

Taking Optogenetics into the Human Brain: Opportunities and Challenges in Clinical Trial Design

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Abstract: Optogenetics, the use of light to control the activity of suitably sensitized cells, has led to major advances in the field of basic neuroscience since it first emerged in 2005. Already, the technique has entered clinical trials for conditions such as Retinitis Pigmentosa. A major focus of interest is the use of optogenetics within the brain, where the ability to precisely control the activity of specific subsets of neurons could lead to novel treatments for a wide range of disorders from epilepsy to schizophrenia. However, since any therapy would require both the use of gene therapy techniques to introduce non-human proteins, and implantable electronic devices to provide optical stimulation, applying this technique in the brain presents a unique set of obstacles and challenges. This review looks at the reasons why researchers are exploring the use of optogenetics within the brain. It then explores the challenges facing scientists, engineers and clinicians wanting to take this technology from the lab into the first human brain, discussing different possibilities for a first-in-human clinical trial from a sponsor, patient and regulatory perspective.

Keywords: gene therapy, implantable device, opsins, first-in-human, neuroscience

Introduction

Optogenetics came to prominence in 2005 following the work of Ed Boyden and Karl Deisseroth.¹ Looking for ways to control the electrical activity of neurons, they followed up on the work on Nagel et al, who had highlighted in 2003 the potential for the algae based cation channel ChannelRhodopsin-2 (ChR2) to depolarize cell membranes following illumination.² To this end Boyden and Deisseroth introduced a ChR2 opsin into a neuronal tissue slice. To their excitement, they were able to induce neuronal activation upon stimulation with blue light.³ Since then there have been numerous advancements made to both the science and technology involved in optogenetics with the number of opsins available to scientists increasing to cover a wide range of functions and characteristics.⁴

Excitatory opsins can be utilised to stimulate activity within neurons whereas inhibitory opsins can suppress activity. Opsins also range in their mode of operation and response speed providing the ability to control neuronal activity with millisecond precision. The range of gene promoters used to generate opsin expression also allows the activity of specific neuronal subtypes to be targeted. This opens up a range of potential opportunities to treat conditions involving abnormal network activity such as migraine and epilepsy as well as signalling disorders such as

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Alzheimer's disease.⁵⁻⁷ However, bringing this novel technology to the clinic presents a number of unique challenges that require specific consideration in trial design and conduct.

Any clinical application of optogenetics requires the use of a viral vector to transduce the target tissue with the chosen opsin. The choice of vector depends upon a number of factors including cell type and accessibility of the target tissue. For readily accessible tissue such as the skin or lung, it may be possible to use repeated transductions, allowing the use of non-permanent treatments. However, introducing vectors to the brain requires a neurosurgical procedure, necessitating use of a vector that ensures long-term protein expression within neuronal cells from a single transduction.

Partly because of these limitations the first optogenetic trials involving neuronal tissue have targeted the retina. These trials have already started to enrol patients. Gensight Biologics are trialling GS030 for Retinitis Pigmentosa which involves the ChrimsonR opsin, a variant of the excitatory channelrhodopsin opsin, delivered into cells via a modified viral vector.⁸ RetroSense Therapeutics have also targeted Retinitis Pigmentosa, using the Channelrhodopsin-2 opsin.⁹ At the time of writing, no results have been published for either study.

Working in the eye means that there is easy access to the relevant tissue. This negates the need for major invasive surgery to introduce the viral vector necessary to transduce and promote opsin expression. The presence of ambient light in the eye also removes the need for an implanted biomedical device to stimulate transduced cells. However, the Gensight therapy includes biomimetic goggles designed to boost light ensuring sufficient optical stimulation of the transduced neuronal cells.⁸

The difficulties involved in transferring optogenetics into clinical studies are highlighted by the progress of its use within auditory systems. The cochlear implant shows that the auditory system, which is relatively accessible to clinicians, can be successfully manipulated through electrical stimulation. However, optogenetic therapies, which could potentially provide greater resolution to patients, are still undergoing preclinical research and testing.¹⁰ Compared to the eye and ear, central nervous system disorders bring further major challenges to the use of optogenetics. The viral vector must be injected directly into the brain during a neurosurgical procedure. The level of expression from a single injection must be sufficient to achieve a clinical effect as repeat injections are not

feasible within the brain. An implantable medical device is also required that is capable of delivering sufficient optical stimulation to produce a clinical effect without damaging the underlying brain tissue.¹¹ Despite these challenges, several groups are currently working towards the first-in-human application of optogenetics in the human brain, and the first human trials are likely to occur within the next decade.

Optogenetics in the Human Brain

As optogenetics is a light-based technique, it is important to understand the behaviour of light within the brain. For optogenetics to be successful, a sufficient volume of brain tissue must be illuminated to achieve a clinical effect without causing damage. A range of opsins are now available which respond to wavelengths ranging from infrared to ultraviolet. Wavelengths of light penetrate brain tissue to varying degrees.¹² Red light is able to travel furthest through tissue, primarily due to lower haemoglobin absorption.¹³ This is beneficial if needing to target a larger volume of cells or when trying to reach cells deeper within the brain. The use of infrared light is, however, limited by the absorption spectra of opsins, with the majority of opsins currently available only responding to light in the blue/green spectrum. These frequencies penetrate the brain poorly, necessitating the use of a fully implanted light source inside the skull.¹⁴ Low light penetration of brain tissue also requires accurate targeting of the implantation location. Failing to precisely target the correct area of the brain may render a therapy useless. However, this should be possible using current imaging techniques such as MRI and transcranial EEG.

It has also been shown that blue light on its own is capable of inducing expression of neuronal-activity-regulated genes affecting cellular activity during periods of continuous exposure over a short period.¹⁵ While this induced transcription has not been seen with red or green light, the need for continual stimulation would not be expected in any therapy, instead utilising short bursts of light which also prevents the build-up of heat from any light source. Therefore, until data suggests otherwise, there is no reason why intermittent blue light cannot be used, especially when this is the natural wavelength for many opsins.

A major benefit of optogenetics is the ability to target opsin expression within specific types of cell.⁴ This is because opsins are introduced into neuronal cells as DNA through viral vectors. Viral vectors are viruses such

as AAV and lentivirus that have been modified to carry a target gene sequence.¹⁶ These modifications also render the viral vector incapable of replication increasing their safety. Certain types of vectors favour the transduction of different cell types, while the use of specific promoter sequences also allows greater targeting. With the use of neuronal-subtype specific promoter sequences, opsin expression can be targeted to specific cell types such as inhibitory or excitatory neurons. One of the most difficult decisions related to optogenetics is identifying the correct combination of cell target, vector choice, promoter region and opsin selection. The choice of which will depend greatly upon the physiological basis of the condition being treated.

Accessing the brain requires significant neurosurgical intervention with accompanying risk, meaning that repeated injections of vector are not a viable option. Therefore, it becomes vital that the viral vector selected can produce long-term expression. Vectors such as AAV introduce the selected DNA sequence into cells in the form of episomes while others like Lentivirus integrate DNA within the host cell chromosome.¹⁷ While both should remain during the lifetime of a cell, only DNA integrated into the host chromosome will be passed on during cell division. Fortunately, the almost lifelong nature of neuronal cells in the brain and the minimal level of cellular division supports the use of either type of vector.

The choice of viral vector is influenced primarily by factors such as their safety and efficacy profile and the size of the DNA payload that they can deliver. On a secondary level, the availability and expertise of suitable manufacturers may also influence the final vector choice. Different viruses may also have different Biosafety classifications, requiring different facilities and training for their safe handling and storage. At present, the viral vector of choice for clinical trials of neurological diseases is AAV.¹⁸ Whichever vector is selected, Investigators must ensure that all institutions from preclinical through to clinical have the expertise and facilities to safely handle such a product.

There are currently no clinical investigations into the use of optogenetics in the human brain meaning that there are a number of currently unanswered questions. What is the long term effect on neurons of retrovirus insertion into the genome, expressing non-human opsin proteins? How will the brain respond to long-term exposure to light? What are the long-term consequences of implanting suitable devices into the brain? As well as the potential

physical impacts, what are the potential psychological impacts for patients involved in any optogenetic clinical trial? And crucially, how do we design and conduct clinical trials that address these questions whilst maintaining the safety of the participants and those around them?

Looking Towards Clinical Trials

At present, any optogenetic therapy in the brain will almost certainly require both a viral vector and an implantable medical device. The viral vector would classify as a Gene Therapy Medicinal Product (GTMP), falling within the Advanced Therapy Medicinal Product (ATMP) regulatory framework.¹⁹ Meanwhile, the device would class as an active implantable medical device (AIMD) within the Medical Device Regulations (MDR).²⁰ The combination of medicinal product and implantable medical device, however, provides complications in regards to clinical trial regulations. A combined advanced therapy medical product is classified by the EU as a product that must “incorporate, as an integral part of the product, one or more medical devices . . .” and the medicinal product “must be liable to act upon the human body with action that can be considered as primary to that of the devices . . .”.¹⁹ That both a GTMP and AIMD are necessary for any optogenetic therapy is without question. If the device were also designed to deliver the viral vector, then it would be classed as a combined product. However if the viral vector is delivered separately, the question of whether it is a single product incorporating both active substance and device or two separate products that are used together becomes unclear and a question for the regulatory authorities. The manner of how a product is developed and presented by manufacturers may also affect classification, necessitating early communications with regulatory bodies during development. In practical terms, the classification is somewhat academic since the level of regulatory scrutiny is the same whatever the classification, but early engagement with the regulator may avoid unnecessary duplication of documentation and delays to approval.

When designing clinical trials, drug studies and medical device studies are normally approached from different perspectives. First-in-human drug studies aim to evaluate a new product and compare how effects seen in pre-clinical studies translate into humans.¹⁹ They are often completed in healthy volunteers with a dose-escalation design. The first participants are given a dose well below the expected level required for efficacy and observed for side effects before a slightly larger dose is given to the next cohort and so on. ABPI guidance suggests a starting

dose no more than 10% of the predicted therapeutic dose.²⁰ The primary end point is safety, determining the safe dosage level, discovering side effects, learning how the body reacts to the drug and how the drug reacts to the body. It is not until later phases that the focus moves onto exploring efficacy in patients and comparing to the current medical gold standard.

According to Regulation (EU) 2017/745 the purpose of a clinical investigation of a medical device is to verify that under normal conditions of use, performance complies with those indicated by the manufacturer.²¹ Any undesirable side effects under normal use are determined and the acceptability of those risks assessed. There is currently no requirement to show a comparison with the current gold standard treatment.

So how does this affect optogenetic therapies with their combination of gene therapy and active implantable medical device? Trials for a Phase 1 medicinal product might expect a low starting dose to check for safety before increasing to greater doses. But what are the ethical considerations in the case of optogenetics? Medicines are normally short-lasting, being processed and removed by the body over time. But once expressed, the expectation is that opsins will remain present for the lifetime of the expressing cell. A dose-escalation trial would require someone to consent to the permanent introduction of a non-human protein into their brain via a surgical procedure. Participants would be taking on long-term personal risk without any prospect of personal benefit only for the advancement of scientific and medical knowledge. The long-term nature of the product makes this unviable from all perspectives.

A key component of safety from the GTMP is not just how neurons respond to expressing opsins but how the cells react upon exposure to light. It is therefore necessary that, in order to collect safety data on the GTMP, the device must also be implanted. This requires a dose at a level expected to obtain a cellular response to the light. Again, implanting a novel medical device into the brain as well as a permanent GTMP without the expectation of being able to see some sort of meaningful interaction is ethically unjustifiable. Therefore, the starting dose used must be expected to be efficacious and a traditional dose escalation approach cannot be used for intracranial injections of permanent gene therapy medicinal products.

While first-in-human drug trials are often in healthy volunteers, it is ethically out of the question to deliver both a permanent gene therapy and to implant a novel device

into such a person. This necessitates the need to move straight to the clinical population for a first-in-human study. Clinical device trials are often conducted from the very beginning in the patient population without comparison to placebo or gold standard. This is often due to the ethical issues involved and the difficulty in blinding participants and clinicians to treatment groups. This makes it vital to thoroughly assess the GTMP during preclinical testing to ensure that sufficient safety and efficacy data is collected before moving into clinical trials as the traditional medicinal early-phase approach of dose escalation is bypassed.

Preclinical studies must allow a proper risk assessment on the safety and efficacy of a first-in-human trial with relevant animal models being used whose biological response is expected to relate to the response in humans.²² No model will compare exactly with the complexity of the human brain and so preclinical work may include a range of models such as rodents, non-human primates, human organotypic tissue slices and *in silico* modelling to build up an understanding of how brain tissue responds. All of these will help to build up a picture of how the human brain might expect to react to an optogenetic therapy. It is up to researchers to decide the type of preclinical testing necessary to justify their clinical plan. Any tests that are used to support a clinical trial should follow the necessary guidance and regulations for gene therapy medical products and active implantable medical devices. However, when testing the combined final therapy, compromises may be necessary as the closest biological animal model may not be suitable for supporting the final human device.

The long term safety and efficacy of any lifelong therapy is difficult to predict without long delays to starting clinical trials. This would come at a huge cost to any developer and to the potential detriment of the clinical population by way of delayed access to potentially new beneficial therapies. There will be a point where the risk-benefit balance falls in favour of moving forward to a clinical trial. However, this does not mean that non-clinical tests should necessarily stop. Running a number of long-term animal studies alongside but slightly ahead of the clinical trial may help identify long-term safety problems before it becomes an issue in humans.

During the clinical trial itself, it is important to monitor for any signs of adverse events. One of the theoretical risks of a GTMP that integrates into the host DNA is insertional mutagenesis resulting in tumour formation.²³

Monitoring of participants for signs of tumour development should be undertaken during any trial, even if the risk is identified as low. Other possible risks from the gene therapy include an immune response towards the vector and opsin proteins as well as cellular damage or toxicity caused by opsin expression.

The standard clinical imaging protocol for observing the brain is an MRI. However, the introduction of a novel implantable device for a first-in-human trial will likely remove this method of scanning as an option. The process of testing and validating medical devices for MRI scanning can be long and expensive. At the point of first-in-human trials, it is generally seen as not worth the developmental cost for getting a device certified MRI safe before it has been shown to be efficacious. However, the risks of exposing a patient with an implant to an MRI scan can be great.^{24,25} The risk of the device being attracted to the magnetic field can be controlled through careful selection of material for building the device. However, the magnetic fields involved in MRI could also induce heating due to the creation of induction currents within a device. An MRI could also result in small movements of the device, movements that could cause cellular damage and scarring which could affect efficacy. The implant may also affect image quality resulting in an inability to detect cellular changes around the implant. An MRI may also potentially cause damage to the implanted device itself resulting in product failure. This may necessitate the use of alternative scanning options such as PET and CT scans which come with their own drawbacks and risks, including exposure of patients to x-rays while not providing the higher level of image definition that can be achieved with MRI.

Any foreign entity introduced into the body provides a risk of damaging tissue or provoking an immune response resulting in cellular inflammation or cell death.²⁶ Similarly, risks associated with implantable devices include immune responses, implant rejection, glial formation and device degradation. The experience of clinically approved implantable devices suggests that it is possible to manage these safely. However, the enclosed nature of the brain and the blood-brain barrier means that it can be difficult to monitor. Inflammatory biomarkers such as interleukins can be monitored for signs of an immune response to the therapy although collection may be difficult.²⁷ Safety elements that check, for example, current leakage or excess temperature build-up can also be built into an implant. While the guaranteed safety of volunteers in any first-in-human study

cannot be ensured, preclinical safety testing, in-study testing and monitoring can minimise risks and maximise safety.

Due to the nature of any optogenetic trial, with permanent changes being made to the brain, the ethical consideration of the psychological impact on patients must also be considered. Patients requiring new experimental therapies are likely to be severely impacted by their condition and to have been so for a number of years. They may have trialled numerous medications or other treatments without success and are likely to be in a vulnerable place mentally.²⁸ With any first-in-human trial, there cannot be any suggestion of benefit put forward to patients. Similarly, while a first-in-human trial will help to identify side-effects, the potential risks involved must also be clearly laid out. Establishing that understanding in patients is vital for informed consent. Because of the very nature of the conditions being treated, it should be noted that some patients may have an impaired ability to give informed consent. Many patients may also struggle with the thought of having an implanted device.²⁹ This may be magnified within neurological conditions. It is particularly important for patients to understand that taking part in a trial may potentially affect the availability of any future treatments. This is particularly pertinent to younger patients who may live to see other future treatments developed during their lifetime. For example, treatment with a gene therapy may preclude patients from future alternative gene therapy treatments.

Optogenetic Trial Strategies

The critical issue for any clinical trial is ensuring the right risk/benefit balance for participants. Being a first-in-human trial, there can be no guarantee of seeing clinical benefit from the therapy. Therefore the participant must enter the study from an altruistic point of view in the expectation that they are helping increase knowledge that will potentially benefit others in the future. This must be clearly explained to ensure that fully informed consent is obtained. It is therefore vital that any data collected in a trial will stand up to scientific scrutiny.

From a scientific perspective, in order to understand how a body reacts to a new therapy, it would be beneficial to be able to remove and analyse transfected cells histologically. For many tissues, such as skin and blood, this is easily obtained. The removal of brain tissue is more difficult and without medical benefit would be unethical. However, for some conditions such as focal epilepsy, resective surgery is a standard option for those who do

not respond to medical treatment. Being able to undergo resective surgery provides a useful tool for a clinical trial. Should any safety concerns be identified then patients will be able to undergo the resective surgery that they might otherwise have received. This would also remove the implanted device and most, if not all, transduced cells. The removed device and tissue could then be analysed to gain a greater understanding of the cellular response to the GTMP and device. However, this may only be an option in the specific population of focal epilepsy patients, and would not be an option for the majority of brain disorders to which optogenetics could be applied.

Early phase studies are often fairly short, collecting initial data to support a second longer and larger study. For an optogenetic trial, this would provide limited data on the successful expression of opsins, safety information on adverse events in response to the surgery and implantation and the ability for an implant to affect opsin expressing cells. Including a longer implantation period within a trial would provide a number of benefits, but at the expense of increased costs and patient commitment. For example, a longer implantation can help to mitigate any potential impact of the surgical treatment on seizure rates as opposed to the therapy. In patients with epilepsy, it has been shown that there can be a short term placebo effect with a reduction in seizures following a craniotomy.³⁰

A longer study will also provide data on how the brain responds over time to the therapy. This is important as long-term data from resective surgery studies and deep brain stimulation (DBS) studies suggests that responses can change over time. The success rate from resective surgery for epilepsy decreases over time, levelling at between 40–50% of people being seizure-free after 10 years.³¹ Conversely, results from implantable devices such as DBS for depression and epilepsy can improve over time.³² For example, the RNS Neuropace closed-loop DBS for epilepsy demonstrated a median reduction in seizure frequency of 53% at two years but which increased to 70% at six years.³³ The SANTE trial, involving an open-loop DBS demonstrated a median reduction in epileptic seizure frequency of 41% at one year, increasing to 69% at five years.³⁴ In the use of neurostimulation devices for headache disorders it can take up to three months to detect changes in headache severity or frequency.³⁵

A successful short-term trial will generally lead on to a bigger, longer trial. However, any initial trial must be long enough to get a strong understanding of whether

treatment efficacy may change over time. Intermittent conditions such as epilepsy or migraine may not provide enough data points over a short period to show efficacy. The risk to a sponsor lies in analysing efficacy data from too short a trial that may falsely suggest that a new therapy is not efficacious. This may result in the closing of trials of therapies that may just require more time. Continuing with further trials requires large investments of time, money and resources. Sponsors must ensure sufficient data is collected to make an informed decision for their own benefit as well as the patient population they are aiming to help. It should be noted, regardless of study length, some form of long-term safety follow-up must be planned to meet the requirements of use of an Advanced Therapy Medicinal Product.¹⁹

When discussing study length, it is important to note that opsin expression does not occur immediately and can take up to six to eight weeks from injection to reach sufficient levels to allow neuronal control. This means that there may be up to two months following GTMP delivery where no impact is to be expected. This can also impact on the timings of surgeries to minimise patient disruption. Ideally both the GTMP and device should be implanted during the same surgery. This would help minimise the number of surgeries required and help ensure that the injection location and implant location are the same. However, during the period when opsin expression is occurring functional testing of the device can be taking place to ensure that the time is not wasted.

A vital factor in the success or failure of a trial is the measure by which success is determined. This bar should be set with the patient in mind and should not necessarily be a physiological measure that might not translate to improved quality of life for patients. If the bar for success is too high a product may be doomed to failure. Set the bar too low and millions may be spent on a therapy offering only minimal benefit. Unless patients are able to detect a noticeable improvement from a product, they may not be willing to accept such an invasive therapy resulting in significant losses for any manufacturer. The key to success lies in early and repeated engagement with patients, their carers and their treating physicians such that the outcome measures selected reflect real world practice and expectations.

Should any benefit or improvement be seen by a participant, sponsors should be in a position to provide continued use of a therapy beyond the planned trial. This may take the form of a long-term extension study. This allows participants to continue to benefit from the therapy

while also providing sponsors with longer safety and efficacy data.

Options to trial either just the gene therapy or implantable device are possible but difficult to justify. Both the GTMP and implantable device are able to function independently (the GTMP will result in opsin expression within neurons and the device will deliver optical stimulation as necessary), but neither will provide any clinical benefit without the other. Any information garnered by a separated trial would not provide any suggestion as to how the combined therapy may work.

Implantation of the device in some form is a possibility but could only be done in specific circumstances. Implanting a full device without the GTMP would entail an invasive procedure that will put the patient at risk without the possibility of any benefit to the patient. For the manufacturer, this may provide data in regards to the surgical process and the ability to record electrophysiological data and translate to optical stimulation. However, due to the lack of participant benefit, the risks of surgery, infection and provoking an immune response amongst others makes this approach difficult to justify.

Some neurological conditions involve surgery as part of standard treatment. This surgery may provide an opportunity to briefly test an implantable device. This should not risk any potential damage to neuronal tissue and is unlikely to allow implantation of the entire device. While this should provide minimal risk to patients, the data it will collect would be basic and depending upon the condition being treated may not be able to show successful implementation of light therapy in response to abnormal neural network behaviour within the brain.

For any single element study, patients would be exposed to a risk through brain surgery for either component. The benefit of any data collected in preparation for a combined therapy trial would arguably be small, compared to well-designed preclinical studies. A first-in-human trial with both aspects of the therapy would still be required, making a trial of either component on its own unjustifiable.

Summary

A review of the benefits and risks suggests that the first clinical study for an optogenetic therapy should be of both the gene therapy and the implanted device together, and should be of sufficient duration to provide meaningful data on safety and efficacy. While a longer trial provides additional risks to the sponsor in regards to time scale and

costs, it should be the sponsor's responsibility to take on this additional risk for the long-term benefit of patients. While benefit should not be expected for an early phase study, patients must also be able to take advantage should any improvement in symptoms be seen. Similarly, for a first-in-human trial, there should be an escape route included in case of severe adverse events such as resective surgery if possible.

A key element in the design and planning of any clinical trial is the involvement of patient groups. Engagement with the clinical population will help to ensure that the trial keeps the patient at its heart and answers questions relevant to them. While changes in biomarkers or tests may suggest a treatment is beneficial, if it does not affect patient quality of life then a treatment is unlikely to be embraced by a patient population.

Developing and testing new therapies is extremely expensive and there is inevitably a financial pressure to identify failing products early, and to get successful products to market as early as possible. Longer studies take time and are expensive, but sponsors are able to build in their own safety points by including mid-trial analyses. However, the early closure of studies due to futility analysis can affect future work on potential therapies. This can be particularly damaging when early analysis is undertaken on small amounts of data.³⁶

Developing first-in-human trials using optogenetics raises a number of issues covering regulatory areas and maintaining the risk/benefit profile from both the patient and sponsor perspective. Ultimately the safety of the patient must be paramount. They are the group with the most to lose and so consideration must be made to minimise risk while allowing the greatest possibility of benefit.

With all of the concerns and difficulties highlighted within this review, it may appear unclear as to why optogenetics is worth pursuing within the brain. Ultimately, it is for the benefit of the patient. That may be the focal epilepsy patient who does not respond to pharmacological treatment and is ineligible for resective surgery or the schizophrenia patient suffering severe side effects to their medication. Pharmacological treatment provides a scattergun approach to cellular targeting and many stimulation implants work on a pre-programmed open-loop basis. Within any organ, the clinical aim should be to deliver therapy only when required and to the exact location it is needed. This is potentially even more necessary within the central nervous system. Optogenetics provides this possibility of targeted, closed-loop treatment. It may be the case that the ethical issues

highlighted preclude the application of optogenetics within the human brain. It is therefore up to researchers to provide enough preclinical data to regulatory authorities to show that this should not occur. With our current knowledge about this technology, it would be unethical not to pursue this challenge to its natural conclusion, wherever that point may be.

Optogenetic therapies for retinal disorders are already undergoing clinical trials and it is only a matter of time before the first trial for a central nervous system disorder is proposed. For these reasons it is crucial to design suitable trial strategies that give the best chance of demonstrating the power of this new technology whilst maintaining patient safety.

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