Journal for Reproducibility in Neuroscience

We need another 3R rule: repeat, repeat, repeat!

Annika Hultén*, Saara Rannanpää

Janssen-Cilag Oy, Vaisalantie 2, 02130, Espoo, Finland
* correspondence: ahulten@its.jnj.com

There is consensus within the scientific community that replication studies are scientifically sound and bring added value and reliability to any discovery. It is also widely acknowledged that replications are not as common as they perhaps should be. The reasons for this vary depending on the stakeholder - here we will discuss the matter from the perspective of the pharmaceutical industry. However, the views expressed here are our own and do not represent the official standpoint of our employer or the industry in general. We will focus this commentary on the issues related to replications of the clinical part of the drug development, as our expertise is most closely related to this area, but the matter is equally relevant and important in the pre-clinical domain.

The development of novel drugs is motivated by the pursuit of more effective, safer, and better tolerated treatment options. The process is formalized and regulated in order to minimize the possibility that any harm comes to any person using the drug and to maximize the possibility that only medications that have proof of a significant benefit over the standard of care are placed on the market. After the initial drug discovery and development, the preclinical stage aims to provide detailed information on dosing and toxicity levels using animal models or in vitro. These are followed by human studies, that are conducted in phases; phase 0/1 focuses on safety and dosage on 10–30 healthy human volunteers, phase 2 on safety and efficacy with a limited number of patients of the disease in question, whereas phase 3 studies are typically large, multicenter trials with hundreds or thousands of patients where the novel drug is compared to the standard of care and/or placebo. In many cases the control in phase 2 and 3 are analogous to a positive or active control, especially if the standard of care has been used for a long time before the study. The health authorities may also require that multiple phase 3 trials are carried out, in order to validate the efficacy and safety profile through replication before market authorization. Moreover, requests for post market authorization commitments to conduct phase 4 trials studies to further evaluate the efficacy and safety of a drug are becoming more common.

As detailed above, the drug development process involves many studies and is typically both long and expensive. The incentive to base business decisions on reliable and replicable scientific data is therefore not only an ethical one, it is also financially important. In other words, it is worth investing money to acquire reliable replicable data, as this is not only a prerequisite for market authorization but will also minimize the financial risks involved in drug development. Replications of clinical human studies are important, as these increase the amount of data on safety and tolerability, confirm (or refute) a previously observed therapeutic effect and offer access to novel treatment options to patients. It is worth noting that, in a sense, the stages of the clinical drug development process is a type of replication setup (especially with regards to phases 2-4), where the following phase replicates the previous phase in a larger sample.

As is currently the case in many, if not most scientific fields, pure replications of clinical studies where every parameter is the same are rare, though some of the reasons for this are unique to the clinical setting. While in theory there are no ethical objections to a replication study in humans, given that (as is standard) the study follows the declaration of Helsinki and is pre-registered, each study must always be carefully evaluated by an independent review board before it starts. For example, it may not be ethical to replicate a pure placebo-controlled trial if there is sufficient evidence of an efficient treatment for the disease. Another major obstacle is the resources needed to collect hundreds or even thousands of patients across the globe, making sure that the protocol is followed identically at every site.

However, there are several ways to conduct studies that at least partially capture the objectives

DOI: https://doi.org/10.31885.jrn.2.2021.1469

of experimental replications. For example, a clinical experiment that in addition to the replication, includes other research questions, such as a novel control group is usually a financially sound way to acquire replication data.

Pharmaceutical companies also often commit to further test the efficacy and safety of their new drugs in long term follow-up studies when applying for marketing authorization or reimbursement. These real-world-evidence studies use observational data (real-world data, RWD) obtained in the routine clinical practice and are important to show that the effect demonstrated in a well-controlled experimental trial replicates in a real-world naturalistic setting. While real-world studies are a cost-effective way to collect data from a population that exceeds the original clinical study, there are limits to what data is available, as the data is observational in nature. For example, in psychiatry treatment outcomes are not measured from laboratory tests, and the questionnaires or the formalized clinical assessment used in the trials may not be commonly used in the clinical practice. Instead treatment effects may need to be approximated from other variables, such as sick leave. In addition to the replication value of RWD, it can also provide new data that is not possible to get from a randomized clinical trial. For example, comorbidities are typically an exclusion criterion in clinical trials, yet it is important that the efficacy and safety of a drug is comparable also in patients with comorbidities. Also, adherence to the treatment is often different between clinical trials with frequent follow-up visits and real-world practice. Nonetheless, evidence generation through RWD is becoming an increasingly important part of value-based healthcare and provides an important way to replicate data.

Another form of replication of clinical data takes place through independent investigator studies. The pharmaceutical company is not involved in these studies but may in some cases provide funding or sponsor the drug being investigated. In contrast to phase 3 clinical trials, these are typically performed in one or a few research centers, and with a substantially smaller study population. Also, these studies tend to have other research objectives that go beyond a pure replication of a previous clinical study, as a replication with a smaller sample size than the original study defeats the purpose of a replication. Their goal is often to close remaining data gaps or to serve as 'proof-of concept' studies that instigate extensive clinical testing, instead of serving as replication-studies themselves.

In the discussion of the value and importance of replication studies, it is sometimes forgotten to highlight that the interpretation of how a replication study impacts the findings of the original study is not always straightforward. If the original study and the (partial)replication vary on one or more factors, caution is warranted in the interpretation (though it does not render the replication useless by any means). Some examples of factors that may make the comparison of two studies very difficult are differences in sample size, effect size, choice of statistical method, duration of the study, background demographic factors or the route and dose of medication. To be able to compare studies with each other, replications studies would benefit from more formalized standards similar to those that are applied in systematic reviews and meta-analyses.

In conclusion, we believe that all stakeholders should strive to remove the barriers that currently make them reluctant to repeat studies. Some barriers are more easily addressed than others. Understanding the importance of replication studies makes science better, and at the end of the day it is the patients that will benefit the most from replication studies, be they in the domain of preclinical compound development or extensive clinical studies. Inspired by the 3R rule for preclinical animal studies (replace, reduce, refine), we advocate for a similar 3R rule for replication studies, that is even easier to learn: repeat, repeat and repeat!

Conflict of Interest: the authors are employees at Janssen-Cilag Oy, and the present article was reviewed by the company prior to submission. The views expressed here are the authors own and do not represent the official standpoint of their employer or the industry in general.