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Globalisation of industry-sponsored clinical trials for breast, lung and colon cancer research: trends, threats and opportunities

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ABSTRACT

Objective Breast, lung, colon cancers are the 'big killers' in oncology. Access to innovative treatments lags behind in low-income and middle-income countries. We investigated the geographic distribution of industry-sponsored trials; and whether results were reported in clinical trial registries.

Methods and analysis We conducted a search in ClinicalTrials.gov by: (i) study type: interventional; (ii) condition: breast, lung, colon cancer; (iii) phases: I–IV; (iv) funder: industry. Trials registered as of 30 June 2018 were extracted; for completed trials, a second extraction was performed on 30 September 2022.

Results We included 4177 trials. Phase I–IV trials involving only high-income countries were 3254/4177 (77.9%), while 923/4177 (22.1%) trials included at least one site in middle-income countries (MICs). Most phase III trials (416/688; 60.5%) involved MICs, including only lower MICs (6/416, 1.4%), only upper MICs (225/416, 54.1%) and lower and upper MICs (185/416, 44.5%). Phase IV trials involved MICs in 45/89 (50.6%) cases. Phase I and II trials included MICs in smaller proportions (72/950, 7.6% and 390/2450, 15.9%, respectively). No trials were run in low-income countries (LICs). Among completed trials, 430 out of 1854 (23.2%) involved MICs. Results had not been entered in the registry in 63.4% (1176/1854) of trials overall and 49.5% (213/430) of trials involving MICs.

Conclusion Trials for breast, lung and colon cancers are increasingly delocalised to countries likely unable to get access to innovative medicines. Furthermore, LICs are not hosting any industry-sponsored trials. Measures are needed to ensure benefit-sharing for trials countries; to improve transparency and to stimulate research addressing the needs of LICs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Globalisation of clinical trials is a well-known phenomenon, both concerning industry-sponsored and non-commercial research.
⇒ Most patients with cancer in low-income (LICs) and middle-income countries (MICs) lack access to innovative treatments, even if MICs are thought to significantly contribute to the advancement of clinical research in this field.

WHAT THIS STUDY ADDS

⇒ Our analysis of the geographic distribution of industry-sponsored clinical trials for breast, lung and colon cancer indicates a significant involvement of MICs in phase III and phase IV trials.
⇒ No clinical trials for breast, lung and colon cancer are run by industry sponsors in LICs.
⇒ A significant fraction of trials fails to report the results in the trial registry.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Research institutions and researchers in MICs should be empowered to take on a leading role in the cancer research agenda.
⇒ The cancer research and development agenda should include LICs, in order to address their specific unmet needs in cancer care.
⇒ Regulatory and legislative measures are required to ensure the availability and affordability of innovative medicines in countries that participated in industry-sponsored trials, and to ensure full transparency on trials results.

INTRODUCTION

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 (nearly one in six deaths). The global cancer burden is expected to be 28.4 million cases in 2040[1] and is increasing most rapidly in low-income and middle-income countries (LMICs). By 2030, about three-quarters of all cancer deaths will occur in LMICs, with one in eight persons receiving a cancer diagnosis in their lifetime. It is estimated that LMICs will account for most of the increase in global cancer burden over the next 50 years (400% in low-income countries (LICs), 168% in middle-income countries (MICs) and 53% in high-income countries (HICs)) due to population growth, increasing life expectancy, increasing urbanisation and changing lifestyles.[2 3] Global health is characterised

by inequality and inequity in cancer care, with only 5% of global resources spent in LMICs.[4] Access to care and innovative treatments lag behind in LMICs: for example, breast cancer survival is particularly low in LMICs due to limited access to early detection and systemic and adjuvant therapy.[5 6] The causes of poor access to adequate cancer care and, more in particular, to cancer medicines vary across LMICs, depending on the economic status and characteristics of health systems. Most LICs suffer from a general lack of well-established and effective cancer care services, including specialists, which are prerequirements for deploying highly specialised medicines. In MICs, where such services and facilities generally exist, innovative medicines 'are often affordable only to certain populations, and good outcomes are reserved for those who can pay for them'.[7 8] Even in presence of political willingness to increase the use of innovative medicines, access often remains unequal within MICs, for example, across different insurance schemes and regions.[9] A session at the European Society for Medical Oncology Asia 2018 Congress provided an overview of the impact that the lack of accessibility and availability of medicines has on LMICs patient outcomes in the treatment of breast cancer, colorectal cancer and lung cancer, indicating that barriers include the lack of government reimbursement, budget allocation for healthcare and quality-assured generic and biosimilar medicines as well as shortages and patent rights.[10] According to Leighl *et al*, the increasing cancer drug prices heavily impact on LMICs, resulting in a 'financial toxicity' seen across cancer types, countries and healthcare systems, and that puts at highest risk new immigrants, visible minority groups, those without private health coverage and the younger patients.[11] Moreover, Ruff *et al* have proposed that a strong collaboration is required between the key stakeholders (including pharmaceutical industry, local national health authorities, WHO and other non-profit and/or humanitarian organisations) in order to develop and grant access to the innovative medicines (such as trastuzumab and imatinib) in LMICs.[12] When it comes to childhood cancer medicines, available evidence suggests indeed that access is highly variable across countries, particularly in LMICs, where the burden of childhood cancer is greatest.[13] Furthermore, access can be dramatically limited in migrants experiencing legal and social vulnerability, and in regions hit by conflicts.[14 15] Striking disparities also exist across HICs. For example, there are significant disparities in the availability of trastuzumab between Western and Eastern Europe, the latter being unable to treat all patients in need.[16]

Clinical trials aim to develop new, innovative medicines that allow to improve the clinical outcomes, and/or the quantity or quality of life in patients with cancer, and that are expected to be up-taken in national health systems, to address the needs of a given population. As such, there is a logical link between clinical trials and, ultimately, the deployment of and access to innovative medicines developed through clinical trials. MICs are increasingly present in the research and development agenda.[17 18] This is consistent with the phenomenon of 'globalisation of clinical trials', that is, the allocation of clinical trials to areas outside the USA and Western Europe.[19–23] 'Globalisation' is an important trend in industry-sponsored trials, particularly in emerging regions of Eastern Europe, Latin America, Asia, the Middle East and Africa.[24] This is per se a welcome phenomenon, given the scarcity of high-grade evidence to guide the application of cancer treatment in LMICs. For instance, research data are needed that take into account the differences between sub-Saharan Africa and resource-rich settings in terms of host genetics and metabolism, tumour biology, endemic burden of infectious pathogens, including HIV and healthcare infrastructure.[25] However, there is little evidence of the actual proportion of clinical trials conducted in LMICs, particularly in the field of non-communicable diseases, and the real size of globalisation might be overestimated. For example, some regions with growing numbers of dialysis patients are poorly represented in multicentre randomised clinical trials, and efforts to boost trial participation are required to ensure that relevant guidance is available to local healthcare providers.[26] In short, a call for more 'global trials' is justified by the need of testing new interventions in a variety of epidemiological settings and populations, and of addressing the health needs of specific communities and health systems. Conversely, globalisation should not be motivated by the 'convenience' of lower costs, easier ethical/regulatory review and easier availability of participants in LMICs.[27]

Therefore, we conducted an exploratory analysis of the globalisation of industry-sponsored, therapeutic phase I–IV clinical trials for the three oncology 'big killers', that is, breast, lung and colon cancers. The specific objectives of our analysis are to describe: (i) the geographic distribution of trials across HICs, MICs and LICs; (ii) the proportion of trials conducted with at least one clinical site in LMICs; (iii) the proportion of trials for breast, lung and colon cancers testing some predefined innovative medicines (namely small molecules, monoclonal antibodies and recombinant fusion proteins), with at least one clinical site in LMICs and (iv) the proportion of completed trials for which results were available in the registry.

METHODS

Search strategy applied in ClinicalTrials.gov

We searched ClinicalTrials.gov, an open-access trial registry (https://clinicaltrials.gov/) maintained by the National Library of Medicine of the US National Institutes of Health (NIH),[18 20 23 28] which is the best known and most widely used registry since the introduction of the International Committee of Medical Journal Editors (ICMJE) requirements for trial registration in 2005.[29–33] Although other open-access registries are accepted by WHO, including the European Union Drug Regulating Authorities Clinical Trials Database (EUDRACT),

ClinicalTrials.gov is generally considered the most comprehensive one.[29 30 34]

Our search modality combined the following fields: (i) study type: interventional studies; (ii) condition/disease: breast cancer, lung cancer, colon cancer; (iii) phases: I–IV; (iv) funder type: industry; (v) first posted: registry inception—30 June 2018. Extraction occurred on 30 June 2018, and information on whether results were posted in the registry was extracted on 30 September 2022 for completed trials.

Inclusion and exclusion criteria for the selection of trial records

We included all therapeutic industry-sponsored trials that tested medicines in breast, lung and colon cancers, and that were registered up to 30 June 2018, irrespective of the trial status ('not yet recruiting', 'recruiting', 'enrolling by invitation', 'active', 'not recruiting', 'suspended', 'terminated', 'completed', 'withdrawn', 'unknown status'). We considered the trial country(ies) and clinical site(s) based on the registry field termed 'listed location countries'. Clinical trials that did not specify study countries and clinical sites were excluded.

For the subanalysis of predefined innovative medicines, we selected a group of small molecules, monoclonal antibodies and recombinant fusion proteins, that at the time of data extraction were either recommended in international guidelines, or in clinical development for lung,[35] breast[36] and colon cancers,[37] according to the NIH National Cancer Institute.

Data extraction from trial records

Two independent evaluators (ABP and LG) screened all clinical trial records in the database according to the inclusion and exclusion criteria. First, we downloaded the raw data in comma-separated values (CSV) format from the registry (https://clinicaltrials.gov). For each clinical trial that met the search criteria, the following variables were extracted: rank, NCT number (trial identifier), title, acronym, status, study results, conditions, interventions, outcome measures, sponsor/collaborators, gender, age, phases, enrolment, funded bodies, study type, study designs, other IDs, start date, primary completion date, completion date, first posted, results first posted, last update posted, study documents and URL. Records that met the inclusion criteria and did not meet the exclusion criteria were extracted and captured in an EXCEL database. Trials for which one evaluator was unsure whether they should be included were discussed by two evaluators, and disagreements were resolved by the involvement of a third evaluator (GG). The variable 'results first posted' was extracted on 30 September 2022, only for trials with a 'completed' status as of 30 September 2022. As the .csv file downloadable from the registry does not contain information on the countries and locations/clinical sites, nor on the trial results, this information was manually extracted from the narrative text in the registry.

Country classification

Countries were classified as LICs, lower MICs (L-MICs), upper MICs (U-MICs), and HICs according to the World Bank classification (fiscal year 2019).[38] This classification is based on the Gross National Income per capita, which was US$995 or less for LICs; US$996–US$3895 for L-MICs; US$3896–US$12 055 for U-MICs; US$12 056 or more for HICs.

Data analysis

We combined early phase I trials into phase I, phase I/II into phase II and phase II/III into phase III. First, we described the geographic distribution of trials and the proportion of trials conducted in LICs and L-MICs/U–MICs for all interventions combined. Then, we described the proportion of trials with at least one clinical site in LMICs; for trials completed as of 30 September 2018, we analysed the proportion of those that had entered their results in the registry. We performed the Pearson's χ^2 test in order to report the statistical significance of our findings. We set α=0.05 to decide whether to reject or not the null hypothesis. Finally, we described the proportion of trials testing selected small molecules, monoclonal antibodies and recombinant fusion proteins for lung, breast and colon cancers. Data analysis was performed using SAS V.9.4.

Patient and public involvement statement

This study is solely based on information publicly available in ClinTrials.gov, therefore, the involvement of patients or the public was not applicable or feasible.

RESULTS

Trial selection

We identified 5448 trial records (breast cancer=2185; lung cancer=2284 and colon cancer=979 trials) that complied with our search criteria. After manual screening/curation, 584 non-therapeutic trials were excluded, and 4864 trial records were assessed for eligibility. Although the ICMJE and the WHO International Clinical Trials Registry Platform require reporting of sites/countries, 365 studies did not report their countries nor sites. After removing them, and after removing 322 duplicate records, we were left with 4177 therapeutic trial records in the final database. The flow diagram of the trial record selection process is shown in figure 1.

Industry-sponsored therapeutic trials for breast, lung and colon cancer with at least one site in low-income and middle-income countries

The total number of clinical trials (n=4177) overall and stratified by phase (I, II, III and IV) included in our study are shown in table 1. Of these, 3254 (77.9%) were conducted exclusively in HICs, while 923 (22.1%) included at least one trial site in MICs (table 1), with 48/923 (5.2%) trials including only L-MICs clinical sites, 603/923 (65.3%) trials including only U-MICs clinical

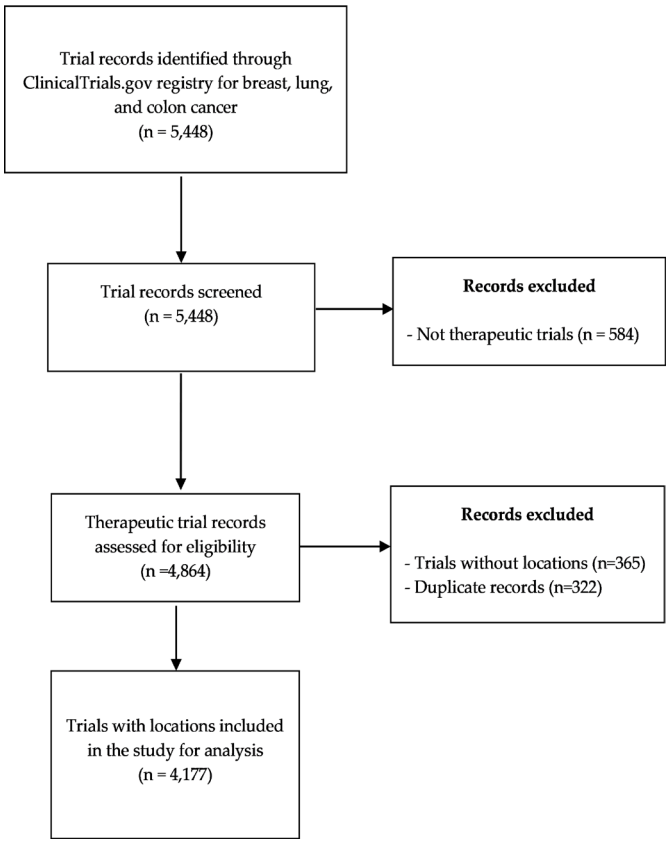

Figure 1 Flow chart for the selection of trials.

sites and 272/923 (29.5%) including clinical sites in both L-MICs and U-MICs (table 2). Out of the 923 trials involving MICs, 311 (33.7%) were conducted only in MICs, while 612 (66.3%) involved both HICs and MICs (table 3). No trials were conducted in LICs. All the proportions showed a statistically significant correlation in all phases of clinical trials with p value <0.001 (tables 1–3), except in the phase II trials that were conducted in only MICs versus HICs and MICs (table 3).

Geographic distribution of industry-sponsored clinical trials for breast, lung and colon cancers conducted in middle-income countries

Lower middle-income countries

The L-MICS that participated in at least one clinical trial, with the number of trials per country, are shown in figure 2A. Most trials with at least one site in an L-MIC were conducted in Ukraine and India (>130 trials). Sixty-two trials were conducted in the Philippines, 31 in Egypt and 22 in Georgia. Vietnam, Indonesia, Pakistan and Tunisia, counted, each, with >10 trials.

The full list of L-MICs with absolute numbers of trials and sites per country are reported in online supplemental figure S1A,B.

Upper middle-income countries

The U-MICs that participated in at least one clinical trial, with the number of trials per country, are shown in the map (figure 2B). The highest number of trials was conducted in China and the Russian Federation (>340 trials). Brazil, Romania, Mexico and Turkey counted, each, with >150 trials; Thailand, South Africa and Bulgaria with >100 trials; Peru, Serbia, Malaysia and Colombia with >50 trials and Lebanon, Bosnia and Herzegovina, Belarus and Guatemala with >15 trials.

The full list of U-MICs with absolute numbers of trials and sites per country are reported in online supplemental figure S1C,D.

Industry-sponsored clinical trials for breast, lung and colon cancers with small molecules, monoclonal antibodies and recombinant fusion proteins conducted in middle-income countries

We specifically looked at trials conducted with selected small molecules, monoclonal antibodies or recombinant fusion proteins, that, in 2018, were either recommended in international guidelines or in clinical development. We included 361 trials with trastuzumab and lapatinib (either breast, lung or colon cancer trials); 317 lung cancer trials with 14 immune checkpoint inhibitors; 527 lung cancer trials with 25 epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) inhibitors and 312 colon cancer trials with 22 EGFR, VEGFR and immune checkpoint inhibitors. The list of the selected molecules for this analysis is available in online supplemental table S1. Out of these trials, those involving at least one clinical site in MICs were 96 for trastuzumab and lapatinib (1 phase I trial; 39 phase II trials; 53 phase III trials; 3 phase IV trials) (figure 3A); 46 colon cancer trials with EGFR, VEGFR and immune checkpoint inhibitors (3 phase I; 11 phase II; 29 phase III; 3 phase IV) (figure 3B); 75 lung cancer trials with immune

Table 1 Industry-sponsored clinical trials for breast, lung and colon cancers involving at least one site in MICs versus HICs only throughout phase I to phase IV

Phases	Trials (n)	MICs	%	HICs only	%	P value
I	950	72	7.58	878	92.42	<0.001
II	2450	390	15.92	2060	84.08	<0.001
III	688	416	60.47	272	39.53	<0.001
IV	89	45	50.56	44	49.43	<0.001
Total	4177	923	22.10	3254	77.90	

HICs, high-income countries; MICs, middle-income countries.

Table 2 Industry-sponsored clinical trials for breast, lung and colon cancers involving L-MICs only versus U-MICs only versus both L-MICs and U-MICs throughout phase I to phase IV

Phases	MICs	L-MICs only	%	U-MICs only	%	L-MICs and U-MICs	%	P value
I	72	4	5.56	63	87.50	5	6.94	<0.001
II	390	30	7.70	282	72.30	78	20.00	<0.001
III	416	6	1.44	225	54.09	185	44.47	<0.001
IV	45	8	17.78	33	73.33	4	8.89	<0.001
Total	923	48	5.20	603	65.33	272	29.47	

L-MICs, lower middle-income countries; U-MICs, upper middle-income countries.

checkpoint inhibitors (5 phase I; 19 phase II; 48 phase III; 3 phase IV) (figure 3C) and 140 lung cancer trials with EGFR and VEGFR inhibitors (5 phase I; 55 phase II; 69 phase III; 11 phase IV) (figure 3D).

Proportion of industry-sponsored completed trials for breast, lung and colon cancers that posted results in ClinicalTrials.gov

Out of 4177 trials, 1854 (44.4%) had been completed by 30 September 2018. We found that 678 out of 1854 (36.6%) trials had posted the results into the registry. When we deeply examined these trials, we found that only 236 out of 1854 trials (12.7%) had their results posted into the registry within 12 months from the primary completion date. As shown in table 4, the results of 1176 trials out of 1854 (63.4%), whether including LMICs or not, had not entered yet in the registry at the time of analysis. Table 5 shows the total number of completed trials with at least one clinical site in MICs by phase that had not entered results into the registry: these were 213 out of 430 (49.5%). All the proportions showed a statistically significant correlation in all phases of clinical trials (tables 4 and 5), except in the phase IV trials that were involving MICs (table 5).

DISCUSSION

The globalisation of trials in cancer research

Our findings indicate that 77.9% (3254/4177) of phase I–IV clinical trials for breast, lung and colon cancer involved HICs only, while 22.1% (923/4177) included at least one site in L-MICs and/or U-MICs. These data suggest that industry-sponsored cancer research is increasingly globalised, in line with previous observations from our group on haematological neoplasia.[18] Although the increase in cancer clinical trials in MICs can be seen positively, there are also reasons for concern.

First, the ICMJE and WHO require that the study sites/countries are reported when clinical trials are registered.[29 30 33] Unexpectedly, our investigation showed that 365 out of 4864 (7.5%) trials did not report countries nor sites, inevitably raising doubts about the completeness and transparency of the information provided.

Second, no trials were conducted in LICs, and only 14 out of 47 L-MICs were involved in trials. In L-MICs, the highest number of trials were conducted in Ukraine (ranked first) and India (ranked second). In contrast, trials were conducted in 30 out of 56 U-MICs. Most trials in this group were conducted in China (ranked first) and the Russian Federation (ranked second). In line with our study findings, a recent study has also obtained similar results in which breast and lung cancer trials are found to be increasingly delocalised to MICs (including India, Ukraine, Russian Federation, Brazil and China).[39] In our study, in terms of both the number of trials and sites/locations, U-MICs outperformed L-MICs by a factor of 5. One possible explanation could be the lack of interest of developers in LICs and L-MICs, due to the low economic profitability of these markets.[26] If the health system is fragile and the population lacks access to health insurance, the sponsors might be less motivated to conduct trials there and to test acceptability and feasibility of innovative medicines in the local context.[40] Other reasons may include lack of adequate

Table 3 Industry-sponsored clinical trials for breast, lung and colon cancer conducted only in MICs versus HICs and MICs throughout phase I to phase IV

Phases	MICs	Only MICs	%	HICs and MICs	%	P value
I	72	57	79.17	15	20.83	<0.001
II	390	133	34.10	257	65.90	0.82
III	416	87	20.91	329	79.09	<0.001
IV	45	34	75.56	11	24.44	<0.001
Total	923	311	33.69	612	66.31	

HICs, high-income countries; MICs, middle-income countries.

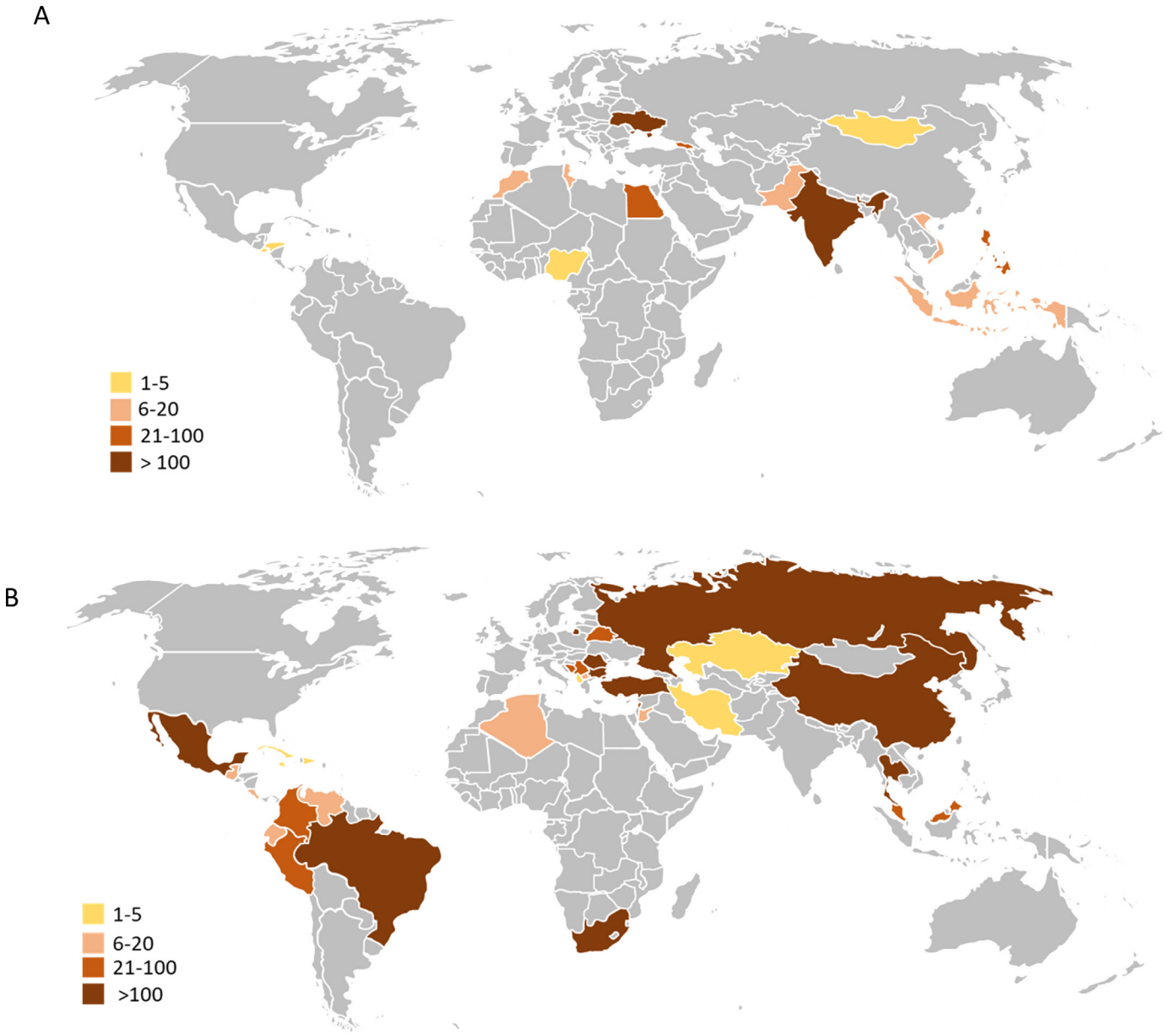

Figure 2 Geographic distribution of industry-sponsored breast, lung and colon cancer clinical trials in MICs. The map shows the geographic distribution of clinical trials in MICs. Different colours represent different numbers of trials per country. (A) Geographic distribution of industry-sponsored clinical trials for breast, lung and colon cancers conducted in L-MICs. (B) Geographic distribution of industry-sponsored clinical trials for breast, lung and colon cancers conducted in U-MICs. L, lower; MICs, middle-income countries; U, upper.

infrastructures; limited financial and human resources capacity; ethical, regulatory and operational barriers; competing demands[41 42]; overwhelming clinical workloads and lack of dedicated research funding.[19 43] A previous study highlighted the lack of leadership of researchers from L-MICs and U-MICs.[42] Lack of local leadership may be linked to 'research parachutism', where researchers from L-MICs and U-MICs, although instrumental in conducting research, are not granted recognition for their work including authorship.[42]

On the other side, several factors may make conducting clinical trials in L-MICs and—particularly—U-MICs attractive to sponsors based in HICs, including lower labour costs, fewer regulatory hurdles and a large pool of potential participants.[44 45] In fact, the increase in clinical trials observed in countries like Ukraine and China has not been exempted from controversies. For instance, the Berne Declaration warned in 2013 about a possible lack of transparency around regulatory compliance of clinical trials conducted in Ukraine,[46] and various authors questioned over time China's medical research integrity.[47 48] These experiences show that the development of the clinical trials enterprise should be preceded by and framed in a robust regulatory and ethics oversight, to ensure protection of participants' rights as

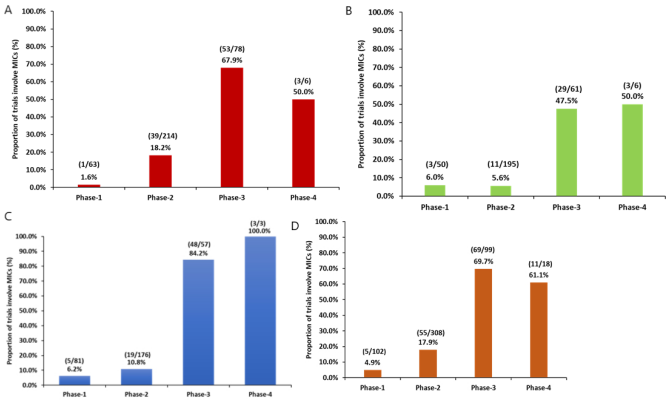

Figure 3 Proportion of industry-sponsored cancer clinical trials (with small molecules, monoclonal antibodies and recombinant fusion proteins) involving at least one site in MICs by study phase. (A) Proportion of industry-sponsored breast, lung and colon cancer clinical trials (n=361) with trastuzumab and lapatinib with at least one site in MICs by study phase. (B) Proportion of industry-sponsored colon cancer clinical trials with EGFR, VEGFR and immune checkpoint inhibitors with at least one site in MICs by study phase. (C) Proportion of industry-sponsored lung cancer clinical trials with immune checkpoint inhibitors. (D) Proportion of industry-sponsored lung cancer clinical trials with EGFR and VEGFR inhibitors. EGFR, epidermal growth factor receptor; MICs, middle-income countries; VEGFR, vascular endothelial growth factor receptor.

well as transparency and accountability vis-à-vis the public.

Benefit sharing in cancer research

In 2021, more innovative anticancer medicines were included in the WHO Model List of Essential Medicines,[49] and various cancer medicines are included in some national lists of LMICs (eg, trastuzumab, rituximab and imatinib in the national list of India, Malaysia, South Africa, Pakistan, Lebanon and Sri Lanka).[50–56] However, their affordability and accessibility are often far from guaranteed in LMICs, especially for innovative medicines[57–59] that are generally not yet available as quality-assured generics or biosimilars,[8 9 60 61] leading to poor clinical outcomes and short survival.[62]

Many MICs contributed to the clinical development of innovative cancer medicines, for example, trastuzumab and bevacizumab. Although our analysis does not provide data on availability and affordability by country, the existing literature shed doubts on the availability and affordability of innovative cancer medicines in those MICs that took part in clinical development.[63] This would contradict the principle of benefit sharing, which requires that benefit from research must be shared with the individuals and communities where research was conducted. The 2013 Declaration of Helsinki states that when a vulnerable population is involved in research, it 'should stand to benefit from the knowledge, practices or interventions that result from the research'. This also relate to socio-economic vulnerability.[64] For example, most patients in Colombia, Mexico, Ukraine, South Africa and Thailand are unable to afford cancer treatment with drugs (co)developed in these regions between 2005 and 2015.[61] This poses multiple ethical problems. On the one hand, there should be upfront reassurance that countries that shared the burden of research would systematically access the (long-term) benefits. On the other hand, patients in MICs will be much more likely to accept being enrolled in trials, knowing that trial participation is the only option to receive treatment with innovative medicines.[58] It is important to uphold the highest ethical safeguards for preventing the exploitation of participants, and of their communities, in MICs.[65] Leading regulators like European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) could contribute to this effort, by requesting developers to submit an 'access plan' for the countries who contribute to the development of a new (cancer) medicine.[18 66]

The impact of geopolitics on cancer research

The impact of the Russian invasion of Ukraine shows that clinical trials in MICs are often conducted in fragile ecosystems. Prior to March 2022, Ukraine was attractive for industry-sponsored clinical trials (in line with the findings of our study, which identified Ukraine as the L-MIC with the highest number of trials): at the beginning of April 2022 ClinicalTrials.gov recorded nearly 400 ongoing trials in Ukraine, in any medical fields, and about 1.5% of the active patient population in Roche trials worldwide was enrolled in Ukraine.[67] Russia's invasion of Ukraine forced pharmaceutical industries to stop recruiting patients for existing trials and put the launch of new trials on hold. The fighting forced the hospitals to stop working on trials, and clinical investigators were called up to care for the wounded people.[67] On 30 Match 2022, the

Table 4 Industry-sponsored completed clinical trials for breast, lung and colon cancers whose results have been posted versus non-posted into ClinicalTrials.gov registry, by study phase

Phases	Trials (n)	Results posted n (%)	Results not posted n (%)	P value
I	386	52 (13.47%)	334 (86.53%)	<0.001
II	1117	452 (40.47%)	665 (59.53%)	<0.001
III	302	149 (49.34%)	153 (50.66%)	<0.001
IV	49	25 (51.02%)	24 (48.98%)	0.03
Total	1854	678 (36.57%)	1176 (63.43%)	

Table 5 Industry-sponsored completed clinical trials for breast, lung and colon cancers conducted in MICs whose results have been posted versus non-posted into ClinicalTrials.gov registry, by study phase

Phases	Trials (n)	Results posted n (%)	Results not posted n (%)	P value
I	17	0 (0.0%)	17 (100%)	<0001
II	210	86 (40.95%)	124 (59.05%)	<0001
III	181	119 (65.75%)	62 (34.25%)	<0001
IV	22	12 (54.55%)	10 (45.45%)	0.69
Total	430	217 (50.47%)	213 (49.53%)	

European Commission, the EMA and the Heads of Medicines Agencies issued an 'advice to sponsors on managing the impact of the war in Ukraine on clinical trials'.[68]

The important role of Ukraine and Russia in cancer trials raises two fundamental questions. First, whether their involvement is driven by capacity-building efforts and collaborative partnerships, or by convenience reasons, where research sponsors gain access to prospective participants in health systems with low costs and fewer regulatory hurdles. Second, what will be the long-term consequences of the Russian invasion of Ukraine. These issues need to be considered by policymakers and the wider scientific community. Healthcare (including cancer care) in Ukraine has systematically deteriorated.[69] For the foreseeable future, it will be difficult for patients with cancer in Ukraine to receive treatment, let alone participate in research. The—for the time being—inevitable decline in trial capacity in Ukraine (and perhaps Russia) may be offset by an increase in trials in other U-MICs and L-MICs with strong cancer research infrastructures (such as Brazil, China and India). However, the need to frame the increase of trials in a robust regulatory and ethics governance, including attention for fair research partnership and for benefit sharing, remains critical also in these other contexts.

Cancer research in registries

Reporting of trial results in the registry is a regulatory requirement. WHO sets requirements for posting clinical trial findings. Results must be made publicly available within 24 months from completion, and posted in a clinical trials registry within 12 months.[70] Section 801 of the FDA Amendments Act requires responsible parties to register clinical trials and submit summaries of results to ClinicalTrials.gov.[71 72] Our analysis included 1854 completed trials (up to 30 June 2018), of which 430 trials involved MICs, and we examined (as of 30 September 2022) whether or not the results of these trials had been posted into the registry. Although International guidelines require to post the trial results into the registry within 12-month period after trial completion, only 12.7% of the trials (236/1854) had their results posted into the registry in this time framework. Moreover, we found that 63.4% (1176/1854) of the trials and 49.5% (213/430) of trials involving MICs had not entered their results in the registry, suggesting a certain lack of transparency. It would seem important that the registry enforced the implementation of this requirement, as well as of the requirement to indicate the trial countries and clinical sites. Timeliness and accuracy of this information is relevant to all trials, and even more for trials involving (L)MICs, to foster transparency and accountability.

Weighing risks and opportunities

The high financial stakes in cancer research and treatment represent both a threat and an opportunity for researchers and participants in resource-poor countries. Participation in trials has the potential to attract more research funding to L-MICs and U-MICs, thus improving research infrastructure, strengthening trial regulation, building new collaborations and providing experience and expertise to researchers who might otherwise lack mentors and opportunities for methodological training. However, the financial implications and the asymmetries of power in research consortia may create an imbalance of power, if the research agenda is unilaterally defined in HICs. Furthermore, the sponsors and other key research stakeholders need to carefully assess the risk of exploitation of research participants and of local researchers, and build in the research plan adequate mitigation measures, including practical provisions for availability and affordability of the newly developed medicines (eg, quick registration, tiered pricing, technology transfer and voluntary licences)—and fair collaborative agreements to prevent research parachutism.[73 74] In some cases, the weak supervision and monitoring mechanisms should also be taken into account: for instance, an analysis of 307 trials conducted in China in the past (2004) reported that 90% of published studies at that time did not have protocol review by a Research Ethics Committee.[75]

The globalisation of cancer clinical trials implies other challenges. First, the trials' geographical distribution needs to be balanced across HICs and LMIs. In the hypothesis that a substantial proportion of patients were included in L-MICs and U-MICs, there might be limited generalisability of results to HICs, where the first regulatory approval is obtained, typically from the US FDA or from the EMA. Internal validity would also be limited if the local standards of care differed systematically across HICs, L-MICs and U-MICs. Threats to external validity might arise from pharmacogenomic differences in populations and other elements of care systems.[20 76] However,

for the time being, the risk is still rather of unbalance in the other sense, implying that results of trials still mainly conducted in HICs might not be informative for LMICs. In particular, the complete absence of LICs in industry-sponsored cancer research implies that we do not know how novel agents would work in these contexts, and indicates a lack of interest for these non-profitable markets.

Limitations

Our study has various limitations. First, we focused on industry-sponsored trials as they are the support dossier for requesting a marketing authorisation and for key post-marketing data. However, key research is also conducted by non-commercial sponsors, especially for paediatric cancer, and it will be important to explore these actors in a next research step. Second, for completed trials, we only checked whether the results were posted in the registry as on 30 September 2022, and we did not check whether completed trials whose results were not posted in ClinicalTrials.gov were published in a peer-reviewed journal or available as preprints. Third, we did not investigate whether the contribution of MIC researchers is duly recognised in the authorship of publications. Fourth, we only searched for studies registered in ClinicalTrials.gov, which may have resulted in an incomplete database missing, for example, studies registered only in the EUDRACT or other WHO-agreed registries. Fifth, we checked whether a clinical trial had at least one MIC clinical site, but we did not examine the absolute number or percentage of participants recruited at these clinical sites.

CONCLUSIONS AND RECOMMENDATIONS

Overall, the substantial (although limited to MICs) globalisation of industry-sponsored cancer trials implies both benefits and risks. Our findings provide some policy-relevant recommendations for cancer research.

To prevent or contrast the potential power imbalance in research, it would be important for health systems in MICs to promote their own cancer research agenda, and to invest in building capacity and capability in clinical cancer research, with the support of external funding mechanisms, including multilateral cooperation and philanthropy,[19] so as to empower researchers to lead research aligned with the needs of their own health systems.[77] There are many excellent examples around the world of how this can be accomplished.[78 79] In addition, there is an important question mark about whether cancer clinical trials conducted in MICs ultimately benefit the broader population from which trial participants are drawn, and whether this research contributes to a strong cancer research ecosystem.[80] National and international policy-makers should cooperate to enforce regulatory measures to ensure availability of these medicines for all those in need, including patients in countries that contributed to the clinical development.

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