

FOCUS ON EUROPE

CLINICAL TRIALS LOCATIONS

Consider Geography

When Choosing Investigative Sites

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With today's time and cost constraints, the pharmaceutical industry is on a constant quest for ways to speed the development of new drugs. Currently, it puts a great deal of thought into the use of modern technology—e-clinical trials. But it gives relatively little consideration to geography.

How many and which countries form the optimal setting for a clinical study? What is the optimal balance between infrastructure, scientific standards, regulatory access and acceptance, good clinical practice adherence, and investigator qualification? Should clinical trials be conducted only where the products' markets are?

It is important to focus on the population in the area surrounding investigative sites to determine whether or not sufficient numbers of subjects can be enrolled in a given time span. The area from which a site can reasonably expect to enroll subjects is called the *catchment area*—here arbitrarily defined as the area from which 95% of that site's regular patients are drawn. The part of a country's total population that lives in the catchment area is called the *catchment population*.¹

Sophisticated clinical trials usually require large hospitals. These in turn require reasonably large cities. Thus, by geographical criteria alone, countries with a high catchment population compressed into a small territory have a higher relative value for clinical investigation than those with a sparse population covering vast territories. In countries where large cities are evenly distributed across

the geographic territory (Germany, for example), the catchment population, relative to the total population, reaches numbers far greater than in countries with an uneven distribution (such as France). The continental United States stands between the two extremes, with centers of gravity in terms of scientific and technological infrastructure and population density along the East and West Coasts and in parts of Texas.

In the context of modern clinical trials, it is helpful to consider modified criteria that reflect the catchment population more concisely—that is, in terms of the number and size of urban centers in comparison to the total population. For this article, we define *urban center* as a city with over 100,000 inhabitants. Germany has 82 such urban centers and a total population of 82 million (over 30% of the total is urban²); France only 32 cities and a population of 59 million (only 14% urban^{3,4}); and, finally, the continental United States (minus Alaska, Hawaii, and Puerto Rico) has some 237 cities and a population of 280 million (26% urban⁵).

Urban centers can also be arbitrarily defined, on the basis of purely geographic criteria, as agglomerations with more than 2,000 people per square kilometer (or more than 1,000 per square mile) in a coherent area of at least 1,000 square kilometers or square miles—a metropolitan area. This view ignores administrative boundaries and merges neighboring cities into meaningful clusters, thus providing a more pragmatic measure for the catchment population considered for clinical trials. Greater New York, Los Angeles, Paris, and the

Rhine-Ruhr and Rhine-Main districts would be such metropolitan areas (Table 1). The larger the population in metropolitan areas, the higher the potential for clinical trials.

Population density and its distribution need to be taken into account. As mentioned earlier, Germany exhibits a relatively even distribution, France and the United States a more uneven distribution. This bears on the travel logistics involved in setting up and monitoring clinical trials. Travel between sites in unevenly populated parts of vast countries is distinctly less productive than in evenly populated areas.

Absolute and relative catchment population

To determine a country's catchment population for clinical trials, one could simply add up the residential population of all urban centers or metropolitan areas. The measure taken depends on the nature of the targeted disease. If we deal with a relatively straightforward protocol for a common disease, we may look at urban centers over 100,000 inhabitants. A more complex protocol and a more unusual target disease calls for metropolitan areas.

The decision is also influenced by the availability of suitably qualified investigational sites. For a straightforward trial in an everyday indication, sites may be abundant and available in every medium-sized city; for a complex trial in a rare disease, sites may be available only in a few specialized academic centers. For common conditions, geography plays a greater role in our considerations; for complex trials, it plays little or no role.

An example: We are located in

Consider the concentration of potential subjects in catchment areas when deciding on locations for clinical trials.

TABLE 1 Population and size of selected countries^a

Country/Area	Total population (millions) ^{2,3}	Urban population ^b (millions) ^{4,5}	Size (sq. km.) ³	Density (people/sq. km.)
Continental United States	280	71.9	8,080,704	35
Metropolitan New York	21.2	9.6	~ 17,300	~ 1,225
Texas	20.9	9.0	695,676	30
Metropolitan Los Angeles	16.4	6.4	~ 13,000	~ 1,262
New Jersey	8.4	0.8	22,590	373
Massachusetts	6.3	1.1	27,337	232
Montana	0.9	0	380,850	2.4
Germany	82	25.2	357,022	230
Rhine-Ruhr agglomeration	11.1	7.3	9,776	1,132
Mecklenburg-Vorpommern	1.8	0.1	23,171	77
France	59	8.3	543,965	108
Metropolitan Paris	9.3	3.4	1,160	8,017
Corse	0.3	0	8,680	30

^aSelected areas represent extreme examples. Figures are rounded.
^bCities over 100,000 inhabitants.

New York City and are planning a trial in the United States.

- In one case, our database identifies 500 suitable sites, and we require at least 20. Southern New York state, New Jersey, and Connecticut appear to be the preferred territory.
- In another case, our database identifies 100 suitable sites, and we require at least 80. Our territory will have to be the entire United States.

When looking at international trials, even the definitions of *urban center* and *metropolitan area* may have to be adapted to each country, taking into account the prevailing traffic and transportation infrastructure.

U.S. subjects may find it normal to travel in their own cars over considerable distances; so the U.S. definition of a metropolitan area may be relatively extensive. To the contrary, European subjects are more likely to depend on public transportation to travel shorter distances; consequently, a European metropolitan area is a more aggregate entity.

The U.S. Office of Management and Budget defines *consolidated metropolitan statistical areas* (CMSAs) on the basis of entire counties, *primary metropolitan statistical areas* (PMSAs) as the cores of CMSAs, and simple *metropolitan statistical areas* (MSAs). It has separate definitions for New England.⁶ Similarly, the German

Statistische Bundesamt (Federal Statistics Office) defines 13 metropolitan areas (*Verdichtungsräume*) more narrowly on the basis of municipalities, using more refined administrative criteria: “Coherent agglomerations of several communities, each with more than 150,000 inhabitants.”⁷ Neither definition is satisfactory, because both mix geographic with administrative criteria.

A definition on purely geographic grounds is better suited to describing subject availability. A metropolitan area would then be a “coherent area with a total of more than 500,000 inhabitants and an average population density of more than 1,000 persons per square kilometer.”⁸

Whatever the definitions, their apparent variations mirror socio-geographic differences between the countries. For international clinical trials the bias is negligible; what is important is that the definitions describe equivalent access to potential subjects. In that respect, metropolitan areas so different in terms of size, absolute or urban population, or population density as Greater Paris and Los Angeles, the Rhine-Ruhr area, and Greater New York (Table 1) resemble each other nevertheless in terms of subject accessibility.

But geography is only one of many components that eventually determine a country’s composite overall

value for clinical investigations. For clinical studies to be carried out efficiently, many nongeographical factors also have to be considered—established contacts to investigational facilities, culture, social coherence, language, ethnic structure, scientific education, investigational interest, regulatory impact, technology, logistic and organizational infrastructure, methodologic and ethical feasibility, political climate, quality, marketing, and competitive strategy. We may even be tempted to consider personal preferences (“Is the site in sunny California?”) or personal pressures (“Enrollment speed alone determines the magnitude of my next pay raise”).

Absolute and relative catchment populations must therefore be differentiated. Absolute catchment is an objective criterion identified purely on the basis of geographical analysis. Relative catchment recognizes all other nongeographical factors and is mixed with subjective factors. The disparity between the two is often striking.

Eastern Central Europe

Geographical obstacles. Eastern Central Europe (also popularly called Central and Eastern Europe) has seen a massive influx of clinical studies in the past decade. One might wonder if geographical considerations support this trend. Eastern Central Europe comprises 15 independent countries of the former Soviet sphere of influence. Neither of these countries today belongs to the Community of Independent States (CIS). The territory is only moderately populated while highly segmented.

The map shows most countries distinctly smaller than their relatively large Western European comparators (Tables 1 and 2). The 15 countries cover an area 3.76 times that of Germany, their population totals 1.57 times that of Germany, and their urban population is 1.33 times Germany’s. Fifteen different languages prevail, 15 different regulations for clinical trials, 15 different authorities. Geographic criteria, regulatory access, language, and cultural diversity all suggest barriers to efficient clinical trial implemen-

TABLE 2 Population and size of Eastern Central European countries^a

Country	Total population (millions) ³	No. cities over 100,000 inhabitants ^{3,4}	Urban population (millions) ^{3,4}	Size (sq. km.) ³	Density (people/sq. km.)
Albania	3.3	1	0.4	28,748	116.1
Bosnia/Hercegovina	3.8	6	1.2	51,129	73.7
Bulgaria	8.3	9	2.6	110,994	74.4
Croatia	4.5	4	1.2	56,542	79.6
Czech Republic	10.3	5	2.2	78,866	130.5
Estonia	1.5	2	0.5	45,227	32.1
Hungary	10.1	9	3.0	93,030	108.7
Latvia	2.4	2	0.9	64,589	37.9
Lithuania	3.7	5	1.5	65,301	56.7
Macedonia	2.0	1	0.4	25,713	78.2
Poland	38.7	31	10.1	312,685	123.7
Romania	22.5	18	6.3	238,391	94.4
Slovakia	5.4	2	0.7	49,034	109.9
Slovenia	2.0	2	0.4	20,253	97.9
Yugoslavia (combined Serbia, Kosovo, Montenegro)	10.4	7	2.0	102,173	101.7
Totals	128.8	104	33.5	1,342,675	95.9

^aFigures are rounded.

tation and speak against considering clinical studies in Eastern Central Europe.

Marketing issues. All clinical studies carry an inherent marketing element, even in the early phases of development. Therefore, carrying out studies in countries that represent interesting markets may be a good strategy. Do we expect our trial to help prepare this relatively poor market for our eventual drug product?

Positives. On the other hand, the investigational environment in Eastern Central Europe has some positive factors—cooperative investigators and patients, alleged superb quality of work, lack of concomitant medications, centralized structure of hospitals, and moderate prices.⁹

The relative catchment population depends on the enrollment and treatment duration of the trial. The higher the enrollment rate, the greater the chance that it will offset the drawback of multiple procedures and initial delays in a departmentalized territory. Overall, one might wonder whether Eastern Central Europe really deserves the attention that it currently enjoys.

An example: We plan a trial in Europe. Our protocol requires a total of 500 subjects and a minimum of 10

subjects per site. Because of time pressures, we need to recruit 50 sites.

- We estimate that regulatory procedures in Germany, the Benelux, and Switzerland will take no longer than 4 weeks; we estimate average enrollment at one subject per site per week. Our trial will take 14 weeks to set up and enroll.
- We estimate regulatory procedures in Eastern Central Europe to take 12 weeks; we estimate average enrollment at two subjects per site per week. Our trial will take 17 weeks to set up and enroll.

The relative catchment population in the example thus appears larger in Germany-Benelux-Switzerland than in Eastern Central Europe. The longer the ensuing treatment duration, however, the less important the set-up time and enrollment rate become, and Eastern Central Europe may take the lead in our decision process.

Fact versus fiction

Consider the following questions. Do you properly rate all contributing factors when deciding which country to take on board? Or are you tempted to take only positive factors into the equation, ignoring the negative ones? Do you go where everybody goes, allowing yourself to be governed by

fashion, hearsay, and self-perpetuation? Are your decisions on countries or territories based on fact or fiction? Can you comparatively evaluate absolute and relative catchment populations? Geographical analysis can be a step toward more critical and objective ratings. Simply look on the map.

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