FROM THE ANALYST'S COUCH

Trends in the globalization of clinical trials

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Industry-sponsored clinical research has traditionally been carried out in relatively wealthy locations in North America, Western Europe and Oceania[1]. However, in recent years, a shift in clinical trials sponsored by the biopharma industry to so-called emerging regions, especially in Eastern European, Latin American and Asian countries, has been noted (for example, REFS 2–5). Reasons cited for this shift include the ability to reduce operational costs while recruiting a large number of patients in a timely manner; the establishment of contract research organizations focused on global clinical trials; the rapid pace of growth of market size, research capacity and regulatory authority in emerging regions; and the harmonization of guidelines for clinical practice and research[1,2,4,6,7]. It seems that these factors will continue to be prominent drivers of the globalization process, resulting in the solidification of trends and increased geographic dispersion of drug development operations[6].

Although these trends, and the associated regulatory, public health and economic implications, have been discussed qualitatively and extensively in the literature (for example, REFS 3,5,6,8), we are unaware of any recent Medline-indexed publications quantifying the globalization of biopharmaceutical clinical trials (BCTs; defined as trials assessing small-molecule pharmaceuticals and adjuvants, biologics and vaccines) based on publicly accessible data. This absence reflects in part historical difficulties in accessing comprehensive public data on the location of BCTs. However, owing to new mandates for clinical-trial registration from both the FDA and the International Committee of Medical Journal Editors[9,10], there has recently been a substantial registration influx of ongoing and completed trials into ClinicalTrials.gov. As of January 2007, the site contains detailed descriptions of 36,249 recruiting and completed studies sponsored by the public and private sectors in more than 140 countries[11].

These data registry developments create the opportunity for a more detailed country and region-specific quantitative assessment of the globalization of BCTs, including clinical-trial capacity (the average number of sites per trial); trial density per population; size of trial; global span (regional versus global); and type of trial (early versus confirmatory versus post-marketing). Key results of such an analysis, conducted as described in Supplementary information S1 (box), are presented in FIG. 1 and TABLE 1, with extensive additional data available online (Supplementary information S2 (box), S3 (table), S4 (table), S5 (table), S6 (table)). This study has several limitations, especially concerning uncertainty about the evolving coverage ratio of ClinicalTrials.gov, incompleteness of the records of some trials and its US-centric nature. It is hoped that in the future, the public will have access to a database containing virtually complete coverage of global clinical development operations over time.

Analysis and discussion

Country-specific data on trial participation reveals considerable heterogeneity across geographical regions (FIG. 1, TABLE 1) (Supplementary information S3 (table), S4 (table)). The US dominates by a large margin, having more than eight times the number of trial sites than second-place Germany (TABLE 1). The top five countries are all in traditional regions (North America, Western Europe and Oceania) and together host 66% of all trial sites. Countries in emerging regions (Eastern Europe, Latin America, Asia, Middle East and Africa) are mostly small players when analysed individually (each with less than 2% global share), but as a group they host 17% of actively recruiting sites. Eastern Europe and Latin America generally currently host more sites than Asia. However, emerging nations such as India and China have grown rapidly from an almost negligible base in just several years. Their high average relative annual growth rates (TABLE 1) (Supplementary information S1 (box), S4 (table)), coupled with their very low density of trials and current levels of investment in clinical research infrastructure[12], suggest that they have potential to grow into major players in the future.

Not only do traditional countries tend to have more trial sites, but their trial capacity is generally larger than in emerging economies (TABLE 1) (Supplementary information S3 (table), S4 (table)). Notably, a substantial number of Eastern European, Latin American and Asian nations have capacity approaching that of the traditional regions. Although trial density (FIG. 1) is greatest in the US, Canada and in several Western European countries, it is becoming quite substantial in some Eastern European countries such as the Czech Republic, Hungary and Estonia, but is still low in the more populous emerging countries. The fact that countries of emerging regions are reaching an average number of sites per trial capacity comparable to that in traditional nations suggests that they are increasingly able to offer a competitive number of sites suitable to participate in large global clinical trials.

Assessing the regional distribution by trial type (Supplementary information S5 (table), S6 (table)) reveals that although North American sites comprise 56% of all trial sites, early trials are disproportionately high in North America (62%), whereas confirmatory trials are disproportionately high in Eastern Europe, Latin America and Asia. Post-marketing trials are disproportionately high in Western Europe, and are less frequent in North America, Eastern Europe and Latin America.

In terms of growth rates, 24 of the fastest growing 25 countries are from emerging regions (TABLE 1) (Supplementary information S4 (table)), while 19 of the 25 slowest growing top 50 countries are from traditional regions (TABLE 1) (Supplementary information S4 (table)). Emerging regions grew from less than 8% in the BCTs initiating recruitment in 2002 to 20% of BCT sites that became active in 2006 (Supplementary information S2 (box)).

Overall, these trends have numerous public health, regulatory, economic and medical training implications. The globalization of clinical trials can bring both health benefits and hazards to research subjects and the general population. Potential benefits include diffusion of medical knowledge and effective medical practice, and greater patient access to high ▸

quality medical care. Concerns include the possibly inadequate regulatory oversight of research activities in emerging regions and the difficulty in drawing valid scientific conclusions with pooled data from ethnically and culturally diverse populations. Additional areas of concern include ethical issues involving integrity of the informed consent process and suitability of the clinical research focus, and economic impacts from the shift of geographic allocation of BCTs for the associated countries and companies[3,5,6,8].

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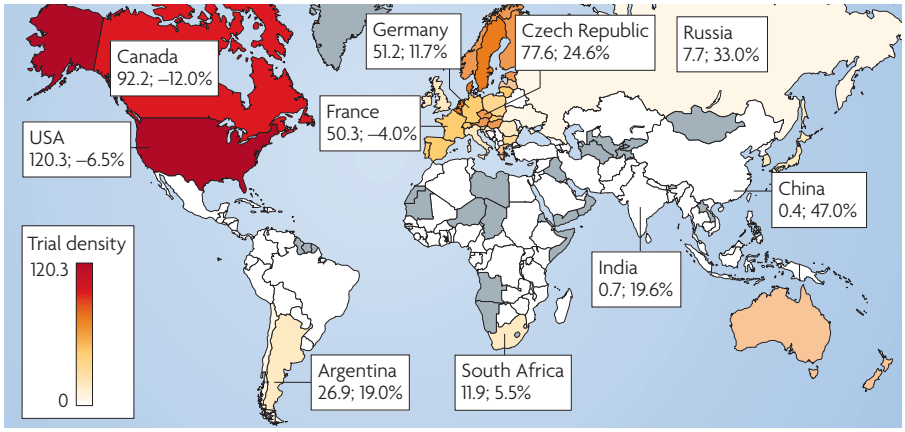

Figure 1 | **Density of actively recruiting clinical sites of biopharmaceutical clinical trials worldwide.** Density is in per country inhabitant (in millions; based on 2005 population censuses); darker orange/red denotes a higher density. The trial density and average relative annual growth rate in percent is shown for selected countries. The countries in grey had no actively recruiting biopharmaceutical clinical trial sites as of 12 April 2007.

Table 1 | **Country trends in participation in biopharmaceutical clinical trials**

Rank	Country	Number of sites	Share (%)	ARAGR (%)	Trial capacity	Trial density
1	United States	36,281	48.7	-6.5↓	43.7	120.3
2	Germany	4,214	5.7	11.7↑	10.9	51.2
3	France	3,226	4.3	-4.0↓	9.6	50.3
4	Canada	3,032	4.1	-12.0↓	8.6	92.2
5	Spain	2,076	2.8	14.9↑	6.8	46.4
6	Italy	2,039	2.7	8.1↑	6.7	34.6
7	Japan	2,002	2.7	10.3↑	33.4	15.7
8	United Kingdom	1,753	2.4	-9.9↓	7.6	29.1
9	Netherlands	1,394	1.9	2.1↑	6.8	85.0
10	Poland*	1,176	1.6	17.2↑	5.3	30.9
11	Australia	1,131	1.5	8.1↑	5.4	54.4
12	Russia*	1,084	1.5	33.0↑	5.8	7.7
13	Belgium	986	1.3	-9.4↓	5.2	94.8
14	Czech Republic*	799	1.1	24.6↑	4.5	77.6
15	Argentina*	757	1.0	26.9↑	4.8	19.0
16	India*	757	1.0	19.6↑	5.8	0.7
17	Brazil*	754	1.0	16.0↑	5.1	4.0
18	Sweden	739	1.0	-8.6↓	5.1	81.0
19	Mexico*	683	0.9	22.1↑	4.0	6.2
20	Hungary*	622	0.8	22.2↑	4.1	62.5
21	South Africa*	553	0.7	5.5↑	4.3	11.9
22	Austria	540	0.7	9.6↑	3.8	65.1
23	China*	533	0.7	47.0↑	5.3	0.4
24	Denmark	492	0.7	9.2↑	4.4	90.3
25	South Korea*	466	0.6	17.9↑	3.4	9.5

*Countries in emerging regions. ARAGR, average relative annual growth rate. Trial capacity is the number of sites in the country involved in large trials (20 or more sites) divided by the number of large trials in the country. Trial density is the number of recruiting sites on April 12th 2007 divided by the country population in millions.