Reverse Lasagna's law: the ethics and undesirable consequences of overbooking patients for trials

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EDITORIAL

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To accelerate recruitment in clinical trials, pharmaceutical companies are increasingly implementing a three-pronged strategy of (i) actively encouraging the general public to participate in clinical trials with novel medications; (ii) overbooking of study sites and countries; and (iii) competitive enrolment of study patients. Whilst such an approach is commercially understandable and clinically laudable because it could potentially accelerate access to new medications, we question the ethics and possible undesirable implications for patients and call for more careful implementation of such a strategy.

We participated in several phase III trials on the prevention of migraine attacks with monoclonal antibodies targeting calcitonin-gene-related peptide or its receptor [1]. The promising efficacy and good tolerability of these medications seen in phase II trials were substantially promoted in the general and social media as well as in medical journals. In addition, the possible introduction of the first-ever class of migraine-specific prophylactic drugs also contributed significantly to the 'hype'. Participants in the phase III trials would receive *verum* in any case in open-label extension phases.

Not surprisingly, expectations were raised and the number of trial volunteers skyrocketed. Such an oversupply is contrary to common experience. Usually, as soon as trials begin, the actual number of eligible patients dramatically drops compared to pretrial estimations, to rise again after the trial has ended [2]. This phenomenon has been known as 'Lasagna's law' since 1979 [3] but is still relevant today [4].

At first glance, an 'inverse Lasagna's law', that is, more eligible patients than expected, seems positive. However, at the same time, an excess of study sites and countries was contracted by the sponsor, and patient enrolment was to be competitive. Inclusion would stop as soon as the overall target number was reached, creating competition among study sites and effectively patients.

We experienced such an abrupt study termination prior to the study target date with three different companies. Highly motivated patients, who already had been prescreened and had received an appointment date for inclusion, suddenly had to be told that 'the trial was overbooked', similar to airline passengers who are told at check-in that the flight is overbooked without receiving appropriate compensation and an apology from the company. Study sites starting later, for example because of delayed ethical approval, had to halt inclusions after only a few of a long list of already planned patients. Understandably, patients were furious, not unusually directing their anger to the study personnel.

In conclusion, whilst appreciating the reasons to speed up inclusion, we are questioning the ethics of the chosen strategy. Effectively, patients were first hyped to participate in the study and then told at the very last minute that they could no longer participate despite extensive initial pre-screening and preparation. Super-motivated patients became seriously disappointed and understandably blamed the study site, not fully aware of the company's role as study sponsor.

In the future, potential participants should be explicitly warned in advance in the informed consent of the risk of exclusion at the very last minute and consequent intense disappointment. Study sites should also be better prepared for the potential impact and consequences of competitive enrolment.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

KEYWORDS

clinical trials, ethics, methodology

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