Global Myeloma Trial Participation and Drug Access in the Era of Novel Therapies

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PURPOSE The globalization of clinical trials has accelerated recent advances in multiple myeloma (MM). However, it is unclear whether trial enrollment locations are reflective of the global burden of MM and whether access to novel therapies is timely and equitable for countries that participate in those trials.

METHODS To assess this, we characterized where MM trials that led to US Food and Drug Administration (FDA) approvals were conducted and determined how often and quickly these drug regimens received approval in their participating trial countries on the basis of country income level and geographic region.

RESULTS A systematic review was conducted to identify all MM clinical trials that met their primary endpoint, enrolled patients outside the United States, and resulted in FDA approval from 2005 to 2019. A total of 18 pivotal MM clinical trials were identified. High-income countries enrolled patients in 100% (18/18) of the trials identified, whereas upper-middle and lower-middle-income countries were represented in 61% (11/18) and 28% (5/18) of trials, respectively. No patients from low-income countries were enrolled. One trial enrolled patients in sub-Saharan Africa, and no trials enrolled patients in South Asia/Caribbean. For drugs/regimens that were approved in their participating countries, the median time from FDA approval to approval was 10.9 months. There were no drugs approved in lower-middle-income trial countries. MM trials leading to FDA approval are generally run in high-income, European, and Central Asian countries.

CONCLUSION There are substantial disparities in where novel therapies are evaluated and where they are ultimately approved for use on the basis of income level and geography.

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INTRODUCTION

Multiple myeloma (MM) is a clonal neoplasm of differentiated B cells (plasma cells) associated with end-organ damage. Despite considerable advances, the disorder remains associated with significant morbidity and causes > 12,000 annual deaths in the United States alone. Compared with White patients, the prevalence of MM in African Americans is increased two- to three-fold, with similar rates seen in African men in Ghana, suggesting a genetic component to this disparity. Unfortunately, there is no definitive cure for MM yet, and most patients remain on treatment indefinitely.[1-6]

Because of the advent and approval of novel therapies and combinations, studies have shown a consistent improvement in 5-year survival rates in the United States and other high-income nations.[7-9]

Regulatory approval of these novel therapies has been accelerated by faster trial enrollment through the globalization of clinical trials.[10,11] Globally, low- and middle-income countries are experiencing an epidemiologic transition from infectious diseases to cancer and chronic diseases.[12] According to the Global Burden of Disease Study 2016, India contributed the third-highest incident cases of MM and deaths from MM after the United States and China. Overall, middle-income countries contributed to the highest incident cases and deaths from 1990 to 2016.[13] This shift has created a mutually beneficial situation for global clinical trials. In wealthy nations, oncologists, patients/advocates, and pharmaceutical companies require the accrual of large numbers of patients to quickly generate the findings needed for regulatory drug approval of novel therapies. In addition, pharmaceutical companies can capitalize on the decreased costs associated with financing a clinical trial outside of the United States. Alternatively, patients in low- and middle-income countries benefit from trial access to therapies that otherwise may not have been available.[14-16] Although socioeconomic and racial disparities in MM treatment have been

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

It is unknown whether treatments for multiple myeloma (MM) are approved for use in the countries that participate in clinical trials leading to US Food and Drug Administration approval.

Knowledge Generated

MM trials are generally conducted in countries that are high-income and located in Europe or Central Asia. However, in the lower-income countries where trials are run, these agents remain unavailable.

Relevance

The under-representation of low-income, South Asian, Caribbean, and sub-Saharan African countries in MM clinical trials continue to exacerbate disparities.

demonstrated within the United States, further research on global disparities in access to MM treatment both in clinical trials and in the real world is needed.[17]

A recent study revealed that drugs are often not approved in the countries where the trials are conducted despite approval in the United States.[18] To our knowledge, the locations of pivotal MM trials have not been studied in aggregate, and it is unknown whether access to novel therapies is timely and equitable for participating trial countries. It is also unknown whether trial enrollment locations are reflective of the global burden of MM. To assess this gap, we sought to characterize where MM trials that led to the US Food and Drug Administration (FDA) approval were conducted and determine how often and how quickly these drug regimens received approval in the respective participating trial countries on the basis of country income level and geographic region.

METHODS

Search Strategy

A systematic review was conducted to identify all randomized MM clinical trials during our study period from 2005 to 2019. Three databases were searched (MEDLINE/PubMed, Embase, and Cochrane Registry of Controlled Trials). The snowballing procedure was performed by searching reference lists of included studies and relevant review articles. Major conference proceedings (American Society of Clinical Oncology, American Society of Hematology, and European Hematology Association) were also reviewed. Two independent reviewers (G.R.M. and K.K.) screened all studies, and any conflict was resolved through mutual discussion. This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[19]

Clinical trials that met their primary end point and led to FDA approval were included. Trials that only enrolled US patients were excluded. Trial countries were defined as locations where clinical trials occurred according to their ClinicalTrials.gov registration. Trial countries with overlapping drug regulatory agencies were kept separate for analysis (ie, European Union). Time lag was defined as the period from FDA approval to drug/regimen approval in the specified trial country.

Geographic regions and income levels for trial countries were defined according to the World Bank Country and Lending Groups classification.[20] For the 2022 fiscal year, low-income countries were defined as those with a gross national income (GNI) per capita of $1,045 or less in 2020; lower-middle-income countries were those with a GNI per capita between $1,046 and $4,095; upper-middle-income economies were those with a GNI per capita between $4,096 and $12,695; and high-income economies were those with a GNI per capita of $12,696 or more.

Two authors (G.R.M. and K.K.) performed and verified all initial data extraction to complete the systematic review. Extracted trials were tabulated using Microsoft Excel (Microsoft, Redmond, WA) and matched with clinical trials registered on ClinicalTrials.gov. We identified the following characteristics of each clinical trial: study name, enrollment start year, trial sponsor, number of patients enrolled, primary end point, and trial countries.

Consistent with previously described methods, another author (R.A.F.) searched the websites of medicines regulatory agencies to determine whether specific drugs/regimens were approved for their studied indications in each trial country.[18] If approved, the year of approval was recorded. Google Translate was used to navigate regulatory websites published in languages other than English. When medicines regulatory agency websites or drug approval databases were unavailable, a search was conducted on the internet (Google and Bing search engines) for pharmaceutical press releases highlighting the desired drug approval information for each trial country. All inconsistencies were resolved via consensus on the basis of available internet information.

Primary and Secondary Outcomes

The primary outcome of our study was to ascertain the median number of countries where trials leading to FDA approval of drugs for MM were conducted and to stratify

those countries on the basis of region of the world and income level.

Secondary outcomes included the proportion of non-US trial countries with drug/regimen approval within 1, 3, and 5 years of FDA approval. The denominator for the proportion of approvals within 3 and 5 years of approval only included regimens that had been approved > 3 and 5 years ago in the United States, respectively, whereas all included studies were included in the 1-year denominator, as greater than a year had passed for all approvals at the time this analysis was conducted. We also measured the median time from US FDA approval to drug/regimen approval in trial countries.

Statistical Analysis

The results are presented in months after FDA approval. We conducted descriptive statistical analyses, including medians and proportions, using Microsoft Excel. Data analysis was conducted from September through December 2021.

RESULTS

Trial Characteristics

The initial search strategy yielded 1,171 results (Fig 1). After excluding duplicates or studies not meeting inclusion criteria and searching conference proceedings, 151 discrete clinical trials were included. When substratified for only those that met their primary end points, enrolled patients outside the United States, and led to FDA approval, a total of 18 clinical trials were identified. The 18 trials are listed in Table 1.

Participation in Clinical Trials

Each clinical trial leading to FDA approval of an MM-directed single-agent or combination regimen enrolled patients in a median of 15 (range 1-33) trial countries outside the United States, including a median of 12 high-income countries and one upper-middle-income country. High-income countries enrolled patients in 100% (18/18)

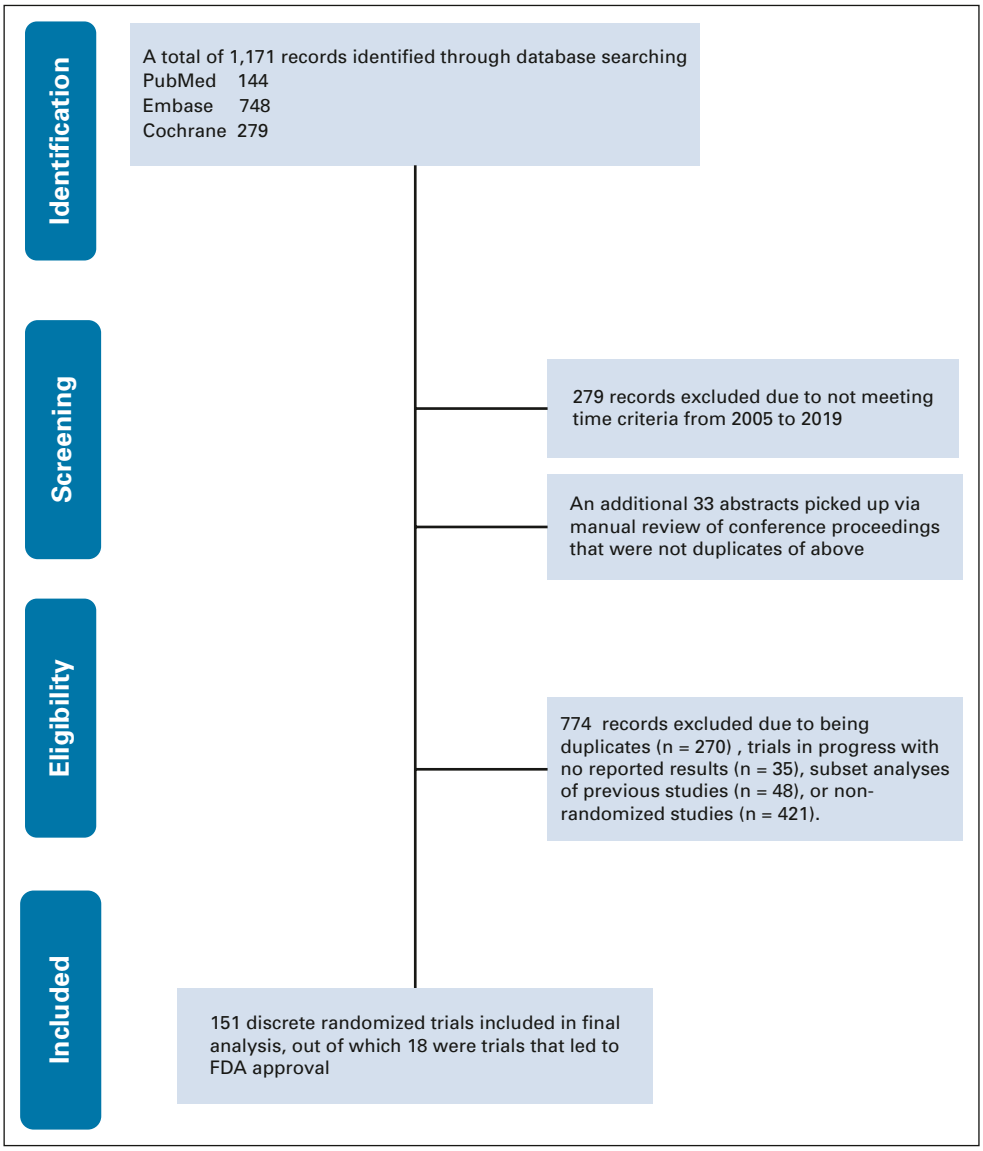

FIG 1. Flow diagram depicting our search strategy and study inclusion.

TABLE 1. Complete List of Included Trials

Trial Details	Year of US FDA Approval	No. of Patients Enrolled	Primary End Point	No. of Non-US Trial Locations	Enrolled Patients in LMICs
Lenalidomide plus Dex for RRMM[33]	2006	351	Time to tumor progression	15	Yes
Bortezomib or high-dose Dex for RRMM[34]	2005	620	Time to disease progression	12	No
Lenalidomide plus Dex for relapsed MM in North America[35]	2006	353	Time to tumor progression	1	No
Subcutaneous versus intravenous administration of bortezomib in patients with RRMM[36]	2012	222	Response rate	3	No
Pomalidomide alone or in combination with low-dose Dex in RRMM[37]	2013	259	Progression-free survival	1	No
Pomalidomide plus low-dose Dex versus high-dose Dex for patients with RRMM[38]	2013	455	Progression-free survival	15	Yes
Lenalidomide and Dex in transplant-ineligible patients with MM[39]	2015	1,623	Progression-free survival	18	Yes
Panobinostat or placebo plus bortezomib and Dex in RRMM[40]	2015	767	Progression-free survival	33	Yes
Carfilzomib, lenalidomide, and Dex versus lenalidomide and Dex in RRMM[41]	2015	792	Progression-free survival	19	Yes
Daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed MM[42]	2018	706	Progression-free survival	22	Yes
Isatuximab plus pomalidomide and low-dose Dex versus pomalidomide and low-dose Dex in patients with RRMM[43]	2020	307	Progression-free survival	22	Yes
Daratumumab, lenalidomide, and Dex for MM[44]	2016	570	Progression-free survival	16	Yes
Daratumumab plus lenalidomide and Dex for MM[45]	2019	737	Progression-free survival	11	No
Elotuzumab therapy for RRMM[46]	2015	761	Progression-free survival, response rate	20	Yes
Daratumumab, bortezomib and Dex versus bortezomib and Dex in RRMM[47]	2018	500	Progression-free survival	14	Yes
Elotuzumab plus pomalidomide and Dex for MM[48]	2018	157	Progression-free survival	9	No
Oral ixazomib, lenalidomide, and Dex for MM[49]	2015	722	Progression-free survival	6	Yes
Subcutaneous versus intravenous daratumumab administration in patients with RRMM[50]	2020	522	Response rate	17	Yes

Abbreviations: Dex, dexamethasone; FDA, Food and Drug Administration; LMICs, low- or middle-income countries; MM, multiple myeloma; RR, relapsed/refractory.

of the trials evaluated, whereas upper-middle and lower-middle-income countries were represented in 61% (11/18) and 28% (5/18) of trials, respectively. Zero low-income countries enrolled patients in these trials.

Outside the United States, trials were most commonly conducted in Canada, France, and Germany (78% [14/18]), followed by Belgium and Spain (72% [13/18]). The geographic regions most represented were Europe and Central Asia (89% [16/18]) followed by North America (78% [14/18]). One trial enrolled patients in sub-Saharan Africa (South Africa) and there were no trials that enrolled patients in South Asia. A complete list of trial countries is listed in Appendix Table A1.

Approval Stratified by Trial

Of all included clinical trials, 22% (4/18) received drug/regimen approval in all their enrolling trial countries within 1 year of FDA approval. This increased to 27% (4/15) and 42% (5/12) at 3 and 5 years after FDA approval, respectively. For drugs/regimens that were approved in their participating trial countries, the median time from FDA approval to trial country approval was 10.9 months (IQR: 4-12 months).

Approval Stratified by Country

Of the 46 participating trial countries, the median approval rate for participating trial countries within 1 year of FDA approval was 71% (180/254), which increased to 77% (123/159) at 5 years. For high-income trial countries, the 1- and 5-year approval rates were 81% (172/213) and 84% (115/137), respectively, with a median time of 9.1 months from FDA approval to approval in trial countries (Fig 2). For upper-middle-income countries, the 1- and 5-year approval rates were 22% (8/36) and 40% (8/20) , respectively, with a median approval time lag of 20.8 months. Of the two low-middle-income countries that enrolled patients

in these trials, Egypt and Ukraine, none of the studied drugs/regimens have received regulatory approval in either trial country to date.

When stratified by geography, we found the highest approval rates for trial countries in Europe and Central Asia with 1- and 5-year approval rates of 83% (151/182) and 84% (96/114) , respectively, and a time lag of 8.3 months. Trial countries in Latin America in addition to sub-Saharan Africa have had zero drug/regimen approvals for the clinical trials in which they enrolled.

DISCUSSION

In the era of novel MM therapies, to our knowledge, there have been no studies characterizing the locations of global MM trials in aggregate and reporting on regulatory approval of studied drugs/regimens in their participating trial countries. In this systematic review, we found that MM clinical trials leading to FDA approval from 2005 to 2019 were primarily run in high-income, European, and Central Asian countries. There were no low-income or South Asian countries that enrolled patients in these pivotal trials, and no approvals were granted in the low-middle-income countries where these trials were conducted. On the basis of our analysis, it appears that countries supporting clinical trials leading to US FDA approval received regulatory approval in other countries in a fairly expeditious fashion. However, our study highlights that there remains a gap in trial participation and access to these pivotal therapies on the basis of country income level and geography. Global oncologists are increasingly sounding the alarm about the potential for exploitation of low- and middle-income countries in the era of multinational clinical trials.[15,16] There is concern that global clinical trials rarely benefit people in the countries where drugs are tested and capitalize on the inaccessibility of standard treatments in low- and middle-income countries to garner trial participation.[21] Our findings confirm that MM trials are indeed global but enroll very few patients in low- and middle-income nations, suggesting that MM clinical trials may be exacerbating disparities in the form of unequal trial participation and access to clinical trials.

This unequal trial participation and access to therapeutics may affect the generalizability of the trial results.[22] People of African descent, for example, have an increased risk of MM and generally experience worse outcomes.[23-25] Studies have also shown that although Black patients account for 13% of the US population and 20% of all new MM diagnoses in the United States, they are under-represented in MM clinical trials, comprising 10.5% of the study populations in US-based trials and only 1.8% in international trials.[26] Even more troubling is the fact that many pivotal MM trials in the modern era do not even report on minority enrollment, and that when trended over time, recruitment of racial minorities has not improved.[27] We observed that there was only one sub-Saharan African country (South Africa) and no Caribbean countries that enrolled in these trials, despite the higher burden of MM in these countries. These disparities in trial representation have the potential to exacerbate health disparities and limit the generalizability of the findings to specific subpopulations including high-risk populations.

There are many opposing forces to balance in the pursuit of ethical global clinical trials. Equipoise must consider study generalizability and minimizing exploitation of low- and middle-income countries. Trial globalization must include increased representation of low- and middle-income in future trials in a fashion that benefits the local population, with the use of contemporary control arms, adequate postprotocol therapies, and efforts from the sponsor to seek approval and provide equitable, affordable, and timely access to a drug if the trial is shown to be successful. However, for these goals to be achieved, they must be matched with policy changes through coordination between national and international regulatory agencies, improvement in local cancer delivery infrastructure, and appropriate drug pricing. Industry can play a pivotal part in this process by helping develop the infrastructure not only to run contemporary, well-designed trials in low- and

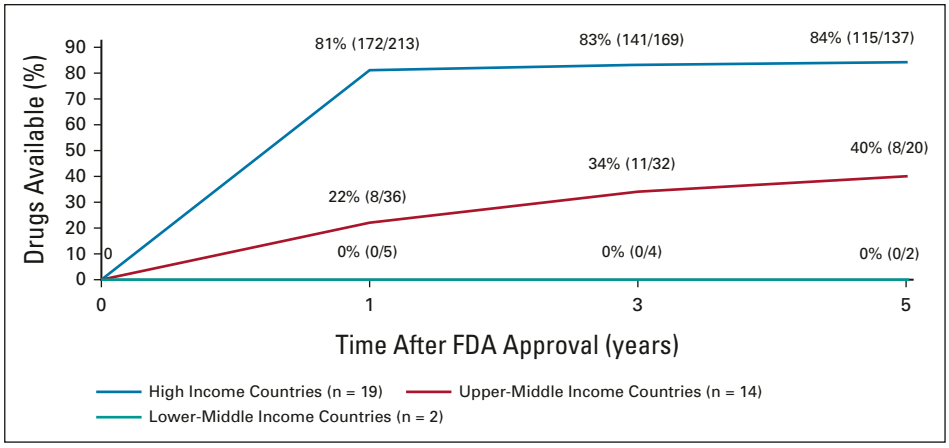

FIG 2. Percentages of myeloma drugs approved for use in their participating trial countries, stratified by income level.

middle-income countries, but also by providing adequate postprotocol therapy and resources for patients after the trial completes.

One can argue that the FDA and worldwide pharmaceutical industry have a moral responsibility to avoid harming clinical trial participants and should at least attempt to secure regulatory approval in countries where drugs are tested.[28] The mechanism to best accomplish these goals remains to be seen. However, there are specific examples regulatory agencies can take to protect their constituents.[29,30] For instance, participating trial countries, especially low- and middle-income countries, could begin to demand that pharmaceutical companies commit to submitting a drug regimen for approval in all trial countries within a specific time frame of FDA approval (ie, 3, 6, or 12 months). Trial countries could also consider aggregating drug marketing and approval activities to streamline the regulatory process and potentially expand the number of new medication offerings available.[28] Although this would take coordination between neighboring/allied nations, and much of the onus would still be on sponsoring pharmaceutical organizations to seek approval in these groups of countries, efforts such as these have the potential to ease the burden of worldwide drug approval and expand drug access, especially in countries that participate in testing. Other opportunities to improve drug access in participating trial countries include increasing government/philanthropic funding for cancer medications, reducing drug prices overall, or developing a single international regulatory body to govern new drug approvals.[31]

Although a cure for MM may soon be in sight for patients living in high-income countries, a large global population of MM residing in low- and middle-income countries remains without access to therapies that have been approved and led to prolonged life expectancy in many high-income countries for many years. This will become increasingly important as newer MM therapeutic modalities currently being developed, such as chimeric antigen receptor therapy and bispecific antibodies, are introduced with significant financial toxicity even in high-income countries.

Although our study examined the drug approval status of different therapeutic combinations, we did not explore other aspects of drug access including funding and/or insurance approvals. Regulatory approval is only one step in the path to drug access, and indeed even where drugs are approved, significant barriers may exist for patients to receive these therapies. Furthermore, we could not clearly determine situations where drug approval was sought and denied. In addition, some trial countries did not have publicly available medicines databases, and we were forced to rely on pharmaceutical press releases for approval information and timing. We reported on the geographic regions of trial countries as a proxy for race/ethnicity but did not evaluate the racial/ethnic composition of each trial cohort, as this has been previously studied.[32] Finally, we did not incorporate the proportions of a total study population represented by each trial country, which could uncover disproportionate involvement in clinical trials for trial countries that do not have access. Future studies should consider the role of funding and the proportion of patients each country contributes to a given trial to identify sponsorship and participation trends that may be affecting drug access.

In summary, our systematic review found that MM trials leading to FDA approval are generally run in high-income, European, and Central Asian countries. There are substantial gaps in where novel therapies are tested and where they are ultimately approved for use on the basis of income level and geography. These findings suggest clinical trials leading to FDA approval in MM may not reflect the global burden of disease and may be exacerbating the established disparities by excluding low-income, sub-Saharan African, Caribbean, and South Asian patient populations.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Complete List of Trial Countries

Trial Country	No. of Trials Enrolled	Income Level	Geographic Region
Hong Kong	1	High	East Asia and Pacific
Singapore	1	High	East Asia and Pacific
Croatia	1	High	Europe and Central Asia
Finland	1	High	Europe and Central Asia
Slovakia	1	High	Europe and Central Asia
Egypt	1	Lower-middle	Middle East and North Africa
Thailand	1	Upper-middle	East Asia and Pacific
Georgia	1	Upper-middle	Europe and Central Asia
North Macedonia	1	Upper-middle	Europe and Central Asia
Lebanon	1	Upper-middle	Middle East and North Africa
South Africa	1	Upper-middle	Sub-Saharan Africa
Norway	2	High	Europe and Central Asia
Bulgaria	2	Upper-middle	Europe and Central Asia
Serbia	2	Upper-middle	Europe and Central Asia
Argentina	2	Upper-middle	Latin America and the Caribbean
Mexico	2	Upper-middle	Latin America and the Caribbean
New Zealand	3	High	East Asia and Pacific
Portugal	3	High	Europe and Central Asia
China	3	Upper-middle	East Asia and Pacific
Romania	3	Upper-middle	Europe and Central Asia
Switzerland	4	High	Europe and Central Asia
Ukraine	4	Lower-middle	Europe and Central Asia
Brazil	4	Upper-middle	Latin America and the Caribbean
Taiwan	5	High	East Asia and Pacific
Hungary	5	High	Europe and Central Asia
Ireland	5	High	Europe and Central Asia
Turkey	5	Upper-middle	Europe and Central Asia
Denmark	6	High	Europe and Central Asia
Japan	7	High	East Asia and Pacific
Austria	7	High	Europe and Central Asia
Republic of Korea	8	High	East Asia and Pacific
Czechia	8	High	Europe and Central Asia
The Netherlands	8	High	Europe and Central Asia
The United Kingdom	8	High	Europe and Central Asia
Israel	8	High	Middle East and North Africa
Italy	10	High	Europe and Central Asia
Poland	10	High	Europe and Central Asia
Australia	11	High	East Asia and Pacific
Greece	11	High	Europe and Central Asia
Sweden	11	High	Europe and Central Asia
Russian Federation	11	Upper-middle	Europe and Central Asia

(Continued on following page)

TABLE A1. Complete List of Trial Countries (Continued)

Trial Country	No. of Trials Enrolled	Income Level	Geographic Region
Belgium	13	High	Europe and Central Asia
Spain	13	High	Europe and Central Asia
France	14	High	Europe and Central Asia
Germany	14	High	Europe and Central Asia
Canada	14	High	North America

