CURRENT MEDICINE

MIDITERRANEAN JOURNALS

2022, Volume 1, ID 610
Original Research
DOI: 10.55085/cm.2022.610

Overview of Phase IV Clinical Trials Targeting COVID-19: Status Report of Studies Registered on the ClinicalTrials.gov Platform

Renato Ferreira-da-Silva [a,b,c], João Miguel Alves [b,c]

[a] Porto Pharmacovigilance Centre, Faculty of Medicine of the University of Porto, Porto, Portugal.
[b] Department of Community Medicine, Health Information and Decision, Faculty of Medicine of the University of Porto, Porto, Portugal.
[c] CINTESIS – Center for Health Technology and Services Research, Porto, Portugal.

Received: 29 Nov 2021;
Revised: 10 Jan 2022;
Accepted: 14 Jan 2022;
Published: 31 Jan 2022

Academic Editor:
Dr. Anoop Kumar

Correspondence: Renato Ferreira da Silva, Porto Pharmacovigilance Centre, Faculty of Medicine of the University of Porto, Porto, Portugal.
Email: renato.ivos@gmail.com

Cite this article as: da Silva RF, Alves JM. Overview of phase IV clinical trials targeting COVID-19: status report of studies registered on the ClinicalTrials.gov platform. Curr Med. 2022;1:610. [https://doi.org/10.55085/cm.2022.610]

Copyright © 2022 **Renato Ferreira-da-Silva R and Alves JM.** This is an open access article distributed under the Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Authors' contributions
The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript, and provided approval for this final revised version.

Funding
This work was financed by national funds and Community funds from the European Social Fund (ESF) through FCT – Fundação para a Ciência e a Tecnologia (Portugal), under the PhD scholarship 2020.10231.BD (DOCTORATES 4 COVID-19) by Renato Ivo Ferreira da Silva.

Acknowledgments
None.

Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this article.

ABSTRACT

Introduction: Phase IV trials evaluate drugs' efficacy, safety, and tolerability in a real-world setting, which may provide evidence related to the safety of approved drugs. This study aimed to characterize the phase IV clinical trials registered at ClinicalTrials.gov targeting COVID-19 and reflect on future needs for post-marketing clinical trials.

Methods: A descriptive cross-sectional study was performed in the ClinitalTrials.gov database with phase IV clinical trials addressed to COVID-19. The search was carried out on March 23rd, 2021, considering search filters for this disease.

Results: A total of 146 protocols were retrieved through a structured search. The results showed the need to promote new, blinded, and larger sample-size phase IV clinical trials. 93.9% of the clinical trials were funded by individuals, universities, and organizations (category "other" funders), and 56.8% were open-label. America and Europe played a more critical role in phase IV clinical trials, with the former leading with 58 trials spread across five countries and the latter with 38 trials in 17 countries. More than two-thirds of the trials (69.8%) included 500 participants.

Conclusions: For the observed period, phase IV clinical trials registered in the ClinicalTrials.gov were dominated by short-term follow-up, open-label designs, small sample sizes, funded mainly by individuals, universities, and organizations, and centered mainly in America and Europe. The methodological features of future studies should be emphasized, namely adequate sample sizes, for which appropriate funding for the implementation of these studies is paramount.

Keywords: COVID-19; Pharmacovigilance, Pharmacoepidemiology, Clinical Trials, Phase IV as Topic, Registries.

INTRODUCTION

Clinical trials play a central role in the study and consequent approval of drugs. Although rigorous pre-marketing studies are required for all new medicines 1,2, the safety profile of a drug at the time of regulatory approval is often incomplete due to some characteristics of phase I–III trials 3, such as sample size/limited number of individuals, short duration/limited follow-up time, strict inclusion criteria and/or exclusion of special populations (e.g., pregnant, elderly or polymedicated), meaning that the characteristics of these drugs are not known in-depth 4. If effectiveness is of great importance in the post-marketing phase, safety is the cornerstone in monitoring the drug's behavior under actual conditions of use. Adverse drug reactions constitute an essential and worrying public health problem associated with high morbidity and mortality, being identified as the fourth and sixth causes of death, after heart disease, cancer, and stroke 5, and are associated with a large share of annual health costs in developed countries 6. In the past, post-marketing research, post-marketing surveillance, and pharmacovigilance were identical concepts to "phase IV studies" as the main activities of regulatory agencies were focused on monitoring adverse drug reactions 7.

However, not all research required by regulatory agencies is focused on safety issues. Phase IV clinical studies can be defined as extensive studies, which may or may not be randomized trials, conducted after a drug is approved by a regulatory agency such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency, often to evaluate additional therapeutic uses and drug's safety over a longer-term than is possible in a phase III trial 4. Compared to pre-marketing phase I–III trials, phase IV clinical studies evaluate the drug in a real-world setting, which may provide evidence to ensure or further refine the safety of approved drugs 3,8,9. Phase IV studies assume methodological variations in the field of pharmacoepidemiologic studies than the preceding clinical trials (early I, I, I/II, II, II/III, III phases), i.e., may have a wider variety of designs 10. Examples of study designs that might fall under the post-marketing research are phase IV clinical trials, practice-based clinical experience studies, large simple trials, equivalence trials, post-marketing surveillance studies such as effectiveness studies, pharmacovigilance studies, and pharmacoeconomic studies 8. However, ClinicalTrials.gov phase IV studies are defined as "clinical trials occurring after FDA has approved a drug for marketing. They include post-market requirement and commitment studies that are required of or agreed to by the study sponsor" 11. Thus, and based on the categorization of this database, only clinical trials in phase IV are considered, leaving out other clinical study designs – such as observational studies - which would also be valid at this phase.

In the current era of the coronavirus disease 19 (COVID-19) pandemic, the development of drugs for this disease, including vaccines, will need to be fast-tracked through the usual pre-licensing development stages12. At issue are drugs approved for COVID-19 and others approved for other therapeutic indications and are now understudied for this disease. However, in the current scenario, the surveillance of COVID-19 drugs in the real-world setting becomes even more paramount. Post-authorization studies for safety and effectiveness complement prelaunch clinical trials and not replacements13.

All these assumptions support the strong need identified for clinical trials in the post-marketing phase (post-authorization safety/efficacy studies) - and not just in the pre-marketing phase - encouraging the realization of randomized and double-blind studies. This study aimed to characterize the phase IV clinical trials registered at ClinicalTrials.gov targeting COVID-19 - new drugs or already approved for other therapeutic indications - and reflect on future needs for post-marketing clinical trials. We focus on variables that are desirable for generating reliable evidence from clinical trials, including sample size and factors associated with randomization and blinding.

METHODS

A descriptive cross-sectional study was performed in the ClinitalTrials.gov database with phase IV clinical trials addressed to COVID-19. ClinicalTrials.gov is a web-based resource that provides easy access to publicly and privately supported clinical studies on a wide range of diseases and conditions and was first launched in February 2000. This public trial registry, maintained by the National Library of Medicine at the U.S. National Institutes of Health (NIH), aggregates several clinical interventions (clinical trials in different phases) and observational studies11. Hence, the ClinicalTrials.gov registry is considered the most comprehensive source for clinical trial information worldwide 14,15,16.

Clinical trials retrieved from a search performed on March 23rd, 2021, applying filters for disease (using the terms Covid19, SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2, 2019-nCoV, 2019 novel coronavirus, Wuhan coronavirus) and study phase (IV) at ClinicalTrials.gov database were eligible for inclusion. Observational studies were not considered for inclusion since this database only considers clinical trials in phase IV of the study type. No sample size was formally calculated since all the survey results were included in the analysis. The variables included were: start date (1st and 2nd semester 2020, and 1st and 2nd semester 2021), expected duration of the study (≤12, 13-24, 25-36, 37-45, ≥46 months), status (not yet recruiting; recruiting; enrolling by invitation; active, not recruiting; terminated; completed; withdrawn; suspended), age of participants (child [birth-17y], adult [18y-64y], older adult [65y+]), primary purpose (prevention, treatment, supportive care, other), intervention type (drug, device, procedure, behavioural, biological, dietary supplement, radiation, diagnostic test, combination product, genetic, other; all kinds of available approaches were considered), anticipated enrolment (0-100, 101-500, 501-1000, 1001-5000, 5001-10000, >10000), masking (open-label, single-blind, double-blind, triple-blind, quadruple-blind), allocation (randomised, non-randomised), interventional model (parallel assignment, single group assignment, sequential assignment, crossover assignment, factorial assignment), founding source (industry, NIH, U.S. Federal, other) and location where the studies are being conducted. The selected variables were obtained from the

database's information, based on the sponsor's and researchers' information in submitting the study on this platform. The variables' absolute and relative frequencies were calculated using descriptive statistics with R version 4.0.4 (R: A language and environment for statistical computing).

RESULTS

A total of 146 protocols were retrieved through a structured search. Most of the clinical trials included were in adults and older adults (91.1%), although a small percentage also included children (4.1%), or just one of the age groups - adults (3.4%) and older adults (1.4%). Overall, the highest percentage of trials were recruiting (49.3%), were expected to start in the first semester of 2020 (46.6%), had an expected duration ≤12 months (64.4%), had treatment as the primary purpose (75.3%), used drugs as single intervention (72.6%), had small sample sizes (0-100 participants; 41.7%), were open-label (56.8%), were randomized (91.5%), were parallel assignment (85.6%) and had funding sources from institutions other than the industry, the NIH, and the U.S. Federal (83.6%). There were also mixed sources of funding from the industry or NIH with funds other than these, even if residual (9.6% and 0.7%, respectively) (Table 1).

The location of the conduction of the clinical trials shows that they are widely distributed across the globe across four continents: America (58 trials in 5 countries), Europe (38 trials in 17 countries), Asia (26 trials in 9 countries), and Africa (13 trials in 5 countries). Twelve clinical trials present no reference to location.

Table 1: Characteristics of phase 4 clinical trials registered at ClinicalTrials.gov targeting COVID-19.

Variables	Studies registered in ClinicalTrials.gov No./Total No. (%)
Start date	
1st semester 2020	68/146 (46.6)
2nd semester 2020	48/146 (32.9)
1st semester 2021	29/146 (19.9)
2nd semester 2021	1/146 (0.7)
Expected duration (months)	
≤12	94/146 (64.6)
13-24	39/146 (26.7)
25-36	10/146 (6.8)
37-45	2/146 (1.4)
≥46	1/146 (0.7)
Status	
Recruiting	72/146 (49.3)
Not yet recruiting	26/146 (17.8)
Completed	19/146 (13.0)
Active, not recruiting	8/146 (5.5)
Enrolling by invitation	8/146 (5.5.)
Withdrawn	7/146 (4.8)
Terminated	4/146 (2.7)
Suspended	2/146 (1.4)
Age of participants (years)	
Adult, Older Adult	133/146 (91.1)
Child, Adult, Older Adult	6/146 (4.1)
Adult	5/146 (3.4)
Older Adult	2/146 (1.4)
Primary purpose	
Treatment	110/146 (75.3)
Prevention	32/146 (21.9)
Supportive care	3/146 (2.1)
Other	1/146 (0.7)
Intervention type	
Single intervention type	123/146 (84.3)
Drug	106/123 (86.2)
Biological	15/123 (12.2)
Dietary supplement	2/123 (1.6)

Multiple intervention type	23/146 (15.8)
Drug | Combination Product	2/23 (8.7)
Drug | Device	2/23 (8.7)
Drug | Dietary supplement	3/23 (13.0)
Drug | Other	12/23 (52.2)
Biological | Behavioral	1/23 (4.4)
Biological | Other	2/23 (8.7)
Dietary supplement | Combination product	1/23 (4.4)
Anticipated enrollment (no. of participants)	
0-100	58/146 (41.7)
101-500	39/146 (28.1)
501-1000	19/146 (13.7)
1001-5000	16/146 (11.5)
5001-10000	3/146 (2.2)
>10000	4/146 (2.9)
Study type	
Interventional	146/146 (100)
Masking	
Open-label	83/146 (56.8)
Single-blind	17/146 (11.6)
Double-blind	16 /146 (11.0)
Triple-blind	13/146 (8.3)
Quadruple-blind	17/146 (11.6)
Allocation	
Randomised	118/146 (91.5)
Nonrandomized	11/146 (8.5)
Intervention model	
Parallel assignment	125/146 (85.6)
Single group assignment	18/146 (12.3)
Sequential assignment	1/146 (0.7)
Crossover assignment	1/146 (0.7)
Factorial assignment	1/146 (0.7)
Founding source	
Industry	9/146 (6.2)
Industry | Other	14/146 (9.6)
NIH | Other	1/146 (0.7)
Other	122/146 (83.6)

Table 2: Geographical characterisation of phase 4 clinical trials registered at ClinicalTrials.gov targeting COVID-19.

Continent	Country	Studies registered in ClinicalTrials.gov No./Total No. (%)
Europe	Netherlands	4/146 (3.0)
	Norway	2/146 (1.5)
	Poland	1/146 (0.7)
	Belgium	2/146 (1.5)
	Czechia	2/146 (1.5)
	Denmark	2/146 (1.5)
	Slovenia	1/146 (0.7)
	Spain	10/146 (7.5)
	Sweden	1/146 (0.7)
	Ukraine	1/146 (0.7)
	United Kingdom	3/146 (2.2)
	France	3/146 (2.2)
	Germany	1/146 (0.7)
	Greece	1/146 (0.7)
	Ireland	1/146 (0.7)
	Italy	1/146 (0.7)

Africa	Mozambique	1/146 (0.7)
	Cameroon	1/146 (0.7)
	Egypt	9/146 (6.7)
	Tunisia	1/146 (0.7)
	Guinea-Bissau	1/146 (0.7)
Asia	Pakistan	4/146 (3.0)
	Qatar	2/146 (1.5)
	Russian Federation	1/146 (0.7)
	Saudi Arabia	1/146 (0.7)
	China	9/146 (6.7)
	Thailand	1/146 (0.7)
	Turkey	1/146 (0.7)
	Hong Kong	1/146 (0.7)
	India	1/146 (0.7)
	Iran	4/146 (3.0)
	Israel	1/146 (0.7)
America	Mexico	3/146 (2.2)
	Argentina	5/146 (3.7)
	Brazil	9/146 (6.7)
	Canada	1/146 (0.7)
	United States	39/146 (29.1)

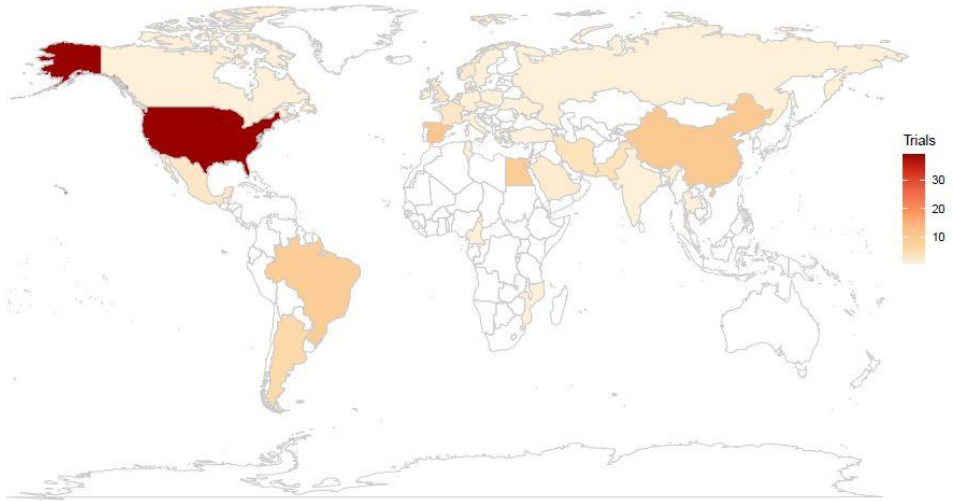

Figure 1. Worldwide distribution of the location of phase 4 clinical trials registered at ClinicalTrials.gov targeting COVID-19.

DISCUSSION

This study provided a descriptive assessment of phase IV clinical trials at a time of pandemic crisis, identifying areas of relative weakness – research gaps - or strength, joining efforts to monitor and analyze the actual use of these products in daily clinical practice. Based on the literature search, we are strongly convinced that this is the first study conducted on the landscape of phase IV clinical trials targeting COVID-19.

Compared to prior analyses assessing the overall quality of the clinical trials landscape 16, our results showed some interesting findings. However, our results characterize the clinical trials that have started just months after the beginning of the COVID-19 pandemic. Even so, many disparities identified in our study are corroborated by previous studies, namely concerns that included a relatively high prevalence of clinical trials with inadequate sample sizes and insufficiently described methodologies 17,18.

First, most randomized, open-label, phase IV interventional studies with a low expected duration (≤12 months). Califfs et al. 16 research revealed that 3.3% of all interventional clinical trials registered from October 2007 through September 2010 were terminated or withdrawn. We identified that 4.8% of the trials were withdrawn and 2.7% were closed, which should be considered without significant concerns. Furthermore, 39.7% of the clinical trials were already complete by March 31st, 2021, so it should be possible to draw positive

or negative conclusions about drugs' efficacy, safety, and tolerability with different action mechanisms.

Second, 93.9% of the clinical trials were funded by individuals, universities, and organizations (category "other" funders), of which 0.7% had accrued financial support from the NIH. Only 15.8% of clinical trials had direct support from the industry, of which 9.6% accumulated from other funding sources. Still, it is interesting to raise hypotheses that motivate the industry to advance to phase IV clinical trials. Regulatory agencies may require them or by industry initiative. In the latter, there may be interest in expanding the portfolio of therapeutic indications of its approved products. In the particular case of COVID-19, a potential interest by the industry is to be expected, as many drugs under study result from "drug repurposing" initiatives for previously approved drugs. Additionally, the centrality of research outputs to academic recognition and promotion creates a much more compelling incentive to undertake research among academics than practice-based health professionals 19,20.

Third, phase IV clinical trials can have several designs, and single-arm, non-randomized, or open-label trials are valid. The most clinical registered trials identified in our analysis were open-label (56.8%). Since most of our trials were not funded by the industry, we would expect blinding to be more significant than open-label trials. We know that academic clinical trials are more likely to use blinding than industry. An earlier analysis crossed ClinicalTrials.gov trials with the European Union Clinical Trials Register, identifying nine phase IV trials targeting COVID-19 21. All randomized controlled trials were aimed at adults and older adults, among which five of the trials were open-label, three were single-blind (participant), and one was double-blind.

Fourth, America and Europe seem to play a more critical role in phase IV clinical trials, with the former leading with 58 trials spread across five countries and the latter with 38 trials in 17 countries. The significant investment in research projects, the wide dissemination of open calls for clinical studies, the encouragement of American and European regulatory agencies to promote new clinical trials, and the strong connection between academia and clinical centers might be potential explanations for these findings. Also, clinical trials registration practices may be done in databases other than the ClinicalTrials.gov registry in many countries.

Compared to pre-marketing trials, phase IV trials evaluate drugs' efficacy, safety, and tolerability in a real-world setting, which may provide evidence related to the safety of approved drugs 22,23. When a broader search is carried out, the number of clinical studies in progress targeting COVID-19 is much higher and needs to be constantly updated 2425. With the approval of new drugs, medical devices, and other health products aimed at the treatment and/or prophylaxis of COVID-19, an increase in the number of phase IV trials is expected, independent research teams at the producers' initiative or by the regulatory authorities.

Lastly, more than two-thirds of the trials (69.8%) include up to 500 participants. Small sample sizes can lead to low power (e.g., difficulty in identifying rare adverse events), compromising the external inference of results. Although small phase IV studies might be used to evaluate the effectiveness of health technology in the form of a drug in special subgroups of patients, the studies that we have reported are not only directed to these populations; therefore, larger sample sizes would be expected 3. Still, clinical trials with small sample sizes are unlikely to be sufficiently informative in other contexts, such as establishing evidence of efficacy or comparing effective treatments for better decisions in clinical practice 26,27,28. Additionally, budget, time, personnel, and other resource limitations can justify not constituting large recruitment pools 29.

This article performed a status report for studies registered on the ClinicalTrials.gov platform specifically targeting COVID-19. Post-marketing studies have been unambitious in their designs, advancing with small samples, brief follow-up periods, and no blinding. Although this analysis has focused on clinical trials, observational and cost-effectiveness studies were also considered, as well as data mining tools and updated safety databases. Additional randomized, blinded clinical trials involving different standard comparators than were used in early phases may be undertaken to differentiate the investigational drug further from other agents 30.

Our research also identified that most post-marketing studies were not industry-funded. However, this trend will be growing, strongly driven by placing new COVID-19 targeting products on the market. In our vision for the future, the pharmaceutical industry must have a more significant commitment to implementing clinical trials in the post-marketing phase, whether they are aimed at COVID-19 or other emerging conditions. Sometimes there may be a lack of interest in promoting these studies at the initiative of market authorization

holders. Companies can adopt a policy of channeling resources to phase III studies, which can be synonymous with introducing new products on the market. However, we must also not forget that phase IV studies can reveal new clinical hypotheses, namely, to explore new formulations, interactions with other drugs, new indications, other patentable innovations, and new population groups such as pregnant women 31.

A final topic of debate that deserves discussion refers to the globalization of clinical research and its registration on multiple platforms 32,33. Although World Health Organization (WHO) provides a portal to many clinical trial registries, notably phase IV clinical trials, no duplication in the registries is recognized, nor are the datasets of interest available for download 34 (e.g., reasons for clinical trials withdrawal).

There are some inevitable limitations in this study. First, it only included clinical trials registered in ClinicalTrials.gov, so other trials not registered in this database were not included. We are aware that we restricted our focus to only one clinical trial registry, potentially underestimating the current evidence. Second, some residual missing data were identified in some fields but without great relevance for the final analysis. Even so, all of these findings raise important issues that must be addressed through systematic and targeted procedures, with improvement in the designs employed in future clinical trials targeting this disease or other emerging public health conditions.

CONCLUSION

We found that post-marketing clinical trials - phase IV - targeting COVID-19 were dominated by short-term follow-up, open-label designs, small sample sizes, funded mainly by individuals, universities, and organizations, and centred mainly in America and Europe. These findings raise questions about the capacity of the phase IV clinical trials to provide sufficient amounts of high-quality evidence in the effectiveness and safety of drugs already approved and available in clinical practice. The methodological features of future studies should be emphasized, namely adequate sample sizes, for which appropriate funding for the implementation of these studies is necessary.

REFERENCES

[1] Englev E, Petersen K. [ICH-GCP guideline: quality assurance of clinical trials. Status and perspectives]. Ugeskr Laeger. 2003 Apr 14; 165(16):1659–62.

[2] Dixon JR. The international conference on harmonisation good clinical practice guideline. Qual Assur. Apr-Jun 1999; 6(2):65–74.
DOI: 10.1080/105294199277860

[3] Gale EAM. Post-marketing studies of new insulins: sales or science? BMJ. 2012 Jun 12; 344: e3974.
DOI: 10.1136/bmj.e3974

[4] Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing Clinical Research. Wolters Kluwer Health; 2013.

[5] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalised patients: a meta-analysis of prospective studies. JAMA. 1998 Apr 15; 279(15):1200-5. DOI: 10.1001/jama.279.15.1200

[6] Bakke OM, Manocchia M, de Abajo F, Kaitin KI, Lasagna L. Drug safety discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993—a regulatory perspective. Clin Pharmacol Ther. 1995 Jul; 58(1):108–17.
DOI: 10.1016/0009-9236(95)90078-0

[7] Hartzema A. Pharmacoepidemiology. Vol 41, 3rd ed. Cincinnati:Harvey Whitney Books; 1998.

[8] Glasser SP, Salas M, Delzell E. Importance and challenges of studying marketed drugs: what is a phase IV study? Common clinical research designs, registries, and self-reporting systems. J Clin Pharmacol. 2007 Sep; 47(9):1074–86.
DOI: 10.1177/0091270007304776

[9] Schmidt LG, Grohmann R, Helmchen H, Langscheid-Schmidt K, Müller-Oerlinghausen B, Poser W, et al. Adverse drug-reactions—an epidemiological study at psychiatric hospitals. Acta Psychiatr Scand. 1984 Jul; 70(1):77–89.
DOI: 10.1111/j.1600-0447.1984.tb01185.x

[10] Wells KB. Treatment research at the crossroads: the scientific interface of clinical trials and effectiveness research. Am J Psychiatry. 1999 Jan; 156(1):5-10. DOI: 10.1176/ajp.156.1.5

[11] Medicine USNLo. ClinicalTrials.gov. [Accessed 2022 Jan 19].
Available from: https://clinicaltrials.gov/ct2/home

[12] Health NIo. Coronavirus Disease 2019 (COVID-19): Treatment Guidelines. [Accessed 2022 Jan 19].

Available from: https://www.covid19treatmentguidelines.nih.gov/whats-new/

[13] Dhanda S, Osborne V, Lynn E, Shakir S. Postmarketing studies: can they provide a safety net for COVID-19 vaccines in the UK? BMJ Evid Based Med. 2020 Oct 21:bmjebm-2020-111507. DOI: 10.1136/bmjebm-2020-111507

[14] Cihoric N, Tsikkinis A, van Rhoon G, Crezee H, Aebersold DM, Bodis S, et al. Hyperthermia-related clinical trials on cancer treatment within the ClinicalTrials.gov registry. Int J Hyperthermia. 2015; 31:609–14. DOI: 10.3109/02656736.2015.1040471

[15] Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet Gynecol. 2013 Nov;122(5):1077–81. DOI: 10.1097/aog.0b013e3182a9ca67

[16] Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007–2010. JAMA. 2012 May 2; 307(17):1838–47. DOI: 10.1001/jama.2012.3424

[17] Meinert CL, Tonascia S, Higgins K. Content of reports on clinical trials: a critical review. Control Clin Trials. 1984 Dec; 5(4):328-47. DOI: 10.1016/s0197-2456(84)80013-6

[18] Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. Lancet. 2005 Mar 26-Apr 1; 365(9465):1159-1162. DOI: 10.1016/s0140-6736(05)71879-1

[19] Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Q. 2016 Sep; 94(3):485–514. DOI: 10.1111/1468-0009.12210

[20] Moher D, Goodman SN, Ioannidis J. Academic criteria for appointment, promotion and rewards in medical research: where's the evidence? Eur J Clin Investig. 2016 May;46(5):383-5. DOI: 10.1111/eci.12612

[21] Canevelli M, Remoli G, Trentin F, Riccardi G, Tariciotti L, Risoleo G, et al. The Pipeline of Therapeutics Testing During the Emergency Phase of the COVID-19 Outbreak. Front Med (Lausanne). 2020 Sep 24; 2020; 7: 552991. DOI: 10.3389/fmed.2020.552991

[22] Gale EAM. Post-marketing studies of new insulins: sales or science? BMJ. 2012 Jun 12; 344:e3974. DOI: 10.1136/bmj.e3974

[23] Glasser SP, Salas M, Delzell E. Importance and challenges of studying marketed drugs: what is a phase IV study? Common clinical research designs, registries, and self-reporting systems. J Clin Pharmacol. 2007 Sep; 47(9):1074-86. DOI: 10.1177/0091270007304776

[24] COVID-19 Clinical Research Coalition. Global coalition to accelerate COVID-19 clinical research in resource-limited settings. Lancet. 2020 Apr 25; 395(10233):1322-1325. DOI: 10.1016/s0140-6736(20)30798-4

[25] Global Data Healthcare. The UK leads Covid-19 clinical investigations in Europe. Clin trial sarena. [Accessed 2022 Jan 19]. Available from: https://www.clinicaltrialsarena.com/comment/europe-clinical-trials-covid-19/

[26] Yusuf S, Collins R, Peto R. Why do we need some large, simple randomised trials? Stat Med. Oct-Dec 1984; 3(4):409-22. DOI: 10.1002/sim.4780030421

[27] Peto R, Collins R, Gray R. Large-scale randomised evidence: large, simple trials and overviews of trials. J Clin Epidemiol. 1995 Jan;48(1):23-40. DOI: 10.1016/0895-4356(94)00150-o

[28] Califf RM, DeMets DL. Principles from clinical trials relevant to clinical practice: part I. Circulation. 2002 Aug 20; 106(8):1015-21. DOI: 10.1161/01.cir.0000023260.78078.bb

[29] Suresh K, Chandrashekara S. Sample size estimation and power analysis for clinical research studies. J Hum Reprod Sci. 2012 Jan; 5(1):7-13. DOI: 10.4103/0974-1208.97779

[30] McEvoy JP, Freudenreich O. CHAPTER 3 - Issues in the Design and Conductance of Clinical Trials. In: McArthur RA, Borsini F, eds. Animal and Translational Models for CNS Drug Discovery. Academic Press; 2008:75-95.

[31] Nikfar S. Safety Testing, Clinical Studies. In: Wexler P, ed. Encyclopedia of Toxicology (Third Edition). Academic Press; 2014:203-204.

[32] Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, et al. Ethical and scientific implications of the globalisation of clinical research. N Engl J Med. 2009 Feb 19; 360(8): 816-823. DOI: 10.1056/nejmsb0803929

[33] Pasquali SK, Burstein DS, Benjamin DK Jr, Smith PB, Li JS. Globalisation of pediatric research: analysis of clinical trials completed for pediatric exclusivity. Pediatrics. 2010 Sep; 126(3):e687-e692.
DOI: 10.1542/peds.2010-0098

[34] Califf RM, Harrington RA. American industry and the U.S. Cardiovascular Clinical Research Enterprise an appropriate analogy? J Am Coll Cardiol. 2011 Aug; 58(7):677-80. DOI: 10.1016/j.jacc.2011.03.048