Sistemske napake kliničnih raziskav

Kljub skrbnemu planiranju in izvajanju kliničnih raziskav se ne moremo izogniti sistemskim napakam v samem postopku raziskave. Omenjene napake v klinični raziskavi lahko vodijo do zaključkov, ki niso realni; razlike lahko povečamo, pomanjšamo ali celo obrnemo. Ugotovitev vzroka napak in njihov obseg so izjemnega pomena za klinično raziskavo. Večja je sistemska napaka ali »bias«, večja je možnost za napačne statistične rezultate. Sistemske napake so tako stalna nevarnost za klinične raziskave. Raziskava, pri kateri je prisotna vsaj ena sistemska napaka, velja za neustrezno.

Kot nesporna velja raziskava, pri kateri je 95 % ali več udeležencev znotraj metod brez sistemske napake (1, 2). Odkritje vzroka za »bias« in obseg ukrepov za njihovo zmanjšanje so za klinične raziskave osnovnega pomena. Kljub skrbnemu načrtovanju in izvajanju se sistemskih napak pri kliničnih raziskavah ne moremo izogniti. Skrb, da jih omejimo, je glavni znak kvalitete raziskave in je obenem najpomembnejša za točnost rezultatov. Kadar »biasa« ne moremo izključiti, je potrebno njegov vpliv na vrednotenje rezultatov oceniti, in to kolikor je le možno natančno. Sistemske napake se ne odpravijo s povečanjem števila preiskovancev, ampak le z zmanjšanjem napak. Odpraviti jih moramo že v samem planiranju raziskave. Randomiziranje in slepi poskusi so najpomembnejši mehanizmi zaščite. V medicinskem raziskovanju najdemo več kot 100 oblik sistemskih napak ali podobnih pojavov (3, 4). Večino teh možnih napak poznamo, saj so bile opisane že pred 50 in 60 leti (2, 5).

GLAVNI VZROKI SISTEMSKIH NAPAK RAZISKAVE

Sistemske napake predstavljajo resen izziv za kvaliteto kliničnih raziskav. Lahko so vzrok, da celo metodično pravilne raziskave vodijo do rezultatov, ki se odmikajo od pravih vrednosti. Statistika je pri prisotnih sistemskih napakah v raziskavi nemočna. Le

Systemic errors in clinical studies

Despite careful planning and implementation of clinical studies, systematic errors occurring during the course of the research cannot be avoided. In a clinical study, such errors can lead to conclusions that are not realistic. These errors can be increased, minimized or even reversed. Finding the cause and scope of such errors are of exceptional importance in a clinical study. The greater the systematic error or 'bias', the greater the possibility for erroneous statistical results becomes. Systematic errors are, therefore, a constant danger for clinical studies. A study is considered to be unsuitable if at least one systematic error is present.

A study is presumably beyond dispute when 95% or more of the results included within the study are without a systematic error (1, 2). The discovery of the cause of the 'bias' and the scope of measures for their reduction are of primary importance for clinical studies. Despite careful planning and implementation, one cannot avoid systematic errors in clinical studies. The concern taken in limiting such errors is a principal indicator of the quality of a study and is simultaneously of the utmost importance for the accuracy of results. When the 'bias' cannot be excluded, it is necessary to assess, as thoroughly as possible, its influence on the evaluation of the results. Systematic errors are not eliminated by increasing the number of examinees, but with the reduction of errors. Such errors should be addressed during the study planning phase. Randomization and blinded experiments are the most important mechanisms of protection against such errors. Nevertheless, more than 100 forms of systematic errors or similar phenomena have been identified in medical studies (3, 4). The majority of these possible errors are known, as they were described between 50 and 60 years ago (2, 5).

MAIN CAUSES OF SYSTEMATIC ERRORS IN STUDIES

Systematic errors represent a serious challenge for the quality of results relating to clinical studies and

obvladovanje napak in ustrezni preventivni ukrepi so pogoj za pravilne rezultate in pravilne zaključke raziskave. Da smo pri tem uspešni, je pomembno, da potencialne vzroke napak odkrijemo, kar pa predstavlja pri vsaki raziskavi zahtevno in težko nalogo.

Sistemske napake se lahko pojavijo v različnih fazah raziskave, to pomeni pred raziskavo, med in po njej. Sistemske napake raziskav v medicini lahko razdelimo glede na šest osnovnih vzrokov, in sicer:

1. izbor literature,
2. zasnova raziskave vključno z izborom raziskovalnih skupin,
3. izvajanje poskusov in dokumentacije podatkov,
4. analiza podatkov,
5. interpretacija podatkov,
6. objava rezultatov.

Večine sistemskih napak se z večjo skrbnostjo pri planu in izvedbi raziskave ne da odpraviti, ampak samo zmanjšati. Ugotavljanje sistemskih napak je osnovni element in podlaga za oceno znanstvene kvalitete.

Neodvisno od tega omogočajo presejalni programi (kot so Cochrane risk of bias tool for randomised trials za randomizirane raziskave, QUADAS 2 za raziskave, kjer se preverja natančnost diagnostičnih testov, ROBIS za sistematične preglede ali ROBIS-1 za nerandomizirane intervencijske raziskave) dobro pomoč pri odkrivanju potencialno možnih vzrokov napak pri kliničnih raziskavah (6, 7, 8).

1. Izbor literature

Izbor literature lahko odločilno vpliva na raziskavo in končne rezultate. Glavni vzroki napake so preferenca določenih tem, preferenca določenih publikacij in preferenca pozitivnih rezultatov. Pri izboru literature se pogosto izbira literatura, ki s svojimi pozitivnimi rezultati projekt podpira. Navdušenje nad raziskovalno idejo lahko vodi do tega, da raziskovalci rezultatov predhodnih raziskav, ki so nasprotni, ne vrednotijo ustrezno. Da preprečimo to obliko biasa oz. napake, moramo literaturo pravilno izbrati, kar lahko zagotovi samo raziskovalec (9, 2, 10–13).

can cause a deviation from true values even in studies that have followed the correct methodology. Statistics are worthless where systematic errors are present in a study. During a study, accurate results and conclusions can be obtained only when errors are managed and appropriate preventative measures are in place. In order to be successful in this, it is important to discover potential causes of such errors in each study. This represents a demanding and difficult task.

Systematic errors can occur prior to the implementation of the study, during the course of the study, and following the conclusion of the study. In clinical studies, six basic causes of systematic errors have been described and include:

1. choice of literature,
2. study design, including the choice of study groups,
3. implementation of experiments and documentation of data,
4. data analysis,
5. interpretation of data,
6. publication of results.

The majority of systematic errors cannot be eliminated through greater care in planning and implementation of a study, but can only be reduced. Finding systematic errors is a basic element and basis for the estimation of the quality of the scientific research.

Independent of this, screening programmes such as the Cochrane risk of bias, QUADAS 2, and ROBIS or ROBIS-1 facilitate good assistance in discovering potential causes of errors in clinical studies (6, 7, 8). The Cocharane programme is useful for randomised trials or studies, while QUADAS 2 is used to assess the quality and diagnostic accuracy of studies. ROBIS and ROBIS-1 are valuable in systematic reviews and non-randomised interventional studies, respectively .

1. Choice of literature

The choice of literature can have a decisive influence on a study and the final results. The main causes of an error include a preference for certain themes, publications, and positive results. Often, literature with

2. Zasnova raziskave vključno z izborom raziskovalnih skupin

Napake pri protokolu raziskave in preiskovancih so tako številne, da so lahko dokazane skoraj v vseh raziskavah. Najpogostejši vzroki napake so usmerjena zasnova raziskave, izvajanje raziskave v določenih specializiranih centrih, različne možnosti dia-gnostičnih postopkov, pozna vključitev obolelih, izbira testiranja, primerjave s prejšnjimi skupinami z napačnimi podatki, napaka v izboru referenčnih standardov, izboru preiskovancev, določitve podskupin itd. (14–17).

3. Izvajanje poskusov in dokumentacije podatkov

Pri pridobivanju in registriranju rezultatov raziskave lahko nastanejo številne težke sistemske napake, večinoma zaradi različne prognoze skupin, sodelovanja udeležencev, izključitve iz raziskave zaradi negativnih rezultatov, zaradi razlik med raziskovalnimi skupinami, zaradi dodatne terapije, vpliva procesa učenja itd. Do sistematske napake rezultatov raziskave pride, če enaki postopki pri različnih skupinah niso izvedeni enako (18).

4. Analiza podatkov

Pri analizi podatkov lahko nastanejo sistemske napake zaradi napake v definiciji pomembnosti podatkov, zaradi izključitve manj ali zelo pomembnih rezultatov, zaradi vključitve bolezni s počasnim potekom, zaradi bolezni, ki se pri bolniku še niso manifestirale, zaradi nezmožnosti spremljanja itd. (19–21).

5. Interpretacija podatkov

Napake zaradi analize podatkov so relativno majhne, so pa pomembne, saj prikažejo končne rezultate raziskave. Glavne napake pri interpretaciji podatkov so napaka zaradi istočasne analize korelacije in vzročnosti, zaradi osebne interpretacije in zaradi retrospektivnih raziskav (2, 22).

6. Objava rezultatov

Sistemska napaka, ki nastane pri objavi rezultatov raziskave, je lahko odvisna od avtorja in tudi od izdajatelja oz. založbe. Najpogosteje je to zaradi osebnih lastnosti avtorja ali avtorjev, zaradi izbora recenzentov, zaradi neobjave rezultatov raziskave. Ključno za

positive results that supports the project at hand is chosen. Enthusiasm for an idea of a study can lead to situations in which researchers do not adequately evaluate opposing results of prior publications. To prevent this form of bias or error researchers have to ensure that literature is chosen correctly (9, 2, 10–13).

2. Study design, including the choice of study groups

Errors in a study protocol and in examinees are so numerous that they can be demonstrated in almost all studies. The most common causes of errors include experimental design (e.g. directional study designs), implementation of a study in specialized centres, variable diagnostic procedures, belated inclusion of the ill, comparisons to data erroneously generated by other research groups, the choice of experimental controls, the choice of examinees, and the determination of subgroups (14–17).

3. Implementation of experiments and documentation of data

During the acquisition of study results, numerous large systematic errors can occur. These are mostly due to variable prognoses of groups, participant cooperation, patient exclusion from a study due to negative results, differences among study groups, the patient's need for additional therapy, the influence of the learning process during the course of the study, etc. Variation during the implementation of study procedures across various groups can also cause systematic errors (18).

4. Data analysis

In data analysis, systematic errors can occur due to an error in the definition of the importance of data, the exclusion of less or very important results, the inclusion of illness with a slow course or which have not yet manifested in a patient, and the incapability of monitoring, etc. (19–21).

5. Interpretation of data

Errors due to analysis of data are relatively small, but are important as they show final study results. Core data interpretation errors are due to simultaneous

preprečevanje sistemskih napak – conditio sine qua non – je registracija kliničnih raziskav v javni bazi podatkov. Pogosteje so objavljeni rezultati tistih raziskav, ki imajo statistično pomembne rezultate. S to napako se srečujejo avtorji pri metaanalizi. Posebno vlogo pa ima statistična napaka pri oblikovanju smernic (23–25).

Če hočemo, da je raziskava uspešna, je potrebno vse potencialne sistemske napake raziskave razumeti, odkriti in označiti. Samo na tak način lahko pridemo do objektivnih realnih rezultatov, ki resnično prispevajo k napredku znanosti v korist človeka. To je še toliko pomembnejše na področju medicinskih znanosti, saj je to področje še posebej občutljivo in so lahko napačni zaključki raziskav vzrok za nepredvidljive posledice.

Cuiusvis hominis est errare, nulius nisi insipientis in errore perserverare. (Cicero)

Vsak se lahko zmoti, a samo bedak bo v zmoti vztrajal.

Prof. dr. Dušica Pahor, dr. med.
odgovorna urednica

analysis of correlation and causation, subjective interpretation of results, and conducting retrospective studies (2, 22).

6. Publication of results

A systematic error that occurs in the publication of study results can depend on an author and also on a publisher or publishing house. This happens most frequently due to the subjective characteristics of an author(s), choice of peer reviewers, and unpublished study results. Crucial in preventing systematic errors, conditio sine qua non, is the registration of clinical studies in a public database. However, studies that have statistically significant results tend to be more frequently published – an error that is revealed during meta-analyses of results. Statistical errors thus play a special role in the formation of guidelines surrounding clinical research (23–25).

In order for a study to be successful, it is necessary to understand, discover and label all potential systematic errors. Only in such a way we can achieve objective and realistic results that contribute to the progress of science. This is extraordinarily important in the field of medical sciences, as this discipline is especially delicate since erroneous study conclusions can cause unforeseeably negative consequences.

Cuiusvis hominis est errare, nulius nisi insipientis in errore perserverare. (Cicero)

Anyone can err, but only the fool persists in his fault.

Prof. Dušica Pahor, MD, PhD,
Editor-in-Chief

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