"Negative" Clinical Trials in Rare Diseases and Beyond: Reclassification and Potential Solutions

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Abstract

Currently, all trials, including those in rare diseases, that do not demonstrate a statistically significant benefit (i.e., $P < 0.05$) on the primary endpoint are classified as "negative". This classification does not take into account a myriad of factors, including whether the trial was sufficiently powered, or had other statistically significant endpoints, or was terminated before completion, or was even initiated. In this paper, I propose reclassification of these trials into 5 categories: true negative, underpowered, inadequate, terminated or uninitiated, and valid. These categories reflect the trial characteristics more accurately and will be more useful to all stakeholders, especially the patients who participated in the trial and their healthcare providers.

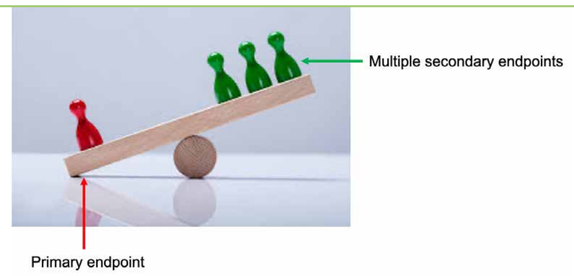
Keywords

"Negative" trials; rare diseases; reclassification; solutions

Background

- Currently, all trials, including those in rare diseases, that do not demonstrate a statistically significant benefit ($P < 0.05$) on the primary endpoint are classified as "negative" **(Figure 1)**.[1-3]
  - The current classification into "positive" and "negative" trials is clearly overly simplistic and potentially a misapplication of statistical analyses.[1-3]
- This classification does not take into account a myriad of factors, including whether the trial:
  - Was sufficiently powered.
  - Had other statistically significant endpoints.
  - Was terminated before completion.
  - Was even initiated.
  - Had other issues not listed above.
- The term "negative trial" itself is very poorly defined and has an obvious undesirable connotation.
  - It raises the specter of failure and suggests that the treatment being evaluated is not effective for that disease.
  - It does not take into consideration the various caveats that may accompany the trial.
- Historically, there is a publication bias toward "positive trials, regardless of disease prevalence.[3-5]
- This is particularly problematic in rare diseases, where there is a paucity of patients.[6,7]
  - In the absence of peer-reviewed publications on "negative" trials in rare diseases, other researchers and sponsors may attempt to conduct trials of similar design for the same disease using the same class of drugs, which would inevitably result in the same "negative" outcomes.
  - This is a phenomenal squandering of the limited resources available in rare diseases, and especially disrespectful of the patients who participate in these trials.

Figure 1: **The disproportionate Impact of Primary Endpoints on Trial Classification**



Objective

- To redefine the term "negative trials" and reclassify these trials more accurately, especially based on their impact on rare disease drug development and approvals.

Methods

- Literature searches of PubMed were conducted using the terms:
  - Search 1: "negative trial" OR "positive trial"
  - Search 2: "rare disease" OR "orphan disease"
  - The searches were limited to clinical trials and restricted to those published in English language.
- The results from search 2 were manually evaluated for whether the primary outcome was met.
  - Trials that did not meet the primary outcome were evaluated for their classification, when available.
  - These reports were also evaluated as to whether there were any extenuating circumstances.

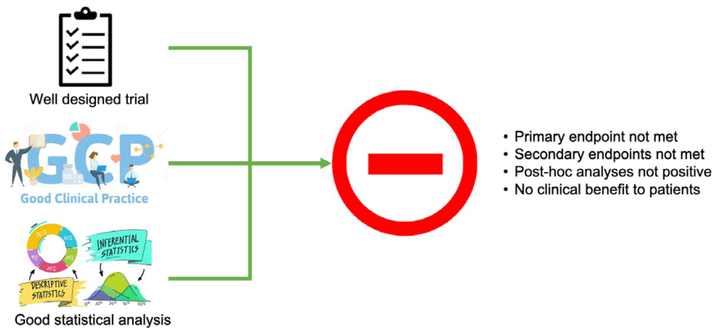
Results

- Based on the evaluations, I suggest 5 categories that more accurately describe the outcomes of the trials, beyond the primary endpoint.

Negative trials

- These are well-designed and well-conducted trials, with outcomes appropriate for the disease population, but do not yield any benefit to patients in any endpoint measured **(Figure 2)**.
- This situation is unusual, although not absent, in rare diseases.

Figure 2: **Negative Trials**



Underpowered trials

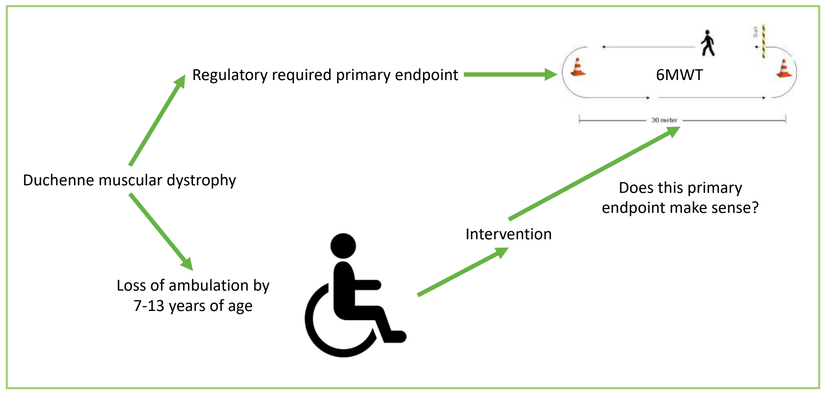
- These are trials in which outcomes are appropriate for the disease.
  - However, they have not enrolled enough patients to determine whether the intervention had a clinically meaningful effect **(Figure 3)**.
- The resulting outcomes can mask a significant treatment effect even when it is real – a type 2 error
- Unfortunately, many rare disease trials fall into this category because of the limited number of patients available and the strict inclusion criteria of trials
  - Furthermore, many of these trials are not completed or not reported when completed.[8]
- This is particularly harmful not only to the participating patients, but also to other patients with this disease.
  - Furthermore, it erodes the confidence of patients in the clinical trial process, making it more difficult to recruit patients for subsequent clinical trials.
- Such trials are at best inconclusive or uninterpretable.

Figure 3: **Underpowered Trials**

Inadequate trials

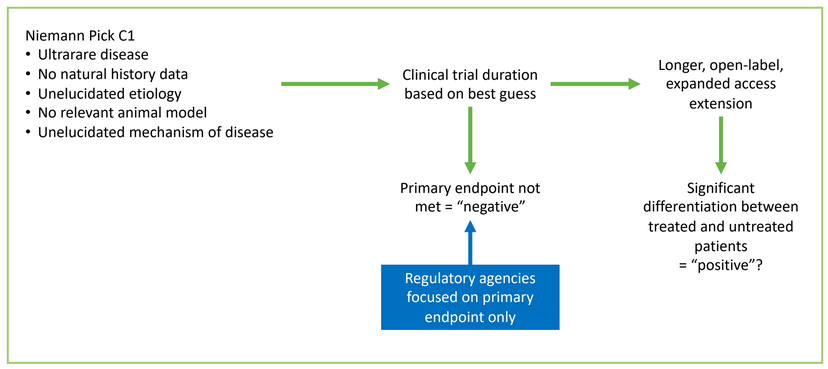
- These are trials in which there is a fundamental defect in the design, which is often identified after the trial is completed.
- Design defects include:
  - Improper primary outcome, eg, the primary endpoint addresses a symptom, but not the underlying disease etiology or mechanism.
  - Inappropriate primary outcome, eg, a primary endpoint that cannot be achieved **(Figure 4)**.
  - Inappropriate treatment regimen, eg, wrong dosage or timing.
  - Inadequate trial duration, eg, too short to demonstrate meaningful clinical outcome **(Figure 5)**.
- Reclassifying these trials as "inadequate" would more accurately describe them.

Figure 4: **Inappropriate Primary Outcome**



6MWT, 6-minute walk test

Figure 5: **Insufficient Trial Duration**



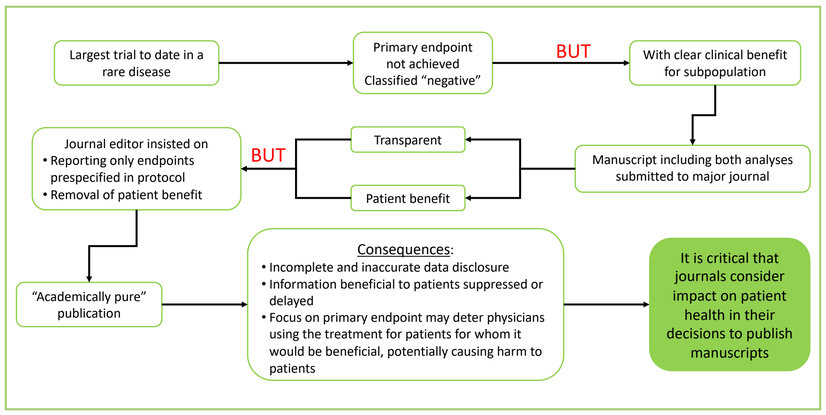
Terminated or uninitiated trials

- Trials in this category are classified as terminated prior to completion or not ever started, despite being registered, and should be classified as such.
- Examples include:
  - Unanticipated safety concerns about treatment arising during trial.
  - Lack of efficacy of treatment.
  - Insufficient or no enrollment of patients.
  - Loss of trial center, eg, due to a natural disaster.
  - Loss of trial sponsorship.

Justifiable trials

- The hallmark of this group is that despite the primary outcome not achieving statistical significance, there is at least one secondary or post-hoc outcome that is clinically beneficial to the patient population being studied.
  - The "negativity" of such trials is limited to the primary outcome.
- Characterizing the whole trial as "negative" is not scientifically or medically accurate nor is it fair to the patients with the disease, their caregivers, the healthcare professionals treating them, the physicians conducting the trial, or the sponsors **(Figure 6)**.

Figure 6: **Justifiable Trials**



Summary

- The 5 new suggested categories are summarized in **Table 1**.

Table 1: **Summary of Proposed Reclassification of "Negative Trials".**

Category		Trial characteristics
1	Negative	Well-designed, well-conducted trial with adequate enrollment, but no benefits of treatment in any endpoint
2	Underpowered	Well-conducted trial, but underpowered to determine whether there was any benefit of treatment under investigation
3	Inadequate	Poorly designed trial that cannot determine whether there was any benefit of treatment under investigation
4	Terminated or uninitiated	Trials that were terminated or not initiated for any reason
5	Valid	Well-designed, well-conducted trial with adequate enrollment, without treatment benefit in primary efficacy endpoint, but with benefit of treatment in at least one other endpoint

Discussion/Conclusions

- Conducting clinical trials in rare diseases remains a daunting challenge.[6,9]
- Trial design becomes particularly problematic in diseases with little, if any, natural history data.
- This situation results in many trials on rare diseases being categorized as "negative" solely on their not achieving statistically significant benefit on the primary endpoint – an overly simplistic view that disregards the complexities of conducting trials in rare diseases.
- Unreported trials due to "negativity" are particularly harmful not only to participating patients but also to other patients with the disease.
- This reclassification may provide guidance to patients, trialists, and sponsors on how to better interpret their data in a more nuanced way than the overly simplified binary "positive" and "negative" categories currently employed.
- This is an important step toward changing the landscape of rare disease trials toward a more positive outlook.

References

1. Gerth van Wijk R. *Allergo J Int*. 2018;27:167-172.
2. Pocock SJ and Stone GW. *New Engl J Med*. 2016;375:861-870.
3. Unger JM, et al. *JAMA Oncol*. 2016;2:875-81.
4. Misemer BS, et al. *Trials*. 2016;17:473.
5. Mlinaric A, et al. *Biochem Med (Zagreb)*. 2017;27:030201.
6. DeWard SJ, et al. *J Genet Couns*. 2014;23:20-28.
7. Ragni MV, et al. *Haemophilia*. 2012;18:e192-e194.
8. Rees CA, et al. *PLoS Med*. 2019;16:e1002966.
9. Augustine EF, et al. *J Child Neurol*. 2013;28:1142-1150.

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