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Applications and The Limitations of Real-World Data in Gene Therapy Trials

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ABSTRACT

There are approximately 7,000 distinct rare diseases that exist affecting 350 million people worldwide, and approximately 80% of those rare diseases are caused by faulty genes. Scientific advances such as the CRISPR/Cas9 genome-engineering system[1] have simplified the pharmaceutical and biotech industry's ability to develop gene therapies especially for single gene mutation disorders. The FDA has more than 700 active INDs for gene and cell therapies and in 2017 approved two cell-based gene therapies — chimeric antigen receptor T-cells (CAR-T) and approved the first gene-therapy product to be administered in vivo which in addition was the first to target a specific rare disease genetic condition. Collins and Gottlieb, of the NIH and FDA respectively, have stated that "*it seems reasonable to envision a day when gene therapy will be a mainstay of treatment for many diseases*"[2].

There are unique challenges associated with gene therapy trials especially in those indications which are rare diseases, such as small patient numbers, lack of detailed knowledge of the disease progression, and definition of suitable endpoints. During the presentation, we discuss how the analysis of real-world data can provide insight and help overcome these challenges and discuss some of the limitations which reduce their acceptance by the regulatory authorities.

Careful consideration is given to the following statistical aspects of a trial

- definition of the study population
- endpoint choice
- use of controls, including historical control data

INTRODUCTION

The natural history of rare diseases is often poorly understood, and the need for prospectively designed, protocol-driven natural history studies initiated in the earliest drug development planning stages cannot be overemphasized[3] …

In this paper, we provide examples of how real-world data (RWD) assists the development of gene therapies by considering the contribution of RWD to conducting adequate and well-controlled studies in this challenging area of clinical research.

Firstly, for those that don't know too much about gene therapy a simplistic introduction is presented, together with the tool that has made the development of gene therapies so much more viable within the past decade, CRISP-Cas9. (For those of you who would like to learn more please see the Recommended Reading section at the end of the paper for some links to short but insightful YouTube clips of this amazing topic in science.)

Then we look at the regulatory requirements for gene therapies including a reminder of what constituents an adequate and well-designed trial. Followed by a discussion of each of these constituents in turn and where appropriate emphasizing how the use of RWD helps meet the requirements. The section ends with a discussion on the limitations of a randomized clinical trial (RCT).

The next main section pulls together the uses of RWD to support gene therapy studies, in terms of conducting an adequate and well-controlled study, as a source of evidence to improve the efficiency of the future clinical trial designs and the use of RWD as historical controls.

In conclusion, parachutes and gene therapy are linked by RWD (Figure 1).

Figure 1. RWD Links Parachutes and Gene Therapy

GENE THERAPY

WHAT IS GENE THERAPY?

Gene therapy uses genes to treat or prevent disease[4] by stopping or slowing the effects of disease on the most basic level of the human body, our genes. Genes are made up of DNA, and act as blueprints to build enzymes and proteins that make the body work. Sometimes a small change is made to a gene, called a mutation, that can change how our proteins work and this can, in turn, cause disease. If gene mutations could be mended this would have a huge impact on the treatment of rare disease as 80% of the 7,000 rare diseases are caused by faulty genes and more people in the world have a rare disease than the population of the US!

Gene therapy is when a correction is made in the body so that the mutated gene no longer causes the disease.

There are several approaches to gene therapy, including:

- Gene Correction: Inactivating a mutated gene
- Gene Transplantation: Introducing a new gene to help fight a disease
- Gene Replacement: Replacing a mutated gene with a healthy copy of the gene

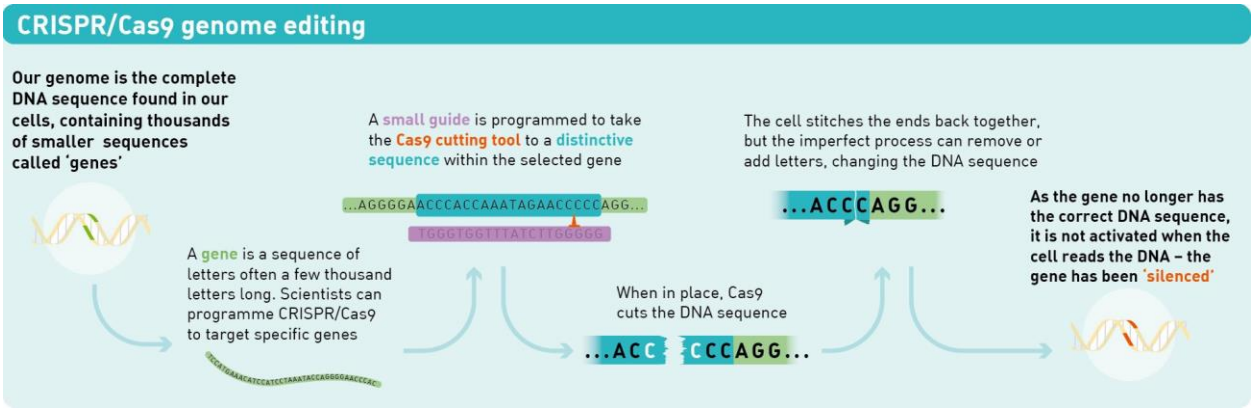
IMPACT OF CRISP/CAS9 TECHNOLOGY

Creating a gene therapy was a complex process requiring much specialised equipement: however just over 5 years ago, the CRISPR/Cas9 genome editing system was demonstrated in eukaryotic cells, establishing a more viable approach to gene therapy for clinical research.

The CRISPR-Cas9 system is recognized as faster, cheaper, more accurate, and more efficient than other existing genome editing methods[5], and in 2018 there were over 360 clinical trials underway in gene therapy[6], and the FDA are expecting to approve 40 gene therapies by 2022.

Gene correction is illustrated using the CRISPR/Cas9 genome editing system in Figure 2.

Figure 2. An Example of CRISPR/Cas9 Gene Editing



Credit: Nigel Hawtin for the Francis Crick Institute

CHARACTERISTICS OF A GENE THERAPY TRIAL

REQUIRED LEVEL OF EVIDENCE FOR GENE THERAPY

Approval of any drug including a gene therapy is based on substantial evidence of the drug's effectiveness and the evidence of effectiveness should be obtained in an identified population from adequate and well-controlled studies. The draft guidance for gene therapy trials in rare diseases[7] goes further and suggests all studies should be designed to be adequate and well-controlled

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"Sponsors should consider designing their first-in-human study to be an adequate and well-controlled investigation that has the potential, depending on the study results, to provide evidence of effectiveness to support a marketing application."[7]

CHARACTERISTICS OF ADEQUATE AND WELL-CONTROLLED STUDIES

An adequate and well-controlled study:

1. includes a suitable mechanism to select subjects who have the disease or condition under study
2. includes a clear statement of objectives ideally with a prospective analysis plan
3. includes a prospective explanation of the variables measured including methods of observation and criteria used to assess the response
4. is designed to provide a quantitative assessment of drug effect by making a comparison with a control
5. includes a suitable method to assign patients to treatment and control group to minimize bias e.g. randomization
6. is designed to minimize bias on the part of the subjects, observers, and analysts of the data e.g. blinding
7. includes an analysis of the results of the study to adequately assess the effects of the drug. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables.

In the following sections, we explore how to incorporate characteristics 1-6 of an adequate and well-controlled study into the design of a gene therapy study and where relevant how to include the use of RWD.

PATIENT POPULATIONS

"has a suitable mechanism to select subjects who have the disease or condition under study"

Gene therapy trials are currently focused on 'simpler' genetic diseases where treatment involves fixing a single mutation of a gene; these types of diseases are called monogenic diseases. WHO estimates that there are 10,000 such diseases.[7] Monogenic diseases tend to have a very low prevalence and often fall into the class of rare diseases. Therefore, the patient population for gene therapy trial is often small, which limits the opportunity for conducting many or large-scale clinical trials.

Interestingly, the patient population for rare diseases to be treated with gene therapy are often heterogeneous resulting in different patient groups experiencing different disease severities and rates of disease progression. This is because different single-point mutations on the same gene are likely to manifest in the same rare disease because the different mutations result in the same protein mal-functioning. Therefore, the patient population can be split into genetic subsets who have the different levels of disease severity and rates of progression.

For many patients, participating in gene therapy clinical trials isn't an option because their immune system recognizes and fights the virus used to deliver the treatment. Until recently, patients with an immune response would be excluded from a gene therapy trial, resulting in up to 80% of patients being excluded.

However, it has been shown that under some circumstances patients with immune response can be given the gene therapy safely and exhibit a degree of efficacy response. Therefore, it is being suggested that patients with an immune response can be included in gene therapy trials. However due to the different response rates, immune response rates should be used as a stratification factor in the study design to act for the different levels of efficacy response in a similar way such as disease characteristics such as severity.

RWD from registry studies including natural history studies can be particularly helpful, providing insight into the identification of patient sub-populations especially:

- Genetic sub-types
- Disease severity sub-types
- Degree of immune response

STUDY OBJECTIVES & ENDPOINTS

"includes a clear statement of objectives ideally with a prospective analysis plan"

"includes a prospective explanation of the variables measured including methods of observation and criteria used to assess the response"

Development of a clear statement of objectives is best achieved when there is a firm scientific foundation, including an understanding of disease natural history. The draft guidance for Rare Diseases: Common Issues in Drug Development Guidance for Industry[8] states that "The natural history of rare diseases is often poorly understood, and the need for prospectively designed, protocol-driven natural history studies initiated in the earliest drug development planning stages cannot be overemphasized."

The type of information that can be gleaned from well-designed natural history studies helps with the construction of clear objectives and hypotheses and development of sensitive and specific clinical outcome measures by gaining an understanding of:

- clinically meaningful outcomes
- variability during the disease
- disease aspects most likely to be life limiting or life altering
- potential prognostic characteristics
- disease manifestations are likely to develop and are likely to persist
- other useful sources of data including clinical examination findings, laboratory measurements, imaging, reports of patient functioning and feeling

CHOICE OF A COMPARATOR

"is designed to provide a quantitative assessment of drug effect by making a comparison with a control"

If feasible a gene therapy trial should include a concurrent control "The randomized, concurrent-controlled trial is generally considered the ideal standard for establishing effectiveness and providing treatmentrelated safety data."[9]

It should be noted that use of a concurrent comparator is moderately uncommon in gene therapy studies. We will explore possible reasons for the lack of their use in the section Limitations of AN RCT as An Adequate and Well-controlled Study. In a recent review of 89 currently recruiting gene therapy studies, 22 (25%) included a comparator (Table 1). The 89 studies were determined from a pre-defined search of www.ClinTrials.Gov on 9 April 2019 with the following filters

1. Recruitment = "Recruiting"
2. Expanded Access = "Available"
3. Study Trial = "Interventional"
4. Funder Type = "Industry"

5. Term = “Gene Therapy” or “Gene Transfer” or “Virus Delivery”

A more common approach to demonstrate effectiveness is to include more than one dose of the treatment in the study design, with a total of 54 (61%) studies conducted in this way in the review (Table 1). Effectiveness in these studies being demonstrated on the basis that “a well-controlled dose-response study is also a study that can serve as primary evidence of effectiveness.”[10]

Table 1. Incidence of Controlled and/or Dose Response Gene Therapy Studies Currently in Recruitment

	Dose Response Study?		
Study includes a Control?	Yes	No	Total
Yes	9 (10%)	13 (15%)	22 (25%)
No	45 (51%)	22 (25%)	67 (75%)
Total	54 (61%)	35 (39%)	89 (100%)

RANDOMISATION AND BLINDING

“has a suitable method to assign patients to treatment and control group to minimize bias e.g. randomization”

“is designed to minimize bias on the part of the subjects, observers, and analysts of the data e.g. blinding”

Randomization is a simple but key feature of conducting clinical research; it is the only method to ensure an unbiased (true and accurate) estimate of a treatment effect. This is because randomization:

- minimizes confounding due to unequal distribution of prognostic factors,
- ensures treatment groups are comparable according to both known and unknown factors
- and minimizes selection bias

“Randomization in early stages of development is strongly encouraged when feasible”[7] for gene therapy studies, but as discussed in the section on Limitations of AN RCT as An Adequate and Well-controlled Study, there can be ethical and practical challenges of conducting a randomized gene therapy trial especially in the later stages of the clinical development program.

Blinding is also a technique used to minimize bias, in this case due to differences in behavior of the participant, or investigator or others involved in the clinical research. The bias stems come from knowledge of the assignment of the treatment group to the patient. The different types of blinding minimize different types of bias for example:

- subject or patient blinding minimizes performance bias
- investigator or clinical staff blinding minimizes assessment bias

When gene therapy treatments include use of surgery or other invasive mechanisms to deliver the treatment, very careful consideration should be given to whether it is ethical to have a sham procedure like the one used for the gene therapy treatment arm given to patients on the control arm.

LIMITATIONS OF AN RCT AS AN ADEQUATE AND WELL-CONTROLLED STUDY

Although a randomized, double-blind, placebo-controlled study is considered the gold-standard design for conducting clinical research, it should be recognized that this design isn’t necessarily the best and only design to be considered for gene therapy studies. There are limitations of a randomized controlled study (RCT) especially those associated with the concept of clinical equipoise[11].

According to the belief of clinical equipoise, no patient should be randomized to a treatment that is known or is thought by the expert clinical community to be inferior to the established standard of care. This provides *'food for thought'* regarding whether an RCT design can be ethical for gene therapy studies, especially for those treatments where a clear efficacious effect has already been demonstrated in a prior study. On the flip side of the same coin, obtaining informed consent from patients in these circumstances also proves to be very difficult and so a randomized study without clinical equipoise is likely to suffer from poor recruitment rates.

USE OF REAL-WORLD DATA IN GENE THERAPY STUDIES

> *"Use of appropriate statistical methods for implementing historical control trial designs can help to reduce the risk of selection bias."*[12]

HOW RWD CAN IMPROVE GENE THERAPY STUDIES

The following list provides some examples where real-world data, especially data from a prospective natural history study, can provide input into a successful clinical development programme for a gene therapy:

- patient populations through
  - the identification and definition of genetic sub-types, disease severity sub-types
  - and the determination of the degree of immune response
- study objectives and endpoints through
  - identifying those disease manifestations are likely to develop and are likely to persist
  - identifying those aspects of the disease that are most likely to be life limiting or life altering
  - the identification and validation of clinically meaningful outcomes
  - estimating the degree and sources of variability during the disease
  - generating hypotheses for testing in randomized controlled trials
- efficiency of the design and analysis through
  - development of prior probability distributions for use in Bayesian models
  - the identification of prognostic indicators or patient baseline characteristics for design enrichment or stratification
- feasibility through
  - examining the impact of planned inclusion/exclusion criteria in the relevant population
  - assessing for geographically distributed research cohorts

RWD FOR A HISTORICAL CONTROL

We saw that the use of a concurrent control is moderately rare (Table 1), but it is possible to compare a gene therapy test drug's results with the results "historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations."[9] This comparator is called a historical control.

The use of historical controls in trials for regulatory purposes is recommended only for special circumstances, such as for those diseases with "and predictable mortality … and studies in which the effect of the drug is self-evident."[9] Both of these circumstances are applicable to certain diseases that are being treated with gene therapies. For example, Cystic Fibrosis has high mortality and a predictable progression, whereas following gene therapy for hemophilia some patients don't require factor replacement for extended periods of time and hence exhibit a life-changing efficacious effect..

There are limitations about use of historical controls that need to be carefully considered; given that "comparability of control and treatment groups at the start of treatment, and comparability of treatment of patients during the trial, cannot be ensured or well assessed."[13]

But given the difficulties of conducting gene therapy studies in rare diseases there has been considerable interest in the concept of 'borrowing' historical control information from previous studies in conjunction with having a concurrent control arm with a fewer number of patients.[12,14] In particular, there is considerable assistance available in the TranCelerate sponsored paper[14] to help the reader gain a better understanding of:

- General principles to consider when incorporating historical control data in a new trial are presented.
- Bayesian and frequentist approaches and how the operating characteristics for such a trial can be obtained.
- …examples of approved new treatments that incorporated historical controls in their confirmatory trials are presented.

CONCLUSION

This paper discusses how by the appropriate use of RWD the regulatory trial process for gene therapies can be accelerated.

However, there are still those who may be concerned by including the use of RWD compared to conducting the gold standard approach to clinical research which is often advocated as the most appropriate choice, namely a randomized, placebo, controlled trial, irrespective of the circumstances. Note we agree that the gold standard is an RCT but just not in all circumstances including for some, or even, most trials involved with gene therapy.

Therefore, we would like to conclude by introducing a 2003 BMJ paper to help us remember to be considered about the use of RWD. The theme of the paper is somewhat satirical but under the right circumstances provides a powerful message "Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials."[15]

Further I leave you with the following thoughts "No randomised controlled trials of parachute use have been undertaken. The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect. Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump."[15]

REFERENCES

1. Barrangou, R. and J.A. Doudna. 2016. "Applications of CRISPR technologies in research and beyond." *Nat Biotechnol*, 34: 933-941.
2. Collins, F.S. and S. Gottlieb. 2018. "The Next Phase of Human Gene-Therapy Oversight." *N Engl J Med*, 379:1393-1395.
3. Rare Diseases: Common Issues in Drug Development Guidance for Industry. 2019. "NATURAL HISTORY STUDIES." Accessed April 12, 2019. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM629579.pdf
4. Your Guide to Understanding Genetic Conditions. 2019. "What is Gene Therapy." Accessed April 9, 2019. https://ghr.nlm.nih.gov/primer/therapy/genetherapy
5. Your Guide to Understanding Genetic Conditions. 2019. "What are genome editing and CRISPR-Cas9?" Accessed April 10, 2019. https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting
6. Alliance for Regenerative Medicine. 2018. "2018 Annual Report." Accessed April 9, 2019. https://alliancerm.org/publication/2018-annual-report/

7. Human Gene Therapy for Rare Diseases Draft Guidance for Industry. 2018. Accessed April 12, 2019. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610802.pdf
8. Human Genomics in Global Health. 2019. "Genes and human diseases: Monogenic Diseases." Accessed April 11, 2019. https://www.who.int/genomics/public/geneticdiseases/en/index2.html
9. Electronic Code of Federal Regulations. 2019. "§314.126 Adequate and well-controlled studies." Accessed April 8, 2019. https://www.ecfr.gov/cgi-bin/text-idx?SID=7be3183a7e7b0882eb3042d4d605319b&mc=true&node=se21.5.314_1126&rgn=div8
10. ICH Topic E4 Dose Response Information to Support Drug Registration. 1994. "GUIDANCE AND ADVICE 4.5" Accessed April 18, 2019. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-4-dose-response-information-support-drug-registration-step-5_en.pdf
11. Freedman, B. 1987. "Equipoise and the ethics of clinical research". N Engl J Med. 317, (3):141–145.
12. Lim J., R. Walley, J. Yuan, J. Liu, A. Dabral, N. Best, A. Grieve, L. Hampson, J. Wolfram, P. Woodward, F. Yong, X. Zhang and Ed Bowen. 2018. "Minimizing Patient Burden Through the Use of Historical Subject-Level Data in Innovative Confirmatory Clinical Trials: Review of Methods and Opportunities." *Therapeutic Innovation & Regulatory Science*. Vol. 52(5) 546-559.
13. ICH Topic E10 Choice of Control Group in Clinical Trials. 2001. "2.5.7 Disadvantages of externally controlled trials." Accessed April 18, 2019. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-10-choice-control-group-clinical-trials-step-5_en.pdf
14. Viele, K., S. Berry, B. Neuenschwander, B. Amzal, F. Chen, N. Enas, B. Hobbs, J. G. Ibrahim, N. Kinnersley, S. Lindborg, S. Micallef, S. Roychoudhury and L. Thompson. 2014. "Use of historical control data for assessing treatment effects in clinical trials." *Pharm Stat*. 13(1): 41–54.
15. Smith G.C. and J.P. Pell. 2003. "Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials." *BMJ*. 327(7429):1459-1461.

RECOMMENDED READING

CRISPR: Gene editing and beyond. 2017. https://www.youtube.com/watch?v=4YKFw2KZA5o This is a 5 min 'pretty' animated clip.

How CRISPR lets us edit our DNA. 2015. https://www.youtube.com/watch?v=TdBAHexVYzc This is a 15 min TED talk presented by Jennifer Doudna who co-invented CRISPR-Cas9.

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