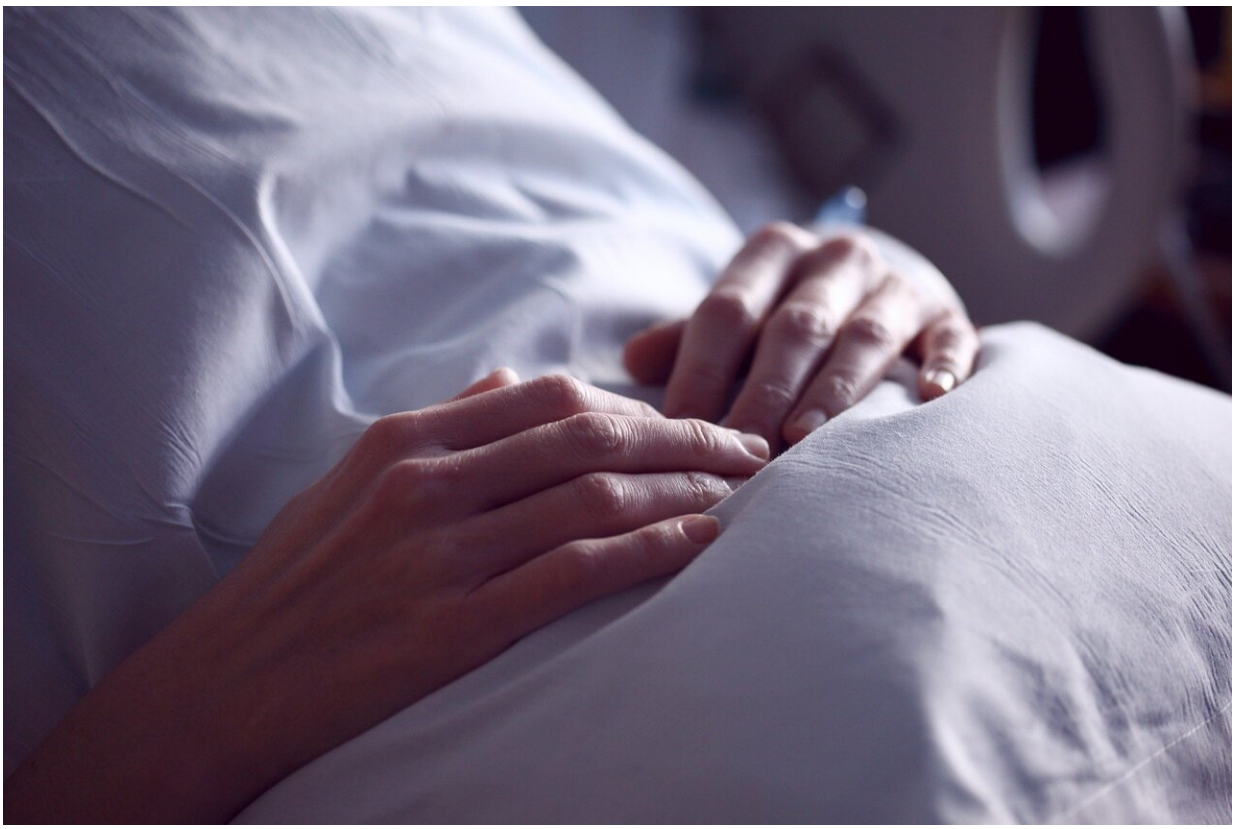
Patients receiving exceptions to participate in targeted therapy trial have similar outcomes to eligible participants

June 27 2024



Credit: CC0 Public Domain

Eligibility requirements for clinical trials help protect patients whose comorbidities may put them at an additional risk of severe harm from

the treatment being tested. Further, they help ensure that analyses are performed on a carefully controlled population, minimizing outliers that could skew the data.

However, the patients who will eventually receive the treatment are not homogeneous. New therapies hitting the market have not always been tested in patients with diverse backgrounds and medical histories. A 2015 study found that 39% of patients treated for renal cell carcinoma in clinical practice would not have been eligible for the trials leading to the approval of the drugs they received.

Among patients in the general population treated with osimertinib (Tagrisso) for non-small cell lung cancer, 62% would have been ineligible for the Phase III trial.

"It is well known that results in an 'ideal' population do not always translate to the real-world population," said Hans Gelderblom, MD, senior author of the study and chair of the Department of Medical Oncology at the Leiden University Medical Center in the Netherlands.

"Eligibility criteria are often too strict, and educated exemptions by experienced investigators can help individual patients, especially in a last-resort trial."

Such exemptions, which allow patients to participate in trials for which they would otherwise be ineligible, may include a lab test slightly outside the eligibility range, a necessary imaging scan completed outside the recommended window, or a tumor that could not be biopsied for safety reasons, Gelderblom explained.

Whether these exemptions—or, by extension, the broadening of clinical trial eligibility criteria—lead to poorer patient outcomes has not been comprehensively studied, Gelderblom said.

Gelderblom and colleagues examined the effect of protocol waivers on patient outcomes in the Drug Rediscovery Protocol (DRUP) trial, a pan-cancer basket/umbrella trial that matches treatment-refractory patients with off-label targeted therapies based on their tumor's genetic profile. Between September 2016 and September 2021, 1,019 patients were enrolled into DRUP, including 82 patients who received a protocol waiver.

The research is published in the journal *Clinical Cancer Research*.

The reasons for waivers were grouped into four categories: eligibility criteria exceptions, out-of-window testing, treatment exceptions, and testing exceptions. The most common waivers granted were exceptions to eligibility criteria, often due to out-of-range lab tests. The second most common waivers granted were for testing exceptions, often exemptions from a biopsy.

At 16 weeks post-treatment, the clinical benefit rate was 40% among patients who received a protocol waiver, compared to 33% among patients who did not receive a waiver. Similarly, the median overall survival among patients who were and were not granted waivers was 11 months and eight months, respectively.

Patients who received waivers were also no more likely to experience severe adverse events (SAEs) than patients who did not receive waivers; SAEs were observed in 39% of patients granted a waiver and 41% of patients without waivers. Gelderblom and colleagues also evaluated the likelihood that each SAE was caused by a protocol waiver in patients who received them.

They deemed the relationship between waivers and SAEs "unlikely" for 86% of patients and "possible" for 14% of patients. The rates of treatment discontinuation due to toxicity or progression during the first

treatment cycle were similar among patients who did and did not receive waivers.

Gelderblom emphasized that while the protocol exceptions studied in this trial were minor, they could have broader implications for the design of clinical trial eligibility criteria. "These findings advocate for a broader and more inclusive design when establishing novel trials, paving the way for a more effective and tailored application of cancer therapies in patients with advanced or refractory disease," he said.

Limitations of this study include a broad diversity in cancer types, treatments, and reasons for protocol exemptions among the assessed patients which, while improving the generalizability of study findings, precluded specific subgroup analyzes.

Further, because the likelihood of clinical benefit was an integral part of physicians' decision to grant waivers, it is possible that patients who received waivers were positively selected for clinical benefit, compared to the general study population.

More information: Jade M. van Berge Henegouwen et al, Maximizing treatment opportunities: assessing protocol waivers' impact on safety and outcome in the Drug Rediscovery Protocol, *Clinical Cancer Research* (2024). DOI: 10.1158/1078-0432.CCR-23-3917