Current Therapeutic Research 86 (2017) 2–8

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/cuthre

Which Benefits Are Mentioned Most Often in Drug Development Publications?

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ARTICLE INFO

Article history:
Accepted 10 October 2017

Key words:
clinical research
clinical trial
direct benefit
ethics indirect benefit
patient benefit
social benefit

ABSTRACT

Objectives: The aim was to identify theoretically expected as well as actually reported benefits from drug development and the importance of individual patient benefits compared to the collective benefits to society in general.

Background: Ethical guidelines require that clinical research involving humans offer the potential for benefit. A number of characteristics can be applied to define research benefit. Often benefit is categorized as being either direct or indirect. Indirect benefits can involve collective benefits for society rather than any benefits to the trial patient or subject. The purpose of this review was to examine which potential individual and societal benefits were mentioned as being expected in publications from government experts and which were mentioned in publications describing completed drug development trial results.

Methods: Literature on research benefit was first identified by searching the PubMed database using several combinations of the key words *benefit* and *clinical research*. The search was limited to articles published in English. A Google search with the same combinations of key words but without any language limitation was then performed. Additionally, the reference lists of promising articles were screened for further thematically related articles. Finally, a narrative review was performed of relevant English- and German-language articles published between 1996 and 2016 to identify which of several potential benefits were either theoretically expected or which were mentioned in publications on clinical drug development trial results.

Results: The principal benefits from drug development discussed included 2 main types of benefit, namely individual benefits for the patients and collective benefits for society. Twenty-one of an overall total of 26 articles discussing theoretically expected benefits focused on individual patient benefits, whereas 17 out of 26 articles mentioned collective benefits to society. In these publications, the most commonly mentioned theoretically expected individual patient benefit was the chance to receive up-to-date care (38.1%). A general increase in knowledge about health care, treatments, or drugs (70.6%) was the most commonly mentioned theoretically expected benefit for society. In contrast, all 13 publications reporting actual benefits of clinical drug development trials focused on personal benefits and only 1 of these publications also mentioned a societal benefit. The most commonly mentioned individual benefit was an increased quality of life (53.9%), whereas the only mentioned collective benefit to society was a general gain of knowledge (100.0%).

Conclusions: Both theoretically expected and actually reported benefits in the majority of the included publications emphasized the importance of individual patient benefits from drug development rather than the collective benefits to society in general. The authors of these publications emphasized the right of each individual patient or subject to look for and expect some personal benefit from participating in a clinical trial rather than considering societal benefit as a top priority. From an ethical point of view, the benefits each individual patient receives from his or her participation in a clinical trial might also be seen as a societal benefit, especially when the drug or device tested, if approved for marketing, would eventually be made available for other similar patients from the country in which the clinical trial was conducted.

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http://dx.doi.org/10.1016/j.curtheres.2017.10.002

Background

The business of doing clinical research involving humans became increasingly common during the last century. During this period not only were several relevant regulations and laws implemented, but the importance of the need to consider the ethical aspects of this activity also became more evident. This led to the development of various ethical guidelines by different government and medical organizations. All of these guidelines focus on the potential for benefit as a requirement for making clinical research involving humans ethically acceptable. The required research benefits can be differentiated by various characteristics and are often categorized into direct or indirect benefits. Indirect benefits are further divided into collective benefits to society, either excluding or including benefits to the trial patient or subject.

Three well-known sets of ethical guidelines that form the basis for conducting clinical research illustrate how the principle of benefit has evolved over time.

The First Ethical Requirements: The Nuremberg Code

The first ethical requirements for drug development in the area of clinical research were developed after the end of the Second World War as a result of the Nuremberg War Crimes Trials—also known as the Doctors Trials. These trials involved illegal human experiments conducted by doctors serving in concentration camps during the Second World War on concentration camp prisoners and led to the adoption of the Nuremberg Code in 1947. This included a set of 10 ethical principles required for conducting human experimentation and was the first official document to include benefit as a requirement for ethical human research. The document states in its second principle that "the experiment should be such as to yield fruitful results for the good of society."[1] This statement suggests that the expected benefit (eg, gaining knowledge about new treatments, medicinal products, or drugs) is for the whole society, not for the individual patients.

A Second Set of Ethical Requirements: The Declaration of Helsinki

Expanding on the Nuremberg Code, the World Medical Association developed and then released the Declaration of Helsinki in 1964. This Declaration was amended several times during the past 50 years as a result of the progress made in clinical research and associated new challenges. The current version (dated from 2013) states in its eighth principle that "the primary purpose of medical research is to generate new knowledge."[2] This definition is similar to the Nuremberg Code statement that the expected benefit of drug development is to society. However, later versions of the Declaration also include another type of benefit; that the research should enable "post-trial access for all participants who still need an intervention identified as beneficial in the trial."[2] For the first time the individual benefit to the trial subjects—and even beyond the end of the clinical trial—was considered as a requirement in an official ethical research document.

A Third Set: The Belmont Report

In 1978 a third official document on ethical requirements for human research was adopted by The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the United States. This document is called The Belmont Report and addresses ethical principles and guidelines for the protection of human subjects participating in all research. The second principle of the Belmont Report, which covers the aspect of beneficence, states that the society should benefit "from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures."[3] "Treating childhood diseases and fostering healthy development" are given as examples of societal benefits.[3] The application of these principles requires that "the term benefit is used in the research context to refer to something of positive value related to health or welfare."[3]

The development of these 3 ethical guidelines resulted in the operationalization of several additional important ethics guidance documents such as the Common Rule in the United States and the Guideline for Good Clinical Practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, which was adopted by the regulatory bodies of the European Union, the United States, and Japan. The standard of Good Clinical Practice was incorporated into law such as in the Regulation EU No. 536/2014 in the European Union and became obligatory for conducting clinical research. This produced an important change in the clinical research approval process. As a result, a clinical trial is only acceptable if the risks and benefits for the trial patients are balanced.

This review was conducted to identify and compare which theoretically expected benefits are identified in articles published by government experts such as at the US National Institutes of Health versus those mentioned in selected published clinical drug development trial report results with respect to the types of benefit mentioned in these documents and to examine whether they focused more on benefits to society or to individual patients or subjects.

Unfortunately, the methods used prohibited any examination of differences in ethical comments in Western versus non-Western countries. This question is important given the increasing globalization of clinical research activity. As noted by Lang et al,[4] "clinical trials are also being conducted across more diverse countries for economic reasons" and factors that are "increasing the wait for lifesaving new interventions," especially for rare disease and health events. Unfortunately this is beyond the scope of this article.

Definition of Benefits

The types of benefits identified were divided into potential individual patient benefits from receiving new treatments, medical devices, or drugs and the general benefits to be potentially gained by society through knowledge obtained from the research. But the societal benefit of clinical research does not only consist of gaining new knowledge of diseases, new treatment methods, drugs, or medicinal products. The influence on the health care system was also considered to be a potential collective societal benefit.

Also, potential benefits to individual patients included both direct and indirect benefits. Direct benefits included those that would result from the patient or subject's use of a new medical treatment, a new drug, or a new medicinal product. The potential benefits of such treatment could also include a decrease "in the severity of symptoms" and thereby an increase in the quality of life or in survival time. Indirect benefits included those resulting from the participation in research without receiving any direct benefits; for example, by being part of a control group. Participants who did not receive the investigation product were still involved in the

product development process by providing the comparative data for proving superiority or noninferiority of a new treatment. They might receive the benefits later, after the market approval of the new treatment or product. Generation of the comparative data needed for a market approval would be impossible without inclusion of patients who accept the risk of being randomized to not receive the new investigational treatment or product. In fact the literature suggests that indirect benefits can also result from trial participation as a control; for example, "the opportunity to meet with other people and feel useful and helpful, or greater access provided to professional care and support" as well as getting monetary reimbursement for participation. In regard to the latter it is important to distinguish between payment and reimbursement. Payment refers to monetary benefits whereby reimbursement addresses only expenses incurred by participants as a result of trial participation.

Although "all research is designed to benefit the public,"[5] only "some procedures offer the patient-subject the prospect of direct benefit."[6] Societal benefit will always exist, whereas individual benefit may only be possible from participation in clinical research.

None of the benefit types discussed are particularly favored in the 3 major ethical guidelines (Nuremberg Code, Declaration of Helsinki, and Belmont Report). Generally, when deciding whether clinical research is ethical, the "potential clinical benefits to participants, if any, and the social value of the knowledge"[5] are combined. Not every clinical trial includes an individual benefit for its participants and unfortunately no "upper limit on the net research risks to which competent adults may be exposed."[5] Therefore, clinical trials can enroll participants only "as long as the risks are justified by the societal value of the research."[5] This means that given a sufficiently important scientific question, some net risk to subjects may be justified,"[6] because "the overarching objective of clinical research is to develop generalizable knowledge to improve health and/or increase understanding of human biology,"[7] and "subjects who participate are the means to securing such knowledge."[7] Therefore, it might appear that the societal benefit of drug development from clinical research take precedence over the individual benefits to the patients or subjects. But is this reflected in publications from governmental experts and selected published clinical drug development trial reports?

Methods

A nonsystematic review of the literature on clinical research benefits was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram and guidance set out by the Centre for Reviews and Dissemination.[8,9] This review focused on narratives and does not claim to be complete.

The search strategy

Literature on research benefit was first identified by searching the PubMed database. Several combinations of key words like *benefit* and *clinical research* or *direct benefit* and *patient and clinical research* as well as *indirect benefit* and *patient and clinical research* were used. Further, synonyms like *advantage* instead of *benefit* and *clinical trial* or *clinical study* instead of *clinical research* were applied. The thematically most promising search string, which was finally used, was the combination of *direct benefit* and *patient* and *clinical research*. Filters such as full text availability, definition of publication date, limited to humans, and articles in English language were used to reduce the search results. The final search was limited to articles published in English between January 1, 1996, and March 31, 2016. A Google (Mountain View, CA) search with the same combination of key words was then done. Here, only the most thematically promising articles were chosen. This search was not limited to only articles in English. The literature identified in the PubMed database and the Google search was then screened by reviewing the titles and abstracts. Articles that were believed to be appropriate, after excluding duplicates, underwent full-text review by the author. The content of the appropriate articles were appraised for which benefits from drug development were mentioned. Articles that did not include any kind of benefit from drug development were excluded. Only articles referring to benefits of drug development were included.

Further, the reference lists of promising articles were screened to identify additional thematically related articles. Any additional articles believed to be appropriate were selected and their full text was evaluated regarding comments on the benefits of drug development trials.

The final review covered publications in English and German language published between January 1, 1996, and March 31, 2016. The search strategy as per Centre for Review and Dissemination Guidance recommended is shown in the **Figure 1**.[8]

All articles identified as suitable for the final review were divided into articles discussing theoretically expected benefits written by experts and published on governmental sites on one hand and into publications reporting completed clinical drug development trial results that included a discussion of study benefits. A similar analysis of both publication types was done to check whether the theoretically expected benefits mentioned by governmental experts were included in publications of clinical drug development trial results.

Documentation in a data extraction form

The data extracted from both publication types were listed in two separate data extraction forms, which were of identical design, containing descriptive details and benefit components (**Table I** and the supplementary tables are included in **Appendix A**). The author, publication year, as well as the topic of the publication were documented as were the benefit components divided into either patient or societal benefit along with a more detailed description of the beneficial aspects mentioned.

Data classification

The benefit components collected in the data extraction forms were classified in subcategories after dividing them into the groups of patient benefits and societal benefits with the frequency of each beneficial aspect enumerated.

In summary, this narrative review was designed to screen the selected literature to identify the benefits most frequently mentioned expected or actual clinical research benefits and to further detail these outcomes.

Results

Analysis of descriptive data

A total of 39 publications were selected and divided into a group of articles discussing theoretically expected benefits and a group of articles reporting actual benefits of a clinical drug development trial. The group focusing on theoretically expected benefits included 26 articles, mostly written by experts, from government sites and 13 articles reporting actual benefits from a clinical drug development trial were mostly written by authors from academia. The descriptive data (**Tables II** and **III**) contain author's name, publication year, and a brief topic description of the article.

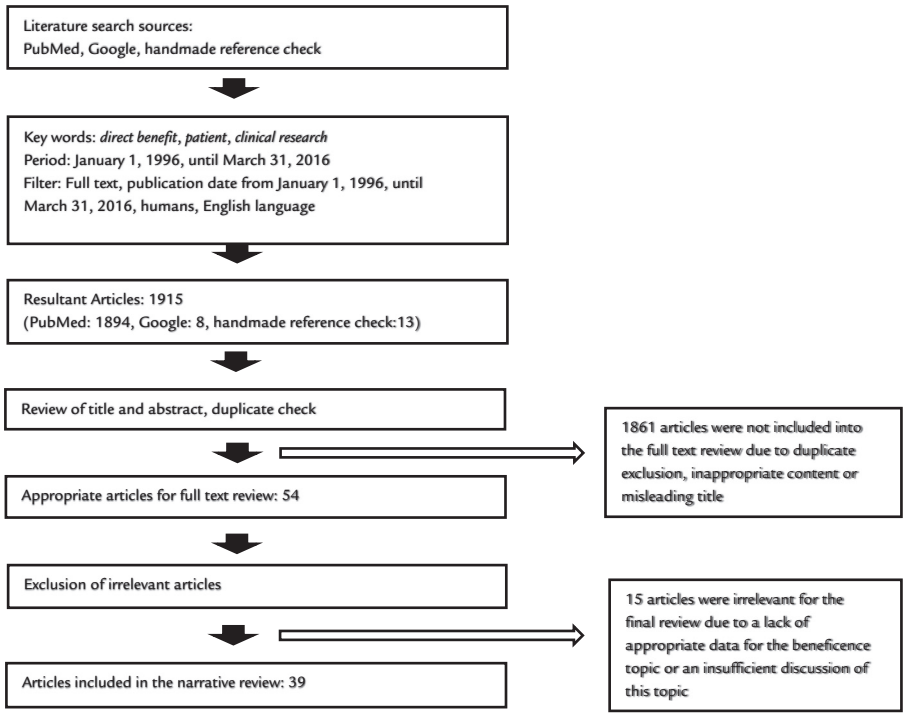

Fig. 1. Preferred reporting items for systematic reviews and meta-analysis flow diagram presenting the search strategy.

Thirty-two of the 39 selected publications used words like *benefit* (n =14), *ethics* (n =6), *effects* (n = 3), and *clinical research* (n = 8) as well as *clinical trial/trial* (n = 20) in their titles.

Analysis of benefit data

In the 39 included articles the benefits from drug development were routinely divided into 2 main classes, namely individual benefits for the patients or subjects and into collective benefits for society.[10] In 12 of the 26 theoretically expected benefit articles both patient benefits and societal benefits were mentioned. Nine of these 26 publications focused on personal benefits and 5 publications focused on societal benefits. In total, 21 out of 26 theoretical benefit publications mentioned personal patient benefits, whereas 17 publications discussed collective benefits to society. In contrast, only 1 of the 13 actual clinical trial reports included both patient and societal benefits while the 12 other publications focused only on personal benefits.

Classification of benefit data

The data in the extraction forms were used to generate percentage frequency scales of mentioned patient and societal benefits per article type. The frequency scale for the theoretically expected benefits articles included only desired benefits, whereas the frequency scale for the clinical drug development trial reports included actual benefits.

The most commonly mentioned theoretically expected societal benefits were the general gain of knowledge about health care, treatments, or drugs (70.6%). The second most commonly mentioned benefits were the subsequent availability of new treatments, technologies, or drugs (29.4%). In 11.8% of these publications, new facilities or clinics, access to medicines, sustainability, and improvement in health care (11.8%); as well as clean water, longer life, cost-effectiveness, and employment or training of medical professionals (5.9%) were additional potential societal benefits. In contrast to these expectations, only 1 of the 13 actual clinical trial reports included a collective societal benefit: General gain of knowledge.

The theoretically expected patient benefits frequency scale is represented in **Table IV**. The most commonly mentioned theoretically expected benefit (38.1%) was the chance to receive up-to-date-care. The second most commonly mentioned benefit was an increased quality of life (33.3%). Other theoretically expected patient benefits were access to health care or provision of treatment or drugs (23.8%), reimbursement for trial-related expenses (23.8%), altruism (14.3%), improved survival time (14.3%), and longer life (14.3%). Other benefits mentioned included improvement of health, knowledge gain, maximization of one's own health, as well as posttrial access to drugs (9.5%), symptom reduction, emotional improvement, contribution to scientific research, decreased morbidity and mortality, and control of the disease (4.8%).

In contrast to the theoretically expected patient benefits listed in **Table IV**, **Table V** represents the frequency scale of the actual

Table I
Examples from the data extraction form covering descriptive details and benefit components of articles discussing theoretically expected benefits.

Author	Year	Topic	Patient benefit	Social benefit	Patient benefit description	Social benefit description
Lemaire F[17]	2004	Patient care vs clinical research	Yes	Yes	Up-to-date care, feeling of altruism, payment	General knowledge
Freedberg K[18]	1995	Effectiveness of prophylaxis for *Pneumocystis carinii* pneumonia in patients with AIDS	Yes	No	Longer life	

Table II
Example from the data extraction form listing descriptive details of articles discussing theoretically expected benefits.

Author	Year	Topic
Lemaire F[17]	2004	Patient care versus clinical research
Freedberg K[18]	1995	Cost-effectiveness of prophylaxis for *Pneumocystis carinii* pneumonia in patients with AIDS

patient benefits specifically mentioned in published clinical drug development trial results. Here, the most commonly mentioned benefit (53.9%) was an increased quality of life. Access to health care or provision of treatment or drugs was the second most commonly mentioned benefit (38.5%), followed by the chance to receive up-to-date care (30.8%). Other important patient benefits were altruism, hope, and trust for cure as well as cost reduction (all 23.1%). Symptom reduction, emotional improvement, and contribution to scientific research were also mentioned (15.4%). Reimbursement for trial-related expenses, improved survival time, longer life, improvement of health, knowledge gain, maximization of one's own health, as well as the opportunity to meet other patients, prolongation of time to progression, closer monitoring, receipt of a second opinion, and an independent handling of future disease (all 7.7%) were other benefits mentioned.

Discussion

By comparing the theoretically expected benefits and the actually reported benefits, it became apparent that individual patient benefit from involvement in a drug development trial was mentioned much more frequently than theoretically required societal benefits. Consequently, it appears that investigators conducting clinical trials concentrate more on what patients who participate in a clinical trial can expect to personally gain from participation rather than on only the collective benefits for society. Perhaps this is because investigators consider societal benefit to be automatically an implicit component of participation because generation of fundamental knowledge about new treatment methods or drugs will be a natural consequence of all trials.

Furthermore, most if not all clinical research should not be approved by an institutional review board or ethics committee or done without aiming to improve the health of at least 1 specific population. However, this aim might not always be achieved by generating fundamental knowledge on diseases, new treatment methods, or drugs. Sustainable access to new drugs or treatment methods, as well as new treatment facilities and additional trained personnel, are potential additional benefits. The theoretically expected collective benefits for society seem to differ from the benefits actually reported in most clinical trial results.

Direct patient benefits

In addition to the collective benefits for society, each individual patient or subject has the right to look for and expect some personal benefit from participating in a clinical drug development trial rather than considering societal benefit as a top priority.[11] When comparing the literature from the late 1990s with more recent literature, it appears that the individual patient benefits expected from participation in human research have become a major requirement for a patient or subject's participation in clinical drug development trials. It is perhaps not surprising that 20 years ago a general improvement in quality of life was among the most commonly expected individual benefits for a participant. Additional fundamental benefits expected include reduction of symptoms, improved emotional and physical condition, and an improved prognosis for extended life expectancy. Access to new treatments or drugs that successfully improve health is also an expected individual benefit. Such benefits were mentioned in both theoretical benefits publications as well as in clinical trial reports and are all direct benefits.

Table III
Example from the data extraction form covering descriptive details of articles listing benefits as reported in publications of completed clinical trial results.

Author	Year	Topic
Lindenstruth K[19]	2006	Beneficial effects of soy trial experience
Lindholm-Olinder A[20]	2015	Effects of acceptance and commitment therapy in patients with type 1 diabetes

Table IV
Classification of theoretically expected patient benefit.

Benefit type	%
Up-to-date-care	38.1
Quality of life	33.3
Access to health care / treatment / drug	23.8
Payment	23.8
Altruism	14.3
Survival	14.3
Longer life	14.3
Improvement of health	9.6
Knowledge gain	9.6
Maximization of own outcome / health	9.6
Posttrial access to drug	9.6
Symptom reduction	4.8
Emotional improvement	4.8
Contribution to scientific research	4.8
Decrease of morbidity / mortality	4.8
Control of the disease	4.8
Hope / trust for cure	0
Cost reduction	0
Meeting other patients	0
Time to progression	0
Closer monitoring	0
Receipt of second opinion	0
Independent handling of future disease	0

Table V
Classification of actual reported patient benefit.

Benefit type	%
Quality of life	53.89
Access to health care / treatment / drug	38.5
Up-to-date-care	30.8
Altruism	23.1
Hope / trust for cure	23.1
Cost reduction	23.1
Symptom reduction	15.4
Emotional improvement	15.4
Contribution to scientific research	15.4
Payment	7.7
Survival	7.7
Longer life	7.7
Improvement of health	7.7
Knowledge gain	7.7
Maximization of own outcome / health	7.7
Meeting other patients	7.7
Time to progression	7.7
Closer monitoring	7.7
Receipt of second opinion	7.7
Independent handling of future disease	7.7
Posttrial access to drug	0.0
Decrease of morbidity / mortality	0.0
Control of the disease	0.0

Indirect patient benefits

Several indirect benefits, regardless of whether from generation of comparative data or from positive treatment effects, might also be expected as a result of a patients' participation in clinical research. These might include a feeling of altruism from participation in clinical research and assistance in the acquisition of new research knowledge, especially when participating patients help discover something useful about their own disease. When this occurs, participants can gain new courage for their further fight against the disease. In addition, participants often have the opportunity to interact with other affected patients in a way that gives them new strength to deal with their illness.

Reimbursement for costs incurred in study participation, including travel expenses and loss of work, can also be considered benefits. However, whether such reimbursement of expenses should be regarded as an indirect benefit for clinical trial participants or not is an ethically very controversial topic. Muthuswamy et al[12] advance the view that reimbursement of expenses is not an individual benefit because it should include only the reimbursement of actual costs incurred and should not serve as an inappropriate incentive for financially less-well-off patients to agree to participation in clinical research. In contrast, Denny et al[13] does not consider such payments as negative as long as they are "considered fair" for patients. In general any reimbursement of expenses or payment should be planned transparently in cooperation with the responsible ethics committee or institutional review board.

Another significant theoretical benefit is the expected long-term access of the participants to any substance, device, or treatment shown to be effective in the clinical trial in which they participated. However, the clinical drug development trial reports reviewed here suggest that short-term improvements were more important for patients compared with any long-term benefits. This aspect is also an ethically controversial topic. According to Lang et al[4] the "post-trial access to medicines and devices are an integral part of […] trust between researchers and the community." Trust is always an important aspect of patients' participation in clinical research regardless of whether patients might expect any direct or indirect benefits. However, González-Saldivar et al[14] stated that participants assigned to the control group often have "the perception that study participants are not protected" and "that in research projects the participant's health is endangered." This suggests that participants who do not receive any of the previously mentioned expected direct benefits may develop distrust in research. The expectation of receiving long-term benefits may be particularly important for compliance with the ethical codices of clinical drug development trials conducted in resource poor countries. From an ethical point of view, the benefits each individual patient receives from participation in a clinical trial might also be seen as a societal benefit, especially when the drug or device tested, if approved for marketing, would eventually be made available for other similar patients from the country in which the clinical trial was conducted.[15]

Limitations

Limitations of this review should be taken into consideration. A small number of studies were included in this nonsystematic review and the analyses were descriptive.

Conclusions

The majority of the included publications emphasized the importance of individual patient benefits rather than collective benefits to society, regardless of whether studies reported theoretical or actual benefits. Short-term patient benefits such as access to treatment, alleviation of symptoms, and improvement of health were emphasized in these studies. However, long-term benefits, including posttrial and postmarketing access to study medications, should be considered. Further, as stated by Limaye et al,[16] "the benefits of […] research should be extended post trial not only to study subjects but to the entire host community." The availability of tested substances or methods is especially important in emerging countries, where the number of clinical trials is increasing annually. Finally, there is a need for monitoring of long-term outcomes to ensure that the expected benefits to individual patients and to society in general are balanced and realized.

Acknowledgment

I would like to thank the journal for its editorial support.

Conflicts of Interest

None

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.curtheres.2017.10.002.

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