# FSHD Case Study - Comparison of a Single-Arm Trial to an External Dataset

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You have been given the opportunity to work as a statistician on a study testing a promising treatment for FSHD (Facioscapulohumeral muscular dystrophy), a genetic condition that causes progressive muscle weakness, primarily affecting the face, shoulder blades, and upper arms. FSHD is a rare disease estimated to affect about 4 in 100,000 people[1]. Currently, there's no cure for FSHD, but healthcare providers recommend ways to ease its symptoms, such as physical therapy, orthotic devices, or surgical procedures to improve shoulders range of motion. The investigational treatment targets the root cause of the disease and has the potential to slow or even halt disease progression. Exciting!

First, your study team set out to perform a randomized placebo-controlled trial. However, due to the fact that the disease is rare, forecasting projects that to recruit enough patients from this population would delay the study by a number of years. In order to speed up the evaluation of the treatment, the study team decides to design an open-label single arm study.

The study team justifies a single arm trial, not only on the grounds that this would speed up the timeline of the study, but also due to their clinical knowledge that for this disease, improvements are generally not observed. If anything, people with the disease generally decline gradually throughout their lifetimes. Therefore, your clinical colleague reasons that even if patients on the treatment arm are observed to exhibit a small improvement or stable trajectory throughout the course of the study, then this observation would lead to promising evidence that the new treatment is indeed helping these patients.

The study team thus decides to proceed with the single arm study of only treated patients. However, your clinical colleague approaches you with an idea for a comparison. They discover that there exists a publicly available natural history registry of the patients that is curated by an external research group. They furthermore found that, in this external dataset, the average change in the primary outcome measure of interest in your study was -3.2 points over a one-year period, which is relevant to your study as you had planned to collect your primary endpoint for each patient at the 1-year mark.

They ask you, "Could we not just compare the average change in the outcome in the natural history data to what we observe in our single-arm study? That is, if the new treatment helps reduce the decline of the patients in the study to be significantly less than -3.2, could we claim that the drug is working?"

You like the idea of using the publicly available natural history data to strengthen the evidence from your single arm study, but given the availability of the external individualized patient data (demographics, clinical variables, etc.), is there a better alternative to the simple comparison to the -3.2 change?

You reach out to a group of your colleagues to discuss. That is you all!

## Task

Collectively draft a response to your clinical colleague. In your response, discuss the simple comparison proposed by your clinical colleague and suggest alternative approaches using causal inference tools to explain your rationale. Provide pros and cons of all proposed approaches.

## Hints

In these contexts, the causal inference literature sometimes proposes to target a causal effect called the "average treatment effect among the treated" defined in counterfactual notation as:

$$\mathrm{E}[\mathrm{Y}^{(\mathrm{a}=1)} - \mathrm{Y}^{(\mathrm{a}=0)} | \mathrm{A} = 1],$$

where $\mathrm{Y}^{(\mathrm{a}=\mathrm{x})}$ is the potential outcome under treatment $\mathrm{x} \in \{0,1\}$ and $\mathrm{A} = 1$ indicates a patient being included in the single arm study where they received the experimental treatment while $\mathrm{A} = 0$ would indicate being in the external control dataset where no treatment was taken.

As you draft your response, you may (but do not need to) use the following prompts as a guide for ideas:

- Explain to your colleague the population for which you would like to investigate the causal effect of treatment. For instance, would you like to quantify the treatment effect in the study population or the registry population? Or both? Justify why.
- Could you use a causal diagram to communicate aspects of this study with your collaborators? Feel free to draw one.
- Given the estimand formally defined in the potential outcomes notation above (or for an alternative one that you believe is more relevant), explain this effect in laymen's terms to your clinical collaborator.
- What assumptions would you have to make in order to identify this causal effect? How would you go about communicating these assumptions to your clinical team? What can you conclude if these assumptions are untestable?
- What analysis method would you consider using? Could you communicate this simply to a non-statistician?
- How would you consider performing a sample size calculation for this single arm trial? What elements would you consider?
- How would you go about interpreting the results of your proposed analysis to a non-statistical collaborator?

References on FSHD:


1. https://www.mda.org/disease/facioscapulohumeral-muscular-dystrophy
2. https://www.fshdsociety.org/
3. https://www.mda.org/disease/facioscapulohumeral-muscular-dystrophy#:~:text=What%20is%20facioscapulohumeral%20muscular%20dystrophy,are%20the%20symptoms%20of%20FSHD?
4. https://my.clevelandclinic.org/health/diseases/facioscapulohumeral-muscular-dystrophy-fshd


When you're done, please email a picture of your results to iscb.causal.symposium@gmail.com and feel free to cc your team members to share the work.