White Paper

Attracting Investment in Clinical Development

How pharmaceutical companies make clinical development location decisions, and what healthcare policy makers can do to attract commercial clinical investment.

SARAH RICKWOOD, Vice President, EMEA Marketing and Thought Leadership, IQVIA
FIONA PEREIRA, Engagement Manager, Brand & Integrated Research Solutions, IQVIA
CAMILA ABELLA GÓMEZ, Intern, EMEA Thought Leadership, IQVIA

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Executive summary

Deciding where to locate clinical trials is a critical and multi-layered investment decision for pharmaceutical companies. Understanding the country selection criteria pharmaceutical companies use is essential for Government policy makers, Regulators and Health authorities to attract clinical inward investments which will generate economic, healthcare and societal value for their local population. This white paper is based on interviews with senior decision makers in pharmaceutical companies responsible for the choices that their companies make about where to locate clinical development. From these interviews, we analyse industry trends and create an Investment Criteria Framework providing actionable recommendations for Regulators, Healthcare policy makers and providers and pharmaceutical companies.

Despite growth in R&D investment, pharmaceutical companies increasingly face challenges to deliver successful and time-efficient drug developments. Success rates, as measured by IQVIA's Clinical development Productivity index, have fallen significantly since 2015[1], with a wide range of issues to blame. These include trialling increasingly complex therapeutics in increasingly defined patient populations, and growing competition for investigator sites and patients in therapy areas, such as oncology, with high levels of innovative activity. They also can include, dependent on country, regulation which slows the set up and execution of trials, and absence of modern digital healthcare infrastructure that can speed patient identification and recruitment. It is critical for a country's healthcare system policy makers to understand the challenges that pharmaceutical companies face when conducting clinical trial to ensure their health system provides differentiated value and attracts more clinical inward investment.

This white paper provides an Investment Criteria Framework with the key factors that pharmaceutical companies assess to decide in which countries to locate their clinical trials, both early and late stage, and the relative attractiveness of different regions and countries against those criteria. These results were derived from anonymous interviews to Heads of Global Clinical Operations and/or Regulatory Affairs of 60% of Large pharmaceutical companies (defined as those in the top 20 of global prescription medicine revenues) and complemented the study with interviews to European mid-sized pharma, and Emerging Biopharma companies (EBPs). This white paper makes strategic recommendations for policy makers and policy influencers by country archetype, with actionable initiatives to accelerate clinical trial activity and promote clinical inward investment.

Multiple reports conclude that clinical trials provide large economic, healthcare system and societal value for countries. In 2021, the top 15 largest pharmaceutical companies by revenue invested $133 billion in R&D expenditure (7.6% CAGR from 2016).[2] 44% of total R&D investment was allocated for clinical trials, of which 27% were invested in Phase III.[3]

US, EU4, UK, Japan, and China hosted 60% of global clinical trials registered in Clinicaltrials.gov in March 2022[4] and accounted for 77% of global sales in FY2021 (IQVIA MIDAS, List price, Rx Only). "Other European" countries conducted 13% of global clinical trials and "Other non-European" countries hosted 27% of global clinical trials, suggesting a clear attractiveness for clinical trials despite their smaller commercial opportunity (i.e., 23% of global sales in FY2021).

In recent years, some pharmaceutical companies have narrowed the number of sites and countries in clinical trials to minimise complexity and increase success rates — which have declined to 5% across all therapy areas in 2021.[5] The underlying drivers are multi-factorial, but pipeline focus on highly specialised treatments for rarer indications, bringing with it increases in trial complexity, is a common factor. It is critical for policy makers to understand the challenges that pharmaceutical companies face conducting clinical trial if they wish to attract more clinical inward investment.

This white paper analyses industry trends and provides an Investment Criteria Framework based on our interviews with Heads of Global Clinical Operations and/or Regulatory Affairs. Our research shows a complex combination of decision drivers for country selection, including Commercial return from the country, trial performance, clinical expertise network, regulatory framework, and disease prevalence. Cost of trial drivers were discussed by interviewees but were not identified as a top priority in the individual country selection criteria (i.e., "quality and speed over costs" or "cost is a consequence of other more relevant factors"). However, as the country set used for a trial will influence overall trial cost, it's sometimes possible that country adjustment will come into play at that point. In short, while some factors such as commercial market size and disease prevalence are largely not influenceable by country policy makers, many factors driving clinical investment decisions are, and factors related to speed, quality and expertise prevail, at the individual country level, over cost.

Pharmaceutical companies establish pre-defined lists of countries, or country archetypes, based on strategic objectives and internal policies: "Cornerstone" countries are defined by commercial and strategic priorities and always include US, EU4, UK, Japan, and China, "Growth" countries are over 150 countries which are considered as optional locations, and "Out-of-scope" countries, where no clinical trials are conducted by the companies we interviewed except in exceptional circumstances such as disease prevalence in those countries constituting all or a

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significant part of global prevalence. While Cornerstone countries will always be considered, policymakers in the very large "Growth" group of countries must understand how they can move up the list pf priorities, and countries currently "Out-of-scope" how they can move into the "Growth" category. Additionally, this white paper provides the interviewees' perceptions about countries' relative attractiveness at a global level (i.e., US, EU4+UK, China, Japan, META, and Australia) and at a European level (i.e., Germany, UK, Spain, CEE, and Nordics).

Our white paper makes specific recommendations for healthcare policy makers in countries falling into the different country archetypes.

- **For "Cornerstone" Countries, an "Accelerate and Collaborate"** strategy will help these countries, most likely to be the site of clinical investment, to capture more share amongst core countries by providing agile and innovative research ecosystem, local regulation which enables rather than hinders clinical trial set up, digital investment to support novel clinical trials design and specialised capabilities, and cross-country agency collaboration to unlock optimization of global R&D.
- **For "Growth" Countries, a "Differentiate and Attract"** strategy is necessary, defining strategic positioning in global clinical trials versus other "Growth" countries based on internal capabilities assessments to identify main source of clinical value-add. Policy makers should also design short-term (e.g., experts network activation, patient awareness, etc.) and mid-term initiatives (e.g., health systems, niche development, etc.) to build relationships and attract more clinical inward investment.
- **Policy makers in "Out-of-scope" Countries: "Ticket-to-Play"** countries need to identify addressable causes for being out of scope and understand the minimum standards required to be considered by pharmaceutical companies and start designing and building the basic digital capabilities and infrastructure to advance towards better healthcare delivery.

Pharmaceutical companies must also be active collaborators in countries' development of clinical trial infrastructure and capacity, through proactive collaboration with Agencies and Associations, feedback, advocacy and support during the development and implementation of new clinical regulatory framework, continuous internal optimisation and investment in digital solutions (e.g., DCT), "Patient voice" as active drivers of trial's journeys and protocols designs, Diversity and Inclusion initiatives, etc.

Clinical trials: A global overview

ECONOMIC AND SOCIETAL IMPACT OF INVESTMENT IN COMMERCIAL CLINICAL DEVELOPMENT

IQVIA Institute's R&D Report 2022 estimated that the top 15 largest pharmaceutical companies by prescription medicine revenues invested $133 billion in 2021 in R&D expenditure, up by 44% from 2016 (Figure 1).[6]
A separate Pharmaceutical Research and Manufacturers' Association America (PhRMA) study showed that of the total surveyed company financed global R&D investment, 44% is allocated for Phase I–III clinical trials, a total of $40bn for a single year, 2020,[7] with Phase III representing $25bn of investment alone (Figure 2).[8]

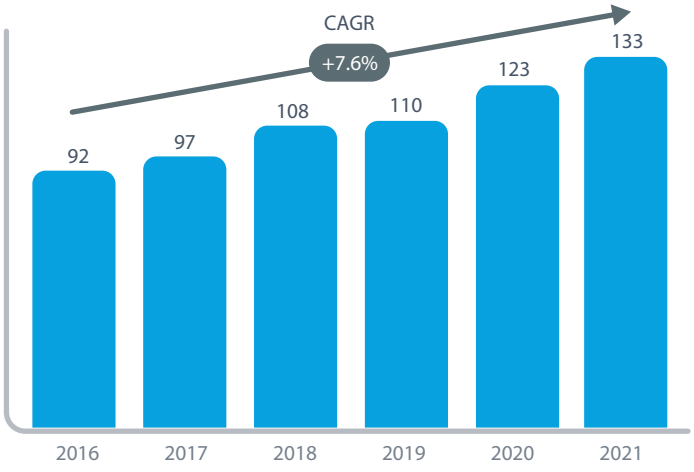
Clinical trials provide huge economic and societal value for countries: early access to new therapeutic treatments for local patients, investment in and new approaches to clinical infrastructure, for example, diagnostic testing, increased direct revenue for hospitals, and world-class talent attraction.[9]

EMEA EXAMPLES OF ECONOMIC AND SOCIETAL IMPACT

- In Barcelona's Hospital Vall d'Hebron, clinical trials represented 18.5% of their total revenue streams in 2020 (€7.46 M), after national grants and industry agreements, as published in annual reports.[10]
- In the UK, IQVIA estimated that its 20% share of all commercial clinical trials the UK delivered — £1.2bn of economic impact in 2020, based on information available in the National Institute for Health and Care Research (NIHR) annual report 2020.[11]
- IQVIA META (Middle East, Turkey, and Africa) estimated that even a 1% increase in global clinical trials market share would generate nearly 4,000 local jobs and help over 10,000 patients participating in trials benefit from cutting edge therapies.[12]

Figure 1: Top 15 large pharma R&D spending, 2016–2021, US $Bn

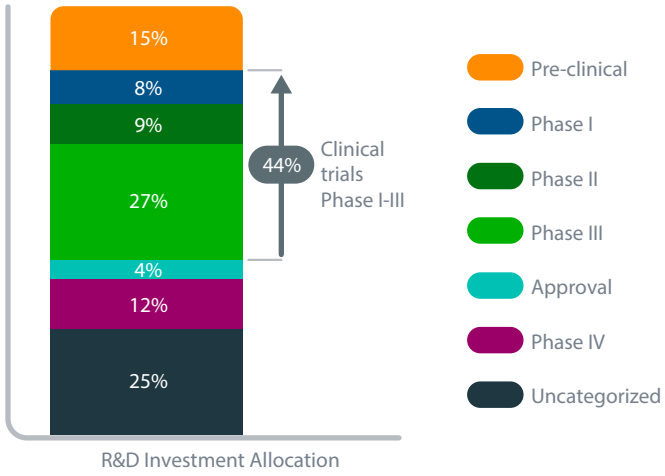
$133Bn in 2021 in R&D expenditure by top 15 large pharma (7.6% CAGR from 2016)
– IQVIA Institute



Source: : IQVIA Institute R&D Trends 2022

Figure 2: R&D by Function in PhRMA member companies, 2020, in %

44% of R&D investment allocated in clinical trials in 2020 (27% allocated for Phase III)
– PhRMA Annual Survey



Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2021.

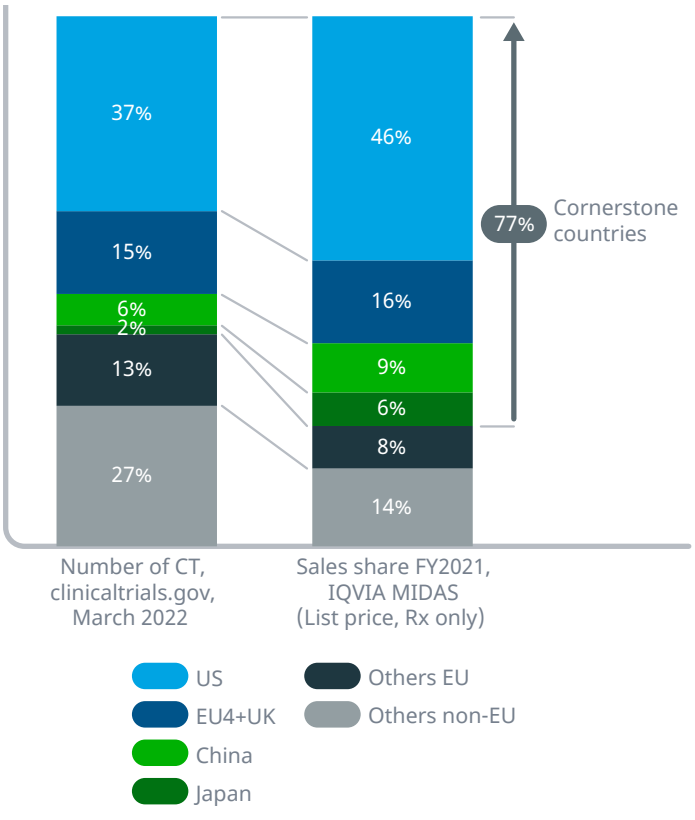
GLOBAL LANDSCAPE AND TRENDS

An obvious possible decision-making factor in the siting of clinical trials might be where commercial return is greatest, and indeed interviewees confirmed that the commercial potential of a county market is a consideration, especially when siting late phase clinical trials, but analysis shows there's no exact match. Comparing the number of clinical trials registered in clinicaltrials.gov[13] versus the total global prescription medicine sales in 2021 (from IQVIA MIDAS, list price, Rx Only), both trial activity and commercial opportunity are highly concentrated in a small number of countries. While the comparison is not exact, as reporting bias on clinical trials likely favours more developed countries, it's clear that commercial potential and clinical activity are not perfectly correlated.

Eight "Cornerstone" countries — by interviewee consensus, US, EU4, UK, Japan, and China — hosted 60% of global clinical trials but generated 77% of global sales in 2021.

"Other European" countries conducted 13% of global clinical trials, and "Other non-European" countries hosted 27% of the total (including Canada with 6%, South Korea with 3%, and Australia with 2%), suggesting a clear attractiveness as location for clinical trials despite their smaller commercial opportunity. Eastern European countries also take a greater share of clinical development activity than their commercial potential alone would predict. Clearly, there are factors other than simple commercial potential at play in the decision-making process.

Figure 3: Number of CT share vs sales share by region



Sources: Clinicaltrials.gov, March 2022, IQVIA MIDAS quarterly sales 2021 (List price, Rx only)

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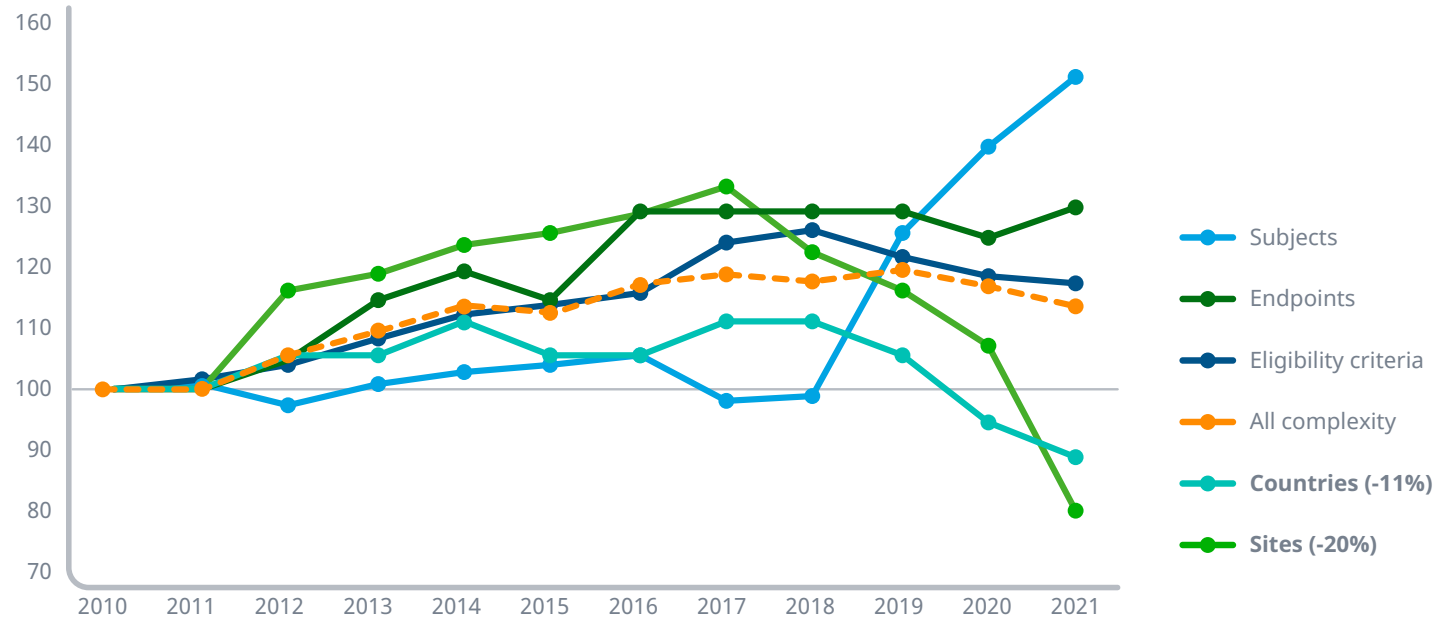
IQVIA Institute R&D Trends 2022 report evidenced that success rate (measured as likelihood of progressing successfully through all development phases) has declined across all therapy areas to 5% in 2021 due to a wide set of drivers, including growing appetite for (or necessity of) clinically high-risk developments with the rise of more complex, often specialty products being developed, higher efficacy and safety requirements, and interruptions in product manufacturing.[14] Pharmaceutical companies have also progressively reduced the number of sites and countries in clinical trials, a trend which started prior to the Pandemic, and is most likely a response to the increasingly specialised nature of the products under trial. 2020 figures should

Figure 4: Clinical trial's elements of complexity indexed to 2010 values, all phases, 2010–2021



Source: Citeline Trialtrove, IQVIA Institute, Jan 2022.
Global Trends in R&D: Overview through 2021. Report by the IQVIA Institute for Human Data.

be regarded as atypical, since they combine massive increases in patient numbers (because of COVID-19 vaccine trials) with reductions in countries and sites that were driven by lockdowns and COVID-19 restrictions (Figure 4).

While the trend to focus on a small number of countries for clinical trials might be understandable, it creates competitive challenges, both for the sites in those countries and for the companies running clinical trials. For the few countries in which pharmaceutical companies tend to retain clinical trials (i.e., "Cornerstone" countries), concentration drives increase in competition and costs for sites and patient recruitment, higher burden and saturation in health systems and possibly longer administrative delays. It is also likely to reduce the number of treatment naïve patients in patient segments targeted by multiple agents in development and

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launched. The countries outside the shrinking core will lose the benefits of clinical investment unless they can improve their attractiveness and move to the front rank of the large "Growth countries" segment by developing a clinical development infrastructure and environment which is differentiated and attractive.

Investment criteria framework: main drivers

Based on our interviews conducted with Heads of Global Clinical Operations and/or Regulatory Affairs of pharmaceutical companies in the Top 20, European mid-sized, and Emerging Biopharma (EBPs) segments, we identified the following drivers for Investment Criteria: Condition Prevalence, Trial Performance, Expertise Network, and Regulatory Frameworks. Pharmaceutical companies prioritise these factors dependent on the underlying asset or study and also the size their footprint as a company. Interviewees did mention clinical trial cost components as part of their criteria, but not as a top priority in country selection (i.e., "we prioritize quality and speed over costs" or "cost is a consequence of other more relevant factors").

A. Prevalence pre-scoping

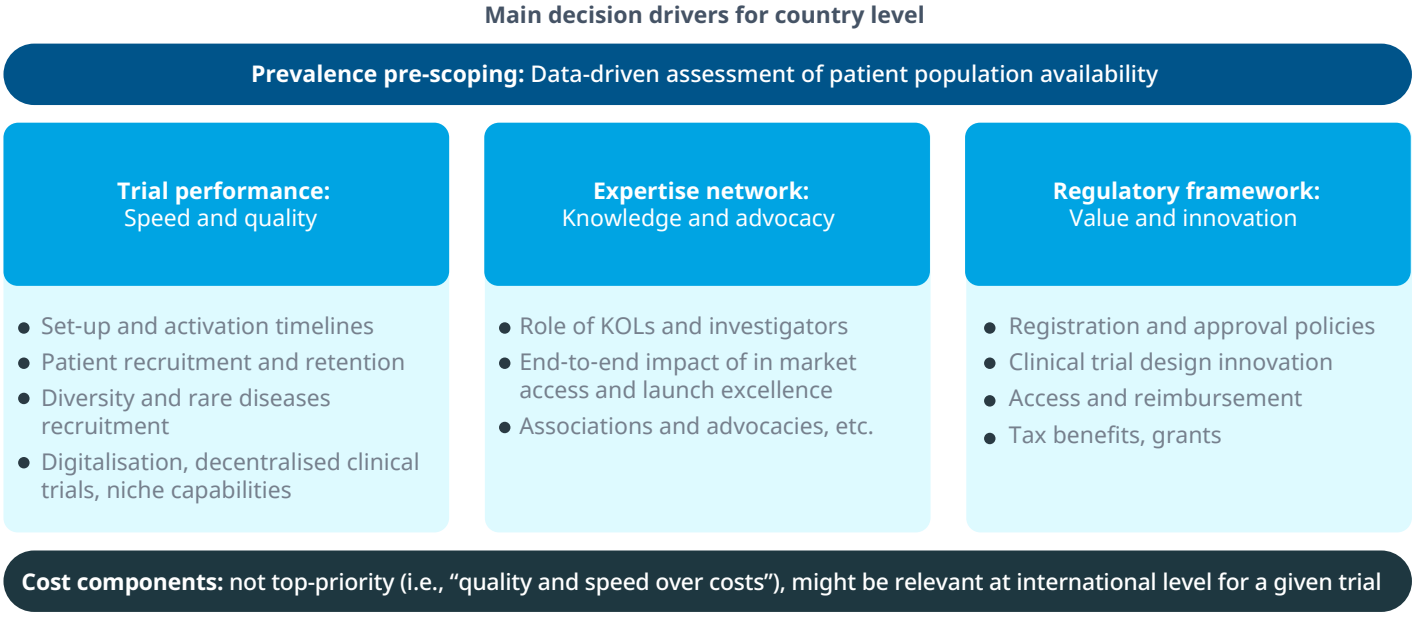
Pharmaceutical companies utilise advanced algorithms and AI/ML to provide an initial scope of countries to consider. Assessments of epidemiologic data, most fundamentally incidence and prevalence of the condition but also diagnosis rates and ease of diagnosis, past and active clinical trials statistics, and even local nutrition and cultural are factors to define the attractiveness and viability of a particular country in the study's protocol.

B. Trial performance: Speed and quality

Speed and quality are the main drivers for country selection criteria for clinical trials. Pharmaceutical companies face a highly competitive environment, in which speed is key to maximise product value and time on the market. Moreover, predictability of the forecasted timelines (e.g., start-up procedure length, site activation speed, and patient recruitment lead times) is critical for the study's design and investment decisions.

Patient recruitment is the key bottleneck our interviewees identified to performance, both in "Cornerstone" countries, where market saturation exists and competition for patients is intense, and in "Growth" countries, where the speed and recruitment of patients varies greatly mostly for other, often

Figure 5: Investment criteria framework: Main drivers assessment



Source: Clinicaltrials.gov, March 2022, IQVIA MIDAS Quarterly Sales 2021 (List price, Rx Only), IQVIA VII Launch Excellence 2022.

healthcare infrastructural, reasons. New technologies can provide timely solutions to optimise recruitment and clinical trial operations. For example, AI/ML driven solutions to take existing Electronic Healthcare record data and analyse it to provide insights on patients who may fit clinical trial inclusion criteria, while maintaining patient privacy through measures such as placing software behind a hospital's own firewall, have been developed and are in active use in healthcare institutions. These can provide a competitive edge in "Growth" countries — differentiating an institution, and, if widely adopted, a country, in an otherwise large pool of possible candidates.

Decentralized Clinical Trials (DCT) are trials blending remote and site-based elements or conducted as fully remote studies[15] and can be an operational solution which can address low patient recruitment rates, proving to expand patient pools, improve recruitment and retention, and reduce burdens in logistics and costs. IQVIA Institute's Digital Health Trends 2021 report estimated a potential reduction of 44–61% on-site visits in Phase II and III, for Decentralised Clinical Trials, depending on the therapeutic area.[16]

Most of the companies we interviewed have so far conducted decentralization only in components of clinical trials, not fully decentralized clinical trials, but they anticipate the direction of travel to be to greater use. Hybrid clinical trials enable pharmaceutical companies to compete in attracting patients by offering a differentiated and attractive patient journey — particularly relevant in indications and countries where recruitment competition is very high and for rare diseases and indications with logistically complex recruitment.

One of the factors impeding the adoption of more effective operational models is the wide disparity in countries' healthcare system digital maturity, from strategy, infrastructure, and implementation. IQVIA EMEA Thought Leadership's white paper "Switching On the Lights" benchmarks digital health systems across EMEA and proposes recommendations by country archetypes (Figure 6).[17] Health systems undoubtedly are moving in the same direction with respect to

Figure 6: Digital health system: Digital maturity archetypes

Source: IQVIA Thought Leadership, Jan. 2022.

digital maturity, but their current level of digitisation, and therefore attractiveness for Decentralised Clinical Trials, is broad. Countries which develop robust digital infrastructure fast will be those best positioned to win a larger share of clinical development activity in the future.

Improving Diversity and Inclusion (D&I) in clinical development was a topic elevated in importance by the Pandemic, and Regulators, lead by the FDA, are imposing stricter criteria for patient selection to right the historic wrong of under-representation of ethnic and minority populations. The FDA demands on reflecting diversity of the actual disease population under study have driven up demand for US-based clinical trials, making "decision increasingly defined by demands of regulators". Other Regulators, specially from "Cornerstone" countries, are expected by our interviewees to follow these diversity requirements. Countries where straightforward recruitment of diverse populations meeting regulator expectations will have another element of advantage.

C. Expertise network: Knowledge and advocacy

Some Emerging Biopharma companies (EBPs) and mid-sized pharmaceutical companies prioritize access to the expertise network over clinical trial speed, to build early relationships with local stakeholders in target markets. The need for knowledge and access to networks becomes increasingly important when entering a new therapeutic area as an unknown, as EBPs which account for the 65% of molecules in R&D pipeline, 80% being single-assets developments,[18] are more likely do. To increase attractiveness as a trial destination for these types of company, country policy makers must explore how they can facilitate an attractive local knowledge network for key therapeutic areas and support entrant company access to R&D hubs.

For Large pharma, the role of Key Opinion Leaders (KOLs) and influential Investigators is also very valuable. Clinical operations and strategic committees are increasingly considering the end-to-end vision of the R&D process and are assessing how the design of the protocols of clinical trials will impact more downstream processes, such as Market Access and Launch Excellence.

However, companies mentioned a need for an "strategic balance" to access Expertise Networks without compromising the speed of clinical trials. Some KOLs were not described as "fast recruiters", and some have competing commitments with other pharma companies. Thus, companies do not always have a systematic approach to engage with KOLs and carefully define their specific roles in the study (e.g., design advisor, steering committee, spokesman, etc.).

D. Regulatory framework: Value and innovation

Regulators can catalyse clinical trial optimization and innovation by launching ambitious initiatives, accepting novel designs and use of real-world evidence.[19] In January 2022, the EMA launched the Accelerating Clinical Trials initiative in the EU (ACT EU)[20] to replace the often-criticised EU clinical trials directive –widely seen by the industry as a slowing clinical development in Europe. In the UK, the MHRA initiated an eight-week consultation in January 2022 to design a "world-class sovereign regulatory environment" for clinical trials.[21]

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In the US, the FDA outlined new strategies to modernize clinical trials, for example, advancing precision medicine,[22] in 2019, and developed guidance to enhance the diversity of clinical trial populations and procedures for Emergency Use Authorization (EUA) and accelerated approval pathways. China's NMPA recently unveiled a 5-Year-Plan to synchronize with Global Drug Approval, proposing rolling data submissions, and published a draft document to accelerate the review of new drug applications (NDAs).[23]

Globally, an increasing range of clinical trial designs were used to support regulatory submissions in 2021, reflecting the diversity of therapeutic innovation approaches to clinical development. For instance, "embracing a seamless path that bypasses the traditional stepwise development paradigm of standalone sequential Phase I, II and III trials", as described in IQVIA Biotech's white paper, "Innovative Design in Early Phase Oncology Studies in JAPAC".[24]

The pharmaceutical industry welcomes these ambitious initiatives for standardisation in criteria and approval procedures and praise an open approach to consultation and co-creation. However, pharmaceutical companies have expressed their concerns about how these implementations will unfold, especially in highly decentralised countries, and how they will address other critical challenges, such as highly restrictive paediatric clinical trials.

Access and Reimbursement is another factor considered when assessing local regulatory frameworks, and companies may use the EFPIA Patients W.A.I.T. Indicator Survey to identify product availability by approval year, rate and time of availability, etc.[25] Finally, tax credits and grants may act as incentives and attract some companied to conduct local clinical trials in some countries, for example, Canada and Portugal, but these are not considered a decisive factor for country selection by our interviewees from pharmaceutical companies.

E. Cost considerations

Cost components of trials were not identified as a top-priority criteria for assessing individual countries in most of our interviews. Even if rigorous cost analysis is performed by companies when assessing trial location, the pressure for fast-speed and high-quality clinical trials drives the final decisions. Comments such as "Time is the most expensive commodity" and "every month missed from forecast costs a lot of money" reflects pharmaceutical companies' need and willingness to pay for accelerate and certain clinical trial timelines. Countries which can deliver speed, by this logic, will be more attractive than those that deliver lower cost but no speed advantages. At the aggregate level, when assessing the cost of a given trial over the basket of countries chosen, cost components may come into consideration and lead to readjustment of the country group.

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Country archetypes and relative attractiveness

COUNTRY ARCHETYPES

Most pharmaceutical companies we interviewed have pre-defined lists of countries for clinical trials based on their own strategic goals and internal policies – which we refer to as "Cornerstone", "Growth" and "Out-of-scope" country archetypes in this white paper.

I. "Cornerstone" countries

"Cornerstone" countries are defined by the commercial and strategic priorities of each company (i.e., US, EU4, UK, Japan, and China). These eight "core countries" are identified in IQVIA's Launch Excellence Series as pivotal for launch success.[26] They hosted 60% of global clinical trials registered in clinicaltrials.gov and generated 77% of global prescription medicines sales in 2021 reported by IQVIA MIDAS.

Pharmaceutical companies described these countries as "must-go" and they will conduct clinical trials in these countries despite their highly competitive and saturated clinical trial environment, complex and stricter regulatory requirements, sometimes lengthy registration and approval timelines, and higher costs. The types of product for which trials are conducted tends to reinforce the status of these Cornerstone Countries- for Cell, Gene and other advanced therapies these countries are most likely to possess the infrastructure necessary to support these trials.

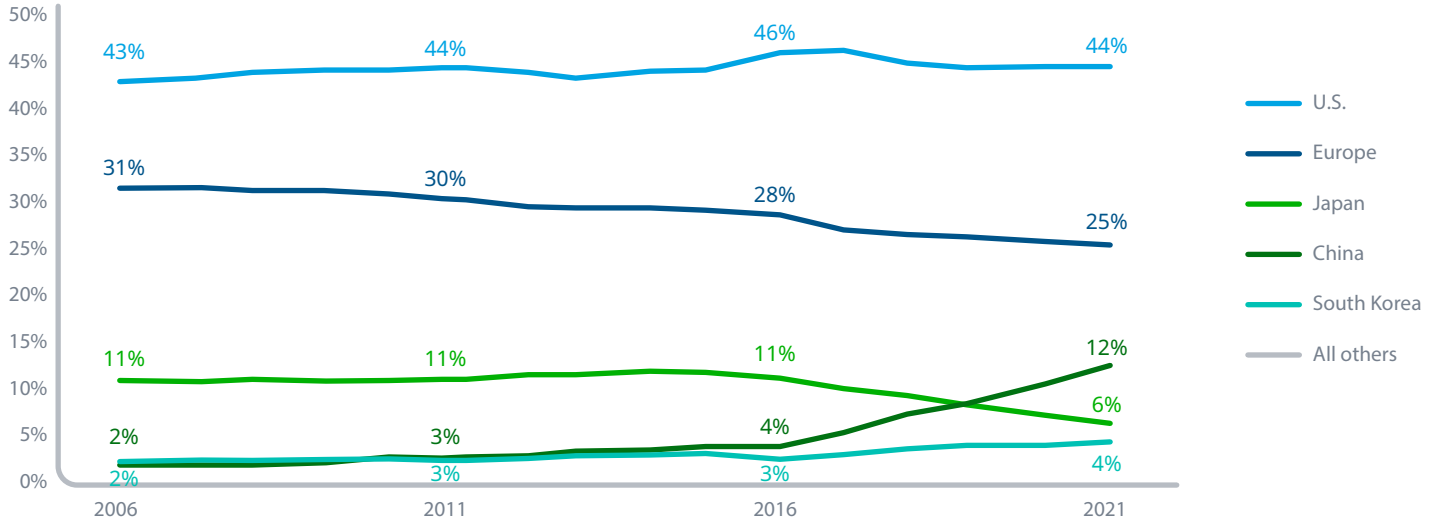
Within this group of countries there is, however, change in the share of inward investment captured. In 2021, EU-headquartered companies R&D pipeline share reduced from 31% to 25% in past 15 years while China rose to 12% up from 4% in 2016 (Figure 8).[27] China's increase in share is mainly driven by the government's regulatory reforms and massive investments in innovation development, while Europe's decline may be explained by the unattractive and complex perceptions on its clinical trials directives (expected to improve by the EMA's new initiatives, ACT EU, launched in January 2022). The US holds its share, driven by a strong perception that the FDA is friendly to Cell, Gene and RNA innovation.

Figure 7: Clinical investment country archetypes. Pre-defined country lists identified: "Cornerstone", "Growth", and "Out-of-Scope" country archetypes

Archetype	Description	Examples
"Cornerstone" countries	• 8 "Cornerstone" countries prioritised by **commercial priority:** 60% of total CT, 77% of global prescription medicine sales in 2021 (List price, IQVIA MIDAS) • Highly competitive and saturated markets. Diversity regulations apply. Changes in their share of inward investment captured	E.g.; US, EU4, UK, Japan, and China
"Growth" countries	• **+150 countries.** 40% of global CT in clinicaltrials.gov. • Three tiers identified by number of clinical trials in 2022 • Multiple local agencies and regulations, creating need for global cooperation initiatives	E.g.,: Canada, South Korea, Australia, Belgium, Netherlands, Denmark, Sweden, Poland, other Eastern European countries
"Out-of-scope" countries	• **Ethical concerns:** No CT in countries with no commercial intent (few exceptions for rare diseases, or those largely prevalent in these countries), (for some) high corruption index, etc. • **Geopolitical factors:** Issues affecting CT stability and continuity.	E.g.: Most low income countries in Africa, Asia, South America

Source: Clinicaltrials.gov, March 2022, IQVIA MIDAS Quarterly Sales 2021 (List price, Rx Only), IQVIA VII Launch Excellence 2022.

Figure 8: Country share of pipeline Phase I to regulatory submission based on company headquarter location, 2006–2021



Source: IQVIA Pipeline Intelligence, Dec 2021, IQVIA Institute, Jan 2022. Global Trends in P&D; Overview through 2021. Report by the IQVIA Institute for Human Data Science.

Not only is it the world's most valuable pharmaceutical market, the US typically accounts for 60% or more of the cumulative first five year sales of New Active Substances.[28]

Emerging Biopharma (EBPs) also play an important role in the global share of pipeline since they accounted for the 65% of molecules in R&D pipeline in 2021.[29] China's EBPs accounted for 17% of the overall EBP innovation pipeline in 2021, up from 6% just five years ago — while both US and Europe-based companies have lost share over the same period.

II. "Growth" countries

Pharmaceutical companies we interviewed considered other +150 countries as optional locations – which we refer to as "Growth" countries. Companies assess each country under rigorous data-driven analytics to identify the most optimal location, depending on a political, economic, and digital infrastructure considerations. "Growth" countries hosted 27% of total number of clinical trials in March 2022[30] but they widely differ in levels of activity, in terms of patient numbers. This is often a function of the disease area for which trials are

Table 1: "Growth" country tier, number of clinical trials registered, March 2022.

"GROWTH" COUNTRY TIERS	NUMBER OF CLINICAL TRIALS (Registered in clinicaltrials.gov)	EUROPE	ROW
TIER 1 (20 countries)	> 4000 CT	Belgium, Netherlands, Denmark, Poland, Switzerland, Sweden, Austria, Russia, Hungary, and Norway	Canada, South Korea, Australia, Israel, Brazil, Turkey, Taiwan, Egypt, India, and Mexico
TIER 2 (13 countries)	2000 – 4000 CT	Greece, Finland, Romania, Portugal, Ukraine, and Bulgaria	Argentina, South Africa, Thailand, Singapore, Hong Kong, Puerto Rico, and New Zealand
TIER 3 (+120 countries)	< 2000 CT	Rest of countries	Rest of countries

Source: Clinicaltrials.gov, March 2022.

conducted in these countries; large numbers of patients can be recruited for trials for specific disease areas where these countries have a large pool of, for example, treatment naïve patients, but they may see no trial activity in other areas, for example, those where cell and gene therapies are being trialled. Cornerstone countries, in contrast, tend to be strong across disease areas.

These "Growth" countries show a clear attractiveness for clinical trials despite accounting for 14% of global sales (IQVIA MIDAS, list price, Rx only). In many cases, attractiveness for clinical trials is well in advance of commercial performance, as for some Eastern European countries. However, ex-EU Growth countries have their own local regulators, creating a need for global cooperation initiatives for clinical trial optimisation (e.g., Orbis Open Research Biopharmaceutical Internships Support[31]) and cross-country clinical trial standardisation (i.e., registration forms, data transfer, import/export, etc.).

III. "Out-of-scope" countries

This list of "Out-of-scope" countries is defined by internal policies driven by ethical concerns and geopolitical factors. Following ethical codes of conduct, some companies do not conduct clinical trials in countries where they have no intention to commercialise (with few exceptions for rare diseases) or in countries with high fraud and corruption index, etc.

Geopolitical issues affecting stability and continuity of clinical trials may cause trials to be paused or cancelled, depending on the local situation. For example, some pharmaceutical companies have suspended new patient recruitments and clinical trial site activations in Ukraine, Belarus, and Russia, while continuing to provide essential medicines and vaccines and drugs to patients already enrolled in studies.[32] These lists are revised and updated periodically to reflect the status of the countries.

COUNTRY RELATIVE ATTRACTIVENESS: INTERVIEWEES' PERCEPTIONS

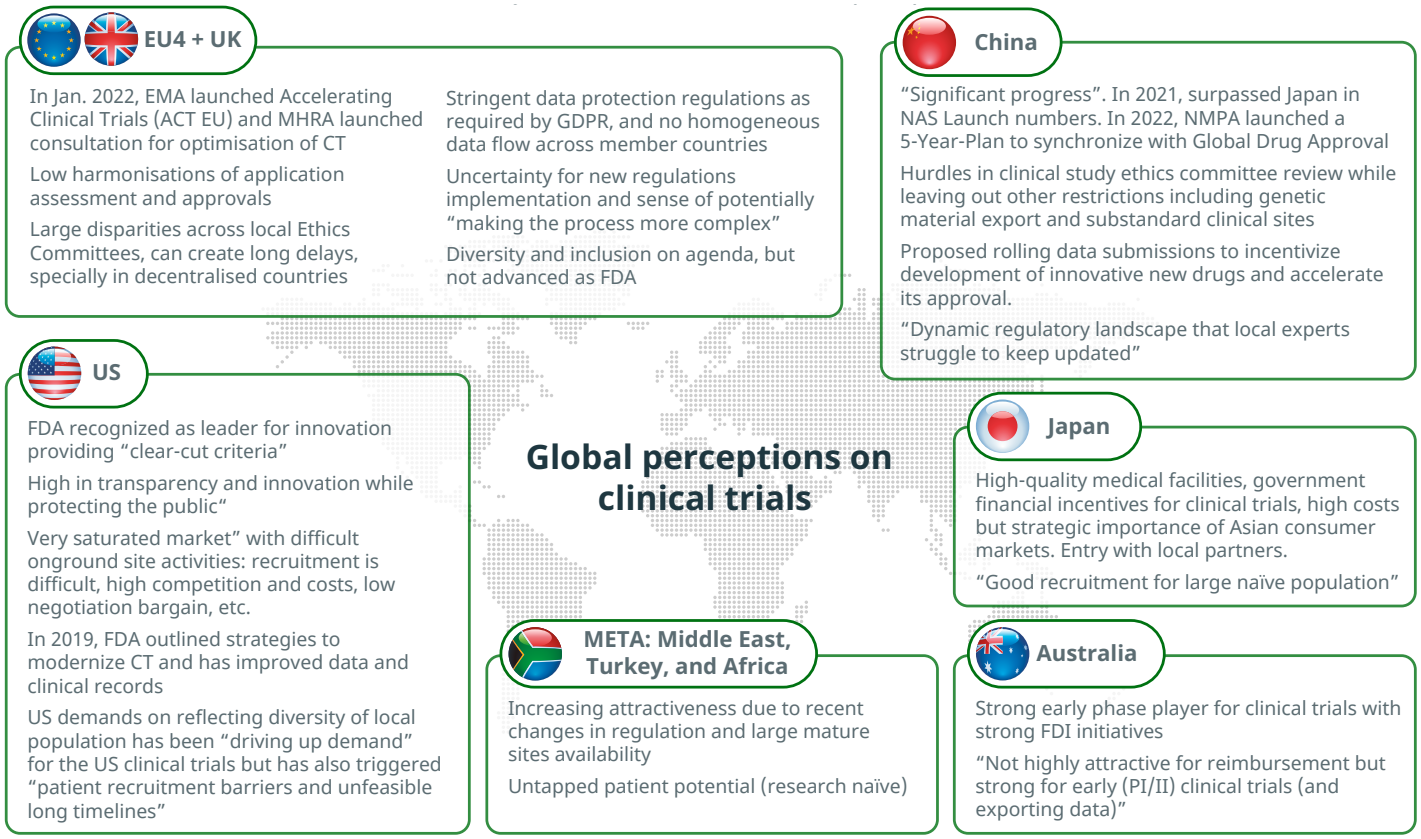
Country qualitative perceptions were collected during the interviews at a global and European level. The following perceptions are specific to each interviewee and reflect current events shaping clinical trials as of March 2022.

I. Global perceptions

The following are the main perceptions of pharmaceutical company interviewees at a global level. As main takeaways:

- For the US, the FDA is recognized as the leader for innovation providing "clear-cut criteria". However, the attractiveness provided by an optimised regulatory framework is offset by the saturated and costly "on-ground" site activities (e.g., recruitment is difficult, high competition and costs, low negotiation bargain, etc.). Companies are therefore caught in a double bind with the US: they must include it and it is also competitive and expensive to run trials.
- In the EU4+UK, the industry welcomes the implementation of new clinical trial initiatives to replace the former clinical trials directive, expecting a boost of EU's clinical trials attractiveness by standardisation, reduction of large disparities withing local Ethics Committees, reduction long delays for registration and approval, especially in decentralised countries, etc.
- China has achieved "significant progress" in NAS Launch but its dynamic regulatory landscape represents a struggle to keep updated, "even for local expert".

Figure 9: Country relative attractiveness: Global perceptions



Source: Interviews, EMEA Thought Leadership.

II. European breakdown

The following are the main perceptions of the interviewees of the most-mentioned European countries in the interviews. The following list is presented in descending order of pharmaceutical market value — it aims to reflect the diverse perspectives of the pharmaceutical companies's senior executive representatives during the first quarter of 2022. Each country is identified with a "Digital Maturity Archetype", defined in the IQVIA's Thought Leadership white paper "Switching On the Lights", in which recommendations are presented for each country archetypes.[33]

Figure 10: Company interviewee perceptions of European countries

COUNTRY DECSRIPTION	DIGITAL MATURITY ARCHETYPE*	INTERVIEWEES PERCEPTION
Germany: Increased complexity and variation in approval process (e.g., variability on Ethics Committees, "IRBs more complicated, more pushback and longer and timelines"). Introduced laws stating voluntarily opt-in to uploading their health data, seen as hampering the adoption of EHRs. Revamped digital health strategy to accelerate path but lack of incentives or legal structure	Builder	→
UK: Highly centralised health system in NHS England, with capacity for decentralised clinical trials. Some respondents concern for current system exhaustion and patient backlog. Strong investments in Biotech Hubs and AI to analyse health data on a national scale and attract top-tier talent. Large opportunity in Omics and a proposed new-born screening programme.	Operator	→
Spain: Increased attractiveness due to new regulation (i.e., "Spain absolute collaboration and dedication", "Shining light"). Collaborates with Pharmacos as advocates for CT. Recruitments speed varies greatly depending on investigators. Comprehensive digital laws but uneven implementation at regional levels. Need to improve CTA approval timelines follow-up questions clarity.	Architect	↗
Nordics: Cultural disposition towards ambitious projects such as whole genome sequencing at a national scale (perceived value in sharing their data). Widespread use of telehealth solutions and AI public sector projects. Omics renowned nationwide programme of whole genome sequencing 60k patients by 2024 and led by the Danish National Genome Centre.	Operator	↗
Other CEE: Region has historically been, and remains, highly attractive for clinical development. Perceptions of increase in number of trials and patients in other CEE countries to offset impact of Ukraine crisis. Fast patient recruitment, high-quality sites and investment in digitisation are main drivers. Poland launched revival plan of €500mn for digitisation though remains "slow approving CTAs".	Architect	→
UKR: Ukraine historically very attractive for clinical trials due to high availability of patients and health system expertise. Company policies to temporarily suspend new patient recruitments and clinical trial site activations as response to Ukraine crisis. Future status uncertain.	Architect	↘

Source: Interviews, EMEA Thought Leadership.

*Note: Archetypes from IQVIA Thought Leadership's white paper "Switching On the Lights: Benchmarking digital health systems across EMEA" analyses and proposed recommendations by country archetypes.

Implications and recommendations

The pharmaceutical industry's global clinical investment will continue to evolve because of multiple complex investment drivers. However, policy makers in country health systems can play a critical role in improving country attractiveness for inward clinical investment. Clinical trials are undergoing rapid changes because of digitisation, decentralisation, and diversity and inclusion drivers, alongside the trend to ever more advanced innovation being trialled.

Policy makers seeking to attract clinical trial investment must respond to these trends by shaping health systems to be able to support these clinical trial needs – and pharmaceutical companies can help shape policy by advocating for the changes they find most helpful and working with health systems to deliver on them.

The following strategic recommendations for regulators and industry associations (e.g., EFPIA, ACRO) provide actionable initiatives to accelerate clinical trials and promote clinical inward investment by country archetype:

- **"Cornerstone" countries:** "Accelerate and Collaborate" strategy aims to capture more share amongst core countries by providing agile and innovative research ecosystem:
  - Correct implementation of new local regulations (i.e., EMA's ACT EU and MHRA's initiatives) with close follow-up and co-creation with pharmaceutical companies and industry associations
  - Digital investment to support novel clinical trials design (i.e., DHS, DCT), niche capabilities (e.g., omics) to support pioneering clinical breakthroughs
  - Cross-country agency collaboration to unlock optimization of global R&D
  - Building on the already established advantage these countries have in providing a strong infrastructure for Cell, Gene and other advanced medicinal product trials.

Figure 11: Main recommendations: Regulators and associations — Actionable initiatives by country archetype

Country archetype	Strategic goal	Actionable recommendations	Further IQVIA references
"Cornerstone" countries	"Accelerate and collaborate"	• Implementation of new local regulations (i.e., ACT EU, MHRA) with close follow-up and co-creation with pharmacos and associations • Digital investment to support novel clinical trials design (i.e., DHS, DCT), niche capabilities (e.g., omics) to support pioneering clinical breakthroughs • Cross-country agency collaboration to unlock optimization of 60% global CT	• Health Tech Trends 2021 • JAPAC innovative design • Omics Investment 2022* • CTQ opportunities
"Growth" countries	"Differentiate and attract"	• **+150 countries.** 40% of global CT in clinicaltrials.gov. • Three tiers identified by number of clinical trials in 2022 • Multiple local Agencies and regulations, creating need for global cooperation initiatives	• Workstreams to boost clinical trials in META • Europe's mid-sized pharma face the 2020
"Out-of-scope" countries	"Ticket-to-play"	• **Ethical concerns:** No CT in countries with no commercial intent (few exceptions for rare diseases, or those largely prevalent in these countries), (for some) high corruption index, etc. • **Geopolitical factors:** Issues affecting CT stability & continuity.	• R&D Trends Report 2022

Source: EMEA Thought Leadership

- **"Growth" countries:** "Differentiate and Attract" strategy focused on developing a strong position to attract clinical trials by providing differentiated value based on internal assessments and definition of roadmap:
  - Perform internal assessments to identify main source of valuable offerings from the main drivers identified in the Investment Criteria, e.g., population/prevalence identification, systems and data maturity, CT sites past performance, HC system capacity, niche capabilities
  - Define strategic positioning in global clinical trials vs other "Growth" countries (e.g., use of matrix performance vs. expertise for competitive benchmark) and build solid offering to capture the attention of pharmaceutical companies (e.g., Nordic's offering for Omics and fully integrated healthcare data, Australia for early phase trials).
  - Roadmap design of short-term (e.g., experts network activation, patient awareness, etc) and mid-term initiatives (e.g., health systems, niche development, etc.) to build relationships and attract inward investment from pharmaceutical companies
- **"Out-of-scope" countries:** "Ticket-to-Play" strategy suggests identifying causes and minimum standards required to be considered by pharmaceutical companies and start designing and building the basic digital capabilities and infrastructure to advance towards a better healthcare delivery.

IMPERATIVES FOR PHARMA COMPANIES

Pharmaceutical companies also play their role in shaping policies which improve attractiveness of a country for clinical trial investment. In some instances, for example, in the formulation of the UK Life Sciences Strategy post BREXIT, circumstances provide a window of opportunity to be listened to by, and engage with, government. But for all countries, continuous work with policy makers both as individual companies but also collectively via industry associations is crucial. Key recommendations for pharmaceutical companies to shape the future of clinical trials are:

- **Open approach and flexibility in the review of countries and sites** to identify new opportunities and capabilities offered by countries and assess new business cases (i.e., cost-benefit analysis).
- **Proactive collaboration with agencies and associations** and timely conversations to design innovative policies (e.g., MHRA's consultation). Quantify value of pharma industry in local countries and convey benefits clearly (i.e., non-technical language, focus on jobs created, benefits to patients).
- **Support and constant feedback during implementation of new initiatives** (e.g., EMA's ACT EU 2022) and lead pioneering novel designs and products to find the right "Product-Policy" combinations.
- **Continuous internal optimisation of clinical trials and investment in digital solutions** to unlock operational bottlenecks and build competitive advantages in patient's journey (e.g., DCT for patient recruitment and retention and reduction of logistics burden in clinical trials) and consider advanced technologies such as blockchain and advanced analytics in EMR.
- **"Patient voice" as active driver of trial journeys** and protocol designs and build strong collaborations with well stablished local advocacy groups to capture insights and provide tailored solutions for patient's journey.
- **Diversity and Inclusion initiatives to reflect real patient population profile** and underrepresented ethnic and minority populations by implementing processes and technologies to conduct optimised inclusive clinical trials and gain a valuable advantage in registration and approval of clinical trials.

Methodology

For this study we undertook primary market research to identify the clinical investment criteria through hour-long qualitative interviews with high-profile pharma executives with investment decision power: Global Heads of Clinical Operations and/or Heads of Regulatory Affairs located in US, UK, France, Germany, Spain, Switzerland, Australia, during 1Q 2022.

Representatives from 60% of Top 20 Large pharmaceutical companies were interviewed to reflect the main drivers of spending in global clinical trials. European mid-sized pharma and Emerging Biopharmas (EBPs, defined as those with less than $500 million in annual sales and R&D spending less than $200 million per year) were also interviewed to complement with insights and challenges from different-sized companies. Additional interviews to Associations (i.e., EFPIA and ACRO) and internal IQVIA experts were conducted to design the discussion guide and complement the analysis and recommendations.

Secondary research from IQVIA Institute reports, MIDAS, R&D pipeline intelligence and external industry Associations and official Health Institutions reports.

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About the authors

SARAH RICKWOOD
Vice President,
EMEA Marketing and Thought Leadership,
IQVIA

Sarah Rickwood has 30 years' experience as a consultant to the pharmaceutical industry. She has an extremely wide experience of international pharmaceutical industry issues, consulting to the world's leading pharmaceutical companies on global issues. She has been Vice President, European Marketing and Thought Leadership in IQVIA for 12 years.

Sarah presents to hundreds of pharmaceutical industry clients every year on a range of global pharmaceutical industry issues, publishing white papers on many topics, including:

- uptake and impact of innovative medicines, and challenges for Launch Excellence
- the impact of the pandemic on medicines markets and Rx launch
- Orphan drugs launch challenges
- Cell and Gene therapies commercialization challenges and opportunity

Sarah holds a degree in biochemistry from Oxford University.

FIONA PEREIRA
Engagement Manager,
Brand & Integrated Research Solutions,
IQVIA

Fiona has over 15 years' experience in delivering commercial and wet-lab research projects in the healthcare and pharmaceutical industries.

Her focus in recent years has been on integrating a variety of research solutions to build global & local atlases of healthcare use. Integrating Data from primary and secondary research within healthcare and government settings to develop insights to drive healthcare policy decision making, and P4 healthcare (preventative, predictive, participatory and personalised).

Fiona holds a PhD in Microfluidics for Biomolecule Analysis and an MSc Health Policy from Imperial College London (ICL). Additionally, she holds an Honorary Research Fellow position at Institute of Global Health Innovation at ICL.

CAMILA ABELLA GÓMEZ
(Intern) EMEA Thought Leadership,
IQVIA

Camila lead this white paper project during her internship in IQVIA, which she completed as part of her London Business School MBA course. Prior to her MBA, Camila worked as a Senior Consultant in Deloitte's Spanish group. She is now Business Insight and Strategy Project Manager- IDRP in Janssen, Spain.

Acknowledgments

The authors of this paper would like to acknowledge the support of the many IQVIANs, pharmaceutical company executives and representatives of industry associations and other bodies for the time and expertise they gave so generously in the creation of this report.

CONTACT US

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