Clinical trials and the COVID-19 pandemic

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"…but why think? Why not try the experiment?..."

John Hunter (1728-1793), in a letter to Edward Jenner.
August 2nd, 1775.

When Galen of Pergamum (2nd c. A.D.), physician, philosopher and experimentalist, sought to ascertain the therapeutic properties of *Theriac*, an antidote of repute against poisons, he resorted to an experiment [1, 2].

Theriac or Theriaca *(Θηριακή* in Greek) was a compound drug, containing in some versions used in antiquity numerous components; Galen's own composition included over 70 ingredients [1, 2]! One of its uses was as an antidote against snakebites, a frequent peril for the Roman armies marching on in sandals.

Galen spent most of his life in Rome and was elevated to Imperial Physician at the court of Marcus Aurelius, who apparently took daily doses of *Theriac*, which among other components included opium [2].

Describing the experiment to his friend Pison [1-3], Galen wrote, "*as I could not possibly conduct a trial on humans, I experimented on roosters*" «…ἡμεῖς μὲν ἐπ' ἀνθρώπων τὴν κρίσην αὐτοῦ ποιῆσθαι μὴ δυνάμενοι, ἐπὶ τινών ἄλλων ζώων τὸ αὐτὸ δρῶντες...».*

For his experiment, Galen, studied two groups of roosters, but he doesn't tell us how many animals he included in each category. Both groups were exposed to poisonous snakebites. All roosters who were fed with theriac prior to exposure to viper bites survived, whereas in the second group that had not received prophylactic Theriac, all roosters died [3].

Not only is Galen's methodology remarkable, preceding the modern randomised trial by eighteen centuries, but more importantly, it is notable for his ethical stance at a time when sensitivities about human rights, prevalent in our times, were largely absent in societies of widespread slavery. For example, Mithridates VI (132-63 bC), the King of Pontus who is credited with the first use of Theriac, tested its efficacy on criminals and slaves [1].

For his experiment Galen used the random allocation of treatment, today's prospective randomised clinical trial, implemented in the evaluation of novel therapies, widely used internationally, particularly in cancer research!

This experimental method used for ascertaining the efficacy of new drugs became established after the second half of the 20th century and is now firmly entrenched as a research tool.

On the other hand, the retrieval of information from observational studies or non-randomised series is considered scientifically inferior and is often dismissed or ignored as irrelevant or anecdotal. Such is the compulsion for the randomised study that in the midst of the COVID-19 pandemic, respected physicians and scientists appeared in the media hesitant to recommend the use of protective facial masks, as there was no evidence of benefit for their use from prospective randomised studies in the general population!

Logic had no place in the argument!

COVID-19, caused by the SARS-CoV-2 new corona virus, brought to the fore the randomised trial, as well as, the ethical dilemmas that surround the allocation of treatment at random, in the face of a devastating pandemic.

Anthony Fauci, distinguished infectious diseases expert and an adviser to the President of the USA, at a recent briefing from the Situation Room of the White House, endorsed categorically and unreservedly the randomised trial for the evaluation of drugs potentially effective against SARS-CoV-2, in patients afflicted with COVID-19.

A few days later on April 8th, 2020, Professor Sotiris Tsiodras, scientific advisor to the Greek Government for COVID-19 and an expert on infectious diseases, when asked by a journalist about chloroquine, he responded, "*Antony Fauci is correct. Nevertheless, we give the drug to everyone, that is, not half of the patients will receive it, and the other half will not*".

If we accept that the randomised trial represents the unique, impregnable method of evaluating new treatments - *several clinicians dispute this dogma* [4-7] - the question arises how will treatments be allocated to patients? According to the Declaration of Helsinki participation of a subject in a clinical trial requires their explicit written consent. Will, a potentially hypoxic patient rapidly deteriorating, be able to understand what is being asked of them, and will that patient be in a position to provide consent? And if that patient refuses to be randomised, what are the options? Is it his/her right to request the active treatment that a fellow patient is receiving in the next bed?

Although the Declaration of Helsinki allows the option of no treatment or even placebo, where no known treatment is available for a certain condition, such as COVID-19, it also emphasizes that "while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects".

Consider now the physicians and nurses on the first line of the battle against the pandemic; to the enormous pressures and risks that they experience daily, they may have to endure the added psychological burden of the randomised trial, knowing that half of their patients are receiving the promising drug, whilst the other half are denied the chance of potential benefit.

When during the Medical Research Council's randomized trial of streptomycin, one senior physician contracted tuberculosis, the Medical Research Council obtained supplies for him outside the trial [8]. In this brief instance of medical history, the equipoise, the scientific imperative, all arguments and other justifications for providing treatment at random, were thrown out of the window in favour of the human factor!

Why is randomization necessary? Because - it is presumed - the process of randomising subjects, protects the study from the selective inclusion of patients with favourable characteristics, thus inadvertently allowing or facilitating a falsely favourable result for the drug or treatment under investigation. However, the process of randomising patients does not necessarily result in the randomisation of the characteristics of their disease [7].

Exactly because of this, at the end of a randomised study, even if the prognostic variables are evenly represented and balanced in the strata, further confirmation of the result is sought with a statistical multifactorial analysis. Such multifactorial analyses can also be applied to a non-randomised group of patients engaged in the trial of a new drug.

Since the middle of the 20th century a generation of physicians have been trained to dismiss, or are incapable of evaluating the validity of a treatment beyond the established etiquette of the randomised study. This, some have argued [7, 9], constitutes intellectual indolence, it is not scientific robustness.

Pandits foresee that the world will be different after the end of this pandemic. Perhaps human ingenuity will seek new investigative methods that will render the randomised clinical trial obsolete, both, on methodological and ethical grounds.

Until then and even if we have to accept the scientific supremacy of the randomised study in the evaluation of novel therapies, the ethical considerations in the unprecedented circumstances of a relentless pandemic demand a more humane approach, befitting the beneficent precepts of the Hippocratic tradition [7, 10].

*complete greek phrase: «τὴν ἀληθῆ τοῦ φαρμάκου κρίσιν εὑρίσκειν πειρώμεθα. ἀλεκτρυόνας γὰρ λαβόντες.....οὕτως αὐτοῖς προβάλομεν τὰ θηρία, καὶ τὰ μὲν εὐθέως ἀποθνήσκει τὰ μὴ πιόντα, ὅσα δὲ πέπωκεν, ἰσχύει καὶ μετὰ τὸ δῆγμα τὴν ζωὴν ἔχει».

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Figure. Pharmaceutical Pot for Theriaca. @ Hospice de Beaune, Hotel-Dieu Pharmaceutical Museum, Photograph by this author.