RETURNING INDIVIDUAL CLINICAL TRIAL DATA BACK TO PARTICIPANTS

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Addressing the ethical and technical challenges of returning meaningful individual clinical trial results to trial participants

It's intuitive to think that returning research results to patients is the right thing to do. A recent publication from the US National Academies of Sciences underlined the importance of returning research results. However, most clinical trials release only aggregate anonymized data through published literature or press releases, and do not release patient-level data obtained in a clinical trial back to the participant.

INTRODUCTION

Participants in clinical trials have intrinsic rights to the clinical data generated on them, yet return of individual data faces multiple barriers, including confidentiality issues in communicating directly with participants, additional burden on over-taxed clinical trial site staff, and navigating complex international and regional ethics committees used by multi-site clinical trials.

Generally speaking, there are three reasons to implement patient-level data sharing with clinical trial participants:

1. **Right to access and right to ownership.** Clinical trials often generate large amounts of data on a participant. There is a fundamental right for the participant to have access to his or her own data. Some of this data may be clinically relevant.
2. **Clinical trial engagement.** Allowing participants to access their study findings and data may help engage the clinical trial participant to feel part of the research process, and lead to greater recruitment in clinical trials.
3. **Possible relevance of clinical trial data to participant health**. People have the right to be an active participant in their (or child's) healthcare. Some data from a clinical trial may, or may not, have relevance to a participant's health.

Summary

This paper outlines the implications of returning clinical trial data in a form that is meaningful to the participant and outlines the ethical and pragmatic challenges. We report on a pilot framework for returning trial data and aggregate data that allows a participant to compare their individual results with their dose group and overall trial.

There are many complexities and challenges that come along with returning results to study participants. This raises an important number of questions including: Should trial participants request return of individual and aggregate data at the time of consenting to participate in the trial? Should a re-consent be done after trial completion at the home clinical trial site? Should a centralized process and ethics review be done to return data from the Sponsor on a global basis? Should the participant have a choice in which results they receive and should education and support be provided to aid the participant in understanding the data returned?

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CHALLENGES

The challenges highlighted in this white paper are:

1. **Ethical implications in returning clinical data.** Confidentiality, GDPR, and distributed vs. central ethics review committees.
2. **Interpretation of trial results by the participant and family.** How is data explained to an individual? Is there actionable data? How can the participant be best educated for sensitive interpretation of experimental data?
3. **Integration of clinical trial data into the participant's medical record**. How is data made 'transportable'.
4. **Barriers in data integrity**. How is data integrity assured in practise?

Both ethics and clinical research communities see the opportunities of return of patient data outweigh the challenges, and are working towards solutions to increase the return individual results. If done correctly, returning data promotes autonomy, provides both clinical and individual relevance and encourages future research participation.

ReveraGen BioPharma

These challenges were investigated by ReveraGen Biopharma, the drug sponsor/ developer in the VISION-DMD clinical trial programme for the innovative new steroid-like drug vamorolone in boys with Duchenne Muscular Dystrophy. Following conversations with patient families during the vamorolone studies, the ReveraGen team developed an approach to provide patient study data directly to participant families, allowing them to share and connect their clinical trial data with their clinical care information. The National Institutes of Health (NIH NINDS) provided an ethics research grant to support a pilot of the approach.

CHALLENGE 1. ETHICAL IMPLICATIONS IN RETURNING DATA

Clinical trial data is research data, and not part of routine clinical care. Clinical trial research results may be inconclusive (either at individual level, or aggregate), and data not typically considered 'clinically actionable' (integrated into care decisions for the participant). The degree of comfort with this level of ambiguity or uncertainty is an 'individual choice'. Consistent with this, a published study showed that not everyone wants to receive their individual clinical trial data (Christensen et al., Journal of Empirical Research on Human Research Ethics 2017; 12:97-106). This raises the question: How can the participant's wishes be acknowledged, and what are the ethical constructs to consider?

Avoiding harm

One of the key ethical principles in both clinical practice and clinical research is avoiding harm. We tend to think about avoiding harm in terms of avoiding physical harm such as side effects but we must also consider psychological harm which should be considered as equally important.

Returning study results could potentially cause both. Psychological harm if participants feel uncertain or anxious when results are returned, for example because they do not understand the data, misinterpret the information or the information makes them feel no action can be taken. Physical harm could occur if individual level results are misunderstood or misinterpreted and lead to inappropriate outcomes such as decisions to switch healthcare treatment.

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CHALLENGE 2. ASSESSMENT OF MEANINGFUL RESEARCH RESULTS

In the case of rare disease research, participants tend to be engaged and active. A large part of the rationale for participating in research is because people are curious about their own and their family's health. People may feel a sense of frustration and loss when clinical studies collect samples and data from them, but do not allow any access to this information, and have no control over who can access the data for future research into their condition.

As the discussion on returning results advances, participants and their families are engaged about the idea of what is meaningful and what is valuable. An individual's needs and preferences should be incorporated into their customised return of results. Participants should have a choice of whether they receive different kinds of results. For example, one participant may be interested in clinical efficacy data, but others may wish to see all laboratory data as well. There are different formats of data that can be returned, such as lists, tables or graphs. Careful consideration should be given to how data is presented to ensure the format is easily understood by participants. Data can be shown relative to others in the trial, or on an individual basis.

Levels of results

There is a global ethical agreement that group level (aggregate) results should be returned to research participants. For example, participants in a study deserve to know what happened during the study, whether the trial met its endpoint, and if the trial succeeded in showing efficacy and/or safety of the study drug. Most argue that people also deserve to receive their individual results when participating in research because it shows respect but also because it increases trust and investment in the research. If people are unwilling to participate in research, the whole research enterprise falls apart. Unfortunately, most drug companies that are carrying out clinical trials are publicly traded and are legally unable to release data to participants before releasing conclusions to the general public. To avoid conflict of interest and delays in returning participant data, timely communication of trial results and interpretation of findings should be relayed to trial participants as soon as possible.

Accessible vs. meaningful

Another challenge is deciding what results to return. There are different kinds of research results and some of them are better understood and more clinically meaningful than others. Often studies obtain a set of results, some of which are well understood and some of which are exploratory and may not yet be well understood by the physicians and scientists leading the study. How do we decide and define when results are meaningful to return? This depends on the type of research, the stage of research, and the individual. Researchers need to understand the meaning of a particular finding, on a basic level, before these types of findings can have meaning to individuals. It can be challenging to articulate to participants what some types of results mean.

CHALLENGE 3. UNDERSTANDING RESEARCH RESULTS

Clinical trial participants should be aware that there is a difference between clinical care and clinical research. In the case of clinical care, healthcare providers develop treatment or management that is directed to the individual patient. The intervention a person receives in clinical care has normally been approved and is well understood. Clinical research is done to develop new knowledge based on the participation of a group of participants. The goal is not to help an individual, although everyone hopes this will happen and can be an outcome of the study. Clinical studies are used to investigate if a new treatment or intervention is safe and /or effective for translation into clinical care.

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Rethinking the meaningfulness of study results

Example I: Four-stair climb

Two researchers timing a child walking up four stairs are very likely to get the same result. But the child may do the test differently on different days, using the handrails one day, and not the next. Thus, the reliability of the evaluator and that of the child can be different. Hopefully, when the child does the test again on the same day, the same investigator should get a similar result. Although many variables are associated with how people do on this test, the test itself is understood and is a very straightforward assessment. It also means something intuitively to parents, walking upstairs is concrete and meaningful to the child's daily activities.

Example II: Interpreting study results

The second example is looking for a chemical in the blood. Although investigators may know the chemical is present in the blood and may understand the chemical structure, we don't necessarily know what it does in the body. This exploratory kind of research might need different laboratory approaches to measure the chemical which could find results that are difficult to interpret that are not directly tied to a health outcome, becoming less meaningful and more challenging to share with participants.

CHALLENGE 4: BARRIERS IN DATA SHARING

Education and support are needed when returning results to patients and their families. This means research teams often have to develop new expertise in making results understandable and accessible. Regulatory barriers as well as practical implementation and cost can make return of results challenging for research teams.

Barriers in sharing data

Sharing study data can be undertaken in several ways. De-identified/anonymised data compiled from a number of different clinical studies, aggregated/combined data from participants in one clinical study, or individual clinical study results, clinical history and electronic medical records. Lack of informed consent can pose a barrier in sharing study data. If not taken into consideration before the start of the study there could be an increased burden on the clinical study sites.

Barriers in data integrity

Data cannot be given until the study is completed. Data needs to be checked and reviewed before being analysed and compiled. While this is important for regulators who are assessing the safety and efficacy of the treatment, it can be challenging for participants who must wait until the study is completed and results analysed before they can find out if they were on the experimental drug/intervention or the placebo, however this is necessary to maintain data integrity.

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(RE)USE OF TRIAL DATA TO DRIVE DRUG DEVELOPMENT

There are currently multiple clinical trials ongoing to develop possible treatments for Duchenne and Becker muscular dystrophy. However, data collected is sometimes kept within drug companies and is often not shared with other companies, researchers or study participants. The inability to share and use existing data damages the already fragmented data collection in this particular rare disease field. This ultimately hampers drug development and possible treatments, as most drug development regulators and Health Technology Assessments decisions are based on evidence (data). There is an urgent need for optimal (re)use of data.

The World Duchenne Organization is advocating for optimal use and reuse of data for drug development, and data collection that is relevant to patients and their families. They support the Duchenne Parent Project Netherlands and Foundation29 in creating an environment where patients have power and control over the use of their own data and who can have access to this called the Duchenne Data Platform.

Duchenne Data Platform

This initiative is a collaboration between Duchenne Parent Project Netherlands and Foundation29. It has been developed to store data in a readable format in a secure environment, so patients and their families have their healthcare information always at their disposal. On the Duchenne Data Platform patients can store and manage their healthcare data from the various healthcare institutions in their own 'locker'. Next to this, they can participate in answering questionnaires, and find answers to frequently asked questions. The platform is available in English, Spanish and Dutch, and is currently being translated in several other languages.

A common approach for return of data in study design is needed to create a unified place for merging study and care data in a format easy to download/upload format, for comparison/merging with existing data. Patient reported outcome measures and placebo data should be made available and patients should decide about the use of their own data. This may lead to well-managed and archived data, gathered in a safe platform that makes standardised data easily accessible (with permission of the individual).

CASE STUDY: REVERAGEN BIOPHARMA'S VAMOROLONE

As part of the VISION-DMD project funded by the European Commission, US National Institutes of Health, and non-profit foundations, several clinical studies are investigating the safety and efficacy of a novel innovative steroid-like drug called vamorolone in boys aged 4-7 years old with Duchenne Muscular Dystrophy. Vamorolone used a venture philanthropy funding model from a large number of DMD patient groups, as well as US and EC grants to ReveraGen BioPharma and Newcastle University to undertake the clinical development.

Following engagement with patients and patient organisations, ReveraGen Biopharma, identified the wish of patient families to access their data, and applied for a U.S. National Institutes of Health Bioethics grant to enable them to develop an approach for the return of patient data to participants. Led by Dr. Laurie Conklin and Dr. Eric Hoffman, the grant was awarded. The return of results project has been initiated, and data returned to about 15 families to date.

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KEY CASE STUDY INNOVATIONS

Key aspects of the project were developed to navigate the barriers noted earlier.

1. Single, central ethics review for worldwide return of results

2. Navigating confidentiality via a firewall within the Sponsor

3. Advertisement of study and ethics consent

4. Surveys of participating families and their physicians

1. **Single, central ethics review for worldwide return of results.** Typically, ethics reviews are done differently at different universities and academic medical centres, and each country has alternative methods. Navigating ethics reviews, while critically important, can take many months at each centre, with extensive redundancy of reviews at all the academic sites participating in the single trial. Instead, a single central ethics committee reviewed the vamorolone return of results for the worldwide study. This reduced burden on academic clinical trial sites, and functionally achieved a 30-fold improvement in efficiencies (compared to independent ethics review at over 30 clinical trials sites).
2. **Navigating confidentiality (GDPR) via a firewall within the Sponsor.** Clinical trials are typically run by a specific pharmaceutical company, termed the "Sponsor", and the Sponsor also owns the data from the trial. While it seems intuitive that the Sponsor just return trial results directly to the participant, there are issues of confidentiality and integrity of data – namely, the Sponsor should not have personal identifying information on the trial participants. To navigate this barrier, ReveraGen identified a single person within the company, herself a parent of a DMD child that had participated in multiple clinical trials, and built a firewall where only this person had patient identifying information. Only this person communicated results to families and had direct contact with families. This 'firewall' effectively navigated GDPR and confidentiality issues.
3. **Advertisement of study and ethics consent.** Using a single central ethics review makes it difficult or impossible for the clinical trial sites to recruit trial participants for return of clinical trial data – this would require ethics review at each medical centre (see #1 above). Thus, the availability of return of results must be communicated to families by some other approach. Here, ReveraGen worked with non-profit stake-holder foundations to advertise the return of results via newsletters and social media outlets. If a family sees the advertisement for return of results, and is interested in participating and receiving their results from the vamorolone trial, then they contact the single person at ReveraGen to initiate participation. The first step of participation is ethical consent of the family, done centrally for families internationally at ReveraGen outside the 'firewall' noted above.
4. **Surveys of participating families and their physicians**. The ongoing ReveraGen study first educates interested families in the different types of clinical trial data, and then conducts surveys to help understand the family's desires for the types of clinical trial data returned, format of data return, and their perceptions of the importance of data return. In parallel, surveys of the physicians caring for the patients and families are carried out to help determine if the single site remote ethics reviews and educational efforts are well received by the clinics, or if unanticipated issues and concerns arise.

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FRAMEWORK FOR RETURNING CLINICAL STUDY DATA

Participant families (as study participants are children) learn of the return of results project through activities of stakeholder foundations, such as the World Duchenne Organization's webinar. If the family is interested in participating, they contact Suzanne Gaglianone, a Duchenne parent, who is the sole ReveraGen employee that has contact and access to contact information of participating families. She has had long-term contact with many of the families, acting as travel coordinator for the vamorolone clinical studies. Thus, takes on the role of coordinator, acting as a firewall between the families and the study team.

To enable patients to realise their data is available, VISION-DMD, the World Duchenne Organization and other Duchenne Foundations have been helping to spread the word about the process. A framework was developed for the return of patient data to thos patient families that expressed their interest in receiving their son's trial data. The coordinator explains the process and emails a consent form for completion. For participants outside of the US this includes a separate GDPR consent. The participant provides their date of birth and study site location, to enable the database manager to provide the coordinator with a study subject number. The coordinator also requires the parent's name and mailing address. This information is stored in a password protected database that only the coordinator can access. The coordinator records who has requested their data but the link between the subject number and personal information provided is not stored.

For non-English speaking participants a phone interpreter is arranged, and all documents are translated in the study participants' native language. Before and after data return, the participant is asked to complete an anonymous survey via email, with questions about the process. These surveys are also translated into the participants native language. The coordinator is responsible for following up on questions and queries or addressing them to the correct person.

Only upon completion of the clinical study, database lock and the clinical study report can data be returned to participants. Data is put onto an encrypted password protected drive that is posted by mail. The password is provided by email to access it.

The drive contains:

1. **A general document** that provides information on the study, the outcome measures used, and links to published manuscripts to access the aggregate patient data from the study in more detail.
2. **An individual data sheet** containing the data collected in the study as a PDF. This provides information on the drug group (i.e. placebo, or treatment arm), the dose, demographics such as weight, height, body mass index and results from the function tests.
3. **A table of the average results** of the participants in their dose group with the participants individual results highlighted for comparison.

Types of data and what, when and how to return it.

1. **Clinical efficacy measures** look at the effectiveness and benefits of the drug. Primary outcome measures are pre-specified as the most important outcome measure, secondary outcome measures are less important.
2. **Clinical safety assessments** measure side effects, adverse events or other health concerns such as stunting of growth.
3. **Biomarkers and blood tests** and other laboratory measures record any other adverse events that are reported during the study.

To ensure the biomarker data is understood and meaningful to participants, a table is provided explaining the different biomarkers collected, an explanation of what the test measures, why it is being used, and its limitations.

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CONCLUSION

There are many complexities and challenges associated with returning individual clinical study results to participants. Participants need to have a choice of whether they receive different kinds of results and should be educated and supported to understand this information.

Study sponsors need to consider the need for data sharing and return of individual data when developing the protocol and patient informed consent forms to ensure that the return of patient data is not hampered by restrictions. Research teams need to develop new regulatory and practical expertise to return individual data results in an understandable format and provide support if required.

References

1. **Christensen et al., Journal of Empirical Research on Human Research Ethics 2017; 12:97-106)**
2. **National Academies of Sciences, Engineering, and Medicine. 2018. Returning Individual Research Results to Participants: Guidance for a New Research Paradigm. Washington, DC: The National Academies Press. https://doi.org/10.17226/25094.**

To ensure patient anonymity, research teams need to ensure an independent data return coordinator acts as a firewall between the parties. Upon return of data, participants should be given options to provide feedback and pose questions about both the data and the process. Both the ethics and clinical research community now lean towards the opportunities outweighing the challenges, working towards solutions and increasingly returning individual results. If done correctly, returning data promotes autonomy and encourages future research participation with both clinical and individual relevance.

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