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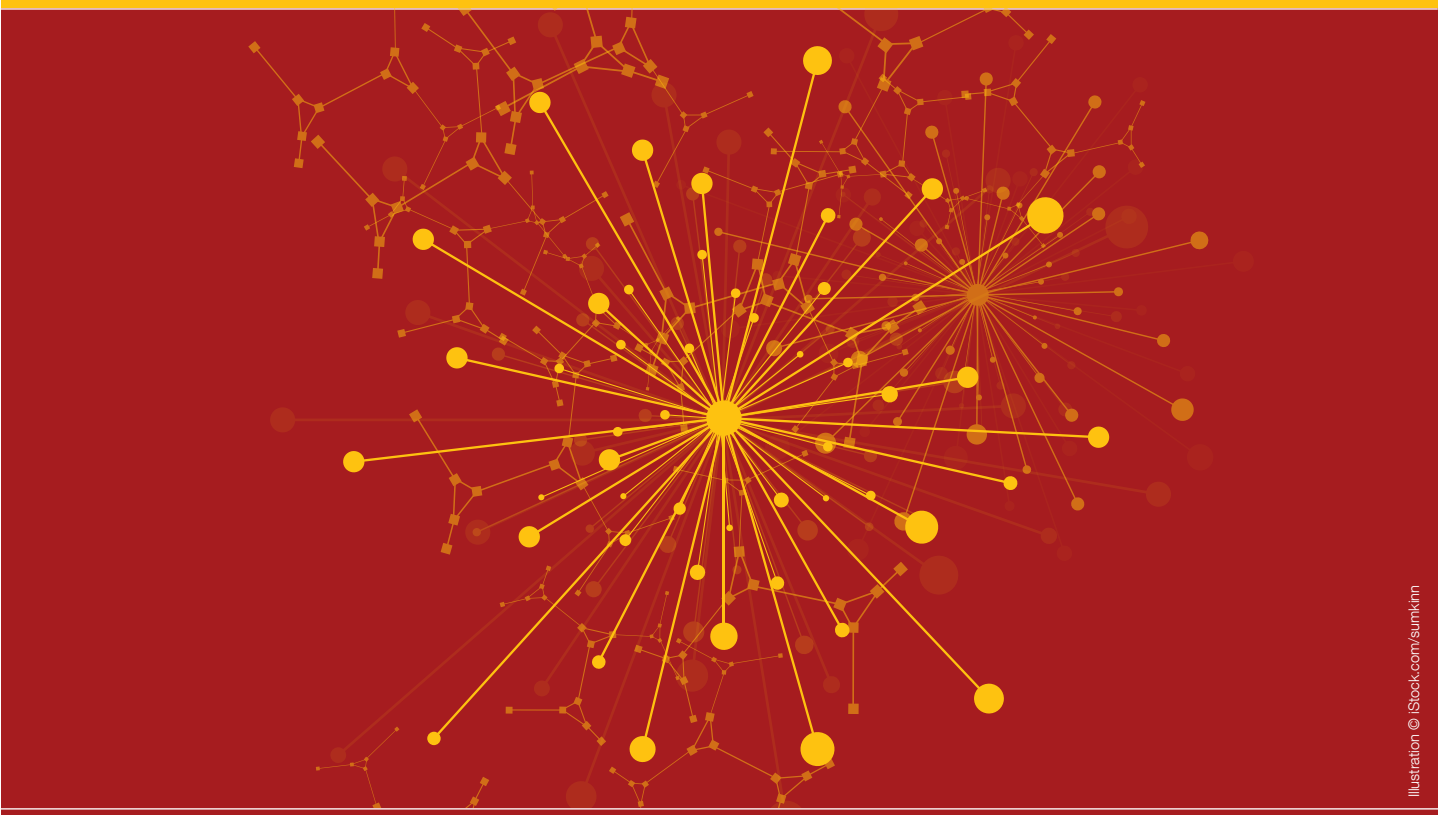

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FUNDAMENTALS OF DESIGNING CLINICAL TRIALS

Part 4: Phase III trial design in oncology and principles of article submission

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Preface

Dear Colleagues

In this special issue we take a look at some of the ways that uses of biomarkers have had on designing, conducting and analyzing clinical trials for lung cancer patients. Prof Lin provides insights into how such trials use biomarkers to select patients for enrollment to make them more efficient, so called enrichment. However, he rightly cautions us to be mindful that such trial designs do not allow biases to creep in and that they must also be considered carefully in what they do not tell us about biomarker negative patients. Prof Lin also explains how there is no longer such a clear line between phase II and Phase III trials and how the emergence of 'umbrella' and 'basket' approaches to trial design further challenge the traditional approaches to clinical trials.

Of course, an important part of undertaking research programs such as clinical trials and their substudies is reporting the outcomes, both positive and negative. Dr Sillaber has a wealth of experience in publishing research and here sets out some basic principles for those wishing to maximize their chances of having their work published in the correct forum where it will receive maximum attention. Connected to this is the invaluable peer review process and I have laid out some key messages related to how to use this to your best advantage to ensure that projects are likely to succeed and therefore get published and ideally contribute to improvements in the lives of patients and their families.

In a world that has more information available to a larger number of people than anytime in human history it is imperative that we take steps to ensure that what we contribute is not just adding to the volume but is capable of reaching our target audience with the most practical information that they can use. I commend this memo-inOncology to you as a vignette that captures a broad range of ideas that I hope fulfils this ideal.

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CSCO

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Chia-Chi Lin

Advances in phase III trial design in oncology

Use of genomic predictive biomarkers

Lung cancer is a model of a malignancy whose management requires the identification of predictive biomarkers in order to tailor therapy. The example of the ISEL and IPASS studies demonstrates the difference the use of a biomarker can make. At the time when the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) gefitinib was investigated in the phase III ISEL trial, the significance of the *EGFR* mutation status for the activity of EGFR TKIs was unknown. Overall, 1,692 patients after one or two prior treatments were randomized to either gefitinib or placebo in a 2 : 1 fashion [1]. In this all-comer population, gefitinib failed to prolong overall survival, which was defined as the primary endpoint.

On the other hand, the randomized, open-label phase III IPASS study was stratified by the *EGFR* mutation status, as this mutation had been identified as an important predictive biomarker in the meantime [2]. A total of 1,217 patients were randomized in a 1:1 manner to first-line gefitinib or standard chemotherapy with carboplatin and paclitaxel. These cohorts had already been pre-selected according to clinical criteria that hint at the presence of *EGFR* mutation: adenocarcinoma histology, non-smoker or former light smoker status, East Asian origin. Indeed, *EGFR*-mutation-positive patients derived significant benefits from gefitinib treatment with regard to progression-free survival and objective response rates. *EGFR*-wild-type patients, on the other hand, fared better with platinum-based chemotherapy than with the EGFR TKI treatment.

Biomarker-stratified design vs. enrichment design

IPASS had a biomarker-stratified design, i. e. the agent in question was evaluated in both biomarker-positive and biomarker-negative populations [3]. Each of these groups received either the EGFR TKI or standard treatment (**Figure 1**). Following IPASS, several trials tested the EGFR TKIs gefitinib, erlotinib and afatinib as compared to chemotherapy in the first-line setting [4–9]. However, these were conducted exclusively in patients with *EGFR*-mutant disease. This study design is called an enrichment design, as only biomarker-positive patients are enrolled (**Figure 1**) [3].

The enrichment design allows for efficient testing of a specific treatment in a biomarker-positive subpopulation, which implies that the sample size required is smaller. On the other hand, trials using this design provide no direct evidence of the clinical utility of the biomarker they are using, and they do not assess the activity of a certain drug in biomarker-negative patients. Profound knowledge of the predictive biomarker is therefore necessary prior to initiating a study using an enrichment design. Convincing evidence that the benefit of the marker is limited to biomarker-positive patients needs to have been established in previous trials.

PD-L1 as a marker for immunotherapy

Another important biomarker for lung cancer treatment is PD-L1 expression, which is predictive for the activity of immunotherapy. The Tumor Proportion Score (TPS) cutoff of 50 % that determines the use of pembrolizumab in NSCLC was chosen based on the observation that the staining intensity does not matter, as long as 50 % of tumor cells are positive for PD-L1 [10].

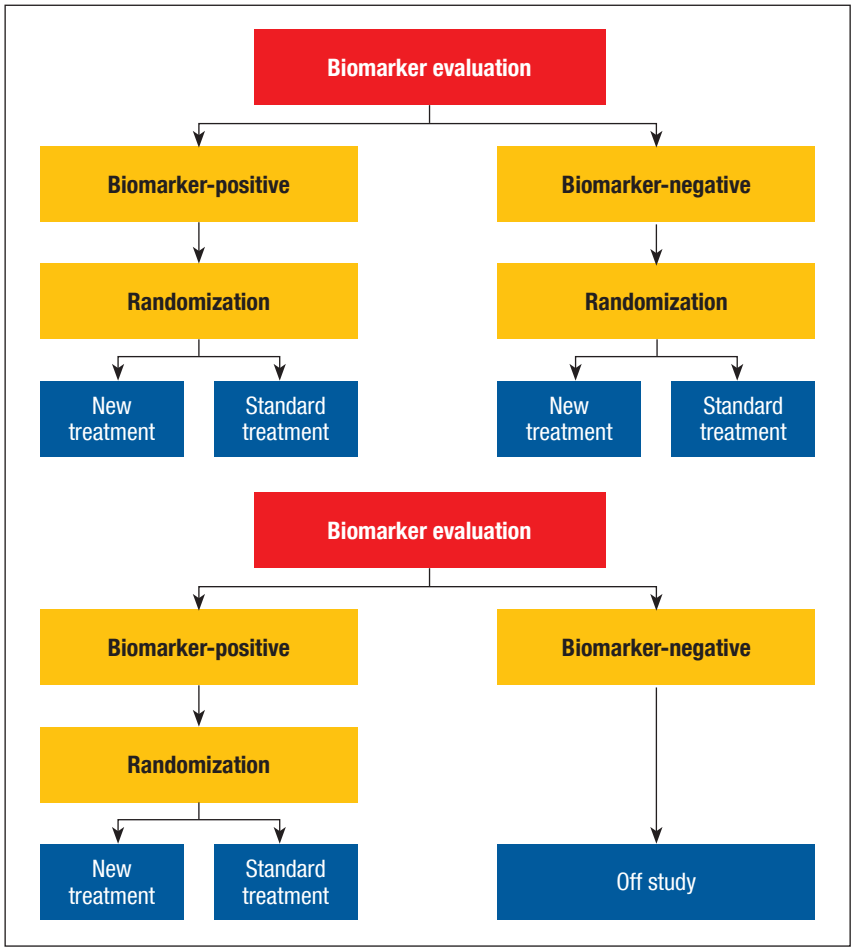

Figure 1: Biomarker-stratified trial design (above) and enrichment design (below)

In the KEYNOTE-001 and KEYNOTE-010 studies, 20 % to 30 % of patients were defined as PD-L1-positive. Indeed, these showed higher response rates in KEYNOTE-001 when treated with pembrolizumab than those with lower PD-L1 expression [10]. This applied to the total population as well as to the previously treated and treatment-naïve cohorts. Likewise, in KEYNOTE-010, the overall survival benefit obtained with pembrolizumab was higher in the subgroup showing PD-L1 TPS ≥ 50 % than in the entire cohort of patients whose TPS ranged above 1 % [11].

Integrated phase II/III clinical studies

An increasing proportion of clinical trials conducted in the setting of drug development programs does not show a clear distinction between phases II and III. Traditionally, phase II studies in the oncology field were single-arm studies providing preliminary information on the activity of a particular treatment, after phase I trials had evaluated the optimal doses and treatment schedules. Phase III studies used to randomize patients into treatment *versus* control groups and to stratify for the pertinent biomarker. Phase II and phase III studies thus had different aims and designs.

Today's phase II trials often commence early on in drug development, after biomarker identification has taken place, and involve the identification of the ideal dose and schedule while at the same time assessing patient responses to treatment (**Figure 2**) [12]. The transition to the phase III part, which serves the purpose of validation, is often seamless, as patient randomization can be preserved. This amalgamated design has both advantages and disadvantages. On one hand, conducting the phase II and III parts in a similar manner will increase efficacy; on the other, regulatory requirements might be difficult to meet.

Adaptive phase II/III trial designs

Basket design

New clinical trial designs have been established to account for the importance of predictive biomarkers. The basket design is histology-independent, but aberration-specific [13]. Basket trials thus include patients with different malignancies, as long as their tumors share the same driver mutation. All of these patients receive the same drug. Analyses can be performed either separately for each entity or for the entire cohort.

For example, the selective small-molecule tropomyosin receptor kinase (TRK) inhibitor larotrectinib has shown activity in a range of adult and pediatric TRK-positive cancers that included salivary tumors, sarcoma, infantile fibrosarcoma, lung cancer, thyroid cancer, colon cancer, melanoma, cholangiocarcinoma, and gastrointestinal stromal tumors [14]. Similarly, patients with endometrial, gastroesophageal, thyroid and neuroendocrine cancer, cholangiocarcinoma, prostate cancer, pancreatic cancer, colorectal cancer and osteosarcoma experienced considerable tumor shrinkage when treated with the anti-PD-1 antibody pembrolizumab [15]. All of these tumors had high microsatellite instability.

Umbrella design

Contrary to the basket design, the umbrella design includes patients with the same histology, while driver mutations differ [13]. Thus, various treatments targeting multiple molecular aberrations can be evaluated in a given tumor type. After the tumor has been analyzed for driver mutations, patients are randomized into several arms that receive specific targeted agents. A notable issue with respect to this design is the need to employ drugs from different pharmaceutical companies. In addition, mutation profiles of tumor types frequently change over time while the trial is still ongoing, which might call for adjustments.

The BATTLE trial was an adaptively randomized study in heavily pretreated lung cancer patients that required tumor profiling with "real-time" biopsies [16]. The biomarker profile assessed included *EGFR* mutation/copy number, *KRAS/BRAF* mutation, VEGF/VEGFR-2 expression, and RXRs/Cyclin D1 expression as well as

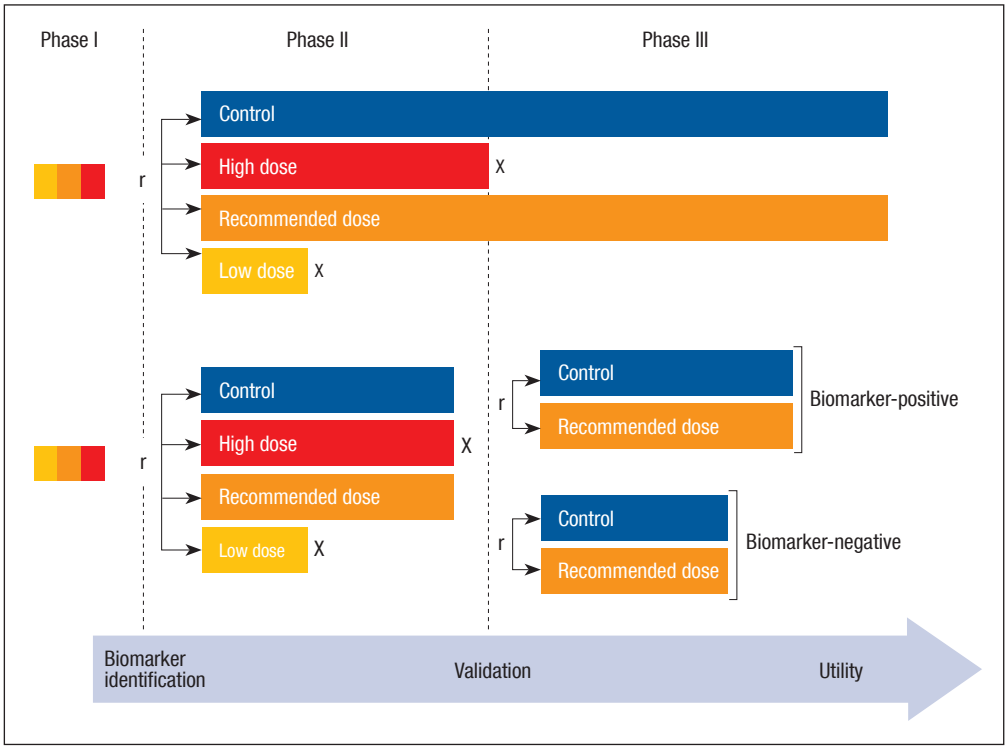

Figure 2: Patient randomization in the continuum of drug and/ or biomarker development

CCND1 copy number. Accordingly, patients were treated with erlotinib, vandetanib, erlotinib plus bexarotene, or sorafenib. BATTLE contained two randomization phases: initial equal randomization (n = 97), which was fixed, and adaptive randomization based on relevant molecular biomarkers analyzed in fresh core needle biopsy specimens (n = 158). As the authors noted, BATTLE took a substantial step toward realizing personalized lung cancer therapy by integrating real-time molecular laboratory findings in delineating specific patient populations for individualized treatment.

LUNG-MAP: umbrella trial containing phase II comparisons

Another renowned umbrella study for lung cancer is LUNG-MAP (SWOG1400) that assessed patients with squamous histology in the second-line setting [17]. Once eligibility was determined, patients underwent screening for mutations and amplifications of interest. They were classified into four groups according to the presence of driver aberrations for *PI3K, CDK 4/6, FGFR,* and *HGF.* Randomization within the PI3K, CDK 4/6 and FGFR groups occurred to either targeted therapy or chemotherapy. In the HGF cohort, the specific treatment was compared to erlotinib. Overall, these were four randomized phase II trials conducted in parallel within mutation-enriched cohorts.

The LUNG-MAP design allows for seamless integration of new cohorts without regulatory approval, as introducing new molecular groups into the protocol was possible via nomination by the Drug Selection Committee. Phase II patients are included in the phase III analysis, thus contributing critical additional length of follow-up. As with other randomized trials, challenges can arise from standard treatments changing, which means that control arms might have to be adjusted. One cohort of the LUNG-MAP study closed prematurely for toxicity concerns when it became apparent that one of the study drugs had caused harm in patients with gastric cancer. Innovative prospective clinical trials that will more clearly define the value of matching targeted agents to genomic alterations are ongoing. ■

Take home message

Biomarker-stratified trials help to identify predictive biomarkers in cancer management, while enrichment studies enable efficient testing of a specific treatment in a biomarker-positive population. Modern oncology trials increasingly show no clear distinction between the phases II and III. Dose finding and assessment of drug activity occur in parallel. Adaptive phase II/III trial designs include the basket trial, which contains patients with different tumors that harbor the same driver mutation, and umbrella trials, which are aimed at investigating different targeted drugs in a single tumor type.

Alois Sillaber

Journal selection and manuscript preparation

Publishing a paper is an important step in a scientist's life, but it has to be preceded by many considerations to make sure that the effort related to it is worthwhile. Even before starting to write, scientists should question their own motives to publish their work. Are the data new and interesting? Is this a current hot topic? Does one's research involve difficult problems? Is the work ready to publish at this point? Is it important to one's career? These questions should be answered satisfactorily before embarking on the project.

TABLE 1
Factors to consider when selecting a journal

Appropriate for one's message?
Publishing frequency
Impact factor
Target audience
Is the journal peer-reviewed?
Who are the editors?
Average time to publication
Rejection rate
Aims and scope
Open access or subscribers-only journal?
Are any payments required?
What types of manuscripts does the journal accept?

Types of manuscripts

- Full articles/original articles represent the most important type of publication. They often contain substantial and significant pieces of complete research.
- Letters/rapid communications/short communications offer quick and early communication of significant and original advances. These are much shorter than full articles; therefore, it is advisable to ascertain limitations in advance.
- Review papers/perspectives summarize recent developments on a specific topic and highlight important previously reported points. Review articles are not the place for introducing new information. They are frequently published on invitation only.
- Case reports give an overview of a case and provide important learning points. However, not every journal accepts them.

Selecting a journal

Given the diversity of available journals, the selection of an adequate journal is not an easy task. It is important to collect as much information as possible and to have some of idea of possible target journals before writing. **Table 1** lists factors to consider in this process. Perform-

ing keyword database searches, browsing publisher websites and reading journal requirements carefully helps to build a list of possible target journals. A necessary step before deciding on the journal is self-evaluation:

- What is the focus of my work?
- Who will be interested?
- How significant are my results?
- Where have similar articles been published?

Being aware of differences among journals, authors should know what their priorities are. Reduction to a short-list and ranking journals according to priority can narrow down choices. Pre-submission enquiries are provided by publishers as a service to authors who wish to confirm that their paper is of interest to a particular journal. It can be helpful to ask one's mentor and colleagues for advice on the type of manuscript, as sometimes outsiders can see things more clearly.

At https://journalsuggester.springer.com/, authors find a tool that provides support in identifying the suitable journal. Upon entry of details such as the manuscript title and the minimum impact factor and selecting the subject area as well as the type of journal, the Journal Suggester will present a list of journals including information for each, such as the time to publication and rejection rates.

The impact factor is the currency of a publication and has relevance for journals, research funders, universities and authors alike. It is calculated using the number of citations divided by the total number of articles published within two years. A listing of impact factors of various journal can be found at the website https://jcr.incites.thomsonreuters.com.

Structure and writing

It is commendable to read the instructions for authors as provided by the publishers at an early stage. Journal guidelines are important for two reasons. For one, not adhering to them can be used by the editors as a reason for rejection. Moreover, if guidelines are observed, time to publication is reduced.

Structure on one hand and writing on the other are important pillars of a good manuscript. The classical structure of a paper is detailed in **Table 2.** Title pages usually contain information on the author(s), affiliation(s), conflict of interest statements, and funding information. Abstracts should be concise and include all variables, but not exaggerate the data. The body of the main text is divided into introduction, materials/ methods, results, and discussion. Tables and Figures need to be provided along with their legends.

With regard to writing, an important point is finding an appropriate and discoverable title. Discoverability represents a significant feature that will make the paper stand out as physicians search for publications online. The paper should be formatted to best showcase the material. A good manuscript contains a clear, useful, and exciting scientific message. The text flows in a logical manner that the reader can easily follow. Most publishers offer language-editing services for scientists who are no native speakers of English.

TABLE 2
Structure of a manuscript

Title, authors, contacts, keywords, conflict of interest statements, funding
Abstract: concise, of appropriate length, includes all variables
Introduction: thorough, conceptual framework, review of the literature, explanation why this particular study is needed
Materials/methods: inclusion of adequate details
Results: detailed description with tables and graphs
Discussion: coverage of findings and implications, pitfalls and necessity of future research
Acknowledgements: citation of funders and other assistance
References: citation of all works in the same area
Tables/figures
Table/figure legends
Appendices

Do's and don'ts

It is highly recommended to observe the following rules of conduct:

- Reply efficiently and in a timely manner to questions, e.g. regarding figure resolution, consent to publish, or language polish
- Use an email address with your institute suffix (no private e-mails)
- Make payments to the publisher promptly, such as the article processing fee or the color figure fee

The following should be avoided:

- Breaking the ethical rules
  - human research (Declaration of Helsinki)
  - clinical tests (ethics committee approval)
  - publishing ethics (Committee on Publication Ethics, COPE)
- Changing the author name(s) after submission
- Fabricating data

The path to publication

After the submission of the article, the chief editor or his associate editor will decide if they accept or reject it. In case of acceptance, the peer review process will start. The author will receive comments from the reviewers and have the possibility of revising and resubmitting the text. Subsequently, another round of revising and resubmitting might take place. If the article is accepted, a proof will be sent to the author, after whose approval the paper will be published. Publishers frequently offer article tracking services that inform the authors about the status of their papers in different stages. ■

Take home message

A manuscript should only be written if the data are relevant to the scientific community. The selection of a journal depends on a number of variables, including the envisaged type of publication, target audience, impact factor, average time to publication, and rejection rate. Author's guidelines should be read early on, and certain rules of conduct need to be observed. Important factors of success pertain to the structure of the text and the quality of writing.

Nik Zeps

The peer review

Clinical research has tangible outcomes that translate into improvements to health care. Besides the improvements to outcomes for patients and development of novel clinical management, a recent evaluation on clinical trials in the academic setting revealed that for every dollar spent there was a 5.1 dollar return based upon savings to the health system and the community; this is something that only very few industries can demonstrate. Given that clinical research is extremely important, it is essential that an efficient and effective peer review process is in place to ensure that high-quality medical progress is maintained. Much of the funding for medical research comes from the taxpayer and the community and there is an obligation to ensure that the money is well spent and researchers are held accountable for any funding they receive.

Peer review, which is a form of criticism that is both subjective and objective, should be constructive and helpful. It should respect the fact that authors who submitted a paper made great efforts in doing so. Therefore, it is not appropriate if reviewers correspond with scientists in a manner that is derogatory to them. At the same time, they should exercise due care when reviewing papers. Editors depend on reviewers to do a thorough job in a timely fashion, which also includes reviewing the literature to ensure the work is presented in its appropriate context, that the statistical modeling is appropriate and robust and that all Tables and Figures are clear, necessary and helpful. An attentive reviewer is more helpful than one who approves of a text that harbors mistakes.

However, Schroter et al. showed that the review process often lacks care [18]. They introduced nine major and five minor deliberate methodological errors into a paper and sent to it 420 peer reviewers. The median number of errors detected by the respondents was only two, and no one managed to spot more than five deliberate errors. Sixteen percent of responders could not find any mistakes at all. This is of great concern and suggests that greater care should be taken in selecting reviewers and that perhaps greater training in how to do a peer review is provided through undergraduate and postgraduate education.

Potential peer review fora that can raise the quality of one's work even before submission consist of colleagues who are engaged in reviewing the research during hypothesis generation, method development, and discussion of results. Collaborations (interdisciplinary fora) are an ideal format for receiving peer review, as well as team meetings, departmental meetings, grant writing workshops, seminars, conferences, community engagement, and stakeholder consultations. ■

Take home message

The review process is aimed at increasing the quality of published research. It should be constructive and helpful and should be performed with care. However, findings show that mistakes tend to be overlooked and that there can be very long delays in getting published.

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