Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Methodological education in response to the quality of COVID-19 publications

1. Introduction

The recent retraction from major medical journals of two articles on coronavirus 2019 disease (COVID-19) [1,2] reminds us that continued education in clinical methodology is an essential part of medicine [3]. Clinicians study and apply the messages coming from the medical literature, influenced by message dissemination and authoritative opinions, but they are rarely offered the chance to be educated or re-educated on the basics of reliable research and on critically appraising [4] the data that support their practice. We recently identified several pitfalls of COVID-19 study designs that typically lead to inconclusive or futile results [5,6]; for example, insufficient power to prove the working hypotheses, soft endpoints subject to assessment bias in the context of open label studies, lack of appropriate comparators, nonrandomised treatment allocation, data duplication or fragmentation, and retrospective analyses of observational data [5]. We here describe common types of clinical studies and the information they are most suited (or unsuited) to provide. We also propose steps for improving the quality of future investigations.

2. Types of studies

2.1. Observational

These look at baseline characteristics – such as age, sex, ethnicity, global distribution - in healthy individuals (epidemiology) or patients (natural history) at a given moment (cross-sectional) or over time (longitudinal). Standardised and prospectively collected environmental, clinical or biomolecular variables can be related to disease incidence or progression or other outcomes. In apparently healthy individuals living in Framingham, Massachusetts, linking certain baseline traits to subsequent adverse events led to the identification of the classical cardiovascular risk factors [7]. Circulating risk markers for cardiovascular diseases, such as fibrinogen, D-dimer, troponin or natriuretic peptides, have been identified in a similar way [8]. Observational studies are suited to describe the natural course of disease development, to identify patho-biological associations, or to discover the effects of specific exposures, by comparing the 'spontaneous' characteristics of those who develop a certain outcome (cases) versus those who don't (controls).

In contrast, observational studies may be highly misleading and are therefore contraindicated to conclude on the consequences of medical interventions. Indeed, *any* human intervention carries a significant risk of (likely appropriate) selection bias. In medical practice, for instance, proton pump inhibitors (PPIs) versus none are given preferentially to comorbid patients, and vitamin K antagonists versus direct oral anticoagulants (DOACs) are given preferentially to patients with advanced renal impairment. Concluding from these behaviours that PPIs cause disease or that warfarin causes renal impairment would be reversing the direction of causality. While observational studies and registries may increasingly become complementary to randomised controlled trials to assess effectiveness and safety of certain interventions in the real world setting, referring to observational studies for the comparison of different treatments can often lead to unreliable conclusions, even after attempts to reduce the impact of treatment-selection bias through propensity-score matching [9]. This was the case of many observational studies that indirectly 'compared' different DOACs and warfarin in patients with atrial fibrillation, producing conflicting, inconclusive results [10,11]. Other examples illustrating the risks of inferring any 'effects' of human intervention from observational studies, particularly retrospective ones, include the early observation suggesting that nurses taking hormone replacement therapy (HRT) fared better than those who did not. Use of HRT likely identified women who were more attentive to their health than those not taking HRT, a difference that may well explain the lower occurrence of cardiovascular events among users, despite subsequent randomised controlled trials showing adverse effects of HRT on stroke and venous thromboembolism [12]. In patients taking clopidogrel, early observations reported that PPI use was linked to adverse cardiovascular events compared to non-PPI use, suggesting adverse clopidogrel-PPI interaction [13]. However, patients on PPI were at higher bleeding risk and likely more comorbid than those non-PPI users, and this may well explain the apparent unfavourable clopidogrel-PPI association, which was not supported by subsequent randomised data [14].

Out of 3802 studies on COVID-19 that have been registered on ClinicalTrial.gov as of October 17, 2020, 1600 (42 %) are observational. A large number of them are assessing the 'effects' of different therapeutic strategies for patients affected by COVID-19. Clinicians should be very careful in interpreting the reported findings and in drawing conclusions from them.

2.2. Interventional

These studies are best suited to compare the effects of treatment A versus treatment B, C, D, etc. They should be large, simple, randomised, meaningful and, if necessary, adaptive [15].

For COVID-19, any proposed treatment that is not specific but is repurposed cannot be expected to provide miraculous results, but rather small to moderate favourable effects. To reliably demonstrate a moderate benefit, several thousand patients are needed. Even small or moderate relative reductions of deaths will produce an enormous impact

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on the absolute number of survivors from a COVID-19 infection. Large numbers are needed to evaluate the effects of a treatment in subgroups, stratified by age, sex, comorbidities, severity of the disease, etc. [5]. COVID-19 is a global problem. Different healthcare systems and socio-economic conditions have an impact on the outcomes of affected patients. These differences can only be revealed by a large, global trial.

With COVID-19, every country has had to enact a form of emergency-disaster medicine. Hospitals have had to change their organisation and structure. Under these circumstances, it is not always possible to follow the usual interpretation of Good Clinical Practice-International Conference on Harmonisation rules. We need to maintain the basic principles that safeguard the rights and safety of patients and the scientific integrity of the study, while putting aside obsessive details. Simplicity is the keyword, and streamlined trials are the appropriate tool. The participation in a streamlined trial should consist of no more than a brief web connection to randomise the patient and to receive the treatment arm. Forget paper documentation with endless forms to complete. Just web inclusion of a small number of relevant variables. The primary and secondary endpoints need to be easy to detect and indisputable, such as hospital mortality or need of mechanical ventilation at hospital discharge. In practice, no more than 10–15 min of activity per patient to adequately complete the study.

Randomisation is necessary to avoid bias when interpretating the results and to avoid fuelling overenthusiastic expectations. A recent NEJM article comprehensively discusses why it is essential to trust randomisation when a benefit/safety profile of a treatment is under investigation [3].

Finally, why adaptive? The dramatic COVID-19 pandemic is incompatible with the usual approaches to drug trial conduction. Scientists and physicians are urged to find out immediate ways to control the aggressive speediness of the infection. Thus, several forced conditions must be considered. First, trials must go straight to efficacy, based on hard endpoints such as all-cause mortality while trying to ensure reasonable safety, and the treatments should be universally applicable. Second, the time required to get results must be as short as possible. Third, the trial design and management should be flexible enough to give the trial's leading committee the chance to identify the most favourable treatment among different non-specific pharmacological hypotheses. The above conditions are extremely challenging. No one can be sure of testing the right drug at the first attempt, in terms of clinically significant effect and universal applicability, so it is reasonable to test several drugs in parallel. No one can be sure about optimal treatment doses and duration to get a permanent effect, so it might be wise to have more than one arm testing different doses and lengths of treatment. Nobody can exclude the testing of ineffective drugs against an infectious agent fully unknown until a few months ago, so interim analyses should closely monitor the study to capture early signals of activity or non-activity or safety concerns, in order to make appropriate decisions. Briefly, the actions, usually pre-planned, in an adaptive design, should be [16]: 1) refining the sample size, 2) abandoning treatments and replacing them with others, 3) changing doses and treatment schemes, 4) changing the patients' allocation ratio to trial arms, 5) identifying patients most likely to benefit and focusing recruitment efforts on them, and 6) stopping the whole trial at an early stage for clear evidence of benefit, harm, or lack of efficacy.

2.3. Looking backwards or forward

Looking back (retrospectively) at existing data means, most likely, that the data were not gathered for that particular analysis. Therefore the data may be untrustable because of missing data, different measuring scales and biases in collecting the data. Looking ahead (prospectively) can minimise the gaps, reduce the degree of heterogeneity and avoid some inevitable biases. COVID-19 examples showing how prospective data can refute earlier conclusions drawn from retrospective analyses include a prospective study of unselected hospitalised COVID-19 patients, in which measurements of established cardiovascular markers did not provide prognostic information beyond that obtained from basic respiratory, haemodynamic, temperature and level of consciousness measures [17]. Earlier retrospective series of hospitalised COVID-19 patients had suggested that biomarkers reflecting cardiovascular disease and inflammation were strongly associated with poor prognosis; however, retrospective studies carry significant risk of selection bias, as the indication for measurements is at the discretion of the treating physician [17]. Prospective randomised trials were able to show lack of benefit and potential harm (by prolonging the QT interval) of hydroxychloroquine [18–20], whereas retrospective case series of hospitalised COVID-19 patients had led to contradictory conclusions, suggesting both benefit and harm [1].

2.4. Pathophysiological

These studies don't necessarily have to be large, as shown by revolutionary medical discoveries, such as Mendel's on recessive and dominant alleles or Koch's on the infective aetiology of tuberculosis, initially based on limited numbers of observations. They should, however, not escape the rigour of being standardised, controlled, prespecified, reproducible internally and by others, registered, and possibly performed by 'blinded' operators.

3. Proposals for improvements

3.1. Urgent methodological re-education

Several years ago an outstanding article [20] strongly recommended the conduction of large, simple, randomised trials when evidence-based data are needed to find effective treatments in clinical conditions of high epidemiological impact. Following the article's recommendation, cardiovascular research changed dramatically, providing in just a few years reliable results on an effective treatment for acute myocardial infarction that modified the management of this condition that, in those days, was burdened by a very high mortality [21,22]. Today, in the days of COVID-19, this lesson seems to be lost. An urgent methodological education/re-education is necessary. Academic institutions and public or private research organisations should promote initiatives to improve knowledge of methodological principles to conduct correct scientific research, remembering that only scientifically valid research can be considered ethical.

3.2. Registry-based randomised clinical trials for therapeutic interventions

The dispersion of resources caused by the conduct of studies with insufficient statistical power and therefore at high risk of being inconclusive could profitably be channelled into the planning of clinical studies of adequate size with sufficient statistical power to produce reliable results. Recent approaches to conducting clinical trials, although obviously acceptable, are very expensive, complex, time consuming and, in some cases, with strong representativeness limitations. A possible solution is the registry-based randomised clinical trial. By including a randomisation module in a large inclusive clinical registry with unselected consecutive enrolment, the advantages of a prospective randomised trial can be combined with the strengths of a large-scale all-comers' clinical registry. This approach could lead to a dramatic increase in the amount of definitive evidence about treatments and at a very reduced cost. Moreover, we might face an innovative ethical paradigm characterised by the expectation that participation in clinical trials is the norm rather than the exception.

In conclusion, in these unprecedented difficult times, critical appraisal and renewed rigour of investigators, journal review bodies and regulatory authorities have never been more welcome.

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Declaration of Competing Interest

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