Methods and Biostatistics in Oncology

Understanding Clinical Research as an Applied Tool

Raphael L. C. Araújo
Rachel P. Riechelmann
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Foreword

It is my pleasure to introduce this volume "Methods and Biostatistics in Oncology—Understanding Clinical Research as an Applied Tool." It is a timely contribution to clinical research in oncology as we experience an unprecedented increase in the number of clinical scientists and clinical studies all around the world. Important advances in our understanding of several topics, such as genomics, immunology, targeted treatments, and biomarkers, capture headlines in the popular press. As translational efforts to use these advances in the clinic intensify, the need for appropriate clinical research methodology has never been greater. It is for this reason that this volume will serve an important need.

Dr. Araújo's and Dr. Riechelmann's editing skills are apparent in the team of authors they have recruited and the topics they have chosen. Each of the book's 20 chapters has been written by one or more internationally recognized experts in the field. The chapters cover substantial ground, starting from a historical introduction and moving on to study design. Several important technical aspects, such as the interpretations of multivariate analysis and survival analysis, and descriptions of case-control and cohort studies, are aptly included. Clinical trial design receives the attention it deserves and emerging fields such as cost-effectiveness and patient-reported outcomes are also included. These chapters can be read sequentially like a textbook, which will be valuable for those who are in the early years of their clinical research training or careers. It would be a mistake, however, to think that seasoned investigators will not benefit from this volume. Since most clinical researchers lack comprehensive formal training in methodology, their knowledge of statistical methods is limited. I would urge them to pick up this volume and read the chapters that interest them. They will find that the chapters are self-contained and not demanding.

My primary advice to the reader is to come back to the chapters as they need to apply the material to their own work. This may, most commonly, be the research they are engaged in. If preclinical work has yielded a result ready for clinical testing, rereading the chapter "How to Design Phase I Trials in Oncology" will reveal the subtleties of the presentation and will, no doubt, increase retention of the knowledge. There are more opportunities to relate this material to work, however. If one is refereeing a paper and the survival analyses are puzzling, if one is mentoring a student who is struggling with a multivariate analysis, or if one is reading an article with a cost-effectiveness analysis there will be much to learn by visiting the relevant chapters.

This book also stands apart because it has a separate chapter for bias (my favorite topic). The word originates from Bias of Priene, one of the seven sages of ancient Greece who thought and wrote a great deal about justice and fairness. It is ironic that we use his name to refer to certain types of prejudice and, in the scientific context, a systematic dissonance between the findings and the truth. Bias is widely recognized as a threat to the validity of a study, to the point that several types of commonly encountered biases have earned their own names, such as selection bias, verification bias, recall bias, etc. Bias is possibly the single most important concept in research methods and yet it might be the most misunderstood one. Bias usually arises from systematic differences between the sample analyzed and the population for which conclusions are drawn. Bias can be due to deficiencies in design; inadequacies in data collection; and legal, ethical, or other constraints. I am heartened to see bias receiving coverage in this volume, because it is even more important to consider bias in the age of big data, where automated data collection and the ability to merge disparate data sources leads to a huge amount of observational data and also makes it more difficult to understand what sorts of biases might have crept in. Some well-publicized failures such as Google Flu Trends and the Boston Pothole Experiment point to the importance and difficulty of detecting biases.

Let me finally make the point that the understanding of research methodology and statistics remains challenging, requiring great intellect and creativity. There is a big gap between results obtained by pushing a button or executing a command in data analysis software, and gaining knowledge and insight from these results, and this gap can be closed only by having a good grasp of research methodology. That is why you should read this book and recommend it to others.

New York, NY, USA Mithat Gönen

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Brief History of the Scientific Method and Its Application in Oncology

1

Vinicius de Lima Vazquez and Raphael L. C. Araújo

1.1 Ancient Science

The first step taken on the way to the scientific method was the cognitive revolution that occurred in our species nearly 70,000 years ago. Within the domain of language, it was possible to create vast collaborations among individuals, with abstract common values. This cognition allowed us to make the first attempts to explain our world, with myths and gods, many of them anthropomorphic. After the agricultural revolution, circa 10,000 BCE, and more recently (1000–500 BCE) with the development of writing and the rise of political and monetary systems, the first attempts to explain nature in a systematic way, and not in supernatural terms, began to flourish.

The first Western thinkers arose in ancient Greece and they utilized the observation of natural phenomena in developing theories based on those observations. Thales of Miletus, one of these pioneers, theorized that water was the origin of all forms in the universe.

The evolution of ancient Greek science took about 700 years and was an astonishing example of how an organized society where free thinking and education are greatly valued can flourish, albeit that education was available only to a minority. This environment gave to humankind great philosophers who enormously influenced our past and present knowledge. Plato and Aristotle were the transcendent figures of their times. Plato gave us, among other brilliant concepts, the concept of dualism and the value of ideas or an ideal world, as well as theories of mathematics. Aristotle, on the other hand, valued observations and gave us rules of nature

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summarized in a methodical way. His six-book collection on logic, *Organon*, which set the basis of rational enquiry, was a tool used for thinking about and understanding nature for more than one thousand years. Aristotle also proposed four kinds of causation in nature: matter (material cause), form (formal cause), agent (efficient cause), and end (final cause). The ancient philosophers also developed a four-element explanation of the constituents of nature (earth, water, air, and fire).

Medicine was a highly intellectual profession in ancient Greece and in the Roman Empire. Galen (Claudius Galenus 129–216 CE) was a prominent Roman physician and philosopher in his time. He made extensive anatomical observations and promoted the theory and the typology of human temperaments according to an imbalance in the four bodily fluids. In parallel to the four elements of nature, the four bodily fluids were regarded as black bile or melancholia, yellow bile, blood, and phlegm. According to his theory, diverse diseases with diverse features and severity would occur in relation to different imbalances. Galen's writings were followed for centuries and were apposite with the classical Greek fundamental idea that the universe is perfect and that what goes wrong is related to deviations of the universal proposal for all things.

1.2 The Middle Ages and the Arabic Influence

Christianity and the disruption of the Roman Empire transferred the development of scientific thought to the Arabic realm, which blossomed in the Middle East during the Middle Ages. Many sciences flourished in this region during that time, with the most dramatic discoveries arising from mathematics and medicine. Some of the lost ancient knowledge was secretly preserved in Catholic monasteries in Europe, while some ancient books were translated into Arabic, and were studied and interpreted in Arab lands as a basis of new discoveries. In the late Middle Ages, many such books traveled back to the West.

Aristotelian thought matched Christian theology. William of Ockham, Siger of Brabant, Boethius of Dacia, and, mainly, Thomas Aquinas (1225–1274) brought a rational approach toward understanding nature, which they saw as a divine creation. In Europe, universities such as the University of Oxford, the University of Paris, and the University of Padova, among the oldest of the European universities, were established and Aristotelian/Galenic thought became solid and traditional. The main assumption was that perfect wisdom belonged to the past, and it was understood that no effort was needed to generate knowledge, but the task was to learn and recover knowledge from the ancients.

1.3 The Renaissance and the New Scientific Method

The new world discoveries in the late fifteenth and early sixteenth centuries shook and irreversibly changed the European way of thinking. The heliocentrism of Copernicus, Galileo's telescope, and other theories and technologies showed a

different version of the natural world. Scholastic Aristotelian thought was not relevant anymore.

In 1543, Andreas Vesalius, in his masterpiece *De Humani Corporis Fabrica*, demonstrated human anatomy in bright new colors. His work was the result of systematic and meticulous dissections of human corpses and showed many differences from the traditional anatomy of Galen. Different from Vesalius, Galen, obeying the Roman law, dissected monkeys, dogs, and other animals, but not humans. Further observations from William Harvey correctly described the circulation of the blood in humans, and the ancient fluid imbalance theory of Galen was disproved. A new way to explain and to explore the complexity of the world was necessary. Could a suitable method be found?

1.3.1 The "Magic" World and Natural Philosophy

Since the Middle Ages, there had been a "magical" way of observing and classifying knowledge related to practical and unexplained phenomena, using methods such as alchemy and theories of magnetism, among others. During the Renaissance, for the first time, these natural or manipulated phenomena started to attract intellectual attention and attempts were made to explain what were previously considered as curiosities or bizarre happenings with occult and supernatural causes by reference to the same forces or laws conceived as governing all of nature. One beautiful example of such intellectual examination was the treatise *De Magnete* (1600), by William Gilbert, where a very well-known technology, utilized by sailors of the time for navigation, was depicted in detail and where Gilbert concluded, in very demonstrative and elegant form, that the Earth is similar to an enormous magnet.

Francis Bacon, in a world very confused by the rupture of the scholastic model, proposed a new method of natural philosophy, later called natural science, with branches such as biology and all life sciences. His *Novum Organum* (new instrument) (1620) was ambitiously intended as a substitute for Aristotle's *Organon*. Briefly, Bacon defined empirical methods to explain nature, using induction after real observations (empiricism) instead of deduction (which is supported by impalpable and weak elements). This became known as the Baconian method; with this method, observations must be as extensive as possible to rule out unexpected manifestations, and the simplest explanation of causation should be sought. Interestingly, the method opened possibilities of new answers for old questions.

Rene Descartes was another great thinker who modeled our methods in sciences. In French society, where skepticism was growing as an answer to the absence of reliable ways to understand nature, he framed his thoughts and arguments to resist the skeptics' attacks. His famous statement *Cogito ergo sum*, translated as "I think, therefore I am", is much better interpreted as "I doubt, or I question, therefore I am". The doubt or question was the first and core principle of the four principles in his method, explained in his famous book *Discourse on the Method* (1637). The first principle can be explained as that a supposition would last only if it could stand after all questions have been asked. In his own words: "The first was never to accept

anything for true which I did not clearly know to be such; that is to say, carefully to avoid precipitancy and prejudice, and to comprise nothing more in my judgment than what was presented to my mind so clearly and distinctly as to exclude all ground of doubt". His other principles are still important in the methods of modern sciences. The second principle is "to divide each of the difficulties under examination into as many parts as possible, and as might be necessary for its adequate solution"; the third, "to conduct my thoughts in such order that, by commencing with objects the simplest and easiest to know, I might ascend by little and little, and, as it were, step by step, to the knowledge of the more complex; assigning in thought a certain order even to those objects which in their own nature do not stand in a relation of antecedence and sequence". And the last principle is "in every case to make enumerations so complete, and reviews so general, that I might be assured that nothing was omitted." Descartes was also a brilliant mathematician, and mathematics is part of the understanding of his method. For him, the sharpness of calculus should be applied to the methods of science, for the precision of results and the search for truth. He contributed to the use of a methodology as an important point to both prove and reproduce experiments. More than this, according to him, precision was the only way to achieve answers. These concepts were powerful and still resound nowadays.

Sir Isaac Newton (1643–1727) was one of the most prominent scientists in human history. His discoveries, in mechanics, optics, mathematics, and other fields, were revolutionary. He demonstrated, with the power of mathematics, the classic laws of mechanics and this was well aligned with the methods of Descartes, paving the way for the modern scientific method.

1.4 The Industrial Revolution and the Birth of Clinical Cancer Research

Modern medicine and the rise of contemporary oncology and clinical cancer research were shaped, as we know today, after the industrial revolution of the nineteenth century. The technology acquired during this period allowed new discoveries to be made and opened possibilities for surgery, radiation therapy, and more recently, the use of antineoplastic drugs.

James Lind from Scotland is considered to be the first physician to have conducted a clinical trial. On a ship, in 1747, when trying to treat widespread morbid scurvy, he designed a comparative study in which twelve sailors with scurvy were allocated to two groups, each with a different diet complement every day. When Lind observed the results, he found that the consumption of oranges and lemons (sources of vitamin C) led to cure of the disease.

The idea of the placebo arrived in the 1800s. Dr. Austin Flint, in the United States, when studying rheumatism, had the idea of giving a herbal "placebo" compound instead of an established medicine. He published details of this experiment in his book *A Treatise on the Principles and Practice of Medicine* (1866). Some patients receiving the "placebo" compound actually improved and he concluded

that this was because of the confidence patients had in the treatment they believed they were receiving.

Controlled, blinded, and '*a posteriori*' randomized trials were first designed and conducted in the late 1940s and 1950s. During that time there were great advances in epidemiology and biostatistics. Ronald Ross, Janet Lane-Claypon, Anderson Gray McKendrick, and others introduced the mathematical method in epidemiology. In the field of oncology, the seminal work of Doll and Hill, in the British Doctors Study (1956), introduced the statistical concept of the hazard ratio and proved that tobacco consumption led to a higher risk of lung cancer. All these concepts and tools in research methods were crucial to the development of modern oncology.

Further, the two world wars had a great impact on the rise of clinical research. The unethical human experiments performed before and during World War II endorsed by the German government were the result of a policy of racial hygiene, in pursuit of a pure "Aryan master race". In 1947, during the Nuremberg War Crimes trials, the Nuremberg Code was established. The Code states that, for any research in humans, the subjects of the research must give their full consent and participate voluntarily, and there must be no unnecessary or unsafe exposure of the participants to any agent or procedure. The Code was based on the principle of giving benefit and doing no harm to the participants. Almost 20 years later, in 1964, the Declaration of Helsinki was made by the World Medical Association and this provided another cornerstone in clinical research practice. The Declaration holds that all research in humans should be based on a scientific background, with putatively more benefits than risks; new treatments should be compared with actual standard treatments, and approval of the project must be obtained from an independent committee of ethics in research (for instance, an institutional review board); there must also be a declaration of any conflict of interest, among other factors.

Historically, the first curative treatment for cancer was surgery. Although it started empirically, far from the modern methods, based on hits and misses, it represented a fantastic advance for modern medicine. At the end of the nineteenth century, William Stewart Halsted, acclaimed by many as the father of surgical oncology, systematically observed the results of his mastectomy surgeries. He noticed that recurrences occurred in a very predictable pattern and he created a new surgical technique, which included a more aggressive approach with resection of the pectoral muscles and the lymphatic nodes from the axilla. This radical (from the Latin word meaning "root") surgery became a model for oncological surgery overall for over a century, and "en-bloc" or "radical" resection remains as a common concept in surgical oncology. Only after the evolution of clinical research methods in the 1980s were new less aggressive surgical methods proposed, showing lower morbidity. These new surgical methods were accepted only because comparative studies demonstrated they were superior to the Halsted methods, with undeniable proof of benefit. For example, Umberto Veronesi, in Italy, and Bernard Fisher, in the United States, conducted randomized trials where they demonstrated that, for localized small breast cancer, local tumor control could be achieved with less aggressive surgery, adjuvant chemotherapy, and radiation therapy instead of total mastectomy.

This led to a paradigm shift in the idea of cancer treatment being exclusively surgical. Fisher proposed that when breast cancer presented an early hematogenous spread, then the lymph node involvement would simply represent systemic disease and not only locally advanced disease. This was the rationale for associated adjuvant treatment after breast surgery. Veronesi advocated breast-conserving surgery associated with adjuvant radiotherapy for local control, as well as chemotherapy for systemic treatment. Both these surgeons emphasized the importance of a multidisciplinary team for an oncological approach in treating cancer patients.

The use of radiation in medicine had a different course; it was described at the end of the nineteenth century by Pierre and Marie Curie, and it was used in oncology in the late 1930s to treat head and neck cancers. In the 1950s the use of cobalt teletherapy offered local treatment for many kinds of cancers. Radiotherapy also progressed to conserving techniques as the technology evolved to deliver doses with more precise techniques made available to give radiation to the target with less toxicity in the path of energy into the tissues.

The use of prospective controlled randomized trials is a milestone for clinical cancer research and for determining the standard treatment. The first such trial was conducted in breast cancer patients in 1968, comparing radical mastectomy (Halsted procedure) associated with thiotepa or placebo. This and other studies in breast cancer were carried out by a multicenter cooperative now called the National Surgical Adjuvant Breast and Bowel Project (NSABP), which Fisher led. These studies showed that better oncologic outcomes could be achieved by using a less radical procedure associated with adjuvant chemo- and radiotherapy, with less morbidity shown as well. With advances in the identification and stratification of clinical presentations of tumors, including clinical and demographic variations among individuals, multicenter trials became increasingly important. Increases in the sizes of study populations and the design and application of large phase III and IV studies clarified the effects of interventions over larger populations and showed more safety. To speed up the long and meticulous process of patient accrual, some studies became international, with dozens of centers involved.

Another successful advance in clarifying the methods involved in research in medicine and oncology was the concept of evidence-based medicine, developed in the 1990s. The scientific evidence of a new treatment or method could now be classified hierarchically according to different evidence levels (Fig. 1.1). This idea spread widely and became an important instrument for clarifying and showing the explicit quality of the research methods utilized in each study.

In parallel with this unprecedented advance, concerns about safety and ethics began to grow. To resolve such diverse concerns, other methods were introduced in the study designs to increase the safety of the participants. Safety monitoring and ethics committees were established, and good clinical practice guidelines policies, as well as a statistical calculus for endpoints and futility or early results presentation, became obligatory parts of experimental research in human beings. More recently, different initiatives have provided guidelines for methods of conducting clinical trials. Scientific and medical journals, government agencies and grants supporters require researchers to follow these guidelines. Some examples are shown in Table 1.1.

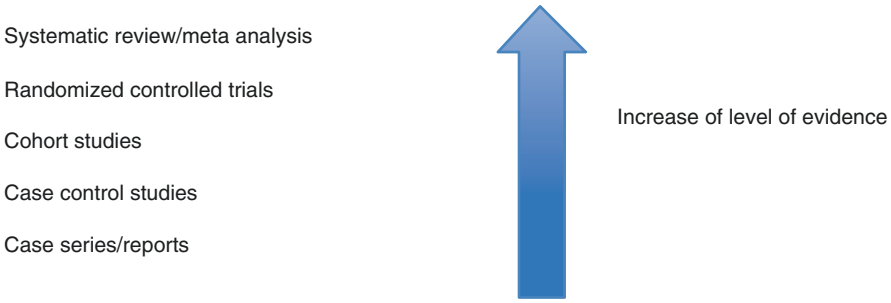

Fig. 1.1 Study design according to evidence-based relevance

Table 1.1 Methodological guidelines indicated for medical research, according to study design

Study design	Guideline
Clinical trial	CONSORT statement and EQUATOR http://www.consort-statement.org http://www.equator-network.org
Epidemiology, qualitative research, and mixed methods	STROBE and SRQR http://strobe-statement.org
Multivariable prediction models	TRIPOD http://www.tripod-statement.org
Routinely collected health data	RECORD http://www.record-statement.org
Systematic review	PRISMA http://www.prisma-statement.org
Quantitative PCR data	MIQE http://www.clinchem.org/content/55/4/611.long
Biomarker and association studies	REMARK http://www.nature.com/bjc/journal/v93/n4/full/6602678a.html

PCR polymerase chain reaction

1.5 The Future

The future of clinical research in oncology is a fascinating matter. Many recent advances in molecular methods and the immune landscape of tumors are bringing complexity to a whole new level. The implementation of next-generation sequencing and the massive output of genome, transcriptome, proteomic, and other molecular data, added to demographic and clinical data—exchanged and collected in the form of multi-institutional data for hundreds or thousands of individuals, some freely available in public consortia—are a challenge for the understanding of big data. Massive amounts of personal information have been collected and are available in real time, and this data, combined with results from the treatment of thousands of patients outside of clinical trials (where the treatment became approved), has led to new visions and new post-approval evaluation of treatments in "real patients", since the patients usually included in clinical trials have to be of good

general clinical status, and clinical situations away from the mean are, in most cases, excluded, for bias control. This colossal data is merging into a new fascinating frontier in oncology: molecular targeted therapy, which, added to new immunology discoveries, provides more personal and precise treatments for patients. New tools in bioinformatics have emerged to enable a search for new solutions to speed up and improve the accuracy of diagnostic and therapeutic interventions.

However, the present methods in use cannot answer many questions prompted by the myriad information gathered. We still do not know the answers we dreamed of in relation to human gene and molecular discoveries for shaping the promise of personalized medicine for each individual cancer patient. Nevertheless, the recent astonishing advances in communication, computation, and artificial intelligence suggest that we are certainly living in a fantastic new era where new—hitherto inconceivable—discoveries may be realized within a lifetime. New approaches in methodology are warranted, and for certain these will arise in the near future.

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Generating a Hypothesis for an Oncology Study

2

Beatriz Teixeira Costa, Isadora Santos Ferreira, and Felipe Fregni

2.1 Introduction

Clinical practice has long been recognized as a profession that combines clinical expertise with scientific evidence. At present, the need to be constantly updated while looking for new alternatives to improve patients' outcomes has transformed clinical research into an essential instrument for healthcare providers. However, the applicability of research findings to routine clinical practice remains incredibly challenging, as it requires in-depth knowledge and critical thinking.

Although the increasing number of studies throughout the past few decades has resulted in a positive impact on patients' lives, many questions remain unanswered. The eager need for breakthroughs and new ideas often makes researchers believe in a great number of misleading studies that do not take into account the basic aspects that characterize well-conducted research. Therefore, the relevance and validity of the studies must be a primary concern, considering that a great amount of scientific data does not always reflect high-quality information.

One of the first steps to be taken in conducting valid clinical research is to ask answerable and interesting questions. At a primary stage, it is fundamental to select a broad topic of interest and deeply explore the available literature in order to draw a line between the existing knowledge and the unknown. A review of published studies allows the recognition of current missing information, also

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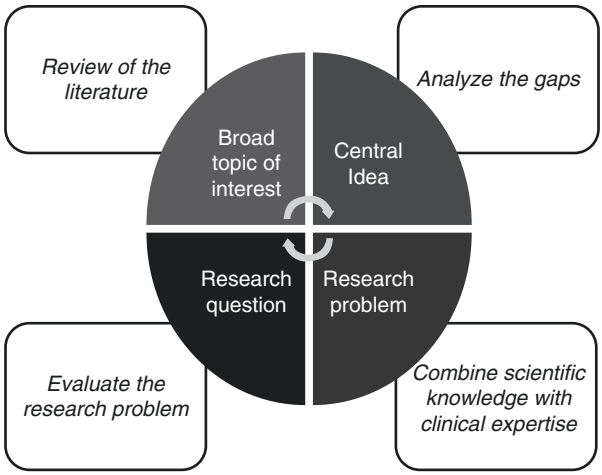

Fig. 2.1 Representation of the process for achieving a good research question

called gaps, and provides an essential rationale for identifying specific issues of importance. Also, it is useful to check clinical trials registrations to search and see what is being researched in the field. Throughout this process, the focus starts to convert a broad topic to a central idea. Thereafter, the combination of scientific knowledge with clinical expertise can be translated into a significant research problem (Fig. 2.1).

Choosing a relevant research problem in oncology is imperative for successfully conducting a study related to preventive, diagnostic, or therapeutic approaches. The challenging task, in fact, is to formulate a precise research question that contributes to and is complementary to the science in oncology. Also, the difficulty lies in finding questions that are simultaneously feasible and interesting. Indeed, questions can also be classified as low- and high-risk questions. Nonetheless, recent advances in oncology research have become a powerful incentive to overcome these barriers, thus leading to the development of well-conducted new studies and making progress against cancer.

2.2 Defining a Research Question

The process of defining a researchable question begins with the evaluation of a research problem and is directly related to the researcher's familiarity with a certain topic. Ideally, the question should be clearly stated at the end of the Introduction and must be as specific as the knowledge the investigator wants to gain. This will allow the investigator to properly answer the question within a given time interval. In addition, it is important to keep in mind that a research question must reflect what the investigator wants to know, an uncertainty about a problem that can be analyzed to obtain useful information.

Although the process is time-consuming and resource-demanding, the researcher should be passionate about the investigation and believe that it is worthwhile in order to fuel the work. In other words, an investigator must believe that, by answering a new research question, useful information will be generated and advances will emerge as a result, regardless of whether the results are in favor of or against the null hypothesis. A well-designed research question should be able to pass the "so what?" test, which indicates how meaningful a research question actually is.

After addressing the importance of a research question, it is fundamental to make sure that it is relevant to both the scientific community and the public, while also meeting certain criteria: it must be answerable and feasible, while increasing knowledge in the field. Even though several aspects must be taken into consideration to achieve an adequate research question, it is indispensable to determine the clinical concerns that should be explored while rationalizing the need for the investigation.

A useful tool suggested by Hulley and colleagues [1] that may guide the development of a successful research question is the FINER criteria (Table 2.1), the use of which increases the potential of developing a publishable study by summarizing five necessary main topics that should be outlined. Accordingly, a research question must be *Feasible*, *Interesting*, *Novel*, *Ethical*, and *Relevant*. In regard to *Feasibility*, the question must address an adequate number of subjects and the researcher must have adequate expertise; the study must be affordable in both time and money, and be manageable in scope. It should be *Interesting* enough to intrigue the investigator, peers, and the community, as well as being a *Novel* source of information that confirms, refutes, or extends previous findings. In addition, it must be *Ethical* so as to preserve the patients' welfare, consequently receiving the institutional review

Table 2.1 FINER criteria for a good research question

F	Feasible	• Include an adequate number of subjects • Follow adequate technical expertise • Be affordable in time and Money • Manageable in scope
I	Interesting	• The answer should intrigue the investigator, peers and scienticic community
N	*Novel*	• Must confirm, refute or extend previous findings
E	*Ethical*	• Amenable to a study that institutional review board will approve
R	*Relevant*	• To scientific knowledge • Clinical and health policy • To future research

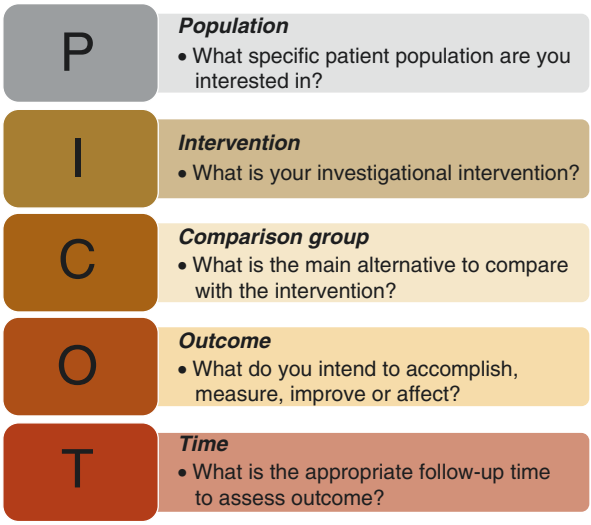

Fig. 2.2 PICOT format for developing a research question

board's (IRB's) approval, and *Relevant* to scientific knowledge, clinical and health policy, and finally to future research.

Whereas the FINER criteria address general aspects of the research question, the PICO format, often mentioned in the literature as the PICOT format (Fig. 2.2), increases the investigator's awareness of the important aspects to mention in the research question, such as the specific *Population* of interest (main criterion). Moreover, this helpful format outlines the effects of a certain *Intervention* by describing the *Comparison group*, *Outcome of interest*, and the amount of *Time* required to assess the outcome:

2.2.1 P (Population)

Population represents the sample of subjects to be recruited for a study; individuals in whom the knowledge is required. For instance, in a study in which the purpose was to "identify circulating microRNAs able to identify ovarian cancer patients at high risk for relapse [2]", the population was *cancer patients in high risk for relapse*.

It is essential to remember that it is not often easy to determine a sample that is most likely to respond to an intervention (e.g., absence of metastasis) and one that can be generalized to patients that are more likely to be identified in daily practice. Other considerations can be dictated by the availability of patients. By addressing questions such as: What is the appropriate age range? Should males and females be included? What about co-morbidities? And Is the type of tumor a relevant factor?, the researcher is able to narrow down the group of individuals that would be the main focus of the study.

One of the key factors to be aware of before defining the population of interest, along with the inclusion and exclusion criteria, is the potential risk of bias, the

internal validity of the results as well as their generalizability. The more rigorous the inclusion and exclusion criteria, and thus the more restricted the target population, the greater their influence on the applicability of the results. Although a restricted population may reduce the risk of null results, thus increasing internal validity, it might also considerably diminish the generalizability of the study. On the other hand, despite representing patients seen in daily practice, a broader population and broader inclusion criteria may have the opposite effect.

Hence, an inadequate definition of the criteria that will shape the population of interest may , as a result, alter the study design, leading to unsuccessful findings and decreasing the chances of achieving clinical significance.

2.2.2 I (Intervention)

Also referred to as exposure, "I" corresponds to the treatment, procedure, therapy, or placebo that will be provided to the patients enrolled in the study. In a study that aims to "evaluate the security and effectiveness of cisplatin with constant dose-intense temozolomide (TMZ) for reduplicative glioblastoma multiforme (GBM) within 6 months" [3], for example, the intervention would be *cisplatin plus constant dose-intense TMZ*. Before designating an intervention to a group of patients, it is important to take into account previous studies, if existent, so as to predict estimates of the study's effect. The following step after ensuring the safety of the exposure is to define, in advance, how to measure its efficacy: using clinical outcomes, surrogates (biomarkers), questionnaires, quality-of-life scales, or other methods. Finally, it is necessary to analyze the financial aspects involved in a certain intervention, counterbalancing its pros and cons, as well as analyzing its cost-effectiveness.

2.2.3 C (Comparison Group)

The comparison group is a group of subjects that resembles the experimental group in several aspects, but who do not receive the active treatment under study. Control interventions may be in the form of a placebo, standard care or practice, a different therapy, or even no intervention. A clear example of "C" is in a study by Middleton et al. [4] that aimed to investigate the clinical efficacy of "vandetanib plus gemcitabine versus placebo plus gemcitabine in locally advanced or metastatic pancreatic adenocarcinoma". In this study, while the active group received vandetanib and gemcitabine, the comparison group received placebo and gemcitabine, which was the standard treatment at that time.

Additionally, a research question could likely change depending on the control groups. In other words, a question that aims to compare one intervention versus another is different from a question that aims to compare one intervention versus no intervention. Therefore, the comparison between groups has large implications in a study and is intrinsically associated with the process of defining participants' exposure to the intervention.