European Journal of Clinical Pharmacology (2018) 74:1001–1010
https://doi.org/10.1007/s00228-018-2474-9

CLINICAL TRIAL

The patient's safety and access to experimental drugs after the termination of clinical trials: regulations and trends

Ricardo Eccard da Silva[1,2] · Angélica Amorim Amato[2] · Thiago do Rego Sousa[3] · Marta Rodrigues de Carvalho[4] · Maria Rita Carvalho Garbi Novaes[2,4]

Received: 9 January 2018 / Accepted: 2 May 2018 / Published online: 12 May 2018

Abstract

Purpose Participants' rights and safety must be guaranteed not only while a clinical trial is being conducted but also when a clinical trial finishes. The criteria for post-trial access to experimental drugs, however, are unclear in various countries. The objectives of this study were (i) to ascertain if there were regulations or guidelines related to patients' access to drugs after the end of clinical trials in the countries selected in the study and (ii) to analyze trends in post-trial access in countries classified by their level of economic development.

Methods This study is a retrospective review. The data are from the records of clinical trials from 2014 registered in the World Health Organization's International Clinical Trials Registry Platform (ICTRP) database.

Results Among the countries selected, provision of drugs post-trial is mandatory only in Argentina, Brazil, Chile, Finland, and Peru. The plans for post-trial access tend to be more present in low- and middle-income and upper middle-income countries, in comparison with high-income countries. Studies involving vulnerable populations are 2.53 times more likely to have plans for post-trial access than studies which do not.

Conclusions The guaranteeing of post-trial access remains mandatory in few countries. Considering that individuals seen as vulnerable have been included in clinical trials without plans for post-trial access, stakeholders must discuss the need to develop regulations mandating the guaranteeing of post-trial access in specified situations.

Keywords Clinical trials · Drugs · Access · Ethics · Continuity of patient care

Introduction

The sponsors of clinical trials have chosen to conduct clinical trials in research centers in less-developed regions, such as South American and Asian countries, rather than in more developed ones such as the United States, Japan, or Europe [1]. The harmonization of the procedures established by the Good Clinical Practices (GCP) among the research centers of various

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-018-2474-9) contains supplementary material, which is available to authorized users.

✉ Ricardo Eccard da Silva
ricardo.eccard@gmail.com

Angélica Amorim Amato
angelicamato@unb.br

Thiago do Rego Sousa
thiago.sousa@tum.de

Marta Rodrigues de Carvalho
marta_rodrigues12@hotmail.com

Maria Rita Carvalho Garbi Novaes
ritanovaes2@gmail.com

[1] Brazilian Health Regulatory Agency (Anvisa), Setor de Indústria Trecho 5, Área Especial 57, Brasília 71250-050, Brazil

[2] University of Brasilia (UnB), Campus Universitário Darcy Ribeiro, Brasília 70910-900, Brazil

[3] Technical University of Munich, Boltzmannstraße 3, 85748 Garching, Germany

[4] Health Sciences Education and Research Foundation (FEPECS), SMHN Quadra 03, Conjunto A, Bloco 1 Edifício FEPECS, Brasília 70710-907, Brazil

countries has contributed to the migration of clinical trials [2]. There are, however, other factors which influence this process of globalization. The process of developing new technologies involves studies which are expensive and time-consuming. As a result, clinical trials have migrated to less-developed regions, principally due to the lower cost of conducting the studies and the greater availability of patients. Although participation in global clinical trials benefits patients from these regions, such as through access to innovative research products for those with serious conditions, it is still necessary to guarantee their integrity, well-being, and rights—as they may be socially and economically vulnerable [3–5].

Participants' rights and safety must be guaranteed not only while the clinical trial is being conducted but also after it has ended. In this scenario, there may be patients who are benefiting from the experimental intervention and who—in the investigator's opinion—should continue to receive the intervention [6]. In many countries, however, the rules for post-trial access have not been established; furthermore, a great many of the regulations in place are unclear in relation to the criteria for providing the products, for how long the products should be provided, at what point provision should be interrupted, and what the responsibilities are of the sponsor, investigator, and host state government [6].

According to the Helsinki Declaration, access to the intervention identified as beneficial in the clinical trial must be guaranteed to all the participants, regardless of whether they were allocated to the experimental treatment or to the control group. That is to say, the patients who were allocated to the control group, at the end of the clinical trial, also have the right to have access to the experimental drug, if this were identified as best in the clinical trial [7]. Also in accordance with this declaration, the clinical trial sponsor, investigator, and government of the host state must participate in the process of the provision to the participants of whichever intervention is identified as being most beneficial during the clinical trial. This declaration states that the responsibility to provide products must be shared between the clinical trial sponsor and the government of the country which hosted the clinical trial [7].

Many countries have guidelines for GCP, providing information on post-trial provision. These guidelines, however, constitute nothing more than recommendations, as compliance is not mandatory [8]. For some patients, the lack of guaranteed post-trial access could have severe consequences—such as, for example, patients with HIV, who can develop resistance to the treatments used in the clinical trial, if access to the same is not guaranteed after the end of the clinical trial [9]. In the context of low- and middle-income countries (LMIC), where a proportion of the population is considered vulnerable and does not have access to healthcare or drugs through the public health system, the lack of post-trial access is concerning, as the treatment provided during the clinical trial may be discontinued permanently [10]. Conducting clinical trials in regions with limited resources, inequalities in health care and vulnerable populations may be characterized as exploitation if—for instance—post-trial access is not guaranteed to the patients who need treatment and who lack access to alternative treatments which may be expensive or unavailable in the country in question [11].

Considering the risks to which clinical trial participants are exposed, and the possibility of harm resulting from discontinuation of the treatment—along with the possibility of benefits to the patients based on the clinical trials' results—importance must be given to post-trial access, although it could be mandatory to provide access to treatment only in cases which meet specific criteria, such as patients who do not have access to alternative treatments for the drug identified as beneficial in the clinical trial [8]. As yet, however, there is no consensus in relation to mandating guaranteed post-trial access [8].

Considering these aspects, the study of (i) guidelines and rules about post-trial access in countries actively participating in international clinical trials and (ii) trends for post-trial access in regions with low incomes and limited resources could contribute to a better understanding of this topic. The present study aimed to ascertain whether the regulations or guidelines of countries situated in the Americas, Asia, or Europe address the obligatoriness of provision of drugs to patients after the end of clinical trials and to analyze trends for access to treatments following the termination of clinical trials in countries classified by their level of economic development.

Methods

Design

The study reported here was a retrospective database review. The data were obtained from the International Clinical Trials Registry Platform (ICTRP) database. The period considered was January 1, 2014 to December 31, 2014. Data collection took place between March 1, 2014 and June 31, 2015.

Information was collected from the EU Clinical Trials Register (EUCTR), which has been a primary registry in the World Health Organization (WHO) Registry Network since September 2011 and contains information on interventional clinical trials on medicines conducted in the European Union or European Economic Area. This database was selected because it includes information on post-trial access: "F. 5 - Plans for treatment or care after the subject has ended the participation in the trial" [12]. In the present study, this information was considered as "plans for post-trial access".

Selection criteria

Inclusion criteria

The study included clinical trials registered in a primary registry (EUCTR) that involved drug interventions in countries with the highest average annual growth rates in a number of clinical trials or the highest trial densities or the greatest trial capabilities.

Clinical trials were selected from countries with (i) the highest trial densities during 2005 and 2012, based on the trial density (annual number of registered clinical trials divided by country population in 2010) [5], (ii) the highest average growth rate in clinical trials [5], and (iii) the greatest trial capabilities (calculated as the mean number of clinical sites in each trial, contributed in large-scale trials in each country) [13]. This strategy led to the inclusion of clinical trials from Denmark, Estonia, Netherlands, Israel, and Finland (criteria i), China, India, Brazil, Egypt, South Africa, Turkey, Ukraine, Colombia, Singapore, Russia, Thailand, and Malaysia (criteria ii), and Argentina, Mexico, Chile, and Peru (criteria iii).

Exclusion criteria

Exclusion criteria include observational studies, devices, and medical procedure studies (Fig. 1).

Data collection

The following information was collected from the EUCTR database: vulnerable populations; patients incapable of giving consent personally; emergency situations; health condition, as classified by the International Classification of Diseases; age group; clinical trial sponsor; development phase; and post-trial access. For information on vulnerable populations, patients incapable of providing consent personally, emergency situations, and post-trial access, the binary system of "yes" or "no" was used. The information on clinical condition, patient's inability to provide consent, emergency situations, and clinical trials involving pediatric population and adolescents was chosen for evaluation in the study, based on vulnerable groups identified in international research ethics guidelines and policies [15].

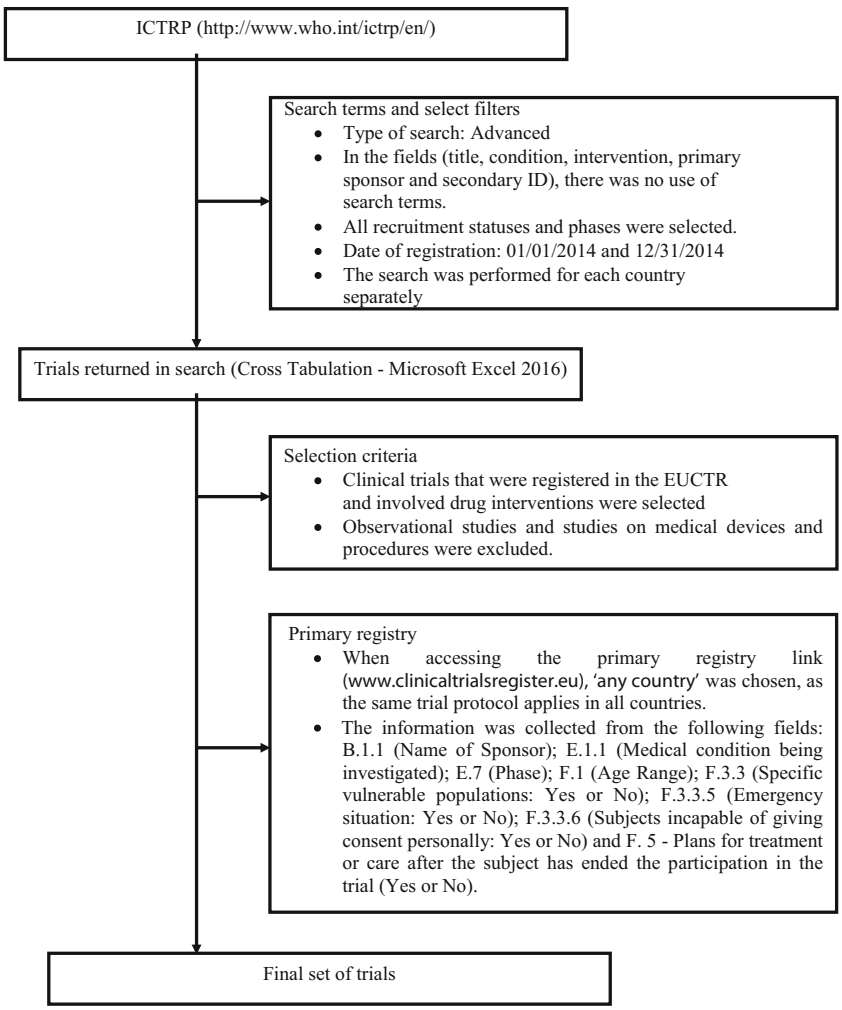

Fig. 1 Steps of search process in ICTRP. Adapted figure [14]

All the steps involved in compiling the list of clinical trials included, along with their characteristics, are described below.

In searching for studies on the platform, it is necessary to follow the steps found in Fig. 1.

No bias control procedure was used.

For quantitative variables, a pivot table (dynamic table in Microsoft Excel 2016) was created, based on a dynamic data source to match the data of the variables. As the vast majority of these are international multicenter clinical trials, that is, trials which took place in multiple countries at the same time, there were a number of repeated trials among the countries involved. When the clinical trials were grouped according to the countries' level of economic development, the repeated clinical trials were excluded. To evaluate vulnerability, information was considered as a comparison of being vulnerable (yes) in relation to not being vulnerable (no). For each variable, the frequency of response between being vulnerable or not was verified. Later, the association between each variable and plans for post-trial access was analyzed.

Data analysis

The clinical trial population's age was classified according to the National Institutes of Health. Age filters include 80 and over, 80+ years; aged, 65+ years; middle aged, 45–64 years; adult, 19–44 years; adolescent, 13–18 years; child, 6–12 years; preschool child, 2–5 years; infant, 1–23 months; and newborn, birth–1 month [16]. The pediatric population was considered as studies that involved newborns and/or infants and/or preschool children and/or children.

Countries were classified according to economic development category as "high-income (HI)", "upper middle-income (UMI)", "lower- and middle-income (LMI)", or "low-income (LIC)" based on their categorization by the World Bank [17]. The World Bank classifies countries into four income groups. Economies were divided according to 2016 Gross National Income (GNI) per capita using the following ranges of income: (i) low-income countries had GNI per capita of US$1025 or less, (ii) LMI countries had GNI per capita between US$1026 and US$4035, (iii) UMI had GNI per capita between US$4036 and US$12,475, and (iv) HI countries had GNI per capita above US$12,476.

Countries were classified according to geographical regions (continental), based on their categorization by the United Nations [18].

The clinical trial sponsor was classified according to the information on the organization's website. The primary sponsor is defined in the WHO ICTRP as the "organization which takes responsibility for the initiation, management, and/or financing of a clinical trial" [19].

Clinical condition was classified as incurable or not by a medical professional.

Statistical tests were used to analyze trends and associations between the main variable "plans for post-trial access" and selected variables: income, vulnerable population, unable to give consent personally, pediatric population, adolescents, emergency situation, sponsorship by pharmaceutical company, existence of legislation in the country, and incurable clinical condition. The Kruskal-Wallis test [20] was used to analyze these trends and associations with different levels of economic development.

For strategy to study the problem, the first step was to organize the data set. The response variable was termed "plans for post-trial access", and the decision was made to work with its original value, i.e., "yes", "no", or "not stated" instead of working with its percentage of occurrence.

The second step was to perform a descriptive analysis followed by a statistical test of dependency. We used rank-based non-parametric statistical tests, such as the Kruskal-Wallis test.

The third step is to quantify the measure of association between each of the influencing variables and the "plans for post-trial access" variable. This was done by computing the odds ratio measure.

This study was approved by the Research Ethics Committee of the Health Sciences College, University of Brasília (Brazil).

Results

The research in the ICTRP returned 15,278 studies. After this, only studies from EUCTR were selected ($n = 1671$). Twenty-five studies were excluded because they did not have information on emergency situations, the plans for post-trial access, the patient's inability to provide consent, or sponsor. A further twenty-two studies were excluded because they were duplicated, that is, the same studies were registered in the same country. After eliminating these studies, the database had 1624 studies (S1 file).

The total number of clinical trials by country were as follows: Netherland (262), Denmark (164), Russia (146), Israel (94), Argentina (92), Ukraine (92), Mexico (91), South Africa (83), Finland (75), Brazil (75), Turkey (61), Chile (58), Colombia (49), Thailand (45), Peru (45), Singapore (44), Estonia (43), China (40), Malaysia (30), India (27), and Egypt (8).

In high-income countries (HIC), 54% of the clinical trials lacked plans for post-trial access. In the LMIC and upper middle-income countries (UMIC), 38 and 38% of trials, respectively, lacked plans for post-trial access.

In the HIC, 55% of clinical trials lacking plans for post-trial access involved vulnerable populations. In LMIC and UMIC, 71 and 76% of clinical trials without plans for post-trial access, respectively, involved vulnerable populations.

In HIC, 20% of the clinical trials lacking plans for post-trial access involved the investigation of cancer. In LMIC and UMIC, on the other hand, 24 and 25% of these clinical trials involved cancer, respectively. Breast cancer and lung cancer are among the most studied in clinical trials lacking plans for post-trial access (Fig. 2).

A total of 7 clinical trials included patients with HIV. Regarding these HIV studies, approximately 43% (3 clinical trials) did not have plans for post-trial access. In relation to the level of economic development, 3 trials were conducted in HIC—only 1 of which had plans for post-trial access. Furthermore, 3 trials were conducted in UMIC, of which 2 trials had plans for post-trial access. In LMIC, there was only one clinical trial undertaken with this population. This trial included plans to provide post-trial access.

A total of 74% of clinical trials lacking plans for post-trial access were sponsored by industry. Other types of sources of financing have also sponsored trials where there were no plans for post-trial access: universities/university hospitals (15%), research center (5%), sponsor investigator (2%) hospitals (1%), research group (1%), and not stated (2%).

In relation to the inclusion of pediatric populations (0 to 12 years old) and the elderly (between 66 and 80 years old and over 80 years old), in clinical trials lacking plans for post-trial access, the results by level of economic development are, respectively, HIC (9 and 67%), UMIC (21 and 81%), and LMIC (12 and 88%).

Regulations and guidelines on post-trial access

Argentina, Brazil, Chile, Finland, and Peru are the only countries, among those selected, where the provision of products after the clinical trials is mandatory. Among these, only Argentina and Chile have a law that regulates the issue (Table 1). Brazil, Chile, and Peru are the only countries where the issue of who shall guarantee the provision is made clear. In the case of Brazil and Peru, the clinical trial sponsor is responsible. In Chile, the institution that obtained authorization to conduct the clinical trial in the country, or the holder of the product registration, is responsible for providing the treatment. In relation to the period of provision, in Brazil, it must be for an unspecified period, or while the patient is benefiting from the treatment. In Chile, provision must take place while the patient is receiving clinical benefits. In Peru, on the other hand, provision must take place until the treatment becomes commercially available and the criteria for the provision of the treatment is the absence of an adequate alternative treatment for the patient. In the other countries (Argentina, Brazil, Chile, and Finland), provision must take place in any situation (Table 1).

Trends in post-trial access

Using a significance level of 1%, the null hypothesis is rejected for the association between the variable of interest "plans for post-trial access" and the influence variables:

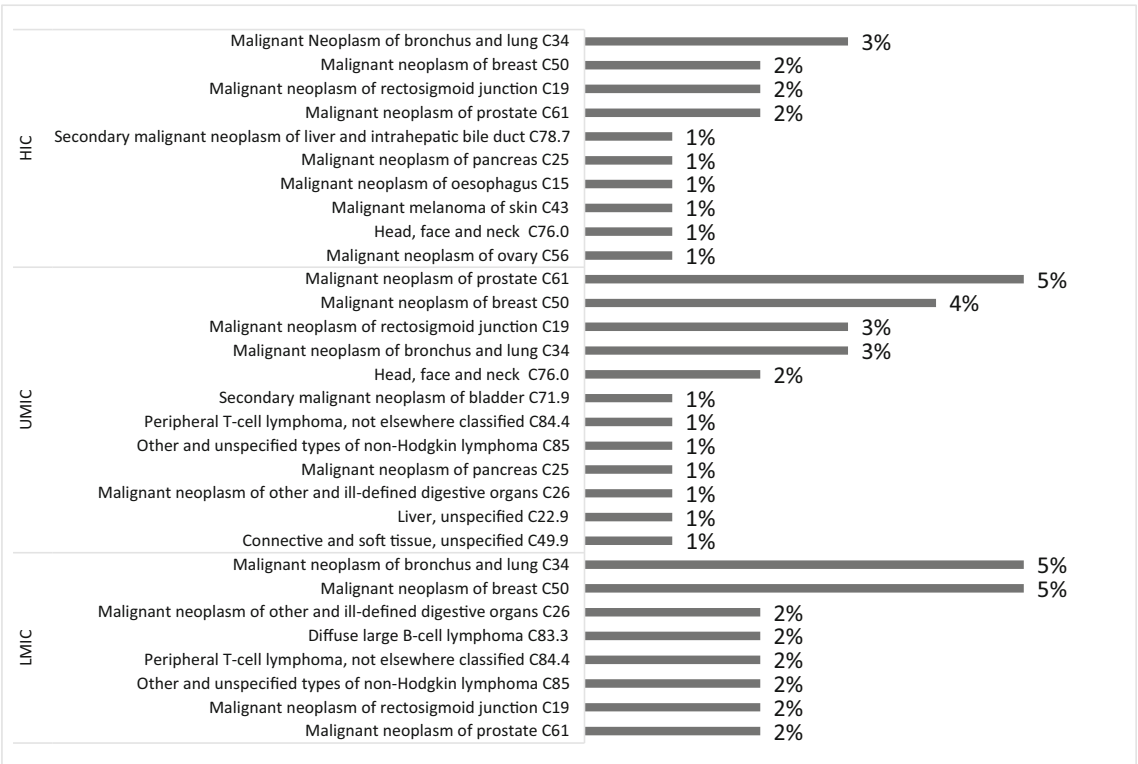

Fig. 2 Proportion of cancer clinical trials that have no plans for post-trial access by clinical condition classified by ICD-10—The EU Clinical Trials Register (2014)

Table 1 Regulations and guidelines on post-trial access

Country	Regulations and guidelines	Content
Argentina	Law No. 26,994/2014, Civil and Commercial Code	Article 58: "(j) to ensure research participants the availability and accessibility to treatments that research has shown beneficial"
	Disposition No. 6677/2010 and Resolution No. 1480/11—Ministry of Health	The research ethics committee which approved the clinical trial specifies the period of provision of treatment. Moreover, this provision must be conceded to the patient until access is guaranteed through other means.
Brazil	Brazilian Health Regulatory Agency (Anvisa). Resolution No. 38/2013	"Art. 15—The provision of treatment after the trial is concluded will be available free of cost to research subjects, for as long as it is beneficial, according to medical criteria."
	National Health Council. Resolution No. 466/2012	"III.3—Biomedical research studies of experimental methods involving human subjects, (…) should (…): (d) Ensure all participants at the conclusion of the study free access by the sponsor, and for an indeterminate period, to the best prophylactic, diagnostic and therapeutic methods the efficacy of which have been demonstrated."
Chile	Law No. 20,850/2015	Article 17: (…) "clinical trial subjects will have the right to continue receiving free of cost the treatment administered from the holder of the 'special provisional authorization for research purpose' or, where appropriate, from the holder of the registration, even when the trial is concluded and while the therapeutic utility remains."
Finland	Finnish Medicines Agency Administrative Regulation Clinical Trials on Medicinal Products No. 2/2012	The trial protocol or the documents appended to the notification must include the following information: "The arrangements for the treatment of patients after the trial (such as gradual discontinuation of the investigational medicinal product, possible replacement by other medication, etc.)."
	European Guideline for Ethics Committee Members (2010)	It recommends that discussions should be held on how the treatments can be made available locally after the clinical trial ends.
India	Guideline for Biomedical Research (2006)	It recommends that clinical trials must be conducted in accordance with the Helsinki Declaration and that post-trial access must be taken into account in the planning of the clinical trial.
Israel	Guideline for Conducting Clinical Trials (2006)	It recommends that the patient should continue to receive the treatment after the closure of the clinical trial, if—in the opinion of the clinical trial's investigator —the patient's well-being depends on this and if there is no alternative treatment available. Provision must not exceed three years, unless one of the following situations should occur: the treatment is approved for commercialization, the product's development is discontinued, the use of the product for a prolonged period could compromise the patient's health, or when the product is not a drug, but, rather, a cosmetic, food, dietary supplement, or herbal product.
Malaysia	Guideline for Application of Clinical Trial Import License and Clinical Trial Exemption (2014)	It recommends that sponsors, researchers, and governments of host countries must guarantee access for all participants to the treatment identified as beneficial. This subject must be discussed with the participants during the process of informed consent.
Peru	National Institutes of Health. Supreme Decree No. 017/2006	"It's the sponsor's responsibility to ensure the access of research subjects, after completion of the study, to preventive, diagnostic and therapeutic procedures that have been beneficial in the study in case there is no other suitable treatment alternative for the patient until the product under investigation commercially available."
Singapore	Operational Guide for Institutional Review Committees (2007)	It recommends that plans must be established to make the product investigated available to the patients after the end of the clinical trial.
South Africa	Guideline to Good Clinical Practices (2006)	It recommends that at the end of the clinical trial, access to the best treatment identified by the clinical trial must be guaranteed to the patients.
Turkey	Guideline to Good Clinical Practices (2015)	It recommends that appropriate treatment and monitoring of the participants must be ensured should the clinical trial be ended early or suspended for any reason.

income, vulnerable population, sponsorship by pharmaceutical company, and incurable clinical condition. There is evidence that a country's income influences the decision to undertake a post-clinical trial there ($p < 0.05$).

Descriptive analysis and the Kruskal-Wallis test showed there to be no association between the variable of "plans for post-trial access" and the variables of "inability to give consent personally", "pediatric population", "adolescents", "emergency situation", and "existence of legislation in the country" ($p > 0.1$).

At a confidence interval of 5%, it can be concluded that plans for post-trial access are 1.73 times more likely to be found in UMIC than in HIC. Furthermore, plans for post-trial access are 1.50 times more likely to exist in LMIC than in HIC.

At a confidence interval of 5%, clinical trials on vulnerable populations are 2.53 times more likely to have plans for post-trial access than clinical trials on non-vulnerable populations. Clinical trials sponsored by pharmaceutical companies are 2.19 times more likely to have plans for post-trial access than clinical trials not sponsored by pharmaceutical companies. Clinical trials involving incurable clinical conditions are 1.41 times more likely to have plans for post-trial access than clinical trials that did not.

Discussion

According to the results, a large majority of the countries selected in the present study do not have regulations on post-trial access. There was a trend for post-trial access to be present in clinical trials undertaken in LMIC and UMIC, in comparison with those with HIC. Furthermore, there was a trend for post-trial access plans in clinical trials involving vulnerable populations and incurable conditions. Clinical trials which lacked plans for post-trial access and which involved vulnerable populations were more heavily concentrated in LMIC and UMIC. Most clinical trials lacking post-trial access plans were sponsored by industry. Other types of sources of financing were also involved, such as universities, sponsor-investigator, hospitals, and research groups. Clinical trials without post-trial access plans and involving pediatric populations were concentrated more in UMIC. Most clinical trials lacking plans for post-trial access included elderly individuals.

The present study's results showed that some countries have guidelines on post-trial access, but the majority of these are not clear in relation to the criteria on provision, the responsibilities of the different parties involved, and the duration of provision. Post-trial access is a controversial topic in the literature. The legislation and guidelines are inconsistent and ambiguous and fail to provide clear information on the situations in which access must be guaranteed, for how long, and who is responsible for the provision [21].

Israel's guide for conducting clinical trials has the most information on the criteria for provision—and for how long this provision is to be maintained. This guideline recommends that the patient should continue to receive the treatment after the closure of the clinical trial, if—in the opinion of the clinical trial's investigator—the patient's well-being depends on this and if there is no alternative treatment available. It does not, however, state who is responsible for the provision. Even international guidelines, such as the CIOMS (Council for International Organizations of Medical Sciences) (2016), do not provide clear guidance on the criteria for provision of treatments after the end of clinical trials. This guide states that the clinical trial's sponsor, and the investigator, must make plans for guaranteeing continued access to those interventions shown to be beneficial. The provision may be ceased when the treatment becomes available through the local health system or after a period of time agreed previously between the researchers, sponsors, and community [22].

At present, the guaranteeing of post-trial access is mandated only in Argentina and Brazil, both of which have regulations on this topic [23]. However, the present study's results showed that, besides Argentina and Brazil, other countries—which were included in this study—have regulations and mandate post-trial access: Chile, Finland, and Peru. The majority of countries where post-trial access is mandatory, therefore, are in the South American region.

In Europe, besides Finland, only the United Kingdom and Portugal have regulations on post-trial access. In the United Kingdom, however, it is not mandatory to provide post-trial access—it is simply the case that the sponsor must provide a rationale for their actions to the research ethics committee and to the participant. This sponsor decides whether or not provision of the treatment will continue in the post-trial scenario [24]. In Portugal, Law 46/2004 obliges the sponsors of clinical trials to provide the treatment free of charge until this is on the market. The treatment must be provided to the patients who do not have other therapeutic options and according to the opinion of the investigator [25].

Provision of treatment while the patient is receiving benefits from it, regardless of whether the product has been registered or incorporated in the local health system, is mandatory in the South American countries (Argentina, Brazil, and Chile), according to our results. The United States of America lacks any regulations on post-trial access, and the sponsor has total power over the decision to provide the treatment or not after the clinical trial has ended [26].

None of the guidelines or regulations of the countries selected in the present study has clear criteria for post-trial access, and they differ regarding the period of provision. The regulations and guidelines do not provide information regarding the situations in which post-trial access is

to be guaranteed—for example, chronic and severe clinical conditions, or conditions where there are no alternative treatments.

According to Harvard University's guideline on post-trial responsibilities, post-trial access should not be mandatory in all situations, but only in cases which meet specified criteria, which should be clear and consistent with the principles of bioethics. Considering the principles of bioethics, such as justice and non-maleficence, the criteria for post-trial access could be (i) serious conditions or conditions with risk to life, (ii) when the discontinuation of the treatment could negatively affect the patient, (iii) when there is no therapeutic alternative available for the patient, and (iv) when there is sufficient information for an evaluation of the risk/benefit [27].

The results of our study showed that industries are more likely than other institutions to sponsor clinical trials that have no plans for post-trial access. However, the results of one already-published systematic review have revealed that of each 10 clinical trials offering continuation of treatment with drugs after the end of the clinical trial, 8 were sponsored by industry [28]. Pharmaceutical companies have a responsibility to provide treatment after the termination of the clinical trial [23]. The present study's results also showed that there are other sources of financing involved in clinical trials that lack plans for post-trial access. In Brazil, although the provision of drugs and treatment by the clinical trial sponsor is mandatory, different sources of financing may be involved in the clinical trial, such as universities, independent research centers, sponsor-investigators, and the government—as shown in the results of the present study. These types of sponsors may not have sufficient resources for continued provision of benefits in the post-trial period [23].

The present study identified clinical trials on cancer which lacked plans for post-trial access. There was, furthermore, a trend for incurable clinical conditions to be investigated in clinical trials that lack plans for post-trial access. Lung cancer and breast cancer are among those studied the most in clinical trials that do not have plans for post-trial access, regardless of the countries' incomes. These results are consistent with already-published studies showing that breast cancer and lung cancer are among the types of cancer which kill most in HIC—and also in LMIC. Other types of cancer, however, such as of the stomach and liver, which are major causes of death in LMIC, have been prioritized little in clinical trials [29]. The patients who participate in these studies have serious clinical conditions and interrupting their treatment can cause them serious harm. Also, in relation to studies on cancer, there is the question of the high costs of oncological drugs, which could reduce access to the treatments in countries with lower levels of economic development [30].

According to the present study's results, 7 clinical trials included patients with HIV. Approximately 43% of these (3 clinical trials) lacked plans for post-trial access. One already-published study showed that in 18 clinical trials involving patients with HIV, all included plans for post-trial access. The majority of these clinical trials were undertaken in clinical centers in developing countries. Over 70% of these trials identified mechanisms through which post-trial access could be obtained. Nevertheless, access in the long-term was not guaranteed [31].

The pediatric population is made even more vulnerable by children's difficulty in assessing risks and benefits and in making decisions on whether to participate in a clinical trial [32]. As children tend to have less ability to think critically, children evaluating whether or not to participate in a clinical trial lacking post-trial access might fail to recognize the possible consequences and risks caused by the interruption of the treatment when the trial ends. Those legally responsible for these participants must participate in the process of obtaining informed consent [33].

According to the present study's results, the pediatric population was included in clinical trials where there were no plans for post-trial access. One study already published in the literature showed that of 18 clinical trials, 5 involved children and adults and 4 involved only children. All these clinical trials involving children had plans for post-trial access [31]. The LMIC and UMIC are among those with the highest percentages of clinical trials lacking post-trial access plans and that involved pediatric populations, according to the results of the present study. The seriousness of the clinical conditions related to levels of poverty, malnutrition, diarrheas, and severe co-morbidities—and the high rate of mortality among children in countries with fewer resources—may be factors related to the greater inclusion of pediatric populations in the clinical trials undertaken in these regions [34–36].

One study already published in the literature, investigating clinical trials registered with the ICTRP in 2005–2013, showed that clinical trials involving children have been concentrated more in HIC. Furthermore, although 98% of the global burden of disease among children is concentrated in LMIC, only 22% of the clinical trials involving children were conducted in these countries. Children are involved in 34% of the global burden of disease; however, children participated in only 15% of these clinical trials. That is, this population continues to be underrepresented in clinical trials [37].

The patients considered vulnerable, that is, who are unable to protect their own interests [38] and who are from countries where access to healthcare is limited, may face more barriers to accessing post-trial access, should this access not be guaranteed by the clinical trial's sponsor [39]. The present study's results showed that vulnerable participants were included in clinical trials where there was no post-trial access. However, there is no information available on the types of vulnerabilities related to these participants.

Most clinical trials without plans for post-trial access included elderly participants, according to the study's results.

This population may be considered vulnerable in participation in clinical trials: for example, some have degenerative illnesses which reduce their decision-making capacity [38]. Although the present study's results show that the elderly population is represented well in clinical trials, the data from the literature indicates that the elderly population is as yet underrepresented in clinical trials, mainly due to cognitive conditions that hinder understanding of informed consent and aspects such as the use of various drugs described in the clinical trials' exclusion criteria [40, 41].

The present study's results showed that there was a trend for clinical trials with post-trial access plans in LMIC and UMIC, in comparison with those with HIC. However, the results also showed that in LMIC and UMIC, there were higher percentages of clinical trials both involving vulnerable populations and lacking post-trial access plans. Although a large majority of clinical trials in the countries had post-trial access plans, it is not known whether the access really was guaranteed, by whom, and for how long. One study published showed that in only 1.3% of clinical trials undertaken in one three-year period, investigating diseases such as malaria, tuberculosis, and AIDS, were post-trial access planned [39]. Another already-published study showed that of 312 clinical trials, only 1% mentioned post-trial access [42]. These data from the literature stand in contrast to the results from the present study, which showed that a large majority of the clinical trials conducted in the countries selected had plans for post-trial access.

Moreover, many patients accept to participate in the studies even though they are aware that, in the post-trial scenario, access to the experimental drug will not be guaranteed. These questions may be related to the lack of clarity found in the guidelines and legislation on the responsibility to continue to provide treatment when the clinical trial has ended. Most countries lack clear rules on post-trial access—and the result of this is that the studies' sponsors (in the most part, pharmaceutical companies) establish their own criteria regarding provision of treatments [23]. It follows that local governments, regulatory authorities, sponsors of clinical trials, and patients must discuss the need to elaborate regulations which mandate the guaranteeing of post-trial access in specified situations—and which take into account the local scenario in each region. These situations of obligatoriness of provision could be aligned with the criteria established by Harvard University's guideline on post-trial responsibilities.

Limitations

The limitations are related to the data which are lacking or incomplete in the databases. As the ICTRP receives data from clinical trials run by providers which meet specified requirements [43], it may fail to consider specified registers which do not meet these requirements. Consequently, there may be clinical trials which were not considered in this study. A further issue is that this study was restricted to clinical trials registered in a period of only one year.

Conclusions

The guaranteeing of post-trial access remains mandatory in few countries, most of which are located in South America. The guidelines and regulations on the topic are not clear in relation to the duration of provision of treatment, the criteria for the provision, or those responsible for guaranteeing the access. The lack of clear criteria in rules and guidelines regarding continued access after the clinical trial may result in the creation of rules by the clinical trial sponsors themselves, based on their own interests. Although plans for post-trial access tend to be more present in LMIC and UMIC, in comparison with HIC, individuals considered vulnerable—that is, who experience difficulty in protecting their own interests—have been included in clinical trials where there were no plans for post-trial access. Therefore, stakeholders involved in clinical trials must discuss the need to elaborate regulations which mandate the guaranteeing of post-trial access in certain situations.

Acknowledgments The authors thank the Brazilian Health Regulatory Agency (Anvisa) (Brasilia, Brazil), Health Sciences Education and Research Foundation (FEPECS) (Brasilia, Brazil), and University of Brasilia (UnB) (Brazil).

Author contributions RES, MRC, and MRCGN made substantial contributions to the study conception and design and to the acquisition, analysis, and interpretation of data. TRS made substantial contributions to the analysis and interpretation of data. AAA made substantial contributions to the conception and design. All authors read and approved the final manuscript.

Compliance with ethical standards

Ethical approval This study was approved by the Research Ethics Committee of the Health Sciences College, University of Brasília (Brazil).

References

1. Atal I, Trinquart L, Porcher R, Ravaud P (2015) Differential globalization of industry- and non- industry–sponsored clinical trials. PLoS One 10(12):e0145122
2. Richter TA (2014) Clinical research: a globalized network. PLoS One 9(12):e115063
3. Li R, Barnes M, Aldinger CE, Bierer BE (2015) Global clinical trials: ethics, harmonization and commitments to transparency. Harvard Public Health Review 5:1–7
4. Hanauer SB (2009) Outsourcing clinical trials. Nat Rev Gastroenterol Hepatol 6:191

5. Drain PK, Robine M, Holmes KK, Bassett IV (2014) Global migration of clinical trials in the era of trial registration. Nat Rev Drug Discov 13(3):166–167
6. Wang DWL, Ferraz OLM (2012) Pharmaceutical companies vs. the state: who is responsible for post-trial provision of drugs in Brazil? Pharmaceutical firms and the right to health. J Law Med Ethics 40(2):188–196
7. World Medical Association (2013) WMA Declaration of Helsinki: Ethical principles for medical research involving human subjects. Available at: http://www.wma.net/en/30publications/10policies/b3/. Accessed 30 Oct 2016
8. Zong ZY (2008) Should post-trial provision of beneficial experimental interventions be mandatory in developing countries? J Med Ethics 34(3):188–192
9. Millum J (2011) Post-trial access to antiretrovirals: who owes what to whom? Bioethics 25(3):145–154
10. Grover S, Xu M, Jhingran A, Mahantshetty U, Chuang L, Small WJ et al (2017) Clinical trials in low and middle-income countries — successes and challenges. Gynecol Oncol Rep 19:5–9
11. Lang T, Siribaddana S (2012) Clinical trials have gone global: is this a good thing? PLoS Med 9(6):e1001228
12. European Medicines Agency - EMA. EU Clinical Trials Register. Available at https://www.clinicaltrialsregister.eu/. Accessed 20 May 2016
13. Thiers FA, Sinskey AJ, Berndt ER (2008) Trends in the globalization of clinical trials. Nat Rev Drug Discov 7:13–14
14. Williams RJ, Tse T, DiPiazza K, Zarin DA (2015) Terminated trials in the ClinicalTrials.gov results database: evaluation of availability of primary outcome data and reasons for termination. PLoS One 10(5):e0127242
15. Bracken-Roche D, Bell E, Racine E (2017) The concept of 'vulnerability' in research ethics: an in-depth analysis of policies and guidelines. Health Res Policy Syst 15(1):8
16. National Institute of Health (NIH). Age filters, 2014. Available at: http://www.ncbi.nlm.nih.gov/books/NBK3827/. Accessed 16 Apr 2016
17. World Bank (2016) World development report, 2016. World Bank, Washington DC
18. United Nations Statistics Division. Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings. Theol Revised 26 September 2016. Available at: https://unstats.un.org/unsd/methods/m49/m49regin.htm#
19. World Health Organization. International Clinical Trials Registry Platform (ICTRP). Glossary. Available at: http://www.who.int/ictrp/glossary/en/. Accessed 14 June 2017
20. Lehmann EL (2008) Nonparametrics: statistical methods based on ranks. Springer Verlag, Berlin
21. Sofaer N, Strech D (2011) Reasons why post-trial access to trial drugs should, or need not be ensured to research participants: a systematic review. Public Health Ethics 4(2):160–184
22. Council for International Organizations of Medical Sciences (2016) International ethical guidelines for health- related research involving humans
23. The Centre for Research on Multinational Corporations (SOMO) (2015) Post-trial access to treatment. Corporate best practices. Pharmaceutical sector. SOMO paper.
24. NHS Health Research Authority (2013) Care after research: a framework for NHS RECS
25. Lei n.° 46/2004. Portugal. Aprova o regime jurídico aplicável à realização de ensaios clínicos com medicamentos de uso humano. Available at: http://www.fcsaude.ubi.pt/comissaoetica/docs/Lei_2004_46.pdf>
26. Klein R (2014) "Post-trial responsibilities". Post-trial responsibilities: ethics and implementation, Harvard Law School, Cambridge, MA. Available at: <http://mrctcenter.org/wp-content/uploads/2015/11/2014-09-18_harvard_mrct_pta_conf_slides_for_session_2.pdf>
27. (2017) Post-Trial Responsibilities Framework. Continued Access to Investigational Medicines. Multi-regional clinical trials center. Brigham and Women's Hospital and Harvard, (Version 1.1)
28. Ciaranello AL, Walensky RP, Sax PE, Chang Y, Freedberg KA, Weissman JS (2009) Access to medications and medical care after participation in HIV clinical trials: a systematic review of trial protocols and informed consent documents. HIV Clin Trials 10(1):13–24
29. World Health Organization (2014) Global status report on noncommunicable diseases 2014. Geneva, Switzerland, 298 p
30. Mano MS, Rosa DD, Dal Lago L (2006) Multinational clinical trials in oncology and post-trial benefits for host countries: where do we stand? Eur J Cancer 42(16):2675–2677
31. Shah S, Elmer S, Grady C (2009) Planning for posttrial access to antiretroviral treatment for research participants in developing countries. Am J Public Health 99(9):1556–1562
32. Caldwell PH, Murphy SB, Butow PN, Craig JC (2004) Clinical trials in children. Lancet 364(9436):803–811
33. Joseph PD, Caldwell PHY, Tong A, Hanson CS, Craig JC (2016) Stakeholder views of clinical trials in low- and middle-income countries: a systematic review. Pediatrics 137(2):e20152800
34. The United Nations Inter-Agency Group for Child Mortality Estimation (2017) The World Health Organization, the World Bank Group and the United Nations Population Division. Levels and Trends in Child Mortality. Estimates Developed by the UN Inter-Agency Group for Child Mortality Estimation. Report 2017. Available online at: http://www.childmortality.org. Accessed 9 Dec 2017
35. Hossain M, Chisti MJ, Hossain MI, Mahfuz M, Islam MM, Ahmed T (2017) Efficacy of World Health Organization guideline in facility-based reduction of mortality in severely malnourished children from low and middle-income countries: a systematic review and meta-analysis. J Paediatr Child Health 53:474–479
36. Rahman AE, Moinuddin MD, Molla M, Worku A, Hurt L, Kirkwood B (2014) Childhood diarrhoeal deaths in seven low- and middle-income countries. Bull World Health Organ 92:664–671
37. Joseph PD, Caldwell PHY, Barnes EH, Craig JC (2017) Disease burden-research match? Registered trial s in child health from low- and middle-income and high-income countries. J Paediatr Child Health 53(7):667–674
38. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. (2014) Tri-Council Policy Statement: ethical conduct for research involving humans. http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf. Accessed 21 Feb 2018
39. Dal-Ré R, Ndebele P, Higgs E, Sewankambo N, Wendler D (2014) Protections for clinical trials in low and middle income countries need strengthening not weakening. BMJ 349:g4254
40. Briggs R, Robinson S, O'Neill D (2012) Ageism and clinical research. Ir Med J 105(9):311–312
41. Herrera AP, Snipes SA, King DW, Torres-Vigil I, Goldberg DS, Weinberg AD (2010) Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. Am J Public Health 100(Suppl 1):S105–S112
42. Cohen ER, O'Neill JM, Joffres M, Upshur RE, Mills E (2009) Reporting of informed consent, standard of care and post-trial obligations in global randomized intervention trials: a systematic survey of registered trials. Dev World Bioeth 9(2):74–80
43. World Health Organization. International Clinical Trial Registry Platform. The WHO Registry Network. Available at: http://www.who.int/ictrp/network/en/. Accessed Jan 2017