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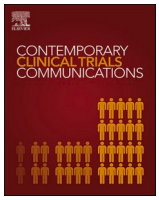

Clinical trials in Bosnia and Herzegovina: Challenges and future perspectives

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ABSTRACT

Background: Clinical trials (CTs) are research investigations in which participants receive medical treatments, interventions, or tests to assess their safety and efficacy. Each planned clinical is registered through local or national medical agencies, which may differ in the amount of administrative and legal procedures. The objective of this study was to systematically analyze the registration process for clinical trials in Bosnia and Herzegovina in comparison to other Balkan countries.

Methods: The search strategy was based using two online databases: Clinicaltrials.gov (CTGR) and Cortellis Clinical Trials Intelligence (cTi). Search engines included studies until 26th April 2021 and countries were compared in terms of the number of studies, status, type, funding, clinical phases and demographic data.

Results: The total number of clinical trials from Bosnia and Herzegovina recorded in the CTGR database was 219, while the cTi database comprised 254 registered studies. The total number of reported clinical trials in CTGR and cTi databases were highest in Serbia (n = 1229, n = 1438), followed by Croatia (n = 1142, n = 1300), and Slovenia (n = 801, n = 948), respectively. However, the highest number of clinical trials per capita is in Slovenia (3.85e-4 in CTGR; 4.56e-4 in cTi), followed by Croatia (2.78e-4 in CTGR; 3.17e-4 in cTi), Serbia (1.41e-4 in CTGR; 1.65e-4 in cTi), and Bosnia and Herzegovina (0.67e-4 CTGR; 0.78e-4 cTi).

Conclusion: Our analysis showed that Bosnia has the lowest number of clinical trials in the Balkans. Furthermore, the registration process is complex and longer than in developed countries. Since the healthcare system has been in a transition in the past decade, clinical trials are underutilized as a tool for the improvement of patient care. The clinical trial registration process could be improved by establishing an ethical committee at the state level and by enabling a parallel submission process to ethical committees and databases.

1. Introduction

Clinical trials (CTs) are research investigations in which volunteer participants are assigned by researchers/investigators to receive one or more treatments, interventions or tests to assess their safety and efficacy [1]. There are several steps and stages of approval in the clinical trials process before a drug or device can be sold in the consumer market. More precisely, clinical trials are conducted in 4 phases (1–4). Phase 1: The study is designed to determine the effects of the drug or device on humans including how it is absorbed, metabolized, and excreted. Phase 2: Studies test the efficacy of a drug or device. This second phase of testing can last from several months to two years and involves up to several hundred patients. Phase 3: Studies involve randomized and blind testing in several hundred to several thousand patients. Phase 4: Studies, often called Post Marketing Surveillance Trials, are conducted after a drug or device has been approved for consumer sale [2].

The first modern randomized controlled trial was performed in 1948, in which researchers have examined the effects of streptomycin on pulmonary tuberculosis. It has been estimated that from this period more than half of all clinical trials were never published [3]. To resolve this issue, the registration of clinical trials has been recommended [4]. The registration of clinical trials has become strongly encouraged

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worldwide, especially after 2005, when World Health Organization (WHO) and International Committee of Medical Journal Editors (ICMJE) that clinical researchers must register their clinical trials to be suitable for publication among member journals [5]. One of the largest databases of clinical trials is ClinicalTrials.gov, which is a governmental web-based resource managed by the US National Institute of Health (NIH). It provides easy access to all registered clinical trials on a wide range of diseases and conditions. By 26th of April 2021, CTGR contained 380,342 research studies in all 50 states and in 204 countries [6]. The rate of study registration has increased over time with voluntary registration of studies by sponsors and researchers together with new policies and laws requiring registration. Another database, Cortellis Clinical Trials Intelligence, was recently established in August 2013 by Thomson Reuters. This is a global clinical-drug-trial intelligence database including coverage of drugs, biologics, diagnostics, and biomarkers. By the 26th of April 2021, cTi contained 412,641 research studies [7].

Clinical studies involve the cooperation between academic institutions, hospitals and pharmaceutical companies. The general trend has been to move many clinical trials to low and middle-income countries. This has raised concerns because of the possible exploitation of disadvantaged populations. Since Bosnia and Herzegovina was in a state of reconstruction since 1995, the introduction of clinical trials has been gradual. No previous study has systematically reviewed and critically analyzed the clinical trial process in Bosnia and Herzegovina. The aim of this work is to systematically analyze the trend in clinical trials in Bosnia and Herzegovina until 26th of April 2021 and compare it with neighboring countries Slovenia, Croatia and Serbia.

2. Methods

The search strategy involved data mining of two online databases: Clinicaltrials.gov and Cortellis.com [6–8]. We used the term "Bosnia and Herzegovina" and for comparison of data "Croatia", "Serbia" and "Slovenia" were used. All the registered information of the entries was downloaded and manually analyzed. All searches were conducted on the same day and the time frame of each database was set until 26th April 2021.

Both Cortellis.com and Clinicaltrials.gov databases were mined for the following parameters: status of clinical trials (not yet recruiting, recruiting, active but not recruiting, terminated and completed), study

Table 1
Total number of clinical trials in ClinicalTrials.gov and Cortellis Clinical Trials Intelligence databases, the number of clinical trials in each of the Balkan countries from January 01, 1983 to April 26, 2021, recruitment status, study type, sex, study phase, and funding sources through two clinical trial registries for Bosnia and Herzegovina, Slovenia, Croatia, and Serbia.

	Bosnia and Herzegovina		Slovenia		Croatia		Serbia	
	CTGR	cTi	CTGR	cTi	CTGR	cTi	CTGR	cTi
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Registry total	380 342	412 641	380 342	412 641	380 342	412 641	380 342	412 641
Local	219 (0.06)	254 (0.06)	801 (0.21)	948 (0.23)	1 142 (0.3)	1 300 (0.32)	1 229 (0.32)	1 438 (0.35)
# Of clinical trials per capita	6.68E-5	7.74E-5	3.85E-4	4.56E-4	2.78E-4	3.17E-4	1.41E-4	1.65E-4
Status								
Not yet recruiting	1 (0.46)	4 (1.57)	12 (1.50)	19 (2.00)	3 (0.26)	26 (2.00)	4 (0.32)	22 (1.53)
Recruiting	26 (11.87)	40 (15.75)	139 (17.35)	229 (24.16)	157 (13.74)	224 (17.23)	163 (13.26)	236 (16.41)
Active, not recruiting	33 (15.07)	39 (15.35)	53 (6.62)	73 (7.70)	96 (8.46)	118 (10.33)	138 (11.22)	158 (10.99)
Terminated	21 (9.59)	27 (10.63)	40 (4.99)	68 (7.17)	85 (7.44)	114 (9.07)	102 (8.30)	147 (10.22)
Completed	126 (57.53)	143 (56.30)	469 (58.55)	538 (56.75)	710 (62.17)	799 (61.46)	753 (61.27)	857 (59.60)
Unknown status	6 (2.74)	1 (0.39)	70 (8.74)	20 (2.11)	66 (5.77)	18 (1.38)	43 (3.49)	17 (1.18)
Others	6 (2.74)	0 (0.00)	18 (2.25)	1 (0.11)	25 (2.18)	1 (0.076)	26 (2.11)	1 (0.07)
Study type								
Interventional	192 (87.67)	227 (89.37)	589 (73.53)	761 (80.27)	971 (85.02)	1163 (89.46)	1 109 (90.23)	1 340 (93.18)
Observational	26 (11.87)	26 (10.24)	210 (26.22)	183 (19.30)	170 (14.88)	135 (10.38)	119 (9.68)	94 (6.54)
Others	1 (0.46)	1 (0.39)	2 (0.25)	4 (0.42)	1 (0.087)	2 (0.15)	1 (0.08)	4 (0.28)
Sex								
Male	8 (3.65)	5 (1.97)	29 (3.62)	26 (2.74)	41 (3.59)	47 (3.61)	39 (3.17)	39 (2.71)
Female	21 (9.59)	22 (8.66)	74 (9.24)	79 (8.33)	65 (6.69)	63 (4.84)	53 (4..31)	69 (4.80)
Mixed sex group	190 (86.76)	227 (89.37)	698 (87.14)	843 (88.92)	1 036 (90.71)	1 190 (91.54)	1 137 (92.51)	1 330 (92.49)
Study phase								
Early Phase 1	1 (0.46)	1 (0.39)	1 (0.12)	1 (0.11)	3 (0.26)	3 (0.23)	1 (0.08)	0 (0)
Phase 1	12 (5.48)	7 (2.76)	22 (2.75)	12 (1.27)	24 (2.10)	15 (1.15)	37 (3.01)	18 (1.25)
Phase 1/Phase 2	NA	5 (1.97)	NA	14 (1.48)	NA	15 (1.15)	NA	24 (1.67)
Phase 2	39 (17.81)	34 (13.39)	102 (12.73)	158 (16.67)	173 (15.14)	204 (15.69)	283 (23.02)	284 (19.75)
Phase 2/Phase 3	NA	10 (3.94)	NA	18 (1.90)	NA	40 (3.07)	NA	52 (3.61)
Phase 3	129 (58.90)	149 (58.66)	226 (28.21)	335 (35.34)	592 (51.83)	716 (55.07)	683 (55.57)	816 (56.75)
Phase 4	11 (5.02)	18 (7.09)	66 (8.24)	158 (16.67)	75 (6.56)	132 (10.15)	66 (5.37)	97 (6.74)
Not Applicable	12 (5.48)	22 (8.66)	194 (24.22)	189 (19.94)	139 (12.17)	130 (10.00)	94 (7.65)	111 (7.72)
Phase not specified	15 (6.85)	8 (3.15)	190 (23.72)	63 (6.65)	136 (11.90)	45 (3.46)	65 (5.29)	36 (2.50)
Funder Type								
Industry	192 (87.67)	214 (84.25)	422 (52.68)	540 (56.96)	840 (77.93)	985 (75.76)	1 066 (86.74)	1 223 (85.05)
Others (individuals, universities, organizations, governments)	27 (12.33)	40 (15.75)	379 (47.32)	408 (43.04)	302 (26.44)	315 (24.23)	163 (13.26)	215 (14.95)

type (interventional or observational), sex (female or male), study phase (early phase 1, phase 1, phase 1/phase2, phase 2, phase 2/phase 3, phase 3 and phase 4) and funder type for all countries.

Additionally, national contribution to world science is shown as a percentage from the total number of studies. Furthermore, the number of conducted studies per capita was analyzed to understand the relationship between the country's population size and the number of registered clinical trials.

The number of clinical trials registered each year was evaluated to get insight into trends in the number of registered clinical trials in the

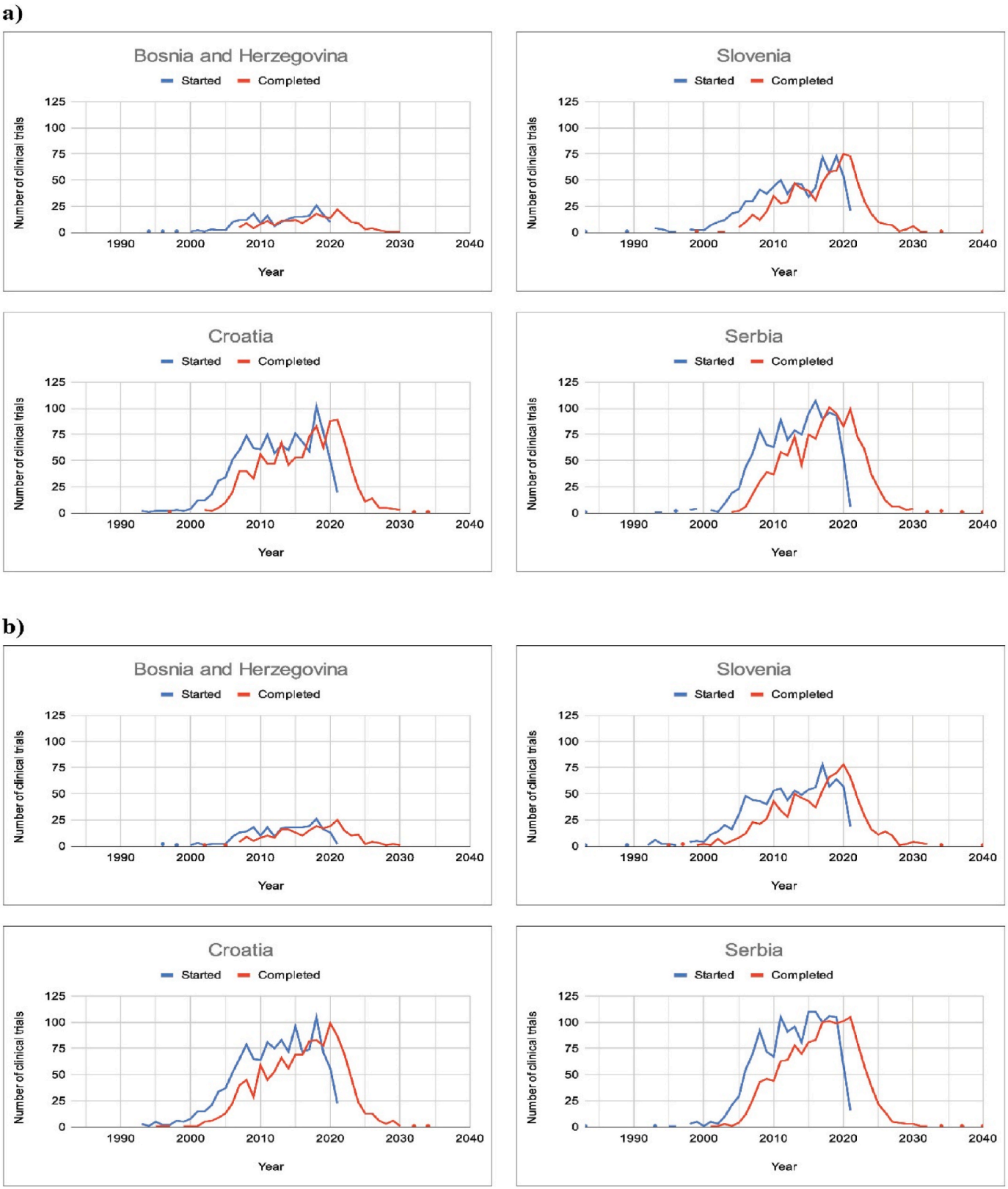

Fig. 1. Recorded clinical trials in a) Clinicaltrials.gov (CTGR), and b) Cortellis Clinical Trials Intelligence (cTi) according to the starting and completion years.

Balkan region, from 1983 (the first year of trial registration in the searched databases) to 2021. These data were plotted along a time axis to observe the registration trend among the bordering countries.

All analyses were done using Microsoft Excel® 2016.

3. Results

Two online public databases, Clinicaltrials.gov (CTGR) and Cortellis.com (cTi), were analyzed in order to determine the number, recruitment status, type, phase and funding source of clinical trials conducted in Bosnia and Herzegovina compared to the other Balkan countries (Table 1). Until 26 April 2021, total numbers of studies included in the CTGR and cTi were 380,342 and 412,641.

Clinical trials from Bosnia and Herzegovina represented 0.06% of total reported clinical trials in CTGR and cTi databases. When it comes to the other countries from the region, 0.2% of clinical trials were from Slovenia, 0.3% of studies from Croatia and 0.3% of clinical trials from Serbia. The highest number of clinical trials per inhabitant is in Slovenia, 3.8e-4 in CTGR and 4.6e-4 in cTi, followed by Croatia having 2.8*10e-4 in CTGR and 3.2e-4 in cTi, Serbia 1.4e-4 in CTGR and 1.6e-4 in cTi, and finally Bosnia and Herzegovina 0.7e-5 in CTGR and 0.8e-5 in cTi. Thus, Slovenia has fourfold higher number of clinical trials per inhabitant compared to Bosnia and Herzegovina.

Recruitment status is different in the two registries. Active recruiting status was registered for 11.8% trials in CTGR and 15.7% trials in cTi for Bosnia and Herzegovina, 17.3% trials in CTGR and 24.2% trials in cTi for Slovenia, 13.7% trials in CTGR and 17.2% trials in cTi for Croatia and 13.3% trials in CTGR and 16.4% trials in cTi for Serbia. Completed status was encountered in 57.5% trials in CTGR and 56.3% trials in cTi for Bosnia and Herzegovina, 58.5% trials in CTGR and 56.7% trials in cTi for Slovenia, 62.2% trials in CTGR and 61.46% trials in cTi for Croatia and 61.3% trials in CTGR and 59.6% trials in cTi for Serbia.

Most interventional studies were conducted in Serbia with 90.2% in CTGR and 93.2% in cTi.

Regarding clinical trial phases, phase 3 was the most common for all countries, even though a significantly lower percentage of phase 3 clinical trials was observed in Slovenia. Least number of clinical studies was classified as early phase 1, a trend observed for all four countries.

In both cTi and CTGR, industry sponsorship predominated for Bosnia and Herzegovina, Croatia and Serbia. Slovenia has pretty much equal contribution from both industry and university/government sectors.

The registration of clinical studies for ex-Yugoslav countries started right after declarations of independences of former republics in 1990s to both CTGR and cTi and with development of new policies and laws in these Balkan countries, registration peaked in 2018 (Fig. 1) [8].

Interestingly, no recorded increase in the number of clinical trials during the ongoing global pandemic of coronavirus disease 2019 (COVID-19) for any of analyzed countries in the last two and half years.

4. Discussion

Bosnia and Herzegovina has its own clinical trial registry agency called “Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina (ALMBIH)” and was established in 2009. Since then, no study has analyzed the scope and types of clinical trials in Bosnia and Herzegovina, especially not done in depth comparison to the other countries from the region.

4.1. Challenge 1: Clinical trial registration and management

The clinical trial registration process starts with the application and subsequent approval from the local ethics committee (EC). There are five existing ECs including University Clinical Centers in Sarajevo, Banja Luka, Mostar and Tuzla as well as the Medical Faculty of the University of Sarajevo. Each EC has its own guidelines for approval with very different timelines and takes anywhere between 1 and 15 months, depending on the local site. This is the longest step in the application process where trials with a limited recruitment phase/recruitment could face serious obstacles. Our proposal would be to establish a unique EC on the state level or create a unique rule book for all EC at the state level, which would reduce the wait time for the approval and expedite the start of the clinical trials.

After EC approval, the application is submitted to ALMBIH, in accordance with the Directives 2001/20/EC and 2005/28/EALMBIH is the state agency that oversees and approves each clinical trial. The timeline for the receipt of the approval is around 5 weeks. Another proposal for the improvement of the approval process would be to allow parallel submission of the application to EC and ALMBIH. Once ALMBIH approval is received, contract negotiations between the sponsor and the local site take place, which can take anywhere between 4 and 6 months [9]. In the most cases, the sponsor is a foreign entity, and legal discrepancies can hinder the start of the clinical trial, which can vary depending on the local site. Import/export license can be obtained within 25 days. Thus, the registration process, from the application to the local EC until contract negotiations and license, can realistically take up to 1.5 years (Table 2), which is a severe hindrance to sponsors. However, due to the limited number of studies in the database as well as the overall difference in approach to the data collection, only CTGR and cTi were used in clinical trial mining and in a depth analysis of Bosnia and Herzegovina, Croatia, Slovenia, and Serbia.

The number of clinical trials in Bosnia and Herzegovina is low compared to neighboring countries. For example, EU states such as Croatia and Slovenia have 4 times more trials per inhabitant than Bosnia and Herzegovina. Similarly, Serbia has more than twice the number of studies than Bosnia and Herzegovina. This data is even more apprehensive considering other countries had less than ten commenced studies prior to 1994, the time when the first clinical trial from Bosnia and Herzegovina was registered in the CTGR registry. Our analysis has confirmed our suspicion that Bosnia and Herzegovina does not utilize the advantages of clinical trial participation.

Within the first 6 months of corona outbreaks more than 2,150 research studies have been registered in CTGR and more than 23,000 publications were indexed in Pubmed [10]. Regardless of an ideal occasion to increase their global contribution in science and join international scientific endeavour in disease comprehension, republics of former Yugoslavia stay exceptionally lethargic regarding COVID-19 research.

4.2. Challenge #2: Participation of healthcare workers

Healthcare in Bosnia is under transition and there are several issues that could be improved in order to increase the number of clinical trials available to patients. For example, cancer patients in Bosnia lack proper access to targeted therapies. Previous studies have shown that patients in Bosnia do not receive timely therapy and that many patients are treated without access to targeted cancer medicines [11–13]. One of the

Table 2
Timeline for the registration process of clinical trials in Bosnia and Herzegovina, Slovenia, Croatia, and Serbia.

	Bosnia and Herzegovina	Slovenia	Croatia	Serbia
Contract Negotiations	4 months	N/A	N/A	N/A
CA	5 weeks	N/A	N/A	N/A
Local EC	5 months	2 months	N/A	N/A
Submission preparation	4 weeks	N/A	N/A	N/A
Import/export licence	Up to 25 days	N/A	N/A	N/A
Total registration time	**12 months**	**2–3 months**	**3–6 months**	**< 6 months**

ways that cancer patients could receive timely treatments is through participation in clinical trials. Thus, the healthcare system in Bosnia needs to integrate the access to clinical trials to be more robust through easier registration process and encouragement of physicians to get involved as investigators because it allows an avenue for further professional advancement.

Besides faster and robust registration, training of clinical trial investigators and team members should be readily available. For more oncology trials, allied health and diagnostic services should be accredited to meet international standards.

Finally, costs of conducting clinical trials since 2001 have grown drastically, a trend hard to follow for countries in development such as Bosnia and Herzegovina [14]. Personnel, drugs, laboratory, and clinical procedures charges are mostly sponsored by industry, while governmental budgets are extremely shrunken for research purposes. If Bosnia joined the EU, thorough system reform would be required to stimulate clinical study conduct in order to follow current research accomplishments from the region.

5. Conclusion

Our analysis showed that Bosnia has the lowest number of clinical trials in the Balkans. Major obstacle in the access to new clinical trials is the ineffective and bureaucratic registration process, which can last from several months to years. To expedite the registration process, establishment of a single ethical committee within the Agency for medicinal products and medical devices could significantly shorten the wait time for trial registration.

Availability of clinical trials benefits both patients and the public. Clinical studies introduce new, effective and cost-efficient drugs to the patients, which is especially important in low resource countries such tas Bosnia and Herzegovina as most patients are having difficulties in securing expensive drugs available in the market. Also, access to the clinical trials data and their results builds trust in medical professionals which is well shaken during COVID-19 pandemic, especially in Bosnia and Herzegovina where vaccine acceptance is only 25.7% [15,16].

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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