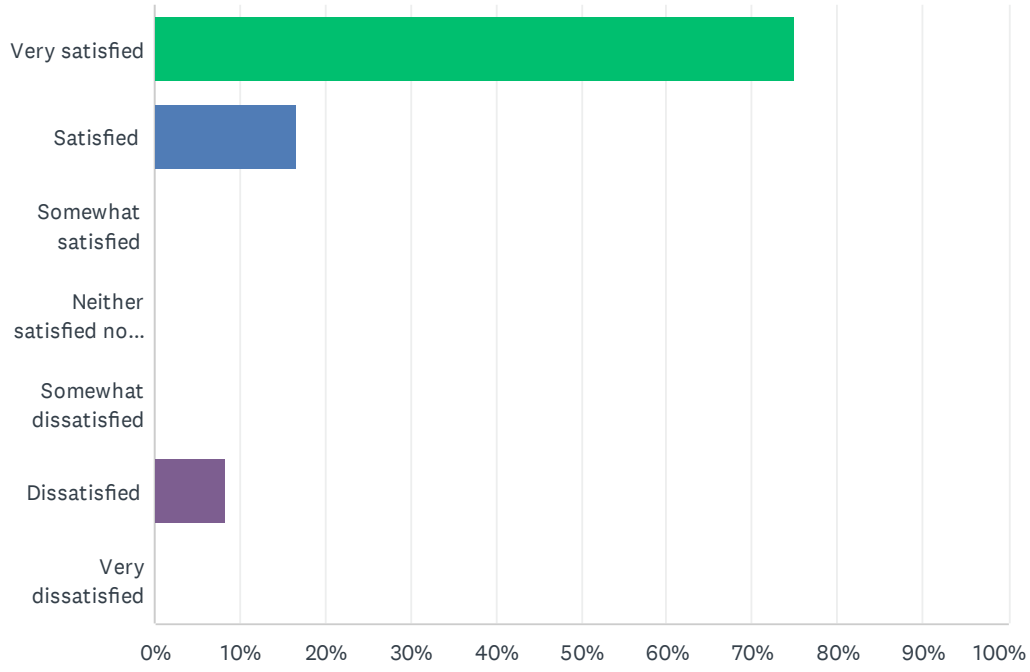
Q4 If it was important to you to receive a summary of data from other trial participants, can you tell us why? You may skip this question if it does not apply.

Answered: 8 Skipped: 4

#	RESPONSES	DATE
1	To stay informed	6/25/2021 12:31 PM
2	Its always great to see how my child was responding to the medication compared to other participants.	6/22/2021 8:49 PM
3	It’s nice to see how it’s doing with every one it’s important to see	6/22/2021 3:53 PM
4	So that I could see how he was doing in comparison with other similar boys.	6/22/2021 3:14 PM
5	To confirm my son belongs in the overall "good band"	6/17/2021 10:34 PM
6	This helps us benchamrk against how our child is doing. If we don't have a benchmark then we do not know if it is benefitting our child or not	6/9/2021 5:23 AM
7	More data more understanding. Comparing results is always helpful.	6/4/2021 11:58 AM
8	To see if others are also seeing good results	6/3/2021 3:29 PM

Q5 How satisfied were you with the delivery of data on an encrypted USB drive by mail?

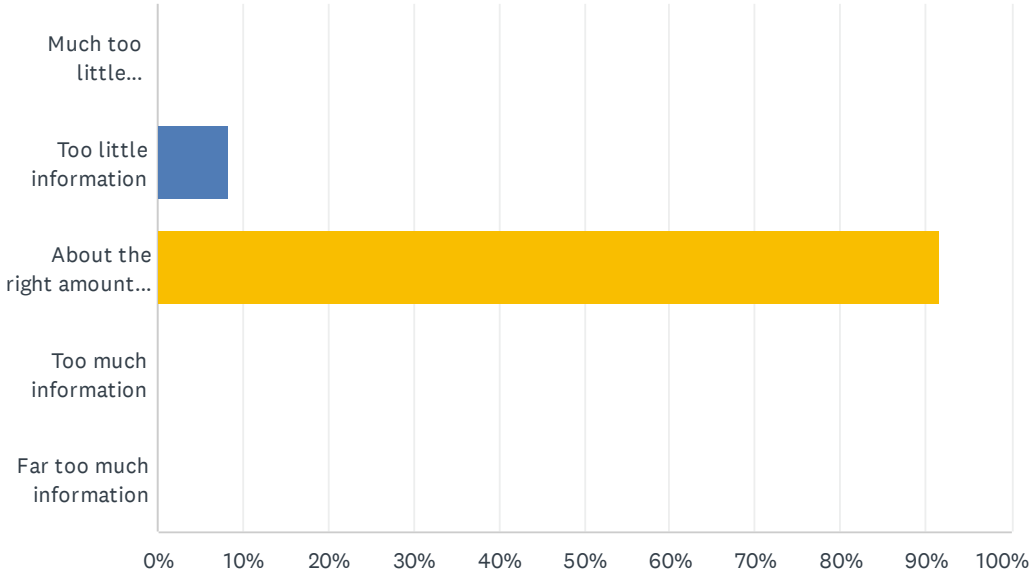
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Very satisfied	75.00%	9
Satisfied	16.67%	2
Somewhat satisfied	0.00%	0
Neither satisfied nor dissatisfied	0.00%	0
Somewhat dissatisfied	0.00%	0
Dissatisfied	8.33%	1
Very dissatisfied	0.00%	0
TOTAL		12

Q6 The amount of information provided was

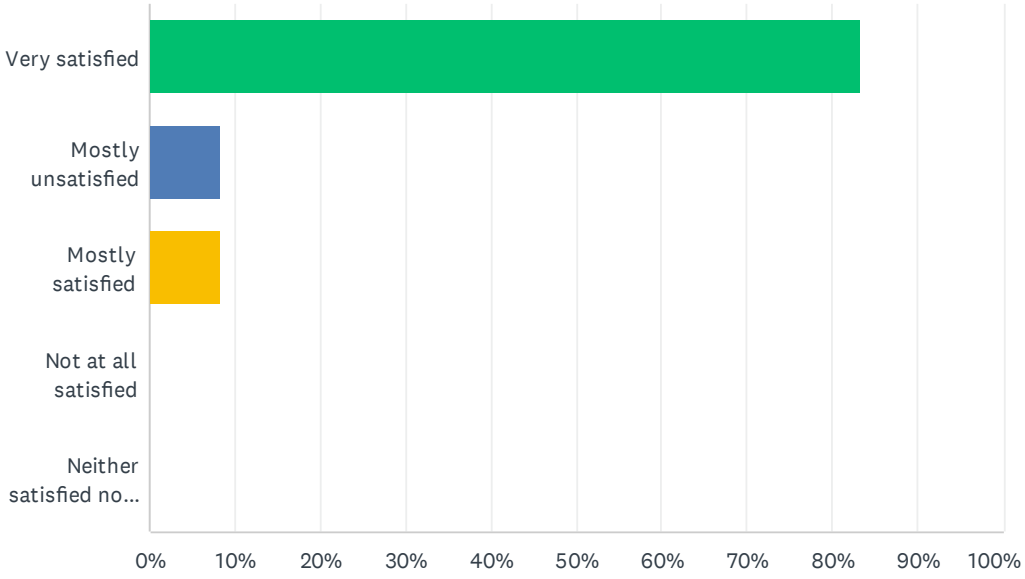
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Much too little information	0.00%	0
Too little information	8.33%	1
About the right amount of information	91.67%	11
Too much information	0.00%	0
Far too much information	0.00%	0
TOTAL		12

Q7 Were you satisfied with return of data to you directly by ReveraGen?

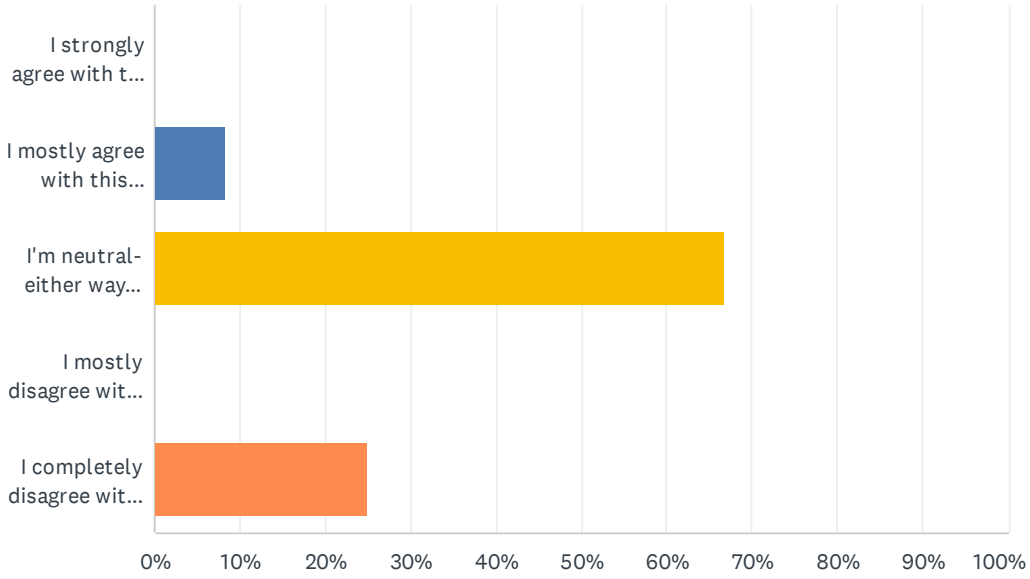
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Very satisfied	83.33%	10
Mostly unsatisfied	8.33%	1
Mostly satisfied	8.33%	1
Not at all satisfied	0.00%	0
Neither satisfied nor unsatisfied	0.00%	0
TOTAL		12

Q8 I would have preferred my child's individual data to be returned by my physician instead of by ReveraGen.

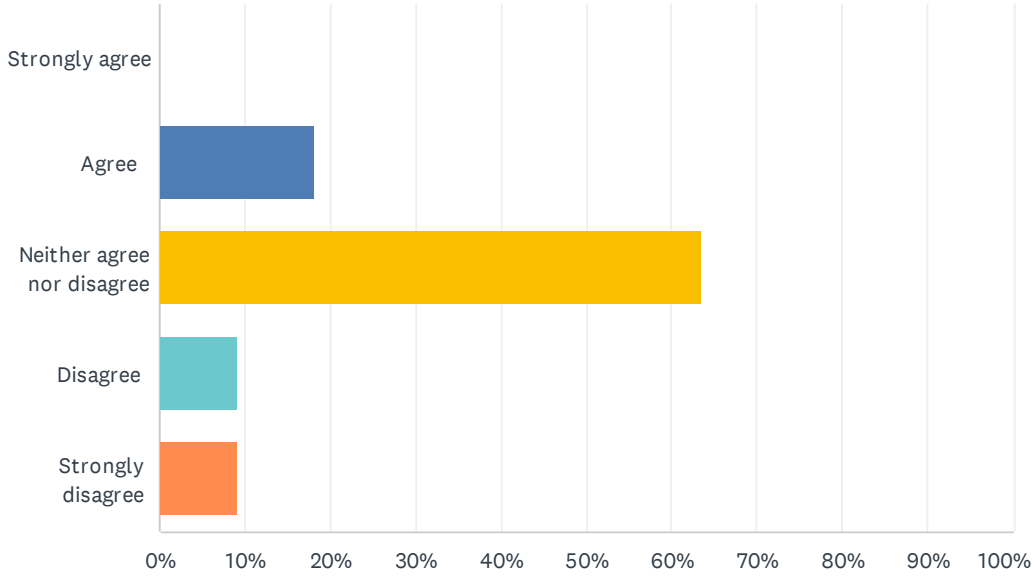
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
I strongly agree with this statement. I would have preferred that my physician returned my son's research data.	0.00%	0
I mostly agree with this statement.	8.33%	1
I'm neutral- either way would be fine.	66.67%	8
I mostly disagree with this statement.	0.00%	0
I completely disagree with this statement. I would prefer to receive my son's data directly from the company.	25.00%	3
TOTAL		12

Q9 I had unanswered questions after receiving the data.

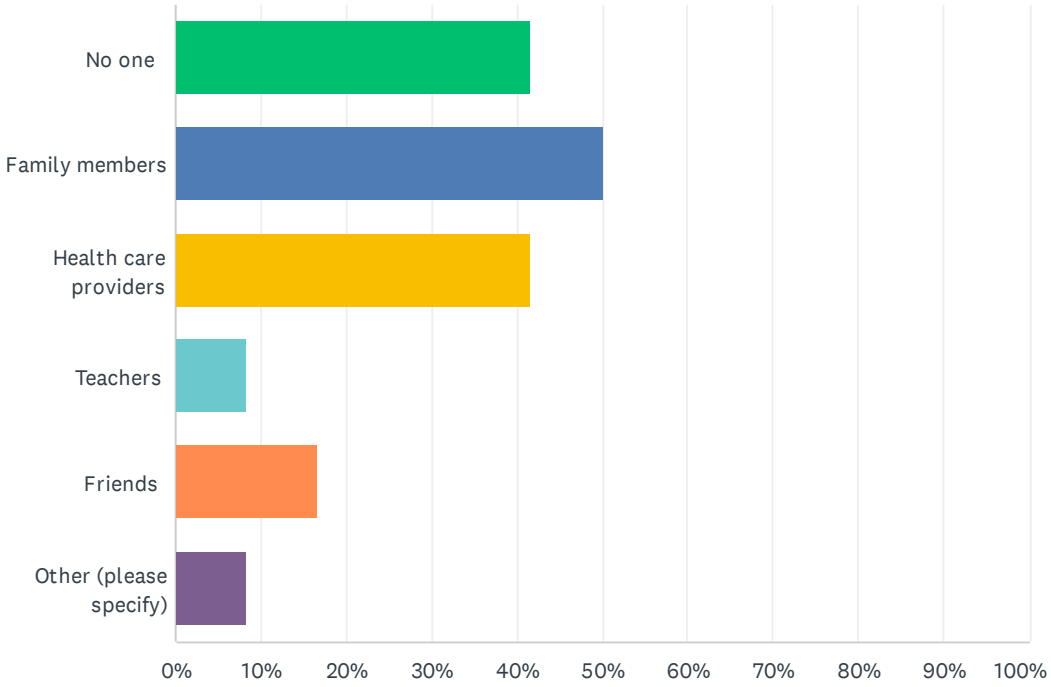
Answered: 11 Skipped: 1



ANSWER CHOICES	RESPONSES	
Strongly agree	0.00%	0
Agree	18.18%	2
Neither agree nor disagree	63.64%	7
Disagree	9.09%	1
Strongly disagree	9.09%	1
TOTAL		11

Q10 Who have you told anyone about the results you received from the ReveraGen? (Choose all that apply)

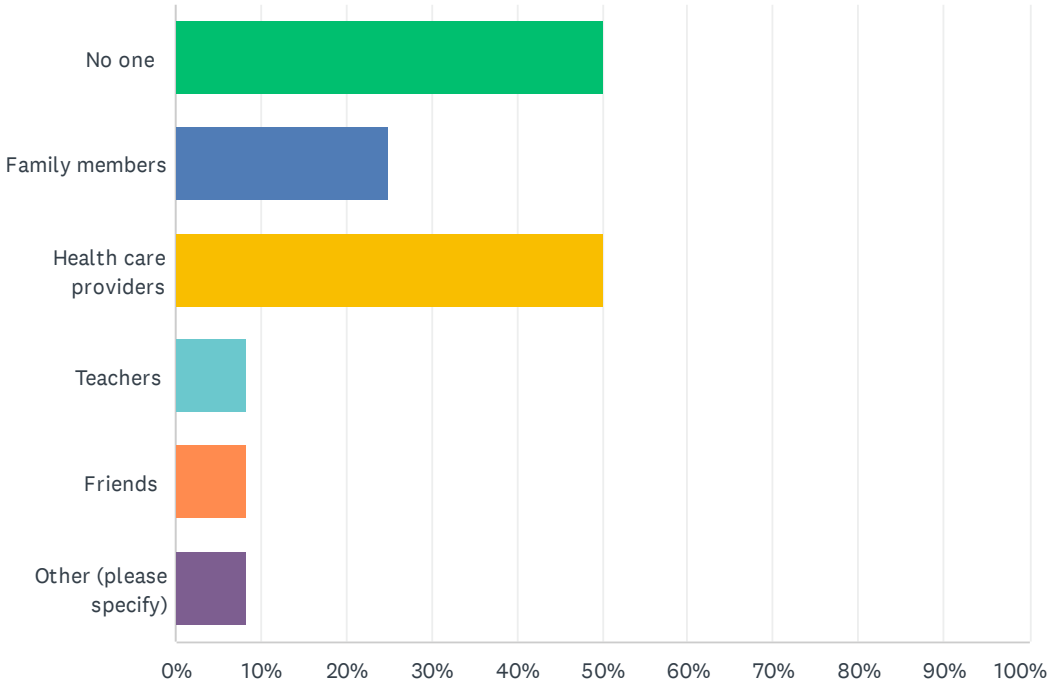
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
No one	41.67%	5
Family members	50.00%	6
Health care providers	41.67%	5
Teachers	8.33%	1
Friends	16.67%	2
Other (please specify)	8.33%	1
Total Respondents: 12		

Q11 Are there other people that you intend to tell about the results you received from ReveraGen? (Choose all that apply)

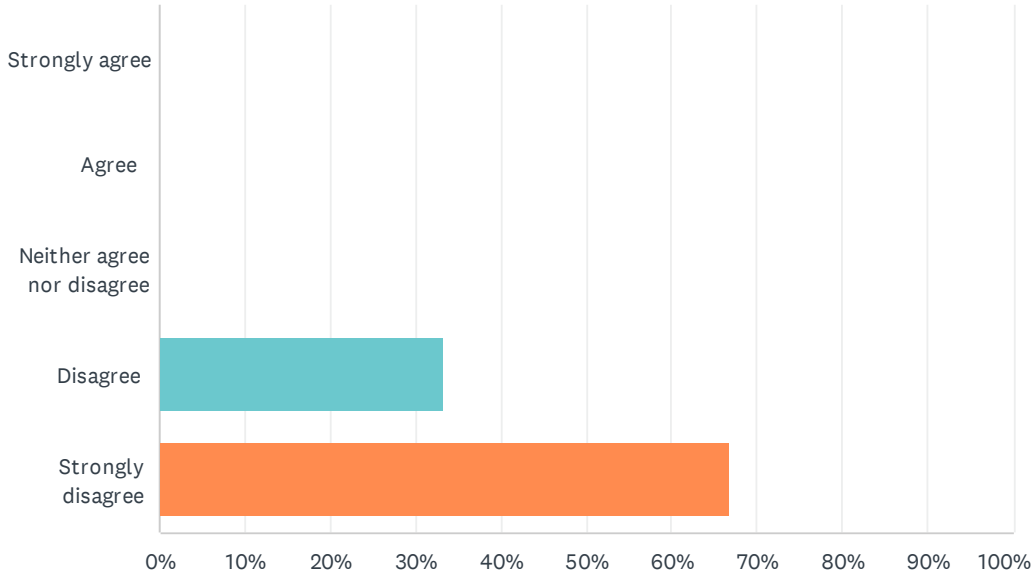
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
No one	50.00%	6
Family members	25.00%	3
Health care providers	50.00%	6
Teachers	8.33%	1
Friends	8.33%	1
Other (please specify)	8.33%	1
Total Respondents: 12		

Q12 I regret having made the decision to participate in this data return study

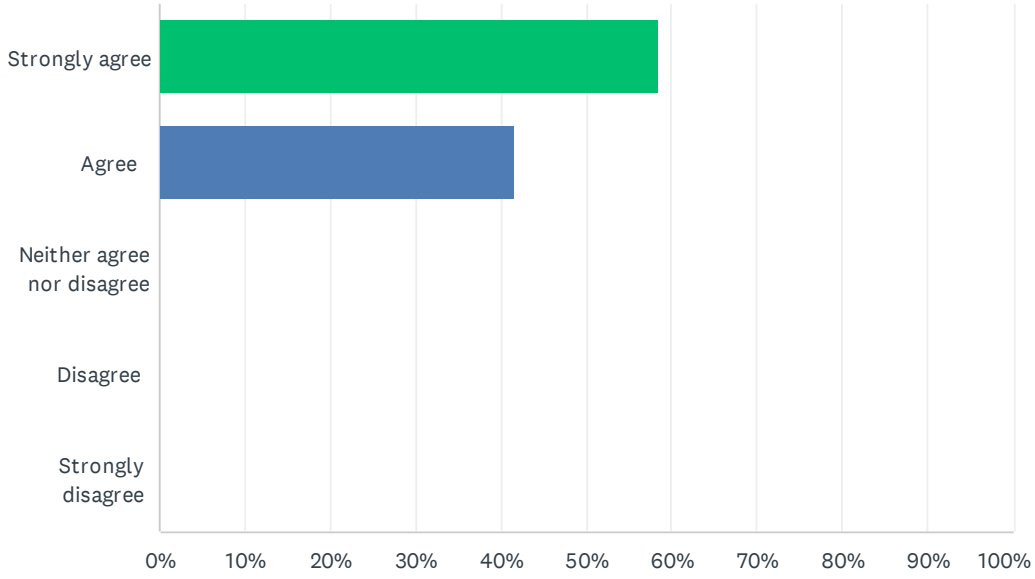
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Strongly agree	0.00%	0
Agree	0.00%	0
Neither agree nor disagree	0.00%	0
Disagree	33.33%	4
Strongly disagree	66.67%	8
TOTAL		12

Q13 If I had to it again, I would participate in this data return study.

Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Strongly agree	58.33%	7
Agree	41.67%	5
Neither agree nor disagree	0.00%	0
Disagree	0.00%	0
Strongly disagree	0.00%	0
TOTAL		12

Q14 If you regret the decision to receive your son's data or felt that the choice did you harm, can you tell us why? You may skip this question if it does not apply.

Answered: 1 Skipped: 11

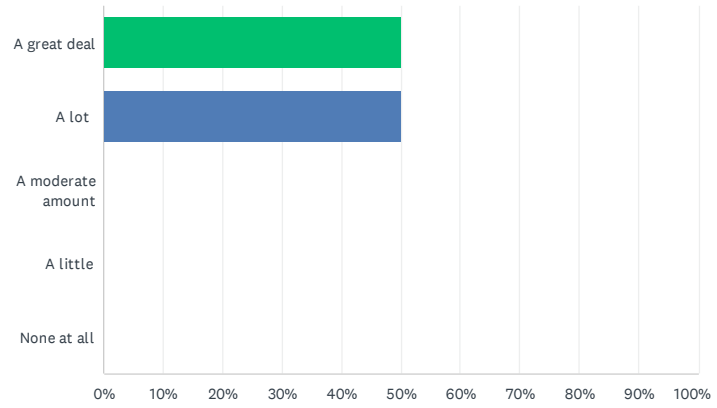
Q15 Do you have any additional concerns, comments, or questions for ReveraGen? You may skip this question if it does not apply to you. Thank you for participating in the survey! Best wishes to you and your family.From the ReveraGen team

Answered: 2 Skipped: 10

Q1 ReveraGen received a Bioethics supplement from the NIH to study a process of returning individual clinical trial data to patient families. We are returning data to study participants after the database is locked, the clinical study report written, and top-line results announced. One of the vamorolone clinical trial participants recently requested their data. We want to understand this issue from a physician perspective- thank you for completing this anonymous survey and answering the following questions._____

much importance do you believe families place on receiving their son's individual clinical trial results?

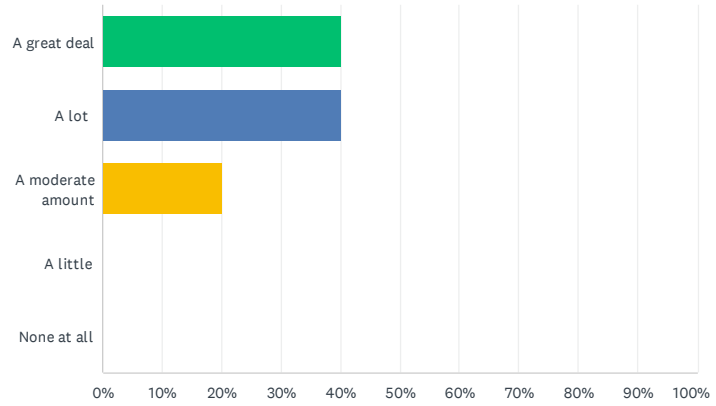
Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
A great deal	50.00%	5
A lot	50.00%	5
A moderate amount	0.00%	0
A little	0.00%	0
None at all	0.00%	0
TOTAL		10

Q2 How much importance do you believe families place on receiving their aggregate clinical trial results?

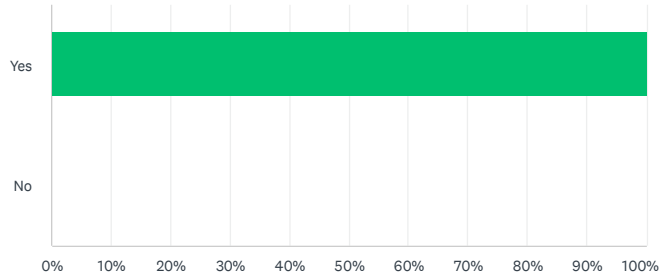
Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
A great deal	40.00%	4
A lot	40.00%	4
A moderate amount	20.00%	2
A little	0.00%	0
None at all	0.00%	0
TOTAL		10

Q3 Do you think a parent/guardian should receive their child's individual clinical trial data if the parent requests it?

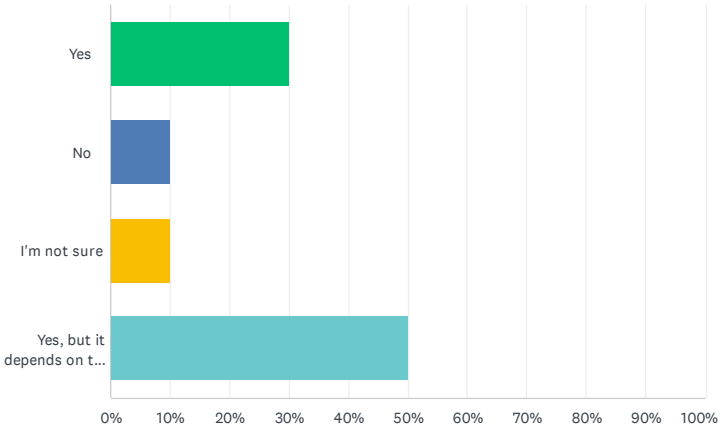
Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	100.00%	10
No	0.00%	0
TOTAL		10

Q4 Do you agree with the concept of a Sponsor returning individual clinical trial data directly to trial participants?

Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	30.00%	3
No	10.00%	1
I'm not sure	10.00%	1
Yes, but it depends on the circumstances	50.00%	5
Total Respondents: 10		

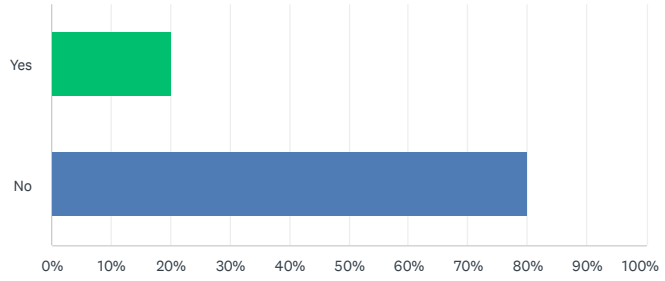
Q5 If you don't agree with the concept of a company returning clinical trial data to participants, can you list your concerns?

Answered: 8 Skipped: 2

#	RESPONSES	DATE
1	after trial is finished, data should be shared	6/21/2021 9:42 AM
2	What's meant by 'clinical trial data'? I don't think getting e.g. ECG, echo or MRI data is very useful and even some of the functional or strength measurements don't mean much to a family. It's a nice option for a family to see clinical trial data, but it would probably be more meaningful to provide them through a healthcare professional, either a doctor or a physiotherapist.	6/21/2021 3:55 AM
3	Has to go through PI, SI and/or site staff	6/21/2021 2:12 AM
4	Interpreting the data and put the individual data in the context of the study results and of a progressive disease might not be easy for all families and can create some false judgement and/or anxiety. It creates some "inequality" as proactive and well informed families are more likely to ask for the data	6/21/2021 1:48 AM
5	Not to disagree with this objective, but to raise the concern that the PI/treating physician for the participant could be blind-sided by the parent contacting the office and requesting an urgent discussion with the physician over an abnormal lab result. How to educate parents on labs/biomarkers/tests that are predicted to be abnormal (due to having DMD)? The poster does not go into this in any detail.	6/20/2021 7:46 PM
6	None	6/20/2021 7:28 PM
7	I agree, but it needs to be done in a thoughtful manner, properly contextualized.	6/4/2021 10:55 AM
8	at the end of the trial, all data should be returned to families. However, on a week by week basis during the trial, I don't favor providing results to individual families.	6/3/2021 2:49 PM

Q6 Are you aware of additional questions/comments/concerns from parents/guardians directed to you/your team following return of their data from ReveraGen?

Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	20.00%	2
No	80.00%	8
TOTAL		10

Q7 If your team received questions/concerns from parents/guardians about the returned data, can you elaborate on what types of questions/concerns they had?This question may be skipped if it does not apply.

Answered: 7 Skipped: 3

#	RESPONSES	DATE
1	Families have heard that data are supposed to be provided, but aren't certain how and when.	6/21/2021 3:55 AM
2	This is still hypothetical but the interpretation of the results, language barrier, cosequences for future therapies sjould be explained by the local physician	6/21/2021 2:53 AM
3	Does not apply.	6/21/2021 2:12 AM
4	It does not apply to a specific situation however it would be important that the clinician is also provided with exactly the same report to be able to answer the questions appropriately	6/21/2021 1:48 AM
5	as above - I anticipate parents will become alarmed over reviewing the labs/test results and where something unexpected comes to their attention. They often lack in context and are unable to sort out what is typical for DMD or a non-significant drug effect.	6/20/2021 7:46 PM
6	N/a	6/20/2021 7:28 PM
7	N/A	6/4/2021 12:07 AM

Q8 Do you have any feedback for ReveraGen on this process? This question may be skipped. Thank you for completing our survey!With best wishes from the ReveraGen team

Answered: 1 Skipped: 9

Research checklist / supplementary file

Checklist of Consensus standards for the reporting of organizational case studies [25 Table 11)]

Reporting item	Page number on which item was reported	Page number of justification for not reporting
Describing the design		
1. Define the research as a case study	2	
2. State the broad aims of the study	2	
3. State the research question(s)/hypotheses	2	
4. Identify the specific case(s) and justify the selection	2	
Describing the data collection		
5. Describe how data were collected	6	
6. Describe the sources of evidence used	8	
7. Describe any ethical considerations and obtainment of relevant approvals, access and permissions	7	
Describing the data analysis		
8. Describe the analysis methods	9	
Interpreting the results		
9. Describe any inherent shortcomings in the design and analysis and how these might have influenced the findings	3	
10. Consider the appropriateness of methods used for the question and subject matter and why it was that qualitative methods were appropriate	15	
11. Discuss the data analysis	15-17	
12. Ensure that the assertions are sound, neither over- nor under-interpreting the data	15-16	
13. State any caveats about the study	3,15	

BMJ Open

Return of participant-level clinical trial results to participants: Pilot of a simplified centralized approach

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-080097.R1
Article Type:	Original research
Date Submitted by the Author:	09-Feb-2024
Complete List of Authors:	Hoffman, Eric; State University of New York at Binghamton, Pharmaceutical Sciences Gaglianone, Suzanne; ReveraGen BioPharma Ketema, Rahel; ReveraGen BioPharma Tu, Wangshu; Carleton University Peay, Holly; RTI International Clemens, Paula; University of Pittsburgh Dang, Utkarsh; Carleton University Conklin, Laurie; ReveraGen BioPharma
Primary Subject Heading:	Ethics
Secondary Subject Heading:	Pharmacology and therapeutics, Patient-centred medicine
Keywords:	ETHICS (see Medical Ethics), Health Literacy, Patient Satisfaction, Clinical Trial

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Return of participant-level clinical trial results to participants: Pilot of a simplified centralized approach

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Abstract

Objectives: Public access databases such as clinicaltrials.gov achieve dissemination of clinical trial design and aggregated study results. However, return of participant-level data is rarely done. A key barrier includes the proprietary ownership of data by the sponsor. Additionally, investigators may not have access to centralized data, and per ICH Good Clinical Practice, must maintain the confidentiality of participants. This study piloted an approach to return both individual and aggregate clinical trial data to parents of children participating in a series of open-label clinical trials. **Setting and Design:** A small biotech company obtained central ethics approval (centralized IRB, non-exempt). The study was advertised via parent advocacy groups. Parents of trial participants were offered the option to contact an employee (coordinator) within the company, requesting return of their child's study results. Ethics approval covered participation in 6 countries. **Interventions**: Contact initiated by the parent enabled the coordinator to obtain informed consent (and separate GDPR consent), with phone translation when needed. Using date of birth and study site location provided by the parent, the data manager reported the participant number to the coordinator. The coordinator retrieved and compiled data, along with an aggregate summary, which was mailed via a password protected and encrypted memory device to the parent. Pre-and post-return surveys were sent to consented parents (n=19; 40% of 48 total trial participants) and investigators. **Results:** Pre-return surveys indicated a request for as much data as offered, in all formats offered. Post-return survey showed high satisfaction with the process and data returned. Survey of the physician site investigators (n=10; 100% participation of investigators) voiced general satisfaction with the process, with some reservations. **Conclusions:** This pilot study demonstrates an innovative, cost-effective, centralized, and labor conservative approach to return of participant-level and aggregate data to participants in studies.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information,

Strengths and limitations of this study

- A strength is the novel approach of return of patient-level clinical trial data to trial participants and their families, directly by the trial Sponsor.
- A strength is the survey of the parents of the trial participants regarding clinical trial data they wished to have returned, the format of this data, and their satisfaction with the process.
- A strength is the survey of physician attitudes regarding the direct communication of the Sponsor and trial participants.
- A limitation is the small number of trial participants (n=19) and physicians (n=10) that participated in this pilot study.

Introduction

Health authorities, academic societies, and patient advocacy groups are increasingly focused on increasing transparency of clinical trial design and conduct, as well as data sharing and data stewardship. This is reflected in the United States 21st Century Cures legislation which supports the National Institutes of Health data sharing mandates [1,2], and is further exemplified by recent European Union Clinical Trial Regulations, which note key initiatives of improving information-sharing and increasing transparency of information related to clinical trials (https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation). Access to participant-level data enables alternative approaches to data analysis, including meta-analyses and modeling to facilitate drug development (e.g. predictive clinical disease progression models, clinical trial simulation tools) [3]. Data siloes, driven by economic and academic incentives, have the potential to undermine development of treatments for rare diseases [4]. Studies demonstrate that most clinical trial participants view data sharing positively, despite some concerns related to confidentiality and data security, awareness about access and control, and potential harms resulting from these risks [5,6].

Clinical trial data disclosure or sharing may take several forms, including the posting of aggregate results on a public or private website, sharing of de-identified data with a 3rd party (for research or other purposes), or return of an individual's personal health data back to them (**Figure 1; Panel A**). Some data collected during a clinical trial are monitored in order to assess a person's well-being during the trial, or response to therapy (e.g. weight, height, clinical chemistries); some of these data could duplicate data found in their medical record or be used by their physician during their clinical care. Other data collected during a trial may be less relevant to their healthcare (e.g. biomarkers and changes in outcome measures that were selected to measure the effect of a drug); often these data are not regularly assessed during the care of a patient. Sometimes these data are not accessible to their physician during the trial

due to use of a central laboratory or a non-CLIA approved laboratory, and even if they are, may not be easily interpreted by the physician because they are exploratory, or intended to assess the pharmacodynamics of a drug. Participants (or parents) may misunderstand that biospecimens are being collected for research purposes only, and not for their direct care.

With the emergence of the General Data Protection Regulations (GDPR) in Europe, there is an acknowledgement that individuals have a fundamental right to ownership of their own personal health data, including data collected during a clinical trial (**Figure 1; Panel B**) [7]. Efforts are underway to enable individual ownership of personal health data through secure 'data lockers', and *FAIR* consensus foundational principles have evolved to create a construct for such data return, ownership, and sharing (Findability, Accessibility, Interoperability, Reusability) [8]. Patient advocacy groups have begun to focus on mechanisms to encourage and implement *FAIR* data lockers for their stakeholders [9]. We hypothesized that the driving principle for a clinical trial participant may be 'a right to know and understand' their personal clinical trial results, and not as much a 'right to own' their clinical trial data. Additionally, while "machine operability" is an imperative for data sharing under GDPR, a recent study of clinical trial participants demonstrated a preference for receiving data by mail and not via a website [10].

We sought to understand parent/caregiver and physician views on return of their child's individual personal health data at the end of an open-label clinical trial. We also sought to develop a cost-effective process for returning clinical trial data directly to participant families, while viewing it as an opportunity to be transparent about how these data were similar or different from data obtained by their physician during clinical care. boys worldwide, with clinical onset around 5 years of age, and progressive weakness and disability. The clinical trials were supported by public funds (National Institutes of Health [USA], and European Commission Horizons 2020 [EU]), and were testing vamorolone, a disease-modifying therapy intended to be

a safer alternative to corticosteroid standard of care. Vamorolone has received regulatory approval from FDA (USA; 2023), EMA (EU; 2023), and MHRA (UK; 2024) based in part on these clinical trials.

In 2019, the Sponsor of the trials, ReveraGen BioPharma, received an Administrative Supplement for Research on Bioethical Issues award from the National Institutes of Health ("Establishing a Cost-effective Return of Results to Parents of Boys in VISION-DMD Clinical Trials"). The goal of this study was to pilot a centralized approach for return of participant-level data to families participating in clinical trials of vamorolone. Here we discuss this pilot process using data from a series of small open-label trials, and present findings from parental and physician surveys, intended to inform application of this process to other studies.

Methods

Patient population and trial design.

This study was focused on participants in two vamorolone trials, VBP15-002 (4 weeks dose-ranging study; NCT02760264) [11], and VBP15-003 (24-week extension study; NCT02760277) [12]. These two trials were sequential open-label trials, with 48 participants with Duchenne muscular dystrophy (DMD), age 4 to <7 years at study entry. VBP15-002 was a multiple-ascending dose study over a 24-fold range of vamorolone doses (0.25 mg/kg/day to 6.0 mg/kg/day), recruited 12 participants in each of 4 dose groups, and was a 4-week safety and pharmacokinetics study (2 weeks on drug, 2 weeks washout). All participants were then enrolled into a 24-week dose-finding study at the same doses (VBP15-003), with motor outcomes at baseline, 12-weeks, and 24-weeks treatment, and laboratory outcomes (safety labs, exploratory biomarkers). In this report we focused on test results reported back to patient families. These included the motor outcomes Time to Stand from Supine velocity (in event/sec), Six-minute

Walk Test (in meters walked), Time to Run/Walk 10 meters (in meters/sec), Time to Climb 4 Stairs (in event/sec), and NorthStar Ambulatory Assessment (total score). Blood laboratory tests (safety biomarkers) assessed in a central laboratory included creatine kinase, osteocalcin, P1NP (N-terminal propeptide of type 1 collagen), CTX1 (C-terminal telopeptide of type I collagen), morning cortisol, fasting insulin and glucose, and glutamate dehydrogenase. Exploratory blood pharmacodynamic protein biomarkers, tested at Somalogic, were CD23, MDC/CCL22, IL22BP, lymphotoxin a1b2, IGFBP2, MMP12.

Patient and Public Involvement Statement

The concept of this study evolved from discussions with parents of patients and advocates at disease-focused conferences. Multiple patient advocacy group leaders, physicians and parents of children with DMD were consulted about the concept of this project, and were asked to comment upon and contribute to the design of the data return and questionnaire content.

Ethics approval and consent of participants.

A single central ethics approval (IRB) was received by the Sponsor (ReveraGen BioPharma, Rockville, MD, USA) for this study through Western IRB (WIRB), as 'expedited review, no continuing review required'. Western IRB (recently renamed WCG; https://www.wcgclinical.com/about/) is an accredited 'central' ethics review panel (not affiliated with a single institution). Clinical trials funded by the US National Institutes of Health now require such centralized ethics review. The approval included advertisement of the study via patient advocacy groups in countries in which enrollment had taken place (USA, Canada, United Kingdom, Sweden, Israel, Australia), and the ability to consent the participant via telephone with use of a telephone interpreter if requested by the parent (**Figure 2; Panel A**). The advertisements included the contact information of a single coordinator employed by the

Sponsor; a strict firewall was established where the coordinator shared no identifying information with any other employee of the Sponsor or others.

Once a trial participant family (parent) contacted the coordinator and requested participation in the return of results study, the coordinator then explained the study and conducted the informed consent process by teleconference. The informed consent was sent via Adobe Acrobat Sign for signature (**Supplemental File 1**). For patients in European countries, a separate GDPR consent was also completed, and signed via Adobe sign. (**Supplemental File 2**). Only those who signed informed consent participated in the return of results study (**Figure 2; Panel A**). Following completion of informed consent, the coordinator collected the following information from the family and stored it in a password-protected, cloud-based file: parent's name, home address, parent's email address, child's study site, child's date of birth. The child's study site and date of birth were provided to the data manager, who identified the study subject number. The data were extracted from the electronic data capture system using only the subject number, and then were presented in a standardized format and converted to a pdf file.

Return of clinical trial results to families was done by sending (by mail) an encrypted and password-protected USB memory device. The memory device used SanDisk Secure Access software (128 bit AES encryption to create a password-protected folder—SanDiskSecureAccess Vault—on the flash drive). Locked files were moved into the SanDiskSecureAccess Vault and only accessed with a password sent separately via email to the family.

Surveys

Three surveys, two for parents, and one for their physicians, were developed, and feedback sought on draft content of surveys from parents, stake-holder foundations, and physicians prior to finalization and dissemination.

The first parental survey was administered after signing of consent to participate in the study, but before results were returned (**Supplemental File 3**). This parental survey was designed to instruct parents on the types of data available from clinical trials (motor outcome, clinical laboratory, exploratory biomarkers), and ask what type of data they were interested in receiving (aggregate, patient-level), and in what data format for data return. The second parental survey was administered after the return of results, to gauge parental satisfaction with the materials received (**Supplemental File 4**).

A third survey was developed to administer to the clinical trial site physicians caring for the patient and patient family that had consented to participate in the return of results (**Supplemental File 5**). The purpose of this survey was to assess the opinions of the physicians regarding the return of patient-level clinical and laboratory data directly from the Sponsor to the parents. The physicians responsible for the participants during the trial also followed the patient for the subsequent 2 years, as all participants enrolled in a 2-year long-term extension study. Thus, the same physician cared for the participant during the trial, and afterwards during the return of results and associated surveys.

Data statement. All data is provided as supplemental files.

Results

Parental attitudes and desires regarding clinical trial return of results. Of the 48 patient families participating in the VBP15-002/003 clinical trial of vamorolone, 19 (40%) responded to advertisements via stakeholder foundations (58% North America [US, Canada], 42% Europe and Israel). We also developed an informational sheet that could be handed out at the clinical trial sites during patient family follow up visits, but clinical trial sites were uncomfortable handing out this informational sheet without their own institutional ethics approval.

The full results of the survey of 19 parents prior to return of results are provided (**Supplemental File 6**). We queried whether aggregate or individual participant level data were important to parents, and the majority (90%) felt that access to both types of data was 'very important'. We then asked if data should be best presented in tabular, or graphical form. Most parents (97%) indicated that receipt of data in both formats was preferred. We then queried what biomarkers were important to report back to parents, giving examples of safety labs (cortisol, insulin, glucose), bone turnover biomarkers (osteocalcin, P1NP, CTX1), and exploratory efficacy biomarkers. The majority of parents responded that they would like all data reported to them.

For the questions "What do you expect you would do with the information returned that summarizes results for all boys in the trial?", most responses acknowledged that the return of data would be for informational purposes only. For "What do you expect you would do with information return on your son's individual results?", most again responded that it would be for informational uses only, although four (of 18) mentioned the possibility of discussing the data with their physician.

Return of results.

Both aggregate and individual (participant-level) were returned to patient parents on a password protected USB memory device sent via the mail. An example report is provided (**Supplemental File 7**). The report included a 2-page educational introduction to aid interpretation of the report. This included definitions of efficacy and safety outcomes, the concept of aggregated data for interpretation of drug efficacy and safety, distinctions between data generated in a research study vs. clinical care. For educational purposes, the report also elaborated on challenges facing Sponsors in terms of return of data, including confidentiality firewalls and risk for parent/patient over-interpretation of research data regarding clinical care. The following 15 pages provided the trial participants individual clinical trial data (motor outcomes, quantitative muscle testing, anthropomorphic data, and laboratory data), as well as his data superimposed

on aggregated data, both as tabular and graphical form for key clinic visits (Baseline, 12 weeks, 24 weeks treatment). The graphical form of data presentation showed each individual in the specific vamorolone dose group (n=12), with their child's data color coded within this group (**Figure 2; Panel B**).

Parent follow-up survey.

Of the 19 families to whom the pre-return survey was completed and results were returned, 12 of these completed the post-return survey (63%). The complete responses are provided (**Supplemental File 8**). The majority of the families were "very satisfied" with both the return of data approach (10/12; 83%), and method of return of data on a password-protected USB memory device (8/12; 67%) (**Figure 3**). One family expressed dissatisfaction with both of these queries (1/12; 8%), but did not provide reasons for their dissatisfaction. Most families (18/19) had no technical issues with receiving the materials on a password-protected USB; one family had technical problems and was mailed a hardcopy of the materials.

When asked if they felt that the return of results was important to them, all (12/12) replied that it was 'very important' (7/12; 58%) or 'important' (5/12; 42%). When given an open-field query for why they felt the data return was important, 10 responded (see **Table 1**). The responses primarily oriented about the importance of knowledge about the trial and being informed about the child's health.

Table 1: Responses of parents of participating children in the clinical trial when asked why they thought that data return was important to them, and their physicians regarding their degree of support of Sponsor direct return of data to families.

Parents of trial participants: Why is trial data return important to them?
Personal knowledge
To be informed

It is a great benefit to be able to see how my son may have responded during the Clinical Trial in all of these areas recorded, In Hopes to see some good benefit from the medication.	
We took a big risk in being in the trial. Want to know if it works and how my son paired with the other boys	
It's nice to see how things are going and not be in the dark	
All data to do with how my son is managing the condition/meds is important	
We would like further understanding about how the trial was going, and what difference it's made to our child as well as the rest of the children	
To understand the clinical help VBP15 provided	
We would like further understanding about how the trial was going, and what difference it's made to our child as well as the rest of the children	
To see actual data of improvement and/ or progression is important. Data helps you to understand if treatment works or not.	
Just to see how our son is doing. We are hopeful he is doing better because if the drug and seeing the results gives us more hope.	
Physician concerns of a Sponsor returning participant-level data to directly to trial participants.	
Supportive	*after trial is finished, data should be shared*
	No comments
Supportive with reservations about timing of delivery	*I agree, but it needs to be done in a thoughtful manner, properly contextualized..At the end of the trial, all data should be returned to families. However, on a week by week basis during the trial, I don't favor providing results to individual families*
Supportive, with reservations about delivery outside of the healthcare or investigative team and interpretation of data	*What's meant by 'clinical trial data'? I don't think getting e.g. ECG, echo or MRI data is very useful and even some of the functional or strength measurements don't mean much to a family. It's a nice option for a family to see clinical trial data, but it would probably be more meaningful to provide them through a healthcare professional, either a doctor or a physiotherapist.*
	Has to go through PI, SI and/or site staff
	Not to disagree with this objective, but to raise the concern that the PI/treating physician for the participant could be blind-sided by the parent contacting the office and requesting an urgent discussion with the physician over an abnormal lab result. How to educate parents on labs/biomarkers/tests that are predicted to be abnormal (due to having DMD)? The poster does not go into this in any detail.
	Interpreting the data and put the individual data in the context of the study results and of a progressive disease might not be easy for all families and can

	create some false judgement and/or anxiety. It creates some "inequality" as proactive and well informed families are more likely to ask for the data

Most parents indicated that it was important to see their child's data in comparison to others in the trial (11/12; 92%) and provided free text justifications that were concordant with increased information exchange is preferred over more narrow information regarding their child. Parents were queried regarding the amount of data provided, and the majority (11/12; 92%) responded that it was "about the right amount of information", and 1 parent reporting that it was too little information.

Parents were asked if they would have preferred their child's data returned to them via their physician, rather than the Sponsor (ReveraGen). Most (8/12; 67%) responded "I'm neutral; either way would be fine"; some responded that they would strongly prefer to receive their child's data from the Sponsor and not their physician (3/12; 25%), and a single parent stated that they mostly agree with their preference for receiving the data from their physician, but not strongly (8%). When the respondents were stratified by North America vs. Europe, there were no differences.

The parents were queried as to whether they had shared the returned data with others. Half of respondents had shared data with family members, 42% with health care providers, 17% with friends, and 8% with teachers; 42% responded that they had not shared the data with anyone. When asked if they would participate in such a return of results study again, all responded affirmatively (12/12). Asked if they had regret regarding participation in this study, all responded that they did not have regret.

Survey of clinical trial site physicians.

Of the 10 physicians that we asked to complete the survey (e.g. those physicians following the 19 patients), all 10 responded. The trial had 12 sites in 6 countries, so this represented 83% of

physicians and sites. The complete responses are provided (**Supplemental File 9**). The physicians were unanimous in their opinion that parents put a great deal of importance on receiving both individual and aggregated trial data, and all physicians affirmed that families should receive this data if requested by the family (**Figure 4**). We asked, "Do you agree with the concept of a Sponsor returning individual clinical trial data directly to trial participants?", most (8/10) were supportive of this, but 5 of these 8 expressed some reservations ("Yes, but it depends on the circumstances"); 1 was not sure, and 1 responded "no". When respondents were stratified by North America vs. Europe, North American physicians (n=6) voiced more enthusiasm for this approach, whereas the European physicians (n=3) were less enthusiastic (**Supplemental File 10**). When asked to elaborate on any concerns of a Sponsor returning participant-level data directly to families, responses are shown (**Table 1**).

Cost effectiveness analysis.

The clinical trials that were the focus of this study were managed via a public-private partnership model, with funding to the for-profit Sponsor (ReveraGen) from the National Institutes of Health and European Commission. The Sponsor contracted with each academic clinical trial site directly (11 sites in 6 countries) and thus had access to all costs associated with contracting of the academic clinical trial sites, ethics review, and participant visits to the site. We estimated costs of the following four models of returning participant-level clinical trial results to clinical trial participants:

- **Current model.** Central ethics review held by the Sponsor, and direct communication with clinical trial participant families.
- **Model 2.** A stand-alone study, with new contracts for return of results between the Sponsor and the participating academic clinical trial centers, inclusive of clinical trial site ethics review, and on-site visit of the participating family for in-person return of participant-level data.

- **Model 3.** Similar to **Model 2**, but with remote (teleconference) delivery of the participant-level clinical trial data by the academic clinical trial site to the study participant. This model does not include patient travel-stay costs to go to the academic clinical trial site.
- **Model 4.** In this model, the return of results is included in the clinical trial protocol from initiation of the contracts with each academic clinical trial center. In this model, the initial costs of the ethics review are covered by the costs for the clinical trial protocol. However, the site would need to remain open (active contract) for about 2 additional years beyond the typical close-out (the clinical trial would need to be completed, data unblinded, and then the return of results initiated). This model assumes in-person delivery of the results to the study participant by the academic clinical trial staff.

The results of this financial impact analysis are shown (**Table 2**). The realized costs associated with data management and reporting (extraction of individual participant data, assembly into participant-specific reports, reporting) was US$78,585, and this was assumed to be a fixed cost across all models. In the Current Model, the focus of this manuscript, there was only the additional incremental cost of a centralized ethics approval held by the Sponsor, for a total cost of US$86,171. The alternative models where participant-level data was returned to participants by the clinical trial sites following those participants were considerably more expensive, with costs driven by the ethics review that would be required at each of the 11 participating sites, the time and effort of clinical site staff, institutional overhead costs associated with site contracts, and (Models 2, 4) the cost of participant travel to and stay near the clinical trial site for in-person return of clinical trial data.

Table 2. Real or predicted costs associated with different return of participant-level data to clinical trial participants.

	Current model	Model 2	Model 3	Model 4
	Sponsor-managed, centralized return of participant level data to participants	New IRB + contract at each trial site for the return of data, inclusive of on-site visit of family (Standalone study)	New IRB + contract at each site to return data to participants, with remote delivery of information (Standalone study)	Return of data included in original clinical trial contract (part of original IRB); extend site contract by 2 years for return of data, on-site visit. (Included in initial protocol)
Sponsor Costs (US$)				
Fixed costs of data management for return of results	$78,585	$78,585	$78,585	$78,585
Central IRB/ethics (Sponsor)	$7,586			
Clinical Site Costs				
Site IRB/ethics	0	$36,900	$36,900	0
Annual IRB renewal Models 2,3: 4 yrs Model 4: 2 yrs[1]	0	$33,580	$33,580	$18,190
Scheduling/ coordinating date entry/query	0	$2,070	0	$2,070
Investigator time	0	$4,830	$4,830	$4,830
Travel	0	$11,323	0	$11,323
Overhead	0	$24,762	$21,040	$9,825
Total	**$86,171.00**	**$192,050.00**	**$174,935.00**	**$124,823.00**

[1] The reduced number of years (2 yrs) in Model 4 is assuming that the IRB costs of the parent clinical trial would be borne by the parent study (not the return of results portion of the study), but the parent study would need to be kept open an additional 2 years.

Discussion

We carried out a centralized return of both participant-level and aggregated clinical trial data to parents of children in an open-label dose-ranging study of vamorolone. Key to our approach was the efficient navigation of human subjects oversight, where we received a single centralized ethical approval for patients worldwide to contact the Sponsor to request the clinical trial data on their child. Our method of alerting patient families of this return of results project was through stakeholder foundations in the 6 countries in which the clinical trial was being conducted (US, UK, Canada, Israel, Australia, and Sweden). As the parents were contacting the Sponsor directly to request information on their own child, the ethical committee felt that it was adequate to remotely consent parents (with a translator if needed), and that the study was "expedited with no requirement for continuing review," much as other survey-type research projects.

The more typical alternative approach of returning clinical trial data to participants is through collaborating clinical trial sites via their health care providers. This would require (in our case) local clinical site ethics approval (12 sites in 6 countries), as well as contracts between the Sponsor and each site to carry out the return of results. Our approach of implementing direct contact between the parents contacting the Sponsor greatly simplified the otherwise complex challenge of returning patient-level clinical trial data to clinical trial participants. Critical to our approach is that the parents initiate contact with the Sponsor, not the Sponsor with parents. Also central to our approach is a 'data/information firewall' within the Sponsor, where only a single employee had direct contact with families, and no de-identifying information was relayed to any other employee of the Sponsor. Additionally, an interpreter in the parents' native language was always made available, and consent forms were translated to the parents' native language.

We queried the attitudes of participating parents both before the return of results, to learn what type of information they felt was important, and how they would like this data to be provided to them. In general, parents expressed a strong desire for as much information as possible, in all formats offered (individual, aggregate; tabular, graphical). Thus, tailoring of information provided to the families was not needed; all families expressed a desire for all information offered. In returning the data to participants' parents, we instructed that this was clinical research data and not generally relevant to the clinical care of their child. Also, we provided tutorials on motor outcome measures, and interpretation of clinical laboratory and exploratory biomarker data. Participant families who participated in the return of results directly by the Sponsor expressed overall satisfaction with all aspects, including the process, the amount of information received, the graphical and tabular presentation, the presentation of both individual and aggregate data, and the manner in which it was received (password protected and encrypted USB memory stick mailed directly to the family). We note that our approach included two factor authentication (direct mail, separate password communication), which is important to maintain privacy and confidentiality.

We found that, of the sample of parents who requested their child's data, most would prefer to obtain the data directly from the Sponsor, or were indifferent to whether they obtained data from the Sponsor or their physician. None of the parents indicated a strong preference for obtaining the clinical trial data from their physician. This finding supports our approach to providing individual-level data directly from the Sponsor. All participants felt that return of data was quite important to them, and parents showed a variable degree of sharing of information with family, friends, teachers and their physicians.

Physician respondents unanimously acknowledged the importance that families place on return of clinical trial data. Some had reservations about return of results without involving clinicians or the clinical site investigators. When physician responses were stratified by North

America vs. Europe, North American physicians were more accepting of the direct return of data participants by the Sponsor (p=0.065; Wilcoxon rank-sum test), although numbers were small and difference not significant (North American physicians n=6; European n=3). These concerns, and potential cultural differences in acceptance by physicians, will need to be further explored and addressed in future return of results approaches.

For parents of children with Duchenne muscular dystrophy, participation in clinical research is a balance of hope and expectations. Parents of children with DMD report a feeling of investment in the trial [13]. In one study, at the termination of a trial in DMD, parents wished for more communication from the sponsor. Some parents felt that when the trial ended, the partnership between the parent and sponsor "broke down" and that the sponsor no longer valued them [14]. Parents describe the significant burdens that participation in clinical trials places on their families [15].

In keeping with the ethical principles of beneficence and autonomy, return of data demonstrates respect for participants' ownership of their health data, encourages family engagement, and fosters increased trust of researchers by patients who are clinical trial participants and their families. Operationally, there is a disconnect, as the clinical trial site personnel and physician have direct contact and responsibility for care for the patient, but typically do not have access to all of the patient's data. Direct industry-patient interaction for returning individual results after trial completion, without the study site/physician interface, has not been common historically due to potential for perceived loss of patient confidentiality, concerns about results interpretation and the potential for clinical follow up for actionable findings if clinicians are not involved, and possible conflict of interest. However, our approach demonstrates that this can be achieved by having an internal coordinator who is not involved in the study conduct, keeps records confidential, and is under a "firewall" of confidentiality when it comes to the study. Another approach could be to use a 3rd party vendor, though this would

increase costs and complexity. Sponsors may perceive the return of results to trial participants as a risk to the participant and the trial, or at least as a distraction to the Sponsor, adding additional time and cost to the drug development process. We have demonstrated that this can be a relatively straightforward process that is not costly and can be done after study completion, and public disclosure of trial data. Alternative models of return of results require contracts between the Sponsor and the participating clinical trial sites, and this adds considerably to the costs and administrative complexity (**Table 2**).

While the current proof-of-concept study is admittedly quite small, we envision that such return of results could be scaled up without additional barriers. Assuming a large multinational Phase 3 trial, either the Sponsor or a contract research organization (CRO) would receive central ethics approval for return of results to trial participants requesting the data (as we have done here). This participant-initiated request would permit de-identification of the subject in the data, and direct return of the data to the participant. The Sponsor could either do this internally with appropriate GDPR firewall (as we have done), or could contract a 3rd party to carry out the process at arm's length.

Not all clinical trial data is relevant to a patient's medical care, and indeed may not add value or be acceptable to add to the participant's electronic medical health record. While clinical trial data is personal health data, it likely has different value to a clinical trial participant compared to their own electronic medical health record. The National Academies of Science (NAS), Engineering, and Medicine convened a committee that published "Returning Individual Research Results to Participants: Guidance for a New Research Paradigm", a process-oriented approach to return of results that considers value to the participants, feasibility of return, and quality of research results [16]. The NAS committee formulated 6 principles to help guide deliberations and development of recommendations presented in their report. One principle was that the potential value of returning individual research results must be carefully considered

along with the trade-offs for research participants, investigators, research institutions, and society. According to the committee, "value" should consider the perspective of the participant (or parent) and might entail clinical utility or personal utility, as well as personal meaning. Thus, *the value of a result is not necessarily tied to its use, as viewed solely through the eyes of the clinician or sponsor.* DMD parents and advocacy groups in the US and European Union clearly indicate that they value provision of individual and aggregate clinical trial results to the study participant.

Recent reviews of efforts to return clinical trial data to participants have found that these are relatively rare and typically only include summarized or aggregate results (not personal participant-level data). Bruhn et al. (2021) studied clinical trials in a period from January 2008 to August 2019 and identified 33 studies involving 12,700 participants that explored returning results to trial participants, and found that aggregate data was returned, without evaluation of what information trial participants wished to receive [17]. Of the 33 studies reviewed, only 2 returned individual data to the participant, and for both of these only 'unblinding' was reported to the participant (not participant-level clinical and laboratory data). A single study provided both individual and aggregate results. Also, the authors noted that there was a general lack of "actively including patients or the public as partners in the development of the dissemination of results". The authors noted that a weakness of their study was relying on literature reports, and this likely underestimated dissemination efforts. Shroter et al. (2019) took an approach of surveying authors of published clinical trials to ascertain efforts to return clinical trial results to clinical trial participants [18,19]. Questionnaires were emailed to 19,321 authors, and analyzed 1,818 responses of authors that had enrolled individual patients. Of these, 498 (27%) had disseminated results to trial participants, but most were aggregate data (academic reports, lay reports). Of the 164 (33%) reporting that individualized data was returned, the type of individualized data was not specified. Raza et al. (2019) queried the UK's research permissions

system for Phase III trials for a 6-year period (2012 to 2017 inclusive), and found that of the 1404 Phase III trials studied, 88% reported the intention to disseminate results to trial participants [20]. However, only ten of the End of Study reports cited dissemination activities, and 6 of these were through a lay summary or letter.

The primary limitation of our study was the small number of families (n=19) and their physicians (n=10) that participated in this study. The clinical trial studied was an open-label Phase 2a dose-ranging and dose-finding study of 48 participants (young children with a rare genetic muscle disease, DMD), and future studies should extend our approach to larger, double-blind placebo-controlled trials in more common disorders (e.g. Phase 3). Future studies will also need to address potential cultural differences in attitudes of both families and their physicians based on country-of-origin, or other factors. Another limitation of our approach is the effectiveness of outreach (advertisement) to the parents of participating children. We had a 40% participation rate (19/48). We do not know if the 60% that did not participate was because they did not hear of the study (e.g. ineffective outreach to them), or if they did not wish to participate. Our ethics approval included an 'informational flyer' that was meant to be distributed to clinical trial sites and provided to patient families, but sites were uncomfortable with distributing this flyer without their own institutional ethics approval. If other Sponsors wish to take our centralized approach, we advise that the informational flyer for direct Sponsor return of data be provided to sites for distribution to trial participants at initial contracting and ethics review and be handed to patients at initial enrollment in the clinical trial, and/or exit from the trial.

In conclusion, there is a strong desire for clinical trial participants to receive patient-level and aggregate returns of clinical trial data to them. Their treating physicians, and stake holder foundations all uniformly acknowledge the importance of return of results to trial participants.

Despite this need, it is largely unmet due to fundamental barriers (pragmatic, financial, organizational, confidentiality, ethics). We have piloted a simplified return of results process that removes most barriers, and we found that trial participants (parents of children in a trial) were highly satisfied with this novel process, and their treating physicians were also generally satisfied while expressing some reservations.

Authors' contribution statement: EPH contributed substantially to concept and study design and drafted the manuscript. SG contributed substantially to study design, data acquisition and interpretation, and reviewed the manuscript critically. RH contributed substantially to data acquisition and interpretation and reviewed the manuscript critically. WT contributed substantially to data interpretation and presentation and reviewed the manuscript critically. HP contributed substantially to concept and study design and reviewed the manuscript critically. PC contributed substantially to concept and study design and reviewed the manuscript critically. UD contributed substantially to data interpretation and presentation and reviewed the manuscript critically. LSC contributed substantially to concept and study design, data acquisition and interpretation and drafting of the manuscript.

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Ethical Statement: This study obtained ethics approval through Western IRB (WIRB), as 'expedited review, no continuing review required' (IRB Tracking ID 20192458). Western IRB

(recently renamed WCG; https://www.wcgclinical.com/about/) is an accredited 'central' ethics review panel (not affiliated with a single institution). All participants gave informed consent before taking part.

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Competing Interest Statement: Dr. Dang received consultancy fees from ReveraGen Biopharma. Dr. Conklin is currently an employee of Johnson & Johnson, but the current work was completed while she was an employee of ReveraGen BioPharma. Dr. Peay was contracted to provide expert insight into study design and interpretation of results. Dr. Hoffman, Ms. Ketema and Ms. Gaglianoni are employees of ReveraGen BioPharma. Dr. Hoffman, Ms. Ketema, and Dr. Conklin are stock holders in ReveraGen BioPharma. Dr. Clemens holds NIH, FDA and foundation grants on vamorolone clinical trials with ReveraGen BioPharma.

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Figures

Figure 1. Models or return of clinical trial results and return of patient-level data. Panel A: Models of return of clinical trial results. Panel B: Models for return of participant level data. Photographs licensed from iStock.

Panel A.

Panel B.

Figure 2. Return of Results Design. Panel A: Overall study design of Sponsor direct return of participant-level and aggregate data to clinical trial participants. Panel B: Example of graphical return of participant-level data, showing the participant's data relative to other participants in the same treatment group.

Panel A.

Panel B.

Figure 3. Post-return of results parental satisfaction. Inner pie: Parental satisfaction with return of data approach utilized by the Sponsor. Outer donut: Parental satisfaction with delivery of the data by mailed, encrypted memory stick.

Figure 4. Physician attitudes towards returning clinical trial data to participating families. Inner pie: Physician agreement with concept of Sponsor returning individual data directly to participants. Outer donut: Physician perception of importance families place on receiving individual trial results.

Supplemental Files:

Supplemental File 1: Consent/Parental Permission and HIPAA authorization to Participate in a Study

Supplemental File 2: Consent For The Processing Of Personal Data From The European Union To Facilitate Return Of Results Per Protocol

Supplemental File 3: Parental Survey Prior to Data Return

Supplemental File 4: Parental Follow-up Survey Post Data Return

Supplemental File 5: Physician Survey

Supplemental File 6: Results of Pre-Return Parental Survey

Supplemental File 7: Example report of data return to patient parents

Supplemental File 8: Results of Post-Return Parental Survey

Supplemental File 9: Results of Physician Survey

Supplemental File 10: Physician agreement with the concept of a Sponsor returning individual clinical trial data stratified by global region

Panel A

Models for return of clinical trial results

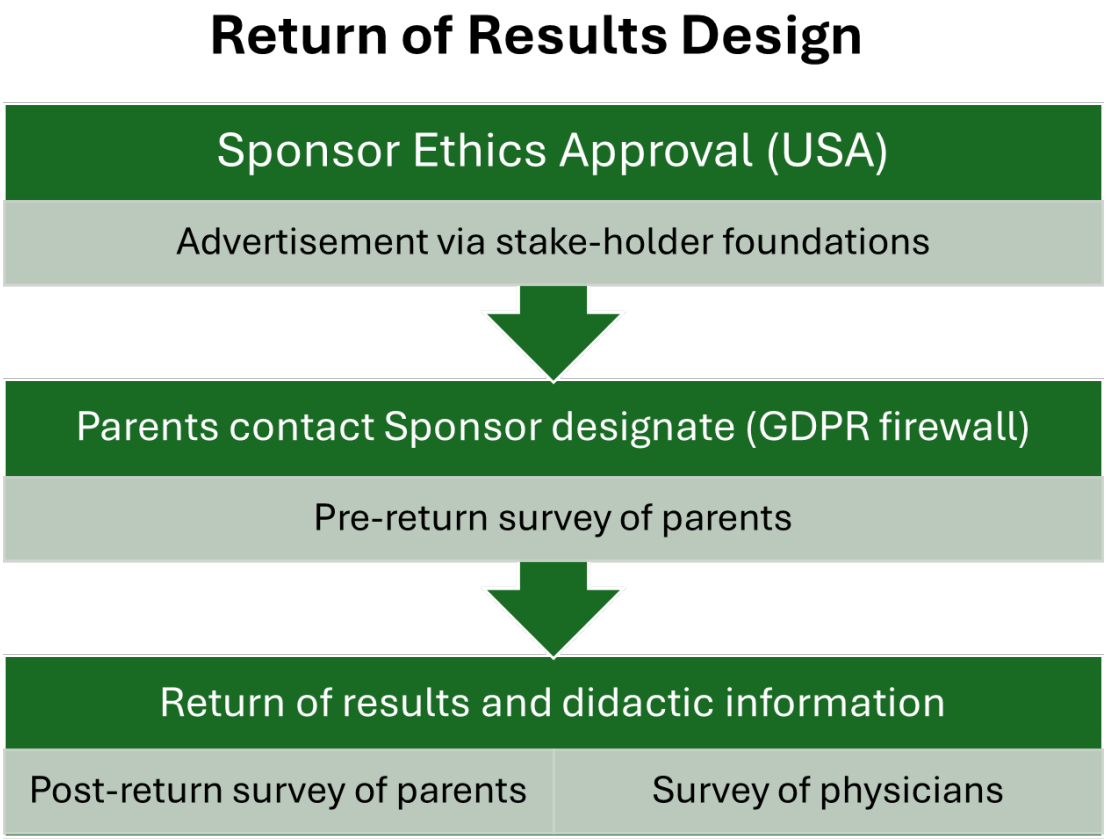
	www.Clinicaltrials.gov	Journal publication	Current study
Data type	• Trial design • Summarized data • Results	• Trial protocol • Data access policy • Anonymized patient-level data	• Personal participant-level data • Summarized data with participant superimposed • Instructional materials
User	• Public	• Academic research	• Participant in trial

Panel B

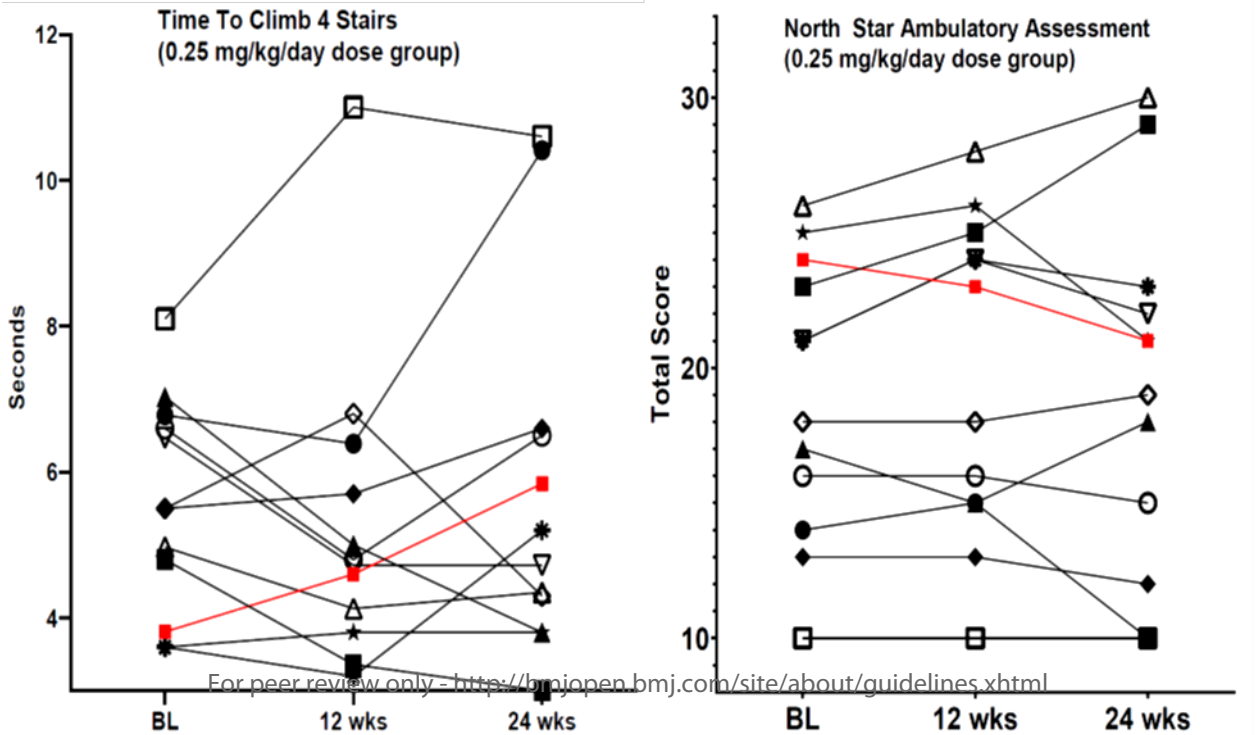
Models for return of participant-level data

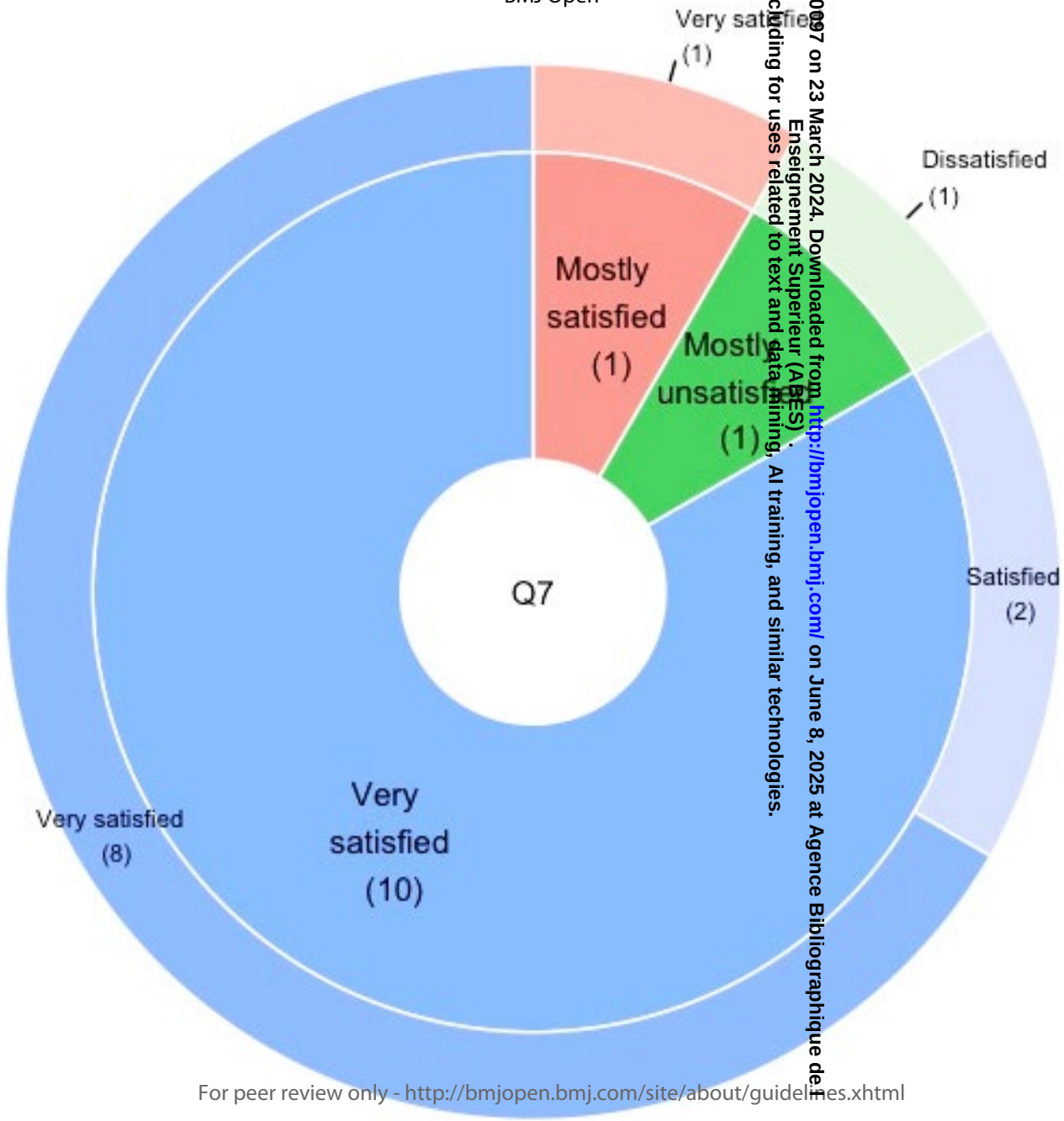
	Trial site participant unblinding	Participant data locker	Current study
Participant learns	• Trial group assignment	• Participant raw data from trial	• Participant raw data • Participant vs. others in trial
Key principle	• Knowledge of intervention	• Data ownership • GDPR; *FAIR*	• Understanding of personal trial data

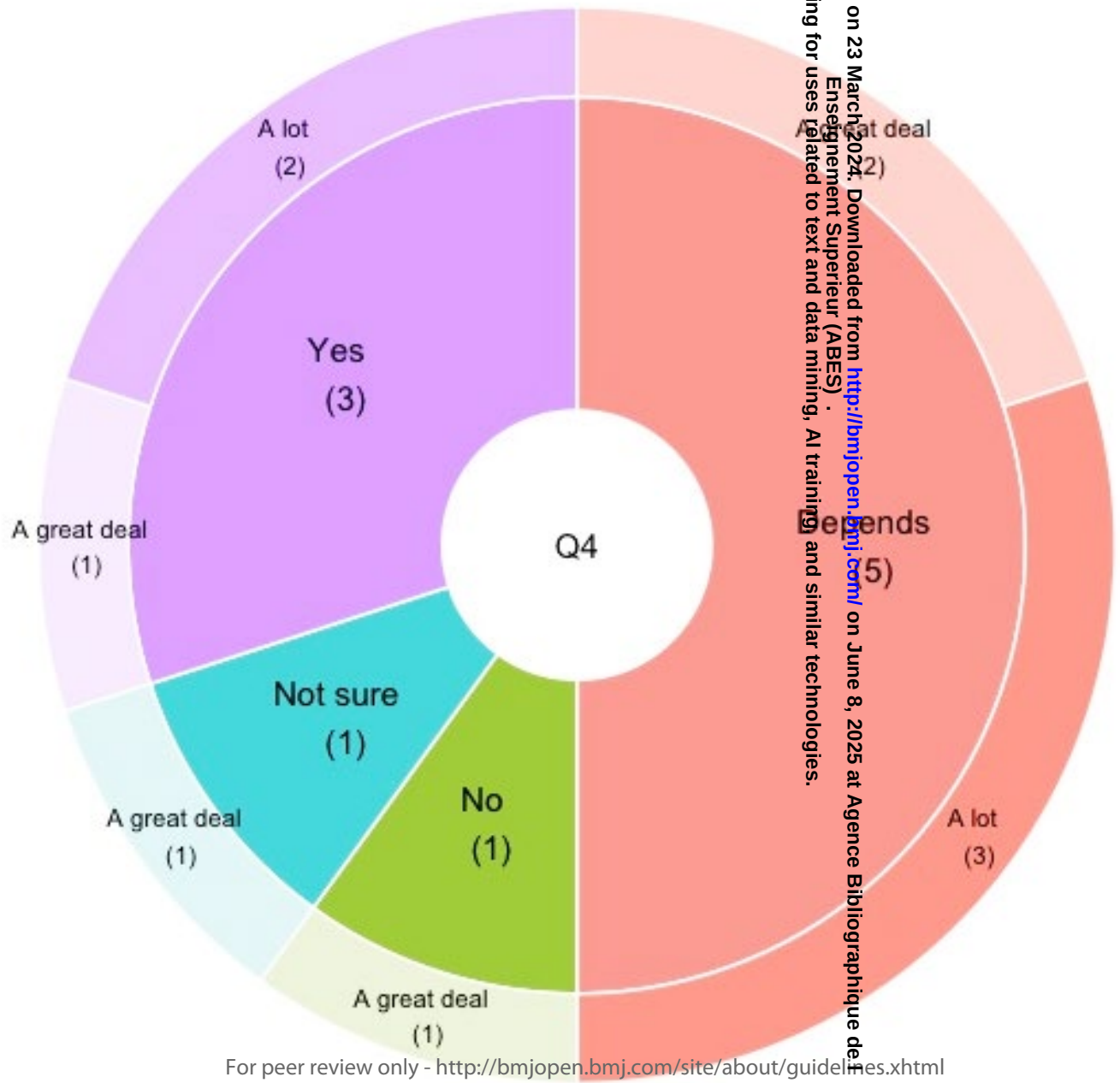
Panel A



Panel B







Place Barcode Label Here

IRB APPROVED
Oct 09, 2019

Consent/Parental Permission and HIPAA authorization to Participate in a Study

Title: Establishing a Cost-effective Return of Results to Parents of Boys in VISION-DMD Clinical Trials

Protocol No.: VBP15-ROR
WIRB® Protocol #20192458

Principal Investigator: Laurie Conklin, MD
155 Gibbs St
Suite 433
Rockille, Maryland 20850
United States

Sponsor: ReveraGen BioPharma

Study is funded by: National Institutes of Neurological Diseases and Stroke (National Institutes of Health)

Study-Related Phone Number(s): 240-672-0295
646-283-1074 (24 Hours)

You are being asked to be in a research study.

Introduction

Return of data to parents/caregivers of participants in clinical trials demonstrates respect for participants' ownership of their health data. However, disclosure of an individual's research results raises many ethical and logistical challenges. There are many questions regarding the perceived and real usefulness of the information, how the data is communicated, the impact of return of results on the well-being of parents and participants, feelings toward the research experience, and subsequent research participation. In a clinical trial with many recruitment sites and patients, the burden on physicians/coordinators may be a concern, and there are challenges regarding re-identification of data, and the need to reconsent if consent for sharing was not part of original consent. Challenges associated with randomized trials include the timing and approach to sharing individual level data. There are

additional regulatory and legal challenges associated with return of research results across international boundaries. To inform this project, we have held discussions with leaders of DMD foundations; all strongly endorsed the value of providing a DMD child's clinical trial data to their parents/guardians

This form is designed to tell you things you need to think about before you decide if you want to participate in this study. **It is entirely your choice. If you decide to participate in the study, you may change your mind at any time.** The decision to participate in this study will not affect any aspect of your son's participation in vamorolone clinical trials. The decision to participate will not cause you to lose any medical benefits you have. If you decide not to take part in this study, your doctor will continue to take care of your son.

Before making your decision:

- Please carefully read this form or have it read to you
- Please ask questions about anything that is not clear

Feel free to take your time thinking about whether you would like your son to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. You are free to refuse to join this research or join now and decide to withdraw later. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled. By signing this form you will not give up any legal rights.

What is the purpose of this study?

The purpose of this study is to evaluate the process of informing patients about re-consent for returning results to the families of trial participants. We will get feedback from stakeholders (parents/guardians, physicians, advocates/foundations), and this information will help to improve the process and design the most ethical and efficient system possible. This system is designed to protect the privacy of trial participants and maintain the integrity of the clinical trial.

As part of the study, the sponsor (ReveraGen BioPharma) will return individual and aggregate research results to the parents/guardians of clinical trial participants.

What will I be asked to do?

You will be asked to complete a survey pre-data return. This will be an anonymous survey—your identity and your child's identity will not be linked to your responses. Responses will be compiled and analyzed together with other people's responses.

Next you will be mailed an encrypted USB drive with your child's data and a summary of the data from all who participated in the trial. You will also be provided with the password to access this drive via email. If you would prefer a paper copy, please let the study coordinator know. After you receive your child's data and a summary of data from all who participated in the trial, you will receive another survey. Again, your identity and your child's identity will not be linked to your responses. Responses will be compiled and analyzed together with other people's responses.

Your physician (the clinical trial investigator at your site) will be notified when you enroll in the study, and he/she will be asked to complete a survey after the data has been returned to you. This will provide information from the perspective of the physician.

You will be asked to directly contact the coordinator at ReveraGen by phone or email if you have questions. This is to maintain confidentiality.

If you have questions about the data and how it relates to your child's health, please discuss with your physician.

What are the possible risks of participating in the study?

Risk of loss of confidentiality:

Your son will only be identified by a study site and date of birth, to protect his confidentiality. At ReveraGen, only a single coordinator will know your identity and communicate with you directly.

Although many precautions are being taken (only identifying your data by your child's birthdate/study site), use of a dedicated coordinator who will be the only one at ReveraGen who knows your identity, there is a risk of loss of confidentiality.

There is a risk of the USB drive being lost. The information on it will be encrypted, and only date of birth/study site will be on the drive with the data (no other identifying information).

Receiving your child's data could lead to distress or confusion. It could raise additional questions. Some questions may be answered by our coordinator. Questions about how this information may or may not impact your child's health. We encourage you to discuss these questions with your physicians.

What are the potential benefits of participating in this study?

A potential benefit of participating in this study is the receipt of your child's data and a summary of compiled results from others in the trial. This research may also help guide our approach to providing data to future subjects in clinical trials.

Will I be compensated for my time and effort?

You will not be offered compensation for participating in this study.

The are no costs associated with participating in the study.

What are my other options?

You have the option not to participate in this study.

How will my confidentiality be maintained?

- A single coordinator at our company will be the only one to know your identity. She will be contacted by you, and will store your child's name, date of birth, address, your email address, and study site (as provided by you) in a password-protected file stored on a cloud-based server.
- The coordinator will request your child's data using only the site location and date of birth as identifiers.

The following entities may review the study records and medical records (including your son's identifying information in rare cases) to make sure that the study is carried out correctly and that we are following the law and protecting the children in the study: US Food and Drug Administration, the study's Coordinating Centers, the study sponsor ReveraGen BioPharma and its representatives, the National Institutes of Health (NIH), and the Institutional Review Board or ethics board overseeing the study activities at Western IRB.

Data obtained from this study may be presented, or published or shared with other investigators interested in DMD. However, nothing shared will contain information that can identify your son.

Contact Information

Contact Suzanne Gaglianone at 609-206-0939 or suzanne.gaglianone@reveragen.com

- if you have any questions about the study

Contact Laurie Conklin at 240-672-0295, 646-283-1074 (24 Hours) or laurie.conklin@reveragen.com

- if you have questions/concerns/complaints about the conduct of the study or if you feel you or your son have been harmed by participating in this research.

Contact the Western IRB at (800) 562-4789

- if you have questions about your son's rights as a treatment recipient.
- if you have questions, concerns or complaints
- If you would like to provide feedback

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Participation in this research requires us to access your son's medical record.

What information may be used and given to others?

The study doctor will get your son's personal and medical information. For example:

- Past and present medical records
- Research records

Who may use and give out information about you?

The study doctor and the study staff.

Who might get this information?

The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information may be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- The institution where the research is being done
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to make sure that the research was done right.

What if I decide not to give permission to use and give out my son's health information?

Then you and your son will not be able to be in this research study.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically.

You may withdraw or take away your permission to use and disclose your son's health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

IRB APPROVED
Oct 09, 2019

When you withdraw your permission, no new health information identifying your son will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

VOLUNTARY CONSENT:
The above information has been explained to me and all of my current questions have been answered.

I understand that I am encouraged to ask questions at any time, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

_____
Child's Name (Print)

_____
Parent or Guardian's Name (Print)

_____
Relationship to Subject (Child)

_____ _____
Parent or Guardian's Signature Date

CERTIFICATION OF INFORMED CONSENT:
I certify that I have explained the nature and purpose of this screening to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____
Printed Name of Person Obtaining Consent

_____
Role in Research Study

_____
Signature of Person Obtaining Consent

_____
Date

ReveraGen BioPharma

CONSENT FOR THE PROCESSING OF PERSONAL DATA FROM THE EUROPEAN UNION TO FACILITATE RETURN OF RESULTS PER PROTOCOL VBP15-ROR/WIRB PROTOCOL 20192458

1. Pursuant to the European Union General Data Protection Regulation ("EU GDPR"), Reveragen BioPharma ("Reveragen"), in its capacity as a data controller and/or processor under the EU GDPR, must obtain your explicit, affirmative, and informed consent before it can collect or process any personal data.

2. Per protocol, return of data will be facilitated through Reveragen's coordinator. Personal information including your child's date of birth, study site, your home address, and phone number will need to be provided to the coordinator.

3. You have the right to withdraw your consent to the processing of your above personal data at any time. However, refusal of consent may make it impossible for Reveragen to carry out the activity of returning data. **If you would like to withdraw consent, please contact the Study Coordinator, Suzanne Gaglianone at suzanne.gaglianone@reveragen.com or 1-609-206-0939**.

4. Reveragen is committed to ensuring the security of your information.

Having read this notice (items 1-4), I, _____, the
[Print Full Name Here]

undersigned, hereby:

☐ **give consent** ☐ **does not give consent**

for the use of the following personal data (of my child and/or myself) for the sole purpose of facilitating the process described in item 2 above.

Son's date of birth : _____

Mailing Address: _____

Phone Number: _____

Signature: _____

Date [Month/Day/Year]: _____

ReveraGen BioPharma

Return of Results parent follow-up survey

Post Data-Return Survey

Thank you for participating in the 'return of patient data' study.

Now that you have received information on your son and the results of the vamorolone clinical trial, we would appreciate your feedback on this process, and how important or useful this information was to you.

1. Please answer the following questions.

How important was it to you to receive your child's individual clinical trial results?

- ◯ Not important
- ◯ Somewhat important
- ◯ Important
- ◯ Very important

2. If it was important to you to receive your son's data, why was this important to you? You may skip this question if it does not apply.

3. How important was it to you to receive a summary of the results from other children in the trial?

- ◯ The most important priority
- ◯ A top priority, but not the most important
- ◯ Not very important
- ◯ Not important at all

4. If it was important to you to receive a summary of data from other trial participants, can you tell us why? You may skip this question if it does not apply.

5. How satisfied were you with the delivery of data on an encrypted USB drive by mail?

- ◯ Very satisfied
- ◯ Satisfied
- ◯ Somewhat satisfied
- ◯ Neither satisfied nor dissatisfied
- ◯ Somewhat dissatisfied
- ◯ Dissatisfied
- ◯ Very dissatisfied

6. The amount of information provided was

- ◯ Much too little information
- ◯ Too little information
- ◯ About the right amount of information
- ◯ Too much information
- ◯ Far too much information

7. Were you satisfied with return of data to you directly by ReveraGen?

- ◯ Not at all satisfied
- ◯ Mostly unsatisfied
- ◯ Neither satisfied nor unsatisfied
- ◯ Mostly satisfied
- ◯ Very satisfied

8. I would have preferred my child's individual data to be returned by my physician instead of by ReveraGen.

- ◯ I strongly agree with this statement. I would have preferred that my physician returned my son's research data.
- ◯ I mostly agree with this statement.
- ◯ I'm neutral- either way would be fine.
- ◯ I mostly disagree with this statement.
- ◯ I completely disagree with this statement. I would prefer to receive my son's data directly from the company.

9. I had unanswered questions after receiving the data.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

10. Who have you told anyone about the results you received from the ReveraGen? (Choose all that apply)

- ☐ No one
- ☐ Family members
- ☐ Health care providers
- ☐ Other (please specify)
- ☐ Teachers
- ☐ Friends

11. Are there other people that you intend to tell about the results you received from ReveraGen? (Choose all that apply)

- ☐ No one
- ☐ Family members
- ☐ Health care providers
- ☐ Other (please specify)
- ☐ Teachers
- ☐ Friends

12. I regret having made the decision to participate in this data return study

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

13. If I had to it again, I would participate in this data return study.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

14. If you regret the decision to receive your son's data or felt that the choice did you harm, can you tell us why? You may skip this question if it does not apply.

15. Do you have any additional concerns, comments, or questions for ReveraGen? You may skip this question if it does not apply to you.

Thank you for participating in the survey!

Best wishes to you and your family.
From the ReveraGen team

ReveraGen BioPharma

Return of Results parent follow-up survey

Post Data-Return Survey

Thank you for participating in the 'return of patient data' study.

Now that you have received information on your son and the results of the vamorolone clinical trial, we would appreciate your feedback on this process, and how important or useful this information was to you.

1. Please answer the following questions.

How important was it to you to receive your child's individual clinical trial results?

- ◯ Not important
- ◯ Somewhat important
- ◯ Important
- ◯ Very important

2. If it was important to you to receive your son's data, why was this important to you? You may skip this question if it does not apply.

3. How important was it to you to receive a summary of the results from other children in the trial?

- ◯ The most important priority
- ◯ A top priority, but not the most important
- ◯ Not very important
- ◯ Not important at all

4. If it was important to you to receive a summary of data from other trial participants, can you tell us why? You may skip this question if it does not apply.

5. How satisfied were you with the delivery of data on an encrypted USB drive by mail?

- ◯ Very satisfied
- ◯ Satisfied
- ◯ Somewhat satisfied
- ◯ Neither satisfied nor dissatisfied
- ◯ Somewhat dissatisfied
- ◯ Dissatisfied
- ◯ Very dissatisfied

6. The amount of information provided was

- ◯ Much too little information
- ◯ Too little information
- ◯ About the right amount of information
- ◯ Too much information
- ◯ Far too much information

7. Were you satisfied with return of data to you directly by ReveraGen?

- ◯ Not at all satisfied
- ◯ Mostly unsatisfied
- ◯ Neither satisfied nor unsatisfied
- ◯ Mostly satisfied
- ◯ Very satisfied

8. I would have preferred my child's individual data to be returned by my physician instead of by ReveraGen.

- ◯ I strongly agree with this statement. I would have preferred that my physician returned my son's research data.
- ◯ I mostly agree with this statement.
- ◯ I'm neutral- either way would be fine.
- ◯ I mostly disagree with this statement.
- ◯ I completely disagree with this statement. I would prefer to receive my son's data directly from the company.

9. I had unanswered questions after receiving the data.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

10. Who have you told anyone about the results you received from the ReveraGen? (Choose all that apply)

- ☐ No one
- ☐ Family members
- ☐ Health care providers
- ☐ Other (please specify)
- ☐ Teachers
- ☐ Friends

11. Are there other people that you intend to tell about the results you received from ReveraGen? (Choose all that apply)

- ☐ No one
- ☐ Family members
- ☐ Health care providers
- ☐ Other (please specify)
- ☐ Teachers
- ☐ Friends

12. I regret having made the decision to participate in this data return study

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

13. If I had to it again, I would participate in this data return study.

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

14. If you regret the decision to receive your son's data or felt that the choice did you harm, can you tell us why? You may skip this question if it does not apply.

15. Do you have any additional concerns, comments, or questions for ReveraGen? You may skip this question if it does not apply to you.

Thank you for participating in the survey!

Best wishes to you and your family.
From the ReveraGen team

Return of Results Site Physician Survey

1. ReveraGen received a Bioethics supplement from the NIH to study a process of returning individual clinical trial data to patient families. We are returning data to study participants after the database is locked, the clinical study report written, and top-line results announced.

One of the vamorolone clinical trial participants recently requested their data.

We want to understand this issue from a physician perspective- thank you for completing this anonymous survey and answering the following questions.

How much importance do you believe families place on receiving their son's individual clinical trial results?

- ◯ A great deal
- ◯ A little
- ◯ A lot
- ◯ None at all
- ◯ A moderate amount

2. How much importance do you believe families place on receiving their aggregate clinical trial results?

- ◯ A great deal
- ◯ A little
- ◯ A lot
- ◯ None at all
- ◯ A moderate amount

3. Do you think a parent/guardian should receive their child's individual clinical trial data if the parent requests it?

- ◯ Yes
- ◯ No

4. Do you agree with the concept of a Sponsor returning individual clinical trial data directly to trial participants?

- [ ] Yes
- [ ] No
- [ ] I'm not sure
- [ ] Yes, but it depends on the circumstances

5. If you don't agree with the concept of a company returning clinical trial data to participants, can you list your concerns?

6. Are you aware of additional questions/comments/concerns from parents/guardians directed to you/your team following return of their data from ReveraGen?

- ◯ Yes
- ◯ No

7. If your team received questions/concerns from parents/guardians about the returned data, can you elaborate on what types of questions/concerns they had?
This question may be skipped if it does not apply.

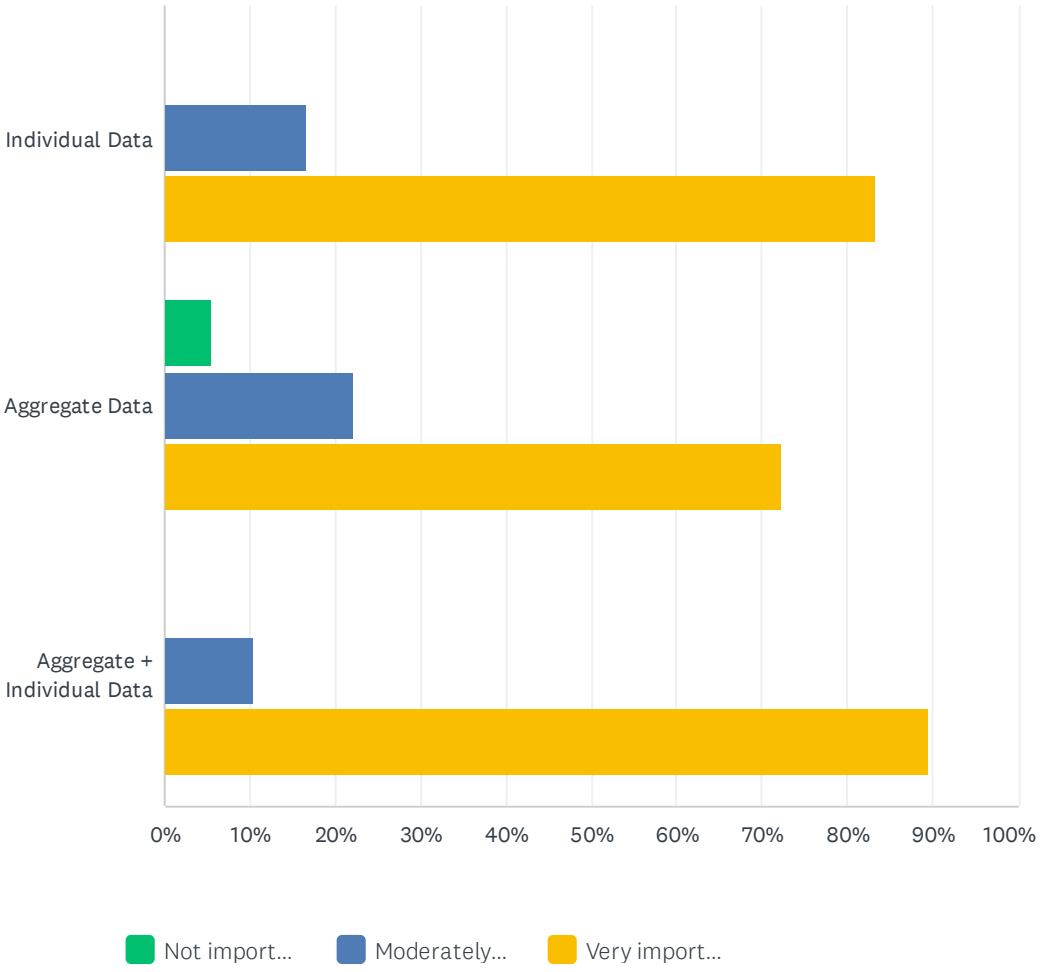
8. Do you have any feedback for ReveraGen on this process?
This question may be skipped.

Thank you for completing our survey!

With best wishes from the ReveraGen team

Q1 1. There are different types of clinical trial data that can be returned:· individual (only your child's data, and no one else's) · aggregate (general findings across trial participants, without specific reference to your son)· aggregate + individual (comparing your son to others, in the form of aggregate data, in the same trial)How important are each of these for you to receive?

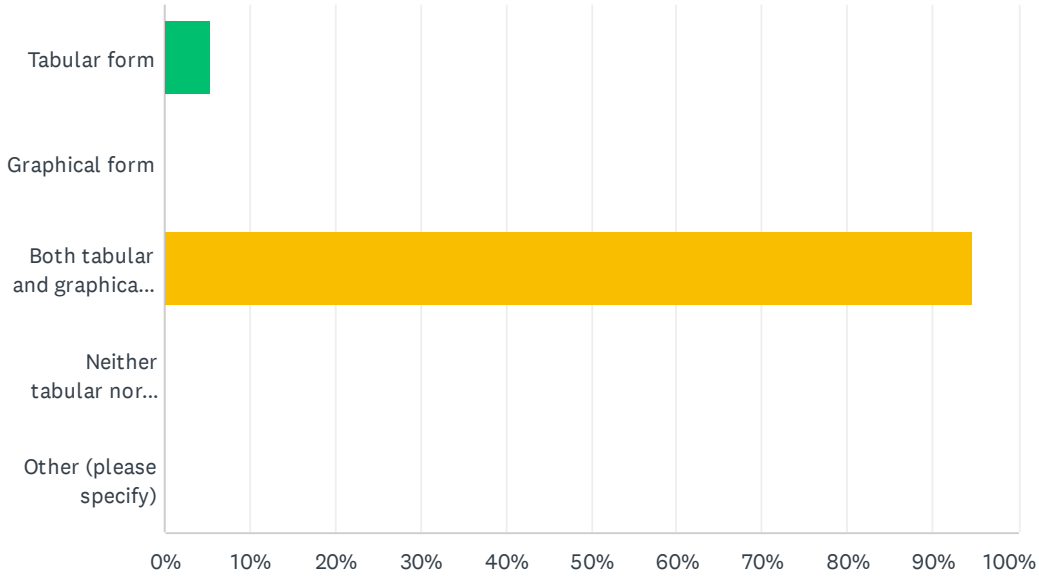
Answered: 19 Skipped: 0



	NOT IMPORTANT	MODERATELY IMPORTANT	VERY IMPORTANT	TOTAL
Individual Data	0.00% 0	16.67% 3	83.33% 15	18
Aggregate Data	5.56% 1	22.22% 4	72.22% 13	18
Aggregate + Individual Data	0.00% 0	10.53% 2	89.47% 17	19

Q2 There are different ways that data from clinical trials can be returned to you: · Tabular. These are numbers in a table. An example is shown below.· Graphical. These show graphs over time. An example is shown below. Of these types, which would you prefer?

Answered: 19 Skipped: 0

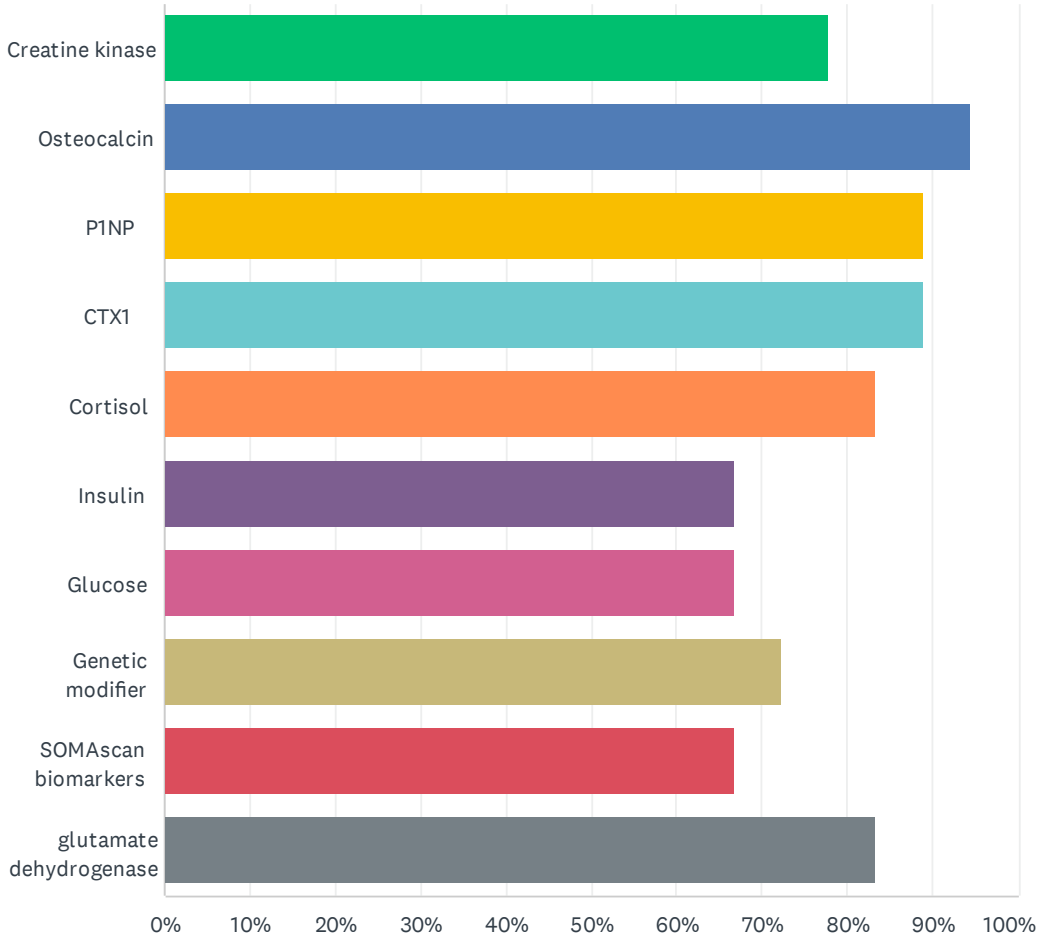


ANSWER CHOICES	RESPONSES	
Tabular form	5.26%	1
Graphical form	0.00%	0
Both tabular and graphical form	94.74%	18
Neither tabular nor graphical form	0.00%	0
Other (please specify)	0.00%	0
TOTAL		19

Q3 Your son generally contributes to 3 types of data collected in a clinical trial:· Clinical efficacy. These are measures of the benefit of the drug. In DMD these are typically measured by timed function tests. An example is the 6-minute walk test.· Clinical safety. These are measures of side effects or other health concerns. An example is stunting of growth.· Laboratory measures. These are often blood tests, typically called "biomarkers". An example is blood sugar.In the vamorolone trials, many different efficacy, safety and laboratory measures were collected and studied.Efficacy and safety information are relatively easy to understand. However, it is important to recognize that the clinical trial information returned to you may not directly impact the clinical care of your child.For laboratory measures, biomarkers may be difficult to interpret and may not be useful to your doctor in your son's medical care. For example, in some cases, we don't know what the "normal" levels of a particular biomarker are in boys with DMD. In some cases the test itself may not be studied well enough to interpret the result in a clinically useful way.A table of biomarkers used in the vamorolone trials is shown below, with a notation of the limitations of the test in the fourth column. As a result of these, and other limitations, none of these tests are recommended for routine use in the care of boys with DMD. However, they are done within the trial to answer a specific question about vamorolone treatment, or for a research purpose (to potentially develop better biomarkers). The term "exploratory biomarker" means that some information is known about the biomarker, but more information needs to be collected before it can be really useful to a physician, or a researcher, or a regulator. Which of the following biomarkers do you feel are important for you to receive, knowing the limitations of the testing (as shown in table above)?

Answered: 18 Skipped: 1

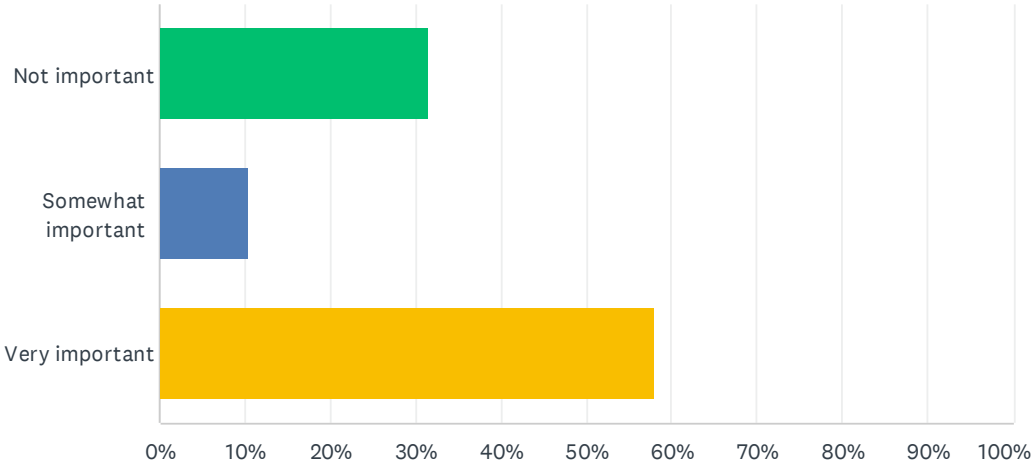
Return of results parent survey



ANSWER CHOICES	RESPONSES	
Creatine kinase	77.78%	14
Osteocalcin	94.44%	17
P1NP	88.89%	16
CTX1	88.89%	16
Cortisol	83.33%	15
Insulin	66.67%	12
Glucose	66.67%	12
Genetic modifier	72.22%	13
SOMAscan biomarkers	66.67%	12
glutamate dehydrogenase	83.33%	15
Total Respondents: 18		

Q4 “Blinding” is a procedure in which you and your son are unaware of which treatment arm you have been assigned to. A clinical trial is often double-blind – this means the doctor, study staff, drug company, and participant all don’t know who is receiving placebo, who is receiving study drug, and at what dose. This is done so that the effects of the drug can be assessed without unconscious bias of the doctor or participant or study staff. If this information is revealed during the study or while the study data are being analyzed, it could lead to bias. How important would it be for you to know what arm your son was in?

Answered: 19 Skipped: 0



ANSWER CHOICES	RESPONSES	
Not important	31.58%	6
Somewhat important	10.53%	2
Very important	57.89%	11
TOTAL		19

Q5 If it is important, why is it important to you?If it is not important, why is it not important to you?

Answered: 14 Skipped: 5

#	RESPONSES	DATE
1	To see if the dose has had an impact on safety and efficacy and discuss with the doctor.	5/27/2021 7:31 AM
2	wasn't important as all of the kids got the vamorolune if I recall correctly (each got at different dosage), and right after everybody got the same dosage.	5/13/2021 6:09 AM
3	This trial was not blind. None of the boys received placebo, and we knew the dose of the Vamorolone our son was getting, all along the trial.	5/7/2021 6:02 PM
4	To know any side effects to look for.	4/28/2021 4:37 PM
5	I would want to know if he was getting the drug to gauge his deterioration to children on other drugs vs no drugs etc.	4/7/2021 1:19 AM
6	We weren't in a blind	9/10/2020 2:34 AM
7	While it cannot change the outcome or results, knowing what arm can validate personal observations. Put to rest many "what-if" questions and scenarios.	8/23/2020 7:04 PM
8	I believe this is the only true way to understand the efficiency of the drug.	8/19/2020 6:32 AM
9	We received Vamorolone from the beginning.	8/18/2020 5:42 PM
10	To know whether or not he was given the medication, or a placebo.	8/18/2020 12:42 PM
11	We would like to know so that we can also gauge any benefits or differences. It is very frustrating not knowing given trials can be for long periods of time	8/10/2020 3:33 PM
12	If my son is in the placebo arm, that means that he'll get the drug eventually in the second leg of the trial. But he'll get the drug later than what he needs, and that is critical.	7/5/2020 1:37 PM
13	I just want to know everything I possibly can.	7/1/2020 2:40 PM
14	It’s important because this drug could have effected his body. We want to know what was or wasn’t effected	1/20/2020 9:06 AM

Q6 What do you expect you would do with information returned that summarizes results for all boys in the trial?

Answered: 18 Skipped: 1

#	RESPONSES	DATE
1	I may not have use for the information right now but in the future if Vamorolone becomes available I can use it to decide if we want to continue	5/27/2021 7:31 AM
2	Will try to see if it works for everybody as a whole, and if not, why it would work for some and not others. I would also also like to see the different effects, if such occur, between dosages.	5/13/2021 6:09 AM
3	I would be happy to know that the trial was successful, and that we had the right decision to join this trial.	5/7/2021 6:02 PM
4	Study it, keep it with medical folder.	4/28/2021 4:37 PM
5	Look it over	4/8/2021 9:48 AM
6	Consider things we may need to do to help our son stay healthy and active. Give me an idea how boys are doing as a whole.	4/7/2021 1:19 AM
7	Compare them to our sons results	12/5/2020 12:52 AM
8	Read and be more informed	9/10/2020 2:34 AM
9	Review and compare how our son aligned with others and stand of care.	8/23/2020 7:04 PM
10	Helps us be more informed and gives us an understanding of what impact the drug is having on an individual level.	8/19/2020 7:32 AM
11	Read it thoroughly to help me understand the efficiency of the drug.	8/19/2020 6:32 AM
12	Comparisons with other steroids treatment.	8/18/2020 5:42 PM
13	For my own knowledge, to get a better understanding of how effective Vamorolone is/was across the board, not only in my son.	8/18/2020 12:42 PM
14	It will help to make a future choice when the medication is approved and available.	8/17/2020 6:04 PM
15	Nothing - we'd just use to bench mark against our son for our own knowledge/piece of mind	8/10/2020 3:33 PM
16	Try to get my younger son enrolled in the next cohorts based on the results of the older one's trials.	7/5/2020 1:37 PM
17	File away in my personal file cabinet after reviewing them.	7/1/2020 2:40 PM
18	Google terms so we understand what terms mean	1/20/2020 9:06 AM

Q7 What do you expect you would do with information returned on your son's individual results?

Answered: 18 Skipped: 1

#	RESPONSES	DATE
1	I will have the information so we can discuss with the doctor if we may want to increase or decrease the dose. I hope to see information that makes me think we were lucky to be in the trial	5/27/2021 7:31 AM
2	For my son I the drug seemed to have worked. I would look at it to see if there were effects I'm not aware of, and to better understand as much as I can his current medical status for the results. Perhaps I'll show the individual results to our doctor to consult, if I'll need to.	5/13/2021 6:09 AM
3	I would read it carefully, and maybe will share it with my son (not sure). and maybe it would be helpful for future trials or approved drugs.	5/7/2021 6:02 PM
4	Same	4/28/2021 4:37 PM
5	To go over it	4/8/2021 9:48 AM
6	Compare his results	4/7/2021 1:19 AM
7	Share them with his doctor	12/5/2020 12:52 AM
8	Read and be more informed	9/10/2020 2:34 AM
9	The data would potentially influence our decision to stay on Vamorolone long term. Also, the results of biomarkers that are not standard may lead us to pursue further intervention with our son's primary medical team.	8/23/2020 7:04 PM
10	Not sure yet. Possibly talk with my son's neuro-muscular consultant about them and the GP.	8/19/2020 7:32 AM
11	Read it thoroughly to see how well my son is doing on the drug in comparison to others.	8/19/2020 6:32 AM
12	Discuss continued use or consider alternative treatments or trials if results are not as expected.	8/18/2020 5:42 PM
13	Be able to make more informed decisions on further participation in clinical trials.	8/18/2020 12:42 PM
14	Understand the effect of the medication on my son's progression based on data.	8/17/2020 6:04 PM
15	Nothing, we'd just use to satiate our own knowledge of his situation which if positive would give us hope and a positive mental mindset	8/10/2020 3:33 PM
16	Correlate to his ambulation. Cause we are seeing a drastic drop in his ambulation since he was moved to Prednisone in March 2020.	7/5/2020 1:37 PM
17	File away in my personal file cabinet after reviewing them.	7/1/2020 2:40 PM
18	Look to see how he compares to the other kids	1/20/2020 9:06 AM

Q8 Is there anything else that you would like ReveraGen to know?

Answered: 16 Skipped: 3

#	RESPONSES	DATE
1	I would like to know if Vamorolone is shown to be helpful, will we be able to continue to get the Vamorolone until it can be approved by public health insurance in Israel	5/27/2021 7:31 AM
2	I have to sons with Duchenne, currently both on Vamorolone. I hope this data may possibly help me better understand why it would seem to work for one and not for the other.	5/13/2021 6:09 AM
3	Even though we don't know the final results, we feel it did good for our son, and hopefully we be available soon for all boys with DMD, and even for other medical conditions, the requires the use of steroids.	5/7/2021 6:02 PM
4	Love the Vamorolone!	4/28/2021 4:37 PM
5	No	4/8/2021 9:48 AM
6	We are happy with the trial and all the work that goes into it! We are hoping it won't cost more than we can afford. That is our biggest fear because we are very positive about Vamorolone.	4/7/2021 1:19 AM
7	We might use this data to decide if we are to continue	9/10/2020 2:34 AM
8	Thank you for pursing the opportunity to release data to families!	8/23/2020 7:04 PM
9	no	8/19/2020 7:32 AM
10	No.	8/18/2020 5:42 PM
11	Thank you for releasing the data; it's much appreciated, especially for those of us who understand how to read and interpret data.	8/18/2020 12:42 PM
12	Estimated time of approval and if it is going to be a good substitute for current steroids regime	8/17/2020 6:04 PM
13	No	8/10/2020 3:33 PM
14	I have absolutely no doubt that Vamorolone helped my older one and was tolerated really well. I am hoping it gets approved in early 2021, so that I can switch both my kids on it. Please keep up your excellent work.	7/5/2020 1:37 PM
15	We are so grateful we were selected to participate in this trial.	7/1/2020 2:40 PM
16	This information is important. I'd like a call to discuss what it is I am looking at	1/20/2020 9:06 AM

ReveraGen BioPharma

Thank you for consenting to participate in a study about the process of returning clinical trial data to patient families. If you have questions about any of the information provided, please reach out to Suzanne Gaglianone at suzanne.gaglianone@reveragen.com.

We are very grateful to your child and to your family for participating in a vamorolone clinical trial, and also for participating in this current data return study.

We look forward to your feedback on a follow-up survey after your son's clinical trial data is returned to you.

As you requested, we are providing individual and aggregate data to you in this report.

Your son participated in VBP15-002 and VBP15-003, trials which have both been completed.

Your son's dose group was 0.25 mg/kg/day.

There are generally 3 types of data on your son that are collected in a clinical trial:

- **Clinical efficacy**. These are measures of the benefit of the drug. In DMD these are typically measured by timed function tests. An example is 6-minute walk test.
- **Clinical safety**. These are measures of side effects or other health concerns. An example is stunting of growth.
- **Laboratory measures**. These are typically blood tests, typically called "biomarkers". An example is blood sugar.

In the vamorolone trials, many different efficacy, safety and laboratory measures were studied.

Efficacy and safety information are relatively easy to understand. However, it is important that this clinical trial information may not have direct impact on the clinical care of your child.

Although we are giving you individual data, these tests are not being done in the trial to measure your son's individual abilities, or how the drug worked or didn't work *in your son.* In order to answer questions about how the drug is working, your son's test results are part of a whole program of multiple studies. Your son's test results are being analyzed as part of a cohort of patients, according to a pre-designed study plan.

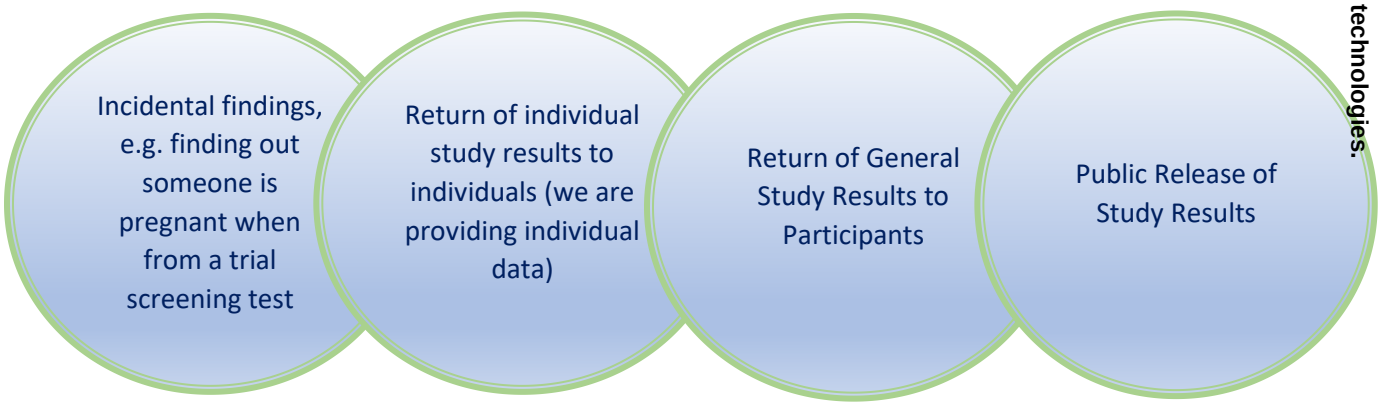
Your doctor doesn't have access to these data and may not be able to interpret them easily. To find out more information about how your son is doing clinically, it is best not to rely on these data, but to speak to your doctors and nurses! Your doctors and nurses know your son as an individual. They know how to take care of children with DMD, and they have a very important

relationship with your son and your family. At ReveraGen, there are researchers and pediatricians who care about helping kids with DMD. But we are not experts in taking care of children with DMD, and we're not supposed to know your son as an individual. Research is different from clinical care- they're both important, but they're kept separate *on purpose*. Your doctor's primary goal is to take the best care of your son and your family that he or she possibly can. As a drug company, we are going through the careful steps that are necessary to see if vamorolone is safe and effective in boys with DMD. If it is safe and effective, we will do our best to make it available to help patients.

So now that this has been stated, we will explain why drug companies don't usually give out their data.

There are different types of data, including incidental findings, individual study results, general study results, and public release of data. Incidental findings that are critical to the patient's health need to be reported to their physician. After a study is complete, often a company needs to publicly release data if there are investors in the company (to avoid getting into legal troubles). Sometimes scientific groups have rules about publishing a manuscript or giving a presentation at a scientific meeting before data is released. Also, it's important for companies not to "promote" their drug to patients or physicians before it's approved by the regulatory agencies to be marketed for a specific group of patients. The regulatory agencies approve drugs after they review all the data and determine that the drug is safe and effective. ReveraGen (and the regulatory agencies) don't know if vamorolone is safe and effective while the trials are still ongoing and before the data is all analyzed. If individual or general study results get released too early, people might misinterpret the data and be either too hopeful or too critical about the drug. Sometimes trial data can be misleading if it isn't presented or interpreted in the right way. And sometimes a drug may look very promising in early trials, but then not work in a placebo-controlled trials.

Many of these tests aren't very important or helpful to your doctor when he or she is assessing the progress of your son. So the doctor may not want to provide the results because they are difficult to interpret out of context from the study, and may not helpful for the care of your son. Giving these results might worry parents or cause them false hope or worry. Many of these results are more important to help researchers assess vamorolone.



Here is your son's Individual Data:

Functional outcome measures before and after treatment with vamorolone

	6-minute walk test	**Time to Stand from the Floor test**		**10-meter run/walk**		**Climb 4 stairs**		**North Star Ambulatory Assessment**
	Distance in meters	In seconds	In velocity (rises/ second)	In seconds	In velocity (meters/ second)	In seconds	In velocity (tasks/ second)	Score
Baseline 30Jun2016	387	7.59	.132	6.37	1.57	3.81	.262	24
12 weeks 17Oct2016	367	Unable to do the test	.000	7.57	1.32	4.6	.217	23
24 weeks 17Jan2017	321	Unable to do the test	.000	8.12	1.23	5.84	.171	21

Here is a table showing the aggregate (rounded average) data for the boys in your son's dose group (0.25 mg/kg/day):

	6-minute walk test	**Time to Stand from the Floor test**	**10-meter run/walk**	**Climb 4 stairs**	**North Star Ambulatory Assessment**
Visit	Distance in meters rounded up to nearest 10	Average seconds rounded up to nearest 0.1	Average seconds rounded up to nearest 0.1	Average seconds rounded up to nearest 0.1	Average rounded up to nearest 1
Baseline	320	6.1	6.5	5.6	19
12 weeks	310	6.9	6.8	5.3	20
24 weeks	300	7.3	6.8	5.8	19

Here is a table of your son's Quantitative Muscle Testing results before and after treatment with vamorolone:

	Elbow extension (pounds)	**Elbow flexion (pounds)**	**Knee extension (pounds)**	**Knee flexion (pounds)**
Baseline	N/A	N/A	N/A	N/A

30Jun2016				
12 weeks 17Oct2016	5.98 8.50	9.97 9.86	18.66 18.55	9.76 9.86
24 weeks 17Jan2017	5.65 5.52	9.24 8.66	10.66 12.31	11.74 12.24

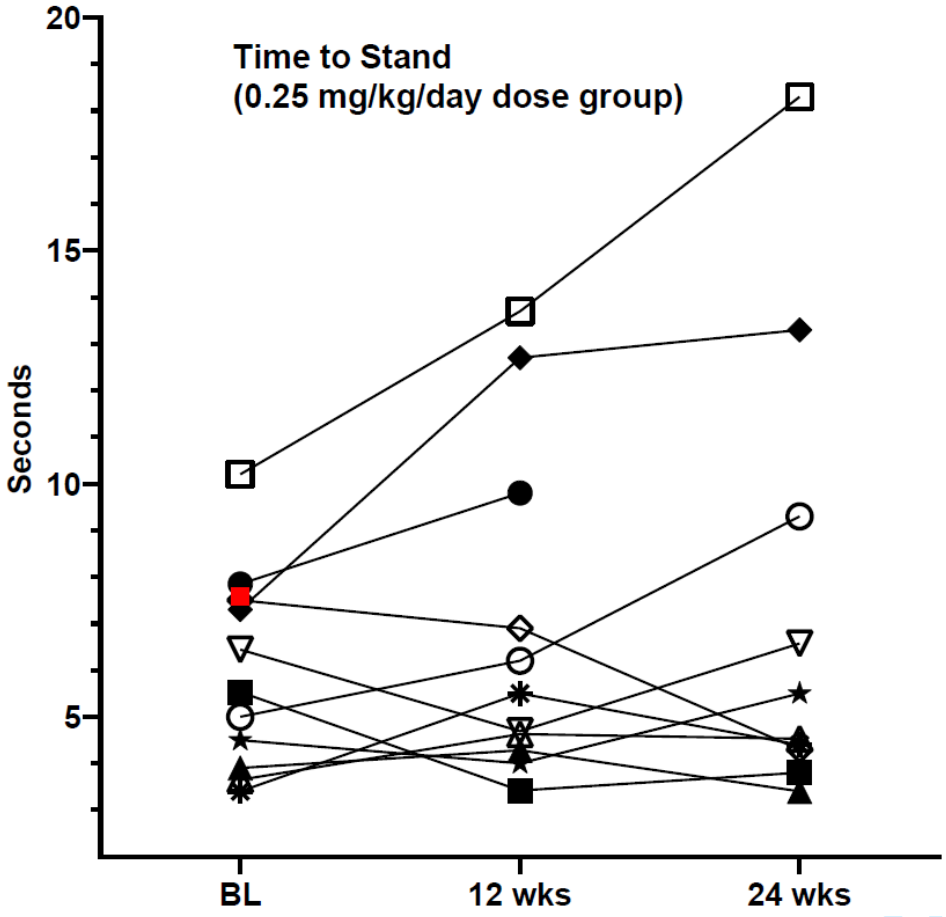
*N/A= data is missing

Here is a table showing the aggregate (rounded average) data for the boys in your son's dose group (0.25 mg/kg/day):

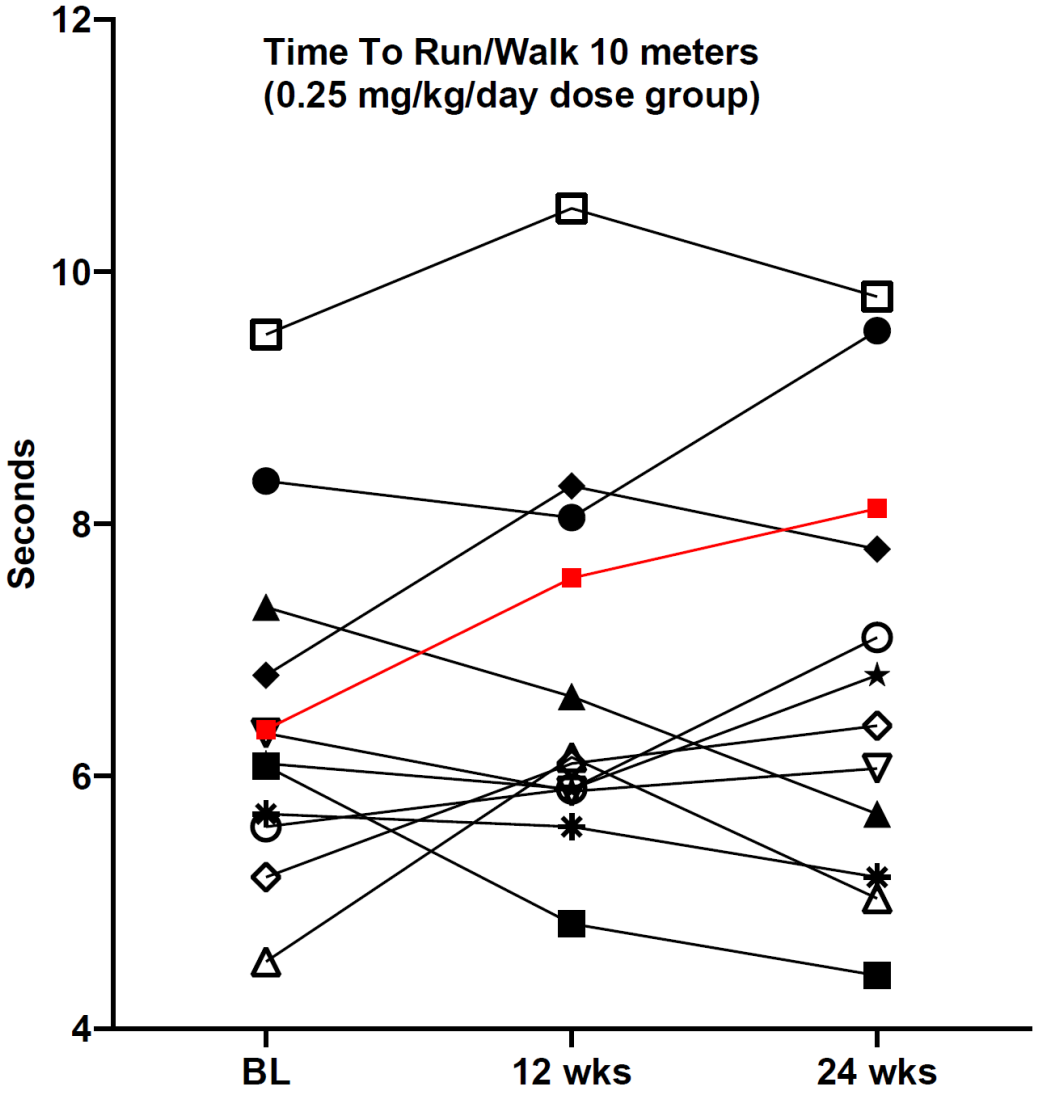
	Elbow extension (pounds)	**Elbow flexion (pounds)**	**Knee extension (pounds)**	**Knee flexion (pounds)**
Baseline	5.2	6.0	10.87	6.961
12 weeks	5.4	6.6	11.82	7.827
24 weeks	6.2	6.1	10.95	8.263

	Weight (kg)	Height (cm)	Body Mass index (BMI) (kg/m^2)
Baseline 30Jun2016	26.2	118	19
24 weeks 17Jan2017	29.6	122.1	19.9

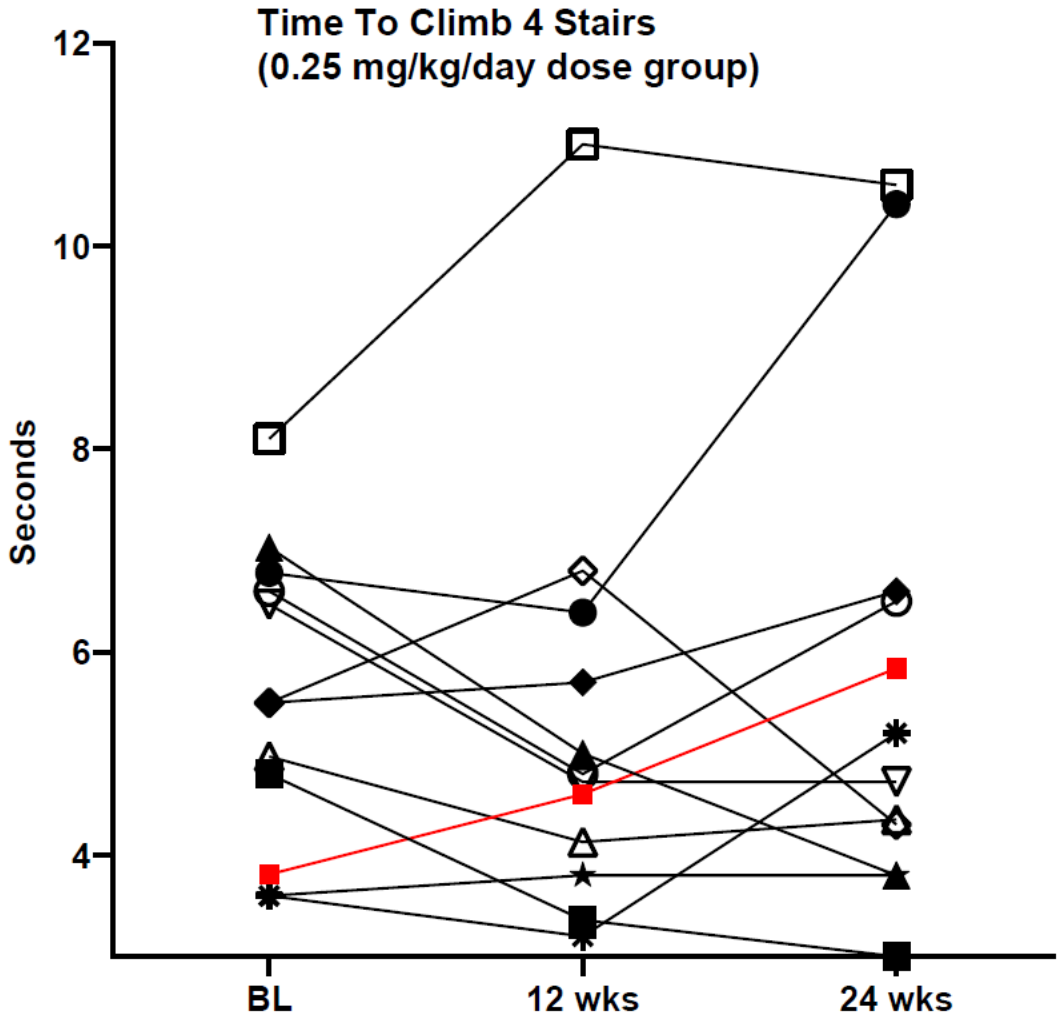
Time to Stand from the floor test, measured in seconds.
Your son's results are noted by the red square. Only one square can be seen because it was reported that your son was unable to do the test at 12 and 24 weeks.



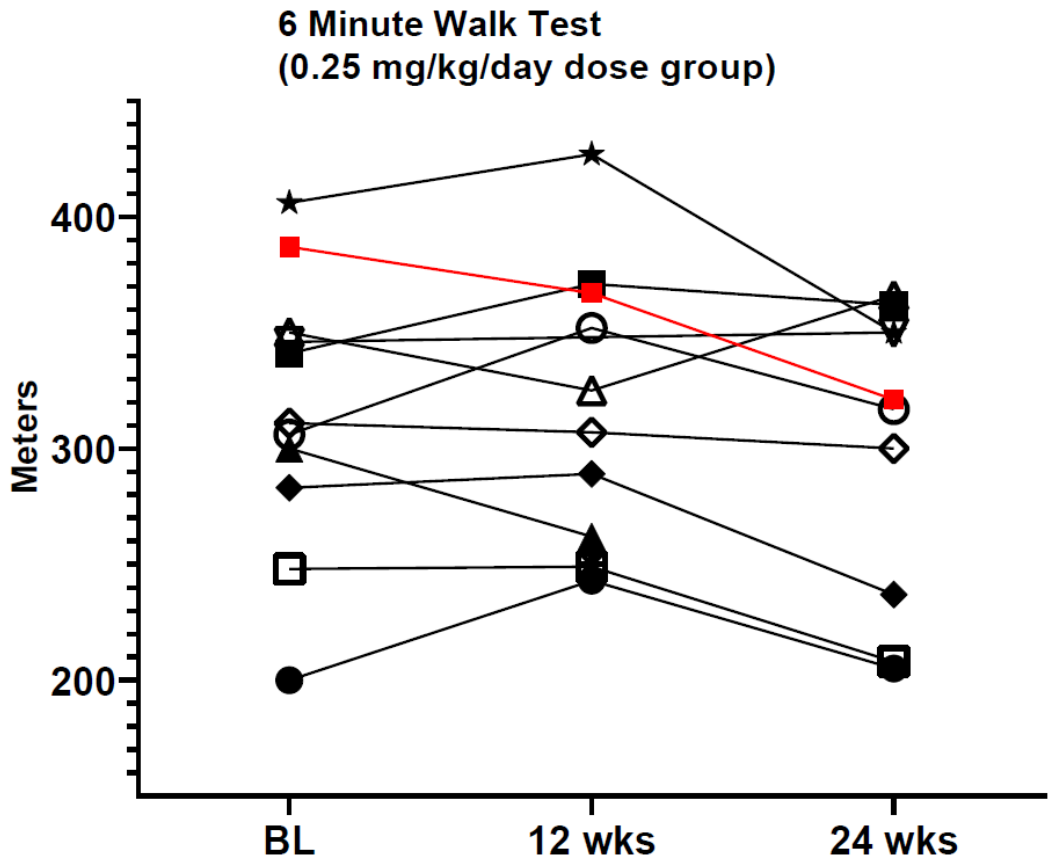
Time to Run/Walk 10 meters test, measured in seconds.
Your son's results are noted by the red square.



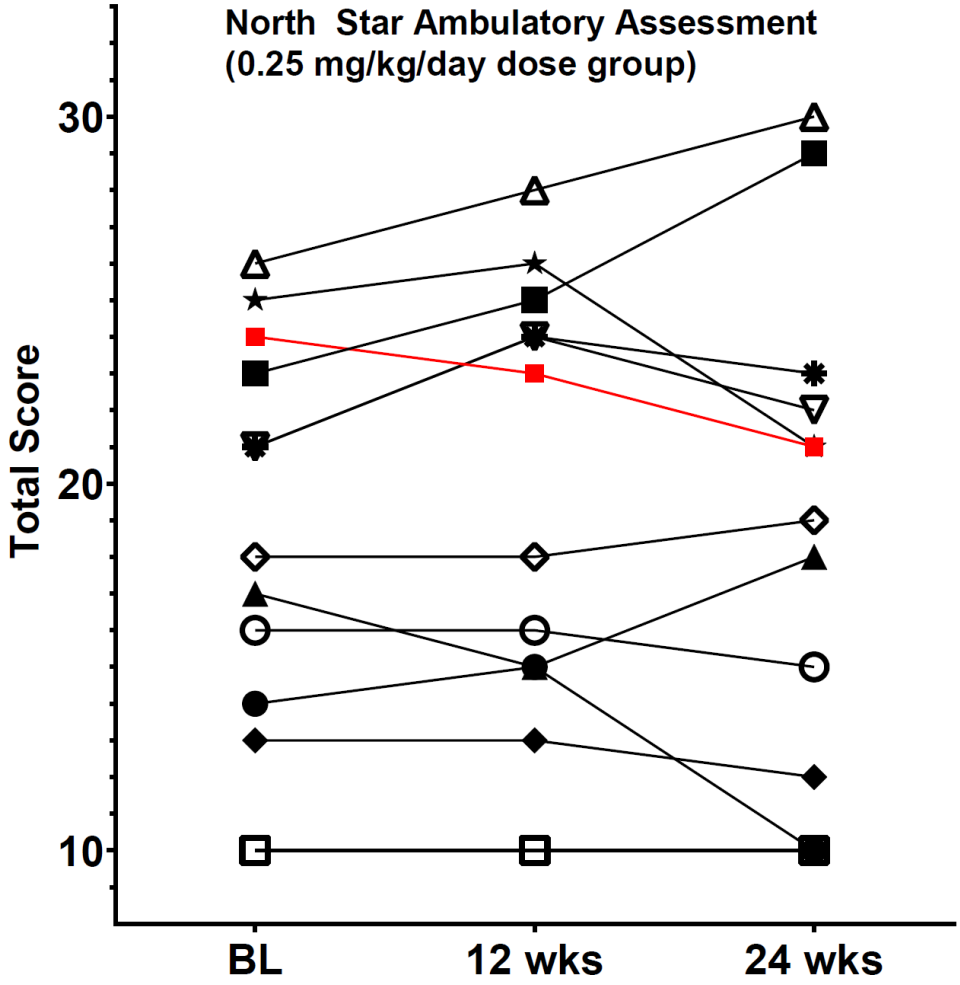
Time to Climb 4 Stairs Test, measured in seconds.
Your son's results are noted by the red square.



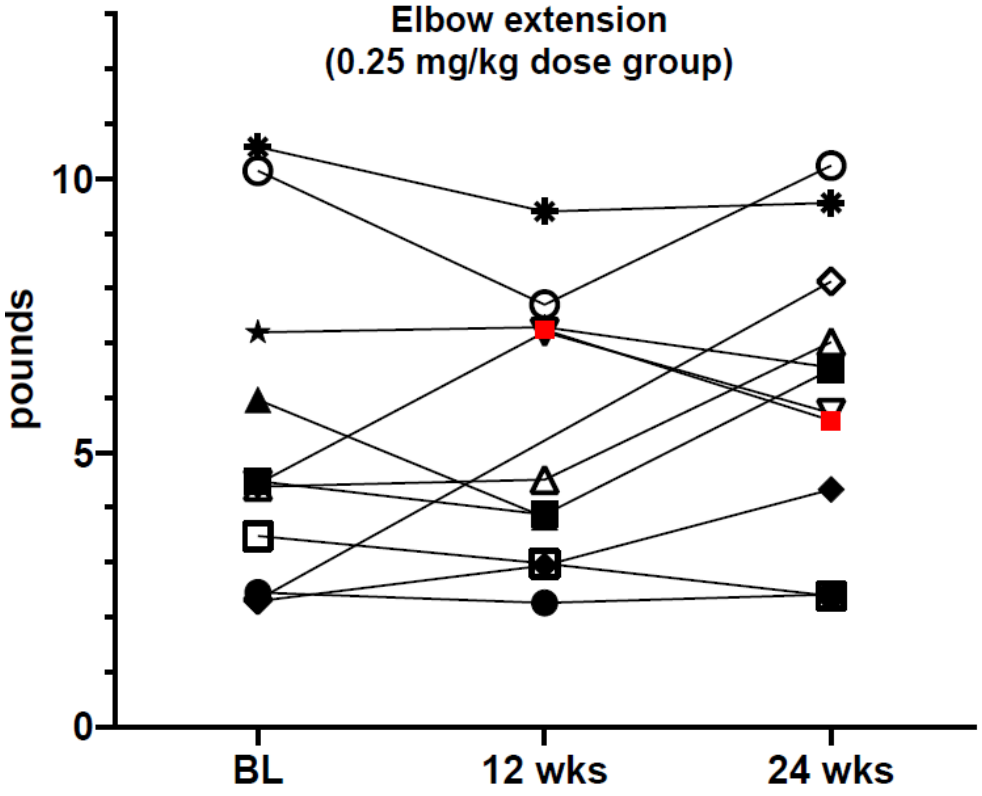
6 Minute Walk Test, measured in meters.
Your son's results are noted by the red square.

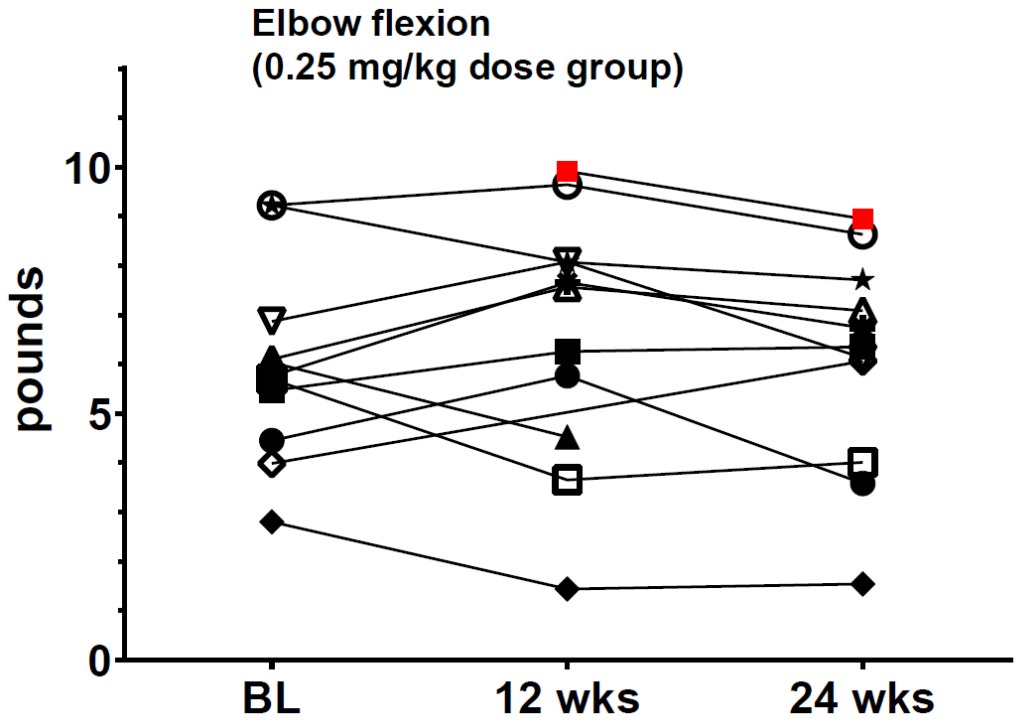


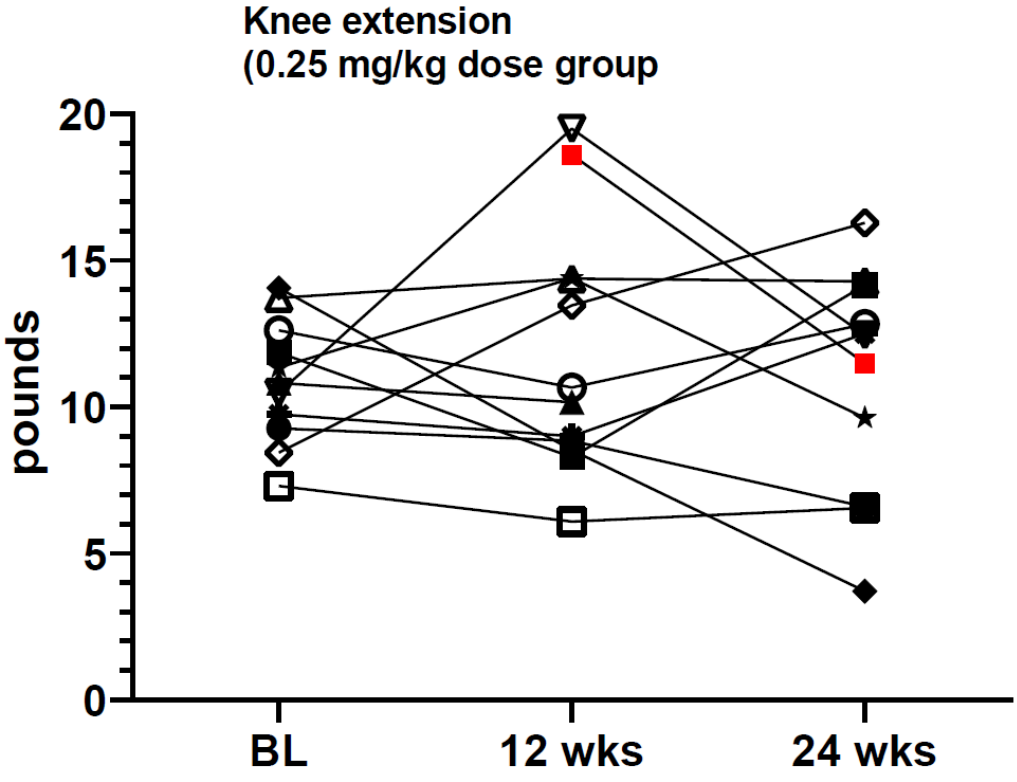
North Start Ambulatory Assessment score.
Your son's results are noted by the red square.

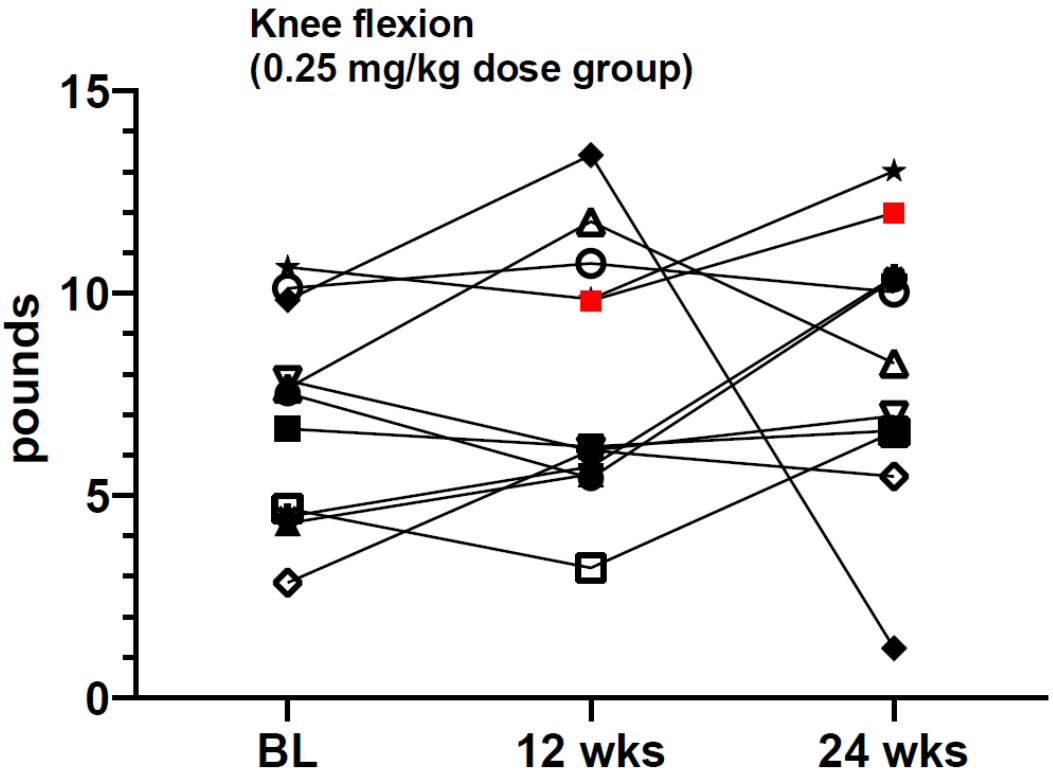


Quantitative Muscle Testing (elbow extension, elbow flexion, knee extension, knee flexion)
Your son's results are noted by the red square.









Biomarkers

For laboratory measures, biomarkers may be difficult to interpret and may not be useful to your doctor in your son's medical care. For example, in some cases, we don't know what the "normal" levels are in boys with DMD. In some cases, the test itself may not be studied well enough to interpret it in a clinically useful way.

A table of biomarkers used in the vamorolone trials is shown below, with a notation of the limitations of the test in the fourth column. As a result of these, and other limitations, none of these tests are recommended for routine use in the care of children with Duchenne muscular dystrophy. However, they are done within the trial to answer a specific question about vamorolone treatment, or for a research purpose (to potentially develop better biomarkers).

Blood test	What is the test measuring?	Why is ReveraGen testing this?	Some limitations of the test	Does your doctor typically order this test in the clinic?
Creatine kinase	Leakiness of muscle	To determine if vamorolone may change	Often quite variable from day-to-day in a person.	Often used as a diagnostic screening test.

		leakiness in DMD muscle.		
Osteocalcin, P1NP (N-terminal propeptide of type 1 collagen)	Bone formation	Part of evaluation of vamorolone's effect on bone (along with x-rays, growth monitoring, keeping track of bone fractures)	Varies depending on a person's age. Can be impacted by a drug, or by DMD itself, or by lack of growth for some other reason. Interpreted along with other bone biomarkers, x-rays, and growth (not by itself).	No
CTX 1 (C-terminal telopeptide of type I collagen)	Bone loss	Part of evaluation of vamorolone's effect on bone (along with x-rays, growth monitoring, keeping track of bone fractures)	Varies depending on a person's age. Can be impacted by a drug, or by DMD itself, or by lack of growth for some other reason. Interpreted along with bone formation biomarkers, x-rays, and growth (not by itself).	No
Cortisol	Adrenal suppression	Part of evaluation of effects of vamorolone on the adrenal glands (along with an additional ACTH stimulation test in VBP15-004, monitoring for symptoms associated with adrenal suppression).	Varies depending on time of day that blood was drawn. Test doesn't tell how well the adrenals will respond to stress or illness.	Not usually- a child on chronic corticosteroids will likely have a low morning cortisol. All children who become seriously ill, or need surgery while taking steroids should be given "stress dose steroids". As we don't know about the effects of vamorolone on the adrenal glands yet, we ask parents/physicians to take this same precaution for children in vamorolone trials.
Fasting insulin/glucose	Low blood sugar,	Part of the evaluation of	Varies depending on whether child is	Sometimes.

	insulin resistance	effects of vamorolone on insulin resistance	fasting or not. Not a challenge test (like an oral glucose tolerance test). Not diagnostic of diabetes.	
Genetic modifiers	Differences in specific DNA sequences in your child.	To determine if certain genetic differences may affect the way a child responds to vamorolone (both efficacy and safety)	This will be done for research purposes. We are not certain when this data will become available.	No. There isn't yet enough known about genetic modifiers to make them useful in the clinic.
Glutamate dehydrogenase	Liver toxicity	To determine the effects of vamorolone on the liver.	This test is still experimental in patients with Duchenne muscular dystrophy.	No.

Here are your son's biomarker results. These tests have been done for research purposes only- to see how treatment with vamorolone affects these blood tests.

	Osteocalcin (bone formation)	P1NP (bone formation)	CTX1 (bone resorption)
Baseline 30Jun2016	52.6	1024	906
24 weeks 17Jan2017	54.4	1031	1455

	Result At Baseline	Result at Week 24-29	Low-High Range
Cortisol (mcg/dL)	4.4	3.2	2-17
Hemoglobin A1C (%)	4.9	4.9	4-6
Glucose (mg/dL)	79	87	60-99
Insulin	4.5	7.7	n/a
Glutamate dehydrogenase	4.8	5.5	0-<7
Creatine kinase (U/L)	42458	24246	18-158

ReveraGen not have genetic modifier data yet- these tests have not yet been run.

ReveraGen conducted a research study to evaluate how "exploratory" blood biomarkers change from before to after treatment with vamorolone for 2 weeks. We chose to look at inflammatory proteins in the blood that have been shown to change quickly after treatment with corticosteroids (in patients with different diseases, including DMD). These data are reported in "Relative Fluorescence Units", abbreviated RFU, which is how the test measures the protein level. A dose-responsive change was seen in 6 of the biomarkers. Your son's results are here at baseline and 2 weeks, followed by the aggregate data from the study, which showed Your son is in the 0.25 mg/kg dose group. It's important to remember that these biomarkers are not adequate to show efficacy of vamorolone in boys with DMD, but changes in these proteins may be an indication of vamorolone's anti-inflammatory activity in the body.

This is an example of test that is only done for research purposes. They haven't been tested well enough to use them in the clinic and aren't available for your doctors to run. It is not possible for us or your doctors to use these tests to explain anything about your son's medical condition or progress.

The results of your son's exploratory biomarker testing are shown here.

Note that are focusing on the 6 biomarkers that importantly showed a dose response to vamorolone in the study (on average, bigger changes were seen in kids who were taking higher doses).

Protein	Baseline RFU	2 Week RFU	Change from Baseline
CD23	7530.2	7221	- 309.1
MDC/CCL22	2604.2	2649.3	+ 45.1
IL22 BP	5192.7	4618.9	-573.8
Lymphotoxin a1b2	466.4	517.3	+50.9
IGFBP2	405.4	352.5	-52.9
MMP12	6421.9	6081	-340

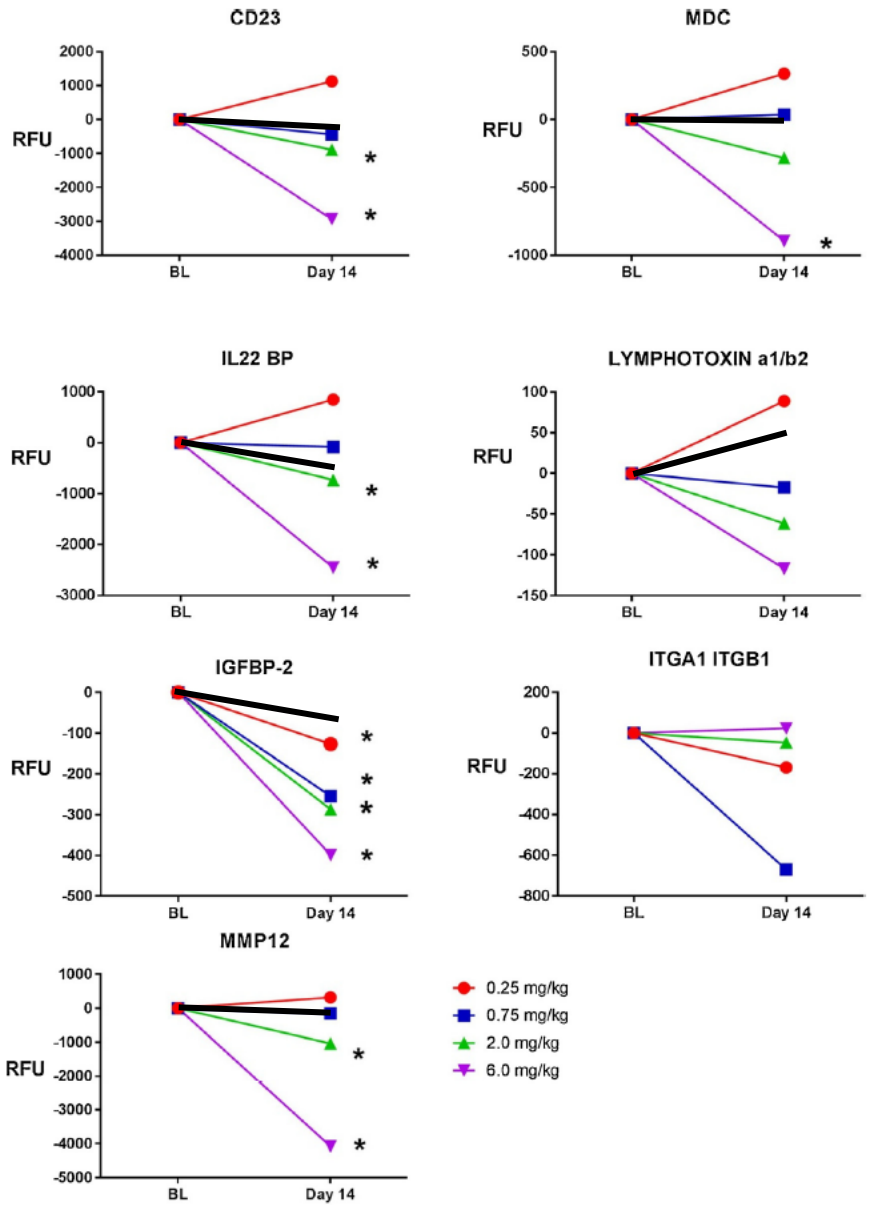
RFU= relative fluorescence units; MDC = macrophage derived chemokine (aka CCL22); IL22 BP = Interleukin 22 binding protein; IGFBP2= insulin growth factor binding protein 2; MMP12 = matrix metalloproteinase 12

The average results from the boys in the 0.25 mg/kg/day dose group (your son's dose group) are shown here for these same biomarkers:

Protein	Average Baseline RFU for 0.25 mg/kg/dose group	Average 2 Week RFU for 0.25 mg/kg/dose group	Average Change from Baseline for 0.25 mg/kg/dose group
CD23	8824	9951	+ 1127
MDC	2458	2796	+ 338
IL22 BP	6261	7110	+ 849
Lymphotoxin a1b2	471.0	559.9	+ 89
IGFBP 2	6261	7110	+ 849
MMP12	3421	3746	+ 324

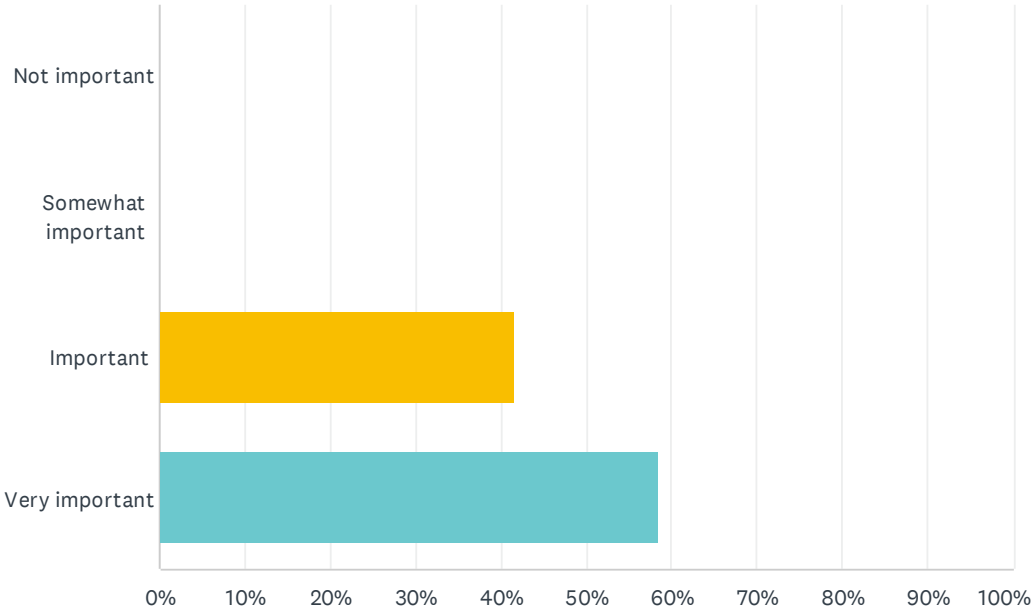
RFU= relative fluorescence units

Here these same data are shown above in graphical form. Each line shows the *average* change in RFU from baseline (red line = 0.25 mg/kg/day dose group; blue line 0.75 mg/kg/day dose group; green line 2.0 mg/kg/day dose group; purple line 6.0 mg/kg/day dose group). The 0.25 mg/kg/day dose group is your son's dose group. A black line represents an approximation of your son's data.



Q1 Please answer the following questions.How important was it to you to receive your child's individual clinical trial results?

Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Not important	0.00%	0
Somewhat important	0.00%	0
Important	41.67%	5
Very important	58.33%	7
TOTAL		12

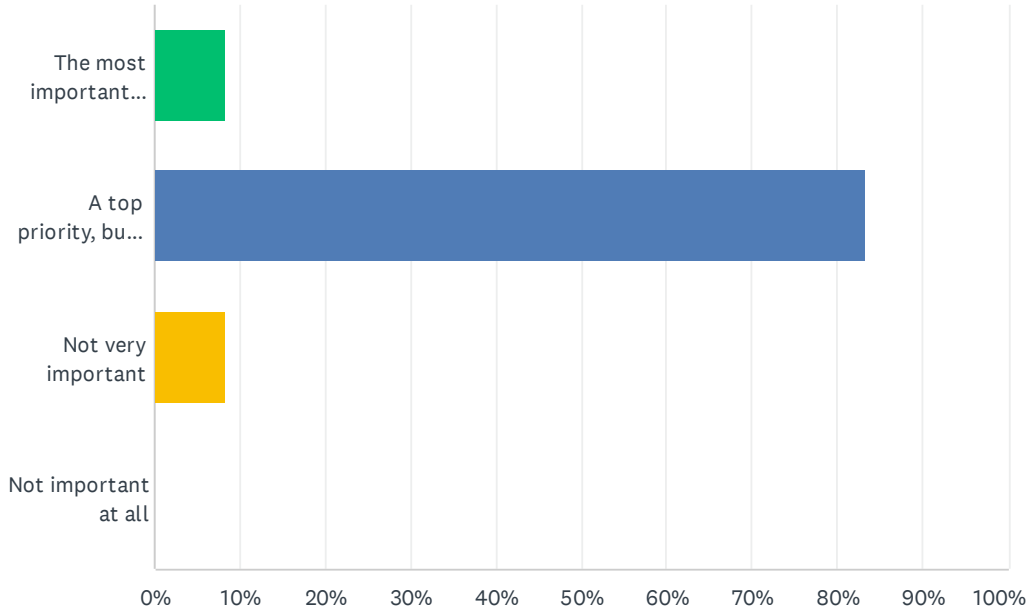
Q2 If it was important to you to receive your son's data, why was this important to you? You may skip this question if it does not apply.

Answered: 10 Skipped: 2

#	RESPONSES	DATE
1	Personal knowledge	6/29/2021 4:56 PM
2	To be informed	6/25/2021 12:31 PM
3	It is a great benefit to be able to see how my son may have responded during the Clinical Trail in all of these areas recorded, In Hopes to see some good benefit from the medication.	6/22/2021 8:49 PM
4	We took a big risk in being in the trial. Want to know if it works and how my son paired with the other boys	6/22/2021 4:29 PM
5	It’s nice to see how things are going and not be in the dark	6/22/2021 3:53 PM
6	All data to do with how my son is managing the condition/meds is important.	6/22/2021 3:14 PM
7	To understand the clinical help VBP15 provided	6/17/2021 10:34 PM
8	We would like further understanding about how the trial was going, and what difference it's made to our child as well as the rest of the children	6/9/2021 5:23 AM
9	To see actual data of improvement and/ or progression is important. Data helps you to understand if treatment works or not.	6/4/2021 11:58 AM
10	Just to see how our son is doing. We are hopeful he is doing better because if the drug and seeing the results gives us more hope.	6/3/2021 3:29 PM

Q3 How important was it to you to receive a summary of the results from other children in the trial?

Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
The most important priority	8.33%	1
A top priority, but not the most important	83.33%	10
Not very important	8.33%	1
Not important at all	0.00%	0
TOTAL		12

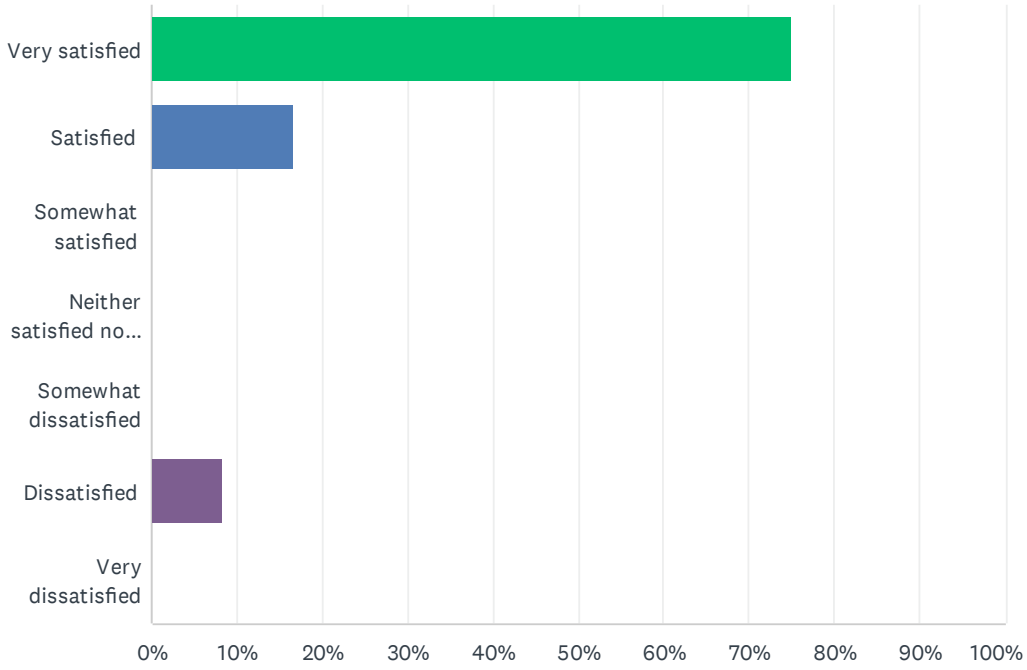
Q4 If it was important to you to receive a summary of data from other trial participants, can you tell us why? You may skip this question if it does not apply.

Answered: 8 Skipped: 4

#	RESPONSES	DATE
1	To stay informed	6/25/2021 12:31 PM
2	Its always great to see how my child was responding to the medication compared to other participants.	6/22/2021 8:49 PM
3	It’s nice to see how it’s doing with every one it’s important to see	6/22/2021 3:53 PM
4	So that I could see how he was doing in comparison with other similar boys.	6/22/2021 3:14 PM
5	To confirm my son belongs in the overall "good band"	6/17/2021 10:34 PM
6	This helps us benchamrk against how our child is doing. If we don't have a benchmark then we do not know if it is benefitting our child or not	6/9/2021 5:23 AM
7	More data more understanding. Comparing results is always helpful.	6/4/2021 11:58 AM
8	To see if others are also seeing good results	6/3/2021 3:29 PM

Q5 How satisfied were you with the delivery of data on an encrypted USB drive by mail?

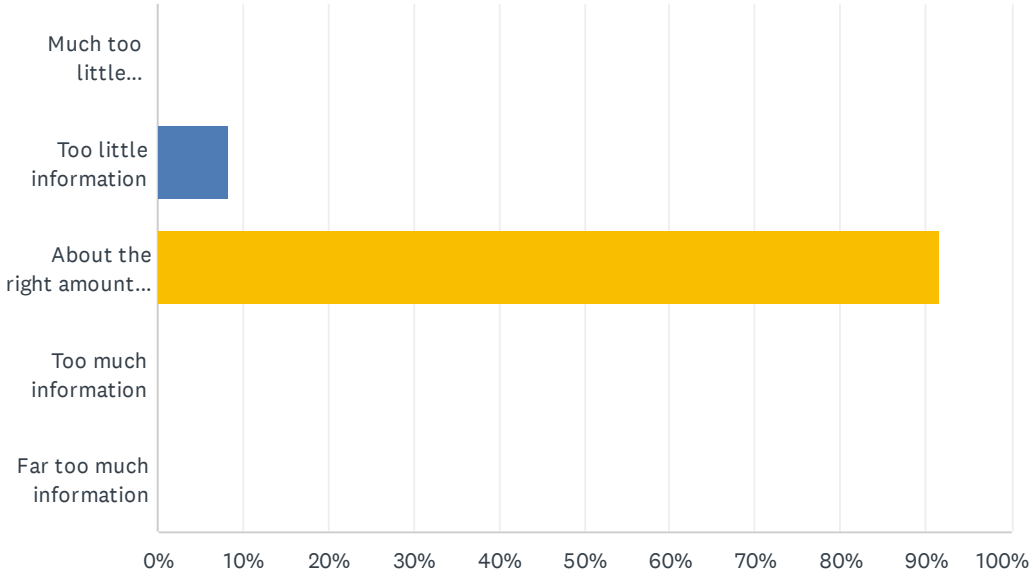
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Very satisfied	75.00%	9
Satisfied	16.67%	2
Somewhat satisfied	0.00%	0
Neither satisfied nor dissatisfied	0.00%	0
Somewhat dissatisfied	0.00%	0
Dissatisfied	8.33%	1
Very dissatisfied	0.00%	0
TOTAL		12

Q6 The amount of information provided was

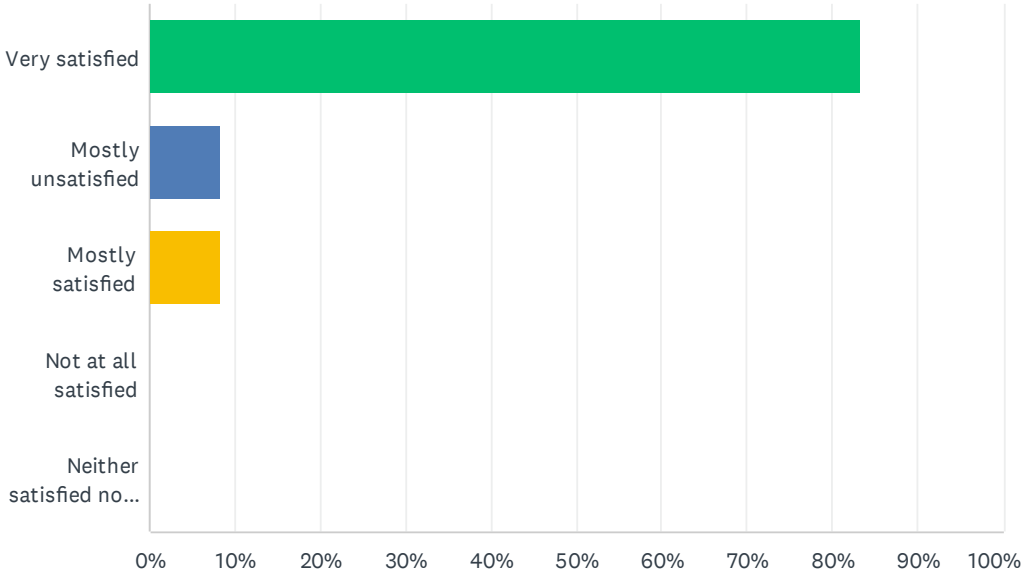
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Much too little information	0.00%	0
Too little information	8.33%	1
About the right amount of information	91.67%	11
Too much information	0.00%	0
Far too much information	0.00%	0
TOTAL		12

Q7 Were you satisfied with return of data to you directly by ReveraGen?

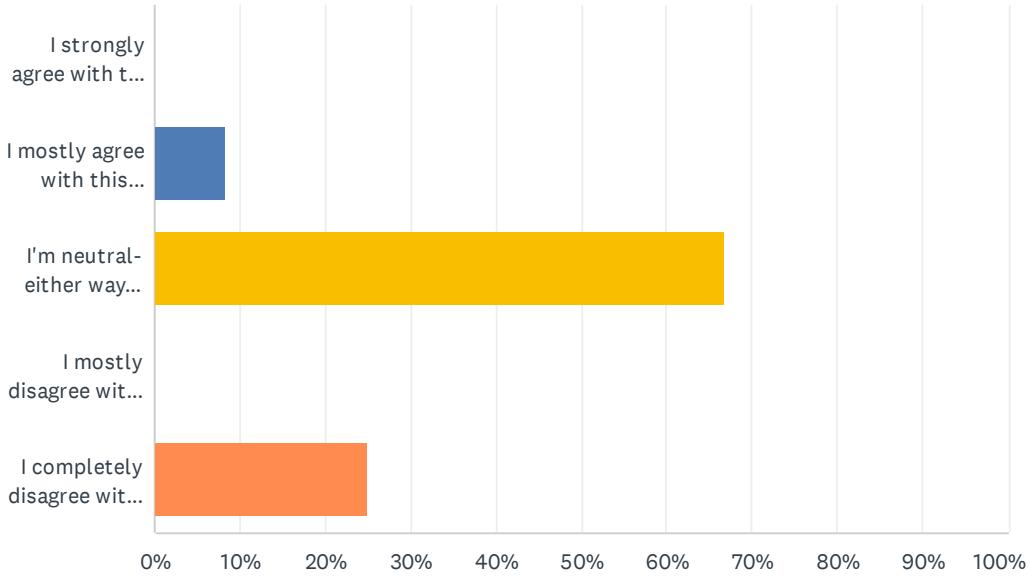
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Very satisfied	83.33%	10
Mostly unsatisfied	8.33%	1
Mostly satisfied	8.33%	1
Not at all satisfied	0.00%	0
Neither satisfied nor unsatisfied	0.00%	0
TOTAL		12

Q8 I would have preferred my child's individual data to be returned by my physician instead of by ReveraGen.

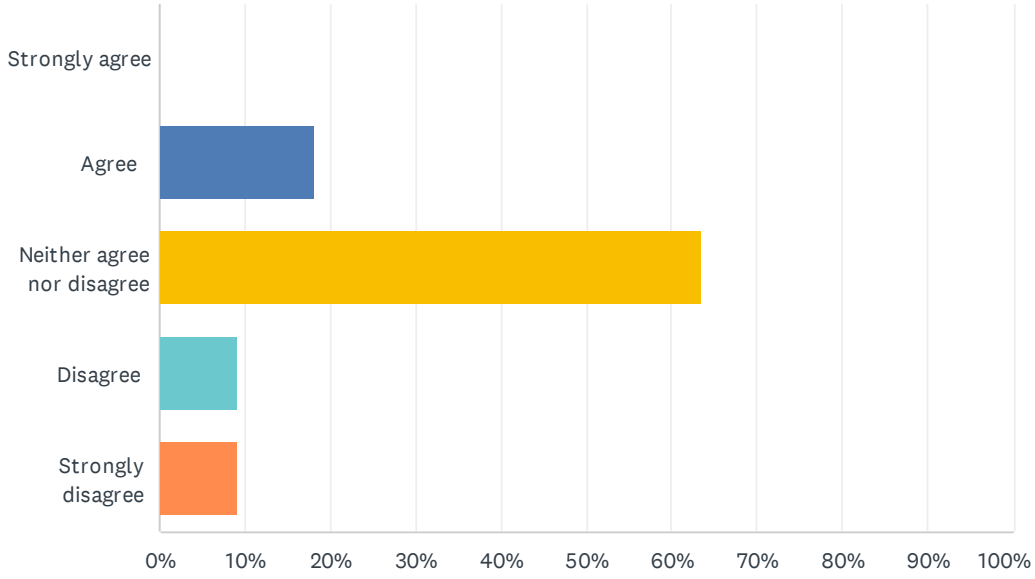
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
I strongly agree with this statement. I would have preferred that my physician returned my son's research data.	0.00%	0
I mostly agree with this statement.	8.33%	1
I'm neutral- either way would be fine.	66.67%	8
I mostly disagree with this statement.	0.00%	0
I completely disagree with this statement. I would prefer to receive my son's data directly from the company.	25.00%	3
TOTAL		12

Q9 I had unanswered questions after receiving the data.

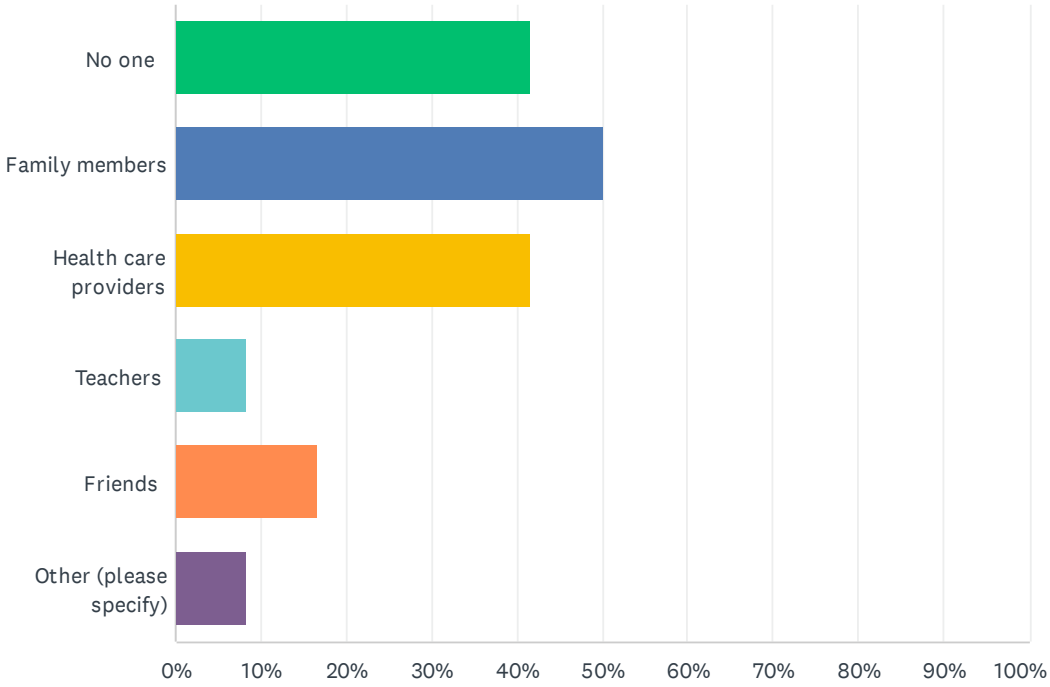
Answered: 11 Skipped: 1



ANSWER CHOICES	RESPONSES	
Strongly agree	0.00%	0
Agree	18.18%	2
Neither agree nor disagree	63.64%	7
Disagree	9.09%	1
Strongly disagree	9.09%	1
TOTAL		11

Q10 Who have you told anyone about the results you received from the ReveraGen? (Choose all that apply)

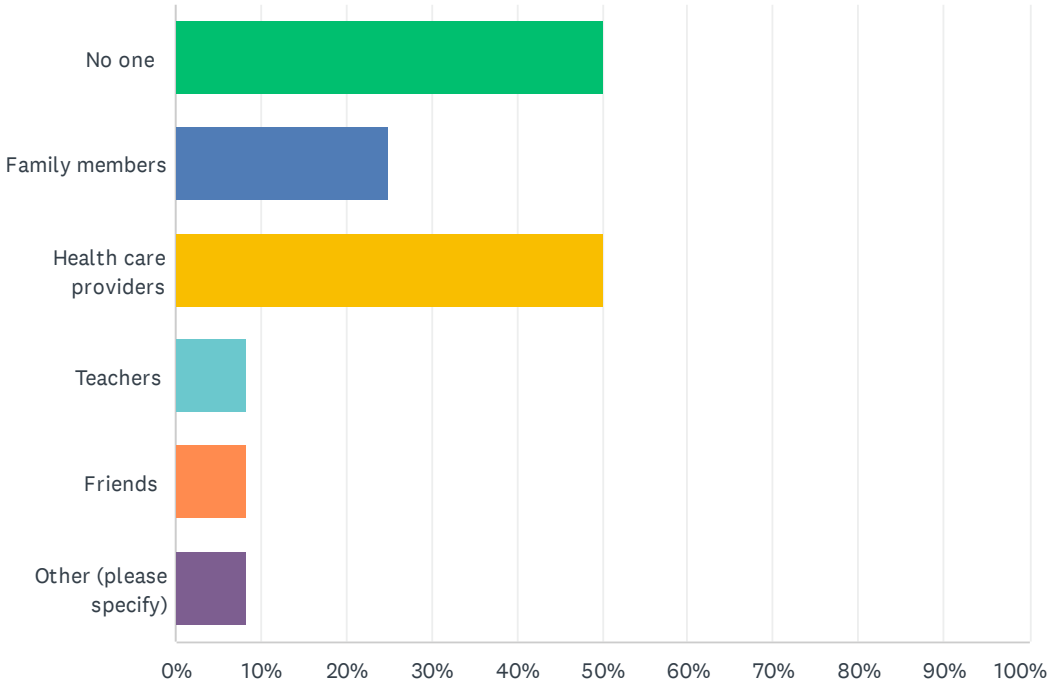
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
No one	41.67%	5
Family members	50.00%	6
Health care providers	41.67%	5
Teachers	8.33%	1
Friends	16.67%	2
Other (please specify)	8.33%	1
Total Respondents: 12		

Q11 Are there other people that you intend to tell about the results you received from ReveraGen? (Choose all that apply)

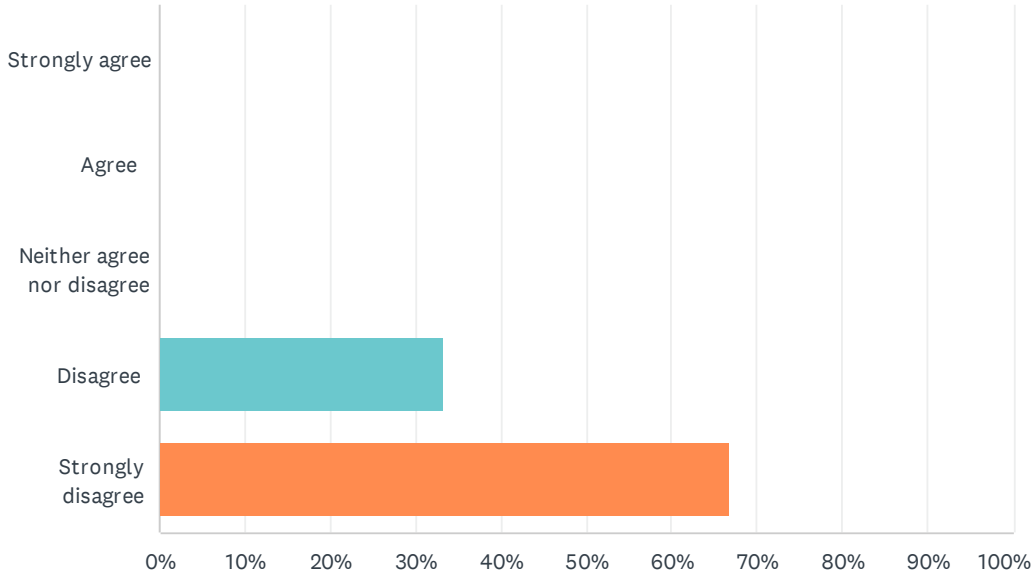
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
No one	50.00%	6
Family members	25.00%	3
Health care providers	50.00%	6
Teachers	8.33%	1
Friends	8.33%	1
Other (please specify)	8.33%	1
Total Respondents: 12		

Q12 I regret having made the decision to participate in this data return study

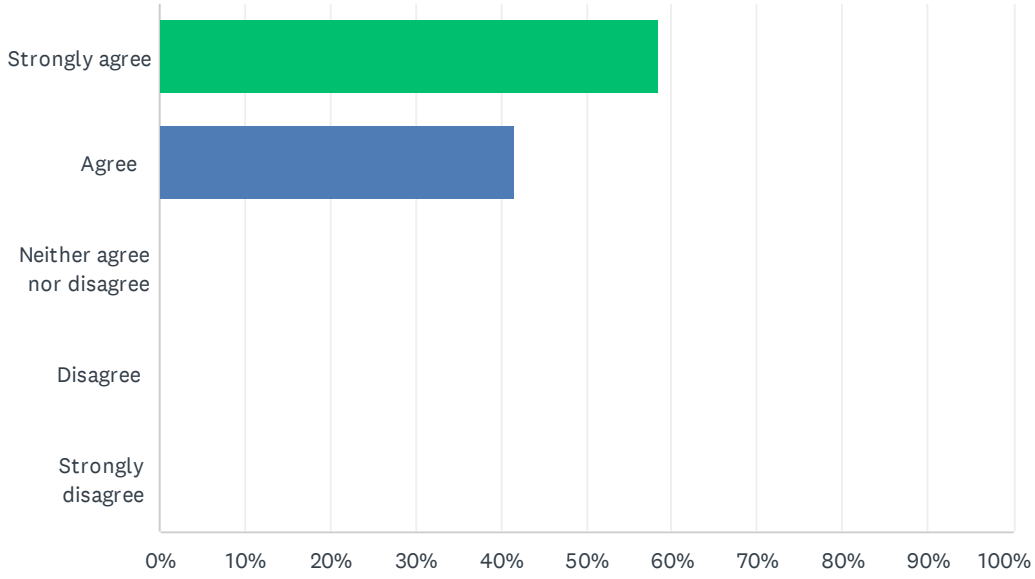
Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Strongly agree	0.00%	0
Agree	0.00%	0
Neither agree nor disagree	0.00%	0
Disagree	33.33%	4
Strongly disagree	66.67%	8
TOTAL		12

Q13 If I had to it again, I would participate in this data return study.

Answered: 12 Skipped: 0



ANSWER CHOICES	RESPONSES	
Strongly agree	58.33%	7
Agree	41.67%	5
Neither agree nor disagree	0.00%	0
Disagree	0.00%	0
Strongly disagree	0.00%	0
TOTAL		12

Q14 If you regret the decision to receive your son's data or felt that the choice did you harm, can you tell us why? You may skip this question if it does not apply.

Answered: 1 Skipped: 11

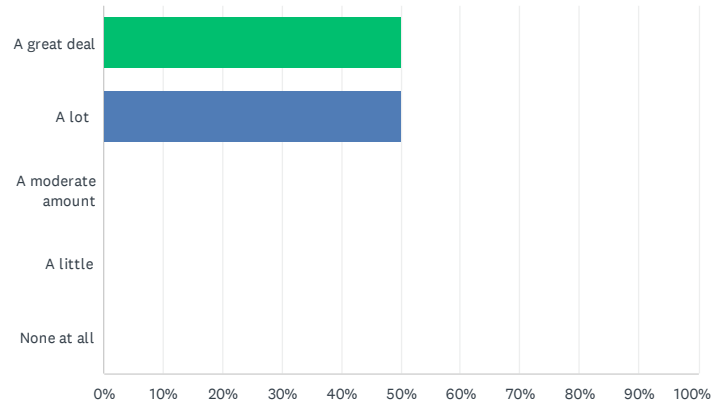
Q15 Do you have any additional concerns, comments, or questions for ReveraGen? You may skip this question if it does not apply to you. Thank you for participating in the survey! Best wishes to you and your family.From the ReveraGen team

Answered: 2 Skipped: 10

Q1 ReveraGen received a Bioethics supplement from the NIH to study a process of returning individual clinical trial data to patient families. We are returning data to study participants after the database is locked, the clinical study report written, and top-line results announced. One of the vamorolone clinical trial participants recently requested their data. We want to understand this issue from a physician perspective- thank you for completing this anonymous survey and answering the following questions._____

How much importance do you believe families place on receiving their son's individual clinical trial results?

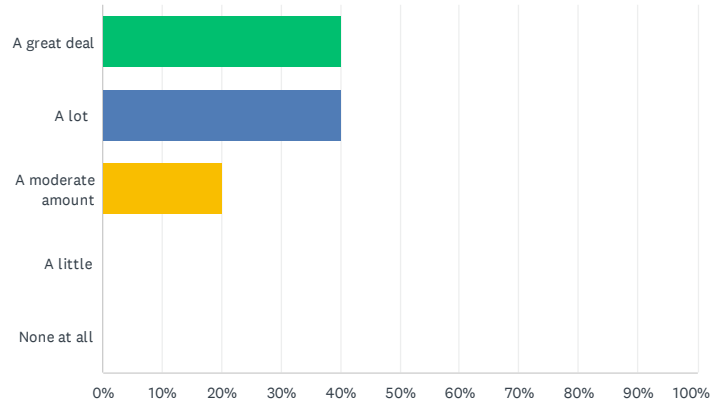
Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
A great deal	50.00%	5
A lot	50.00%	5
A moderate amount	0.00%	0
A little	0.00%	0
None at all	0.00%	0
TOTAL		10

Q2 How much importance do you believe families place on receiving their aggregate clinical trial results?

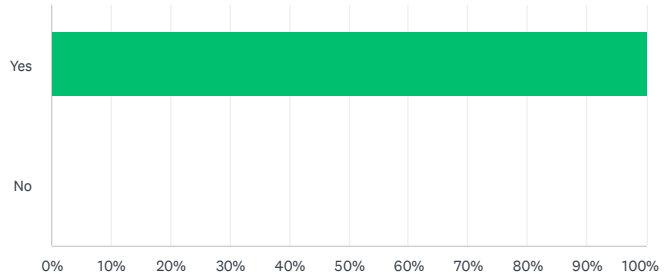
Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
A great deal	40.00%	4
A lot	40.00%	4
A moderate amount	20.00%	2
A little	0.00%	0
None at all	0.00%	0
TOTAL		10

Q3 Do you think a parent/guardian should receive their child's individual clinical trial data if the parent requests it?

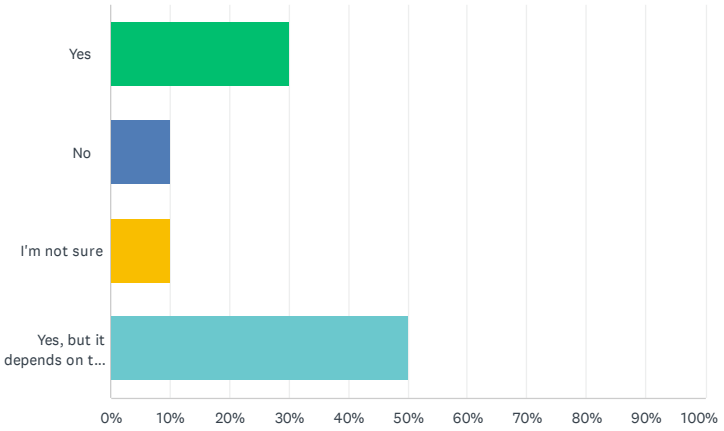
Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	100.00%	10
No	0.00%	0
TOTAL		10

Q4 Do you agree with the concept of a Sponsor returning individual clinical trial data directly to trial participants?

Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	30.00%	3
No	10.00%	1
I'm not sure	10.00%	1
Yes, but it depends on the circumstances	50.00%	5
Total Respondents: 10		

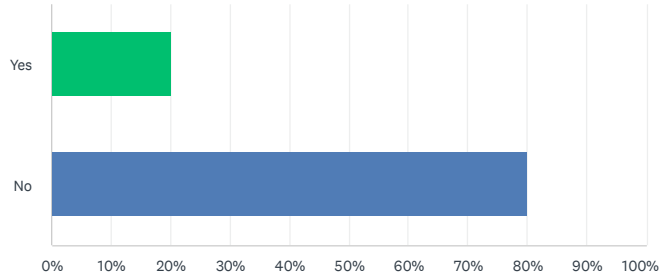
Q5 If you don't agree with the concept of a company returning clinical trial data to participants, can you list your concerns?

Answered: 8 Skipped: 2

#	RESPONSES	DATE
1	after trial is finished, data should be shared	6/21/2021 9:42 AM
2	What's meant by 'clinical trial data'? I don't think getting e.g. ECG, echo or MRI data is very useful and even some of the functional or strength measurements don't mean much to a family. It's a nice option for a family to see clinical trial data, but it would probably be more meaningful to provide them through a healthcare professional, either a doctor or a physiotherapist.	6/21/2021 3:55 AM
3	Has to go through PI, SI and/or site staff	6/21/2021 2:12 AM
4	Interpreting the data and put the individual data in the context of the study results and of a progressive disease might not be easy for all families and can create some false judgement and/or anxiety. It creates some "inequality" as proactive and well informed families are more likely to ask for the data	6/21/2021 1:48 AM
5	Not to disagree with this objective, but to raise the concern that the PI/treating physician for the participant could be blind-sided by the parent contacting the office and requesting an urgent discussion with the physician over an abnormal lab result. How to educate parents on labs/biomarkers/tests that are predicted to be abnormal (due to having DMD)? The poster does not go into this in any detail.	6/20/2021 7:46 PM
6	None	6/20/2021 7:28 PM
7	I agree, but it needs to be done in a thoughtful manner, properly contextualized.	6/4/2021 10:55 AM
8	at the end of the trial, all data should be returned to families. However, on a week by week basis during the trial, I don't favor providing results to individual families.	6/3/2021 2:49 PM

Q6 Are you aware of additional questions/comments/concerns from parents/guardians directed to you/your team following return of their data from ReveraGen?

Answered: 10 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	20.00%	2
No	80.00%	8
TOTAL		10

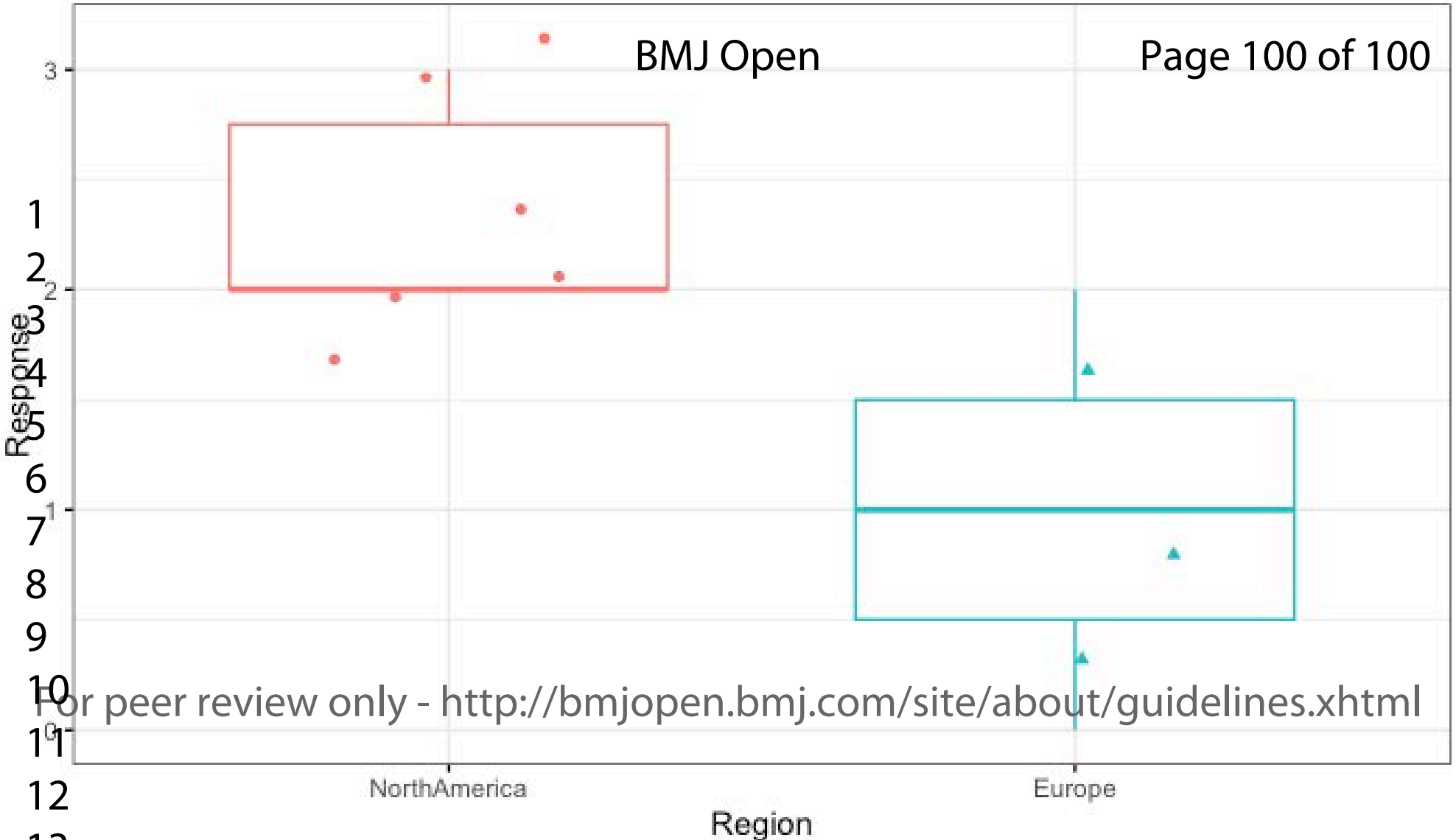
Q7 If your team received questions/concerns from parents/guardians about the returned data, can you elaborate on what types of questions/concerns they had?This question may be skipped if it does not apply.

Answered: 7 Skipped: 3

#	RESPONSES	DATE
1	Families have heard that data are supposed to be provided, but aren't certain how and when.	6/21/2021 3:55 AM
2	This is still hypothetical but the interpretation of the results, language barrier, cosequences for future therapies sjould be explained by the local physician	6/21/2021 2:53 AM
3	Does not apply.	6/21/2021 2:12 AM
4	It does not apply to a specific situation however it would be important that the clinician is also provided with exactly the same report to be able to answer the questions appropriately	6/21/2021 1:48 AM
5	as above - I anticipate parents will become alarmed over reviewing the labs/test results and where something unexpected comes to their attention. They often lack in context and are unable to sort out what is typical for DMD or a non-significant drug effect.	6/20/2021 7:46 PM
6	N/a	6/20/2021 7:28 PM
7	N/A	6/4/2021 12:07 AM

Q8 Do you have any feedback for ReveraGen on this process? This question may be skipped. Thank you for completing our survey!With best wishes from the ReveraGen team

Answered: 1 Skipped: 9



Research checklist / supplementary file

Checklist of Consensus standards for the reporting of organizational case studies [25 Table 11)]

Reporting item	Page number on which item was reported	Page number of justification for not reporting
Describing the design		
1. Define the research as a case study	2	
2. State the broad aims of the study	2	
3. State the research question(s)/hypotheses	2	
4. Identify the specific case(s) and justify the selection	2	
Describing the data collection		
5. Describe how data were collected	6	
6. Describe the sources of evidence used	8	
7. Describe any ethical considerations and obtainment of relevant approvals, access and permissions	7	
Describing the data analysis		
8. Describe the analysis methods	9	
Interpreting the results		
9. Describe any inherent shortcomings in the design and analysis and how these might have influenced the findings	3	
10. Consider the appropriateness of methods used for the question and subject matter and why it was that qualitative methods were appropriate	15	
11. Discuss the data analysis	15-17	
12. Ensure that the assertions are sound, neither over- nor under-interpreting the data	15-16	
13. State any caveats about the study	3,15	