MOJ
MEDITERRANEAN
ONCOLOGY
JOURNAL

NOVEMBER 2011
Issue 1 ■ Volume 1

THE OFFICIAL JOURNAL OF MEDITERRANEAN
MULTIDISCIPLINARY ONCOLOGY FORUM

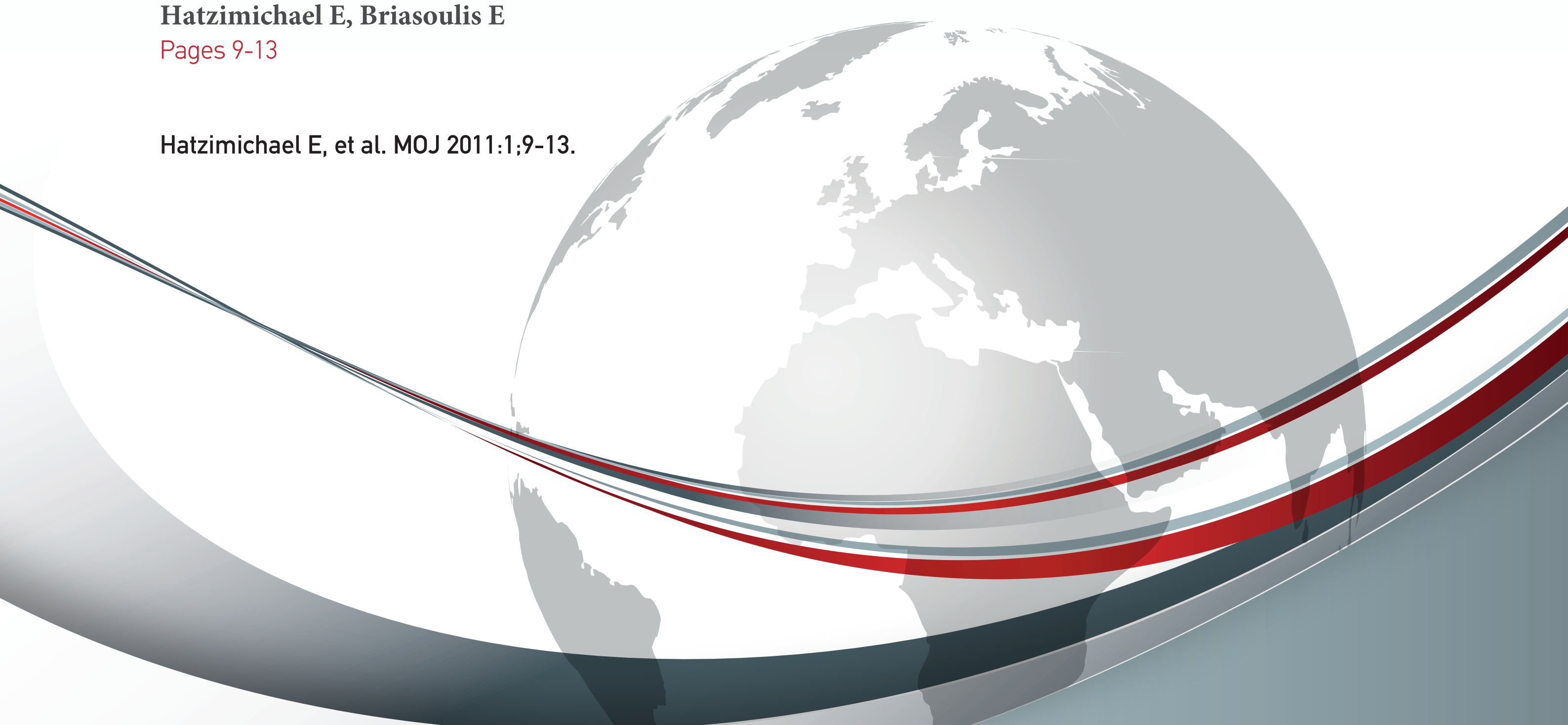
Controversy

Attitudes of people, authorities and doctors towards clinical cancer research: high expectations, neglected responsibilities and minimal involvement outline a hazy picture. Can we do any better?

Hatzimichael E, Briasoulis E

Pages 9-13

Hatzimichael E, et al. MOJ 2011:1;9-13.



MMOF

Attitudes of people, authorities and doctors towards clinical cancer research: high expectations, neglected responsibilities and minimal involvement outline a hazy picture. Can we do any better?

Hatzimichael E[1,2], Briasoulis E[1,2]

[1]Academic Department of Hematology, Ioannina University Hospital, Ioannina, Greece, [2]Cancer Biobank Center, University of Ioannina, Greece

Received 20 September 2011; accepted 15 October 2011

Introduction

We are entering the second decade of the 21st century, and despite an unprecedented explosion in cancer research, advances in the therapy of advanced-metastatic cancer is making hesitant steps forward while cancer morbidity remains, as a whole, almost unaffected [1,2]. In this milieu of active research, peoples' expectations are running high as the media and tabloids regularly overtone news reporting that "scientists" are close to discovering a miraculous ”cancer drug", which might shortly "become available" to the public. This rhetoric discloses a deep misconception about the processes that regulate the development and approval of new therapies and critical deficiencies in understanding clinical research, which is a sine-qua-non tool to this process.

Interestingly, relatively poor accomplishments of clinical research in the developing countries, and sluggish improvements on non-communicable diseases at a global level, central to which includes cancer, led the United Nations General Assembly of September 16th 2011, to issue a statement, which urges and encourages countries to:
a) establish alliances and networks to bring together national, regional and global actors, including academic and research institutes, for the development of new medicines, vaccines, diagnostics and technologies,
b) promote national and international investments for health,
c) strengthen national capacities for quality research and development in a sustainable and cost-effective manner,
d) incentivizing innovation, and
e) support and facilitate non-communicable disease-related research and its translation to enhance the knowledge base [3]. In addition to this, the awaited World Health Report 2012 of the WHO entitled "No health without research" attempts to demystify clinical research and promote clinical research programs [4].

Examining clinical cancer research publications, as sourced in PubMed, one can easily recognize a serious underrepresentation of non-EU Mediterranean countries over the last 15 years, (with the exceptions of Israel, Turkey and Lebanon) when compared to European countries and the US. (Figures 1A & 1B) Investigation of this issue can lead to the identification of possible causative associations, which are related to (but not limited to) an underrepresentation of clinical cancer research in several low-income countries, and assist in identifying factors that may help improve such disparity.

The community

All people want and deserve to receive the most effective and safest therapies when they are necessary. However, public expectations, pushed by the lay-media regarding the yield(s) of modern cancer research, are running high [5]. In daily clinical routine practice making medical decisions on optimal therapy for each individual cancer patient is not always possible because of a lack of convincing medical evidence [6]. Medical evidence originates from clinical trials [7], and the participation of cancer patients in clinical trials (necessary to generate sufficient evidence) is dismally low [8,9]. In the US, the vast majority of people are either unaware of clinical trials or they have several misconceptions towards them including: fear of getting a placebo in place of an actual treatment, belief that standard treatment is better than what they would be offered in a clinical trial; and the fear of being a «guinea pig» [10,11]. The situation can hardly be better in countries where people do not have access to clinical trials, in populations who had never been exposed to clinical trial promotion, and in societies that are unwilling to accept disclosure of unmasked prognosis or even diagnostic information to their patients [12-14]. Moreover, the attitudes of the public towards clinical research and the evaluation of the risks and benefits of any given therapy may differ according to various cultural and health contexts [15-17].

The low enrollment into clinical trials appears to be a major hurdle for the advancement of cancer research being developed into achievements that move into routine clinical practice. It is suggested that authorities, scientific bodies and medical personnel must collaborate intensely in order to promote understanding [18] and transform societal attitudes toward clinical research with the aim to improve the attractiveness of clinical research for the general public [15]. Several attempts are already being made in this direction. The National Cancer Institute (NCI)

***Corresponding author:** Evangelos Briasoulis, Academic Department of Hematology & Cancer Biobank Center, University of Ioannina, Greece
E-mail: ebriasou@me.com, www.imol.edu.com

has initiated a program called the "Continuing Umbrella of Research Experiences (CURE)", which offers a training and career development continuum to enhance diversity in cancer research and focuses on broadening the cadre of underserved investigators engaging in cancer research. CURE begins with high school students and fosters scientific, academic and research excellence throughout the trainee's education [19]. This is an excellent paradigm of bringing clinical research education to a community level.

The patient

A survey conducted in the US indicated that the primary problem with accrual is not actually the attitudes of patients, but the unavailability of an appropriate clinical trial and the disqualification of large numbers of patients in the pre-screening phases [20]. Moreover, the pool of willing patients is further reduced by the reluctance of some physicians to engage in the process of accrual [20].

In order to get enrolled onto a clinical trial, each patient must sign a study (trial) specific informed consent for voluntary participation. However, only a few participants can sufficiently understand the information written on the rather highly specific (non-laymen's) trial-specific materials provided. Furthermore, the perception deficiencies seem to be caused in most cases by informers rather than the participants [21]. In order to obtain an informed consent for participating in a clinical trial, patients must first be instructed about the nature and practical utility of clinical research [22]. That means they should understand what clinical trials are, how they function, the risks and benefits of participation and how their participation may affect the medical decisions made at a personal level [23]. This has been shown to be a painful process in certain clinical settings [24]. Secondly they should to be clearly informed about the disease they are affected from, their disease status and about possible clinical outcomes when treated with available options on the grounds of approved drugs before being informed about the possibility of participation in a clinical trial [18].

Quality of provided information

A major hurdle in enrolling cancer patients into clinical trials is the clearness and the quality of information provided and the willingness and efficiency of involved medical staff to communicate appropriate information to the patient. Unfortunately, the information given and the way this is provided often fails to meet the guidelines of the Declaration of Helsinki and deficiencies experienced in perception are commonly caused by informers rather than the participants [21]. A recent investigation on the patient information sheet of the AML16 trial indicated that upfront performance-based user testing, could significantly improve provided information to a fit-for-purpose level.

Patient information sheet & Informed Consent

It is advised that the information included in "clinical trial information sheets", is disclosed in accordance with national and local ethics committees. Such information should be as plain as possible matching the standard literacy level of the target population. Poverty, a poor educational background, and the complexity of the information provided to the patients may question the validity of the procedure, especially in vulnerable cancer patients, which appears to be most common in developing countries. An investigation conducted in Mexico found characteristically that the consent forms were difficult to understand by half of the patients they were handed to, and most doctors agreed that the forms were not comprehensible to the patients. The average length of the documents analyzed was 14 pages, and the average readability score of the target population was low [26].

The authorities

The development of clinical trials is usually a long and arduous process, in which regulatory bodies and authorities are heavily implicated. A strong relationship on account of long development times and accrual performance has been demonstrated, which obviously has a negative impact in translating scientific knowledge to improvements being delivered with respect to basic therapeutic options [27].

Several issues that have been identified are linked to deficiencies in several regulatory bodies. The lack of sufficient knowledge on clinical trial regulatory issues spans the whole spectrum from administrations to single individuals in research institutions worldwide. It has shown that, even in the USA, many institutions do not have staff who understand the regulatory issues involved in managing investigational new drug research, and who knows the institution's obligations [28]. Similar problems are inherent to many health-providing institutions.

The clinician

The key operators of clinical trials are physician specialists, who are expected to have a deep knowledge of the subject at hand. Moreover, it is the medical community that has the ethical responsibility to produce and provide such information to their patient populations. Some basic questions can be raised with this in mind:

- How many doctors are involved in clinical cancer research?
- How many have the essential know-how on clinical trial technicalities and also an in-depth knowledge of clinical questions and prioritization to be addressed?
- How many have the proper communication skills, and sufficient time to introduce cancer treatment trials to patients and get signed informed consents [29]?

Moreover the minimum standards for a medical center to qualify as a quality research site according to the American Society of Clinical Oncology must:

a) Comply with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines,
b) Follow the GSP code, and practice the international ethical and scientific quality standards for designing,

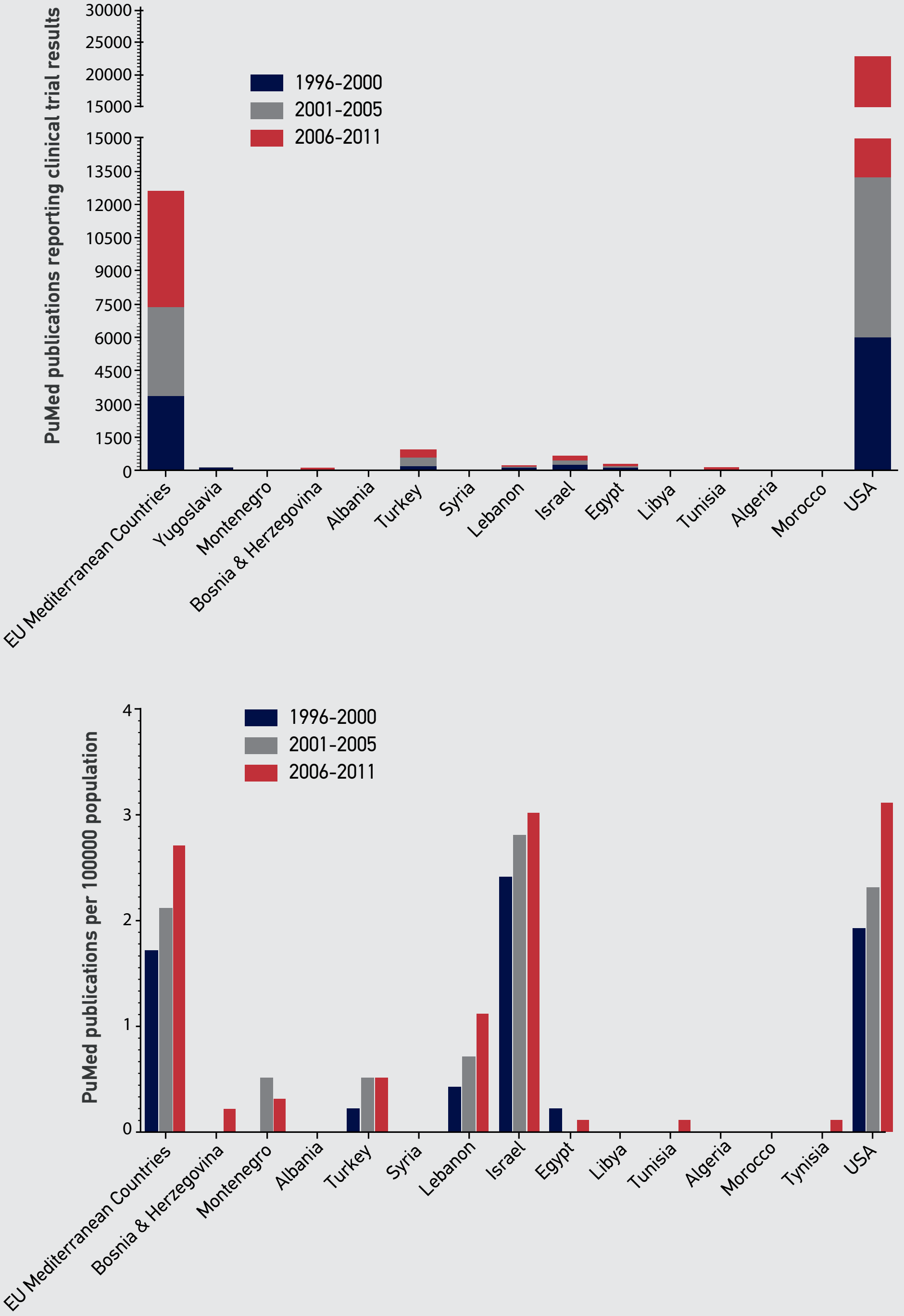


Figure 1.
Clinical trials reported per country (1A) and per 100.000 population outcome (1B). Countries that have a coastline on the Mediterranean Sea are shown in a clock-wise mode starting from the northwest part of the Mediterranean basin. US data are given as a reference. A PubMed search was performed for three consecutive time-periods: 1996-2000, 2001-2005 and 2006-2011. We used the term clinical trial in the "type of article" field and any of: cancer or carcinoma or lymphoma or myeloma or leukemia or sarcoma or melanoma or glioblastoma or tumor/tumour in the "title" field. The search was repeated for each country name in the "affiliations" field. No discrimination was made for registered or randomized trials. The top four Mediterranean countries with regard to absolute numbers of publications in the three time-periods were in descending order Italy, France, Spain and Greece. However, when the number of publications was adjusted to each country's population the top four were Italy, Israel, Greece and France.

conducting, recording, and reporting trials involving human participants and,

c) Demonstrate a minimum accrual activity of 5% [30].

Cancer specialists, whether Medical Oncologists, Hematologists or Radiation Oncologists are the professions that are nominally responsible in carrying out clinical cancer research. The most relevant scientific associations have recognized this need and responsibility, and have reasonably included a training program in conducting clinical research within their proposed training curricula. Characteristically, the joint ESMO/ASCO Task Force in the proposed Global Core Curriculum in Medical Oncology states the following [31,32]:

a) Trainees must be provided an education in the design and conduct of clinical trials,

b) clinical activities should include research involving

patient contact, care, and treatment,
c) research experience for 1 or more years, including international training, is strongly recommended, especially for the oncologists who want an academic career and,
d) they must have exposure to the development and conduct of these trials through international cooperative groups or in-house protocols. That instruction should include the following: clinical trial design, phase I–II–III trials; review of the ethical, regulatory, and legal issues involved in study design; criteria for defining response to therapy; tools used to assess quality of life; basics of statistics, including statistical methods, requirements for patient numbers in designing studies, and proper interpretation of data; toxicity assessment and grading; role and functioning of the institutional review board and ethical committees; experience obtaining informed consent from patients; government regulatory mechanisms of surveillance; instruction in grant writing and information about mechanisms of support for clinical research; cost of therapy and the cost-effectiveness of therapy; instruction in preparing abstracts, oral and visual presentations, and writing articles; and they should be able to critically evaluate the scientific value of published articles and their influence on daily clinical practice. However, these guidelines have not yet been widely adopted and are not consistently or sufficiently embedded in all training programs for many reasons [33].

Similarly, the Joint Royal Colleges of Physicians Training Board of the UK in the "Specialty training curriculum for Haematology" endorses that Haematology trainees should acquire the following clinical research capabilities [34]:
a) to understand and explain the use of trial protocols and the importance of multicentre trials in acute leukaemia;
b) to provide full explanation of appropriate clinical trials and obtain informed consent after discussion with patient and/ or carers,
c) to collect trial data and;
d) to promote participation in trials and research governance. Moreover it is advised for those in specialty training, to take time out of programme to complete a specified project or research degree [34].

The impact clinical trials have on improving cancer therapy and the role doctor's play in this process is well illustrated in the case of acute leukaemia. Acute leukaemias are critically severe at presentation and are still regarded as a rare disease. However, these adverse features have become key factors that prompted doctors to form large collaborative groups, develop successive therapeutic protocols on trial and enroll the majority of their patients in them [35-38]. A similar situation exists in the case of multiple myeloma [39,40].

Undergraduate education on clinical research

It is suggested that medical students should optionally receive early teaching in problem-oriented clinical research and ethical issues and should be reasonably exposed to clinical trials. Hands-on experience during their undergraduate studies have been shown to assist in further understanding the aim to mature their knowledge on the needs and practice of clinical research [41-44].

Conclusions

Currently we are witnessing an exponential increase in cancer biology achievements and molecular target knowledge, but at the same time we are seeing slow improvements in the therapy of advanced/ metastatic cancer. This discrepancy is largely attributed to inherent difficulties of clinical cancer research to follow the more rapidly developing biotechnological advances that are occurring, or in handling the accelerated accumulation in basic research data. Impressive discoveries of basic research hazily reported by news agencies and disseminated by the media lead to misconceptions and promote false expectations among the public. The missing link between basic/ preclinical and clinical science is the low performance of clinical trials. Both the UN and the WHO have identified this as a significant deficiency and are now undertaking, for the first time, initiatives to demystify and promote such research among member states.

Clinical trials in oncology are costly and often slowly progressive. Moreover, they demand large competences in know-how, recourses and specialists. Furthermore, several categories of players with different professional backgrounds and interests need to continuously collaborate and cross-interact over prolonged periods of time to see completion of these studies.

Poor accrual is the single most important negative factor that intervenes with clinical trials achieving their timely goals. Connected to that are trial unavailability, lack of clinical research education and promotion in the community and between health professionals alike. A relatively poor understanding, poor know-how, inefficiencies of involved medical staff, a reluctance of physicians to engage in accrual, and poor co-operation and underpowered regulatory mechanisms are all aspects of a poor reality. These obstacles are evidently more pronounced in low income countries.

We can do better! From a medical association's perspective, such as MOFF, we need to shape interregional and international scientific working collaborations and networks, and to promote public education on clinical research in regard to regulations, basic concepts, mechanisms and procedures. Only in such forums can we muster together all the specialties necessary to accomplish our goals.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.

2. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999;49:33-64, 1.

3. Political declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases. In: Nations U, ed. A/66/L1: ; 2011.

4. World Health Report 2012. 2011. (Accessed at http://www.who.int/rpc/whr2012/en/.)

5. Marshall E. The power of the front page of The New York Times. Science 1998;280:996-997.
6. Duggal R, Menkes DB. Evidence-based medicine in practice. Int J Clin Pract 2011;65:639-644.
7. Wille-Jorgensen P. No clear evidence for adjuvant therapy in people with stage II colon cancer. Cancer Treat Rev 2005;31:147-150.
8. Terry SF, Terry PF. Power to the people: participant ownership of clinical trial data. Sci Transl Med 2011;3:69cm3.
9. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA 2004;291:2720-2726.
10. Doctors, Patients Face Different Barriers to Clinical Trials. Bethesda, MD: NCI at NIH; Assessed 07 Oct 2011.
11. Colon-Otero G, Smallridge RC, Solberg LA, Jr., et al. Disparities in participation in cancer clinical trials in the United States : a symptom of a healthcare system in crisis. Cancer 2008;112:447-454.
12. Fumis RR, De Camargo B, Del Giglio A. Physician, patient and family attitudes regarding information on prognosis:a Brazilian survey. Ann Oncol 2011.
13. Back AL, Arnold RM. Discussing prognosis: «how much do you want to know?» talking to patients who do not want information or who are ambivalent. J Clin Oncol 2006;24:4214-4217.
14. Belvedere O, Minisini A, Ramello M, et al. Information given to cancer patients on diagnosis, prognosis and treatment: the clinical oncologist's perspective. Eur J Cancer 2004;40:1850-1854.
15. Schulman KA. Understanding attitudes toward clinical research. J Ambul Care Manage 2003;26:88-90.
16. Li JY, Yu CH, Jiang Y. Participation in cancer clinical trials as viewed by Chinese patients and their families. Oncology (Williston Park) 2010;79:343-348.
17. Markman M, Petersen J, Montgomery R. Influence of tumor type, disease status, and patient age on self-reported interest regarding participation in cancer clinical trials. Cancer 2006;107:849-853.
18. Behrendt C, Golz T, Roesler C, et al. What do our patients understand about their trial participation? Assessing patients' understanding of their informed consent consultation about randomised clinical trials. J Med Ethics 2011;37:74-80.
19. Franco I, Bailey LO, Bakos AD, et al. The Continuing Umbrella of Research Experiences (CURE): a model for training underserved scientists in cancer research. J Cancer Educ 2011;26:92-96.
20. Comis RL, Miller JD, Aldige CR, et al. Public attitudes toward participation in cancer clinical trials. J Clin Oncol 2003;21:830-835.
21. Lynoe N, Sandlund M, Dahlqvist G, et al. Informed consent: study of quality of information given to participants in a clinical trial. BMJ 1991;303:610-613.
22. Wray RJ, Stryker JE, Winer E, et al. Do cancer patients fully understand clinical trial participation? A pilot study to assess informed consent and patient expectations. J Cancer Educ 2007;22:21-24.
23. Stryker JE, Wray RJ, Emmons KM, et al. Understanding the decisions of cancer clinical trial participants to enter research studies: factors associated with informed consent, patient satisfaction, and decisional regret. Patient Educ Couns 2006;63:104-109.
24. Tait AR, Voepel-Lewis T, Zikmund-Fisher BJ, et al. The effect of format on parents' understanding of the risks and benefits of clinical research: a comparison between text, tables, and graphics. J Health Commun 2010;15:487-501.
25. Knapp P, Raynor DK, Silcock J, et al. Can user testing of a clinical trial patient information sheet make it fit-for-purpose?--a randomized controlled trial. BMC Med 2011;9:89.
26. Verastegui EL. Consenting of the vulnerable: the informed consent procedure in advanced cancer patients in Mexico. BMC Med Ethics 2006;7:E13.
27. Cheng SK, Dietrich MS, Dilts DM. A sense of urgency: evaluating the link between clinical trial development time and the accrual performance of cancer therapy evaluation program (NCI-CTEP) sponsored studies. Clin Cancer Res 2010;16:5557-5563.
28. Wermeling DP. Clinical research: regulatory issues. Am J Health Syst Pharm 1999;56:252-256.
29. Hietanen PS, Aro AR, Holli KA, et al. A short communication course for physicians improves the quality of patient information in a clinical trial. Acta Oncol 2007;46:42-48.
30. Zon R, Meropol NJ, Catalano RB, et al. American Society of Clinical Oncology Statement on minimum standards and exemplary attributes of clinical trial sites. J Clin Oncol 2008;26:2562-2567.
31. Hansen HH, Bajorin DF, Muss HB, et al. Recommendations for a Global Core Curriculum in Medical Oncology. Ann Oncol 2004;15:1603-1612.
32. Hansen HH, Bajorin DF, Muss HB, et al. Recommendations for a global core curriculum in medical oncology. J Clin Oncol 2004;22:4616-4625.
33. Briasoulis E, Kardamakis D. The dawn of Clinical Oncology education in Greece. J Buon 2009;14:327-332.
34. The specialty training curriculum for Haematology. Federation of Royal Colleges of Physicians of the UK, 2011. (Accessed at http://www.jrcptb.org.uk/specialties/ST3-SpR/Pages/Haematology.aspx.)
35. Mengis C, Aebi S, Tobler A, et al. Assessment of differences in patient populations selected for excluded from participation in clinical phase III acute myelogenous leukemia trials. J Clin Oncol 2003;21:3933-3939.
36. Dechartres A, Chevret S, Lambert J, et al. Inclusion of patients with acute leukemia in clinical trials: a prospective multicenter survey of 1066 cases. Ann Oncol 2011;22:224-233.
37. Joffe S. Framing the benefits of cancer clinical trials. Arch Pediatr Adolesc Med 2010;164:293-294.
38. Hehlmann R, Grimwade D, Simonsson B, et al. The European LeukemiaNet: achievements and perspectives. Haematologica 2011;96:156-162.
39. Karjalainen S, Palva I. Do treatment protocols improve end results? A study of survival of patients with multiple myeloma in Finland. BMJ 1989;299:1069-1072.
40. Cavo M, Rajkumar SV, Palumbo A, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. Blood 2011;117:6063-6073.
41. Marshall LL, Frye RF, Jr., Murphy JE. Students' experience in a phase III clinical trial. Am J Hosp Pharm 1990;47:1014, 6.
42. Weed LL. The problem oriented record as a basic tool in medical education, patient care and clinical. Ann Clin Res 1971;3:131-134.
43. Westberg K, Lynoe N, Lalos A, et al. Getting informed consent from patients to take research part in the clinical training of students: randomised trial of two strategies. BMJ 2001;323:488.
44. Kelly E, Nisker J. Increasing bioethics education in preclinical medical curricula: what ethical dilemmas do clinical clerks experience? Acad Med 2009;84:498-504. ■