Benefits of a clinical research strategy for Turkey

A roadmap for innovation-driven growth

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LIST OF ABBREVATIONS

AIFD	Association of Research-Based Pharmaceutical Companies
CAGR	Compound Annual Growth Rate
CEE	Central and Eastern Europe
CRA	Clinical Research Associate
CRF	Case Report Form
CRN	Clinical Research Network
CRO	Contract Research Organization
DR	Dose-Response
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
EU5	United Kingdom, Germany, France, Italy, Spain
FDA	The Food and Drug Administration
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICT	Information and Communication Technologies
IND	Investigational New Drug
IP	Intellectual Property
IPI	Industry Production Index
IPR	Intellectual Property Rights
IT	Information Technologies
MENA	Middle East and North Africa
NHS	National Health Service
NIHR	National Institute for Health Research
OECD	Organization for Economic Co-operation and Development

LIST OF ABBREVATIONS

PMDA	Japan Pharmaceuticals and Medical Devices Agency
PoC	Proof of Concept
PRO	Patient-Reported Outcome
R&D	Research and Development
RCT	Randomized Control Trials
RDP	Regulatory Data Protection
RWD	Real World Data
RWE	Real World Evidence
SMO	Site Management Organization
SSI	Social Security Institution
SUT	Health Implementation Communiqué
TGA	Australian Therapeutic Goods Administration
TİTCK	Turkish Medicines and Medical Devices Agency
TRL	Turkish Lira
TÜBİTAK	Scientific and Technological Research Council of Turkey
TÜSEB	Health Institutes of Turkey
US	United States
UK	United Kingdom
USD	United States Dollars
WEF	World Economic Forum
WHO	World Health Organization
WIPO	World Intellectual Property Organization
YÖK	Council of Higher Education

KEY FINDINGS

MESSAGE 1: CLINICAL RESEARCH IS A KEY TOOL TO ACHIEVE TURKEY'S ECONOMIC POLICY OBJECTIVES

Innovation and R&D are crucial for economic growth, fostering innovation, creating more healthcare resilience, and improving global competitiveness, including clinical trials; recognized in the government's core strategy documents. A clinical trial strategy would allow the government to achieve greater economic development, create more value-added, foster innovation and R&D, reduce the trade deficit, and support a healthier and health-resilient society.

MESSAGE 2: CLINICAL RESEARCH BENEFITS TURKEY'S ECONOMY, HEALTHCARE AND PATIENTS

The current value of clinical research in Turkey is estimated at USD 327.7 million (TRL 1,860.1 million) annually, with direct economic and broader societal effects (healthcare system and patients). Clinical research leads to lower medical costs for research subjects, lower financial burden for the Social Security Institution, additional income and more resilience for the healthcare system and State, and generates employment.

MESSAGE 3: TURKEY HAS A LARGE UNTAPPED CLINICAL RESEARCH POTENTIAL

Turkey ranks 26th globally in terms of the number of clinical trials conducted annually (521 clinical trials in 2019) but when ranked relative to population, GDP and the size of the pharmaceutical industry, Turkey drops in the rankings. This suggests that Turkey has ample opportunity for growth to increase its share of the global clinical research investments.

MESSAGE 4: TURKEY COULD IMPROVE IN KEY FACTORS TO INCREASE CLINICAL RESEARCH ATTRACTIVENESS

While Turkey is doing relatively well on six indicators, there are immediate opportunities to improve in eight other indicators: patient recruitment and easy access to patients, patient awareness, process simplicity, new investigator development, physician incentives, dedicated clinical research staff, foreseeable clinical research costs, and sponsor incentives.

MESSAGE 5: ANALYSIS SHOWS A STRONG CLINICAL RESEARCH STRATEGY POTENTIAL FOR TURKEY

Addressing all improvement opportunities and involving all stakeholders, Turkey could become a regional leader in the Middle East region in 3 to 8 years measured by the number of clinical trials. By adapting to global trends as well, Turkey can further improve and become a leader in the broader region of the Middle East and Central and Eastern Europe, becoming a global top 10 clinical research country in 8 years.

MESSAGE 6: BEING A TOP 10 CLINICAL RESEARCH COUNTRY WOULD MEAN NEARLY TRIPLING ITS NUMBER OF CLINICAL TRIALS

This would lead to annual total clinical research value of USD 1,130.1 million (TRL 9,675.4 million), and approximately 70,000 patients enrolled in clinical trials annually by 2027. Up to 12,700 investigators would be involved in more than 1,600 clinical trials. The annual value of innovative medicines provided to Turkish patients would reach USD 650.9 million (TRL 5,572.4 million).

KEY POLICY RECOMMENDATIONS

1. **Establish a central patient database:** Establish an anonymous patient database which lays out numbers of patients by region and/or healthcare institution and by detailed health information.

2. **Design a patient referral system:** Establish a patient referral system across healthcare institutions. Ensure that this system is accessible for physicians and other relevant healthcare staff.

3. **Raise public awareness:**
   - » Run public awareness campaigns to raise awareness of the patient and public benefits of clinical research.
   - » Publish detailed information on upcoming and ongoing clinical trials on a publicly accessible website and communicate new clinical research to related patient associations.

4. **Streamline and centralize documentation and ethics committee submission:**
   - » Standardize documentation required by institutions, ethics committees and other authorities in the submission phase.
   - » Streamline document submission through an online system which related parties can access so that submissions are made online with one set of standard documents.

5. **Reinforce implementation of ethical review standards:** Ensure the implementation of high standards in ethical review across all ethics committees.

6. **Build an investigator network:** Establish a database which lays out the network of physicians trained and experienced in clinical research and interested in primary investigator roles.

7. **Increase capacity in a wider range of institutions:** Build and increase clinical research capacity in all the relevant institutions with access to patients.

8. **Provide formal education, academic incentives, and career advancement opportunities:**
   - » Train healthcare staff in clinical research through courses and graduate degrees on clinical research.
   - » Revise regulations to include clinical research for academic and career advancement.
   - » Amend regulations to include clinical research in physician performance evaluation.

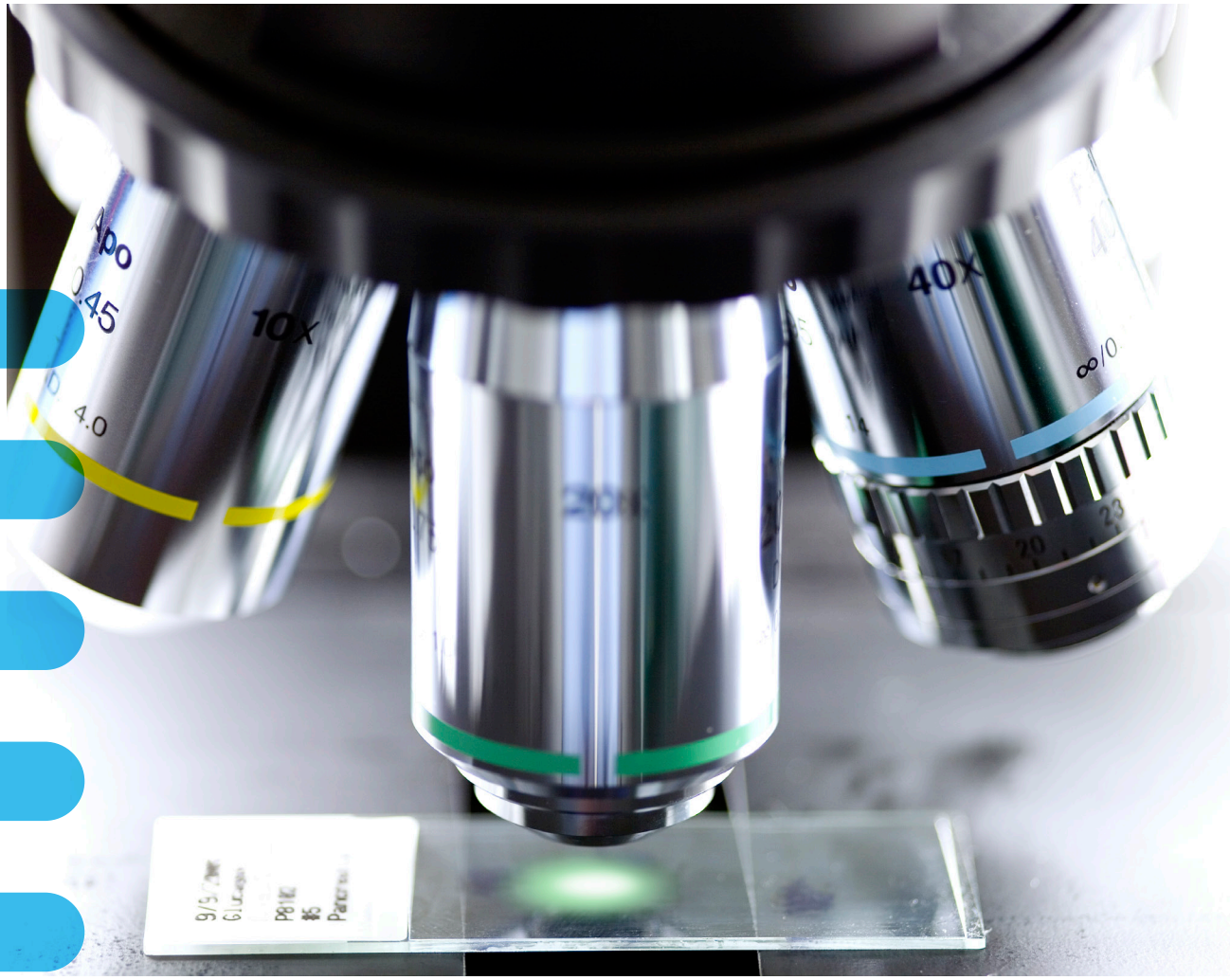
9. **Revise R&D regulations:**
   - » Ensure that a pre-approval clinical study is considered R&D even if only one phase is conducted in Turkey.
   - » Ensure that not only investigators employed as permanent hospital staff but also co-investigators working under temporary contracts are eligible for R&D incentives.

10. **Establish clinical research centers with dedicated staff:** Establish new or revamp existing clinical research centers to employ full-time healthcare and administrative staff dedicated to clinical research.

11. **Improve accounting systems in healthcare institutions:** Revamp healthcare institutions' accounting systems ensuring the correct itemization and invoicing of clinical research costs.

12. **Increase incentives for companies to run clinical research in Turkey:**
   - » Increase direct incentives for sponsors and contract research organizations that run clinical research in Turkey.
   - » Increase direct funding for startups or other companies that have limited or no capacity to fund their clinical research.
   - » Streamline the regulatory review submission of drugs of which Phase III clinical research has been done in Turkey.
   - » Provide strong sponsor incentives and intellectual property protection for clinical research to improve Turkey's relative attractiveness.

EXECUTIVE SUMMARY



POLICY CONTEXT

The vision of the Turkish government is to make Turkey a stronger and more prosperous country which produces greater value and shares welfare more equitably. Building a strong and stable economy is considered as one of the key dimensions of this vision. To achieve it, the government has laid down its key policy objectives and tools in several core policy documents. In particular, the 11th Development Plan (the Plan) details the components of the ultimate goal of economic growth and development and lays out a detailed policy plan to achieve this goal. Policy priorities established in these strategic documents include fostering innovation and increasing global competitiveness, productivity, exports, inward investments, production and employment, while reducing the current account deficit and improve financial stability. The 2020-2022 New Economic Program (Midterm Plan) and the 2020 Annual Program of the Presidency of the Republic set out specific actions to realize the policy objectives of the Plan. In particular, the Annual Program asks: "*How can the national R&D environment be promoted to help foster innovation and increase Turkey's competitiveness in the international arena?" and "How can Turkey become an economic leader in the region, linking the EU with the Middle East?*".

Figure A: Key policy documents of the Turkish government

POLICY DOCUMENT	TIMELINE	
11th Development Plan	2019-2023	Medium-term
2020-2022 New Economic Program	2020-2022	Medium-term
2020 Annual Program of the Presidency of the Republic	2020	Short-term

The specific target for Pharmaceuticals in the Plan is to increase the country's competitiveness and move it higher up in the global value chain. Innovation and R&D are considered crucial for this purpose and several policy targets are presented to promote innovation in the industry. Recognizing the critical role of clinical research in the pharmaceutical R&D process, the Plan puts forward a specific policy target to address this area: making Turkey a regional leader in clinical research.

STUDY OBJECTIVES

With this policy context as a driver, this study looks at the potential benefits for Turkey of a clinical research strategy and makes recommendations on how to implement such a strategy successfully.

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Against the backdrop of consensus reached by the public and private sectors in the strategic importance of pharmaceuticals, especially with respect to the R&D link into global value chains, this report is timely and instrumental in making a strong case that focusing on clinical research is the best strategy. Turkey already has a considerable base in conducting clinical research with the potential to triple its size in the medium term. Turkey does not have to wait for one or two decades to climb up to the Top-10 of the global rankings in pharmaceutical R&D. Concentrating on clinical research and getting the policies right, the country is well positioned to make considerable progress in the next 3 to 8 years.

Turkey already has a considerable base in conducting clinical research with the potential to triple its size in the medium term.

This report is comprehensive, comparative and inclusive in its nature, based on a very extensive literature review, analysis of quantitative data, while making extensive use of insights and knowledge garnered through in-depth interviews, first-hand conducted surveys, and broad stakeholder inputs. A clinical research strategy can only be implemented successfully if all stakeholders needed for different elements of the approach engage and

cooperate. Believing in the importance of ownership of the issue by all stakeholders, this study was designed from start to end as an inclusive one to reflect multiple aspects of the clinical research domain by consulting with major actors in the field: government officials, industry, regulators, as well as think tanks and academics. To this end, 60 people in- and outside of Turkey – from among the different actors – were interviewed to better understand the reality of clinical research in practice. A comprehensive workshop with the participation of 55 people representing the diverse nature of stakeholders was held in October 2019, providing important inputs into developing recommendations for reaching the objectives set out in government policy papers through a clinical research strategy.

Figure B: Clinical Research stakeholders in Turkey

CLINICAL RESEARCH IN FIGURES

The pharmaceutical industry in Turkey, put forward in the referred strategy documents as one of Turkey's key strategic industries, is worth USD 7.7 billion (TRL 43.8 billion), with locally produced drugs making up 49.4% of the total market value. A third of the local production value belongs to the products of international pharmaceutical companies and the rest to national companies. Turkey exports USD 1.2 billion worth of pharmaceutical products to more than 160 countries around the world. It is estimated that nearly 37,000 people are employed in the pharmaceutical industry – approximately a third employed by international companies and the rest by national companies – with additional employment in the surrounding industries. [2,3,4,5,37]

R&D investment in the Turkish pharmaceutical industry reached USD 86.0 million in 2017, growing at a compound annual growth rate (CAGR) of 4.7% between 2009 and 2017. The number of accredited R&D centers grew from 1 in 2008 to 33 in 2019. As of 2017, the number of people employed in these centers was 1,399. Despite the growth in local R&D investments, however, the estimated ratio of Turkish pharmaceutical industry R&D spending to the total pharmaceutical market size in 2018 remains below 1.5%, well behind the global estimated ratio of 14.9%. [4,12]

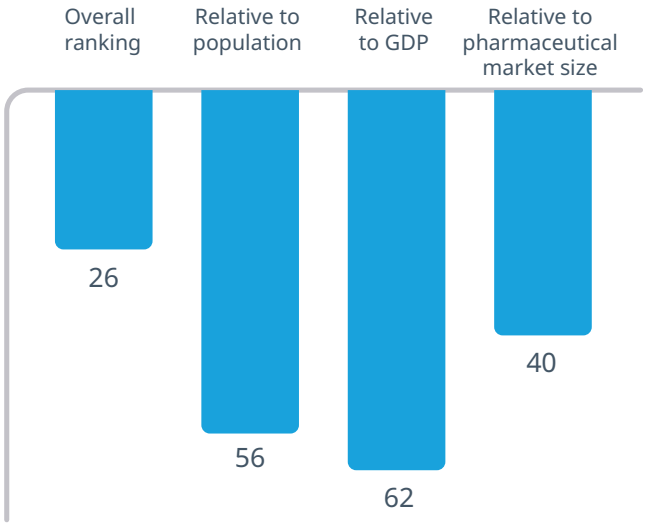
Total annual R&D expenditures of pharmaceutical and biotechnology companies worldwide reached USD 178.9 billion in 2018 – growing by 4.2% annually between 2010 and 2018, which corresponds to 21.6% of total worldwide and 23.8% of non-generic worldwide prescription sales revenues.

The pharmaceutical industry differs in key aspects from other industries: it is the most R&D intensive sector globally, and pharmaceutical R&D is long-term, expensive and high-risk. Developing a new drug lasts 10 to 15 years, costs USD 2.6 billion (including the cost of failures) on average, and only 1 or 2 out of 10,000 potentially successful compounds ultimately become a medicine. Clinical trials hold the largest share in pharmaceutical R&D investments. Phases I, II and III trials (which take place prior to the regulatory review submission of the drug candidate) make up 50.2% of the total R&D investment. When Phase IV trials (i.e. clinical research that takes place after marketing authorization) are included, the total investment in clinical research corresponds to 61.6% of the overall pharmaceutical R&D investment. [6,7,8,9,16,17,56]

Pharmaceutical R&D is long-term, expensive and high-risk.

As of June 2019, 16,720 industry-sponsored clinical trials (Phase I through IV) were ongoing worldwide. With 521 active trials, a number that has been stable since 2013, Turkey holds the 26th place globally. When correcting for the size of the country, however, Turkey drops in the rankings: to 56th place when corrected for the size of the population; to 62nd place when corrected for the size of gross domestic product (GDP), and to 40th place when corrected for the size of the pharmaceutical market.

Figure C: Turkey's global ranking in the number of active clinical trials

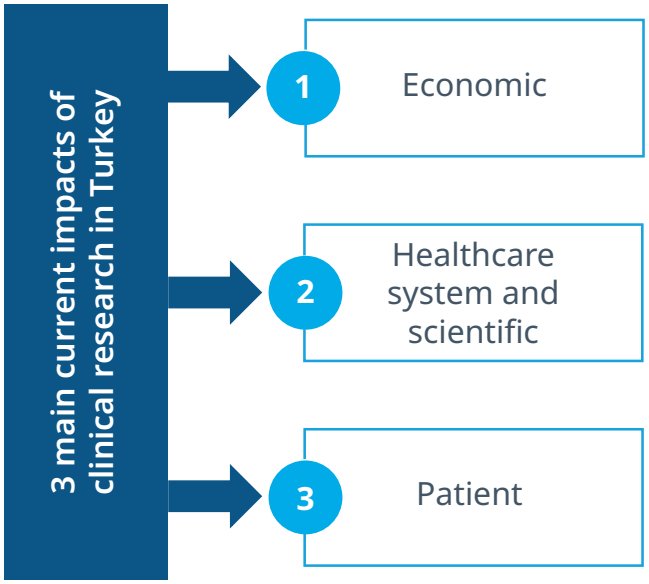


This points to an important opportunity for Turkey to increase the number of clinical trials conducted in the country and gain a greater share globally. To realize the 11th Development Plan target of becoming a regional leader in clinical research, Turkey would need to double its total number of clinical trials to lead the Middle East region, or nearly triple it to lead in the broader region of the Middle East and Central and Eastern Europe. The latter would also place Turkey among the Top-10 of global leaders in clinical research.

CURRENT IMPACT OF CLINICAL RESEARCH

Clinical research provides several benefits to the country, which can be grouped under three main areas: economic, healthcare system and scientific, and patients.

Figure D: Current impact of Clinical Research in Turkey



At the moment, the total economic value of clinical research run in Turkey is estimated at USD 327.7 million (TRL 1,860.1 million) annually as of June 2019, corresponding to 0.3% of the total global clinical research economy. This total amount includes both the clinical research investment in Turkey, which is estimated as USD 139.0 million (TRL 788.8 million), and the added value of the innovative medicines provided to clinical trial subjects, which is estimated as USD 188.7 million (TRL 1,071.3 million). Since industry-sponsored clinical research in Turkey is largely conducted by multinational pharmaceutical companies, most of the money spent

on clinical research is considered as foreign direct investment. This means the clinical research investment of USD 139.0 million (TRL 788.8 million) made in Turkey directly contributes to a macro-economic equilibrium which is one of the key targets of the New Economic Program. This direct investment consists of five key components: reduced financial burden for the Social Security Institution (SSI) thanks to the medical costs of clinical research subjects undertaken by sponsoring companies totaling USD 46.4 million (TRL 263.5 million), additional income to the healthcare system amounting USD 23.4 million (TRL 133.0 million), direct income to the state of USD 6.2 million (TRL 34.9 million), value of the employment generated thanks to clinical research estimated as USD 44.4 million (TRL 251.8 million), and other direct economic contribution of nearly USD 18.6 million (TRL 105.7 million). In addition, clinical trial research could lead to a higher value of Turkish exports (not higher quantities) which would reduce the trade deficit, improving the current account equilibrium, a key target of the New Economic Program.

From a healthcare system and scientific perspective, clinical research impacts not only healthcare professionals and institutions, but also startups in the pharmaceutical industry. As indicated above, clinical research saves the SSI USD 46.4 million (TRL 263.5 million) per year. In addition, it has a positive effect on healthcare professionals as engagement in clinical research increases their state-of-the-art understanding of diseases and latest potential treatments because of exposure to novel scientific developments, allows them to link to wider (international) research networks, and know of better ways to treat patients with rare diseases. And, specifically from a scientific perspective, it impacts them through increased prestige, reputation and scientific publications, gaining experience in rigorous scientific discipline and practices, first-hand exposure to the novel scientific developments, career advancement opportunities and access to a wider scientific network. On the other hand, clinical research benefits startups through its contribution to the pharmaceutical R&D infrastructure and research capabilities. To support pharmaceutical R&D activities and elevate the scientific contribution of clinical research, the 11th Development Plan emphasizes clinical research as an R&D activity. According to the Plan, all clinical research conducted before product registration will be considered within the scope of R&D without any pre-condition (11th Development Plan, 366.1). The Plan also declares that pharmaceutical product developers, especially researchers at universities, will be provided with information programs on incentives and intellectual property rights to accelerate the commercialization process. (11th Development Plan, 363.5)

The 11th Development Plan emphasizes clinical research as an R&D activity.

From a patient perspective, it is estimated that approximately 21,700 subjects are currently enrolled in clinical research in Turkey. Participation in clinical research mainly provides patients receiving the investigational drug with the benefit of early access to innovative treatments and of potentially better health outcomes. In addition, with medical professionals engaging more in clinical research, working on state-of-the-art scientific medical developments, also for patients in Turkey that are not enrolled directly in clinical research, potential new treatments are more known and thus general access could be enhanced.

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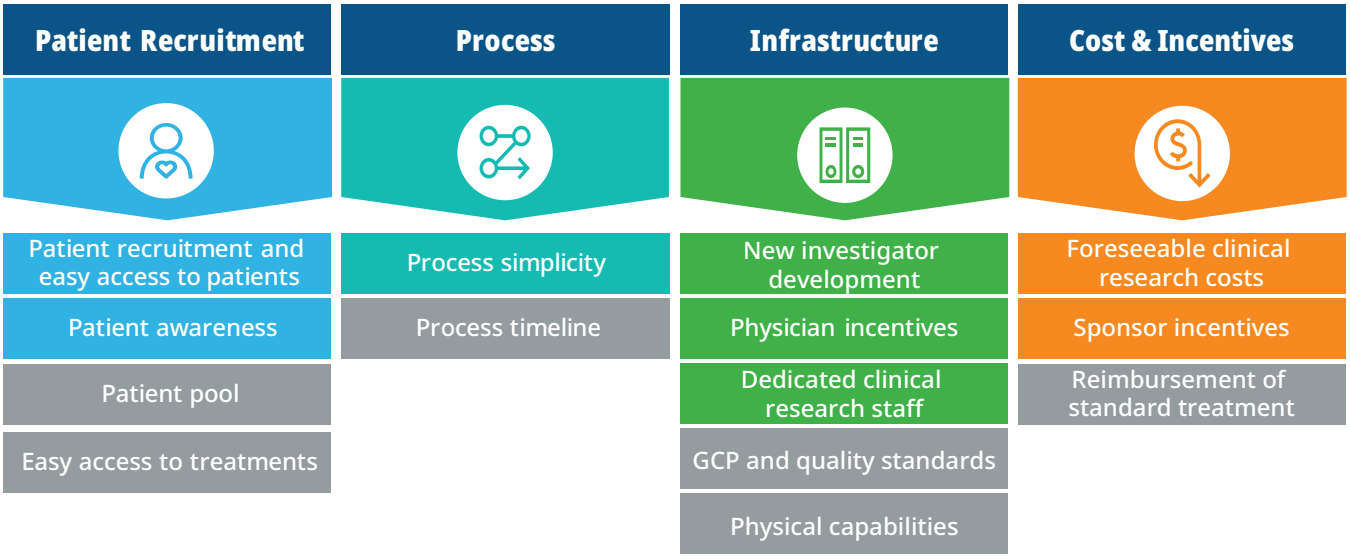
FACTORS FOR CLINICAL RESEARCH ATTRACTIVENESS

We identified fourteen key factors that contribute to a country's attractiveness for clinical trial inclusion, as shown in Figure E. We have grouped them under four pillars – patient recruitment, process, infrastructure, and cost and incentives. These factors impact the country's attractiveness through fast and flawless study set-up and execution. When Turkey is assessed in terms of each of the fourteen factors, eight major improvement opportunities stand out to have the potential to support the growth of clinical research in Turkey.

Figure E: Factors determining country attractiveness for clinical research*



Source: In-depth interviews; IQVIA Survey; IQVIA Analysis

* Factors shaded in grey have been identified as well-performing areas where no immediate action is recommended.

- The Patient Recruitment pillar consists of the attractiveness factors concerning the speed and ease of patient enrollment in clinical trials. Of the four factors under this pillar, Turkey has improvement opportunities in "*patient recruitment and easy access to patients*" and in "patient awareness" to speed up patient enrollment in clinical trials.
- Under the Process pillar are "*process simplicity" and "process timeline*", concerning the processes of regulatory and ethics committee submission and review processes. Building on Turkish Medicines and Medical Devices Agency's (TİTCK) major improvements in this regard, there is further opportunity to simplify the ethics committee submission and review processes.
- The Infrastructure pillar captures the factors concerning all critical dimensions of clinical research infrastructure in a country. To increase clinical research capacity, Turkey has opportunities in "*new investigator development*", improving "physician incentives" and employing "*dedicated clinical research staff*" in healthcare institutions.
- The Cost & Incentives pillar includes three factors concerning not only the cost of conducting clinical research but also its accounting and budget planning as well as the incentives that encourage innovative pharmaceutical companies to conduct more clinical research in Turkey. In this regard, Turkey has the opportunity to improve on clinical research costs and incentives, including regulatory data protection (RDP).

GLOBAL TRENDS IN CLINICAL RESEARCH

Beside these improvement opportunities, emerging clinical research trends around the globe pose further possibilities for growth in this area. These are important if Turkey aims to become a global Top-10 leader in clinical research. The use of digital health data, patient-reported outcomes (PRO), real world evidence (RWE) and predictive analytics as well as artificial intelligence, and access to pre-screened pools shape the present and near future of the global clinical research environment. Combined with the development of innovative drugs targeting complex diseases and conditions and with the availability of biomarker tests, the use of these new developments is changing the regulatory landscape globally. [28]

Turkey has already picked up and gained traction in some of these global trends (e.g. the use of digital health and mobile technologies, PROs), while it has the opportunity to improve its infrastructure to adapt

to other trends. By adapting to the shift into new types of drugs and complex treatments relatively quickly, Turkey has started to build the fundamental clinical research experience to support the New Economic Program policy target of realizing projects for the development of value-added precision and transformational drugs targeting cancer, chronic and rare diseases. On the other hand, there is still ample room to improve efficiency and productivity in clinical research processes in Turkey to gain a competitive edge globally – in part to be addressed via Turkey's digital transformation (a critical tool in the 11th Development Plan) and in part by providing sufficient R&D-supporting incentives.

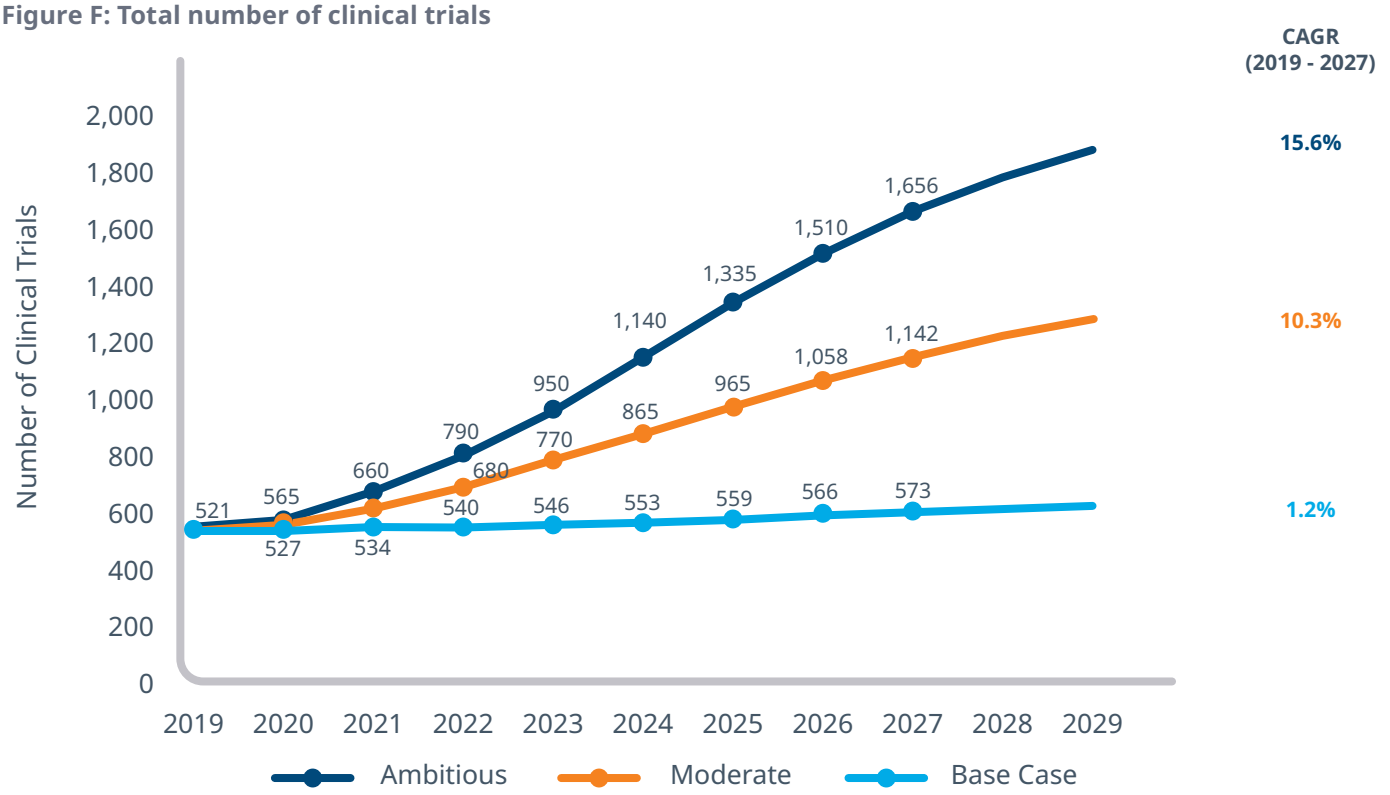
GROWTH SCENARIOS FOR CLINICAL RESEARCH IN TURKEY

The Turkish government has made a clear commitment to increase Turkey's competitiveness in the international arena and innovation has been elevated as an important means to achieve this goal. When its current global position and its growth potential in clinical research are considered, Turkey has ample room for growth in this area to meet its potential. In order to become a prominent country in clinical research, it needs to strengthen its infrastructure and deliver on the basic requirements that impact Turkey's attractiveness in this field. The potential impact of taking necessary steps in this regard have been evaluated in three different scenarios:

- **Scenario 1 –** Base Case Scenario: No major actions are taken. The total number of clinical trials grows at the same CAGR of the last 5 years. In this scenario Turkey does not improve its clinical research standing globally or regionally.
- **Scenario 2 –** Actions are taken in all identified improvement areas. The total number of clinical trials doubles after 8 years (which is the time needed to implement all the actioned improvements and see their full impact on the total number of trials). In this scenario Turkey becomes a regional leader in the Middle East in clinical research
- **Scenario 3 –** Ambitious Growth Scenario: Not only all fundamental actions are taken in all the improvement areas, but also extra steps are taken to incorporate and anticipate global clinical research trends effectively, and incentives are strengthened. The total number of clinical trials triples after 8 years. In this scenario, Turkey just enters the global Top-10 of most important clinical research countries, making it the leader in the broader region of the Middle East and Central and Eastern Europe.

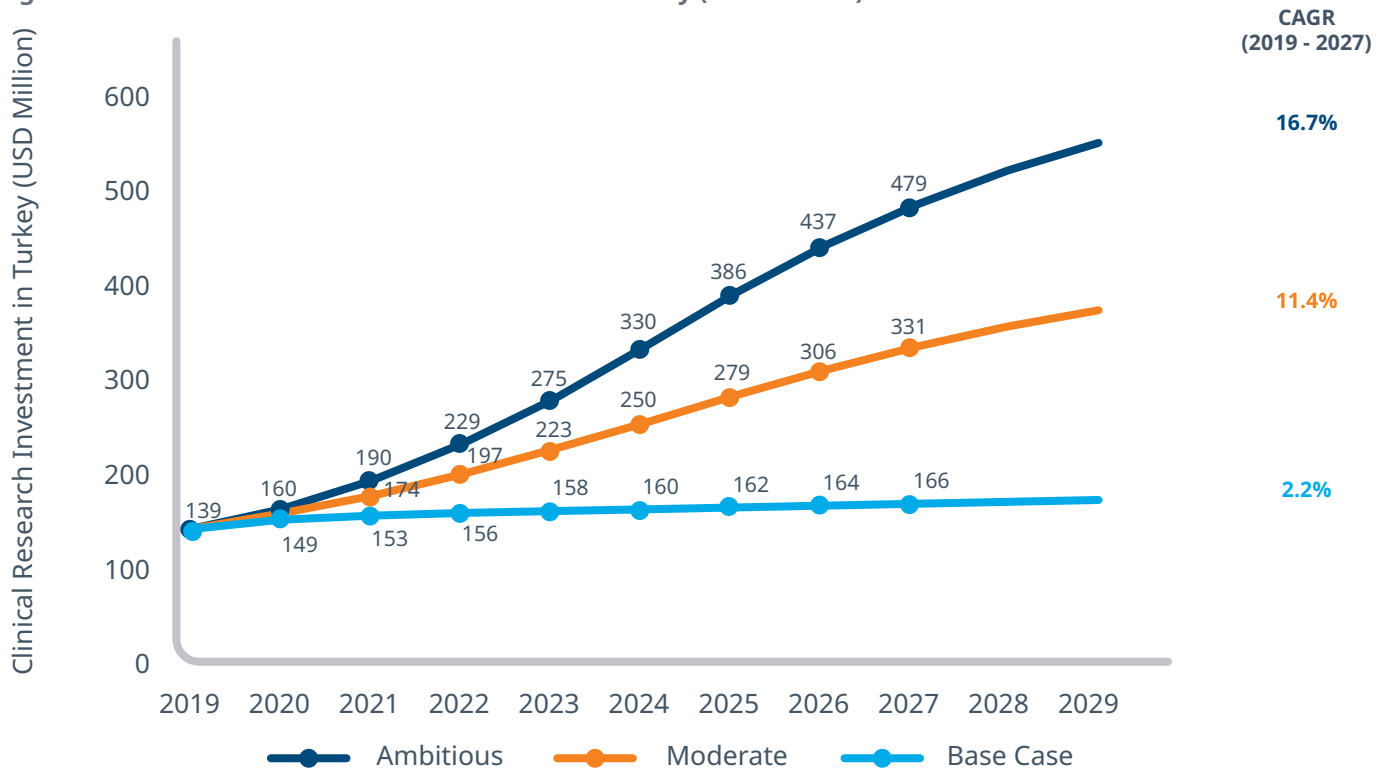
In the baseline scenario, as shown in Figure F, the annual growth rate in the number of clinical trials is 1.2%, increasing the number from 521 in 2019 to 573 in 2027. Turkey will – in this scenario – fall behind its global and regional competitors. In the moderate and ambitious growth scenarios, growth is expected to arrive at a steady state in 8 years and then level off to match global clinical trial growth over time. In the moderate growth scenario, the average annual growth rate in the first 8 years is 10.3% leading to 1,142 clinical trials in 2027. The largest growth in clinical trials is in the ambitious growth scenario, leading to 1,656 clinical trials, more than triple the current number.

Figure F: Total number of clinical trials



When we look at the economic effects of these increases in clinical trials, the effects are very clear. Figure G shows the evolution of the investment value of focused clinical research strategies. The initial investment of USD 139.0 million (TRL 788.8 million) in 2019 increases to USD 165.8 million (TRL 1,419.1 million) in 2027 in the baseline scenario. But it increases much more to USD 330.5 million (TRL 2,829.6 million) in 2027 in the moderate growth scenario and to USD 479.2 million (TRL 4,103.0 million) in the ambitious growth scenario.[1]

Figure G: Size of clinical research investment in Turkey (USD million)



[1] See Appendix 2 for inflation and exchange rate assumptions.

Achieving the ambitious growth scenario would place Turkey among Top-10 countries in terms of the total number of clinical trials and among the Top-6 or -7 countries (right behind the United States, United Kingdom, Spain, Germany, Canada, France and Italy) in terms of the number of new trials in 2027. This would mean nearly 70,000 patients enrolled in clinical trials, reducing the financial burden of three times as many patients as in the base case scenario for the SSI. In the case of a moderate growth, Turkey would join the Top-15 countries in the number of total clinical trials and new clinical trial registrations in 2027. In both cases, the growth in clinical trials would come along with an increased capacity in the workforce, involving a greater number of physicians in trials as investigators and generating new job opportunities specifically in contract research organizations, site management organizations, and sponsor companies.

Achieving the ambitious growth scenario would place Turkey among Top-10 countries in terms of the total number of clinical trials.

Figure H does not include the potential impact of a stronger clinical research strategy for the resilience of the Turkish healthcare system and public health in times of health emergencies. More clinical trial activities would place Turkey more at the innovative frontline in the R&D process for finding new treatments and cures – e.g. in the coronavirus pandemic situation.

Figure H: Summary of impacts for each scenario in 2027 [2]

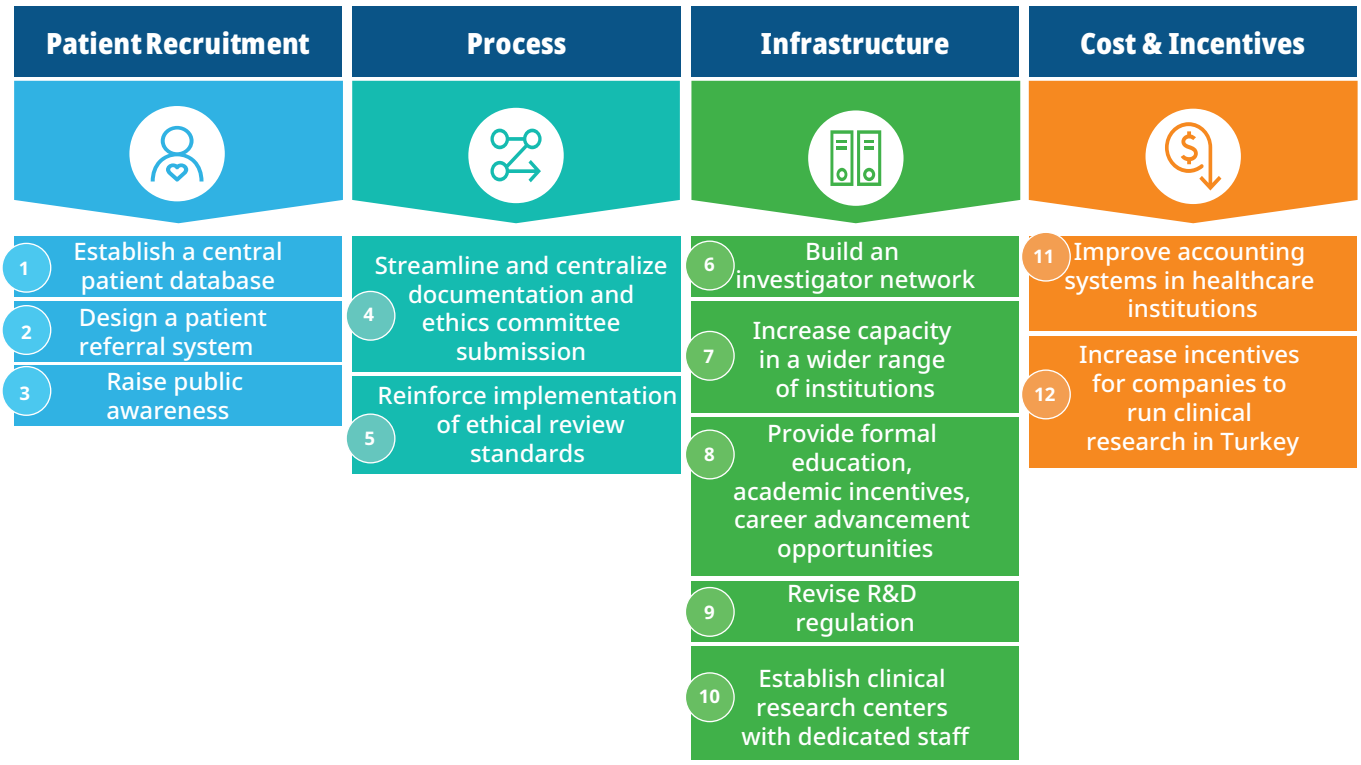
IMPACT	BASE CASE	MODERATE GROWTH	AMBITIOUS GROWTH
Economic impact (USD Million)			
Total investment in Turkey	165. 8	330.5	479.2
Reduced burden for SSI	55.4	110.4	160.1
Additional income to the healthcare system	27.9	55.7	80. 8
Value of generated employment	52.9	105.5	153.0
Other economic contribution	22.2	44.3	64.2
Total economic impact (USD million)	**390.3**	**779.4**	**1,130.1**
Healthcare system and scientific impact			
Number of trials	573	1,142	1,656
Annual number of new trials	120	296	448
Number of investigators	3,300-4,400	6,600-8,800	9,500-12,700
Patient impact			
Number of patients	23,903	47,661	69,109

[2] See Appendix 2 for inflation and exchange rate assumptions.

Recommendations for Turkey to enhance clinical research

To address the opportunities in all the improvement areas, a total of 12 recommendations for action steps have been developed. While grouped under specific improvement areas, most of the recommendations have the potential to impact multiple areas.

Figure I: Recommended actions



1. **Establish a central patient database:** Establish an anonymous patient database which lays out numbers of patients by region and/or healthcare institution and by detailed health information such as diagnosis, treatment, special conditions and genetic disorders.

2. **Design a patient referral system:** Establish a patient referral system across healthcare institutions. Ensure that this system is accessible for physicians and other relevant healthcare staff, includes information on upcoming and ongoing clinical trials and allows patient referrals between institutions.

3. **Raise public awareness:**
   - » Run public awareness campaigns to raise awareness of the patient and public benefits of clinical research and to overcome common prejudices.
   - » Publish detailed information on upcoming and ongoing clinical trials on a website that is publicly accessible and communicate new clinical research to related patient associations, which can in turn relay such information to their members.

4. **Streamline and centralize documentation and ethics committee submissions:**
   - » Standardize documentation required by institutions, ethics committees and other authorities in the submission phase.
   - » Streamline document submission through an online system which related parties can access so that submissions are made online with one set of standard documents.

5. **Reinforce implementation of ethical review standards:** Ensure the implementation of high standards in ethical review across all ethics committees.

6. **Build an investigator network:** Establish a database which lays out the network of physicians trained and experienced in clinical research and interested in primary investigator roles.

7. **Increase capacity in a wider range of institutions:** Build and increase clinical research capacity not only in university hospitals but also in other institutions that have access to a large patient pool.

8. **Provide formal education, academic incentives, and career advancement opportunities:**
   - » Train healthcare staff in clinical research through courses and graduate degrees on clinical research in medical, dentistry and nursing schools.
   - » Revise regulations to include clinical research in academic and career advancement criteria.
   - » Amend regulations to include clinical research in physician performance evaluation.

9. **Revise R&D regulation:**
   - » Revisit the coverage of the R&D regulation for clinical research so that a pre-approval clinical study is considered within the scope of R&D even if only one phase is conducted in Turkey.
   - » Revisit the coverage of the R&D regulation for clinical research so that not only investigators employed as permanent hospital staff but also co-investigators working under temporary contracts are eligible for R&D incentives.

10. **Establish clinical research centers with dedicated staff:** In healthcare institutions where clinical research is conducted, establish clinical research centers or revamp the existing ones to employ full-time healthcare and administrative staff dedicated to clinical research.

11. **Improve accounting systems in healthcare institutions:** Revamp healthcare institutions' accounting systems ensuring the correct itemization and invoicing of clinical research costs.

12. **Increase incentives for companies to run clinical research in Turkey:**
   - » Increase direct incentives for sponsors and contract research organizations that run one or more phases of a drug's clinical research in Turkey.
   - » Increase direct funding for startups or other companies that have limited or no capacity to fund their clinical research.
   - » Speed up the regulatory review of drugs of which Phase III clinical research has been done in Turkey, by streamlining the submission process.
   - » Provide strong sponsor incentives and intellectual property protection for clinical research to improve Turkey's attractiveness in relative terms vis-à-vis Top-10 competitors.

FINAL COMMENT

Clinical research poses a major opportunity for Turkey in terms of enhancing economic development, attracting greater foreign direct investment, increasing domestic value-added, reducing the trade deficit, strengthening the resilience of the Turkish healthcare system in times of health emergencies, and creating a more innovation-focused economy, by means of only moderate domestic investment requirements aimed at improving or building new infrastructure, and creating strong framework policies.

Clinical research poses a major opportunity for Turkey in terms of enhancing economic development, attracting greater foreign direct investment, increasing domestic value-added, reducing the trade deficit, strengthening the resilience of the Turkish healthcare system in times of health emergencies, and creating a more innovation-focused economy.

When correcting for the size of Turkey's economy, population or pharmaceutical market, it is evident that Turkey has ample room for growth in the number of trials to take its fair share in global clinical research. Taking the recommended actions with the collaboration of all related stakeholders would help the country reach this goal and become a regional or even global leader in clinical research. What is needed to make the leap in clinical research is full engagement and collaboration of all stakeholders (i.e. government, industry, regulators). This will then be a huge step towards achieving the economic and industrial targets set in the government's policy documents.

1. INTRODUCTION

1.1 Objectives of the study

The objective of this study is to identify the value and importance of clinical research as an element in the strategy to achieve government objectives for the Turkish economy overall, for the Turkish healthcare system, and for Turkish patients. The contribution of this study is not only the combination of an in-depth analysis matching policy objectives to the role the regulator and R&D intensive pharmaceutical industry could play to support. The research and fact-finding sections also allow this study to offer recommendations and suggestions on how cooperation between the Turkish government, the regulator and the innovative pharmaceutical industry in a clinical research strategy for Turkey could be a win-win relationship for all, with patients and the Turkish economy as the final beneficiaries. In addition, it is clear that a strong clinical research strategy also has a bearing on a country's healthcare system's agility in times of health pandemics, like Covid-19.

1.2 Turkish national policy objectives

The Turkish government has made a clear commitment to realize its vision of making Turkey a stronger and more prosperous country which produces greater value and shares welfare more equitably. Building a strong and stable economy is considered as one of the key dimensions of this vision. For a strong and stable economy, the government has envisioned a growth model focusing on productivity and export-orientation, specifically in prioritized industries – one of which is pharmaceuticals and medical devices. [1]

The authorities have set out a range of policy objectives that they want to achieve with respect to economic growth and development in general as well as in the field of pharmaceuticals and medical devices industry. In particular, the Turkish government priorities are laid down in several core policy documents that include the 11th Development Plan, the 2020-2022 New Economic Program, the 2020 Annual Program of the Presidency of the Republic, and the 2019-2023 Strategic Plans of the Ministry of Health and the Ministry of Industry and Technology. [1,39,48,49,51]

Policy priorities for Turkey emerging from these strategic documents include achieving a macroeconomic equilibrium, fostering innovation and increasing competitiveness, productivity, production and employment. In order to achieve these government objectives, it is possible to use a range of policy tools. These are driven – at the policy level – by Turkish government stakeholders, but they require the buy-in and support from multiple actors, including the private sector, in order to have the intended positive effects on the ground.

In Chapter 2, we elaborate more extensively on the Turkish national policy objectives, because the main question is how pharmaceutical research and development (R&D), and specifically clinical research, can best support and help to advance them.

The size of the Turkish pharmaceutical market was USD 7.7 billion (TRL 43.8 billion) in 2019.

1.3 Role of the pharmaceutical industry in Turkey

The pharmaceutical industry is an important industry for Turkey and for its objectives from an economic, healthcare system, scientific and patient perspective.

From an economic perspective, the size of the Turkish pharmaceutical market was USD 7.7 billion (TRL 43.8 billion) in 2019, with more than 37,000 people estimated to be employed in the industry directly, and many more indirectly. Between 2010 and 2018, pharmaceutical production has grown at a rate well above total industry production, with a growth rate of 102.4% in the Industry Production Index (IPI) for pharmaceuticals versus 67.5% for overall industrial production. Pharmaceutical industry exports grew by 93.7%, reaching USD 1.1 billion in 2018. [2,3,4,5]

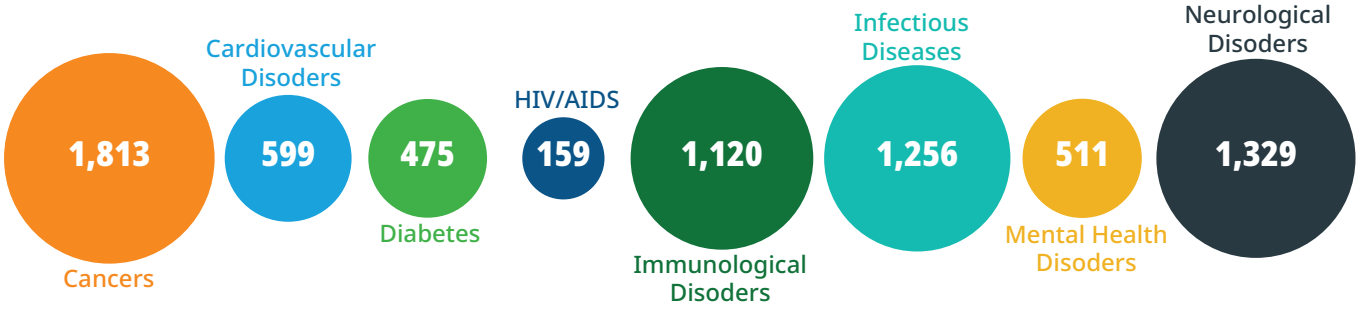
From a healthcare perspective, medicines constitute approximately 20% of the total healthcare spending in Turkey. The pharmaceutical industry helps physicians and healthcare staff stay up-to-date with the latest

treatment methods and technologies through clinical research, product detailing and sponsorship in scientific activities. The industry contributes to the enhancement of public health not only by providing innovative treatment methods to address disease areas and help fight pandemics, but also through patient support programs which raise awareness of issues such as chronic diseases, compliance and disease prevention. In the long term, innovative treatments and greater public health help to decrease hospitalization rates and overall treatment costs, reducing the financial burden on the healthcare system.

From a scientific perspective, in recent years, several R&D initiatives to develop innovative, original molecules in Turkey have been launched and have received positive outcomes. The pharmaceutical industry has provided support for these initiatives to contribute to the development of pharmaceutical R&D activities and innovation in the country.

From a patient perspective, the pharmaceutical industry's pipeline of innovative medicines provides hope – globally and in Turkey – in terms of a better quality of life and even of unprecedented complete cures. With the industry's current pipeline as shown in Figure 1, there is hope for Turkish patients with cancer, diabetes, HIV/AIDS, immunological disorders or infectious diseases for a complete cure or improved quality and/or duration of life. In Turkey, patients can have access to the latest treatments and most innovative medicines through approved drugs in the market, named-patient programs, and clinical research activities.

Figure 1: Innovative medicines pipeline



Source: Health Advances analysis: Adis R&D Insight Database, March 2015

1.4 Structure of the study

This study is structured as follows.

In Chapter 2, we focus on short- and longer-term economic and health objectives of the Turkish government, including links to the relevant strategic policy documents.

In Chapter 3, we highlight the relevance of the innovative pharmaceutical industry in Turkey and how the innovation process to develop new medicines works in detail.

In Chapter 4, we look at the process of clinical research overall, the size and composition of clinical studies, and the clinical research infrastructure in Turkey, in particular its relative strengths and weaknesses.

In Chapter 5, we describe the global clinical research trends and identify opportunities for Turkey in adopting them.

In Chapter 6, we focus on the current benefits for Turkey and develop growth scenarios for a focused clinical research strategy and identify their potential impact for Turkey.

In Chapter 7, we identify the factors that impact a country's attractiveness in global clinical research and assess Turkey's performance in terms of these factors.

In Chapter 8, we make recommendations on how to execute a clinical research strategy and reap the potential benefits of it, including suggestions for cooperation between the different healthcare system actors to the benefit of Turkey as a whole and its patients.

2. TURKISH POLICY OBJECTIVES

In this Chapter, we detail Turkey's overall economic policy objectives as well as the specific healthcare and pharmaceutical industry goals.

2.1 Turkey's economic and industrial policy objectives

Economic growth and development are the overarching themes in all strategic policy documents put out by the Turkish government over the past years. While the 11th Development Plan details the components of this goal and lays out a detailed policy plan to achieve it, the 2020-2022 New Economic Program and the 2020 Annual Program of the Presidency of the Republic set out the policy objectives and tools for specific actions.

THE 11TH DEVELOPMENT PLAN

From an economic perspective, the 11th Development Plan focuses specifically on achieving a strong and stable economy and increasing competitive production and productivity. The targets set out in the plan aim to achieve a sustainable growth model led by the manufacturing industry and based on exports, with a specific focus on increased productivity. Private sector investments will be channeled to value-added initiatives increasing productivity and competitiveness through technological transformation in the production industry, specifically in prioritized industries. While attracting foreign direct investment is targeted to help reduce the current account deficit, investments in innovation, R&D and new product initiatives are expected to have positive returns and increase Turkey's competitiveness internationally.

In the development plan, the high-priority industries have been identified as Chemistry, Pharmaceuticals and Medical Devices, Machinery, Electronics, Automotive, and Rail System Vehicles. The goal is to improve technology, innovation, product quality and productivity, transform industrial capacity to become more competitive, and increase value-added production in all these industries.

THE 2020-2022 NEW ECONOMIC PROGRAM

The 2020-2022 New Economic Program has a similar economic objective as the 11th Development Plan overall: achieve an economic transformation for sustainable growth and equitable sharing, with a focus on production and productivity. Financial stability and a current account equilibrium are core elements of the program and several policy targets and tools are set out to address these objectives. The Program aims to reach a current account equilibrium and achieve 5.0% annual growth throughout the program period, as a result of the planned actions that are part of economic transformation.

The goal of the 11th Development plan is to improve technology, innovation, product quality and productivity, transform industrial capacity to become more competitive, and increase value-added production in all these industries.

2020 ANNUAL PROGRAM OF THE PRESIDENCY OF THE REPUBLIC

The 2020 Annual Program of the Presidency of the Republic shares the same objectives as the 11th Development Plan and lays down a solid set of actions for 2020 to address the Plan's policy targets.

Given the objectives mentioned above, the crucial questions for Turkey are how they can best be achieved:

- How can a macroeconomic equilibrium be achieved?
- How can the national R&D environment be promoted to help foster innovation and increase Turkey's competitiveness in the international arena?
- How can productivity and production in goods and services be increased?
- How can overall employment opportunities and the quality of employment be increased?
- How can Turkey become an economic leader in the region, linking the EU with the Middle East?

2.2 Turkey's healthcare objectives

Turkey's healthcare policy objectives are captured in the 11th Development Plan, 2020-2022 New Economic Program, 2020 Annual Program of the Presidency of the Republic and the 2019-2023 Strategic Plan of the Ministry of Health as follows.

Figure 2: Key policy documents of the Turkish government

POLICY DOCUMENT	TIMELINE	
11th Development Plan	2019-2023	Medium-term
2020-2022 New Economic Program	2020-2022	Medium-term
2020 Annual Program of the Presidency of the Republic	2020	Short-term

The specific target for Pharmaceuticals and Medical Devices is to increase the country's competitiveness and move it higher up the value chain through innovation and R&D.

THE 11TH DEVELOPMENT PLAN

In the Plan, the specific target for Pharmaceuticals and Medical Devices is to increase the country's competitiveness and move it higher up the value chain through innovation and R&D. Several policy targets are laid out to promote innovation in the industry. The Plan recognizes the critical role of clinical research in the pharmaceutical and medical device R&D process and sets out specific policy targets to address this area:

- Become the regional leader in clinical research;
- Define all pre-approval clinical research within the scope of R&D, without additional conditions, and differentiate R&D incentives for clinical research;
- Raise public and stakeholder awareness of clinical research;
- Add experience in clinical research to performance, academic assignment and advancement criteria;
- Increase membership in networks which will improve Turkey's international visibility in order to increase the share received from international clinical research funds (e.g. European Union funds, National Institutes of Health funds, etc.).

THE 2020-2022 NEW ECONOMIC PROGRAM

In addition to the industrial strategy elements of the 2020-2022 New Economic Program, the program also emphasizes healthcare system objectives that are meant to support financial stability and that relate to innovation in healthcare:

- Launch projects in the field of precision and transformational medicine to develop effective, original and value-added products for the early diagnosis, treatment and prevention of cancer, chronic and rare diseases;
- Develop and manufacture vaccines, medicines, medical devices and diagnosis kits of strategic importance to increase our international competitiveness and reduce reliability on imports, and increase the clinical research potential of public hospitals in the development of biotechnological/ biosimilar drugs;
- Provide investment incentives for R&D and production development activities of priority products identified in high-priority industries including also the pharmaceutical industry, as part of the implementation of the Technology-Oriented Industry Drive Program.

2020 ANNUAL PROGRAM OF THE PRESIDENCY OF THE REPUBLIC

Several action steps laid down in the Program aim to address policy targets about pharmaceutical and medical device R&D and innovation as well as clinical research in specific. Beside various action steps to

promote and incentivize pharmaceutical and medical device R&D activities, four actions have been laid out to address clinical research:

- Organize eight regional clinical research awareness meetings;
- Launch activities to raise awareness and increase knowledge of clinical research;
- Contact decision-makers and hospital managers to initiate trainings on clinical research;
- Revise the code of academic advancement and assignment.

In addition to these strategic policy documents, strategic plans of the Ministry of Industry and Technology, TİTCK and Health Institutes of Turkey (TÜSEB) also address the overall objective of promoting innovation and R&D in the pharmaceutical and medical devices industry with specific policy targets and tools in their areas of operation.

2019-2023 STRATEGIC PLAN OF THE MINISTRY OF HEALTH

The ultimate goal of the Ministry of Health is defined as protecting and improving citizens' health and ensuring that every citizen can access high-quality healthcare services equitably. The detailed goals laid down in the strategy document relate to this ultimate goal as well as the government's objectives of promoting the country's socioeconomic development, improving local technologies and increasing production. One of the targets set for this purpose is to promote R&D and innovation and increase local production and exports in healthcare via an attractive market for clinical research. TÜSEB is given responsibility for the actions planned in this regard. Regarding clinical research, the plan recognizes that Turkey has room for improvement in terms of its share in global clinical trials and in terms of the coordination and know-how in clinical research processes. The strategies and needs pertaining to clinical research laid down in the plan include:

- Improve the clinical research infrastructure, develop a qualified workforce and provide incentives to develop clinical research centers and activities and support R&D activities in pharmaceuticals;
- Provide specific support for R&D activities in prioritized healthcare products such as drugs, vaccines, diagnostic kits and biomedical equipment;
- Collaborate with other related government institutions to ensure that greater R&D and technology support is provided to the healthcare industry.

In line with the policy targets set in the above mentioned strategy documents, in its 2019-2023 Strategic Plan, TÜSEB defines its strategy in promoting and supporting R&D activities in healthcare, lays out a detailed action plan and sets performance indicators. [52]

The pharmaceutical industry in Turkey is worth USD 7.7 billion (TRL 43.8 billion).

2.3 Current environment for Turkey's pharmaceutical industry

The pharmaceutical industry in Turkey is worth USD 7.7 billion (TRL 43.8 billion), with locally produced drugs making up 49.4% of the total market value. A third of the local production value belongs to the products of international pharmaceutical companies and the rest to national companies. Turkey exports USD 1.2 billion worth of pharmaceutical products to more than 160 countries around the world. It is estimated that nearly 37,000 people are employed in the industry – approximately a third employed by international companies and the rest by national companies – with additional employment in the surrounding industries. [2,3,4,5,37]

R&D investment in the Turkish pharmaceutical industry reached USD 86.0 million in 2017, growing with a CAGR of 4.7% between 2009 and 2017. However, the estimated ratio of Turkish pharmaceutical industry R&D spend to the total pharmaceutical market size in 2018 remains under 1.5%, well below the estimated ratio globally of 14.9%. [4,12]

A key driver of the growth in the industry's R&D investment was the issuance of The Law on Supporting Research and Development Activities (Law No. 5746) in 2008. The law defines R&D activities and stakeholders as well as allowances, exceptions, support and incentives for such activities. The number of accredited R&D centers in the pharmaceutical industry, 1 in 2008, has grown considerably since then to reach 33 in the last quarter of 2019. As of 2017, the number of people employed in these centers was 1,399 of which 80.0% had an undergraduate degree or higher. [12]

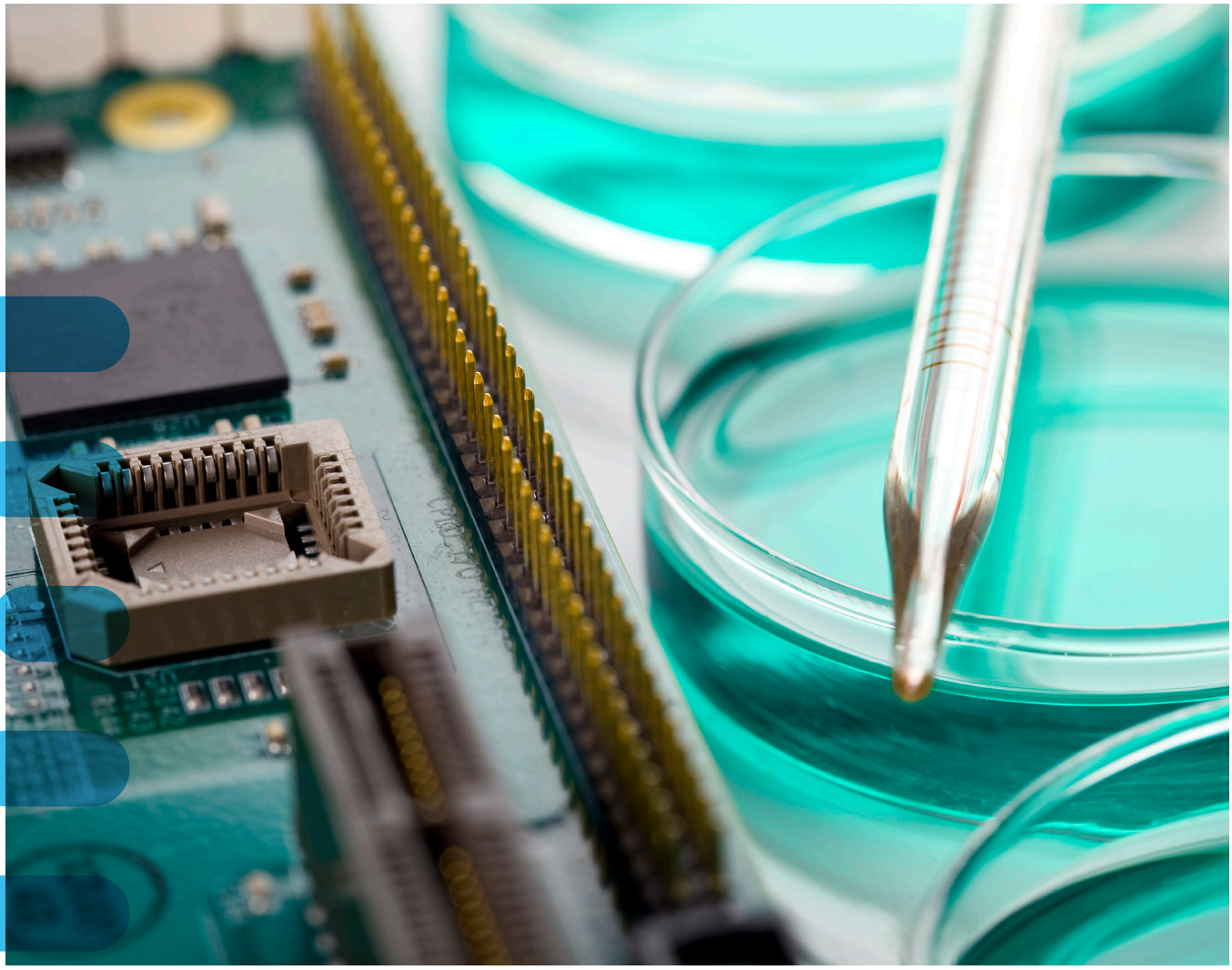
The estimated ratio of Turkish pharmaceutical industry R&D spend to the total pharmaceutical market size in 2018 remains under 1.5%, well below the estimated ratio globally of 14.9%.

While investing in R&D centers, the industry players also built partnerships with universities for the development of new medicines and medical technologies. The focus of the industry's R&D activities has been shifting over the years from building on existing molecules in the past to developing biosimilars, innovative delivery methods, new treatments, fixed dose combination drugs and new production methods today. [38]

From an academic perspective, the Council of Higher Education (YÖK) supports the development of researchers in high-priority areas for scientific development, who will be employed not only in academics but also in public and private sectors. One of the most important initiatives launched by the institution is the "100/2000 YÖK PhD Scholarships Project". The purpose of the project is to expand the researcher pool in the country. For this purpose, the program has provided 4,250 PhD students with scholarships since its launch in 2017, supporting them for their research activities in various areas including in medicines and cancer research. [53]

As evidenced by World Economic Forum's (WEF) 2019 Global Competitiveness Index, Turkey is in a competitive position globally in terms of its research institutions' prominence: Turkey ranks 19th globally in this regard which is in line with the country's 18th position globally in total GDP. It has, however, further room for growth in terms of its global position in the overall research and development index (38th). Similarly, according to World Intellectual Property Organization's (WIPO) statistics, residents' patent applications by population in Turkey grew with a fast pace (CAGR of 10.3%) between 2009 and 2018, reaching 94 resident applications in 2018. However, the country has further opportunities for growth as it ranks 32nd globally in this regard. With the government's dedication and initiatives to foster innovation in various industries, including pharmaceuticals, Turkey has the potential to improve its international competitiveness and become a prominent actor in innovation and new product R&D. [13,14]

3. INNOVATIVE MEDICINES: R&D PROCESS AND VALUE



The R&D process to develop innovative medicines is a long and complex endeavor. It is important to clearly show how this process works and the value it brings in order to make appropriate policy recommendations at the end of this report.

3.1 Innovative medicines R&D process

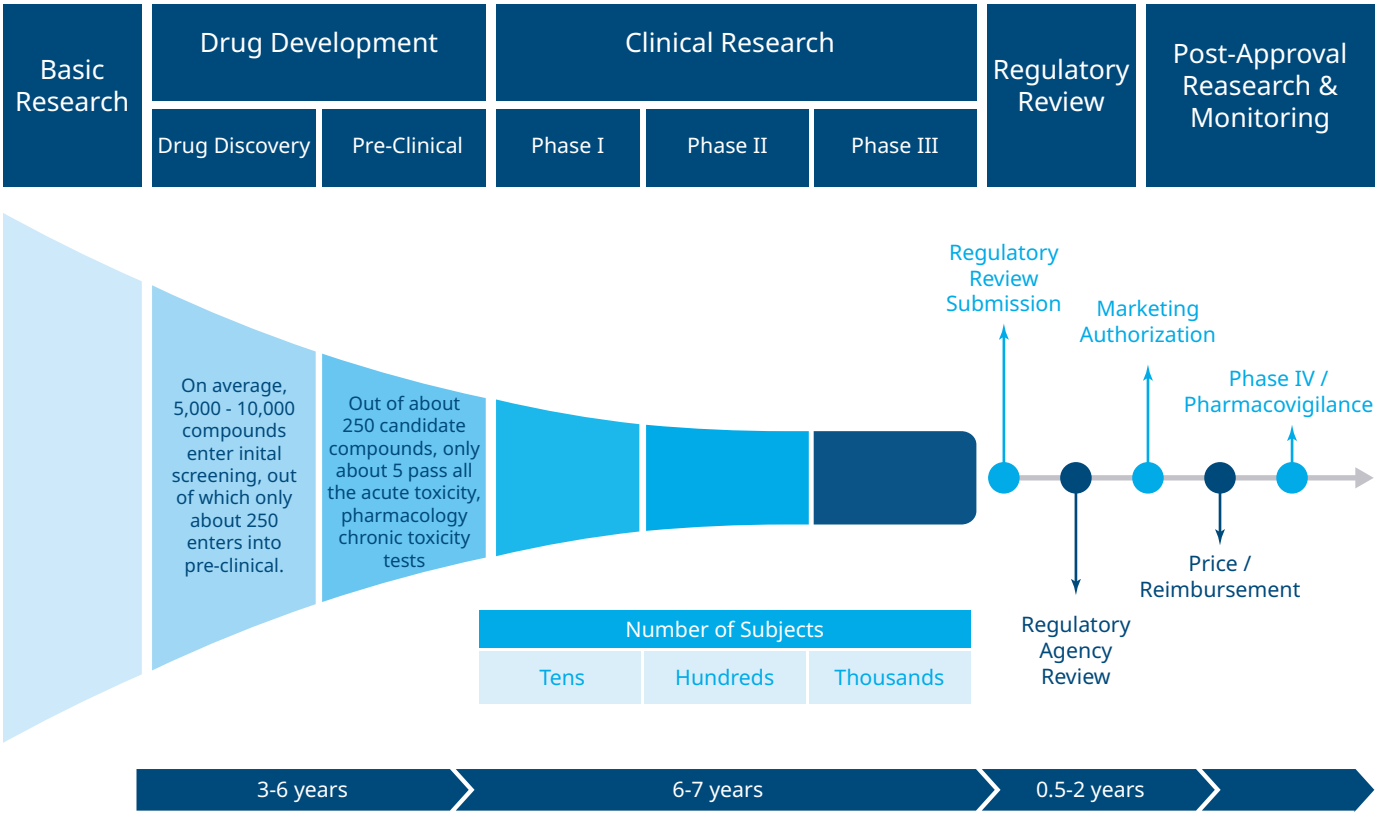
The R&D process for innovative medicines consists of four main phases: drug discovery and pre-clinical testing, clinical research, regulatory review, and post-approval research and monitoring. The process begins with the identification of a therapeutic target and screening through thousands of compounds and continues with pre-clinical and then clinical testing. Following the regulatory body review, only one medicine receives regulatory approval and proceeds to manufacturing. [6,7,9,10,55]

The R&D process for innovative medicines consists of four main phases: drug discovery and pre-clinical testing, clinical research, regulatory review, and post-approval research and monitoring.

DRUG DISCOVERY

The very first step to develop a new medicine is identifying the therapeutic target: a point within a biological mechanism of action that scientists can target with a therapeutic intervention. Once the therapeutic target is determined, thousands of compounds are screened to select a set of leading compounds which 'hit' this target. In the next step, these lead compounds are optimized – the molecules' drug-like characteristics are improved – before they are passed through to the pre-clinical phase.

Figure 3: Pharmaceutical R&D process



Source: IQVIA adaptation of 1. EFPIA. Phases of the Research and Development Process. 2. PhRMA. Biopharmaceutical Industry Profile 2016. 3. US Food and Drug Administration. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

In pharmaceutical drug discovery, on average, 5,000-10,000 compounds enter initial screening, out of which only about 250 make it into the next step: pre-clinical testing.

PRE-CLINICAL TESTING

Following the selection of candidate compounds in the initial screening, pre-clinical development begins with patent application for such compounds. Before drug candidates can be tested in humans, they must go through pre-clinical testing conducted in laboratory environment and on animals. Insofar, animal testing is still required and cannot be done in alternative ways, but the pharmaceutical industry is fully committed to the key principles of 3Rs (i.e. reducing the number of animals used, refining the experiments to minimize the impact on animals, and replacing animal experiments wherever possible with alternatives). The purpose of pre-clinical testing is to assess the drug candidates' working mechanism and safety. Three main tests are carried out: acute toxicity testing (which means single-dose testing to identify the short-term adverse effects of the drug candidate), pharmacology testing (which means testing to determine the biological effects of the drug candidate) and chronic toxicity testing (which means testing to determine the long-term effects of the drug candidate). Out of about 250 candidate compounds, only about 5 pass all the acute toxicity, pharmacology and chronic toxicity tests conducted in this phase, proceeding to the next phase – clinical research in humans. Pre-clinical testing – combined with drug discovery – can last 3 to 6 years. [54]

The purpose of clinical research is to prove the drugs' safety and efficacy in humans.

CLINICAL RESEARCH

The purpose of clinical research is to prove the drugs' safety and efficacy in humans: demonstrate that the new drugs work to treat diseases and conditions in humans. For this purpose, three phases of clinical research are conducted before a medicine can be ready for regulatory review and approval:

- Phase I studies are usually conducted in healthy humans to test drug safety and dosing ranges;
- Phase II studies are conducted with patients that have the target condition, testing drug safety and efficacy;
- Phase III studies conducted within a larger population of patients with the target condition, testing safety and efficacy of the drug.

Clinical research is a critical part of the overall pharmaceutical R&D process, lasting 6-7 years on average and making up half of the new product R&D investment. [6,7,9,10,17,55]

REGULATORY REVIEW AND MARKETING AUTHORIZATION

Once the safety and effectiveness of the drug candidate is established through clinical research, it becomes ready for regulatory review. The sponsoring pharmaceutical company submits a new drug application to the regulatory body of the country where the product will be marketed. These bodies are, for example, Turkish Medicines and Medical Devices Agency (TİTCK) in Turkey, Food and Drug Administration (FDA) in the United States, European Medicines Agency (EMA) in the European Union and Pharmaceutical and Medical Devices Agency (PMDA) in Japan. Often, multinational pharmaceutical companies market a new drug first in the United States, European Union or Japan, and thus submit their first application to FDA, EMA and/or PMDA. The regulatory body reviews all the pre-clinical and clinical evidence with scrutiny before granting a marketing authorization for the new drug.

POST-APPROVAL RESEARCH AND MONITORING

Following the regulatory body approval (and pricing and reimbursement decision), the new drug becomes ready for manufacturing. This is the phase where post-manufacturing surveillance begins: companies collect long-term, real-life safety and efficacy data on larger patient populations.

3.2 Pharmaceutical industry characteristics

The core aspect of the pharmaceutical industry stemming from the R&D process described above and setting it apart from other sectors, is that research and development (R&D) into new medicines and treatments is a lengthy, expensive, and risky process. From initial molecule screening to obtaining regulatory approval to sell a medicine in a market, it takes between 10 to 15 years, depending on many factors, including the speed of regulatory approval procedures. Only one in 10,000 screened molecules eventually obtains regulatory approval, while only 11.8% of drugs entering the clinical research phase result in an approved medicine. The total trajectory from molecule to bringing a new medicine to the market costs USD 2.6 billion on average – including the cost of failures, according to an analysis published in 2016. [6,8]

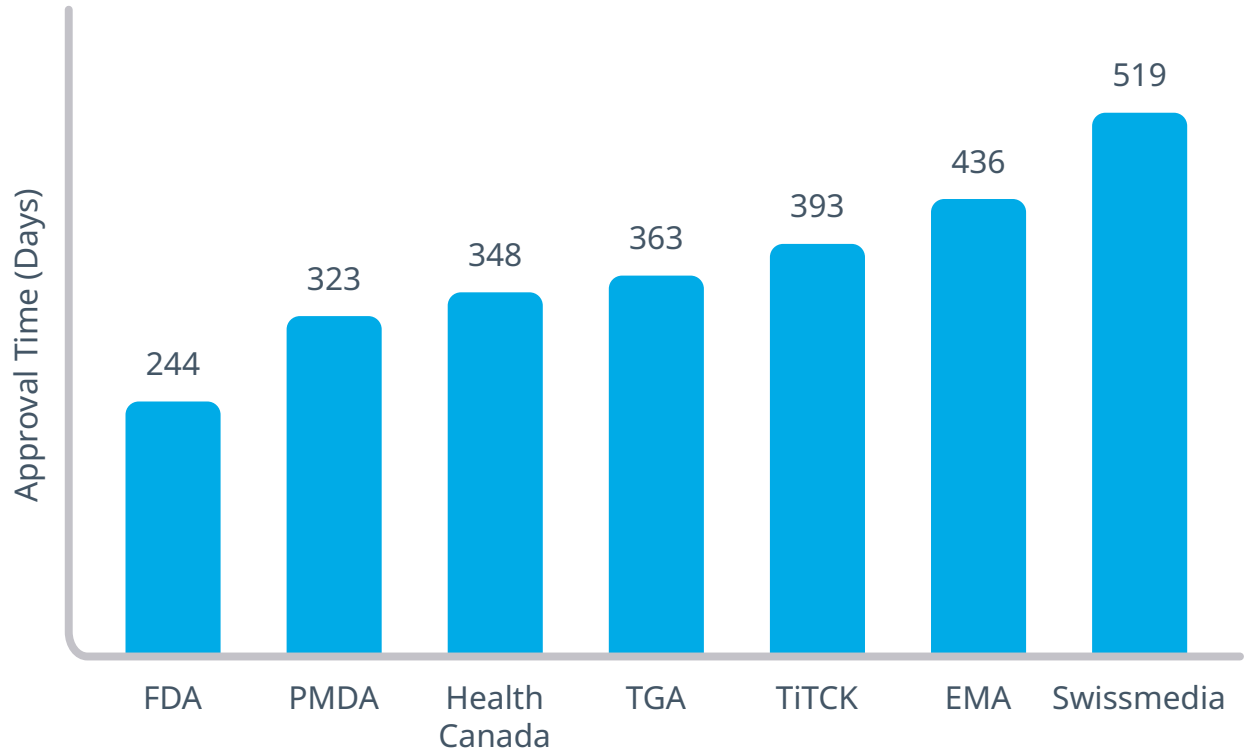
From initial molecule screening to obtaining regulatory approval to sell a medicine in a market, it takes between 10 to 15 years.

LONG TIME PERIOD NEEDED TO DEVELOP NEW MEDICINES

The development and testing of new drugs take a long period, followed by a lengthy regulatory review process (as well as time-consuming pricing and reimbursement processes). The pre-clinical development phase consisting of drug discovery and pre-clinical testing typically lasts 3 to 6 years overall, followed by the clinical research phase which typically lasts 6 to 7 years in total. Once all the pre-clinical and clinical evidence is ready, the drug candidate enters the regulatory review process which typically lasts 0.5 to 3 years.

The drug development part of the innovative medicine is finished with Phase III clinical research after 9 to 13 years (which excludes the time for regulatory approval). How long after and if at all a patient gets access to the innovative drug – and whether it is reimbursed – then depends on the speed of regulatory approval in a market as well as pricing and reimbursement procedures and decisions. Including regulatory approval, and if reimbursed, the time to develop an innovative medicine and get it to patients typically ranges from 10 to 15 years.

Figure 4: Regulatory review timelines (number of days) [4]



Source: 1. Rodier C, Bujar M, McAuslane N, Liberti L. 2019. R&D Briefing 70: New drug approvals in six major authorities 2009 -2018: Focus on Facilitated Regulatory Pathways and Orphan Status. Centre for Innovation in Regulatory Science. London, UK; 2. Ministry of Health. 2019-2023 Strategic Plan. 2019.

According to a report on new drug approvals between years 2009 and 2018, FDA had the shortest approval times[3] among six major regulatory authorities: FDA, EMA, PMDA, Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA). In 2018, the median approval time was 244 days for FDA, 323 days for PMDA, 348 days for Health Canada, 363 days for TGA, 436 days for EMA and 519 days for Swissmedic. Based on the data reported by the Ministry of Health in their 2019-2023 Strategic Plan, the average approval time for new drugs was 393 days in 2017. [15,39]

Disruptions and policy shocks are difficult to absorb and will never show up negatively immediately because of the long investment horizons.

Because of these long timelines in the industry, a stable and predictable investment and macroeconomic as well as policy climate are essential. Disruptions and policy shocks are difficult to absorb and will never show up negatively immediately because of the long investment horizons. But eventually they lead to internal company decisions to divert R&D away from markets that are more volatile towards more stable markets.

HIGH FAILURE RATE

A rigorous screening is applied to every step of the pharmaceutical R&D process where, of a total of 5,000-10,000 compounds in the initial screening phase, only 1 drug candidate receives regulatory approval in the final stage. This high failure rate is a critical characteristic of the pharmaceutical R&D process as the obligation to meet strict criteria in each phase of the process ensures that new medicines add value to patients should they make it onto the market.

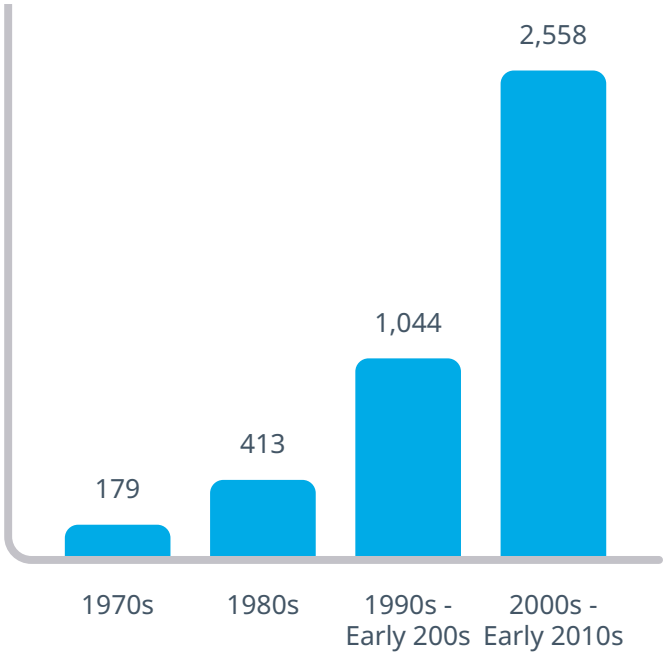
Because of the high failure rates in the industry, a solid regulatory process is needed together with a stable and predictable investment and macroeconomic environment as well as policy climate. Moreover, the costs of failures should be included as part of the costs for developing successful medicines that reach patients.

Of a total of 5,000-10,000 compounds in the initial screening phase, only 1 drug candidate receives regulatory approval in the final stage.

HIGH INVESTMENT COSTS

Average cost of developing a new drug (including the cost of failures) has more than doubled in only a decade, reaching USD 2.6 billion half way the 2010s vs. USD 1.0 billion in early 2000s. This is mainly due to the fact that new medicines increasingly target more difficult and complex diseases which are costly to address, thanks to the advance of medical science and technology which has led to a better understanding of disease mechanisms and greater capabilities to develop innovative medicines. For example, the latest gene therapies are reshaping the field of medicine, providing full cures to patients. Indeed, an average of 70% of medicines in development globally have the potential to be first-in-class medicines. [6,8,56]

Figure 5: Average cost of developing a drug (USD million) [5]

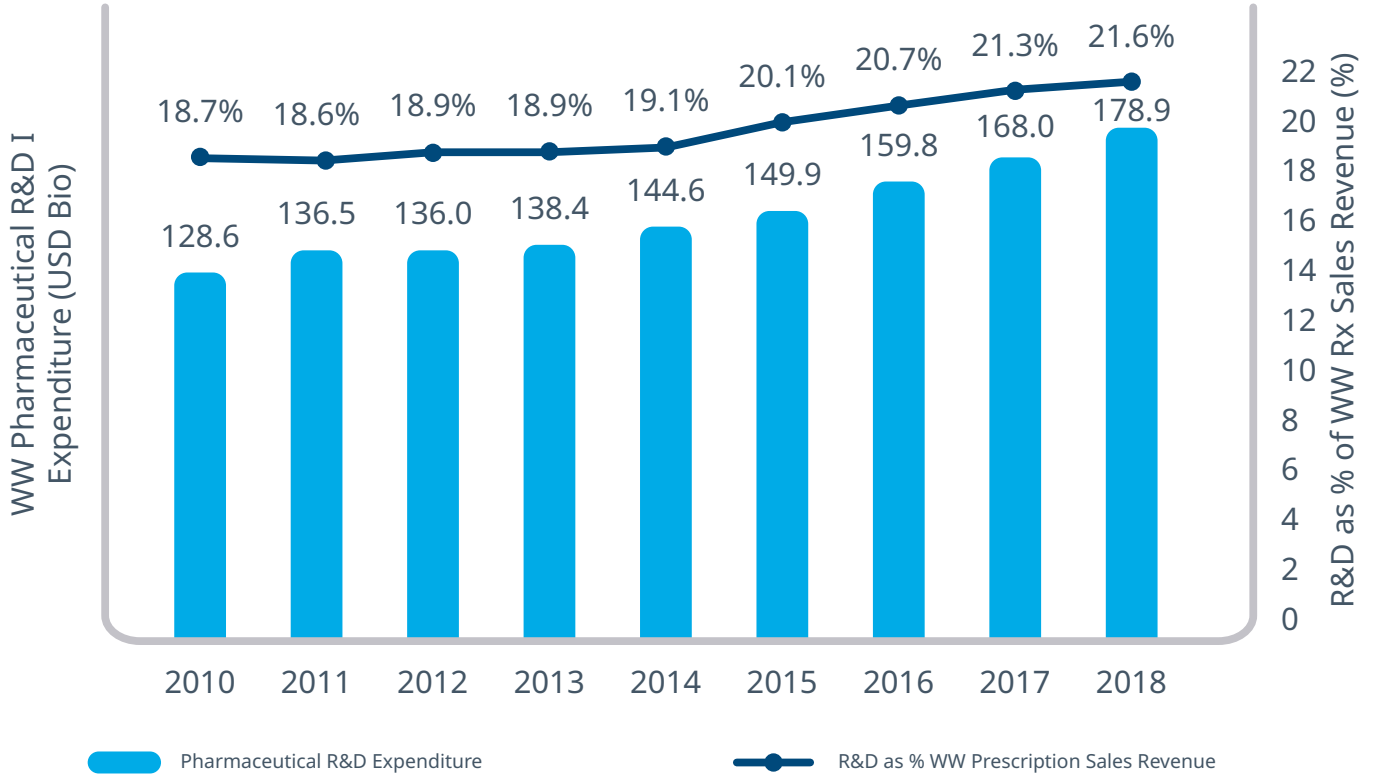


Source: DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Econ. 2016; [47: 20-33.]

[3]Approval time was calculated as the time between the date of submission and the date of approval by the agency. This time includes agency and company time. EMA approval time includes the European Commission time.
[4]Median for FDA, EMA, PMDA, Health Canada, Swissmedic and TGA approval times, average for TİTCK approval time.
[5]Includes the cost of failures.

R&D investments are vital for pharmaceutical companies. In Europe, pharmaceuticals and biotechnology are the most R&D intensive industry cluster, ahead of the software and computer services, technology hardware and equipment, automotive, and electronic and electrical equipment industries. [40]

Figure 6: Pharmaceutical R&D expenditure and share in prescription sales revenue



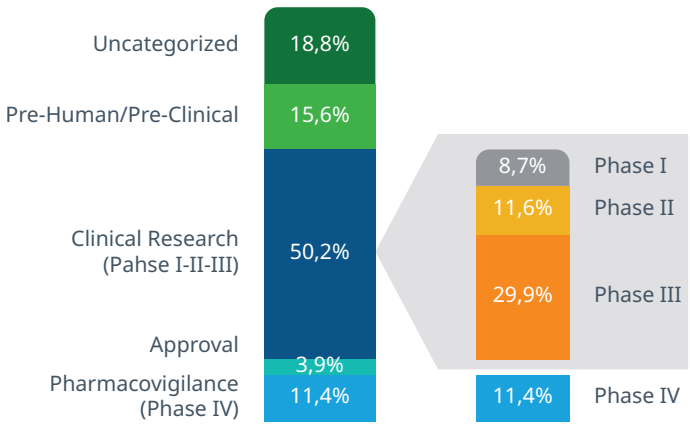
Source: EvaluatePharma World Preview 2019

R&D investments play a major role in the economy of pharmaceutical companies, with about a fifth of their worldwide prescription sales revenue going back into R&D investment. Worldwide R&D spending of pharmaceutical and biotechnology companies grew at a CAGR of 4.2% between 2010-2018, reaching USD 178.9 billion in 2018, equivalent to 21.6% of their total worldwide and 23.8% of their non-generic worldwide prescription sales revenue. [16]

In the overall R&D process, 50.2% of financial investments is directed into Phase I-II-III clinical research, with a total of 61.6% spent on Phase I through Phase IV studies. Phase III clinical research makes up almost half of all clinical research investment (Phase I through Phase IV) because of the large patient samples and often complex designs. [17]

In the overall R&D process, 50.2% of financial investments is directed into Phase I-II-III clinical research.

Figure 7: Pharmaceutical R&D investment by function



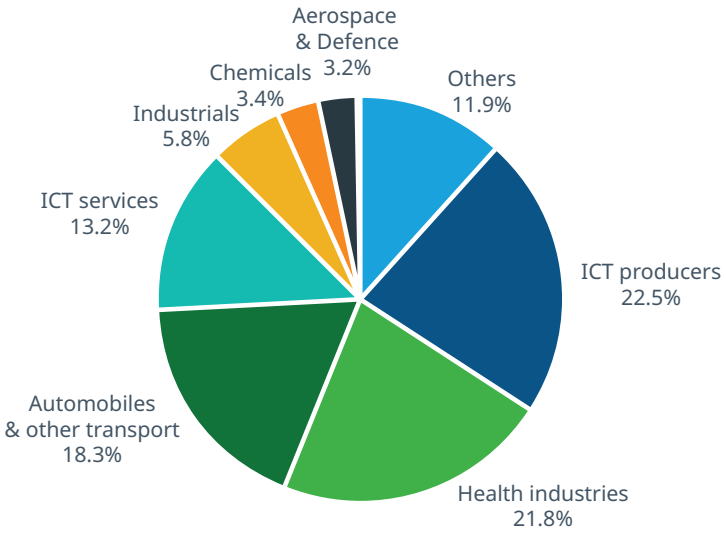
Source: PhRMA Annual Membership Survey 2018

The long time period needed to develop new products and bring them to market, high failure rates and high investment costs for pharmaceutical R&D make it critical to have a strong and clear IP and incentive system in the markets to ensure continued investment in the research and development of new therapies.

CONTRIBUTION TO INNOVATION

The pharmaceutical industry is a key player in the global innovation environment. In 2016, the size of the global R&D investments totaled USD 739.4 billion, with health industries[6] making up 21.8% of the total investment. In the European Union, the share of health industries was even higher with 23.4%. On a global basis, after Information and Communication Technologies (ICT) services, health industries were the industry with the highest R&D growth (6.9%) in 2016 compared to the year before. [21]

Figure 8: R&D specialization of companies by industry



Source: 2017 EU Industrial R&D Investment Scoreboard

The share of the pharmaceutical industry in total R&D investments in Turkey was 1.6% in 2016 and 1.8% in 2017. Overall, Turkey is considered as a "moderate level innovation" country with investments in innovation across industries growing in recent years but starting from a low base. [12,21,22]

Another indicator of the pharmaceutical industry's contribution to innovation is the number of patents granted. Despite long time periods needed for developing new medicines and high investment costs associated with new drug development, in 2018, more than 39,000 patents were granted in the industry globally, placing pharmaceuticals within top-15 industries in this regard. The number of pharmaceutical patents granted in the same year in Turkey was 83, placing the industry within top-3 in the country. [14]

In 2018, more than 39,000 patents were granted in the industry globally, placing pharmaceuticals within top-15 industries in this regard.

EMPLOYMENT

It is estimated that more than 6 million people are employed in the pharmaceutical industry worldwide, with 765,000 of them employed in Europe. Nearly 15% of the industry employment in Europe is estimated to come from R&D jobs. [4,18,19]

As detailed in Section 2.3, in Turkey, nearly 37,000 people are estimated to be employed in the industry, with 1,399 of them reported to be employed in pharmaceutical R&D centers.

[6]Health industries consist of pharmaceutical and biotechnology industries.

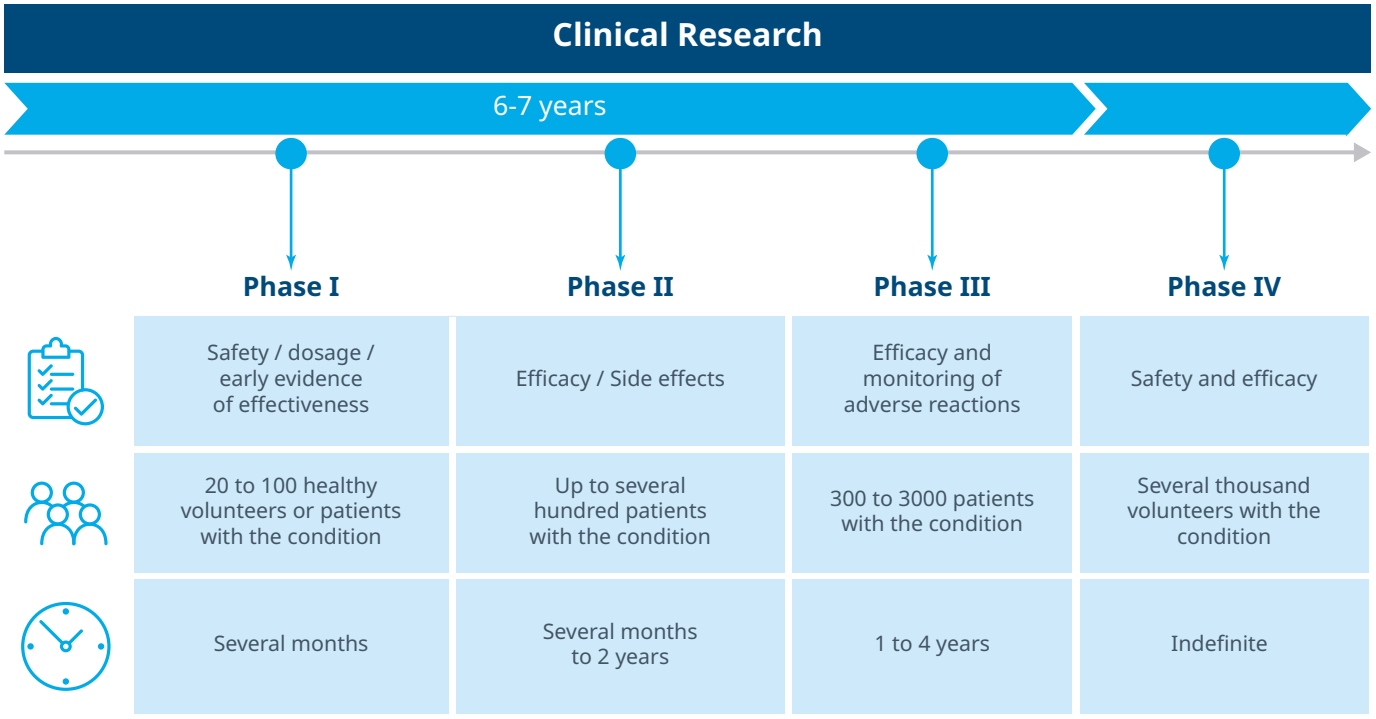
4. CLINICAL RESEARCH GLOBALLY AND IN TURKEY

Clinical trials are the core component of the innovative R&D process to develop new medicines and treatments. In this chapter, we show how clinical research phases work overall, what is tested in each phase, and how clinical research is done in Turkey.

4.1 Clinical Research phases

Clinical research consists of four phases: typically, the first three must be completed before a new drug application can be submitted to the regulatory authority, and the fourth begins after regulatory approval and manufacturing. [7] This is shown in Figure 9.

Figure 9: Phases of Clinical Research



Source: US Food and Drug Administration. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

PHASE I

Phase I clinical studies are usually the first studies where the experimental drug which has passed the pre-clinical phase is conducted in humans. They are typically human pharmacology studies which aim to evaluate the treatment's safety, determine a safe dosage range and identify side effects. Key questions answered in these studies are safety and tolerability, pharmacokinetics, pharmacodynamics, the drug's interactions (with other drugs, with food and drink, etc.), and whether the medicine is active.

Phase I studies are usually conducted in a small number of healthy volunteers (20 to 100), although some may be conducted in actual patients with the target disease or condition (e.g. cancer treatments) since the drug candidate may be too toxic to be given to healthy patients. Participating subjects may be compensated in accordance with local laws.

Phase I studies are often conducted at dedicated Phase I clinical research centers. This phase of clinical research overall lasts several months, making up 14.1% of total clinical research investment and 8.7% of the overall R&D investment. Approximately 70% of experimental drugs entering Phase I clinical research move to Phase II.

PHASE II

Phase II clinical studies are usually the first studies where an experimental drug is administered to

[7] Possibilities also exist to submit marketing authorization applications on limited indications for conditional approval based on Phase II data, as detailed in Section 5.1.

patients with the target disease or condition. They are typically therapeutic exploratory studies which aim to test the drug's efficacy, i.e. whether it treats the intended disease or condition, and to further evaluate its safety. Key questions for the Phase II studies are effect and dosing in patients, safety in patients, pharmacodynamics, and how the next research phase should be designed in terms of endpoints, target population, concomitant medication use, etc. Phase II studies which aim to show that an experimental drug treats the intended indication in a particular patient population are called Proof of Concept (PoC) studies, while those which aim to gather information on the best dosage levels and schedules are called Dose-Response (DR) studies.

Phase II studies are conducted with up to several hundreds of patients with the disease or condition. Participants are usually selected based on strict inclusion criteria to ensure a relatively homogenous study population, which enables a more rigorous interpretation of study results.

While individual studies in this phase are typically short, lasting only several weeks or months, the entire phase overall lasts several months to 2 years. Phase II clinical research makes up 18.8% of total clinical research investment and 11.6% of the overall R&D investment. Only about 33% of experimental drugs which enter this phase move to Phase III.

PHASE III

Phase III clinical studies are confirmatory therapeutic studies which aim to confirm the efficacy and safety of the experimental drug in a large patient population. In this phase, researchers confirm the drug's effectiveness, monitor its side effects, compare it to commonly used treatments or placebo, and collect information which will allow it to be used safely.

Phase III studies are conducted typically with between 300-3,000 patients with the disease/condition, in many countries. Beside their experimental design, their patient sample size and definitions are also critically important so that the detailed information gathered from these studies can be properly interpreted and meet the requirements of regulatory authorities.

Because of the importance of Phase III outcomes in regulatory authority review and approval, these studies make up the most complicated and expensive part of the R&D process. The phase overall lasts 1 to 4 years and makes up 48.6% of total clinical research investment and 29.9% of the overall R&D investment. Only about 25%-30% of experimental drugs which enter this phase move on to regulatory review.

Because of the importance of Phase III outcomes in regulatory authority review and approval, these studies make up the most complicated and expensive part of the R&D process.

PHASE IV

Phase IV clinical studies are usually conducted after a drug or treatment has received marketing authorization from the regulatory authority. The purpose of these post-authorization safety studies is to collect additional information about side effects and safety, long-term risks and benefits, and/or how well the medicine works when used more widely than in Phase III clinical trials. Collecting these real-life pharmacovigilance data may be voluntary or imposed by regulatory authorities.

Phase IV studies are long-term evaluations conducted on several thousands of patients who have the disease or condition. They make up 18.5% of total clinical research investment and 11.4% of the overall R&D investment. [6,7,10]

4.2 Global clinical research studies

Globally, more than 16,700 industry-sponsored active clinical studies were recorded as of June 2019. 42.0% of these are Phase II trials, while nearly a quarter are Phase III. When considering patient enrollment, however, the patient share of Phase II trials remains at 23.3% while Phase III trials make up 55.0% of total patient enrollment. This is due to the larger scale of the trials in Phase III compared to earlier Phases. The overview of the number of clinical studies and patient enrollment shares are presented in Figure 10.

The share of Phase IV studies remains at 10.4% in all industry-sponsored clinical research. This is because Phase IV studies are often sponsored by funders outside the industry. Industry-sponsored studies make up 21.4% of all Phase IV research run globally and 13.6% of total global Phase IV patient enrollment. The number of patients enrolled in Phase IV clinical trials is substantially lower than in Phase III.

Figure 10: Global active industry-sponsored studies & patient enrollment

PHASE	CLINICAL STUDIES (% SHARE)	PATIENT ENROLMENT (% SHARE)
Phase I	23.1	5.8
Phase II	42.0	23.3
Phase III	24.5	55.0
Phase IV	10.4	15.9
TOTAL Number	**16,720**	**4,364,485**

Source: www.clinicaltrials.gov

Figure 11: Global active Phase IV studies and patient enrollment by sponsorship

SPONSORSHIP	PHASE IV CLINICAL STUDIES (% SHARE)	PHASE IV PATIENT ENROLLMENT (% SHARE)
Industry-Sponsored Research	21.4	13.1
Non-Industry Sponsored Research	78.6	86.9
TOTAL Number	**1,737**	**671,002**

Source: www.clinicaltrials.gov

Looking at the geographical distribution of all industry-sponsored clinical research, the regions with the largest number of active studies are North America, Europe and East Asia (driven by China and South Korea). The top five countries with the largest number of active clinical studies are the United States, United Kingdom, Spain, Germany and Canada, while Turkey is in 26th place. More than half of all industry-sponsored clinical studies globally are conducted in the United States.

When the number of studies in each country is scaled to population size, GDP and pharmaceutical market size, the picture changes in favor of mid-sized countries, mostly from Central and Eastern Europe. Among these countries are some with well-established economies, healthcare systems and clinical research infrastructure such as Belgium, Denmark, The Netherlands, Austria and Israel, and others with economies and healthcare systems that are developing quickly such as Hungary, Poland, Estonia and Bulgaria. In the last two decades, clinical research has gained a strong presence in Central and Eastern European (CEE) markets with emerging economies and healthcare systems, as it provides specific healthcare benefits to patients and scientific and economic benefits to healthcare professionals and institutions.

In these scaled rankings, Turkey is placed lower in the list than when simply measured by the total number of active studies: 56th place in active studies by population, 62nd place by GDP, and 40th place by

market size, as shown in Figure 12. This shows that there is a lot of potential for Turkey with respect to clinical research. The lower rank when looking at clinical research per person in Turkey shows that Turkey could be expected to run more clinical research than it does at present. This is even more pronounced when we look at clinical research corrected for Turkey's GDP and corrected for market size. The latter indicator (40th place by market size versus 26th in number of clinical trials) suggests that Turkey's pharmaceutical market at the moment is much more a 'low-value production driven' than an 'innovation driven' pharmaceutical market, showing very large clinical trial potential. [4,29]

Turkey's pharmaceutical market at the moment is much more a 'low-value production driven' than an 'innovation driven' pharmaceutical market.

For Turkey to achieve its target of becoming a regional leader in clinical research, the country would need to more than double its number of total active studies and new clinical study registrations to take the 15th position in global ranking. For a more ambitious target of becoming a global Top-10 player in clinical research, Turkey would need to nearly triple its clinical research size in both terms.

When considering new clinical trial registrations in Top-5 countries and in the global Top-20 countries in Turkey's region, new registrations have increased in the United Kingdom, Spain, Hungary and Israel. Beside these countries, growth has rather been visible in Asia Pacific countries which previously were smaller clinical research markets. This shows not only the growing popularity of previously smaller markets but also the growing competition among these markets and developed ones in getting new clinical research.

Turkey has been among the Top-30 countries in new clinical study registrations since 2013 when the number of new registrations increased by 40% in only one year, reaching nearly 122. While its number of new registrations has remained stable since 2013, Turkey is still in 22nd place with respect to new registrations in 2018.

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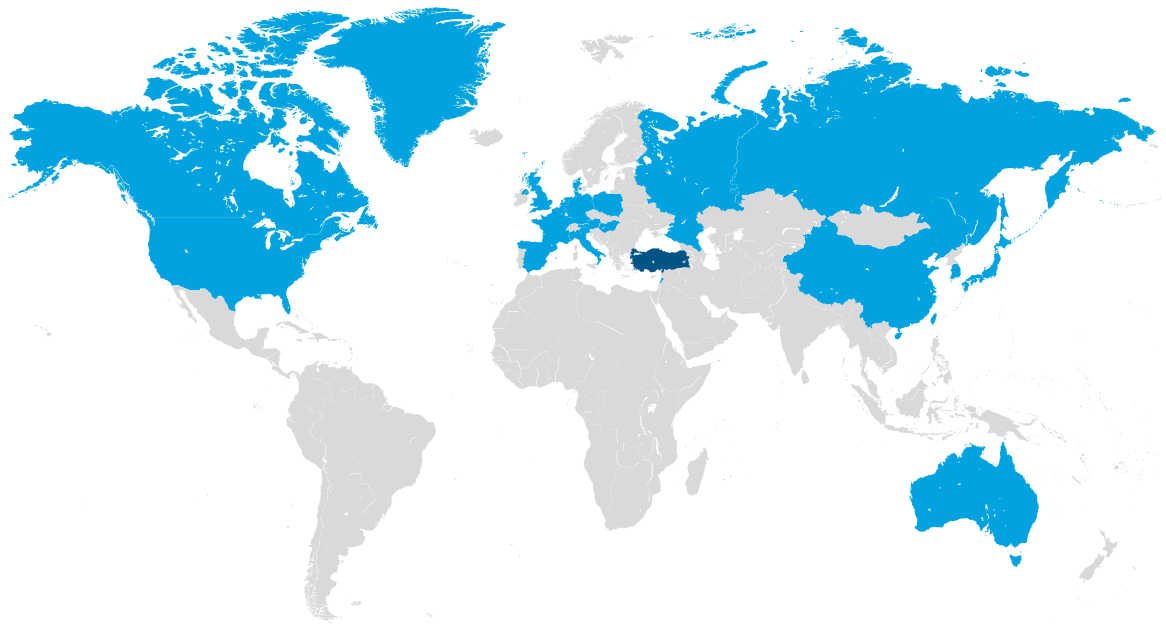


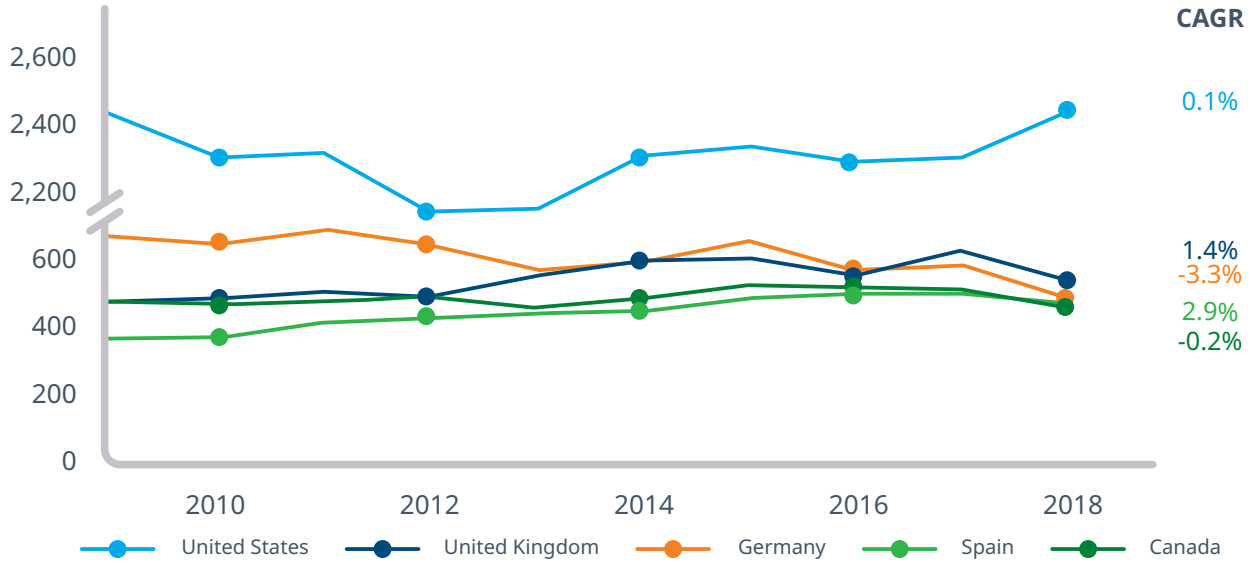
Figure 12: Top-20 countries in the number of active Clinical Research

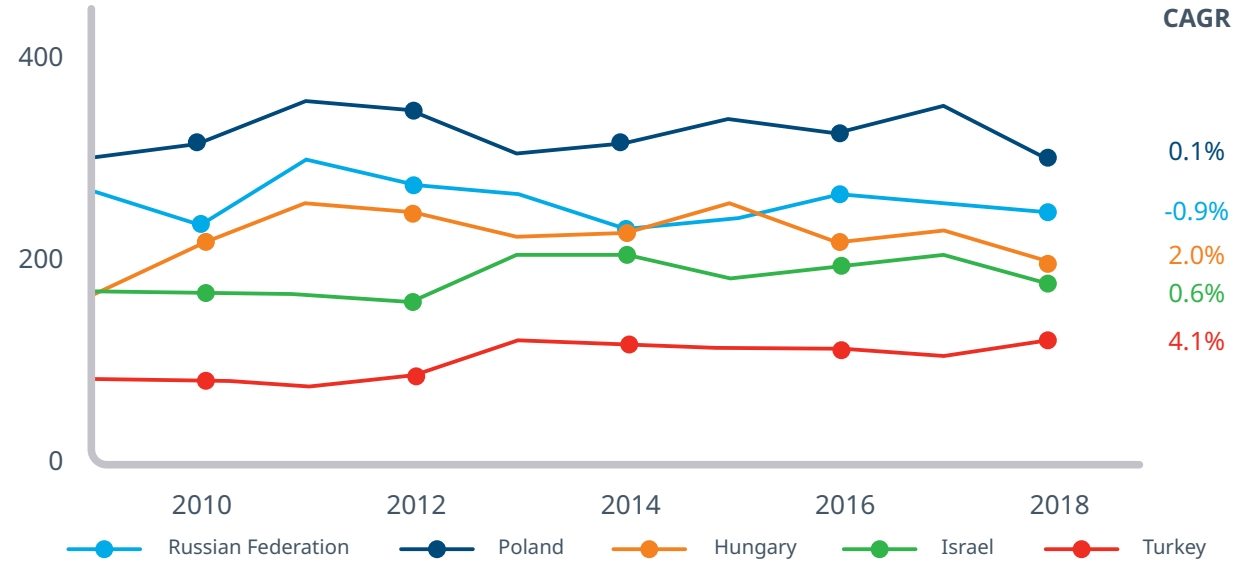
RANK	NEW CLINICAL STUDY REGISTRATIONS (2018)		ACTIVE CLINICAL STUDIES (JUNE 2019)		ACTIVE STUDIES BY POPULATION (PER MIO PEOPLE)		ACTIVE STUDIES BY GDP (PER USD BIO)		ACTIVE STUDIES BY PHARMA MARKET SIZE (PER USD MIO)	
	World	4,407	World	16,720	World	2.2	World	0.2	World	14.9
1	United States	2,436	United States	8,997	Estonia*	129.0	Bulgaria*	8.0	Israel	522.4
2	United Kingdom	568	United Kingdom	2,250	Belgium	119.8	Georgia	6.7	Singapore	344.4
3	Germany	514	Spain	2,248	Israel	113.0	Estonia*	6.5	Hungary	308.7
4	Spain	495	Germany	2,246	Denmark	112.2	Serbia	6.2	Georgia	305.5
5	Canada	488	Canada	2,155	Hungary	89.2	Hungary	6.2	New Zealand	267.3
6	France	430	France	2,130	Latvia*	82.4	Moldova	5.3	Serbia	263.4
7	China	424	Italy	1,851	Austria	80.7	Latvia*	5.2	Denmark	210.5
8	South Korea	374	China	1,672	Netherlands	71.1	Ukraine	4.4	Belgium	208.8
9	Australia	373	South Korea	1,568	New Zealand	69.1	Lithuania*	4.0	Netherlands	195.0
10	Italy	352	Australia	1,478	Puerto Rico	68.0	Bosnia	3.4	Ukraine	191.6
11	Belgium	326	Belgium	1,378	Bulgaria*	65.9	Croatia*	3.2	Bosnia	168.7
12	Poland	303	Poland	1,290	Lithuania*	65.3	Slovakia	3.0	Poland	167.1
13	Japan	284	Netherlands	1,215	Switzerland	61.0	Belgium	2.8	Slovakia	166.1
14	Netherlands	266	Japan	1,085	Finland	60.6	Israel	2.7	Hong Kong	145.1
15	Russia	246	Russia	989	Singapore	60.1	Gambia*	2.7	Taiwan	143.0
16	Taiwan	207	Israel	955	Sweden	59.7	Poland	2.5	Austria	134.3
17	Hungary	201	Taiwan	897	Australia	59.7	Puerto Rico	2.4	Sweden	128.1
18	Israel	179	Hungary	864	Canada	58.3	Greece	2.2	Iceland	125.8
19	Denmark	146	Austria	706	Ireland*	57.3	Romania	2.1	Romania	119.8
20	Austria	133	Brazil	705	Norway	54.2	Portugal	2.0	Finland	118.6
	22nd Turkey	**122**	**26th Turkey**	**521**	**56th Turkey**	**6.4**	**62nd Turkey**	**0.6**	**40th Turkey**	**71.7**

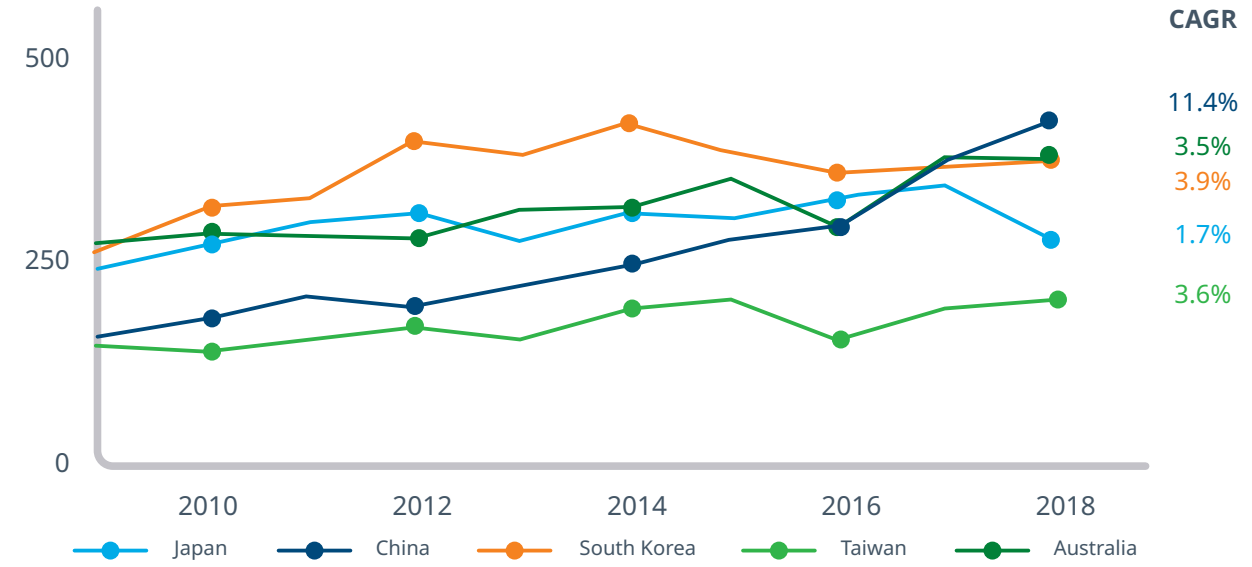
Sources: 1. www.clinicaltrials.gov; 2. United Nations Statistics; 3. IQVIA Market Prognosis.

*Pharmaceutical market size data is not available.

Figure 13: New clinical trial registrations







Source: www.clinicaltrials.gov

4.3 Clinical research studies in Turkey

As of June 2019, a total of 1,086 interventional clinical studies were actively conducted in Turkey, 521 of which were industry-sponsored Phase I through Phase IV studies. Those studies which are not defined as Phase I-IV (i.e. defined as "Not Applicable" on www.clinicaltrials.gov) tend to be mostly academic studies or studies on non-pharmaceutical products.

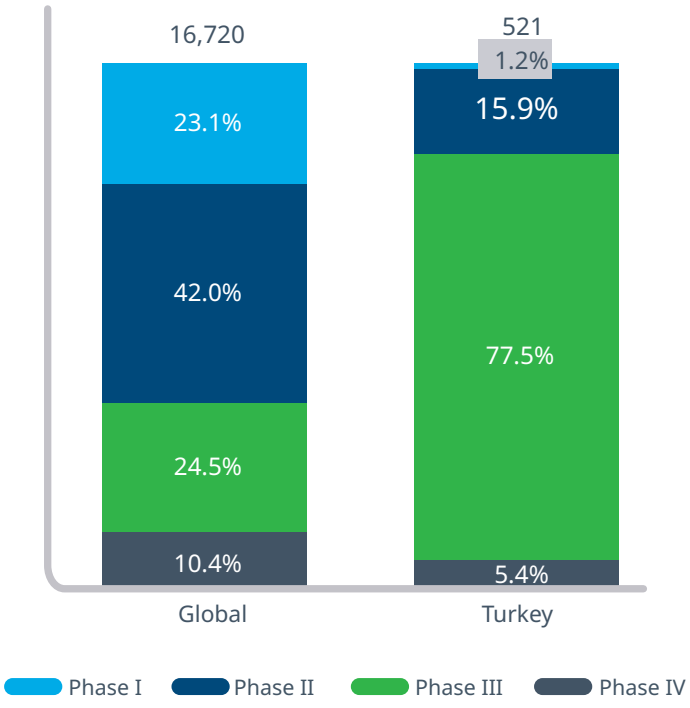
Focusing on industry-sponsored Phase I-IV interventional clinical research, 77.5% are Phase III studies (versus 24.5% globally) while 15.9% are Phase II (versus 42.0% globally). The share of Phase I studies in Turkey is below the global share in relative terms – 1.2% in Turkey versus 23.1% globally.

Figure 14: Interventional clinical studies in Turkey

SPONSORSHIP	PHASE I-IV	NOT APPLICABLE	TOTAL
Industry-Sponsored Research	521	18	539
Non-Industry Sponsored Research	138	409	547
TOTAL	**659**	**427**	**1086**

Source: www.clinicaltrials.gov

Figure 15: Active industry-sponsored clinical studies



Source: www.clinicaltrials.gov

It is not surprising to see a low share of Phase I trials in Turkey versus globally, since these trials often take place in countries where original molecules are developed. However, Turkey has been building the infrastructure to attract more Phase I trials to the country, as detailed in Section 4.5.

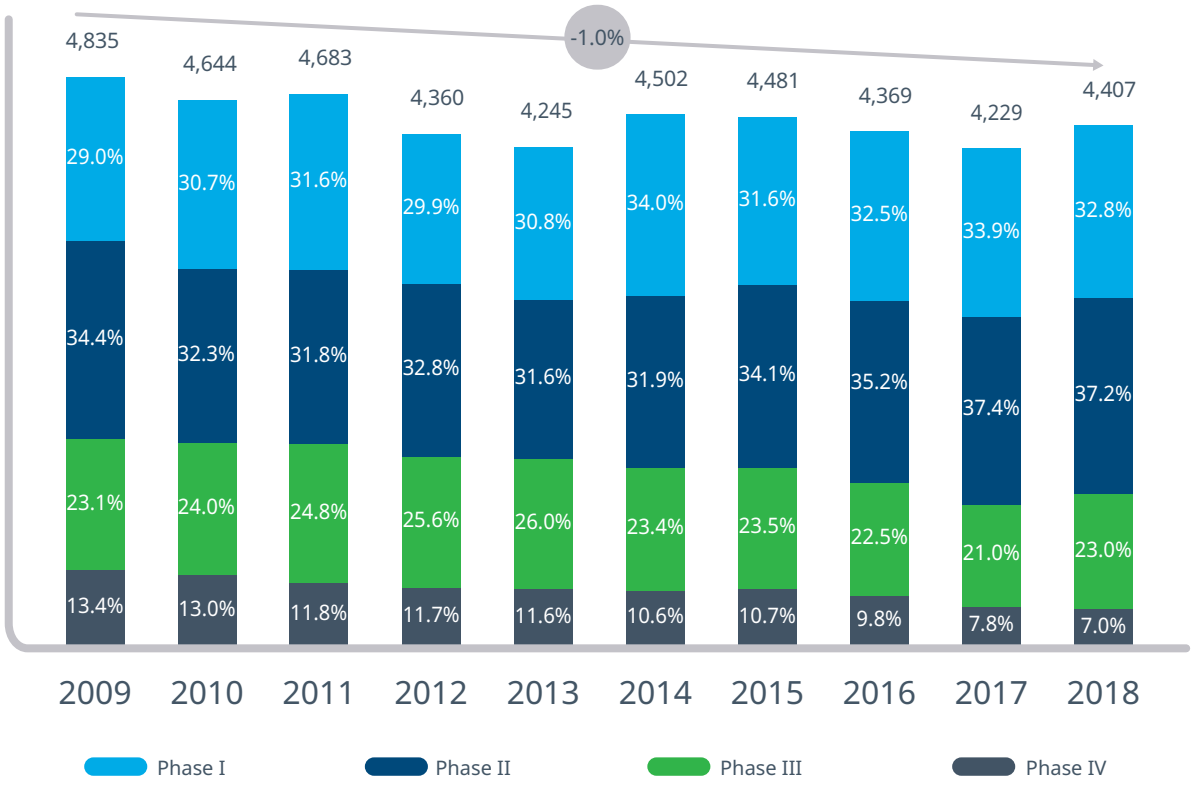
In Phase II trials, on the other hand, speed is a critical factor. Thus, pharmaceutical companies prefer conducting Phase II trials in countries which can deliver the fastest results without compromising on quality of data. It is often more likely that a country where the Phase II trial of a drug in development has been conducted will also attract the Phase III trial of the same investigational product. Given the current number of Phase II trials taking place in Turkey, there is opportunity for the country to increase these trials, which would likely drive a growth also in the number of incoming Phase III trials.

Over time, new study registrations have remained relatively stable globally (-1.0% between 2009 and 2018) while slowly increasing in Turkey (by 4.1% between 2009 and 2018 – driven mostly by the 2013 one-year growth). Study distribution by phase has remained relatively stable over the years. This has meant that Turkey's share in global clinical trials has gone from 1.8% in 2009 to 2.8% in 2018.

The reason for this growth is the shift in new clinical trial registrations which happened in 2013, driven by the regulatory process improvement that took place between 2008 and 2013 and the clinical research regulation issued in 2013. The process which involved input from all stakeholders including the pharmaceutical industry representatives was completed in 2013, resolving all the critical process roadblocks at the time. This was received positively by the sponsor companies who were following the regulatory improvement process closely. As a result, the number of new registrations which was flat between 2009 and 2012 grew by 40.2% in 2013 and has remained stable since then.

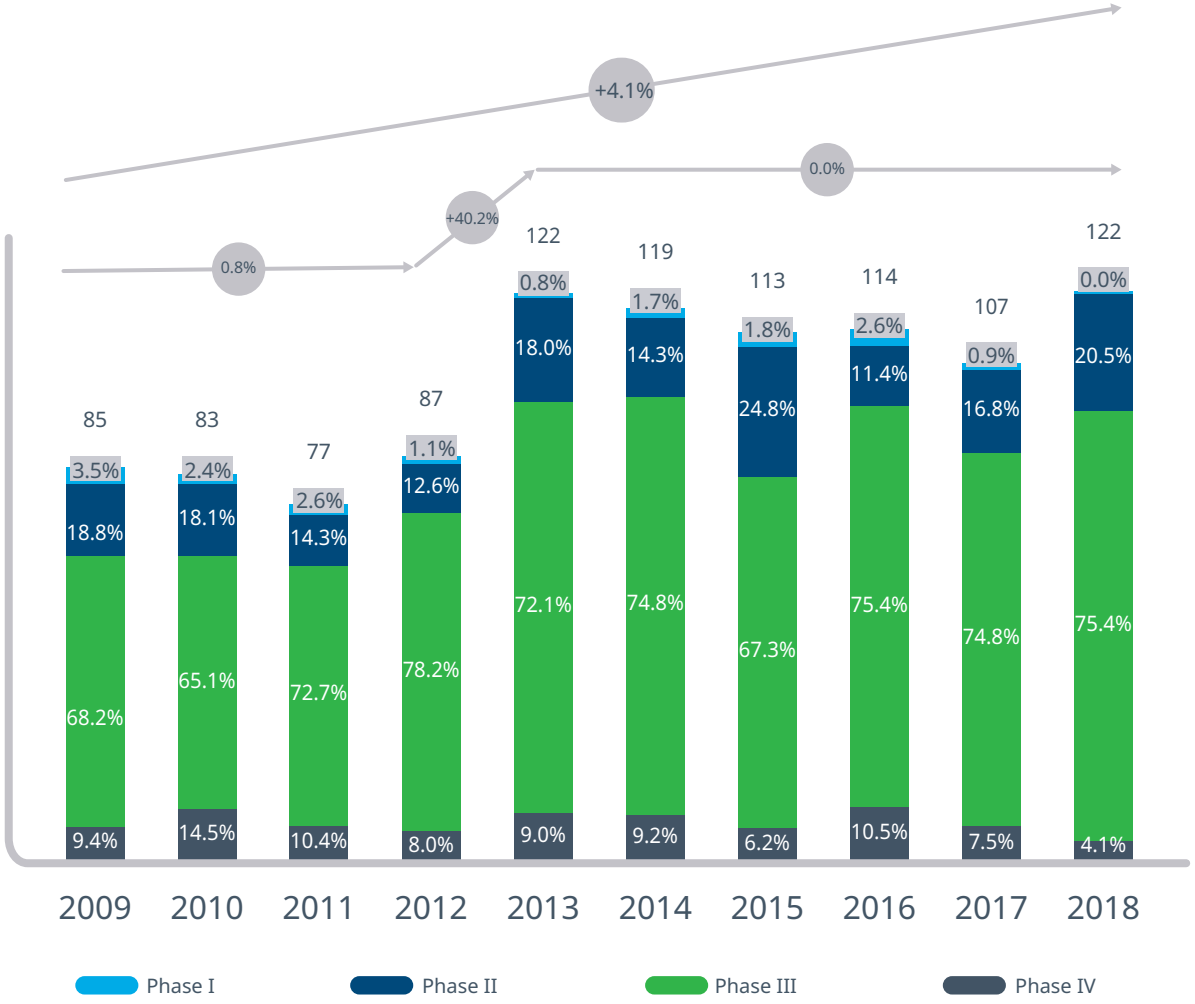
In Turkey, the number of new registrations which was flat between 2009 and 2012 grew by 40.2% in 2013 and has remained stable since then.

Figure 16: New registrations of industry-sponsored clinical studies globally



Source: www.clinicaltrials.gov

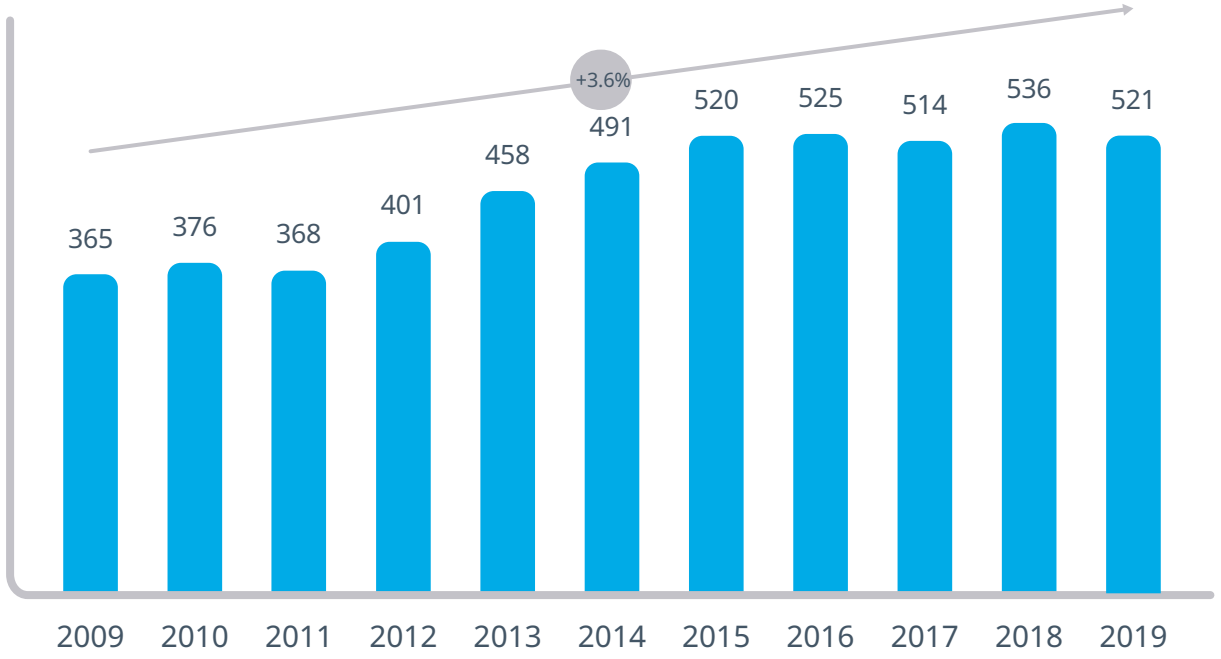
Figure 17: New registrations of industry-sponsored clinical studies in Turkey



Source: www.clinicaltrials.gov

In line with new registration growth, the total number of active studies has also grown in Turkey over time with a CAGR of 3.6% between 2009 and 2019. The driver of the growth rate in clinical research during this period was the shift in new registrations which took place in 2013. Considering that an average clinical trial in Turkey lasts 3 to 5 years, the total number of clinical studies grew with a high pace for 3 years following the initial shift in new trial registrations. As the number of new registrations per year has remained stable since 2013, there has been no growth in the total number of studies each year after 2015.

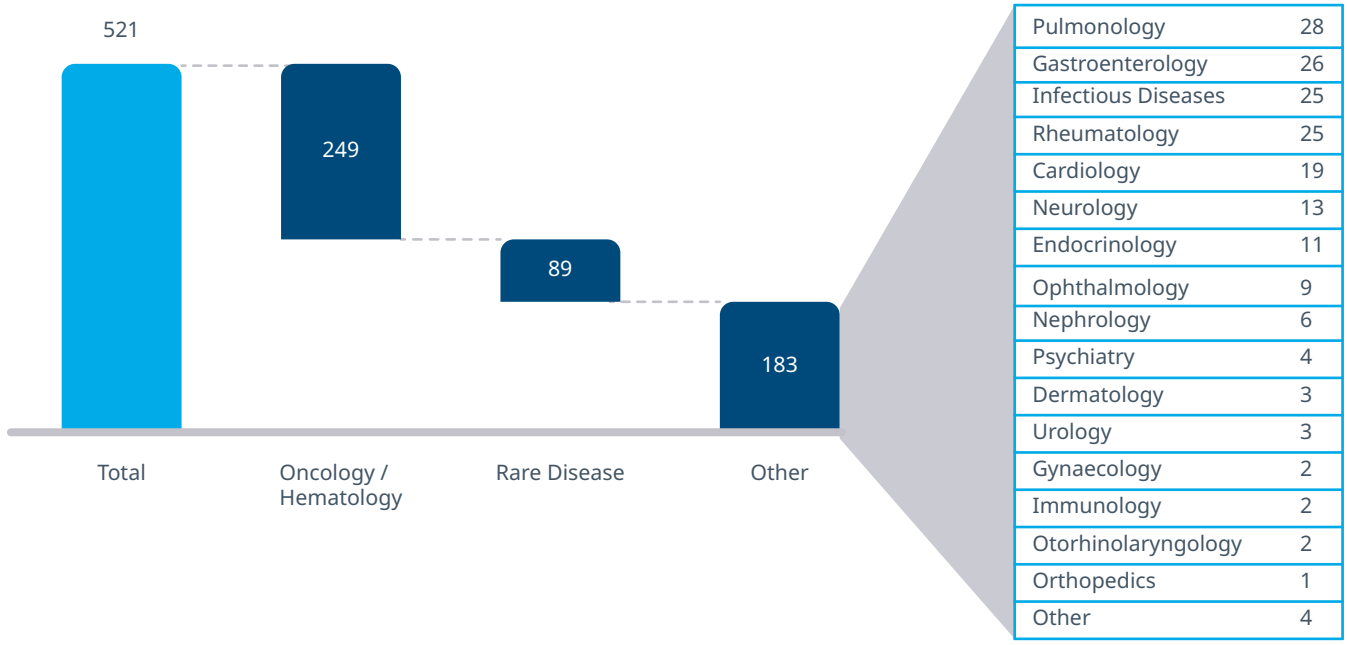
Figure 18: Active industry-sponsored clinical studies in Turkey



Source: www.clinicaltrials.gov; IQVIA analysis

In terms of therapy areas, oncology and hematology together constitute the largest portion of active clinical studies in Turkey with a share of 47.8% (249 clinical studies), followed by rare diseases with 17.1% (89 clinical studies).

Figure 19: Therapy area distribution of industry-sponsored clinical studies



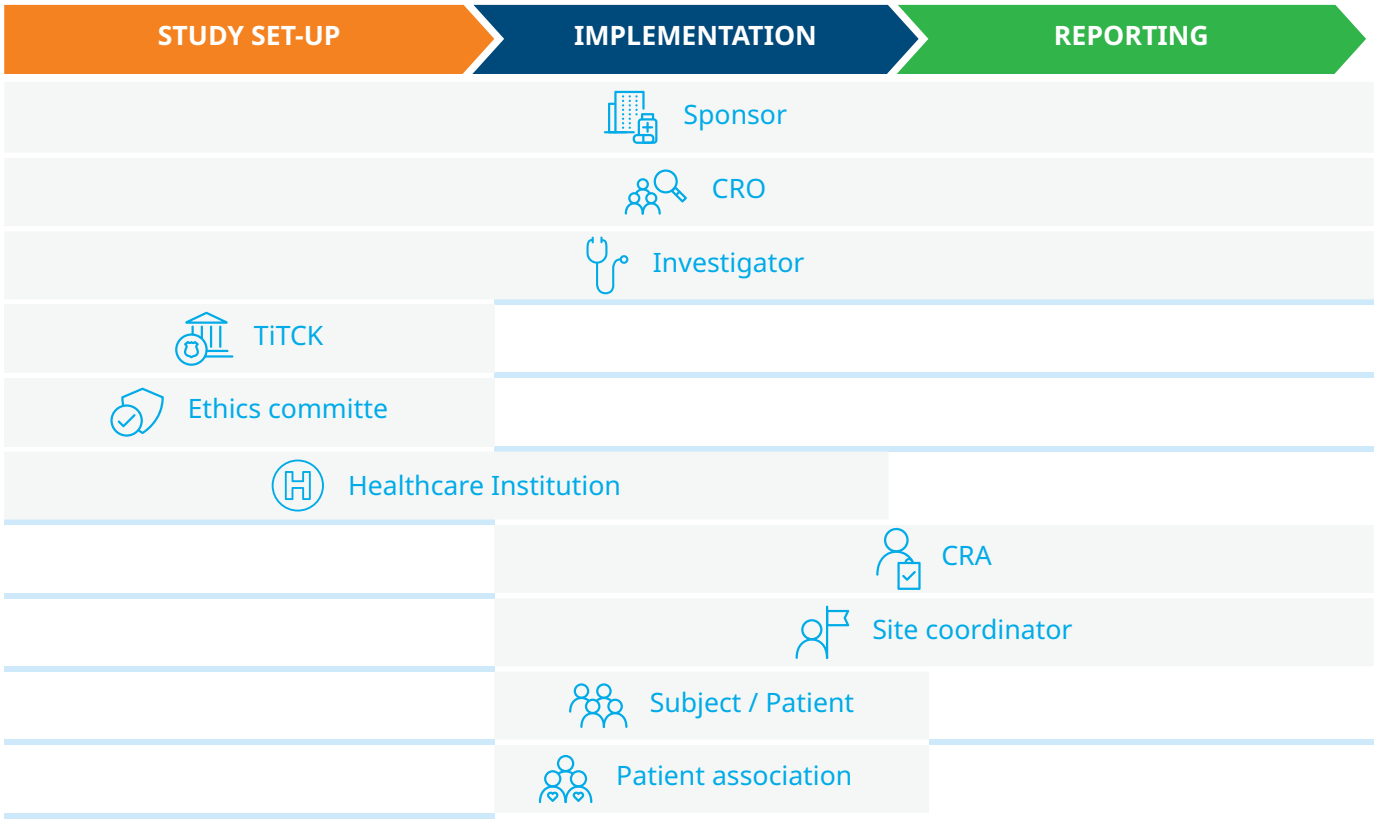
Source: www.clinicaltrials.gov; IQVIA analysis

4.4 Clinical research structure and process in Turkey

To lay out the clinical research structure and process in Turkey, we conducted extensive desk research and 22 in-depth interviews between May and July 2019 with stakeholders representing the government, healthcare institutions including hospital management and ethics committees, investigators, professional and patient associations, contract research organizations (CRO) and sponsor companies, as detailed in Appendix 2.

Overall, there are multiple stakeholders who are involved in different stages of clinical research and collaborative work between them plays an important role in ensuring clinical research quality. While some of the actors such as the sponsoring company, CRO and the primary investigator are involved throughout the entire process, others get involved in only some of the stages. Some of the stakeholders presented in Figure 18 are closely associated. For example, clinical research associates (CRA) are CRO or sponsor company employees and site coordinators are often employed by CRO or site management organizations (SMO). However, to highlight their specific roles in the process, they have been listed separately.

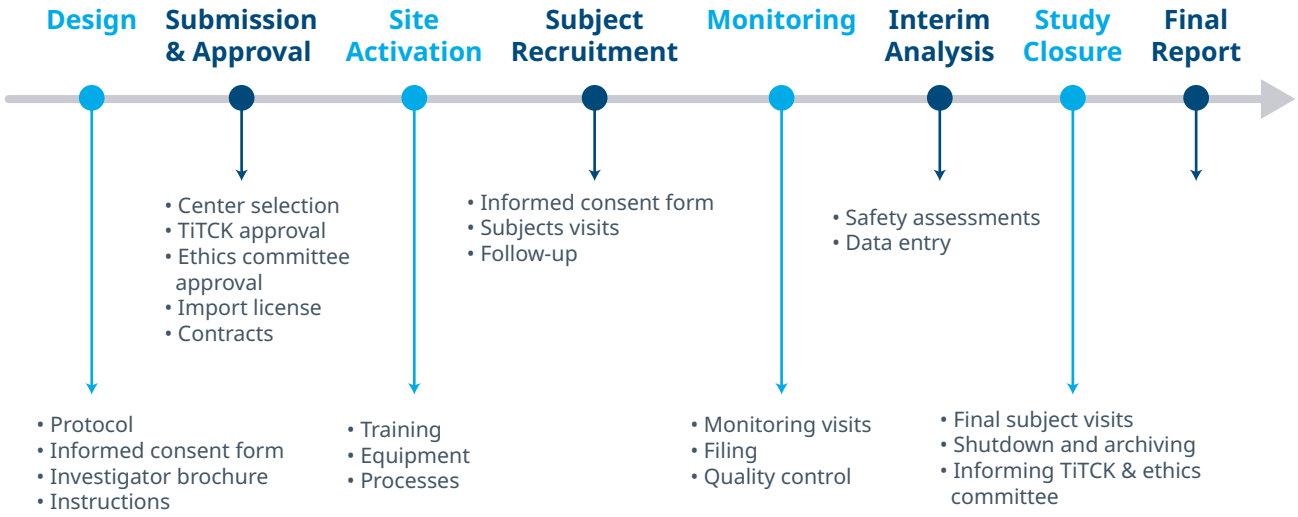
Figure 20: Stakeholders in Clinical Research in Turkey



Source: IQVIA Analysis

The process of setting up and conducting clinical research in Turkey is identical for all studies, regardless of the study phase, indication or sponsor type. It consists of eight stages from 'Design' to 'Final Report' as depicted in Figure 21.

Figure 21: Clinical Research process



Source: IQVIA Analysis

Appendix 1 provides greater detail on clinical research stakeholders and their roles as well as the detailed steps in the clinical research process in Turkey.

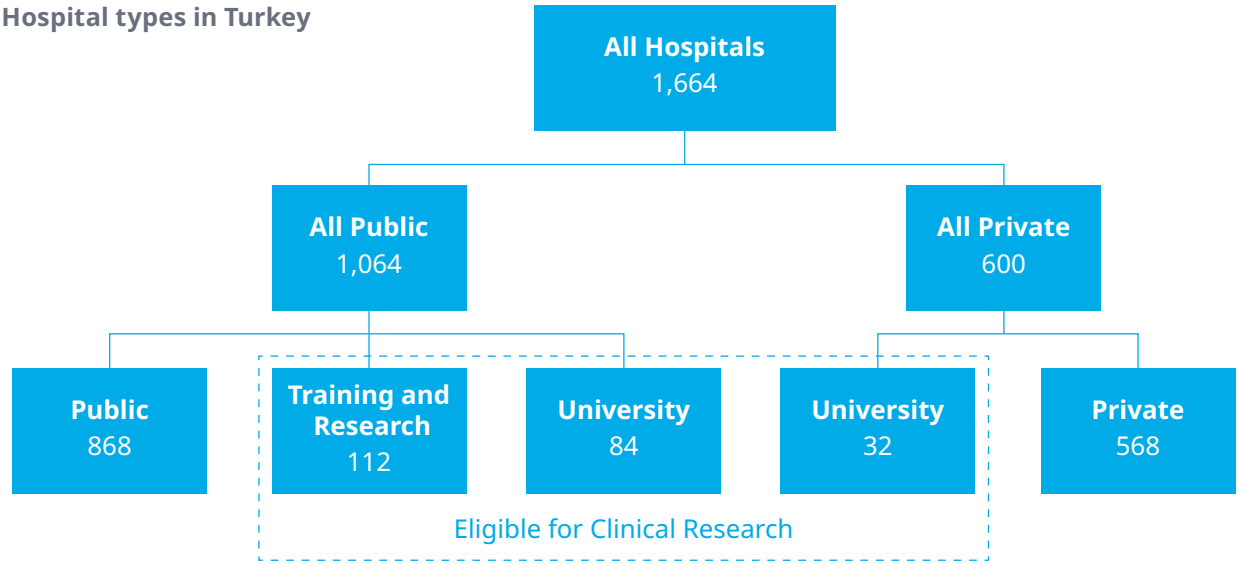
4.5 Clinical research infrastructure in Turkey

In Chapter 3, we shortly presented elements of the overall innovation infrastructure in Turkey. Here we focus on the clinical research infrastructure. There is a need for a well-established clinical research infrastructure for a country to be successful in attracting clinical research. Key components of such infrastructure are the healthcare infrastructure, clinical research workforce, information technologies (IT) infrastructure, legal infrastructure, standard of care, physical infrastructure, and the incentive mechanism.

HEALTHCARE INFRASTRUCTURE

While there are 1,664 hospitals in Turkey, with the majority of them being regular public or private hospitals, clinical research is run mainly in public and private university hospitals and training and research hospitals – including city hospitals which comprise training and research hospitals. The total number of these institutions in Turkey is 228, 116 of them being university hospitals. When we look at the distribution of clinical research by healthcare institutions in 2019, we find that the majority of trials are run in university hospitals.

Figure 22: Hospital types in Turkey



Source: IQVIA OneKey database

Figure 23: Top-15 Clinical Research sites in Turkey

TOP-15 SITES (ACCORDING TO THEIR ESTIMATED SHARE IN THE OVERALL CLINICAL RESEARCH LOAD)	ESTIMATED SHARE IN TOTAL CLINICAL RESEARCH LOAD (%)
Hacettepe University Medical Faculty	10-15
Ege University Medical Faculty	10-15
Ankara University Medical Faculty	8-13
Kocaeli University Medical Faculty	8-13
İstanbul University Cerrahpaşa Medical Faculty	8-13
Gazi University Medical Faculty	7-12
Akdeniz University Medical Faculty	5-10
Karadeniz Technical University Medical Faculty	4-9
Acıbadem Adana Hospital (Acıbadem University)	4-9
Mersin University Medical Faculty	4-9
Ondokuz Mayıs University Medical Faculty	4-9
Dokuz Eylül University Medical Faculty	3-8
Trakya University Medical Faculty	3-8
İstanbul Medeniyet University Göztepe Education and Research Hospital	3-8
Marmara University Pendik Training and Research Hospital	3-8

Source: IQVIA Analysis

University hospitals hold the largest share in Phase II, III and IV clinical research and all of the top-15 clinical research sites, based on their share in the overall clinical research load, are affiliated with a public or private university hospital.

The relative strength of university hospitals compared to training and research hospitals in clinical research in Turkey can be explained by several factors. First, the patient load in training and research hospitals is heavier than in university hospitals, reducing the time that physicians can allocate to each patient. Clinical research is a time-intensive process and the per patient time is considerably more limited in training and research hospitals. Therefore, physicians in these institutions often cannot dedicate enough time to clinical trials beside their outpatient clinic duties, also driven by the current pay-per-patient performance system. Second, university hospitals are perceived by patients as more specialized and scientific. With no effective gatekeeping mechanism in the healthcare system, patients with more complex diseases or conditions tend to go directly to university hospitals, hoping to receive more specialized treatment from expert physicians. Therefore, although the patient load is heavier in training and research hospitals, accessing the right patients in cases of more specialized diseases or conditions tends to be easier for university hospitals. [50]

Although the patient load is heavier in training and research hospitals, accessing the right patients in cases of more specialized diseases or conditions tends to be easier for university hospitals.

Phase I clinical research is conducted at 8 accredited centers across Turkey. These centers, as reported by TİTCK, are listed in Figure 24.

Figure 24: Phase I Clinical Research centers in Turkey

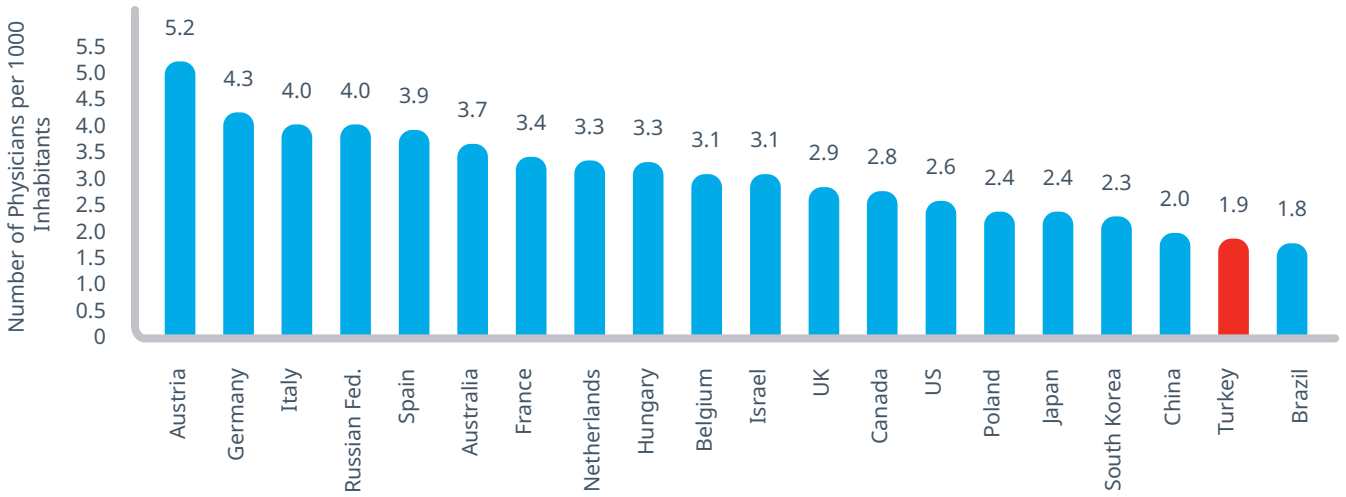
PHASE I CLINICAL RESEARCH CENTERS
Ege University Research and Application Center of Drug Development and Pharmacokinetics (ARGEFAR)
Dokuz Eylül University Phase I Clinical Research Center
Ege University Medical Faculty Paediatric Hospital, Pediatric Hematology Clinic
Erciyes University Hakan Çetinsaya Good Clinical Practice Application and Research Center
Gazi University Hospital, Department of Paediatric Metabolism
Koç University Hospital Phase I Clinical Research Center
University of Health Sciences, Ankara Abdurrahman Yurtaslan Oncology Training and Research Hospital Phase I Center
University of Health Sciences, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital

Source: www.titck.gov.tr. Accessed November 2019

CLINICAL RESEARCH WORKFORCE

Investigator: According to 2018 data, there are about 157,000 physicians in Turkey, of which 83,000 are specialists. The number of physicians per thousand people in Turkey is only 1.87, behind all of the top 20 clinical research countries except Brazil. [36]

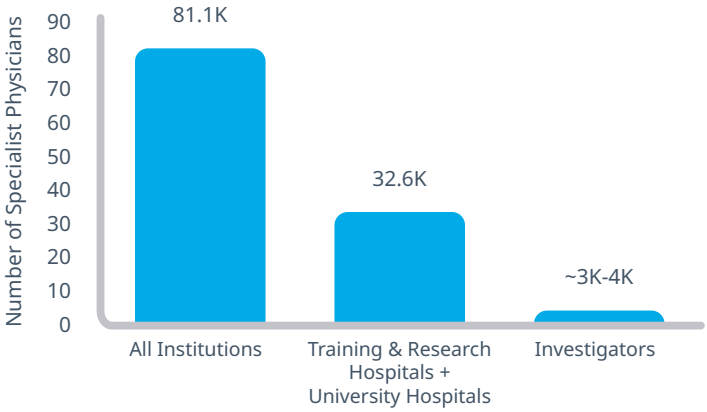
Figure 25: Number of physicians in Top-20 Clinical Research countries and Turkey



Source: OECD Health Data 2018

The number of specialist physicians in all the healthcare institutions in Turkey is nearly 81,000 with about 32,600 of them working at university and training and research hospitals. The number of specialist physicians involved in clinical research as investigators is estimated to be in the range of 3,000 to 4,000, with 10% to 15% of them assuming primary investigator roles.

Figure 26: Number of specialist physicians and investigators in Turkey



Source: IQVIA Analysis

When selecting investigators for a particular clinical trial, sponsor companies or CROs often choose to work with investigators with whom they have worked in the past, who are already recognized in the clinical research environment, and who have the potential to recruit patients fitting the specific study requirements. When a physician is contacted by the sponsor or CRO to be an investigator but is not available, he or she often refers them to other physicians. This system of selecting investigators, however, carries the risk of overlooking physicians who have less experience in clinical research but wish to advance in the field, or those who have worked as investigators in several studies and wish to take on the role of principal investigator.

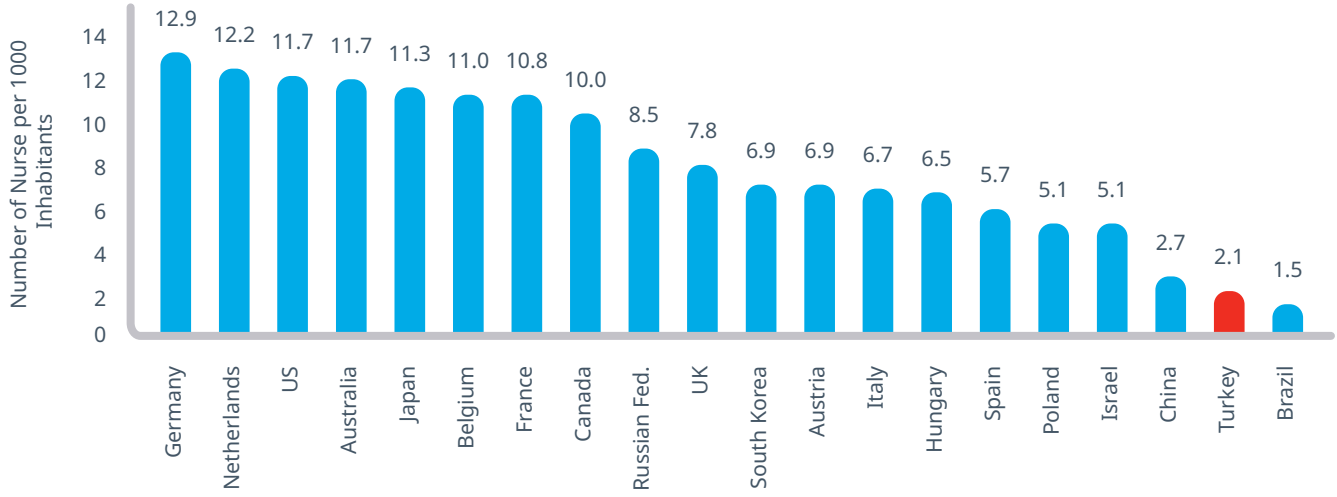
Recently, a Clinical Research Center was founded within the TÜSEB organization. One of the goals of this center is to connect investigators who wish to run clinical trials with healthcare institutions where they will conduct these trials, and to ensure that such trials are tracked and supported by TÜSEB.

One of the goals of TÜSEB's Clinical Research Center is to connect investigators who wish to run clinical trials with healthcare institutions where they will conduct these trials.

Clinical Research Staff: Assistant doctors, nurses, site coordinators and office assistants are the staff involved in the clinical research process, assisting the investigator throughout the process.

When compared to top clinical research countries, nurses, like physicians, also carry a considerably heavy patient load – the average number of nurses per 1,000 inhabitants is only 2.1 in Turkey, less than half of the average in all the top 20 clinical research markets except Brazil and China.

Figure 27: Number of nurses



Source: OECD Health Data 2018

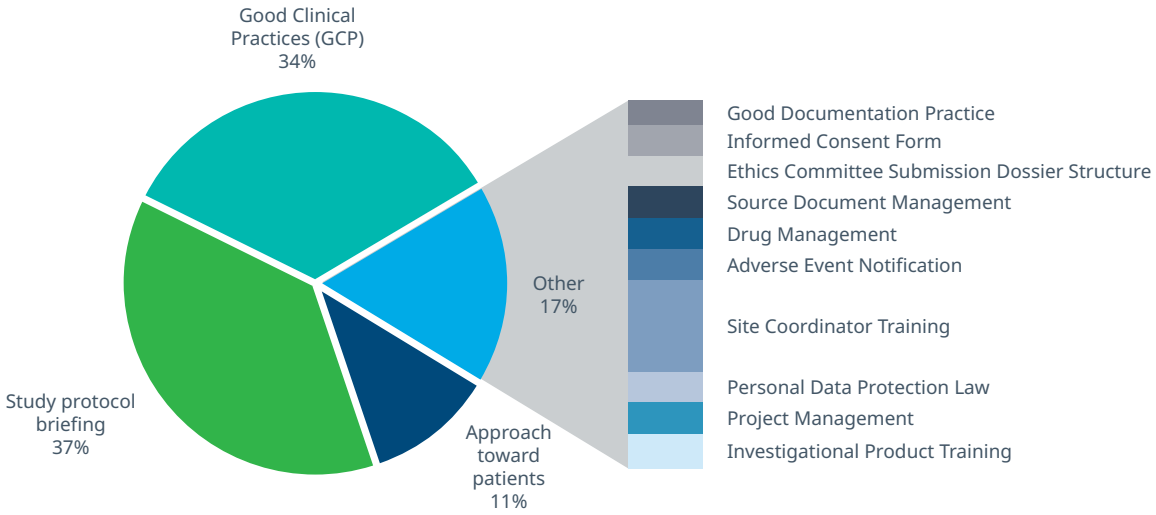
Staff retention is one of the biggest problems that investigators face in Turkey, as high turnover means repeated training programs, thus greater time and effort spent on junior staff. Due to restrictive regulations and limited resources, healthcare institutions cannot provide enough support to clinical research teams in terms of staffing. Indeed, in public healthcare institutions, site coordinators cannot be employed by the institution, thus need to be contracted, and nurses cannot dedicate their full time to clinical research due to their patient treatment duties.

Staff retention is one of the biggest problems that investigators face in Turkey, as high turnover means repeated training programs.

Investigators and clinical research staff participate in various trainings, some of which are mandatory. Investigators need to have special knowledge of basic principles of clinical research, protocol design, ethical and regulatory requirements and Good Clinical Practices (GCP) before they can be eligible to conduct clinical studies. Clinical research staff, too, participate in relevant trainings sponsored by pharmaceutical companies or CROs, which help with more effective management of clinical research at site level.

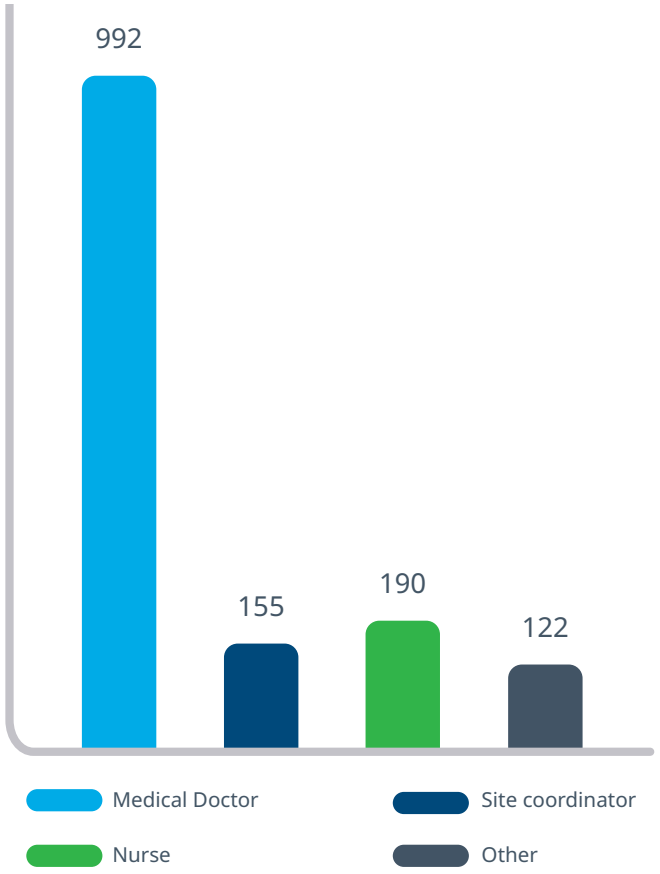
In the IQVIA survey which was conducted in June and July 2019 with participation of 17 companies who are members of the Association of Research-Based Pharmaceutical Companies (AIFD) and who have clinical research operations in Turkey, a section was dedicated to investigator and clinical research staff trainings that companies held in the country. When companies were asked about the trainings given in the last year; we found that trainings covered a variety of topics related to clinical research. In addition, healthcare personnel who participated in the trainings included not only the physicians but also the nurses and site coordinators who contribute to the clinical research. In this way, trainings not only contribute to the clinical research infrastructure but also to the overall healthcare ecosystem of the country.

Figure 28: Overview of the industry-sponsored training topics



Source: IQVIA Survey

Figure 29: Total number of participants in all the trainings organized[8]



Source: IQVIA Survey

INFORMATION TECHNOLOGY INFRASTRUCTURE

Although most of the hospitals have individual databases where patient – and in some cases clinical research – records are kept, there is no standardized clinical study, investigator or patient IT database system to serve clinical research activities in Turkey. The tools available to assist sponsor companies and/or CROs during patient recruitment (e.g. portals, databases) are one of the most important country selection criteria. Lack of a centrally and systematically maintained clinical research database tends to slow study set-up and patient recruitment times and is one of the challenges in Turkey. [43]

LEGAL (REGULATORY) INFRASTRUCTURE

Turkey has a well-established clinical research regulation and regulatory authority, TİTCK. There are various laws, regulations and national as well as international guidelines related to clinical research, which have been established in line with European Union standards. These clearly define the relationship with the patient as well as patients' rights in clinical research. The main laws, regulations and guidelines applied at national level are as follows;

Turkey has a well-established clinical research regulation and regulatory authority, TİTCK.

- **The Regulation Regarding Clinical Trials:** As defined in its Article 1, "the purpose of this regulation is to coordinate the methods and principles concerning the assurance of scientific and ethical standards as well as the protection of the volunteering subjects' rights in the design, operations, data collection, reporting, validity and other subject matters regarding clinical trials to be conducted on volunteering human subjects, within the framework of international agreements as well as European Union standards and good clinical practice."
- **The Turkish Penal Code, Article 90:** It clearly states which conditions should be met to avoid criminal responsibility in the scientific experiment, based on consent. According to the article, when it is understood that the implementation of known medical interventional methods will not yield results, research with therapeutic purposes, in accordance with scientific methods and based on patient consent is not defined as a crime. The informed consent must be in writing based on adequate information on the nature and results of the research and the treatment should be carried out by a specialist physician in a hospital setting.
- **Fundamental Law on Healthcare Services, Supplementary Article 10:** This law deals with more detailed issues such as the scope, purpose, informing the patient and contribution of the clinical study.
- **Personal Data Protection Law:** Refers to the Fundamental Law of Healthcare Services Article 10, Turkey/Data Protection Law and regulation on Clinical Trials on the use of personal data obtained through clinical research. As per this legislation,

[8] The total number of participants is based on responses from 15 pharmaceutical companies.

monitors, auditors, ethics committees, regulatory agencies and other health authorities can access patients' original medical records. However, all information will be kept confidential and patients or their legal representatives will grant permission for such access by signing an Informed Consent Form. All records that can reveal a patient's identity will be kept confidential and will not be released to the public. Patients' identities will be kept confidential even if research results are published.

- **Local Good Clinical Practice:** The principles of GCP in use are based on the Helsinki Declaration with adaptations required by the local environment. All persons conducting clinical research should possess the respective qualification, training, and experience to perform the study-related tasks in compliance with rules for Good Clinical Practice.

STANDARD TREATMENT

In Turkey, reimbursement conditions of standard treatments accepted by the SSI are defined in the Health Implementation Communiqué (SUT) and implemented in a standard manner in public and private healthcare institutions. In case of clinical research, in some trials, the definition and reimbursement of standard care are clear and in line with those accepted by the SSI. In others, the definition of standard treatment provided in the study protocol may not be sufficiently detailed or may conflict with that accepted by the SSI, in which case questions may arise regarding how and by whom the cost of such treatment should be covered.

PHYSICAL INFRASTRUCTURE

Adequate physical infrastructure including physical space, equipment, archiving facilities, storage facilities for biological samples and research drugs, uninterrupted electricity supply, etc. are necessary to conduct clinical research. While some of the clinical research centers across the country are fully-equipped and accredited, others have room for improvement in terms of physical infrastructure, specifically in terms of adequate space.

INCENTIVE MECHANISMS

Clinical research provides an additional income opportunity for participating physicians who carry out research on a regular basis. However, to obtain this income, the physician must allocate considerable time and effort to clinical research.

Investigators play an important role in the clinical research process. The more they get involved in clinical trials, the greater the experience they gain in protocol implementation, thorough data collection, recruiting and retaining subjects, and ensuring safety; and thus, the more qualified they become for future research. Consequently, physicians who become experts in clinical research get the opportunity to provide consultancy services to the industry in the area of clinical research and new product launches.

Currently, there is no binding clarity or uniformity across institutions in terms of which clinical research should be considered within the scope of R&D, thus definitions and interpretations vary by institution.

Investigator fees in clinical research are paid by the sponsor company or the CRO directly to the healthcare institution where the investigator is affiliated. Hospital management transfers a certain amount of this income to the revolving fund and gives the other part to the investigator. Income is accumulated in the hospitals' revolving funds and transferred to the hospital budget as additional income to be spent not just on clinical research-related needs but on all needs.

In addition, the healthcare institution invoices the sponsor or CRO for all the research-related medical costs (tests, diagnostics, examinations, additional treatments, etc.) at a rate which is approximately three times higher than the discounted Social Security Institution (SSI) rates. The difference between these two rates is considered as additional income generated for healthcare institutions.

Incentive distribution

The decision on how the investigator fee will be distributed is made by the individual healthcare institution's management, and there is no standard practice on this across institutions. In regular clinical research, about 30% to 50% of the investigator's fees are passed on to investigators. The investigators are subject to income tax on this income. If the clinical research is formally considered within the scope of R&D, however, then 85% of the investigator fee is transferred to the investigator, which is exempt from income tax according to the R&D regulation.

Currently, there is no binding clarity or uniformity across institutions in terms of which clinical research should be considered within the scope of R&D, thus definitions and interpretations vary by institution.

The relevant R&D regulation by the Ministry of Industry and Technology is an interpretation of the Frascati Manual [9] published in 2002. According to the regulation, for a clinical study to be considered within the scope of R&D, at least two phases of the investigational product's clinical research should be conducted in Turkey before the drug is licensed. [25,26]

> *"In applying this regulation, the following activities are not considered within the scope of R&D and innovation activities: ...*
>
> *d) Clinical studies not carried out in Turkey at least two stages prior to drug production permit and clinical studies after production permission..."*
>
> *— Ministry of Industry and Technology. Regulation Concerning the Implementation and Supervision of the Law No. 5746 on Supporting the Research, Development and Design Activities, Article 5, Paragraph d*

According to the Higher Education Law, on the other hand, all industry-supported studies (Phases I, II, III) run in university hospitals can be considered as R&D activities. Some university hospital managements refer to this law when evaluating clinical research and determine the amount of fees accordingly, while others refer to the abovementioned regulation by the Ministry of Industry and Technology. [27]

> *"Within the scope of university-industry cooperation, revenues obtained as a result of Research & Development, design and innovation projects and activities are collected in a separate account of circulating capital. No deduction shall be made from these revenues... 85% of the income to be paid to the investigator working in this context is paid to the investigator without any tax deduction... The projects and activities to be evaluated within this scope are decided with the permission of the university administrative board in accordance with the application of the investigator."*
>
> *— Higher Education Law No. 2547, Article 58, Paragraph K*

The Frascati Manual published in 2015, on the other hand, establishes that Phase I, II and III clinical trials can all be classified as R&D while Phase IV trials can be treated as R&D only under certain circumstances.

[9] The Frascati Manual is a globally accepted manual on the measurement of scientific, technological and innovation activities, which provides guidelines for collecting and reporting data on research and experimental development. Within these guidelines, the manual also provides definitions regarding which activities in different areas can be treated as R&D.

"Before new drugs, vaccines, devices or treatments can be introduced onto the market, they must be tested systematically on human volunteers to ensure that they are both safe and effective. These clinical trials are divided into four standard phases, three of which take place before permission to manufacture is granted. For the purposes of international comparison, by convention, clinical trial phases 1, 2 and 3 can be treated as R&D. Phase 4 clinical trials, which continue testing the drug or treatment after approval and manufacture, should only be treated as R&D if they bring about a further scientific or technological advance."

— Frascati Manual, 2015

Which definition will be used and how it will be implemented, mainly depends on the healthcare institution's own approach to clinical research and revenue distribution. Although there are efforts to standardize these definitions, one clear definition has not yet been decided upon at the writing of this report. Because progressing from Phase I to Phase II or III clinical trials is dependent on outcomes of the research, and cannot be guaranteed or predicted by the sponsor or CRO, this ambiguity regarding the R&D definition likely impacts the a priori decision whether to conduct clinical research in Turkey as it may not be possible to claim the offered R&D incentives (because a subsequent stage may not occur). This leads to unpredictability and uncertainty on procedures and incentives that could have a negative effect on clinical research activities in Turkey.

5. GLOBAL CLINICAL RESEARCH TRENDS

5.1 Global clinical research trends

Along with advancing technology and the opportunities it provides, it is expected that there will be changes in the traditional understanding of clinical research. While some of these innovations have already begun to be used, others are still emerging. We will shortly explain the eight global clinical research in order to incorporate them when looking at the future impact of clinical research for Turkey in the next Chapter. [28]

1. Application of Digital Health / Mobile Technologies
2. Increased Focus on Patient-Reported Outcomes
3. Emergence of Curated Real-World Data Sources
4. Use of Predictive Analytics and Artificial Intelligence
5. Shifts in Types of Drugs Being Tested
6. Availability of Biomarker Tests
7. Changes in the Regulatory Landscape
8. Availability of Pools of Pre-Screened Patients / Direct-to-Patient Recruitment

APPLICATION OF DIGITAL HEALTH / MOBILE TECHNOLOGIES

With the advance of digital health technology, mobile health applications, wearable sensors, telemedicine and other software tools have begun to be used in clinical research. These new technologies enable tracking of patient-reported outcomes (PROs) and experience measures, monitoring of patients in a real-world setting in real-time, novelties in disease monitoring, remote management of clinical assessments, and increased patient engagement and compliance.

The use of novel digital health technologies is expected to impact clinical development positively in the following ways:

- **Improve the capture of drug efficacy and safety data:** Centralized patient monitoring is expected to increase in the coming years. Digital biomarkers and real-world data captured in real time offer novel endpoints which can help to identify more meaningful real-world benefits and may replace some of the traditional clinical endpoints and patient-reported outcomes.

- **Facilitate the collection of PROs:** By making it easier for patients to complete than traditional questionnaires, and by enabling reminders, digital tools will likely make data reported by subjects more accurate, improve data quality, and increase patient engagement to increase timeliness of data reporting and reduce missing data points.
- **Improve patient safety within a clinical study setting:** Patient experience data delivered in real time will increase the success rate of clinical studies through a more rapid adverse event alert system, facilitate studies in high-risk populations, enable drug developers to stop studies with negative signals much faster, and allow for more complex study designs.
- **Enable virtual patient visits and site-less study formats, improving patient experience:** By reducing the number of required patient visits to study sites, digital tools enabling virtual assessments can help improve the patient experience, make patient participation more convenient, and reduce patient drop-out rates in clinical research. They can also have additional benefits in cases like clinical research in infectious diseases where the patient is generally advised not to visit the clinic, or when there are conditions which limit patient mobility, or for studies

which require frequent follow-ups or which are conducted at remote sites.

INCREASED FOCUS ON PATIENT-REPORTED OUTCOMES

Since patients are more accessible through different channels than in the past, patient outcomes and experience measures are increasingly included in study designs of clinical research. This enables the inclusion of the information about such outcome measures on drug labels and helps provide a more holistic view of drug benefits, especially in terms of quality of life and function. As the value of information reported by patients increases, the collection of PRO measurements will increase and mobile ePROs and wearables will facilitate the flow of this information.

Since patients are more accessible through different channels than in the past, patient outcomes and experience measures are increasingly included in study designs of clinical research.

PROs are expected to impact clinical research in multiple ways:

- **Provide additional views of drug efficacy and safety outside clinical settings:** Between 2012 and 2016, 70% of the indications for drugs approved by the FDA and EMA included PRO data in their regulatory submissions. PROs are becoming an important component of clinical research across therapy areas. Patients now can report outcomes, symptoms or functions not only in clinical settings but also outside the hospital. This provides a more complete view of the effects of a drug and patients' real-world experience and reduces clinical research bias (especially relevant for Phase II clinical research).
- **Become more accepted by regulatory bodies and influence drug labeling:** Although PRO endpoints have already been included in clinical research, regulatory authorities are becoming open to approve novel PRO endpoints and including them on drug labels. In certain therapy areas, quality of life assessments and new endpoints obtained through PROs are expected to be used in some new approvals.
- **Track adverse events and patient perception of drugs after approval:** PROs can help track safety and adverse events of a new drug in large-scale, real-world post-approval studies once a new drug goes to market. These data are more likely to capture the drug's actual effects, including adverse events, which may impact the patient's daily life.

EMERGENCE OF CURATED REAL-WORLD DATA SOURCES

In recent years, the healthcare industry's use of big data on real-world patient experience has increased. This real-world evidence can be collected widely and robustly through various sources such as electronic health records kept by healthcare institutions or other parties, medical claims data and disease registries, and they can help understand more about drug outcomes, patient experience and response and the course of a disease outside a controlled clinical research setting.

It is expected that real-world evidence will impact clinical research in the following ways:

- **Help manufacturers design studies with optimal protocol specifications:** Real-world data can help demonstrate an investigational drug's effect in a real-world setting, which may differ from the results found in clinical research, and impact protocol design. Especially in new disease segments or rare diseases, it can help to identify the right sample size, patient selection criteria and endpoints to detect a targeted treatment effect.

- **Serve as comparators and virtual control arms in clinical studies:** Instead of performing a traditional placebo-control study, patients receiving a therapy are matched to historical controls or prospectively matched to patients represented in real-world data sources. As a response to ethical concerns or recruitment challenges in clinical research in certain conditions or disease areas, such hybrid real-world data / randomized-control trial (RWD/RCT) studies have been received positively. Indeed, the FDA has signaled that it will accept the use of RWD for initial approvals of new drugs addressing high unmet needs.

Evidence-based insights can be obtained through predictive technologies such as artificial intelligence and machine learning.

USE OF PREDICTIVE ANALYTICS AND ARTIFICIAL INTELLIGENCE

Evidence-based insights can be obtained through predictive technologies such as artificial intelligence and machine learning. Artificial intelligence helps to predict future outcomes and generate new hypotheses using data on disease populations, drug candidates, and patient and physician groups. Thanks to its use, decisions are optimized by establishing a link between predictive analysis and available data. Insights generated through the combination of RWD with predictive analytics and artificial intelligence help to optimize the design of clinical study protocols and improve the quality and efficiency of studies.

In particular, it is expected to have the following impacts:

- **Generate new hypotheses to test clinically:** RWD databases will be used to generate new hypotheses with the help of AI and predictive analytics, and these hypotheses will then be validated through prospective clinical studies. In other words, clinical studies will be supported by evidence before they begin, which will ensure higher rates of success.
- **Speed up enrollment by guiding patient identification:** Protocol-ready patients who were previously registered in RWD databases and who fit the study protocol requirements can be better identified through predictive analytics. This helps accelerate the recruitment process in clinical studies and ease access to the patient population. In addition, it helps with identifying which center is most likely to recruit the desired patients and perform faster, thus aiding the choice of centers for clinical research in advance.

SHIFTS IN TYPES OF DRUGS BEING TESTED

From symptomatic therapies that reduce residual disease symptoms, the types and mechanisms of action of the drugs under development are evolving into disease-modifying therapies which slow or stop the progression of the disease. These treatments include the new generation of cell-based biotherapeutics, gene therapies and regenerative drugs. The development and production of biologicals has become increasingly easy. Changing types of drugs are expected to lead to improvements in patient life expectancies and overall patient quality of life and could revolutionize the standard of care in various therapy areas.

New drugs under development are expected to have multiple effects on clinical research:

- **Use of non-traditional development pathways with increased study complexity but accelerated timelines:** In some new curative therapies, the traditional Phase I to Phase III study approach is being replaced by different, novel study designs. Adaptive trials which start as a single Phase I study and then expand to collect all information required for registration are one of them. In addition, studies for

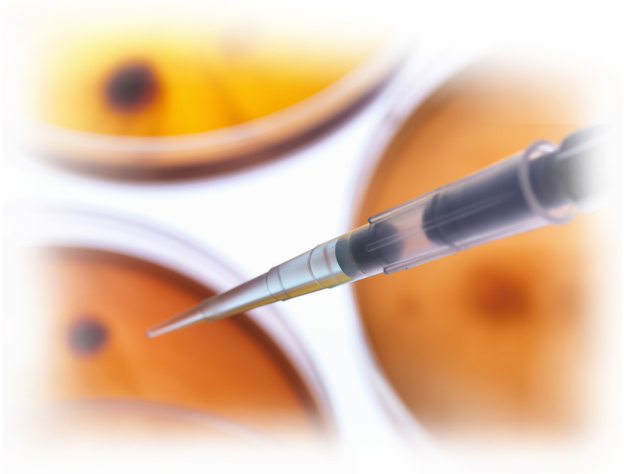
novel curative therapies with high response rates can result in approval with testing only on a few patients.

- **Include more disease-modifying drugs that will lengthen study duration and alter endpoints:** In clinical research for disease-modifying drugs, the focus is shifting to the early and preclinical stages of the disease. In case of detected changes in endpoints used in studies for disease-modifying agents, increased biomarker measurement might be necessary through laboratory testing and imaging over time. Therefore, the documentation of the change throughout the course of the disease will lengthen trial duration.
- **Several therapy areas may see a shift to biologics from small molecule therapies for the first time:** Studies for the use of biologics in new treatment areas will increase. Normally, studies for biologics are more complex than traditional small molecules, but this will be the opposite in areas such as infectious diseases. Because of its targeted use, patients are expected to potentially have less risk of side effects and adverse events.

Predictive biomarkers help to identify patient subgroups according to their susceptibility to a particular disease.

AVAILABILITY OF BIOMARKER TESTS

With a greater knowledge of the etiology and genetics of diseases, a better understanding of biomarkers has emerged. Linked to patients' genetic and metabolic profiles, tumor genetics and disease pathology, biomarkers can indicate the stage of a disease and help to identify its subtype. Predictive biomarkers help to identify patient subgroups according to their susceptibility to a particular disease, help to determine whether the disease is expected to progress more slowly or faster, and can be used for patient screening. Therefore, predictive biomarkers help with the development of targeted drugs for narrower patient subgroups.



A greater use of biomarkers in clinical research is expected to have several impacts:

- **Alter patient eligibility criteria to narrower populations and decrease sample sizes:** As studies on new drugs are increasingly targeted toward specific indications and patient subsets, biomarkers are expected to be of greater use to stratify patients into subgroups. While tighter inclusion criteria may enable smaller sample sizes in clinical studies, they can also lead to recruitment challenges, as it will become more difficult to find the patients who match all the recruitment criteria.
- **Slow approval for drugs with companion diagnostics:** When evaluating new biomarkers in clinical trials, companion diagnostics may be needed. Therefore, the approval process may slow down as regulatory rules are needed to develop companion diagnostics.
- **Strengthen drug efficacy signals and reduce side effects:** Use of predictive biomarkers in patient selection for clinical research will enable the enrollment of the right patient group, increasing the likelihood that the efficacy signals will be correct, thus reducing the risk of study failure.
- **Enable novel study designs including basket trial designs:** With the use of predictive biomarkers in clinical research, different study designs will emerge. Many clinical studies are expected to be conducted in smaller sample sizes, unlike in the past. In addition, an increase in basket trials (trials that measure the effect of one drug on a single mutation across a variety of tumor types) is expected.

CHANGES IN THE REGULATORY LANDSCAPE

In recent years, a number of legislations and guidelines have been introduced to enable the regulatory authorities, such as the FDA and EMA, to adopt a wider range of drug development approaches. While allowing new designs, these changes promote the implementation of innovations such as risk-based monitoring, use of RWD within studies, and the use of digital health technologies, electronic records and electronic signatures. In addition, the European Union's Clinical Trials Regulation aims to standardize data reporting and clinical study applications to conduct clinical research in the European Union, and to provide the appropriate environment for improving study efficiency.

All these changes in the licensing environment are expected to have the following effects on clinical research:

- **Increase the likelihood of approval by promoting use of biomarkers and other technologies:** According to experts, the use of biomarkers is expected to lead to changes in regulatory approval as they become more widespread. Furthermore, it is expected that emerging regulations will enable more options in certain therapy areas, especially in clinical research of disease-modifying drugs linked to predictive and carrier biomarkers.
- **Help accelerate drug development:** With clinical studies reducing the legal requirements for standard data types to prove the safety and efficacy of a drug, it is expected that the drug development process will accelerate in some therapy areas. Since this change in regulatory requirements is a sensitive subject covering the safety and efficacy of the drug, it is necessary to ensure that the quality of the work is high in terms of study design which complies with related regulations, helping the delivery of solid results.
- **Promote the uptake of RWD and RWE in clinical research design:** Although regulatory authorities, such as the FDA and EMA, have begun to accept the use of RWE and RWD, randomized control studies are still the gold standard for evidence in regulatory submissions. RWD will be valuable for use as comparator arms and for providing evidence on safety or efficacy. In addition, RWD post-approval studies tracking long-term safety may be used in the early approval of certain products like vaccines in cases of epidemic outbreaks.

Companies with databases of patients who have given consent for their data to be used for clinical research provide patient pools which can be leveraged in recruitment for clinical studies.

AVAILABILITY OF POOLS OF PRE-SCREENED PATIENTS / DIRECT-TO-PATIENT RECRUITMENT

Companies with databases of patients who have given consent for their data to be used for clinical research provide patient pools which can be leveraged in recruitment for clinical studies. Such data which may include behavioral and lifestyle information, genetic information, medical status, age, sex and location often accelerates the patient recruitment process. In addition, the relationship between patients and clinical research is getting closer thanks to accessible platforms that allow patients to be aware of clinical research, such as increased use of social media and online patient forums.

All of these are expected to bring the following positive effects:

- **Reduce study duration:** Patient recruitment targets are expected to be reached faster as the recruitment process will be accelerated thanks to patient pools consisting of pre-screened patients. Thus, with a potentially lower screening failure rate, this may lead to a shortening of the clinical research process.
- **Increase patient flows to sites:** Patient flows to centers are expected to improve as pre-screened patient pools and patient awareness grow. This will be critical in many disease studies, especially in those with patient screening difficulties such as allergy

and autoimmune studies, and additional pools are expected to be established for these therapy areas.

- **Improve time to clinical study initiation and enable early market availability:** Pre-screened patient pools will shorten the time of product launch, as they will enable clinical research to start faster, thus giving the investigational product the chance to be on the market earlier. In addition, it will be much easier than in the traditional approach to work in areas where physician-patient relationships during patient recruitment is more sensitive, like in the case of rare diseases.

5.2 Adoption of global Clinical Research trends in Turkey

Some of the abovementioned trends such as the use of digital health and mobile technologies, patient-reported outcomes and the shift in types of drugs have already started to be picked up in Turkey, although they all have ample room to develop and mature.

Turkey appears to have started to build the fundamental clinical research experience to support the New Economic Program policy target.

Of the reported global clinical research trends, Turkey has adapted relatively fast to the shift in the types of drugs. Especially in recent years, among the main drivers of the growth in clinical studies in Turkey have been oncology and immunotherapy studies, driven by multinational Phase III studies. Besides, even though biological agents are reimbursed by the Social Security

Institution, Turkey has become a successful country in patient recruitment for biosimilar drug studies. From this perspective, Turkey appears to have started to build the fundamental clinical research experience to support the New Economic Program policy target of realizing projects for the development of value-added precision and transformational drugs targeting cancer, chronic and rare diseases.

Considering the other trends, however, while digital health technologies are already in use in Turkey to a certain extent, site-less study designs are new to clinical research taking place in the country. Similarly, other emerging trends such as the use of real-world data, predictive analysis and pre-screened patient pools in clinical research still have to gain traction. For example, RWD is collected manually, and major problems exist in the infrastructure: there is no standard database used by hospitals and there are incorrect and missing codes in historical patient databases. There is an opportunity to set up electronic systems to provide access to more comprehensive data, and to use blinded data in portals which can be established in hospitals. When it comes to processing large amounts of data, in recent years, most developed countries have already begun to formulate national artificial intelligence strategies, while Turkey has not progressed much in this regard. The country still has a limited infrastructure and know-how to allow the combined use of predictive analytics and artificial intelligence to impact clinical research.

In addition to the lack of comprehensive patient databases for clinical research use, there are also no pre-screened patient pools in hospitals in Turkey. Patient screening is conducted by scanning the paper archives, recruiting among already known patients, or accessing the limited electronic databases of hospitals, if any.

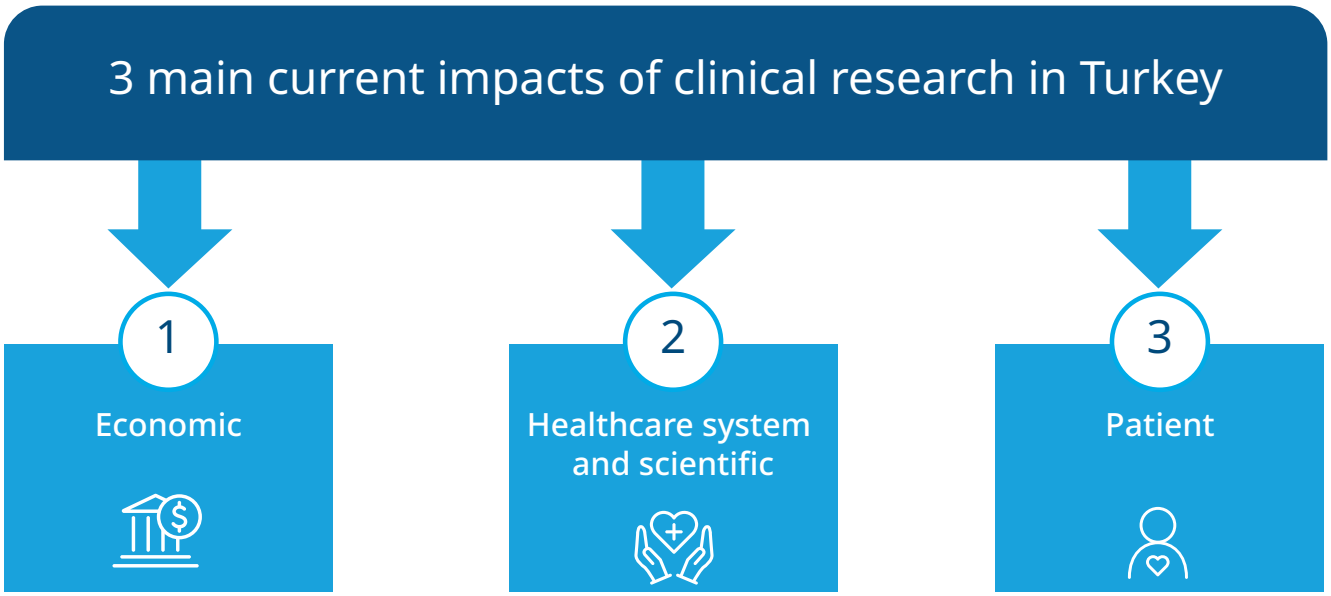
The 11th Development Plan establishes digital transformation as one of the critical means to achieve greater competitiveness and productivity in prioritized industries, one of which is pharmaceuticals. Beside the development of digital systems delivering on the industry players' needs, the importance of the development of artificial intelligence and predictive analytics tools has also been emphasized. Implementing digital transformation as well as incorporating the other global trends in clinical research in Turkey would not only help increase efficiency and productivity in the entire clinical research process, but would allow Turkey to increase its international competitiveness in this field structurally, helping it to become a significant player in the global clinical research market.

For an effective adoption of the emerging trends in clinical research, all parties running research in Turkey must comply with local laws and regulations, while – at the same time – Turkey continues to be open to learn from and take onboard global best practice developments. Above all, this ensures the safety and well-being of patients participating in clinical studies. On the other hand, like in other countries, the regulatory landscape in Turkey has opportunity to adapt to innovative study designs which have come along with the shift in drug types and with the use of new technologies and real-world evidence in clinical research.

6. IMPACT OF CLINICAL RESEARCH FOR TURKEY

With a large network of operations and stakeholders involved, clinical research goes beyond its core purpose of proving the safety and efficacy of a new medicine, thus helping patients with new products and treatments. In addition to these direct healthcare, scientific and patient impacts, clinical research also creates short- and long-term economic value in the country where it is conducted. These impacts are presented in Figure 30.

Figure 30: Current impact of Clinical Research in Turkey



Source: OECD Health Data 2018

Clinical research overall makes up 61.6% of global pharmaceutical R&D investment, corresponding to nearly USD 110.2 billion in 2018. This large cost is driven by its size and complexity, as clinical research involves millions of patients, healthcare professionals and other stakeholders worldwide and a complex network of operations.

Evaluating the impact of clinical research in Turkey, this Chapter is structured as follows. In Section 6.1, we look at the current economic relevance of clinical research for Turkey. Section 6.2 looks at the healthcare and scientific impact of clinical research, and Section 6.3 at the impact of clinical research for Turkish patients.

6.1 Economic impact

In countries like Turkey where industry-sponsored clinical research is largely conducted by multinational pharmaceutical companies, most of the money spent on clinical research is considered as foreign direct investment which has a direct positive effect on the country's current account. However, the overall economy of clinical research in Turkey should be evaluated not only in terms of financial flows entering the country, but also in terms of the value of employment generated thanks to clinical research, revenues created for the Turkish government, and the economic activity surrounding clinical research.

In order to understand the dynamics of the clinical research economy in Turkey and to estimate its size and contribution to Turkey's economic development, we used extensive desk research complemented with a survey among AIFD member companies (conducted between June and July 2019) and in-depth interviews with key stakeholders, including the Turkish government and Turkish regulator.

17 AIFD member companies participated in the survey where detailed financial data were collected on 73 recently-completed or ongoing clinical trials representing the clinical trial universe in terms of trial phase, therapy area and cost structure. Data were checked thoroughly for anomalies and 4 trials were left outside the analysis for being outliers or having incomplete information, and all data were anonymized

before the detailed analysis of the final sample of n=69 trials. To have a more accurate estimation of the total market size in Turkey, average patient numbers and annual per patient costs were calculated for each trial and therapy area, and therapy areas were grouped by their levels of average annual per patient costs. Survey data were extrapolated to the total universe of clinical trials in Turkey, using average per study patient numbers and per patient costs by therapy area group and active industry-sponsored clinical trial numbers in Turkey – N=521 studies registered on www.clinicaltrials.gov as of June 2019 and coded by IQVIA for therapy areas. Given the clinical trial sample size of the survey and the total universe of industry-sponsored clinical trials in Turkey, the analysis had a margin of error of 11% at 95% confidence level.

Total economic value of the clinical research run in Turkey is estimated as USD 327.7 million (TRL 1,860.1 million) annually as of June 2019, corresponding to 0.3% of the total global clinical research economy. This total amount includes both the clinical research investment in Turkey, which is estimated as nearly USD 139.0 million (TRL 788.8 million), and the added value of the innovative medicines provided to clinical trial subjects, which is estimated as USD 188.7 million (TRL 1,071.3 million).

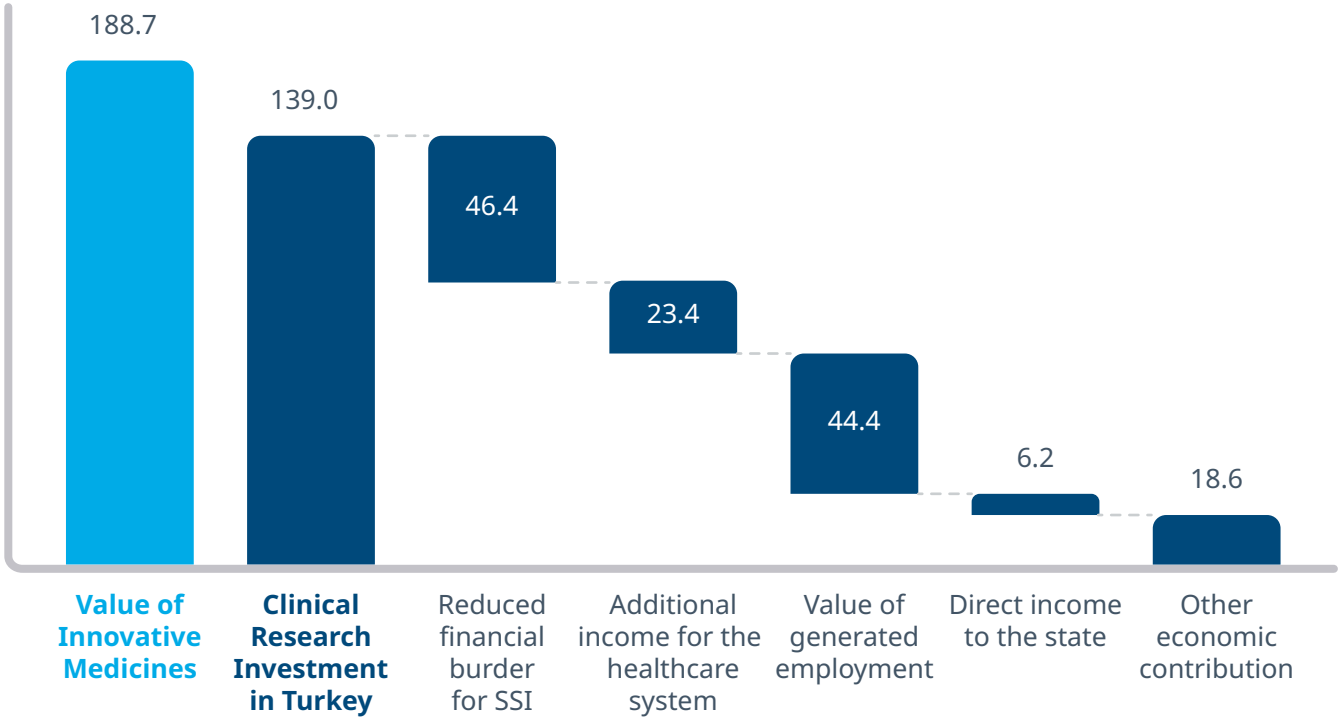
The clinical research investment of USD 139.0 million (TRL 788.8 million) in Turkey corresponds to 1.8% of the total size of the Turkish pharmaceutical industry – down from 2.6% in 2015, and 0.02% of Turkey's GDP in 2019. It is estimated that the clinical research investment in Turkey has grown with a CAGR of 12.3% in local currency since 2015, given clinical trial numbers, patient participation and inflation rates over time, but its growth has remained behind that of the total pharmaceutical industry in Turkey.[10]

Figure 31: Clinical Research investment in Turkey over time (USD million)

Source: IQVIA Analysis

[10] See Appendix 2 for inflation and exchange rate assumptions.

Figure 32: Economic value of Clinical Research in Turkey (USD million)



Source: IQVIA Survey (June-July 2019); IQVIA Analysis

VALUE OF INNOVATIVE MEDICINES

This represents the added value of the novel medicines that are provided to the subjects in clinical research, who would otherwise be treated with standard therapy or receive no treatment – in cases where no other therapy currently exists.

The reduced financial burden of medication for SSI totals to USD 41.8 million (TRL 237.3 million).

98.5% of industry-sponsored clinical research conducted in Turkey are run by multinational companies. Therefore, most of the investigational drugs provided to subjects in these trials are imported. Based on the cost analysis carried out through the IQVIA survey, the value of the drugs imported to Turkey through clinical research has been estimated as USD 188.7 million (TRL 1,071.3 million).

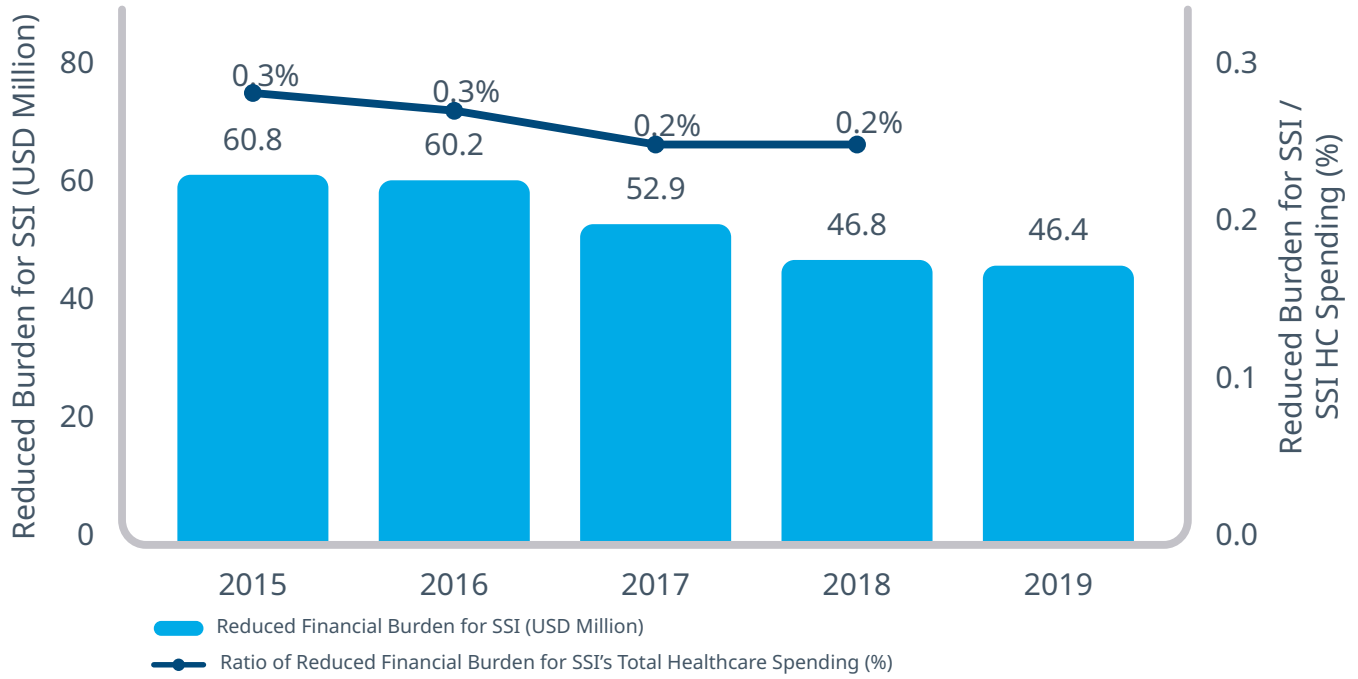
REDUCED FINANCIAL BURDEN FOR SSI

This represents the total medical cost of clinical research subjects, for which the SSI would otherwise be responsible – calculated at SSI discounted rates. In Turkey, 99.8% of the population is covered by the Universal Health Insurance Scheme which provides residents with access to healthcare and medication subsidized by the state. In the event of clinical research, on the other hand, the sponsoring company assumes all the medical cost (medication, consultations, diagnostics, laboratory tests, etc.) associated with the specific clinical study, as detailed in the study protocol. Medical costs that are not associated with the clinical study are supposed to be paid to healthcare institutions by the SSI.

With the ongoing clinical studies, this total financial burden of USD 46.4 million (TRL 263.5 million) is taken off the SSI every year.

If there would not be any clinical research in Turkey, all the medical costs currently paid by the sponsoring companies would be the responsibility of the SSI. Assuming that the nearly 21,700 patients enrolled in clinical research would use the standard therapy for their specific diseases or conditions (instead of some using the research drug) and continue with their routine exams, all at SSI's discounted rates, SSI's financial burden from these patients would amount to USD 46.4 million (TRL 263.5 million) per year. With the ongoing clinical studies, this total financial burden is taken off the SSI every year.

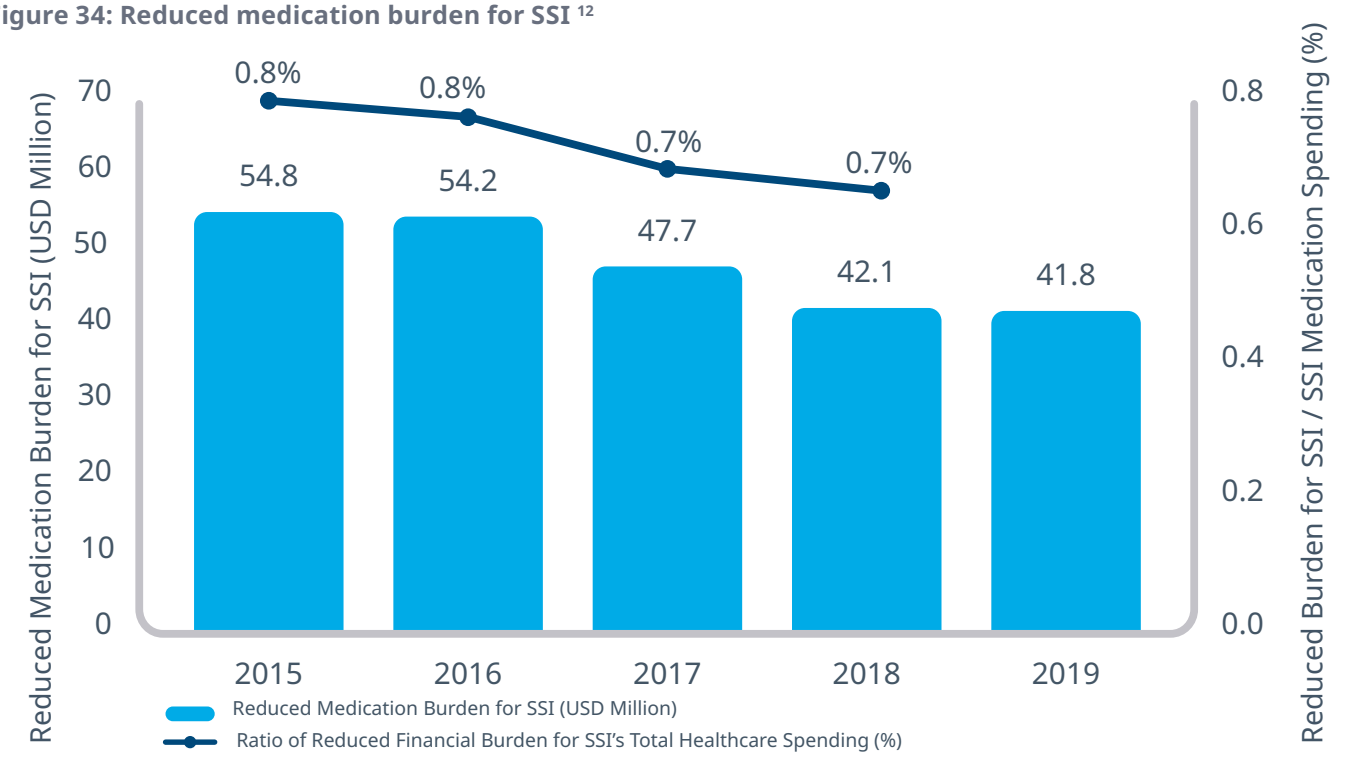
Figure 33: Reduced financial burden for SSI [11]



Source: SSI Annual Report; IQVIA Analysis

The reduced financial burden of medication for SSI totals to USD 41.8 million (TRL 237.3 million) making up 90.1% of the total financial burden taken over through clinical research. In terms of their ratio to SSI spending, the total financial burden taken off SSI through clinical research corresponds to 0.3% of SSI's total annual healthcare spending, while medication cost taken off the institution corresponds to 0.7% of its total annual spending on medication. Considering the number of active clinical studies over time, the financial burden taken off SSI has remained stable in recent years. [6,29]

Figure 34: Reduced medication burden for SSI [12]



Source: SSI Annual Report; IQVIA Analysis

[11, 12] See Appendix 2 for inflation and exchange rate assumptions.

ADDITIONAL INCOME FOR THE HEALTHCARE SYSTEM

This component consists of investigator fees, incremental income of healthcare institutions from medical costs of clinical research subjects, and ethics committee submission fees.

In all clinical trials, investigator fees, which are defined in the study protocol as fees per patient visit, are paid directly to the institutions where the clinical trial is held. Institutions then distribute this amount between the revolving fund and clinical research staff at their pre-defined rates.

On the other hand, for patient diagnostics and laboratory tests conducted as part of clinical research, institutions charge clinical research companies nearly three times the discounted rates that they would charge the SSI – and these fees are even higher at clinical research sites in private hospitals. This difference in such fees can be considered as additional income generated for institutions thanks to clinical research.

Altogether, additional income generated for healthcare institutions from these clinical research-related sources amounts to USD 23.4 million (TRL 133.0 million) per year.

In addition to investigator fees and additional income generated from tests and diagnostics, institutions with own ethical committees also receive application fees for all the ethical committee applications submitted. Altogether, additional income generated for healthcare institutions from these clinical research-related sources amounts to USD 23.4 million (TRL 133.0 million) per year.

VALUE OF GENERATED EMPLOYMENT

The value of the employment generated through clinical research consists of site coordinator payments and salaries of other people employed at CROs and in clinical research departments of sponsor companies.

In our analysis, investigators and other healthcare and hospital personnel were not counted as part of the employment generated thanks to clinical trials since clinical research is considered as their secondary duty and there are virtually no healthcare professionals or hospital personnel dedicated to clinical research in Turkey.

The total estimated value of the employment generated through clinical research is TRL 251.8 million (USD 44.5 million) annually.

Desk research conducted by IQVIA shows that the total size of the labor force generated through clinical research is approximately 1,400 people – nearly 720 clinical research associates and managers, 470 site coordinators, 160 regulatory and start-up managers and other personnel, and 35 clinical research directors and upper management personnel are employed by CRO, SMO and sponsor companies in Turkey.

Payments made to site coordinators are a direct cost item for clinical studies and data on this was collected per study in the IQVIA survey and extrapolated to total number of studies in Turkey. On the other hand, insight into average wages of other clinical research employees, by level and area of expertise, was gathered through key stakeholder interviews and desk research.

A detailed analysis of site coordinator payments and other employee salaries shows that the total estimated value of the employment generated through clinical research is USD 44.4 million (TRL 251.8 million) annually. The methodology used in the analysis has been detailed in Appendix 2.

DIRECT INCOME TO THE STATE

This is made up of customs and import taxes and TİTCK submission fees. Medication imported for clinical research purposes is subject to import taxes and customs fees, which are considered as direct income to the state. Considering import taxes and customs fees

as well as submission fees paid for TİTCK submission in the study setup phase, direct annual income to the state is estimated to be around USD 6.2 million (TRL 34.9 million).

OTHER ECONOMIC CONTRIBUTION

Besides investments, direct payments to the state and healthcare institutions and sector employee salaries, clinical research generates additional economic effects through other operational spending, impacting other industries. These operational items include spending on office space and operations, storage, travel and accommodation in Turkey, meetings and trainings held in Turkey, shipping of drugs and equipment, communication and IT, legal and other consulting, research-related insurance paid in Turkey, etc. The total of this spending is estimated as USD 18.6 million (TRL 105.7 million) per year.

When the induced effect of clinical research is taken into consideration, the economic impact can be expected to be even greater.

The direct investment of USD 139.0 million (TRL 788.8 million) consisting of the five components mentioned above reflects the money that is spent in the country. When the induced effect of clinical research (i.e. greater contribution to labor force due to better health outcomes and earlier access to innovative treatments, additional spending by those employed in clinical research roles, etc.) is taken into consideration, the economic impact can be expected to be even greater.

A recent analysis by the Clinical Research Association in Turkey shows that if Turkey attracted clinical trials with higher per-patient average costs in all the indications, the total value of clinical research conducted in the country would nearly double. This shows the added value of attracting clinical research on innovative drugs which require the use of advanced clinical trial methods and tools.

6.2 Healthcare system and scientific impact

As detailed in Secion 6.1, clinical research provides monetary benefits to the healthcare system: it reduces the SSI's financial burden by USD 46.4 million (TRL 263.5 million) per year and generates an additional income of USD 23.4 million (TRL 133.0 million) to the healthcare system. Beyond monetary, clinical research also has non-monetary impacts on the healtchare system and the scientific environment in Turkey.

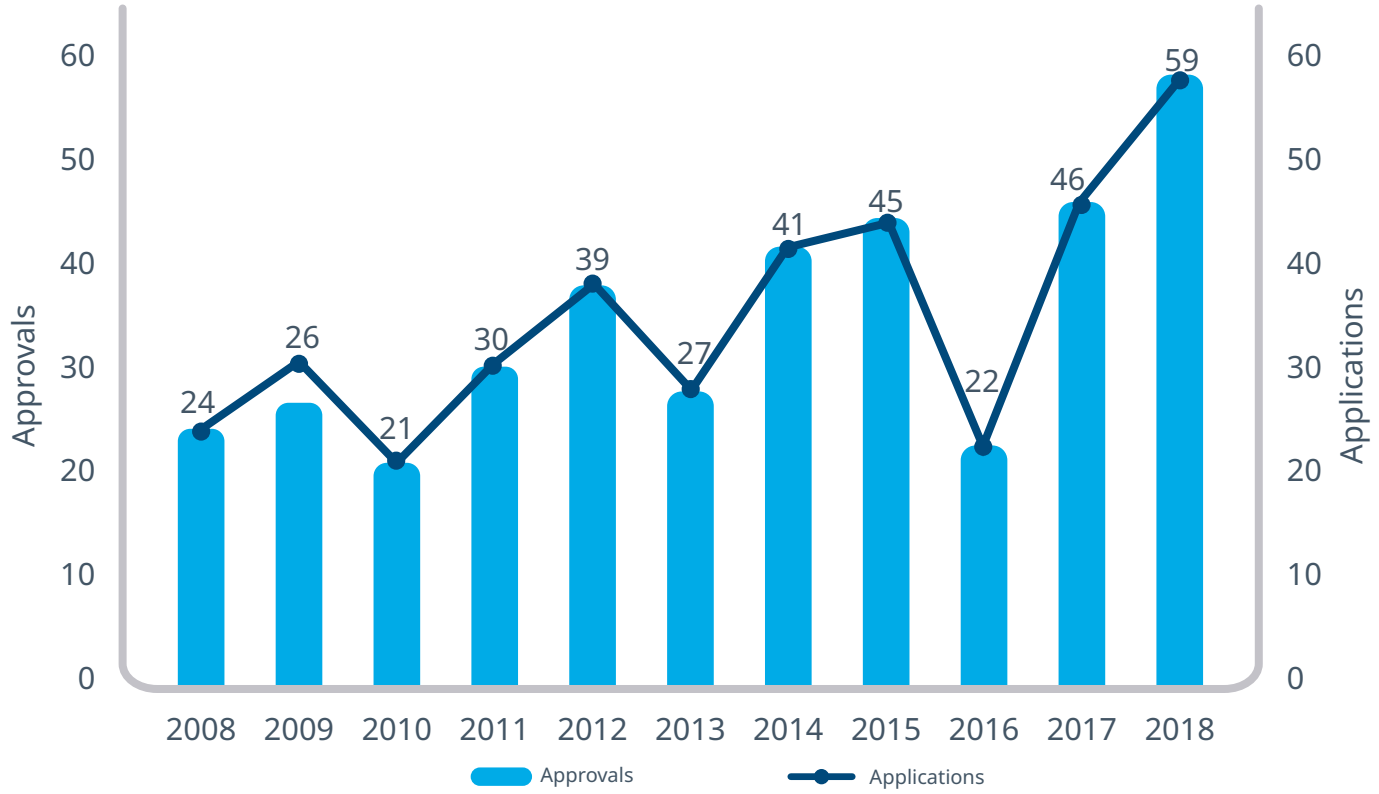
BENEFITS FOR HEALTHCARE PROFESSIONALS

Clinical research investigators play an important role in the development of products for use in different diseases and seek cures for chronic and degenerative diseases while improving public health around the world. The development of innovative treatments has been on the rise globally and the number of clinical studies that are required is increasing consequently. These innovative treatments require innovative and often more complex approaches to clinical research, which in turn require greater clinical research expertise and capabilities.

The development of innovative treatments has been on the rise globally and the number of clinical studies that are required is increasing consequently.

Although the growth of the total number of clinical trials has remained flat globally, the composition of countries where clinical trials are conducted has been changing. In recent years, new countries have emerged in the clinical research sector, gaining strength in clinical trials for not only established but also innovative treatments. One of the benefits these countries have enjoyed through growing clinical research is the impact on the scientific infrastructure, specifically on healthcare professionals.

Figure 35: Novel drug and biologics license applications & approvals (NDA & BLA)



Source: FDA Website

In 2018 alone, the US FDA approved 59 new molecular entities and new biologics licenses and over 40 new applications were submitted for review. Just ten years ago, the number of approvals was 24, less than half the 2018 total. Because the sum of FDA approvals (and, in turn, the amount of clinical research) has increased in the last several years, there has been a dramatic increase in the need for qualified physicians to be part of the clinical studies conducted for these drugs. Many of the novel drugs approved are important for their potential positive impact in terms of quality of medical care and public health.

Healthcare professionals with different roles are needed throughout the entire clinical research process to develop a new product. Regardless of whether they lead a study as principal investigator or take part in it as co-applicant or other healthcare personnel, every role and every professional is essential to patient recruitment and delivery of studies.

Taking part in clinical research, especially in those for innovative treatment methods, contributes both to educating and training the healthcare professionals involved in clinical trials.

Taking part in clinical research, especially in those for innovative treatment methods, contributes both to educating and training the healthcare professionals involved in clinical trials. The main advantages gained by physicians who conduct clinical research are the following:

- Scientific publications and increased prestige and reputation
- Career advancement
- Better treatment decisions
- Participatory role in the evolution of medicines

Scientific publications and increased prestige and reputation

Clinical research provides physicians with the opportunity to gain visibility and reputation in the scientific arena. Clinical research investigators often appear as authors or co-authors of research-related articles in reputable scientific journals. This helps them to be recognized as thought leaders in their respective countries and internationally.

Clinical research investigators often appear as authors or co-authors of research-related articles in reputable scientific journals.

A structured review of clinical research publication trends in PubMed between 1995 and 2015 showed that top-30 publishing countries generated 94.6% of all publications and 98.1% of core clinical journals globally. According to this analysis, Turkey was ranked 31st in "systematic review" and "meta-analysis" categories with 55 publications, while the country was ranked 18th in the "clinical trial" category with 671 publications and 17th in "all publications" with 19,963 publications. The country leading the list in all publications, "clinical trial" and "systematic review" categories was the United States (323,047, 11,095 and 3,654 publications, respectively), followed by United Kingdom, China and Germany. [44]

Physicians involved in clinical research also build close connections with patients who participate in their studies, as they follow up with them closely and regularly during the monitoring process. Moreover, as investigators, physicians are more likely to follow new and innovative treatments closely, which in turn increases their reputations in the eyes of patients.

In addition, a survey published in the United States in 2018 showed that online reviews are quickly becoming an important factor in patients' healthcare decisions. The survey revealed that online reviews influence the decision of 66.3% of patients when they are searching for medical care.

Online reviews are quickly becoming an important factor in patients' healthcare decisions.

Clinical research provides an opportunity for Turkish physicians and scientists to gain prominence in reputable international literature.

Career advancement

As the pharmaceutical industry focuses more on clinical research in today's world, the demand for physician-scientists around the world is increasing. Nevertheless, running clinical research with the current infrastructure and capabilities is perceived to be challenging by healthcare professionals in Turkey. The common belief among experienced investigators is that only a small number of younger physicians is interested in clinical research due the challenges and disadvantages when compared to other career advancement opportunities.

However, with the increasing need for clinical practice to test today's pharmaceutical innovations and because of increasingly complex studies, it is likely that demand for competent physician-scientists for clinical research will increase. When the countries where clinical research is conducted are compared, a shift in favor of the markets emerging in this field is recognized. In this sense, there is an opportunity for Turkey to become an important player in this sector globally, and for Turkish physicians to adopt clinical research as an increasingly important career opportunity. This will also contribute to retaining the trained healthcare workforce in the country by providing them new career opportunities.

The conduct of clinical research requires meticulous work by healthcare professionals in all stages of a trial – from study setup to patient visits, data collection and reporting. Especially for younger professionals, this helps them gain experience in rigorous scientific discipline and practices.

In addition, being active in clinical research provides healthcare professionals, specifically physicians, with the opportunities to build international networks,

collaborating with healthcare professionals from different parts of the world. In Turkey, physicians who assume investigator roles in clinical trials gain the opportunity to publish more articles in scientific journals and participate as co-authors in several articles, thanks to their involvement in clinical research. At national and international congresses, they have a voice in the clinical research environment and take important steps for their career development. Many physicians who participate in clinical research from Turkey have had the opportunity to increase participation in prestigious congresses and globally recognized publications.

Better treatment decisions

The data obtained by physicians participating in clinical studies is based on evidence rather than on personal experience. Therefore, when a physician is involved in clinical research, this objective and evidence-based information will be available for use in planning the treatments of patients who will later consult with him or her. Participation in trials enables physicians to develop their competencies and disciplines of objective evaluation since they will be more familiar with rare and specific cases.

Participatory role in the evolution of medicine

Therapies are developed for people's health and, to apply these treatments on people, healthcare professionals must first know about them. Being involved in the studies of new therapies before they come onto the market and being involved in the development process of these therapies, contributes to the investigator's professional development. In addition to enabling physicians to contribute to the development of potential new treatment methods that are important for public health, clinical research increases the level of awareness for innovative treatments and keeps physicians abreast of the latest treatment advancements. It is possible that increasing the number of physicians participating in clinical research in Turkey will have a positive impact on public health. This is because, when new treatments come onto the market, physicians involved in prior clinical research will have already gained experience with such treatments, and thus will be able to prescribe them for patients successfully right away.

BENEFITS FOR HEALTHCARE INSTITUTIONS

Although it seems that the investigator who conducts clinical research has a central role during the research process, one of the most important factors determining the motivation of the investigator to conduct clinical research is the healthcare institution with which he or she is affiliated. Although physicians often choose to take part in these studies because of their professional network or scientific interests, the inadequacy of centers may prevent them from taking this step.

The contribution of clinical research to the institutions where it is conducted is considerable but still the most important issue raised by the physicians in charge is the insufficient support of their institutions. Even minimal contributions such as supporting physicians in examinations and treatments made during the clinical research process, providing space for archives where patient records are kept, and providing the clinical researcher with personnel and access to the patient increase the motivation of the investigator. This, in turn, benefits the healthcare institution as well. Based on the interviews conducted with both hospital management and physicians, the following measurable and unmeasurable contributions of clinical research to hospitals/centers have come into prominence:

- Additional value propositions
- Equipment and donation
- Higher patient engagement

Additional value propositions

Clinical research benefits the hospital personnel who are involved in the research activities. Being involved in clinical research designed in different ways provides different benefits for healthcare personnel. Infrastructure support generated through clinical research helps improve the working environment and conditions of the hospital staff also beyond the clinical research itself, which potentially leads to a greater dedication and loyalty.

When the number of trials conducted in an institution and that of physicians involved in clinical research increases, the need for site coordinators and nurses will increase. Basically, because of clinical research

facilitation, the hospital will become an institution with more science and research-oriented people.

Because of clinical research facilitation, the hospital will become an institution with more science and research-oriented people.

Equipment and donation

In cases where the equipment in the clinical research center does not meet the requirements for the clinical research to be conducted, the missing equipment is supplied through donations by the study sponsor. This can sometimes be a cabinet in the archive room, but it can also be technical equipment of significant value. Although some of the donations are temporary, i.e. for use throughout a specific clinical trial, others are permanent. These contributions become even more meaningful when the institution faces budgetary challenges. In addition, many technology and digitalization steps are integrated more quickly into clinical research centers. For example, "electronic patient logs" can be one of them. Without clinical research, some of these issues (e.g. digitalization) would likely not be considered as a priority and would not be maintained by the hospital.

Higher patient engagement

Patients participating in clinical research have more knowledge of their health status than the average person and develop a more comprehensive understanding of their disease. They develop a stronger relationship with their physicians, thus build greater confidence in the hospital/center where the research is conducted. This, in turn, results in increased patient retention for institutions. Increasing the prestige of and confidence in the hospital in the eyes of the patients also contributes to the hospital's reputation in the clinical research arena. Hospitals with more patients take advantage of the large and diversified patient pool and take a more favorable position for further clinical research.

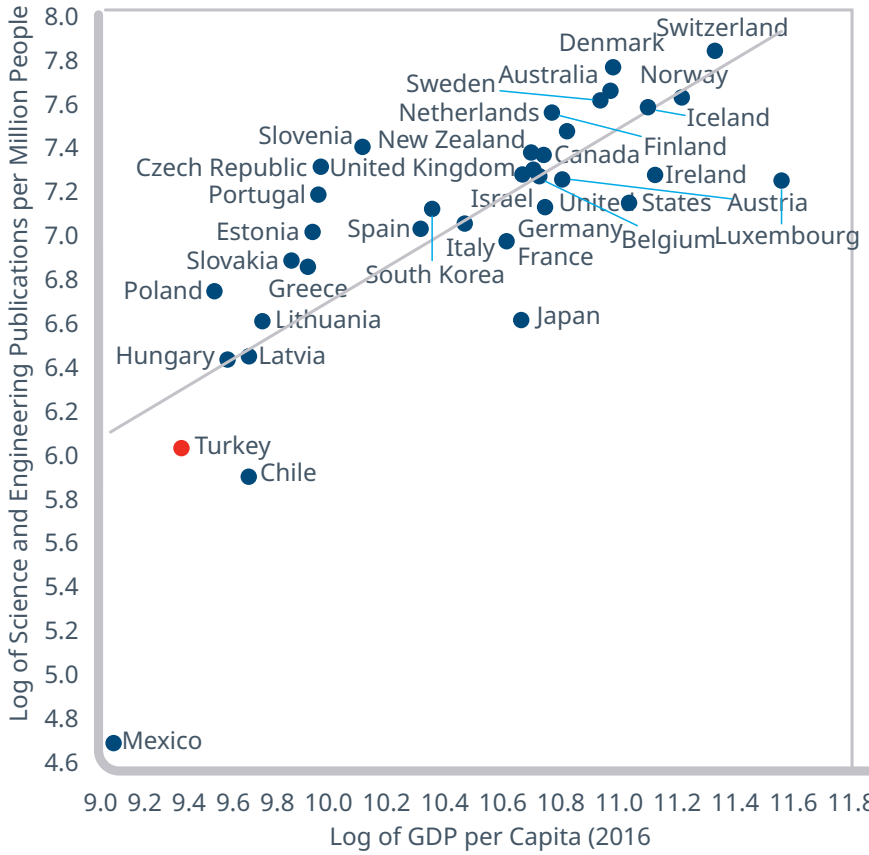
SCIENTIFIC INFRASTRUCTURE

Scientific output is strongly correlated with a country's level of development (in terms of GDP per capita) as is shown in Figure 36: countries with higher levels of GDP per capita also deliver more science and engineering publications per million people (in 2016). Although this is a correlation and not a multiple regression analysis, thus the causality between the two variables is not clear, a clear link between innovation and GDP per capita is established.

Clinical research has a major positive impact on building scientific infrastructure and improving know-how of basic research and the development of innovative healthcare products. Healthcare professionals involved in clinical research activities tend to be more open to scientific development as they become part of the development process of various innovative treatments. With an increasing number of innovative, breakthrough products entering the pipeline in recent years, pharmaceutical R&D, especially clinical research, has become more complicated. The growing use of more complex and innovative methodologies throughout the R&D process has increased the need to work with more competent and scientifically equipped healthcare professionals along the process.

In countries where pharmaceutical R&D is in its early stages of development, clinical research is mainly driven by multinational companies. In these countries, the majority of clinical research consists of later phase (i.e. Phase III) studies: large-scale studies which multinational pharmaceutical companies conduct in diverse geographies. Although mostly managed from abroad, these studies help these countries grow in clinical research focus and expertise. As they build more experience in clinical research over time, these countries develop infrastructure and capabilities which enable them to run also more specialized studies like Phase I research.

Figure 36: Scientific output by country in OECD



Source: National Foundation Survey for the number of science and engineering publications in 2016; United Nations Statistics data for population and GDP per capita (2016)

SUPPORT FOR INNOVATIVE START-UPS

Establishing a clinical research infrastructure which enables testing a drug candidate all the way from Phase I through Phase IV is the first step into developing pharmaceutical R&D capabilities in a country. Even if companies in a country are competent at developing new molecules, a country cannot succeed in bringing such molecules to market unless it has the capabilities to test them on humans in various phases following pre-clinical research. Therefore, if a country aims to take a leap in pharmaceutical innovation, the first step is to ensure the establishment of a solid clinical research infrastructure. [24]

From this perspective, clinical research plays a critical role in Turkey's scientific advancement in pharmaceuticals in line with Turkey's economic development and industrial policy objectives. Turkey has built clinical research experience in various therapeutic areas over the years. However, most of this experience is focused on later phase studies (see Figure 14) and carried out by large pharmaceutical multinational companies. While these studies are critical to maintain and increase, it is also important to build more capabilities, experience and competent workforce to run earlier phases of clinical research. With established clinical research capabilities, Turkey can receive higher return on its pharmaceutical R&D investments, increasing its competitiveness in the international arena through original molecules and increased high-value industry exports, reducing *inter alia* Turkey's trade deficit.

If a country aims to take a leap in pharmaceutical innovation, the first step is to ensure the establishment of a solid clinical research infrastructure.

Case Study: RS Research

RS Research is a pharmaceutical company developing next generation nanomedicines on innovative drug delivery platforms for targeted cancer therapy.

The venture capital-funded company was co-founded by Prof. Dr. Rana Sanyal, who is a professor at the Department of Chemistry at Boğaziçi University, and by the entrepreneur Sena Nomak in Istanbul in March 2015. The company's business model which was developed by Boğaziçi University's Center for Life Sciences and Technologies (LifeSci) allows the company to leverage the center's established infrastructure and the center to collect additional funds to support the sustainability of the platform.

Leveraging this infrastructure, RS Research developed a globally patented, novel nanomedicine platform for drug delivery. The drug candidates in the company's pipeline, targting a range of cancer types, combines the effectiveness of chemotherapy with the precision of tumor targeting.

The leading drug candidate in the company's pipeline received Investigational New Drug (IND) approval from TİTCK in 2017, becoming the first drug that has been developed nationally in Turkey from the very first stage of its R&D process and moving onto the clinical research stage.

Phase I clinical research of the drug candidate is planned to be conducted in Turkey, at the University of Health Sciences, Ankara Abdurrahman Yurtaslan Oncology Training and Research Hospital Phase I Center.

Sources: 1. https://rsresearch.net/media/; 2. Işıtır, T. The World's Healing Power. The Turkish Perspective, Issue 68, p.39-43. March 2016

Under the coordination of the Presidency of the Republic, Turkish government has included original drug development in its agenda and set action plans to achieve this goal. Among its 2023 targets is to implement a "start-up" model which will pave the way for developing a "national drug."

The purpose of this model is to create an innovation environment through a "start-up pool" which will bring together molecule inventors, investigators from the state, universities, techno-cities, small-scale companies, and big pharmaceutical companies. This "start-up pool" will also bring together national drug and medical device candidates with active ingredient plants, artificial intelligence and health technologies.

According to the medium-term road map built as part of this plan, domestic large pharmaceutical companies will buy candidate molecules at the very beginning of their development and try to convert them into "national drugs". Companies will carry out their R&D activities on their sites built in techno-cities which are established within universities.

In addition, conferences will be held each year to have a selection of projects presented and to bring inventors, start-up companies and manufacturers together. Inventors who develop molecules will have the opportunity to interact with potential buyers in person, sell them their molecules or build partnerships with them.

The 11th Development Plan published in August 2019, too, has addressed these initiatives, also emphasizing clinical research as an R&D activity. According to the plan, all clinical research conducted before the receipt of product license will be considered within the scope of R&D without any pre-condition (11th Development Plan, 366.1). The plan also declares that pharmaceutical product developers, especially researchers at universities, will be provided with information programs on incentives and intellectual property rights to accelerate the commercialization process. (11th Development Plan, 363.5)

So far, the Scientific and Technological Research Council of Turkey (TÜBİTAK) and TÜSEB have provided

support for R&D activities on innovative medicines of which the molecules are developed in Turkey or medical devices of which the protoypes are buuilt locally. With this purpose, specifically TÜSEB has issued calls for collaboration with inventors and begun evaluating the incoming project proposals.

At this point, besides the initiatives on government-supported drug discovery and pre-clinical activities, Turkey also needs to be ready to clinically test its national drug candidates fast and thoroughly once they pass the pre-clinical phase. For this to happen, the country's clinical research infrastructure, capacity and skills need to improve significantly.

6.3 **Patient impact**

Although it seems like the core of clinical research is developing drugs, the primary and sole purpose of all pre-clinical and clinical trials is to prove that the drug/therapy in development is beneficial to patient health, and is safe and effective. Patients are at the center of clinical research as well as of the entire pharmaceutical industry. Clinical research has many implications for the patients involved such as:

- Better health outcomes
- Easy access to innovative treatments
- Improved quality of the healthcare services provided
- Motivation of contributing to public health

We estimate that nearly 21,000 patients are currently enrolled in clinical research in Turkey.

We estimate that nearly 21,700 patients are currently enrolled in clinical research in Turkey, 13,100 of them being test group patients and 8,700 control group, corresponding to 0.5% of global patient enrollment. Figure 37 shows the estimated total patient enrollment from 2015 to 2019 in Turkey.

Figure 37: Patient enrollment in Turkey

Source: IQVIA Analysis

BETTER HEALTH OUTCOMES

Clinical research is critical to bringing a new medicine to market– without clinical trials, new drugs cannot have sufficient clinical evidence to prove their safety and efficacy on humans, thus to enable their approval by regulators.

Clinical research plays an important role also in improving patients' quality of life and, especially in cases of terminal diseases, their lifespan. Patients receive the best quality care and benefit from the most advanced, life-saving treatment methods when they participate in clinical research. Besides, it has been proven through studies that the health outcomes of the patients participating in clinical research are improved regardless of whether they are in a placebo or a test group.

In addition, in certain cases, clinical research is conducted not to bring a new product to market but to prove a different use of an existing active pharmaceutical ingredient, which changes the method or frequency of administering a drug, leading to better health outcomes.

EARLY ACCESS TO INNOVATIVE TREATMENTS

Clinical research allows patients to benefit from alternative and innovative therapies that can only be available to those participating in clinical trials. Next to the advantage of receiving an innovative and, in many cases, unique therapy at no cost, patients who receive an investigational drug in a clinical trial become the ones who access it first, well before regular patients, who can start using it only after its regulatory approval and manufacturing. In some cases, this can even have life-saving effects if patients have life-threatening diseases or conditions which are cured or put into remission thanks to the investigational drug.

Clinical research allows patients to benefit from alternative and innovative therapies that can only be available to those participating in clinical trials.

In addition, patients participating in clinical research are followed with the utmost attention – they are under close supervision, and regularly evaluated for a large number of criteria established in the study protocol. Due to protocol requirements, these patients often need to go through extensive tests and examinations which are arranged by clinical research personnel, minimizing the time that is spent on these operations. In addition, patients are insured as part of the clinical research. They are provided with close medical attention by clinical research personnel and it is possible for them to access the research personnel at any time.

IMPROVED QUALITY OF THE HEALTHCARE SERVICES PROVIDED

Delivering on the healthcare needs of its citizens challenges the government in keeping the healthcare system financially sustainable over the long term. Clinical research supports the delivery of high-quality healthcare services not only for patients who participate in clinical research, but also for other patients by generating additional income for the state and healthcare institutions and by reducing the financial burden on the social security system, thus by generating additional financial resources to be spent on sustaining the quality of the healthcare system.

MOTIVATION OF CONTRIBUTING TO PUBLIC HEALTH

Patients who agree to be enrolled in clinical research have a very useful role and responsibility on behalf of the medical profession. By being a part of the process, patients become one of the most important contributors to the immediate introduction of the drug under development because of the clinical research in which they have participated. Drugs must have gone through clinical research to get approval and get on the market, and this process would not be possible if patients did not agree to participate in these trials. For this reason, regardless of whether the product subject to clinical research is innovative or generic/biosimilar, participating patients have the rightful pride of contributing to public health. Even in the clinical research of products such as biosimilars and generics, they can indirectly contribute to reducing the budget for drug expenditure, thus actually to saving budget for innovative research and development activities.

Case Study: Real Patient Success Story

A patient born in 2014 was diagnosed with Haemophilia A when he was 7 months-old, after his parents consulted with a pediatric hematology out-patient due to bruises on his body. He was first given protective treatment to be applied twice a week but, in time, his symptoms reappeared in the form of bleeding.

Drugs used to stop the bleeding triggered the development of an inhibitor which caused other complications that were treated with other licensed drugs. However, to avoid the risk of bleeding, the patient had to live an isolated life. Unlike his peers, he could not play in the playground or go to school, and had to wear a helmet, elbow pads and kneepads at all times. At home, in order to avoid accidents and protect the patient from hard and sharp objects, his family had to cover all the surfaces in his living area with sponges.

When the pediatric hematology clinic treating the patient was selected for a clinical study on a new subcutaneous biological agent developed for Hemophilia A indication, the patient and his condition were found to be in accordance with the protocol and he was included in the study with the consent and request of his family. As a severe Haemophilia A patient, before he was enrolled to the study, he had gone through 8 bleedings in the last 24 weeks with two of them resulting in hospitalization.

At he beginning of the study, he was administered the same dose of subcutaneous medication twice a week for a total of 4 weeks. After 4 weeks, the dose was reduced and he continued with a low dose for 8 weeks. Since there was no bleeding during this period, he kept receiving the same dose and is still using it. In this process, the family was given training on how to administer the drug at home and they began applying it at home moving forward.

The patient received 117 doses of medication for the first 27 months of the study, and the number of hemorrhages that occurred was three, all of which were ceased without the need for any bleeding medication.

Since the first application, the patient's quality of life has improved and he can now continue his daily life without the need for helmets, elbow pads or kneepads. He can play with his peers in the playground and participate in sports activities without any worries. Now, the patient can even get dental filling without the fear of bleeding, nor any additional medicine.

If the patient had not had the opportunity to participate in this clinical research, he would not have achieved the quality of life he has today, since the investigational drug he uses is not yet registered and marketed in Turkey.

Hemophilia A, also called factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by missing or defective factor VIII, a clotting protein.

People with hemophilia A often, bleed longer than other people. Bleeds can occur internally, into joints and muscles, or externally, from minor cuts, dental procedures or trauma. How frequently a person bleeds and the severity of those bleeds depends on how much FVIII is in the plasma, the straw-colored fluid portion of blood.

Source: Prof. Dr. Bülent Antmen, Cukurova University Medical Faculty

7. TURKEY'S COUNTRY ATTRACTIVENESS IN CLINICAL RESEARCH

The last decade has been of critical importance in the field of clinical research for Turkey. A series of initiatives, including new laws and regulations, have been launched since 2008 to remove the road blocks and improve the clinical research environment. With a solid regulatory infrastructure at European Union standards, Turkey has become a stronger candidate as a site for multinational clinical studies.

The last decade has been of critical importance in the field of clinical research for Turkey.

Currently, Turkey is ranked 26th among all countries in terms of the total number of ongoing industry-sponsored clinical studies. However, as explained in Section 4.2, when the number of studies relative to the size of GDP and to that of the pharmaceutical market are considered, Turkey falls far behind in the rankings – 62nd in the former and 40th in the latter. Several outstanding barriers play an important role to explain this gap. As they remain, they discourage the selection of Turkey as a site for multinational studies and clinical research in the country.

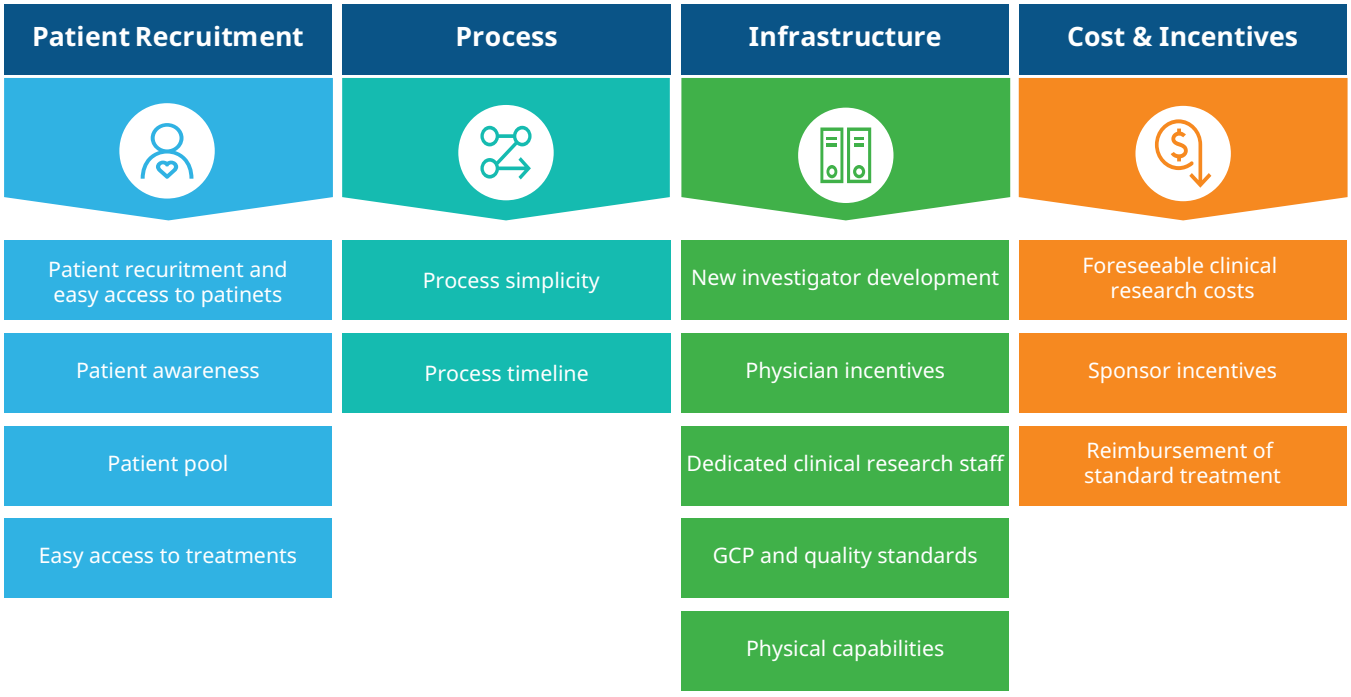
7.1 Factors determining country attractiveness for clinical research

To identify the factors impacting a country's attractiveness for multinational clinical research, we conducted in-depth interviews with key opinion leaders as well as clinical research and pharmaceutical industry experts in Turkey and abroad and dedicated a section in the IQVIA survey to the drivers of country selection in multinational industry-sponsored clinical research.

14 factors overall impact a country's attractiveness for multinational clinical research.

Although they can be further detailed, these factors can be assessed in 14 key themes, as shown in Figure 38, grouped under four overarching themes – patient recruitment, process, infrastructure, and cost and incentives. These 14 factors overall impact a country's attractiveness for multinational clinical research through fast and flawless study set-up and execution.

Figure 38: Factors determining country attractiveness for clinical research



Source: In-depth interviews; IQVIA Survey; IQVIA Analysis

Patient Recruitment consists of four factors, all impacting the speed and efficiency of recruitment in the country. Patient recruitment and easy access to patients is about how easily potential subjects can be searched for and accessed through resources in place such as databases and patient referral systems. Patient awareness plays an important role communicating with and recruiting the potential subjects who have been accessed. The size and characteristics of the available patient pool have the potential to impact the ease of patient access, thus the speed of recruitment. Finally, easy access to treatments tends to have an inverse relationship with the ease of recruitment as patients who have more limited access to treatments tend to have greater motivation to participate in clinical research.

Submission Process has two components. Process simplicity concerns the efficiency of the overall documentation, submission and review processes for regulatory authorities, ethics committees and other authorities. Process timeline, on the other hand, is about the overall time spent for these processes.

Infrastructure consists of five factors concerning the investigators, clinical research staff, quality standards and physical infrastructure. New investigator development is about having an expanding network of physicians who are interested and experienced in clinical research. Physician incentives increase investigators' motivation in building a clinical research career. Dedicated clinical research staff play an important role in the successful implementation of research operations. GCP and quality standards are critical to not only high-quality trial execution but also patient safety. Physical capabilities are clinical research site capabilities including building infrastructure and research equipment.

The Cost & Incentives pillar has three dimensions. Foreseeable clinical research costs are critical to sponsoring companies as they need to have a clear understanding of the estimated research budget in each country for a thorough planning of the overall trial budget. Sponsor incentives provide a motivation for start-ups and other sponsors for selecting a specific country for multinational clinical research. The reimbursement of standard treatment costs of control group subjects by a country's social security system can be a determining factor in country selection for multinational clinical research, specifically in case of selection between countries with similar conditions otherwise.

Evaluating Turkey against the above factors that determine a country's attractiveness for clinical research is one of the core components of this study. In order to do so, we used a multi-pronged approach of literature review, a survey, and in-depth interviews.

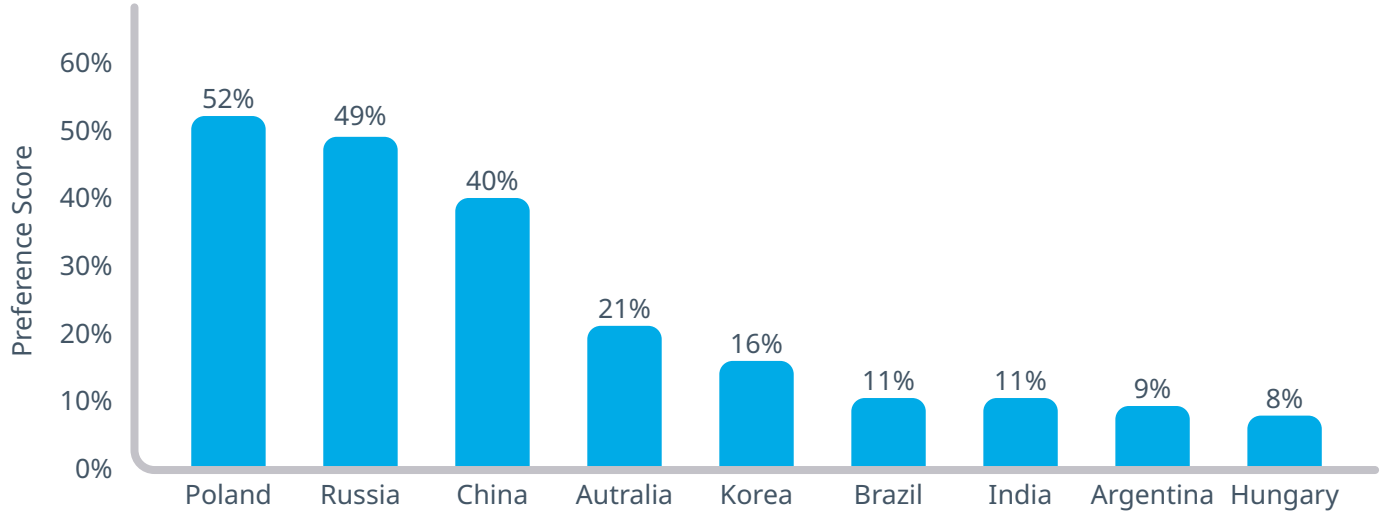
These methods corroborate each other and allow us – when taken jointly – to clarify Turkey's performance on each of these factors. This in turn allows us to identify where the main areas for improving the clinical research climate in Turkey are, helping us to make appropriate policy recommendations for the Turkish government, Turkish regulators, industry, and other stakeholders.

IQVIA SURVEY ON COMPANY CHOICES FOR CLINICAL RESEARCH DESTINATIONS

In the IQVIA survey, which is part of our multi-pronged approach, and which was conducted in June-July 2019 with the participation of AIFD member companies who have clinical research operations in Turkey, a section was dedicated to the drivers of country selection in multinational industry-sponsored clinical research. The survey was completed by 17 AIFD member companies.

When respondents were asked about which countries outside the US, Canada, Japan and EU5 countries were preferred the most by their companies in multinational clinical research, the top-3 countries mentioned were Poland, Russia and China. Turkey was not mentioned in the top-3 preferred countries outside of the US, Canada, Japan and EU5 by any respondent company. These findings are in line with the earlier statistics indicating Turkey occupies the 22nd place in number of clinical trials globally, while the country ranks lower when scaled to population size, GDP, pharmaceutical market size.

Figure 39: Top-3 preferred countries outside of the US, Canada, Japan and EU5

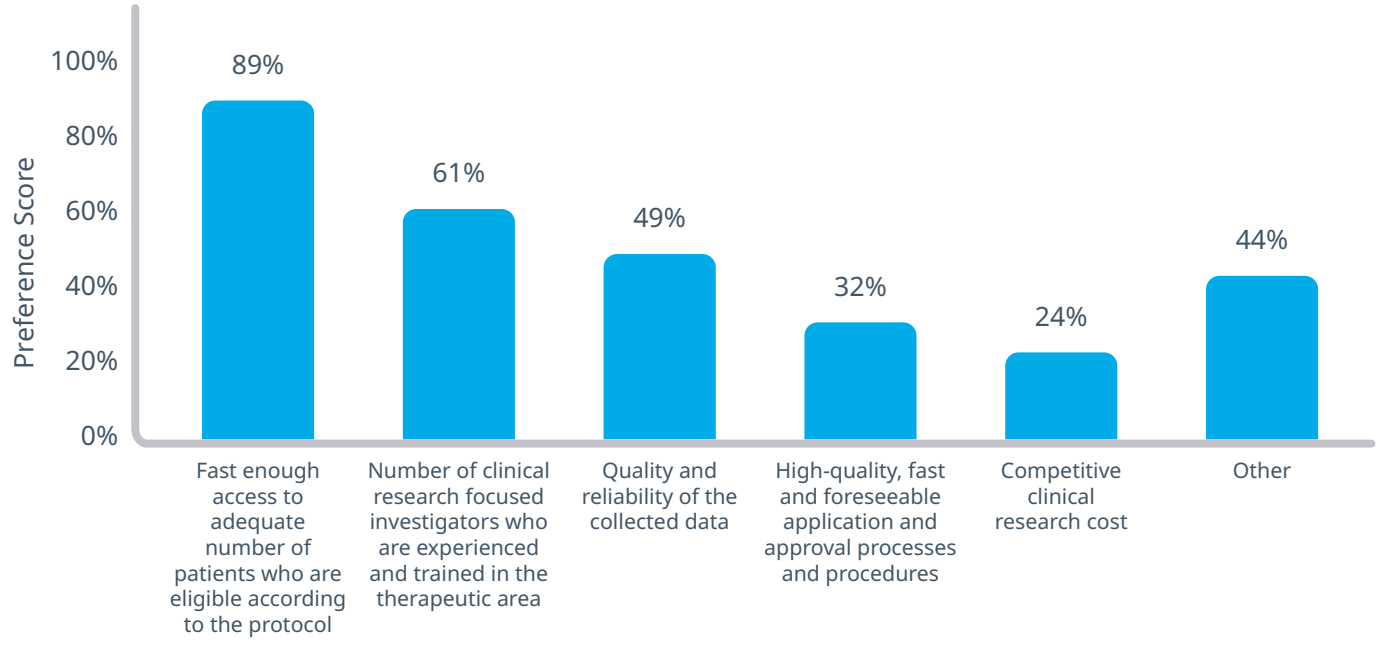


Source: IQVIA Survey

When asked about the top-5 criteria considered while making the country selection for clinical research, the following factors presented in Figure 40 emerged as the most important ones:

- Fast enough access to adequate number of patients who are eligible according to the protocol;
- Number of clinical research-focused investigators who are experienced and trained in the related therapeutic area;
- Quality and reliability of the collected data;
- High-quality, fast and foreseeable submission and approval processes and procedures; and
- Competitive clinical research cost.

Figure 40: Top-5 criteria companies consider for country selection

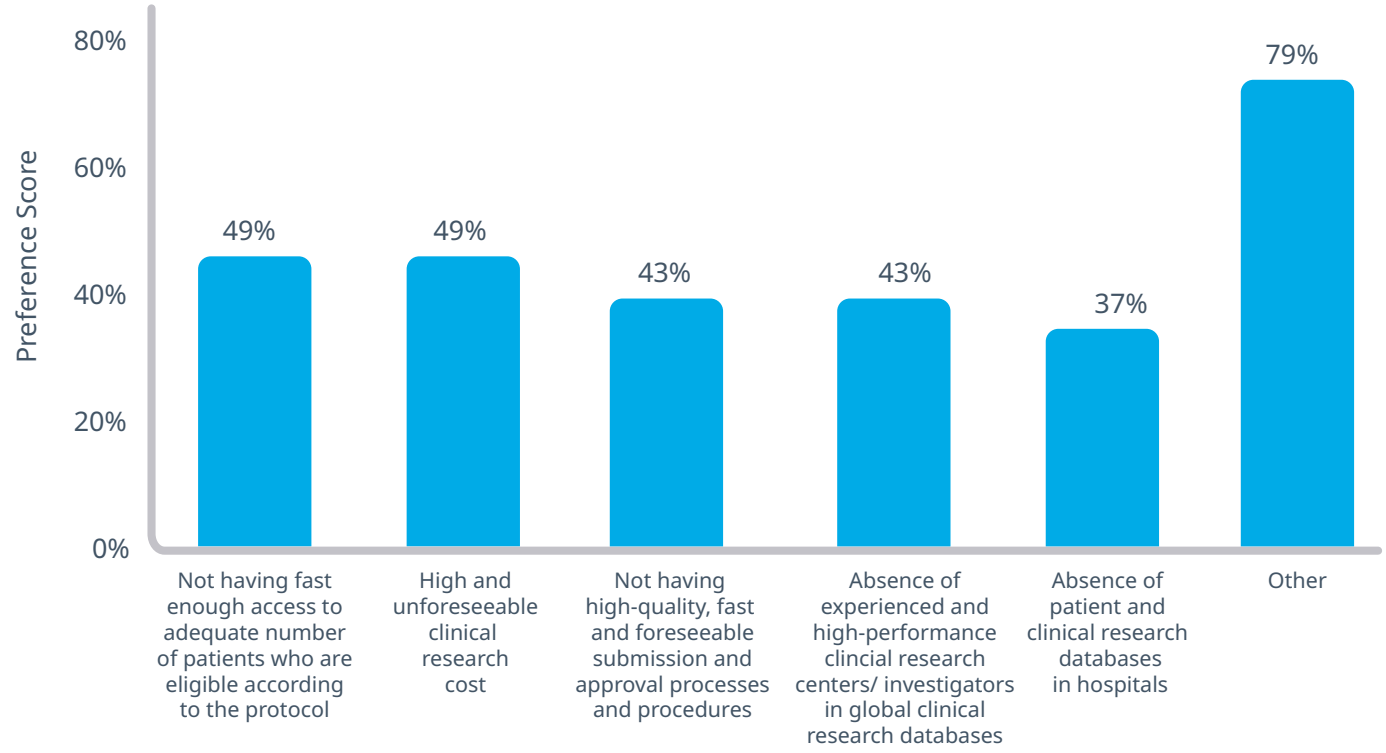


Source: IQVIA Survey
Other includes; presence of experienced and high-performance clinical research centers/ investigators in global clinical research databases, presence of technically equipped clinical research centers, enough size of qualified workforce, and quality of the healthcare service provided to patients.

According to the survey results, the following factors were important for not choosing Turkey as a destination for clinical research (in ranked order):

- Not having fast enough access to enough patients who are eligible according to the protocol;
- High and unforeseeable clinical research costs;
- Not having high-quality, fast and foreseeable submission processes and procedures;
- The absence of experienced and high-performance clinical research centers / investigators in global clinical research databases; and
- Absence of patient and clinical research databases in hospitals.

Figure 41: Top-5 reasons why Turkey is not/less preferred in global Clinical Research

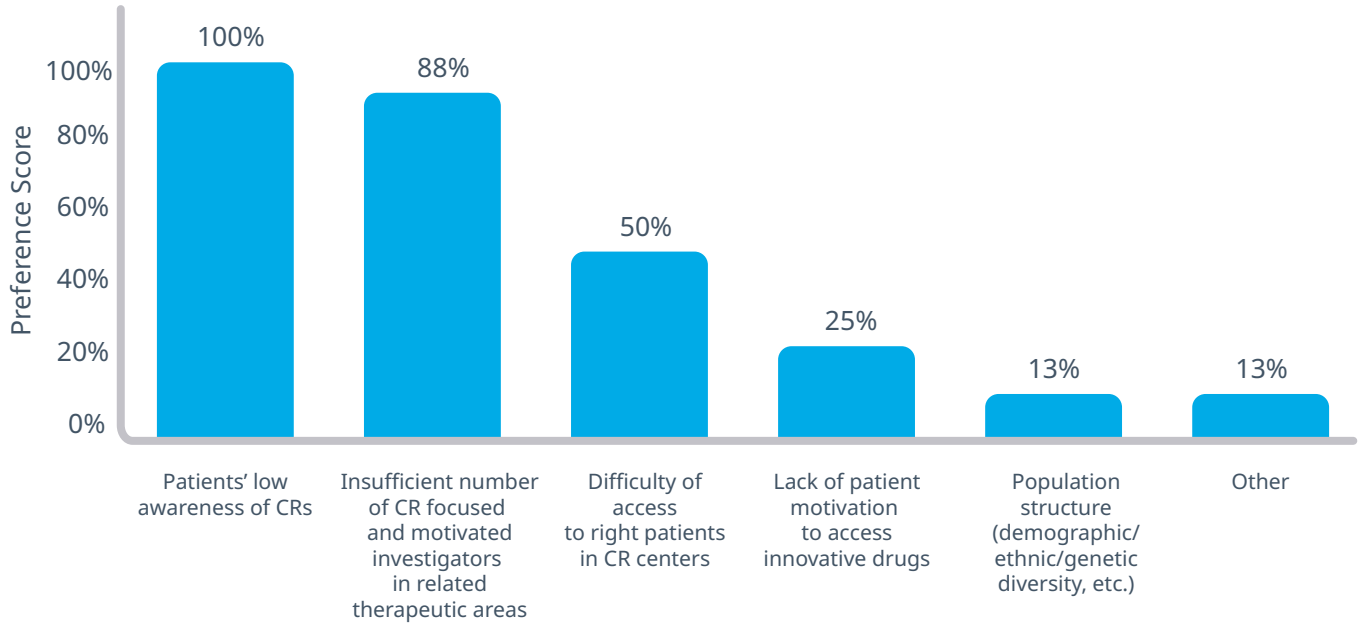


Source: IQVIA Survey

Other includes; insufficient number of technically equipped CR centers, lack of quality and reliability of the collected data, insufficient size of qualified workforce, quality of the healthcare service provided to patients, and covering the standard treatments and examinations not within the scope of the study from the working budgets.

It is important to note that not having sufficiently fast access to enough patients has been raised as the main issue in Turkey, despite the country's large and diverse population and its healthcare system which allows patients to access secondary and tertiary healthcare institutions directly. Top reasons underlying this matter, which came out of the survey, are perceived as patients' low awareness of clinical research, insufficient number of clinical research-focused and motivated investigators in related therapeutic areas, and difficulty of access to right patients in clinical research centers. While clinical research is well-established in a limited community of healthcare institutions and physicians, it is evident that there is an opportunity to use Turkey's large physician pool to access the right patients more effectively.

Figure 42: Factors determining slower access to patients in Turkey



Source: IQVIA Survey

7.2 Turkey's attractiveness for clinical research

Turkey's performance in each of the country attractiveness factors presented in Figure 38 was evaluated based on IQVIA survey and in-depth findings as well as literature review, through an analysis of the country's position relative to other countries in its region and the opportunity to take action in the related attractiveness factor to improve its competitive position versus other countries in multinational clinical research. Figure 43 summarizes the outcome of this analysis.

Figure 43: Evaluation of Turkey's performance in terms of country attractiveness factors

	COUNTRY ATTRACTIVENESS FACTOR	TURKEY IS IN A FAVORABLE POSITION RELATIVE TO COMPETITOR COUNTRIES	TOTAL
PR1	Patient recruitment and easy access to patients		
PR2	Patient awareness		
PR3	Patient pool		
PR4	Easy access to treatments		
PO1	Process simplicity		
PO2	Process timeline		
IN1	New investigator development		
IN2	Physician incentives		
IN3	Dedicated clinical research staff		
IN4	GCP and quality standards		
IN5	Physical capabilities		
CI1	Foreseeable clinical research costs		
CI2	Sponsor incentives		
CI3	Reimbursement of standard treatment costs		

Source: IQVIA Survey

PR1. PATIENT RECRUITMENT AND EASY ACCESS TO PATIENTS

In Turkey, clinical research is carried out mainly in public and private university hospitals and training and research hospitals. When private institutions are set aside, there are 116 university hospitals and 112 training and research hospitals around the country.

The total number of annual patient visits to these institutions was nearly 175 million in 2018. Training and research hospitals were responsible for 72.0% of these visits. Although their per institution annual patient visit load is almost 3 times as that of university hospitals, training and research hospitals fall behind university hospitals in terms of the number of clinical trials conducted. This is mainly due to the fact that physicians in training and research hospitals can dedicate more limited time to clinical research when compared to their counterparts in university hospitals due to their heavy patient load and that patients with special conditions often choose to visit university hospitals to receive treatment.

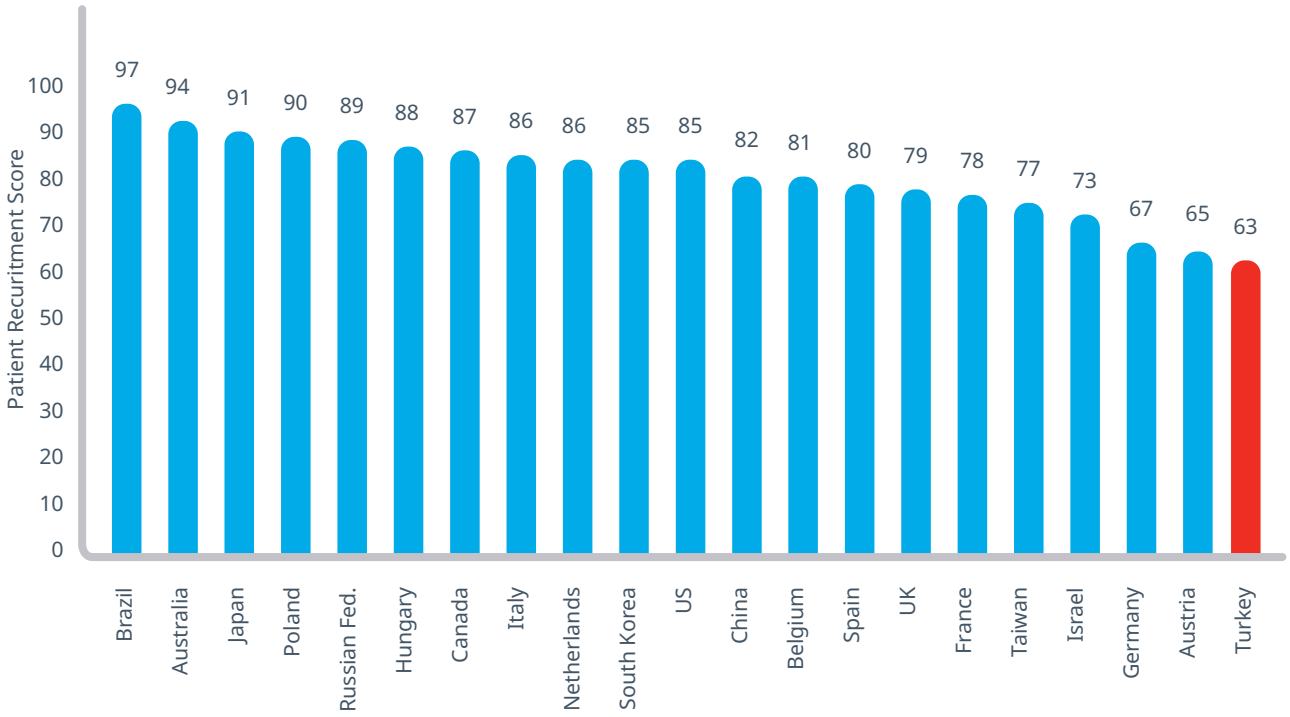
Turkish patients have easy and nation-wide access to healthcare services.

With a population of 83 million people and a Universal Health Insurance Scheme with 99.8% coverage, Turkish patients have easy and nation-wide access to healthcare services. However, lower patient loads in university hospitals and likely low referral rates between institutions working on clinical research stand in the way of reaching the full patient potential for clinical research.

Patient Recruitment Performance Score calculated for nearly 860 ongoing or recently completed clinical studies in top 20 countries and Turkey shows the countries' rate of success in achieving their patient

enrollment targets in the latest 18 months as of September 2019. Based on the performance scores, Turkey remains behind the top countries in terms of patient recruitment relative to expectations, even in those with lower out-of-pocket healthcare spending such as France and Netherlands. In nearly all these countries, health insurance schemes cover almost all the population, although coverage structure and the quality of healthcare services may vary.

Figure 44: Patient recruitment performance score in Top-20 countries and Turkey



Source: IQVIA Analysis; IQVIA Pharma Pricing & Reimbursement Country Guides (September 2018-June 2019); OECD Health Data 2018

One of the top clinical research countries with similar universal health insurance scheme coverage and out-of-pocket healthcare spending as in Turkey but a higher Patient Recruitment Performance Score is the United Kingdom. The country's success in patient recruitment is driven by multiple factors such as comprehensive central and hospital-based patient databases and experienced site personnel.

In the UK, the National Institute for Health Research's (NIHR) Clinical Research Network (CRN), established within National Health Services (NHS) and primarily funded by the Department of Health and Social Care, enables high-quality research by providing additional funding as well as resources such as clinical research staff, training, and information systems. This UK system enables the employment of dedicated staff in clinical research sites, which reduces turnover and increases research experience and know-how at site level. Based on experience and lessons learned from previous research, site staff work more efficiently in reaching out to patients eligible for the specific clinical studies. [41]

This UK system enables the employment of dedicated staff in clinical research sites, which reduces turnover and increases research experience and know-how at site level.

In cases where there is a need to search for patients in a wider patient network, CRN and hospital databases are available. CRN has a comprehensive central database including detailed patient and research data, which it leverages to support researchers, CROs and

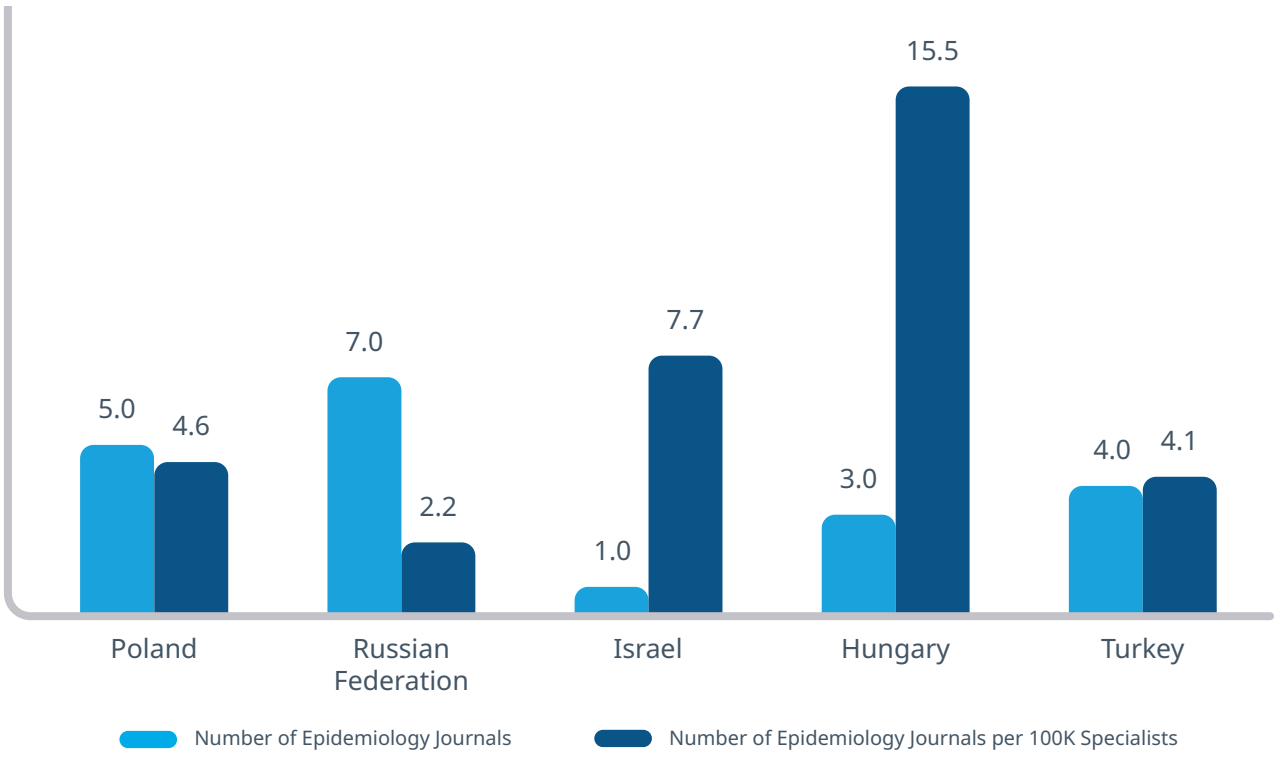
sponsor companies in the process of patient access and feasibility. Beside the CRN's central database, hospitals keep detailed historical patient records which enable them to access the right patients fast and efficiently.

The lack of large-scale local epidemiological studies in a variety of acute and chronic diseases remains as a barrier for Turkey.

When evaluating the patient access potential in a candidate country, multinational companies running clinical research also consider the total size of the patient population in that country, with the target disease or condition. For this purpose, availability of accurate epidemiological data plays an important role in estimating patient potential in the country and selecting it as a candidate for multinational clinical research. The lack of large-scale local epidemiological studies in a variety of acute and chronic diseases remains as a barrier for Turkey, as multinational studies are taken as a reference for incidence and prevalence rates. This potentially leads to an underestimation of the patient potential for certain hereditary diseases and genetic disorders which are likely to be seen at higher frequency in Turkey. [31]

The International Epidemiological Association commissioned a paper series in 2013, evaluating the population health and status of epidemiology in the WHO European Region. The article on Region I – which covers Turkey together with 20 other countries in Eastern Europe, Western Asia and South-Central Asia – analyzes epidemiological research and publications in each country. The article shows that Turkey remains behind the top clinical research countries in its region in terms of the number of epidemiology publications in total, and especially per specialist physician. [32]

Figure 45: Number of epidemiology journals



Source: Mati Rahu, Vasiliy V Vlassov, Frank Pega, Tatiana Andreeva, Pinar Ay, Aleksei Baburin, Vladimír Bencko, Péter Csépe, Anita Gębska-Kuczerowska, Martina Ondrušová, Joseph Ribak, Population health and status of epidemiology: WHO European Region I, International Journal of Epidemiology, Volume 42, Issue 3, June 2013, Pages 870–885, https://doi.org/10.1093/ije/dyt054

At this point, the lack of a well-established patient database network stands out as another barrier against easy access of target patients. In Turkey, the Ministry of Health and Social Security Institution have various databases which keep records of patient data – the Ministry of Health's e-Nabız database which keeps records of all citizens' health information and medical background, the SSI's e-Prescription database which keeps records of all Universal Health Insurance-related transactions in healthcare institutions and pharmacies, and the National Record System which tracks medical records in a limited number of therapy areas selected by SSI. However, neither of these databases is open to use for clinical research purposes. On the academic institution side, hospitals do not have consistent database systems which can be effectively be used to get easy access to patients.

PR2. Patient awareness

Accessing eligible patients is the first step into including them in clinical research, while informing them about the study and convincing them to participate is the second.

40% of surveyed adults did not understand clinical trials.

When patient awareness of clinical research and its benefits to the patient and to public health is high, patients tend to be more likely to participate in research. According to an article published in the Journal of Clinical Oncology, the results of a survey conducted in the United States showed that 40% of surveyed adults did not understand clinical trials. The most common concerns raised about clinical trials were patients' perception that clinical research participants were "treated like guinea pigs," the effectiveness or side effects of tested drugs, uncertainty of research organizations, receiving a placebo vs treatment, the delay of treatment approval or availability, additional costs or insurance issues, and the time commitment to participate. After being exposed to information and being educated about these concerns, however, 32% of surveyed adults had a more favorable perception of clinical trials and indicated that they would be willing to participate in one if asked to do so. [33]

Patients' prejudice against clinical studies stands out as a barrier against enrollment also in Turkey where there is a common perception that clinical research treats patients as guinea pigs and that confidential patient information collected through research may be used for other purposes. Especially given the fact that most of industry-sponsored clinical research is led by multinational pharmaceutical companies, there is a tendency to believe that large multinational companies run their tests-on-human in developing and underdeveloped countries and then market their products and earn money in developed countries.

Beyond the fact that there have been virtually no large-scale initiatives to date to build patient awareness, mainstream media have played a role in building a negative public perception through misinformation on clinical research.

Although patients overcome their prejudices, and even search for studies themselves, for example in cases of clinical research on innovative therapies for rare or terminal diseases or conditions, there is no specific source where they can access detailed information on ongoing or upcoming research for which they may be eligible.

In South Korea, patients gather information on clinical research through patient associations and the KoNECT website. Korea National Enterprise for Clinical Trials (KoNECT) is a non-profit organization funded by the Korean Ministry of Health and Welfare, which aims to advance and promote the country's clinical research capabilities. Beside the organization's various initiatives, its website serves as a meeting point and source of information for all key stakeholders. [42]

Patients with special conditions or rare diseases in South Korea receive information on clinical research through patient associations on a regular basis.

Patients with special conditions or rare diseases in South Korea receive information on clinical research through patient associations on a regular basis. Associations share the information of new clinical studies on the related disease or condition, which are

posted on the KoNECT website. Patients who hear about new studies through the associations can visit the KoNECT website for more details. On this website, they can access basic information on all ongoing and upcoming studies, including patient eligibility criteria, recruitment status, research sites, and the primary investigator's contact information.

Another means to raise patient awareness on new clinical studies is advertising them on mainstream media or on billboards, as practiced in the United Kingdom. By ethical standards, these advertisements only serve the purpose of informing patients on the existence of specific clinical studies and refrain from promoting participation. In the UK, such advertisements are used effectively in raising patient awareness of new clinical research.

PR3. Patient pool

With its large and diverse population and a high prevalence of several chronic and rare diseases, Turkey has a large patient pool which could be eligible for clinical trials. Therefore, this country attractiveness factor was not identified as an improvement opportunity for Turkey.

With its large and diverse population and a high prevalence of several chronic and rare diseases, Turkey has a large patient pool which could be eligible for clinical trials.

PR4. Easy access to treatment

99.8% coverage of the universal healthcare system in Turkey makes it easier for Turkish patients to access treatment. While this could potentially reduce patient motivation to participate in clinical research, it is a strength of the Turkish healthcare system. Thus, this country attractiveness factor would not be considered as an improvement area for Turkey.

PC1. Process simplicity

Over the last decade, TİTCK has made major improvements to the submission and review processes, simplifying the process and shortening timelines. While submissions to TİTCK are simple and straightforward, the process on the ethics committee side of the clinical research process still has room for improvement.

There are a total of 120 clinical research ethics committees set up in healthcare institutions around Turkey. Although the basic requirements for the committees and the standards of the application process are pre-defined by TİTCK, there are complexities in their application, review and approval processes.

Two major issues stand out as complicating the ethics committee application process: documentation and submission. Beyond the application forms standardized by TİTCK, many committees continue to request additional forms and documentation, all with their own formats and specifications. And while applications to TİTCK are submitted online, applications to ethics committees are still submitted in hardcopy documents and forms. Further standardization in the submission phase is needed to increase efficiency of the overall process.

Based on TİTCK requirements, each ethics committee consists of 7 to 15 members with various areas of expertise. While the majority of the members are supposed to be healthcare professionals who are specialist physicians or hold a PhD degree, the committees are also required to include a member with a law degree and one who is not a healthcare professional. Specialists should preferably include those who have previous experience in multinational clinical research as an investigator, a pharmacologist, and a biostatistician, next to a member who works in the biomedical field and, if possible, an expert in medical ethics or deontology. Regardless of their areas of expertise, all members should receive or have received training on good clinical practice and basics of clinical research.

Committees typically gather once or twice a month to evaluate the applications, and members typically do not receive any income or payment for their participation.

With so many ethics committees around the country, inconsistencies and complications in ethics committee reviews arise. The main reason for this is the varying levels of clinical research experience as well as knowledge and understanding of ethics and study protocols both across and within committees.

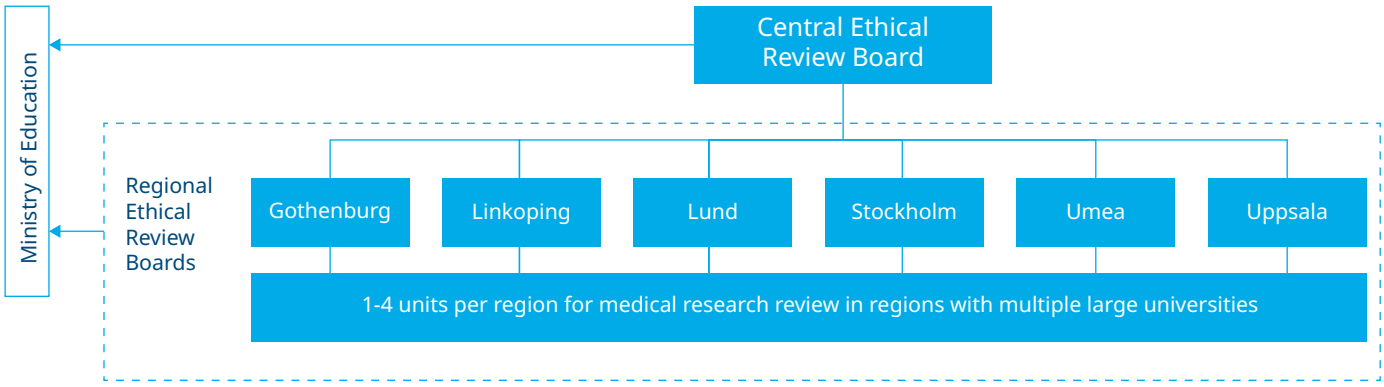
In healthcare institutions that are active and experienced in clinical research, ethics committees have a thorough understanding of clinical research and protocol design, good clinical practices and related regulations.

In healthcare institutions that are active and experienced in clinical research, ethics committees have a thorough understanding of clinical research and protocol design, good clinical practices and related regulations. Reviews by such committees are usually quicker and protocols approved by them often receive either only a few comments or direct approval by TİTCK, which ensures a fast review and approval process overall. However, committees with members who are relatively new to clinical research and to protocol review, often tend to spend more time on review or reject protocols which are in fact in line with ethical standards, especially in cases of complex study designs. Protocols approved by such committees also tend to receive more amendment requests from TİTCK, complicating the process and adding to the review and approval timelines. While, in Turkey, the timeline for ethics committee review and approval is 60 days on average, the timeline may go down to as short as 15 days in case of review by experienced committees, and up to 4 to 5 months for some reviews by committees with less experience.

To increase consistency and efficiency in ethics committee reviews and approvals, there is need to bring all active ethics committees and committee members to the highest level of knowledge of clinical research, good clinical practices, protocol design and ethics, to track their performance (e.g. review timelines, amendment requests, etc.) in detail, and to build an ethics committee network which would enable effective communication between committees.

In Sweden, the ethical review setup involves the Swedish Ethical Review authority, divided into separate regional research ethics committees. There is also one central ethics committee, and both are responsible to the Ministry of Education. All of the six large universities in the country have a regional research ethics committee and, in regions where a number of large universities exist, these regional committees may involve one to four different units for medical research review. Although mostly located in university premises, the regional committees have their own administration and economy. And while they may get administrative support from the university, their internal work is completely independent from the university. [34,35]

Figure 46: Swedish ethical review authority



Source: Government Offices of Sweden, https://www.government.se/government-agencies/ethical-review-boards-etikprovningsnamnderna/; European Network of Research Ethics Committees (EUREC), http://www.eurecnet.org/information/sweden.html

The central ethics committee, on the other hand, oversees controversial issues delivered by regional committees and acts as an appeal body for complaints about regional committee decisions. Regional committees consist of 15 members each, 10 of them being representatives with scientific backgrounds and the rest from the public. Committee members are provided education by the Swedish Research Council, and regional committees arrange annual educational activities for their own members.

Consistency between regional committees in terms of education and experience is ensured through a number of regular networking activities between committees, including chairmen meetings, seminars for chairmen and scientific secretaries, all-members seminars arranged by the Swedish Research Council, and discussion meetings with committee representatives regarding issues related to laws and regulations.

The submission process for ethical review in Sweden has been standardized and streamlined through standard forms and a digital platform.

The submission process for ethical review in Sweden has been standardized and streamlined through standard forms and a digital platform called Prisma, which will soon be replaced by a more effective digital system. The close network and consistent quality of regional ethics committees and the uniformed and efficient submission process help with meeting the standard 60-day approval timelines across the country.

PC2. Process timeline

In recent years, TTCK has taken important steps to make considerable improvements in regulatory submission and review timelines. Therefore, our analysis concluded that there was very limited room for immediate improvement in this regard.

IN1. New investigator development

It is estimated that only around 10% of specialist physicians in university and training and research hospitals in Turkey are involved in clinical research as investigators and only between 10% and 15% of them as primary investigators. Limiting clinical research in the country to a small network of experienced investigators is one of the key reasons for this low level of involvement. [6]

Study setup and patient recruitment timelines play a critical role in site selection for new research, where CROs and sponsor companies often prefer to work with sites and investigators known for fast setup and recruitment. Especially when selecting a primary investigator, companies tend to contact directly those with whom they have collaborated in the past. The result is that the primary investigator circle is relatively closed and does not expand to increase the number of investigators.

In fact, although it helps to speed up study timelines in the short term, working with a small network of investigators is potentially a disadvantage for CROs and sponsor companies in the long term, because it limits their capabilities to access a wider patient potential in future studies. Inside the Turkish system, not having enough visibility for the process of investigator selection is a barrier for younger physicians who have worked in clinical research and wish to advance in this field. The longer-term impact is that it reduces their motivation to pursue a career in clinical research.

Institutions, especially university hospitals, in Middle Eastern and North African (MENA) countries have handled the same problem by establishing an investigator database where they list physicians on staff who have received GCP training and are interested in taking part in clinical research as investigators. The database is regularly updated and made accessible to all CRO and sponsor companies for primary investigator selection. Once new physicians with GCP training get experience in a clinical study as a sub-investigator, CROs reach out to them to offer them the role of primary investigator in new clinical research. And once such physicians become primary investigators, the opportunity is born for new sub-investigators on their teams. This circle allows CROs to continuously connect with new investigators and grow their investigator network, and thus grow the overall clinical research capacity.

Physicians tend to perceive clinical research only as a "side job" that provides prestige, wider network and some additional income.

IN2. Physician incentives

The heavy patient load per healthcare professional is one of the issues challenging the Turkish healthcare system. This heavy patient load puts pressure on physicians to focus their efforts on their primary role of providing healthcare services. Given the fact that also their main income comes from such healthcare services, physicians tend to perceive clinical research only as a "side job" that provides prestige, wider network and some additional income.

Investigators or other healthcare staff are not allowed to receive direct payments from CROs or sponsoring companies for their enrollment in clinical research. Investigator payments in clinical research are made to healthcare institutions who distribute the amount between the hospital's revolving fund and the investigator. The investigator then pays income tax on these earnings and often chooses to share part of the remaining net income he/she receives among healthcare staff involved in the specific study. However, there is not a standard ratio across institutions for the distribution of investigator payments – as explained before – between the revolving fund and the investigator. Similarly, it is up to the investigator to share this income with other staff or not.

The portion of the payments which goes to the revolving fund is not spent only on clinical research needs and staff. Thus, the amount that clinical research staff receive from this income is almost negligible.

Considering the challenges of clinical research and the fact that physicians are only to a very limited extent rewarded in career advancement for their clinical research activities, many physicians prefer generating additional income by running more patient examinations instead of running clinical research.

In different countries around the world, physicians' incentives to participate in clinical research varies. While in some countries, investigators receive virtually no monetary incentive, in some others they receive almost the entire investigator fee themselves. Figure 47 shows the diverse approaches in various countries.

Figure 47: Investigator incentives by country

COUNTRY	INVESTIGATOR DOES NOT RECEIVE INCENTIVES OF MATERIAL VALUE, INCLUDING MONETARY INCENTIVES	INVESTIGATOR RECEIVES MONETARY INCENTIVE		
		INSTITUTION RECEIVES MAJORITY	INVESTIGATOR RECEIVES MAJORITY	INVESTIGATOR RECEIVES 100%
United States*				●
United Kingdom	●			
Spain		●		
Germany				
Hospitals	●			
Private research clinics*				●
Italy	●			
South Korea			●	
Australia			●	
Poland				
Public institutions			●	
Private institutions**		●	●	●
Russian Federation				
Separate contracts with institution and investigator			●	
Single contract with institution		●		

* Investigators receive investigator fees and pay other expenses including research staff out of this amount. ** Distribution of the monetary incentive depends on the proprietary structure of the clinical research site in terms of who the owner is and how taxation has been set up.
Source: IQVIA Analysis

IN3. Dedicated clinical research staff

Employment of clinical research staff stands out as one of the key hurdles against growing clinical research in Turkey. This is due to the heavy patient load of the healthcare staff and to the laws and regulations in place.

As detailed in Section 4.5, physicians and nurses in Turkey have a considerably heavy patient load. And by laws and regulations, the primary role of physicians, nurses and other healthcare staff employed in public institutions is providing healthcare services. Supporting clinical research, on the other hand, can only be an additional role. Thus, in the current situation, it is virtually impossible in public healthcare institutions to employ dedicated healthcare staff for clinical research.

Common practice to meet part of the staff need in the country is by contracting site coordinators who undertake all the operational workload. Their employment on site, however, is complicated. First, site coordinators cannot be employed directly by healthcare institutions and, due to their contracted

employee status, they should in fact not be given access to confidential patient data, nor be allowed to stay on site after work hours or without being escorted by an institution employee. In fact, healthcare institutions can hire site coordinators as their own employees, which would solve part of the problems with contracted site coordinators. However, headcount is a critical barrier in these institutions, which would limit the number of hires, and thus timely and effective execution of clinical research. Another perceived risk relates to the additional departmental duties, and thus workload, that site coordinators might be assigned to if they were to be hired directly by the institutions.

In countries like Italy and the United Kingdom, dedicated clinical research staff including study nurses and site coordinators are employed and assigned to specific studies directly by the institution.

Although operational work is undertaken by site coordinators, tasks involving patient intervention can only be executed by healthcare staff. Given their heavy patient load, healthcare staff can only dedicate limited time to clinical research.

Varied and heavy workload of the healthcare staff and the high turnover rate among site coordinators due to their difficult work conditions prevent experience from building among research staff on site, impacting the speed and quality of the studies. As a consequence, scarce human resources often lead to the underutilization of clinical research capacity at sites.

In countries like Italy and the United Kingdom, dedicated clinical research staff including study nurses and site coordinators are employed and assigned to specific studies directly by the institution. The study nurse system is relatively new in Italy and more actively used in clinical research on advanced therapy areas such as Oncology and Neurology. In the UK, on the other hand, the system has a longer history and is well-established. The employment of focused study nurses and the overall low turnover rate of the research staff enable building experience and know-how in clinical research sites, increasing speed, quality and efficiency in study setup and execution.

IN4. GCP and quality standards

With initiatives taken in recent years, clinical research regulations in Turkey have matched European Union standards in terms of GCP and quality. In addition, Turkey is often in a competitive position relative to developed clinical research markets in terms of patient compliance with treatment, lost-to-follow-up rates and quality of data.

IN5. Physical capabilities

While many healthcare institutions in Turkey have very limited capabilities in terms of physical space for clinical research centers, they also have limited opportunity to create more space within their current structures, little room to improve in this regard. City hospitals which are being established around the country pose an opportunity to provide more space for proper clinical research centers.

Our analysis shows that, in universities and training and research hospitals, efforts to improve physical capabilities would provide lower incremental return relative to other improvement opportunities.

CI1. Foreseeable clinical research cost

High and unforeseeable clinical research costs are one of the top two reasons why Turkey is not preferred by companies as a country for multinational clinical research, according to our survey.

Unforeseeable costs make it difficult to set budget estimates for clinical trials upfront, complicating the financial planning of trials by sponsors. To ensure a thorough financial planning throughout the study cycle, sponsoring companies prefer conducting research in countries where total trial budgets can be estimated more accurately.

The key activity which ensures foreseeable clinical research cost is a thorough contract negotiation with institutions in the study startup phase. Ideally, this negotiation should specify in detail all the cost items and terms of billing which may arise throughout the study protocol. Any details that are not included in the contract may later cause conflicts between the institution and the CRO or sponsor company running the study, leading to unforeseeable added costs and even delays in study timelines. Therefore, a thorough negotiation of the contract helps with a fast and flawless execution of the research.

In Turkey, due to the heavy workload and inadequate clinical research exposure of the personnel in healthcare institutions, contract negotiation comes across as a critical problem in study setup and execution. Contracts are often negotiated by hospital management personnel who are not sufficiently familiar with clinical research or by investigators themselves who are not experts in finance and accounting procedures. Therefore, contract terms are often not fully negotiated nor detailed as thoroughly as they should, leading to billing and payment problems and delays throughout the execution phase. In certain cases, this even leads to legal conflicts between the CRO and the institution or contractual conflicts between the CRO and sponsoring company.

In terms of contract negotiation timelines in different institutions, university hospitals initiate the process right away while training and research hospitals wait for TİTCK's protocol approval before initiating negotiations. In comparison to university hospitals, this lengthens the start-up timeline for training and research hospitals by 2 to 3 months.

In the United Kingdom, contract negotiation is strictly regulated and constitutes one of the key steps for the initiation of a clinical study. In each clinical research site, there is knowledgeable personnel who have specific experience in contract negotiation for clinical research, which ensure a thorough negotiation process. Although this lengthens setup timelines, once the contract terms are agreed upon, the study runs flawlessly, with no unforeseeable costs which arise throughout the study.

In Denmark, Trial Nation works as a network which serves as an interface between the industry and researchers, and manages coordination with all clinically relevant units and departments in the country.

In Denmark, Trial Nation, which is a formal national collaboration between the five Danish regions aiming to attract more clinical research to the country, works as a network which serves as an interface between the industry and researchers, and manages coordination with all clinically relevant units and departments in the country. One of the services that the organization offers is a legal network which aims to ensure that contracts are negotiated smoothly and efficiently with the regions acting as a united negotiation party in relation to industry. It is only necessary for sponsor companies or CROs to contact one of the legal consultants who are in close contact with hospitals and clinical research sites, and this one legal consultant then negotiates across all five Danish healthcare regions. Sponsor companies or CROs may negotiate their own templates or use the Danish Regions' standard template. When they use the legal network for contract negotiation, they only enter one negotiation and avoid having to negotiate with every single site in the country, sidestep administrative burdens, and speed up contract assessment timelines. On behalf of the company or CRO, the legal consultant coordinates all the negotiations.

While the negotiation of company- or CRO-specific

templates takes longer than that of the Danish Regions' standard template (10 days to approval), use of templates still shortens negotiation timelines and, once they are agreed upon, specific templates receive legal approval faster than in the case of single contract negotiations. The use of such a legal network helps to ensure more thorough contract negotiations while keeping the timelines as short as possible.

Another driver of unforeseeable clinical research cost in Turkey is the reimbursement of certain cost items by the Social Security Institution.

Currently, common perception is that all the medical costs of the subjects – whether associated with clinical research or not – should be covered by the sponsoring company. However, sponsoring companies are in fact responsible only for the medical costs associated with clinical research as detailed in the study protocol. All other medical costs of the patient – i.e. all the medical costs that are unrelated to clinical research – are supposed to be reimbursed by the Social Security Institution.

Beside this misconception, coding in the financial systems of healthcare institutions is another issue that stands out in the billing process. While some institutions have solid financial system infrastructures that allow for detailed coding of clinical trial activities and cost items, others are unable to set up accurate coding systems. This results in mistakes in the billing process. For example, cost items which are supposed to be reimbursed by the SSI may be billed to the CRO or the sponsoring company.

Mistakes in billing are not driven only by initial coding mistakes in financial systems. Because of the abovementioned misconception, the institution's personnel do not know exactly which financial codes to use for specific cost items or tend to bill all the medical costs of a subject regardless of whether such costs are associated with clinical research or not. Dealing with the correction of wrong billing takes time and effort, and often results in added, unforeseeable costs paid by CROs and sponsor companies.

CI2. Sponsor incentives

Competitive clinical research costs are among the key criteria that companies consider in country selection and, as explained above, high and unforeseeable costs remain as barriers against growth of clinical research in Turkey.

Next to a fast study setup and patient recruitment, financial incentives, too, are important to maintain lower clinical research costs.

Next to a fast study setup and patient recruitment, financial incentives, too, are important to maintain lower clinical research costs. These incentives are typically provided in the form of tax exemptions or subsidies.

In Turkey, such incentives are mainly granted under the umbrella of R&D classification for certain types of clinical research. Clinical trials considered within the scope of R&D become exempt from income and import taxes. However, the terms of which trials should be considered within the scope of R&D remain unclear since there is inconsistency between different definitions used in regulations by different government offices, namely the Ministry of Industry and Technology and the Council of Higher Education. This leads to ambiguity as to whether the R&D classification in clinical research only applies when two phases of clinical research are conducted in Turkey or not. Because it is not possible to tell upfront whether one or more stages of clinical research will be conducted in Turkey (as a next stage of clinical research depends on positive results

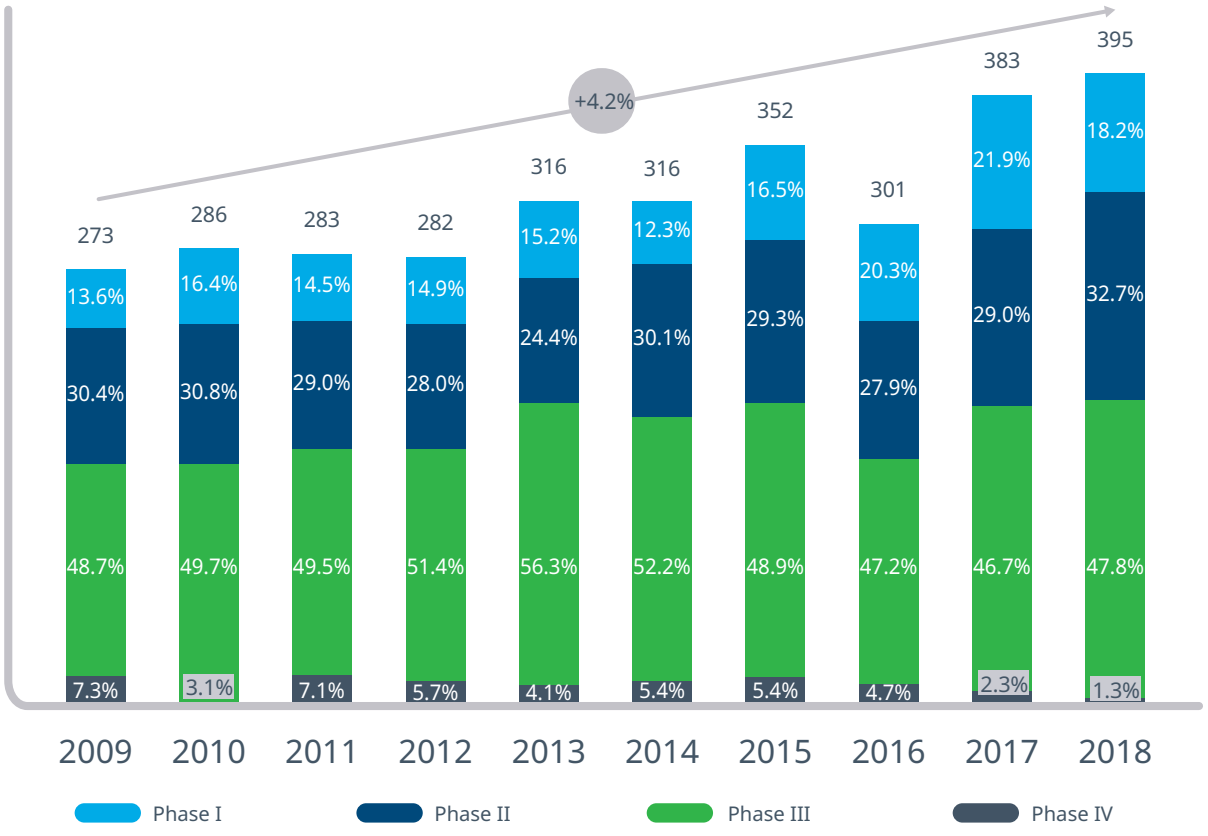
from the stage before), this ambiguity has a deterring effect on starting clinical research in Turkey.

In studies which have been defined within the scope of R&D, the sponsor benefits from waived import taxes on study drugs that are imported from abroad. A more meaningful financial benefit is for the investigator and other healthcare staff: in clinical studies with R&D status, a greater portion of the investigator fee is passed on to the study investigator, and – on top of that – this fee is exempt from income tax. Investigators start paying income tax on their income from R&D status clinical research only after they pass an annual income threshold.

Beyond the limited scope of R&D definition for clinical research and inconsistencies in its coverage and implementation, R&D status incentives for clinical research appear to have more impact on the investigator end and less on the sponsor. Therefore, the effect of attracting more clinical research, especially from budget-constrained, smaller sponsor companies, remains limited. To increase country attractiveness in multinational clinical research, Turkey could avail to offering a wider variety of financial incentives benefiting sponsor companies.

In Asia Pacific, Australia has become successful using financial incentives for sponsor companies to attract multinational clinical research. With the purpose of becoming a clinical research hub in its region, the country has launched initiatives not only to increase efficiency and reduce costs in the startup process, but also to provide greater financial benefits in the form of tax breaks for sponsoring companies who complete all phases of a clinical research – i.e. Phases I, II and III – in Australia. These tax breaks provide a 43.5% refundable R&D tax benefit for eligible companies with annual revenues below $20 million Australian dollars, and a 38.5% non-refundable R&D tax offset for those with annual revenues above $20 million Australian dollars. The efforts have specifically focused on attracting earlier phase clinical research from smaller biotechnology companies for whom cost effectiveness is a critical driver. The introduced tax breaks have led to considerable growth in earlier phase research in recent years, specifically from Chinese biotechnology startups, as is shown in Figure 48.

Figure 48: New registrations of industry-sponsored clinical studies in Australia



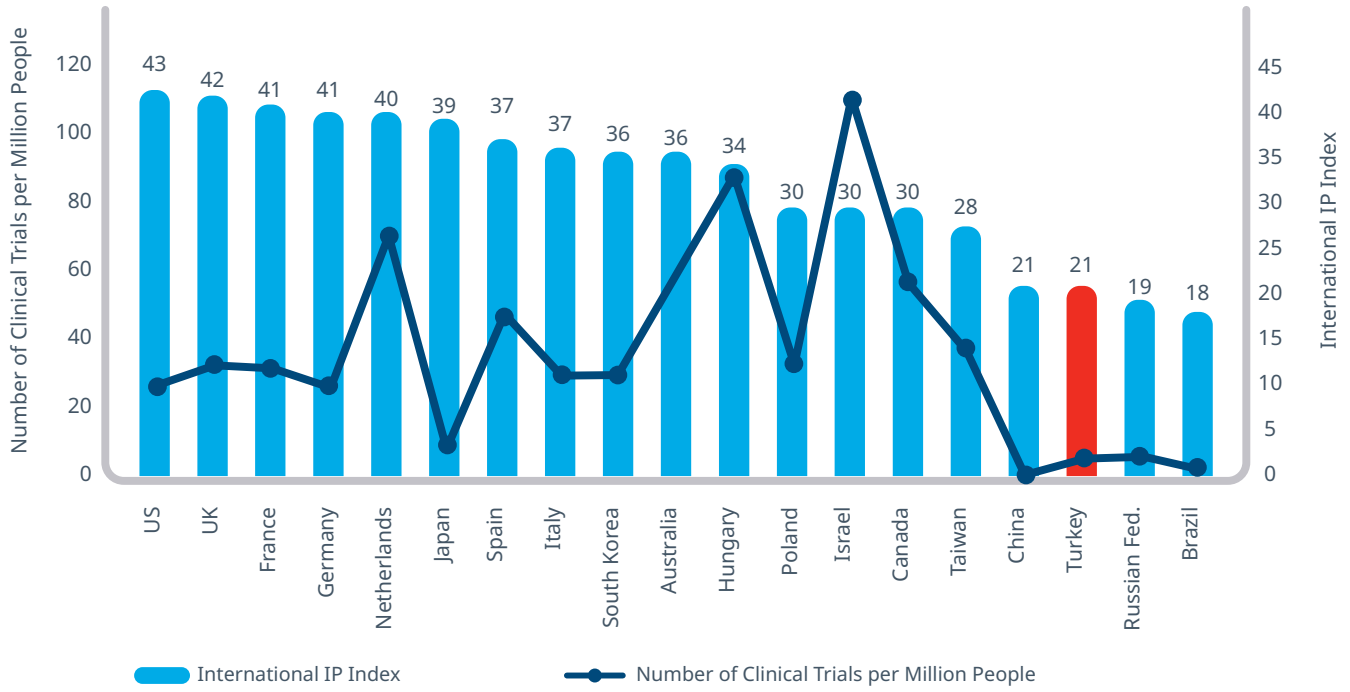
Source: www.clinicaltrials.gov

Beyond financial incentives, other types of incentives also play an important role in sponsors' country selection for multinational clinical research, especially for those countries that are clinical research leaders. One of such incentives is the assurance that intellectual property (IP) rights, in particular regulatory data protection (RDP), are clearly defined in laws and regulations, protected by regulatory authorities, and in line with global best practice. A solid incentives framework is an important element for a positive

A solid incentives framework is an important element for a positive climate for innovation, encouraging investment.

climate for innovation, encouraging investment. Figure 49 shows that the number of clinical trials per person in a country tends to be higher in countries with stronger IP infrastructure. [47]

Figure 49: Quality of IP protection versus number of clinical trials



Sources: 1. www.clinicaltrials.gov; 2. United Nations Statistics; 3. Global Innovation Policy Center. U.S. Chamber International IP Index. February 2019.

Considering other non-financial incentives, one that is provided to the sponsoring companies to attract more clinical research to Turkey concerns the focused review of submissions for marketing authorization and TİTCK's regulatory efficiency.

CI3. Reimbursement of standard treatment costs

Clinical trial protocols often detail which treatment costs should be covered by the sponsoring company and which ones by other insurance schemes. The reimbursement of the standard treatment costs of a control group in a clinical trial varies by country, as presented in Figure 50. Therefore, it is often difficult to set a standard in terms of how these costs should be reimbursed.

Figure 50: Reimbursement practices by country

COUNTRY	INVESTIGATOR DOES NOT RECEIVE INCENTIVES OF MATERIAL VALUE, INCLUDING MONETARY INCENTIVES	OUT-OF-POCKET EXPENDITURE AS A PERCENT OF CURRENT HEALTH EXPENDITURE	REIMBURSEMENT OF CONTROL GROUP STANDARD TREATMENT COSTS		REIMBURSEMENT OF TREATMENT COSTS WHICH ARE NOT RELATED TO CLINICAL TRIAL OR NOT SPECIFIED IN STUDY PROTOCOL		
			PUBLIC SOCIAL SECURITY OR COMPULSORY HEALTH INSURANCE	STUDY SPONSOR	PUBLIC SOCIAL SECURITY OR COMPULSORY HEALTH INSURANCE	STUDY SPONSOR	OTHER
Turkey	Public	16%		●	●	●	
Australia	Public	19%	●		●		
Bulgaria	Public	48%	●	●	●		
Denmark	Public	14%		●			●
France	Public	10%		●	●		
Germany	Compulsory	12%	●		●		
Poland	Public	23%	●	●		●	
Romania	Public	21%	●	●	●		●
Russia	Compulsory[13]	40%	●	●	●		
South Africa	Public & Private	8%	●	●	●		●
South Korea	Public	33%		●	●		
Spain	Public	24%		●	●		
Sweden	Public	15%	●		●	●	●
Ukraine	Public	54%		●	●		
United Kingdom	Public	15%	●		●		●

Source: IQVIA Analysis; The World Bank.

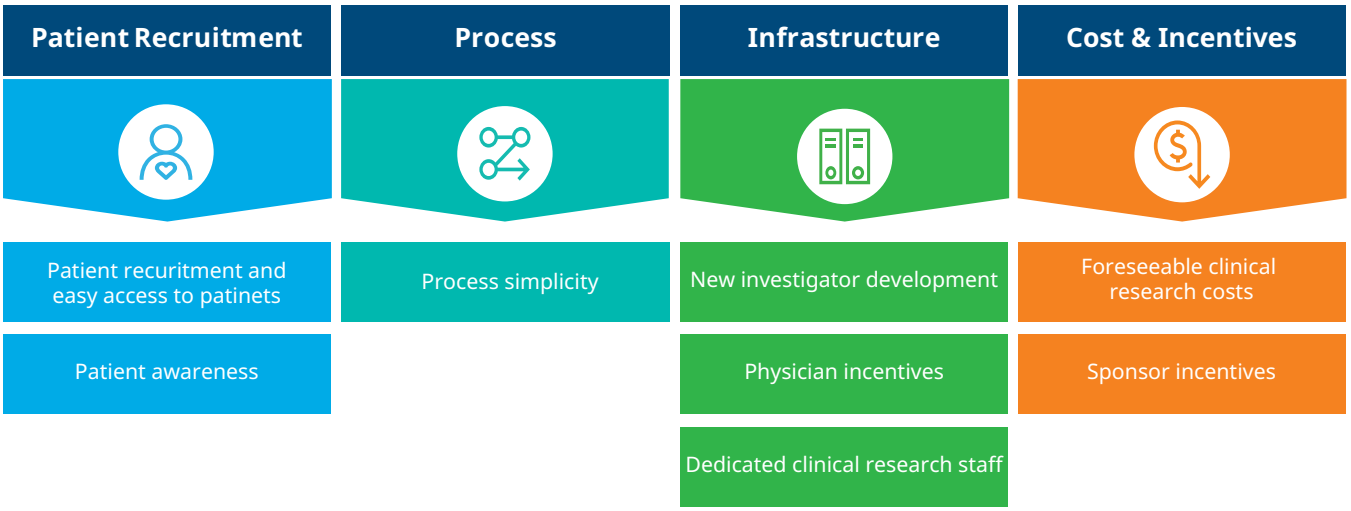
[13] 80% of the public are covered by the public social security system, 20% by private insurance.

In Turkey, while the reimbursement of standard treatment costs by the Social Security Institution can be an area of opportunity to provide the country a greater competitive edge in multinational clinical research, the analysis shows that a more immediate opportunity lies in being in line with majority of other countries in terms of the reimbursement treatment costs which are not related to the clinical trial or which are not specified in the study protocol. This has been discussed in greater detail as part of the evaluation of foreseeable clinical research costs (CI1).

7.3 Summary

Based on this detailed analysis, overall, eight major improvement opportunities which have the potential to support the growth of clinical research in Turkey were identified.

Figure 51: Opportunity areas for Turkey



Source: In-depth interviews; IQVIA Survey; IQVIA Analysis . 80% of the public are covered by the public social Security system, 20% by private insurance.

8. POTENTIAL BENEFITS OF A FOCUSED CLINICAL RESEARCH STRATEGY

The Turkish government has made a clear commitment to increase Turkey's competitiveness in the international arena and innovation has been elevated as an important means to achieve this goal. For the pharmaceutical industry, developing original molecules in Turkey has been set as the ultimate innovation objective. Pharmaceutical R&D is a lengthy and costly process where clinical research plays a critical role: it makes up more than half of the costs of the overall R&D process and investment and a new molecule cannot receive marketing approval without solid clinical evidence.

For a country to have a prominent place in clinical research rankings, it needs to have a well-established infrastructure and deliver on the basic requirements that impact country attractiveness in this field.

The complex nature of clinical research involves multiple stakeholders throughout a complicated process, requiring a strong infrastructure for a successful implementation. For a country to have a prominent place in clinical research rankings, it needs to have a well-established infrastructure and deliver on the basic requirements that impact country attractiveness in this field.

Globally, Turkey is 17th in terms of pharmaceutical market size but ranks 26th in terms of the total number of clinical trials. This report has defined fourteen factors that impact a country's attractiveness in clinical research from a patient recruitment, process, infrastructure and cost and incentives perspective, and identified eight of them as areas where improvements could still be made to stimulate clinical research. In Chapter 9, we will propose a set of clear and concrete actions which would help the stakeholders and policymakers deliver on this clinical research opportunity area.

8.1 Growth scenarios

Embarking upon a focused clinical research strategy – in addition to the policy plans Turkey already has put forward in its strategic plans – is going to require a clear vision, resources, and cooperation between multiple stakeholders who are interdependent to make it work. It is for this reason, and for the reason of indicating whether this would be a strategy that could significantly and realistically help Turkey in its economic development, healthcare system, scientific and patient objectives, we develop three possible future scenarios, from a baseline case to a most positive case, of how – following such a clinical research strategy – clinical research could develop in Turkey, with ensuing effects:

Embarking upon a focused clinical research strategy is going to require a clear vision, resources, and cooperation between multiple stakeholders who are interdependent to make it work.

- **Scenario 1:** Base case scenario: the total number of clinical trials grows at the same average growth rate as has been the case over the past five years;
- **Scenario 2:** Pharmaceutical market capacity scenario: bringing Turkey's clinical research activities up to the level of its pharmaceutical market capacity in 8 years;
- **Scenario 3:** Global Top-10 scenario: making Turkey a Top-10 global player in clinical research in 8 years.

It is assumed that it would take approximately 3 years to fully implement structural changes in the clinical research system in Turkey. From that point on, given that a clinical trial in Turkey lasts 3 to 5 years on average, the total number of trials would be expected to reach the target level in 5 years. In total, it would

take nearly 8 years from the beginning of the implementation of policy recommendations detailed in Chapter 9 to reach scenario targets. It is expected that growth will level off after 8 years and annual growth rate of the number of clinical trials will merge to global average over time unless new or recurring actions are taken in later years.

For each of the abovementioned scenarios, we show the potential impact on the number of clinical trials conducted in Turkey, total patient numbers enrolled in clinical research, the total value of clinical research in Turkey, the size of the clinical research investments in Turkey, and the reduced financial burden for the SSI.[14]

Scenario 1: Base case scenario (no change)
If no further actions were taken regarding clinical research, Turkey would be expected to continue to grow at its current 5-year average pace of 1.2%. Given that only limited actions have been taken regarding clinical research in Turkey since 2013, this average growth rate would be a proper estimate for a no-action growth scenario.

Scenario 2: Pharmaceutical market capacity scenario (modest clinical research growth scenario)
Turkey ranks 26th in terms of total number of clinical trials in the world at the moment. But Turkey's ranking when taking into account the size of Turkey's pharmaceutical market is only 40th place. This ranking differential suggests that Turkey is a lower-value added (low-price) producer of medicines. If Turkey were to bring its clinical research capabilities to the same level as its pharmaceutical market capacity by implementing the suggested policy recommendations, Turkey's clinical research should more than double in number. Currently, the ratio of total investment in clinical research in Turkey to the size of the Turkish pharmaceutical market is 4.2%, while the ratio of global clinical research investments to the global pharmaceutical market size is 9.2%. So, for Turkey to grow from 4.2% to 9.2% (an increase of 119%) means also a more than doubling of the amount of clinical research conducted in the country. This would make the country the regional leader in terms of the total number of clinical trials in the Middle East.

Scenario 3: Global Top-10 scenario (ambitious clinical research growth scenario)
Turkey ranks 22nd in added clinical research in 2018 and 26th in terms of total number of clinical trials in the world at the moment, with Turkey's ranking corrected for pharmaceutical market size falling behind to 40th place globally.

Turkey would have the potential of becoming a Top-10 global player in clinical research.

If Turkey properly implemented the core clinical research recommendations, but in addition also focused on and incorporated global clinical research trends (e.g. digitalization, predictive analytics, AI) as explained in Chapter 5, and improved its incentives framework for the R&D driven pharmaceutical industry, Turkey would have the potential of becoming a Top-10 global player in clinical research. Figure 52 shows, in terms of new clinical study registrations, active clinical studies, active studies by population, active studies by GDP and active studies by pharmaceutical market size what increase in clinical research would be needed in Turkey to achieve global top-10 status (based on Figure 11 in Section 4.2):

- For Turkey to take 10th place in new clinical trial study registrations of 2018, the country should go up by a factor 2.9 to reach the level of Italy (currently 10th place) of 352.
- For Turkey to take 10th place in active clinical studies by 2022 (assuming an average of 3-4 years for a clinical study), reaching the level of Australia (currently 10th place with 1,478) the total number of active clinical studies should increase 4.3 times.
- For Turkey to take 10th place in active studies by population, the total number of clinical trials should increase by a factor 10.6 to reach the level of Puerto Rico (currently in 10th place).
- For Turkey to take 10th place in active studies by GDP, clinical research should increase by a factor 5.4 to reach Bosnia (currently in 10th place) with 3.8 clinical studies per billion USD GDP.

[14] Inflation has been taken into account when calculating value growth. See Appendix 2 for inflation and exchange rate assumptions.

- Finally, for Turkey to take 10th place in active studies by pharma market size, clinical research should increase by a factor of 2.7 to reach Ukraine (currently in 10th place) with 215 clinical research per million USD pharmaceutical market size.

With a three- to fourfold increase in clinical research, Turkey would solidly enter the global Top-10 for a range of global indicators. In this ambitious scenario, we therefore assume a 3.2 time increase in clinical research in Turkey to simulate Turkey's global clinical research ambition, which would make the country the regional leader in terms of the total number of clinical trials in the broader region of the Middle East and Central and Eastern Europe.

With a three- to fourfold increase in clinical research, Turkey would solidly enter the global Top-10 for a range of global indicators.

Figure 52: Top-10 status for Turkey in Clinical Research

RANK	NEW CLINICAL STUDY REGISTRATIONS (2018)		ACTIVE CLINICAL STUDIES (JUNE 2019)		ACTIVE STUDIES BY POPULATION (PER MIO PEOPLE)		ACTIVE STUDIES BY GDP (PER USD BIO)		ACTIVE STUDIES BY PHARMA MARKET SIZE (PER USD MIO)	
	World	4,407	World	16,720	World	2.2	World	0.2	World	14.9
9	Australia	373	South Korea	1,568	New Zealand	69.1	Lithuania*	4.0	Netherlands	195.0
10	**Italy**	**352**	**Australia**	**1,478**	**Puerto Rico**	**68.0**	**Bosnia**	**3.4**	**Ukraine**	**191.6**
11	Belgium	326	Belgium	1,378	Bulgaria*	65.9	Croatia*	3.2	Bosnia	168.7
Now	**22nd – Turkey**	**122**	**26th – Turkey**	**521**	**56th – Turkey**	**6.4**	**62nd – Turkey**	**0.6**	**40th – Turkey**	**71.7**
10	**Turkey – Sc3**	**350**	**Turkey – Sc3**	**1,500**	**Turkey – Sc3**	**68**	**Turkey – Sc3**	**3.4**	**Turkey – Sc3**	**192.0**
	Factor	**2.9**	**Factor**	**4.3**	**Factor**	**10.6**	**Factor**	**5.4**	**Factor**	**2.7**

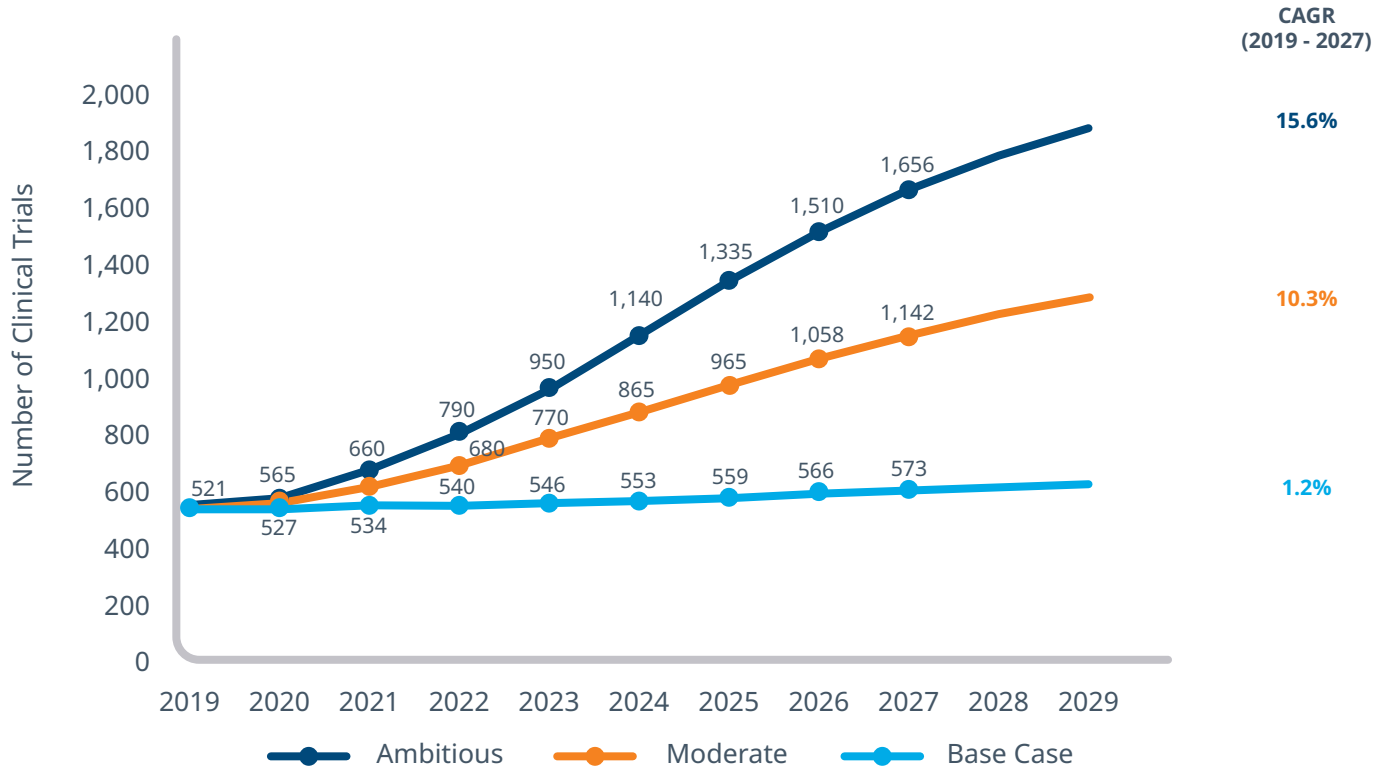
* Pharmaceutical market size data is not available.
Sources: www.clinicaltrials.gov; United Nations Statistics; IQVIA Market Prognosis

8.2 **Results and analysis**

TOTAL NUMBER OF CLINICAL TRIALS ONGOING

If clinical research continued to grow at its current pace, the total number of trials would reach 573 in 2027. To reach the fair share target in 8 years, Turkey would need to have a total of 1,142 clinical trials in 2027, assuming that the total number of clinical trials globally would continue to grow at its current pace. To reach the ambitious target of becoming a Top-10 player globally in 8 years, the total number of trials in Turkey would need to be 1,656 in year 2027.

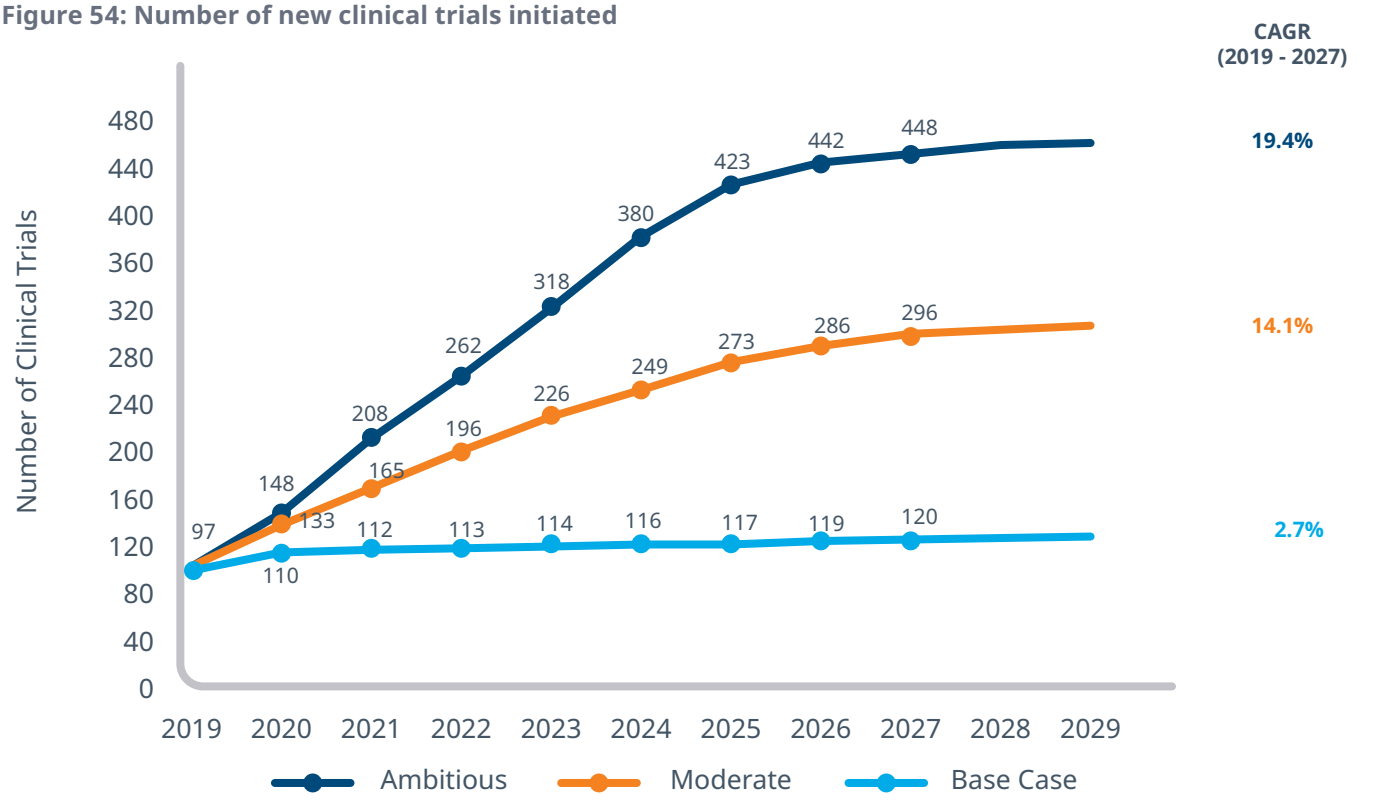
Figure 53: Total number of clinical trials



NEW CLINICAL TRIALS INITIATED

With the total number of clinical trials growing at its historical pace, the number of new trials per year would become 120 within eight years. In the ambitious scenario, the number of new trials per year would reach 448 in year 2027. In the moderate scenario where the fair share would be reached in eight years, on the other hand, the number of new trials per year would be 296 in year 2027.

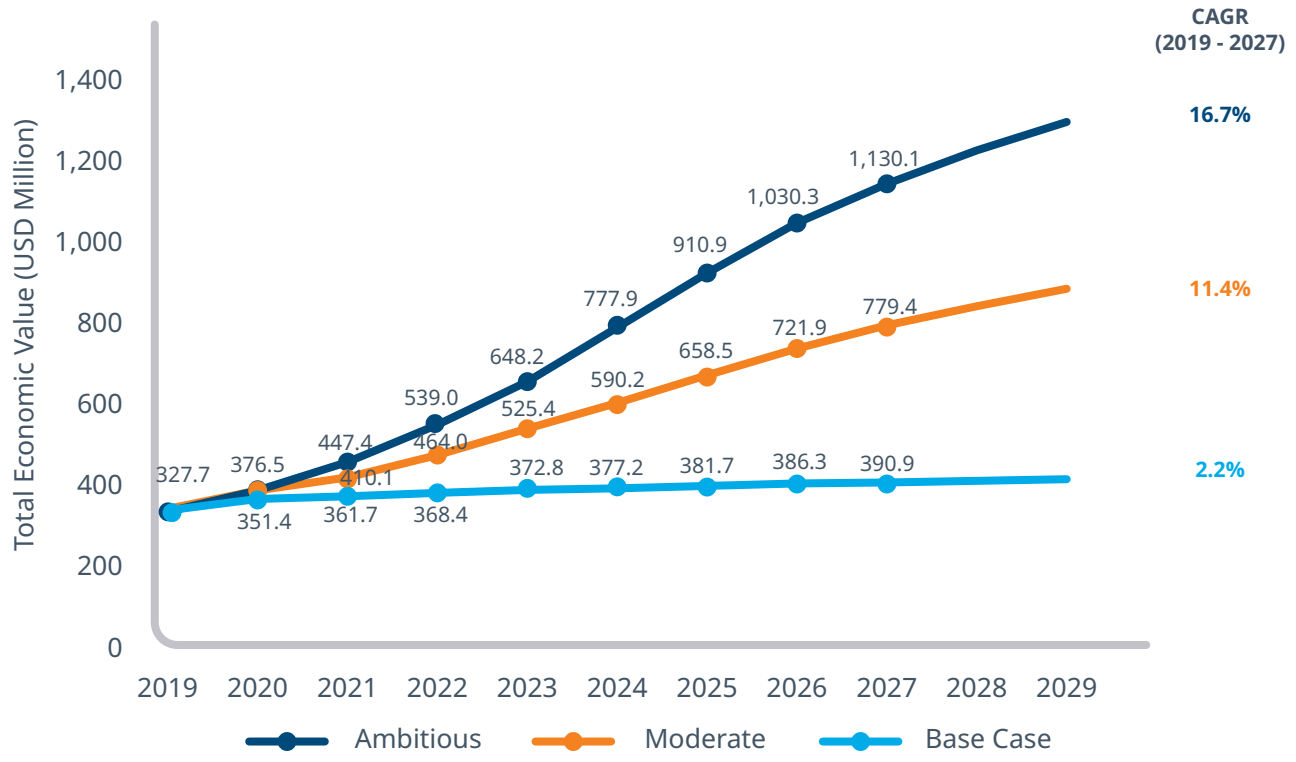
Figure 54: Number of new clinical trials initiated



ECONOMIC VALUE OF CLINICAL RESEARCH IN TURKEY

In the base case scenario, the total value of the clinical research run in Turkey would reach USD 390.9 million (TRL 3,346.4 million) in 2027, creating a cumulative value of USD 2,990.3 million (TRL 21,807.7 million) between 2020 and 2027. The annual size in 2027 would reach USD 1,130.1 million (TRL 9,675.4 million) with a cumulative value of USD 5,860.5 million (TRL 44,279.3 million) in the ambitious scenario. In the moderate scenario, on the other hand, the annual value in 2027 would be USD 779.4 million (TRL 6,672.7 million) with a cumulative value of USD 4,516.0 million (TRL 33,730.8 million). [15]

Figure 55: Total economic value of Clinical Research in Turkey (USD million)



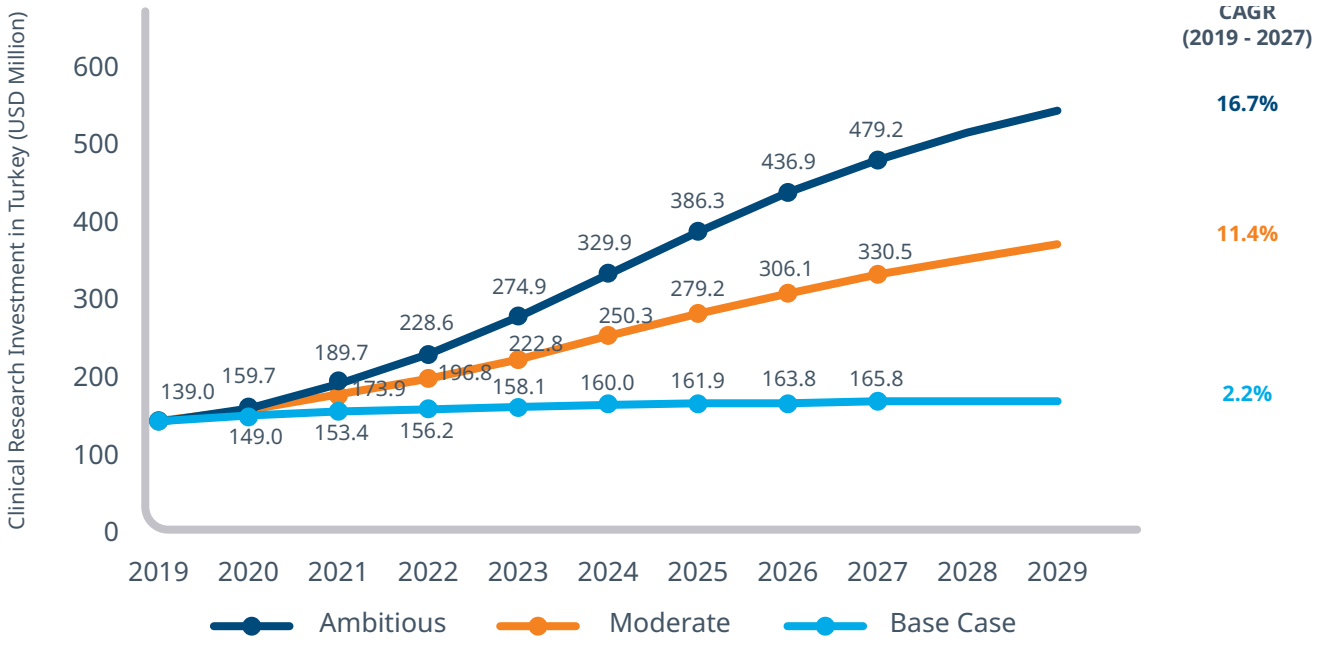
The annual clinical research investment in Turkey would reach USD 479.2 million (TRL 4,103.0 million) in case of the ambitious scenario with an 8-year cumulative value of USD 2,485.2 million (TRL 18,777.1 million) by 2027.

SIZE OF CLINICAL RESEARCH INVESTMENT IN TURKEY

With a clinical research volume growth at its historical pace, the total clinical research investment in Turkey would reach USD 165.8 million (TRL 1,419.1 million) in 2027 with a cumulative value of USD 1,268.1 million (TRL 9,247.8 million) between 2020 and 2027. The annual clinical research investment in Turkey would reach USD 479.2 million (TRL 4,103.0 million) in case of the ambitious scenario with an 8-year cumulative value of USD 2,485.2 million (TRL 18,777.1 million) by 2027. In the same year, the annual investment would reach USD 330.5 million (TRL 2,829.6 million) in the moderate scenario, with a cumulative value of USD 1,915.1 million (TRL 14,303.9 million) for the period between 2020 and 2027. [16]

[15, 16] See Appendix 2 for inflation and exchange rate assumptions.

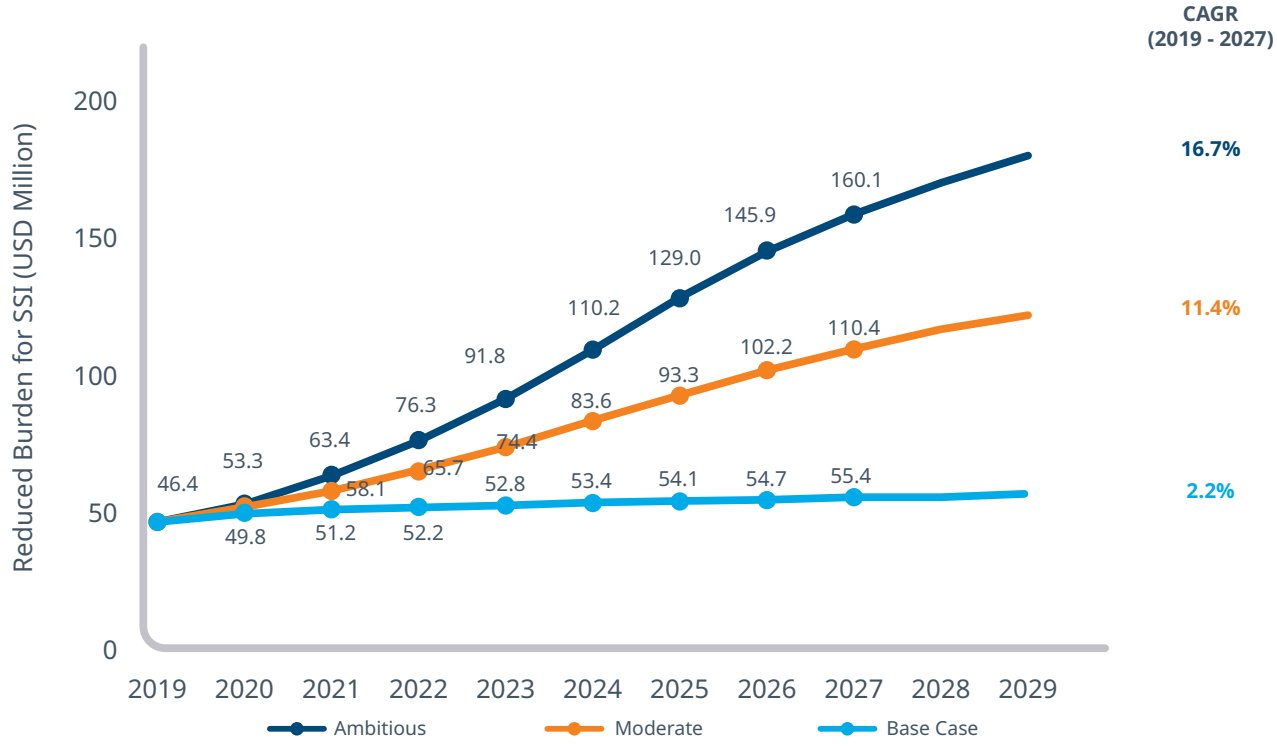
Figure 56: Size of Clinical Research investment in Turkey (USD million)



REDUCED FINANCIAL BURDEN FOR SSI

The reduced financial burden for SSI annually would reach USD 55.4 million (TRL 474.0 million) in 2027, if the total number of clinical trials grew at its historical pace. In this case, the cumulative burden reduced for SSI between 2020 and 2027 would be USD 423.5 million (TRL 3,088.7 million). In case of an ambitious growth, the annual burden reduced for SSI would reach USD 160.1 million (TRL 1,370.3 million) in 2027, with a cumulative burden of USD 830.0 million (TRL 6,271.4 million). In case of a moderate growth scenario, the annual burden reduced for SSI would become USD 110.4 million (TRL 945.1 million) with a cumulative burden of USD 639.6 million (TRL 4,777.4 million) between 2020 and 2027. [17]

Figure 57: Reduced financial burden for SSI (USD million)



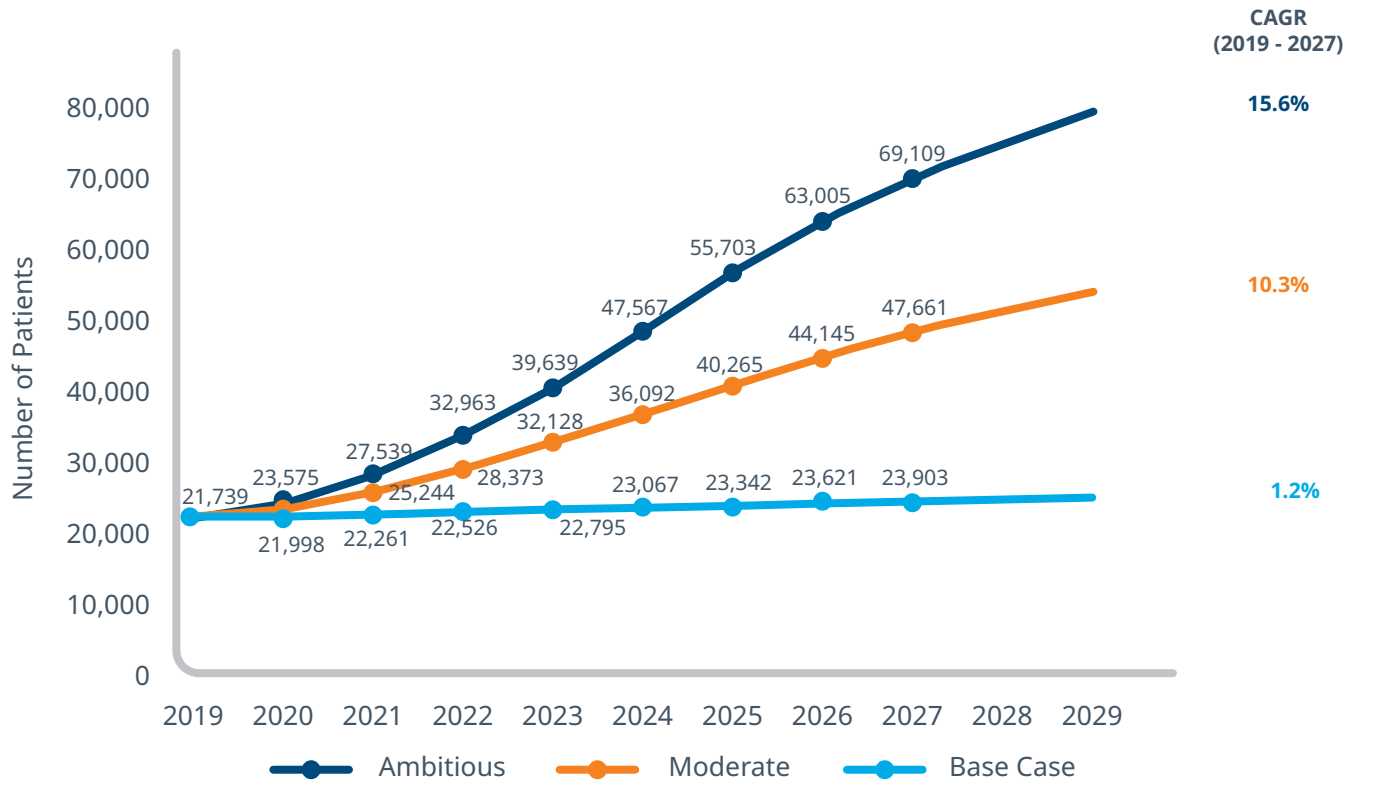
[17] See Appendix 2 for inflation and exchange rate assumptions.

TOTAL NUMBER OF PATIENTS IN CLINICAL RESEARCH

In case of growth at historical pace, the total number of patients in clinical research would reach 23,903 patients in 2027 (10.0% higher than in 2019). In case of an ambitious scenario, the total number of patients in clinical research would more than triple its 2019 level, reaching 69,109 in year 2027. In case of a moderate growth scenario, the total number of patients in clinical research would reach 47,661 in 2027 (119.2% higher than in 2019).

In case of an ambitious scenario, the total number of patients in clinical research would more than triple its 2019 level, reaching 69,109 in year 2027.

Figure 58: Total number of patients in Clinical Research



INNOVATION, DISEASE AREAS AND HEALTHCARE PANDEMICS

In addition to these quantified benefits of a clinical research strategy, there are also several intangible effects like improvement of the overall innovation climate in Turkey, access to state-of-the-art research techniques and medicinal innovations. These help to make the Turkish healthcare system more resilient and ensure that affected patients, through clinical trial research, have faster access to latest treatments. In particular, in situations related to specific disease areas and when addressing global healthcare pandemics (e.g. Covid-19), having the research infrastructure and climate has very large potential benefits.

8.3 **Summary of the results**

Considering the impact of clinical research on different grounds, growth of clinical trial activities in Turkey would have a positive impact on the country overall, as summarized in Figure 59.

From an economic perspective, a greater volume of clinical research would increase the inflow of foreign direct investment. In the moderate scenario of doubling the annual number of ongoing clinical trials by year 2027, the annual inflow of foreign direct investment would be expected to exceed USD 0.3 billion (TRL 2.8 billion) with the 8-year cumulative inflow of USD 1.9 billion (TRL 14.3 billion). In the ambitious scenario of tripling the annual clinical research volume by the same year, the cumulative 8-year foreign direct investment would be expected to reach USD 2.5 billion (TRL 18.8 billion).

A key component of the economic growth driven by clinical research would be the growth in research-specific employment – increasing the number of clinical trials would necessitate to increase the number of people working on the management and field operations of clinical research.

Similarly, the clinical research volume in the country would increase not only the direct income to the state but also the other economic contributions of clinical research including the spending on trial logistics, transportation and lodging, meeting and training expenses, office expenses and other spending.

Figure 59: Summary of impacts for each scenario in 2027 [18]

IMPACT	BASE CASE	MODERATE GROWTH	AMBITIOUS GROWTH
Economic impact (USD million)			
Total investment in Turkey	165.8	330.5	479.2
Value of employment	52.9	105.5	153.0
Other economic contribution	22.2	44.3	64.2
Healthcare impact (USD million)			
Reduced burden for SSI	55.4	110.4	160.1
Additional income to the healthcare system	27.9	55.7	80.8
Scientific impact			
Number of trials	573	1,142	1,656
Number of investigators	3,300-4,400	6,600-8,800	9,500-12,700
Patient impact			
Number of patients	23,903	47,661	69,109
Value of innovative medicines (USD million)	225.1	448.9	650.9

Regarding the economic impact of clinical research on the healthcare system, a growing number of clinical trials would directly increase the additional income generated for the system. At the same time, the financial burden for SSI would be further reduced thanks to an increasing number of patients participating clinical research, thus a larger volume of patient treatment costs covered by the sponsoring companies. The cumulative value of the

A greater volume of clinical research would increase the inflow of foreign direct investment.

[18] See Appendix 2 for inflation and exchange rate assumptions.

burden reduced for SSI would be nearly USD 0.6 billion (TRL 4.8 billion) for the 8-year period between 2020 and 2027 in the moderate growth scenario and reach USD 0.8 billion (TRL 6.3 billion) in case of an ambitious growth in clinical trials.

A growing number of clinical trials would directly increase the additional income generated for the system.

Beyond its economic contribution to the system, a growing volume of clinical research would also help to improve the quality of healthcare services and extend the experience, global network and visibility of healthcare professionals involved in research. For the number of clinical trials to grow, approximately 6,600 to 8,800 physicians would need to assume an investigator role to carry the total trial load in the moderate scenario, 9,500 to 12,700 in the ambitious scenario. This would mean doubling or tripling the number of physicians who would be exposed to such global network and greater visibility.

Thanks to its contribution to the scientific environment – pharmaceutical innovation in specific, a growing clinical research infrastructure in Turkey would support the local original molecule development efforts and provide low-cost clinical testing alternatives – relative to international alternatives – for local start-ups. Therefore, a growing clinical research environment in the country would have an induced positive effect on value creation through local pharmaceutical innovation.

From a patient perspective, an increasing volume of clinical research would mean a greater number of patients benefiting from innovative treatments which provide positive health outcomes. The estimated 8-year cumulative value of such innovative treatments received in clinical trials would be above USD 2.6 billion (TRL 19.4 billion) in a moderate growth scenario for clinical research and nearly USD 3.4 billion (TRL 25.5 billion) in case of an ambitious growth.[19] If Turkey becomes a regional leader in clinical research, a larger number of clinical trials on innovative treatments will be conducted in the country, which will make Turkey a cutting-edge treatment center in its region, potentially attracting volunteering subjects also from other countries in the region.

Clinical research growth trend in the last decade in Turkey shows that highly anticipated structural changes lead to major shifts in the number of incoming trials while periods of no major action result in a steady state. To realize its goal of becoming a regional leader in clinical research, Turkey needs to clearly identify the current roadblocks and improvement opportunities, create a solid action plan to address them, and be determined to implement such plan to bring all the critical structural changes to life.

A growing volume of clinical research would also help to improve the quality of healthcare services and extend the experience, global network and visibility of healthcare professionals involved in research.

A successful implementation of the required structural changes would likely drive a growth in clinical research at the level defined in the moderate scenario. For a more aggressive growth as defined in the ambitious scenario, Turkey would need to go beyond the basics and take additional steps to adopt the latest global trends in clinical research so that it gains a competitive edge relative to the key players in its league.

[19] See Appendix 2 for inflation and exchange rate assumptions.

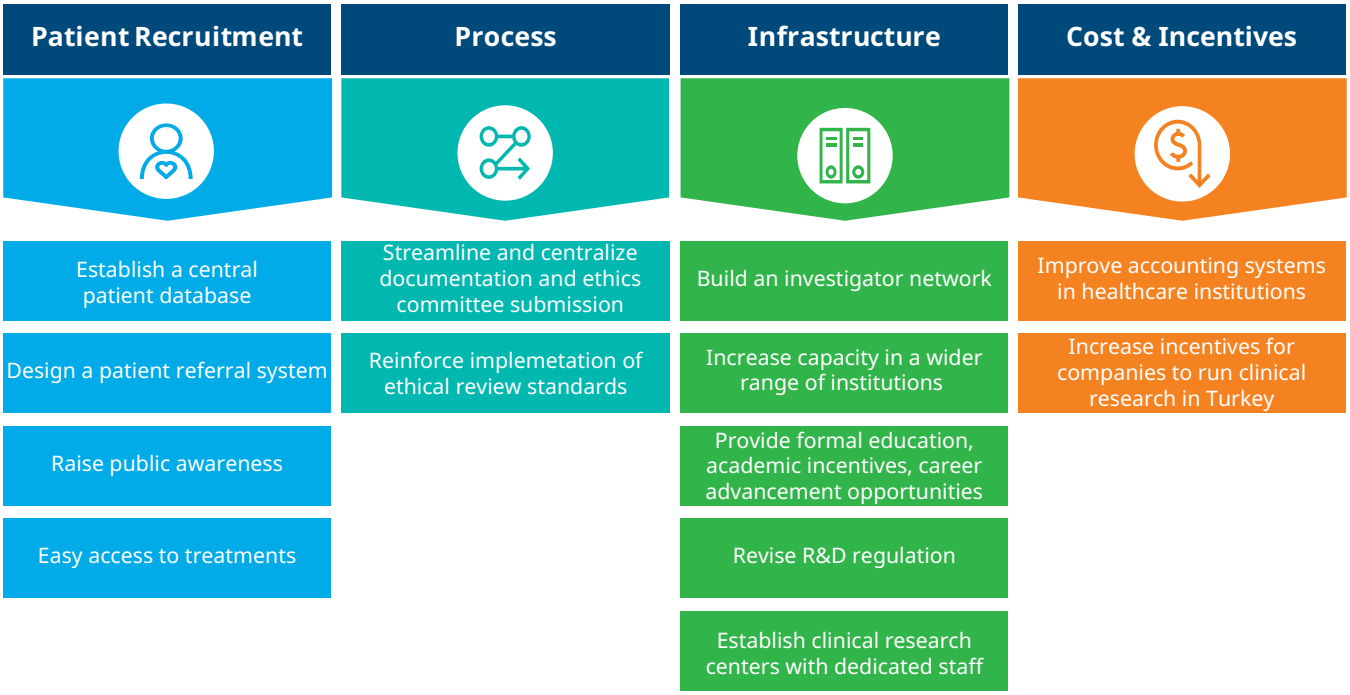
9. RECOMMENDATIONS

A series of action recommendations addressing the improvement opportunities discussed in Chapter 7 of this report have been developed by IQVIA, with input from key stakeholders in the country.

A workshop was conducted in October 2019, with participation of 55 key stakeholders – key opinion leaders, government officers from the Ministry of Health, Ministry of Industry and Technology, and Ministry of Trade, representatives from clinical research, CRO, site coordinator and patient associations, and industry representatives.

With insight and input received from the key stakeholders, 12 recommendations were developed and grouped under the four key improvement areas defined earlier – patient recruitment, process, infrastructure, and cost effectiveness.

Figure 60: Recommended actions



In terms of patient recruitment, three recommendations have been developed – establishing a central patient database and designing a patient referral system, both with the purpose of accessing the right patients more easily and raising public awareness to overcome common prejudices against clinical research and to inform patients of the ongoing clinical studies.

Two recommendations have been developed to address two different process improvement opportunities – streamlining and centralizing documentation in submission to reduce paperwork and shorten timelines in the overall submission process and reinforcing the implementation of ethical review standards by all ethics committees to ensure high standards across committees.

For the improvement of the clinical research infrastructure, five recommendations have been developed to address improvement opportunities in terms of new physician enrollment, physician incentives and employment of dedicated clinical research staff – building an investigator network to access new physicians for primary investigator roles, increasing clinical research capacity in a wider range of institutions, providing formal education as well as academic incentives and career advancement opportunities to attract more healthcare professionals to clinical research and to keep them in the field, revising the R&D regulation to improve incentives for physicians, and establishing clinical research centers with dedicated staff to address multiple improvement opportunities in infrastructure.

Finally, two recommendations have been developed to address costs and incentives – improving the accounting systems in healthcare institutions to ensure correct itemization and invoicing of clinical research costs and

providing robust incentives in line with global standards for companies who consider running clinical research in Turkey.

While grouped under specific improvement areas, however, most of the recommendations have the potential to impact multiple areas.

Figure 61: Impact of recommendations on improvement opportunities

	RECOMMENDATION	PATIENT RECRUITMENT AND EASY ACCESS TO PATIENTS	PATIENT AWARENESS	PROCESS SIMPLICITY	NEW INVESTIGATOR DEVELOPMENT	PHYSICIAN INCENTIVES	DEDICATED CLINICAL RESEARCH STAFF	FORESEEABLE CLINICAL RESEARCH COSTS	SPONSOR INCENTIVES	REAL-WORLD DATA	DIGITALIZATION
1	Establish a central patient database	●								◐	●
2	Design a patient referral system	●									●
3	Raise public awareness		◐								
4	Streamline and centralize documentation and ethics committee submission			◐							●
5	Reinforce implementation of ethical review standards			◐							
6	Build an investigator network				●						●
7	Increase capacity in a wider range of institutions	●			●						
8	Provide formal education, academic incentives and career advancement opportunities				●	●	◐				
9	Revise R&D regulation				●	●			◐		
10	Establish clinical research centers with dedicated staff	●		●			◐	◐			
11	Improve accounting systems in healthcare institutions			◐				◐			●
12	Increase incentives for companies to run clinical research in Turkey								◐		

The recommendations have been evaluated in terms of their overall impact on clinical research in Turkey and the difficulty of implementing them. While all the recommended action points are expected to have a relatively high impact overall, some structural or operational changes carry the potential of a greater impact than others. On the other hand, such changes may also be more difficult or require longer timelines to implement.

One of the recommended actions with the highest expected impact is establishing clinical research centers with dedicated staff. This is because the successful implementation of such a structural change would not only have a positive effect on all four improvement areas but also mean a shift in the mindset – the perspective that clinical research requires its own resources would be accepted by all stakeholders, specifically by healthcare

institutions. Implementing this wide-scale structural change, however, would be difficult and require a long time. Similarly, establishing a patient database or referral system would have a major impact on how patients are accessed and recruited but various barriers would need to be overcome for their successful implementation.

On the other end of the spectrum are recommendations which are expected to have a medium to high overall impact on clinical research but would be easier to implement. Among these recommendations are revising the R&D regulation, building an investigator network and raising public awareness.

Recommendations concerning structural changes, those which have regulatory, technological or other pre-requisites, or those which require the ownership of multiple stakeholders would take longer to fully implement. While immediate action can be taken and results received on the recommendations of lower difficulty, timelines for others should be defined considering their overall impact on the clinical research environment, their impact on other action recommendations, and the stakeholders who will lead them.

Figure 62: Level of impact and difficulty of recommendations

Figure 63: Recommendation timelines

	RECOMMENDATION	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
1	Establish a central patient database												
2	Design a patient referral system												
3	Raise public awareness												
4	Streamline and centralize documentation and ethics committee submission												
5	Reinforce implementation of ethical review standards												
6	Build an investigator network												
7	Increase capacity in a wider range of institutions												
8	Provide formal education, academic incentives and career advancement opportunities												
9	Revise R&D regulation												
10	Establish clinical research centers with dedicated staff												
11	Improve accounting systems in healthcare institutions												
12	Increase incentives for companies to run clinical research in Turkey												

ESTABLISH A CENTRAL PATIENT DATABASE

Establish an anonymous patient database which lays out numbers of patients by region and/or healthcare institution and by detailed health information such as diagnosis, treatment, special conditions and genetic disorders.

The most efficient and comprehensive method to set up such a database is to leverage the e-Nabız database by Ministry of Health or the e-Prescription database by Social Security Institution. Currently, citizens using the e-Nabız system to manage their health information authorize the Ministry of Health to use their records anonymously for national and international health research purposes. With clinical research defined within this scope, relevant data in the system can be accessed by authorized clinical research staff and used anonymously to identify the potential for eligible patients across the country.

Similarly, the e-Prescription database as well can be used to identify this potential. In either case, full compliance with the personal data protection law should be a pre-requisite. To protect the safety of data, access to such anonymous data can be given to relevant employees of the Ministry of Health or Social Security Institution, to relevant staff in healthcare institutions, or to limited users at CRO and sponsor companies, with special authorization by related government institutions.

If e-Nabız and e-Prescription systems cannot be leveraged for various reasons, an alternative, nation-wide patient database can be set up from scratch with the specific purpose of supporting patient search for clinical research.

At a healthcare institution level, individual patient databases or institution extensions of the national database can be set up to enable authorized healthcare staff track records of their patients and search for patients eligible for specific clinical studies.

This comprehensive database system at national and institutional level would ease the overall process of identifying patient potential and recruiting eligible patients for specific studies.

DESIGN A PATIENT REFERRAL SYSTEM

Establish a patient referral system across healthcare institutions. Ensure that this system is accessible by physicians and other relevant healthcare staff, includes information on upcoming and ongoing clinical trials and allows patient referrals between institutions.

Currently, physicians often learn about ongoing clinical research in other healthcare institutions through their individual professional network. Therefore, patients who would benefit from specific clinical studies which are not run in the institution that they visit often cannot be referred to the study of interest.

An online patient referral network which would be established by the Ministry of Health, share detailed information on upcoming and ongoing clinical research and connect healthcare professionals from all institutions around the country would allow physicians refer patients to studies in other institutions or clinical research staff ask for patient referrals from other institutions. This would ease access to patients eligible for specific clinical studies regardless of the institution where they get diagnosis or receive treatment for their condition.

RAISE PUBLIC AWARENESS

Run public awareness campaigns to raise awareness of the patient and public benefits of clinical research and to overcome common prejudices.

A public awareness campaign endorsed or directly run by the Ministry of Health would aim to communicate what clinical research means, how it is run and how it benefits patients, the broader society and the country overall. The campaign would be run on multiple platforms including mainstream media and online platforms, to raise awareness in specific target groups as well as broader public. The ultimate goal of the campaign would be to overcome wide prejudices against clinical research, make patients consider clinical research as a viable option in their treatment journey, and motivate them to ask their healthcare professionals about clinical studies for which they may be eligible.

Publish detailed information on upcoming and ongoing clinical trials on a website that is publicly accessible and communicate new clinical research to related patient associations, which can in turn relay such information to their members.

Currently, per clinical research regulations, TİTCK lists all the approved or in-review clinical studies in Turkey on their Clinical Research Portal. The former version of the portal provided information only on the name, primary investigator, coordinating healthcare institution and the approval status of each study. With its recently developed version, the portal now provides greater detail on each study including the phase of the study and target patient population. In this new version, adding each study's recruitment status and its contact information for the coordinating center would allow patient associations track and search for information on clinical research on their specific conditions.

To ensure effective communication of new clinical studies with potentially eligible patients, the Ministry of Health can inform related patient associations on the relevant studies so that they can share such information with their members and encourage them to visit the Ministry's clinical research portal for more information.

STREAMLINE AND CENTRALIZE DOCUMENTATION AND ETHICS COMMITTEE SUBMISSIONS

Standardize documentation required by institutions, ethics committees and other authorities in the submission phase.

While some of the documents required by different authorities in the submission phase are already standardized, various authorities continue to ask for additional documentation, complicating the process and lengthening the timelines. A full standardization of documentation requirements would resolve some of these complications. With the collaboration of the related departments within the Ministry of Health, including TİTCK and the Public Hospitals Authority, documents required by ethics committees, healthcare institutions and other healthcare authorities can be streamlined so that one standard format is used for documents which are common across authorities and that redundant documentation is eliminated.

Currently, although not required by regulations, provincial directorates of health services impose extra steps in the process for clinical research conducted in public hospitals. A thorough communication of the overall standardization would also ensure streamlining the submission process on the public hospitals end.

Streamline document submission through an online system which related parties can access so that submissions are made online with one set of standard documents.

An online submission system like the one for TİTCK submissions can be established so that companies planning clinical research can make all their ethical review and institution submissions online. If the system will be a single centralized one for all ethics committees, companies can make all their ethics committee submissions through one single system, and each authority can have their own space and be given access only to the submissions or documents directed to them. If the system will be set up at institutional level, a customized version of one overarching online system developed by the Ministry of Health can be set up separately for each institution. In this case, companies would have to submit ethics committee applications at institutional level, but through websites with similar interfaces.

While the former solution would save greater time and effort to applying companies in the submission phase, both solutions would help improve the overall process of submission.

REINFORCE IMPLEMENTATION OF ETHICAL REVIEW STANDARDS

Ensure the implementation of high standards in ethical review across all ethics committees.

To ensure greater standardization of review processes across ethics committees around the country, TİTCK can keep review process statistics of all ethics committees in a central database. An effective follow-up of the review statistics at committee level would

help the authorities identify the roadblocks overall and by each committee and develop actions to resolve such roadblocks.

This would contribute to reducing complications which arise during the ethical review process, especially of complex study protocols, and to speeding up review timelines.

BUILD AN INVESTIGATOR NETWORK

Establish a database which lays out the network of physicians trained and experienced in clinical research and interested in primary investigator roles.

The database should include a list of physicians by institution and specialization and provide the detailed curriculum vitae of each physician in the network, including information on their relevant education, training and experience. Rather than individual lists by healthcare institutions, a national list easily accessible by all sponsor and CRO companies would be a more effective solution.

The Clinical Research Coordination Center recently established by TÜSEB to connect clinical research centers and investigators with sponsor companies with the purpose of facilitating the conduct of clinical research in suitable sites by experienced investigators can potentially serve this purpose.

If TÜSEB's coordination center cannot be leveraged for this purpose and if it is difficult to establish one single network covering both university and public hospitals, as the two types of institutions are overseen by different governmental authorities, two separate physician network databases can be set up in parallel – one by the Council of Higher Education to cover the university hospitals and one by the Public Hospitals Authority to cover the public hospitals.

Establishing a physician database for clinical research investigators would help sponsor and CRO companies extend their network of primary investigators to new physicians, increasing capacity for additional clinical research.

INCREASE CAPACITY IN A WIDER RANGE OF INSTITUTIONS

Build and increase clinical research capacity not only in university hospitals but also in other institutions that have access to a large patient pool.

Currently, most of clinical research in Turkey takes place in university hospitals although there is a large patient population visiting public hospitals as well. To capture a greater potential of eligible patients, clinical research capabilities can be increased in public hospitals – both training and research hospitals and the newly-established city hospitals.

In the current state, healthcare professionals and other staff in public hospitals have a very heavy workload. A pre-requisite to increase clinical research capabilities in these institutions would be to revisit their workload and the other resources which would be assigned to clinical research. In cases where the healthcare and other staff employed in the institution cannot bear the additional workload generated by clinical research, additional staff can be hired permanently or temporarily, as institutions' income growth driven by additional clinical research would potentially compensate for the additional cost of employment.

As a result, increasing clinical research capabilities in a wider range of institutions would not only increase the number of clinical studies that can be run in the country or the number of patients who can participate in clinical research, but also the number of people who are employed in institutions running clinical research.

PROVIDE FORMAL EDUCATION, ACADEMIC INCENTIVES, AND CAREER ADVANCEMENT OPPORTUNITIES

Train healthcare staff in clinical research through courses and graduate degrees on clinical research in medical, dentistry and nursing schools.

Undergraduate and graduate level courses on clinical research can be opened in medical, nursing and dentistry schools as well as faculties of pharmacy and science to teach its basic principles and practices.

Serving as an introduction to clinical research, these courses can help to raise future healthcare professionals' interest in this area.

For those who would like to specialize in clinical research in their career, graduate degree education can be made available in such schools, providing a comprehensive education covering all the theoretical and practical subjects that a specialized clinical researcher should master – study design, protocol design, local and international laws and regulations, clinical research ethics, finance and accounting of clinical studies, etc.

Revise regulations to include clinical research in academic and career advancement criteria.

While clinical research activity brings prestige and reputation to the involved physicians, current regulations do not formally recognize it as an academic or career advancement criterion. A change in regulations to define it as an advancement criterion for all the involved healthcare professionals would provide them a greater motivation to specialize in clinical research and help them achieve their medium to long-term academic or career path goals.

Amend regulations to include clinical research in physician performance evaluation.

Beside academic and career advancement, considering clinical research activities as a criterion also in physicians' performance evaluations would increase their motivation to dedicate time and effort to clinical research. This would require a change in the regulation defining the activities which are considered as criteria in physicians' performance evaluations. The regulatory change would help physicians achieve their short-term performance goals.

REVISE R&D REGULATION

Revisit the coverage of the R&D regulation for clinical research so that a pre-approval clinical study is considered within the scope of R&D even if only one phase is conducted in Turkey.

The R&D regulation to which the Ministry of Industry and Technology currently refers defines clinical research within the scope of R&D only if two or more of the Phases I-II-III clinical research of a drug in development are conducted in Turkey. Changing the regulation to provide R&D status to any pre-approval clinical research phase, even if only one phase is conducted in Turkey, would increase the motivation of both the healthcare professionals involved in research and the multinational companies sponsoring it.

The change in the regulation would benefit the healthcare professionals through a greater portion of the investigator fee passed on to them, which would also be exempt from income taxes to a certain extent. On the sponsoring companies end, imported test drugs would be exempt from import taxes in clinical studies which are defined within the scope of R&D.

Revisit the coverage of the R&D regulation for clinical research so that not only investigators employed as permanent hospital staff but also co-investigators working under temporary contracts are eligible for R&D incentives.

A change in the R&D regulation which would allow co-investigators working under temporary contracts benefit from the R&D incentives provided to healthcare professionals would increase their motivation to participate in clinical research, helping increase the overall healthcare staff capacity for clinical research.

ESTABLISH CLINICAL RESEARCH CENTERS WITH DEDICATED STAFF

In healthcare institutions where clinical research is conducted, establish clinical research centers or revamp the existing ones to employ full-time healthcare and administrative staff dedicated to clinical research.

The centers should employ dedicated staff who have received or should receive training or education on clinical research and GCP and have full knowledge of related research processes. All staff should have clear, pre-defined roles, and be experts in their areas.

Regulations should be revisited to allow nurses employed in the centers to be fully dedicated to clinical

research patients and all dedicated healthcare staff in the centers to receive a share of the incentives together with the investigators.

Administrative staff in the centers should include site coordinators, finance and accounting staff and other staff required for flawless clinical research operations from contract negotiation to reporting.

A system of such fully dedicated centers would improve all steps of clinical research operations in healthcare institutions including contract negotiations, study setup, patient recruitment and accounting; help to reduce research staff turnover thanks to greater motivation and loyalty; and help to keep experience and knowhow within the institution over time.

IMPROVE ACCOUNTING SYSTEMS IN HEALTHCARE INSTITUTIONS

Revamp healthcare institutions' accounting systems ensuring the correct itemization and invoicing of clinical research costs.

In contrast to majority of healthcare institutions where accounting systems cannot separate clinical research patients' research-related costs from their other healthcare costs, a few institutions which have set up systems with this capability have made progress in differentiating between research-related costs and others, addressing invoices to the correct party responsible for payment – CRO or sponsor company vs. SSI.

Revamping accounting systems in all healthcare institutions to have capabilities of perfect cost itemization would help prevent most of the financial coding and invoicing mistakes in healthcare institutions and increase foreseeability of clinical research costs.

For the use of such improved accounting systems to reach full success, clinical research-related cost items should be identified precisely in study protocols, the party responsible for the payment of each cost item should be clearly defined, and staff who are fully trained in accounting, coding and invoicing of clinical research cost items should be employed by the institutions.

INCREASE INCENTIVES FOR COMPANIES TO RUN CLINICAL RESEARCH IN TURKEY

Increase direct incentives for sponsors and CROs that run one or more phases of a drug's clinical research in Turkey.

Direct incentives like tax advantages can be provided to companies conducting clinical research in Turkey. These advantages can be gradual with greater advantages provided to smaller-scale companies or companies which conduct more than one phase of a drug's clinical research in Turkey, aiming to increase both the total number of studies and the variety of study phases as well as companies conducting clinical research in the country.

Increase the quality of the framework of incentives for sponsors and CROs.

The overall incentives framework (i.e. protection of IP, including Regulatory Data Protection – RDP) is strongly correlated with more clinical research. For Turkey to become a regional or even global leader, and support clinical research, assurance that intellectual property rights are clearly defined in laws and regulations in line with global best practice and enforced is an important element for a positive climate for innovation that encourages investment.

Increase direct funding for startups or other companies that have limited or no capacity to fund their clinical research.

To support pharmaceutical R&D activities in the country, direct research funding by TÜBİTAK, TÜSEB or other sponsoring institutions can be provided to startups and other companies who do not have adequate resources and capacity to fund and conduct their clinical research in Turkey.

Speed up the regulatory review of drugs of which Phase III clinical research has been done in Turkey, by streamlining the submission process.

Some of the documentation requested by the Ministry of Health in regulatory submissions for Phase III clinical studies and for drug approvals are in common. Therefore, companies which submit applications

for the approval of drugs of which Phase III clinical research has been conducted in Turkey currently prepare the same documents in both submissions.

Eliminating this duplication of common documentation for drugs of which Phase III clinical research has been conducted in Turkey would help speed up the drug approval process for such products. This would, in turn, act as a motivator for sponsor companies to run their Phase III clinical research in Turkey.

Provide strong sponsor incentives and intellectual property protection for clinical research to improve Turkey's attractiveness in relative terms vis-à-vis Top-10 competitors.

The overall incentives framework (i.e. protection of IP, including Regulatory Data Protection – RDP) is strongly correlated with more clinical research. For Turkey to become a regional or even global leader, and support clinical research, assurance that intellectual property rights are clearly defined in laws and regulations in line with global best practice and enforced is an important element for a positive climate for innovation that encourages investment.

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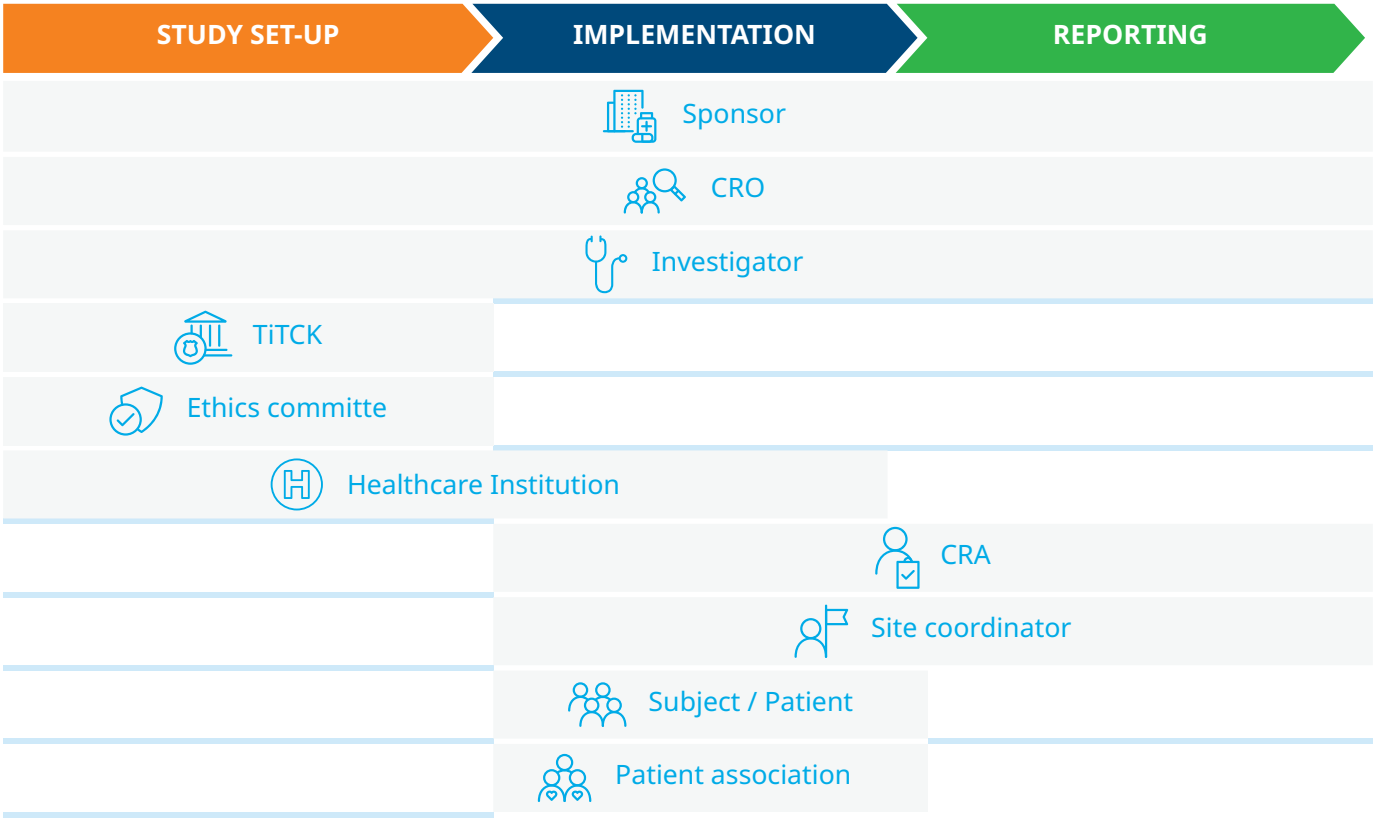
APPENDICES

Appendix 1: CLINICAL RESEARCH STRUCTURE IN TURKEY

A1.1 Stakeholders and their roles

There are multiple stakeholders who are involved in different stages of clinical research and collaborative work between them plays an important role in ensuring clinical research quality. Some of the stakeholders presented in Figure 64 are closely associated but they have been listed separately to point out their specific roles in the process.

Figure 64: Stakeholders in Clinical Research in Turkey



TİTCK (TURKISH MEDICINES AND MEDICAL DEVICES AGENCY)

TİTCK is the regulatory body overseeing clinical research in Turkey through its Department of Clinical Research. The Department is responsible for carrying out regulatory operations for all investigational and observational clinical research on medicines, in accordance with international agreements, European Union standards and Good Clinical Practices. TİTCK approval is mandatory to initiate a new clinical research in Turkey.

ETHICS COMMITTEE

Beside TİTCK, an ethics committee approval is also mandatory for study initiation. Ethics committees are independent committees established in healthcare institutions which run clinical research. Their role is to evaluate clinical research applications from a scientific and ethical standpoint in order to protect the rights as well as health, safety and well-being of the subjects participating in the research. Currently, there are 120 ethics committees in Turkey, with nearly half of them located in the three big cities – Istanbul (38), Ankara (18) and Izmir (7).

SPONSOR

The sponsor of a clinical research is a person, an institution or an organization responsible for initiating, conducting or financing the clinical research. In Turkey, 91.6% of all Phase I-III and 23.1% of all Phase IV interventional clinical studies are sponsored by the pharmaceutical industry.

CONTRACT RESEARCH ORGANIZATION (CRO)

CROs are companies that provide sponsor companies with contracted clinical research services from study set-up to execution, monitoring and reporting. CROs are independent organizations that work in accordance with the principles of the OECD's Good Clinical Practice (GCP). Sponsors may transfer all or part of their duties related to clinical research to the CROs based on specific contracts.

CLINICAL RESEARCH ASSOCIATE (CRA)

CRA is a sponsoring company or CRO employee who is the main contact person with clinical research centers. In the name of the sponsor, the CRA monitors the progress of a clinical study and whether the study is in accordance with the research protocol, standard working methods, Good Clinical Practice (GCP) and related regulations. Where necessary and relevant, CRAs are responsible for the following activities for the research and the research center, depending on the sponsor's needs:

- Manage the communication between the sponsor and the site coordinator, principal investigator or other investigators;
- Ensure that staff and facilities, including laboratories and equipment, are safe and appropriate for conducting the research and that they remain so throughout the study;
- Ensure that a written informed consent is received from all the subjects before they participate in the study;
- Check whether adverse events, concomitant medications and conditions which have occurred during the same period are reported in accordance with the study protocol and Case Report Forms (CRF);
- Inform the principal investigator of any deviations from or violations of the study protocol, standard operating methods, GCP and related regulations, and take steps to prevent the recurrence of detected deviations or violations;
- Submit a written report to the sponsor following a visit to the research site or notification about the research.

INVESTIGATOR

According to regulations and the Good Clinical Practice (GCP) Guideline for Turkey, "investigator" and "principal investigator" are defined as follows: A **principal investigator** is "*a physician or dentist who has completed the specialization or doctorate education in the related field and is responsible for conducting the research*." **An investigator** is "*a person who is involved in clinical research under the supervision of the principal investigator*."

Based on our estimations, the number of investigators who are involved in clinical research in Turkey is between 3,000 and 4,000. It is estimated that only a minority of these investigators are involved in clinical research on a continuous basis while others take part in clinical trials only occasionally. Investigators are the members of the team assigned by the principal investigator to work at the research site and they are responsible for the implementation of critical research-related methods and/or taking important decisions about the research. The following are the main responsibilities of an investigator during a clinical research process:

- Documenting all adverse events that occur during the course of the clinical research;
- Supervising the proper handling, administration, storage, and destruction of investigational products;
- Informing subjects about the risks; anticipated benefits; and any alternative treatment options they have;
- Ensuring a sufficient number of qualified personnel and adequate facility conditions are available to conduct the research correctly and safely within the agreed time period.

SUBJECTS

Subjects are patients or healthy individuals who participate in a clinical study with their own or their legal representative's written consent. In clinical research, it is essential to inform the subjects and to obtain written consent. Subjects do not get compensated for their participation in Phase II and III studies. Participant compensations for subjects who participate in Phase I research, on the other hand, are low but adequate, considering ethical reasons.

There are some important responsibilities subjects have, which are important for ensuring patient safety during a clinical study:

- The subject is expected to visit the center (the healthcare institution where the clinical study is conducted) in accordance with the study protocol;
- The subject is expected to use the study medication as instructed by the investigator and inform the investigator about every missing dose;
- The subject is expected to inform the investigator about all the unexpected events, medications used or discontinued outside of the study routine, medical interventions, doctor appointments and hospitalizations.
- The subject is expected to inform the monitor about his/her state of health even though he/she leaves the clinical trial in accordance with the written consent provided at the beginning of trial participation, or even if he/she withdraws the written consent.

PATIENT ASSOCIATIONS

Patient associations are advocacy groups that support the rights and interests of the patients and their relatives and that offer advice to patients to improve their healthcare experiences. Although the sponsor company or CRO does not contact patient associations directly, patient associations play an intermediary role in raising patient awareness about clinical research and its potential benefits.

SITE COORDINATORS

Site coordinators are qualified people often employed by CRO or SMO companies, who are assigned to a clinical research center upon the request of the principal investigator, independently from the sponsor. Their responsibility entails carrying out the research procedures such as organizing the research files and preparing the subjects for their visits. Based on our employment analysis, it is estimated that there are nearly 470 site coordinators taking role in clinical research in Turkey.

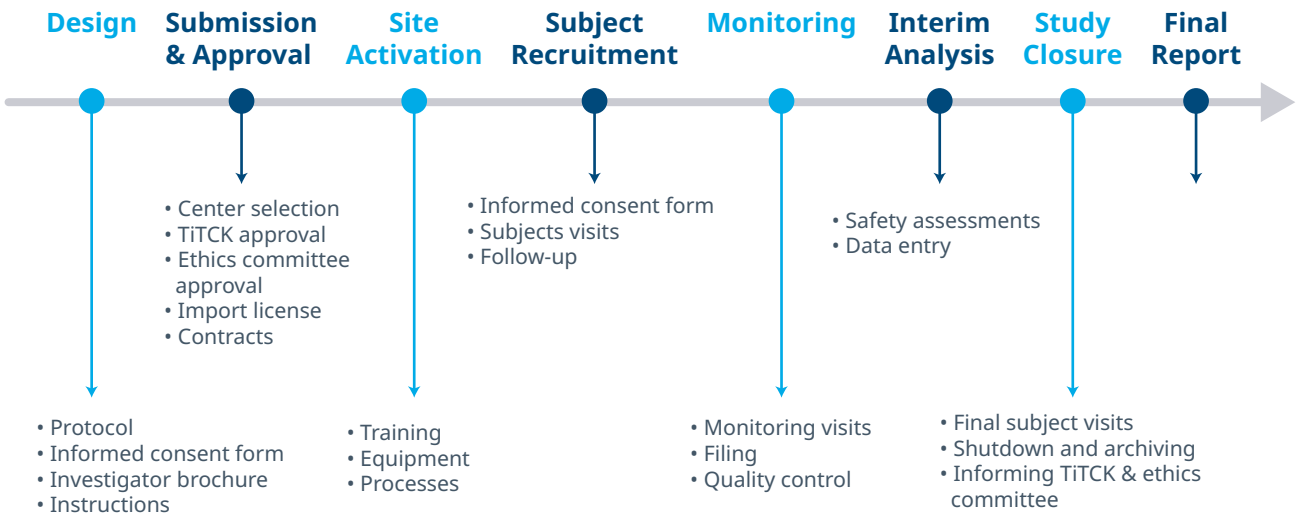
HEALTHCARE INSTITUTIONS

Healthcare institutions – often universities or training and research hospitals in Turkey – are the locations where clinical research is conducted. Healthcare institutions contribute to clinical research mostly by providing investigators with physical space and/or financial resources to conduct research. While private institutions can also provide staff support, due to the regulations in Turkey, public institutions are not allowed to dedicate full time of the healthcare personnel (e.g. nurses, etc.) to support investigators in clinical research. While there are a total of 1,664 hospitals in Turkey, clinical research can be conducted only in a minority of them.

A1.2 Clinical Research Process in Turkey

The process of setting up and conducting a clinical research in Turkey is identical for all studies, regardless of the study phase, indication or sponsor type. It consists of eight stages from 'Design' to 'Final Report' as depicted in Figure 65.

Figure 65: Clinical Research process



Source: IQVIA Analysis

STEP 1: DESIGN

This is the first stage in the process where the study is defined and some of the key documents are designed. The first one of these is the study protocol which defines the purpose and scope of the study and describes who is eligible to participate, details about tests, procedures, medications and dosages, the length of the study, and which information will be gathered. In clinical research sponsored by multinational companies, study protocol is often designed abroad. After the protocol is designed by the sponsor company or the delegated CRO, an informed consent form (ICF) is prepared for patients or volunteers explaining all relevant details pertaining to their participation. The investigator's brochure is a document that explains the routes the drug has gone through in previous stages of product development and is updated in every phase of the drug's developmental journey. Finally, instructions include the study's clinical operation plan to be implemented by the sponsor or CRO.

STEP 2: SUBMISSION & APPROVAL

'Center selection' is the first step into the submission and approval stage: the sponsor company or the CRO runs a feasibility study to select the sites where the study will be conducted, considering their capabilities for the specific research. In global clinical studies, this also means country selection, as countries with more of the qualified sites are prioritized. Upon feasibility approval, a physical site selection visit is made to the candidate centers.

For clinical research to be formalized in Turkey, it needs to receive both a TİTCK and an Ethics Committee approval. The applications to TİTCK and Ethics Committee are made in parallel to speed up the process. However, TİTCK expects the Ethics Committee's approval before it completes its evaluation for regulatory approval. The Ethics Committee where the application is submitted is typically the one at the healthcare institution of the principal investigator. If there is no active ethics committee in such institution, then the application is submitted to the nearest one geographically. Once both approvals are received, an import permit is required if the investigational product (IP) to be used in clinical research will be imported.

Prior to site initiation, necessary documents (researchers' curricula vitae, documentation on GCP training for Turkey, signature page indicating acceptance of the protocol, etc.) are collected from the centers, and a three-party contract is signed between

the investigator, CRO/sponsor company and the healthcare institution.

STEP 3: SITE ACTIVATION

Upon site activation approvals, site visits are made to confirm that the selected sites are ready to involve subjects in the study. Trainings are given, and processes are explained to the entire research team at the center, and equipment required for the study are checked.

STEP 4: SUBJECT RECRUITMENT

Each study protocol has guidelines for who can or cannot participate in the study. These guidelines, called eligibility criteria, describe characteristics that must be minimally shared by all participants. The criteria differ from study to study. Criteria may include age, gender, medical history, current health status and lab values. Informed consent is the process of providing potential participants with important facts about a clinical research before they decide to participate. The ICF is signed by the subject and investigator. Investigators start carrying out the study in accordance with the protocol, GCP and the Declaration of Helsinki. During the screening period, the subjects are checked for eligibility and, if eligible, randomized and subsequently included in the study. After the study ends, patients' safety follow-up is performed by the same site.

STEP 5: MONITORING

The sponsor company or CRO periodically monitors and reports on whether the right subjects are being recruited for the study, the right protocol is applied, and side effects monitored. It is checked whether everything in the subject's file is properly documented, and the study file is kept properly.

STEP 6: INTERIM ANALYSIS

The sponsor company or CRO performs an interim analysis by locking the database while the work is still in progress. Whether the data entry and analysis are made in accordance with the protocol is checked at the moment the database is 'locked'. A safety assessment is also performed which feeds into a decision moment where it is decided whether to continue or terminate the study. The interim analysis can be carried out one or more times throughout the study.

STEP 7: STUDY CLOSURE

The study is closed at all sites after the last patient's last visit. The responsible CRA collects the entire study documentation and confirms the destruction of drugs. Upon confirmation of study completion, the CRA takes a copy of the required documents and closes the site.

STEP 8: FINAL REPORT

Usually, the final report is written by the sponsor after the end of the study. Once completed, it is sent to the study sites to be kept on study file and submitted to the regulatory authority.

Appendix 2: METHODOLOGY

In addition to extensive desk research, multiple methods have been used to collect data and to gather in-depth insight and key stakeholder engagement.

IQVIA SURVEY

A quantitative online survey was conducted with AIFD member companies between June and July 2019.

The objective of the survey was to collect detailed financial data on clinical trials conducted in Turkey, gather information on member companies' donations and training activities related to clinical research, and identify the drivers of country selection for multinational clinical research.

In line with research objectives, the survey consisted of three sections:

- **Section 1:** Financial Data on Clinical Trials
  In this section, each respondent was asked to enter financial data on a maximum of 5 ongoing or recently closed clinical trials. For each trial, 14 questions were asked to cover all the cost items in detail as well as information on sample size, length of trial and therapeutic area. For recently closed trials, respondents were asked to enter cost information for the entire duration of the trial. For ongoing trials, they were asked to estimate total costs for the total planned duration of the trial, based on costs incurred to date, planned trial duration and planned total sample size.
- **Section 2:** Activities Related to Clinical Research
  This section included 5 questions on clinical research-related trainings that were organized, and donations made by member companies within the last year.
- **Section 3:** Multinational Clinical Research
  In this section, 6 questions were asked regarding the companies' approach to country selection for multinational clinical research.

17 AIFD member companies participated in the survey where detailed financial data were collected on 73 recently-completed or ongoing clinical trials representing the clinical trial universe in terms of trial phase, therapy area and cost structure. Data were checked thoroughly for anomalies and 4 trials were left outside the analysis for being outliers or having incomplete information, and all data were anonymized before the detailed analysis of the final sample of n=69 trials. To have a more accurate estimation of the total market size in Turkey, average patient numbers and annual per patient costs were calculated for each trial and therapy area, and therapy areas were grouped by their levels of average annual per patient costs. Survey data were extrapolated to the total universe of clinical trials in Turkey, using average per study patient numbers and per patient costs by therapy area group and active industry-sponsored clinical trial numbers in Turkey – N=521 studies registered on www.clinicaltrials.gov as of June 2019 and coded by IQVIA for therapy areas. Given the clinical trial sample size of the survey and the total universe of industry-sponsored clinical trials in Turkey, the analysis had a margin of error of 11% at 95% confidence level. The results of this analysis were used in Chapter 6 of this report.

The analysis of the data collected in Section 2 of the survey provided detailed understanding of clinical research-related trainings and donations, and the results of this analysis were used in Chapter 4 of this report.

Data collected in Section 3 of the survey were analyzed to provide greater understanding of the drivers of country selection for multinational clinical research in global terms and specifically for Turkey. The output of this analysis as used in Chapter 7 of this report.

ANALYSIS OF EMPLOYMENT GENERATED BY CLINICAL RESEARCH

To complement the economic analysis carried out with data collected in the IQVIA survey, an analysis was made to estimate the total value of employment generated in Turkey thanks to clinical research.

In the first step, the list of CRO companies in Turkey was defined and all the employees working in such companies were identified through a detailed search on the LinkedIn website. Similarly, all the possible job

titles related to clinical research in sponsor companies were identified and searched for on the same website.

In the second step, the data were cleaned to compile the job titles of similar levels and responsibilities under the following representative job titles and the total number of employees for each title was identified:

- Site Coordinator
- Clinical Trial Assistant
- Clinical Research Associate
- Regulatory and Start-up Associate
- Manager
- Director
- Other (i.e. support roles in CRO companies)

Considering that not all employees would have a LinkedIn profile, it was assumed that the total number of employees was 10% higher than the total number of employees identified through the website search. Thus, the employee numbers per job title were multiplied by 1.1 to acquire a better estimate of the total size of the clinical research-related employment in Turkey.

In the next step, the salary range for each job title was identified through competitive intelligence. Based on these ranges, average salaries were calculated for all positions except site coordinators – for which total value data were acquired through the IQVIA Survey.

In the final step, average salaries were multiplied by the numbers of employees with related job titles to calculate the total value of employment generated through clinical research.

IQVIA BENCHMARK COUNTRY SURVEYS AND IN-DEPTH INTERVIEWS

To set a benchmark for Turkey in terms of country attractiveness factors, two surveys were conducted with IQVIA's clinical research leads in a total of 17 countries in August and November 2019. Beside the surveys, in-depth interviews were conducted with 10 countries to gather deeper insight into specific characteristics of their clinical research environment and infrastructure. A list of the surveyed and interviewed countries is provided in Figure 66.

Figure 66: Country surveys and interviews

COUNTRY	SURVEY	INTERVIEW
Australia	●	●
Bulgaria	●	●
Croatia	●	
Denmark	●	
Germany	●	●
Greece		●
Italy	●	
Middle East and North Africa	●	●
Poland	●	●
Portugal		●
Romania	●	
Russia	●	●
Serbia	●	
South Africa	●	
South Korea	●	●
Spain	●	
Sweden	●	
Ukraine	●	
United Kingdom	●	●

The information gathered in these surveys and interviews was used in Chapter 7 of this report.

IN-DEPTH KEY STAKEHOLDER INTERVIEWS

In the early phases of constructing this report, several interviews with 26 representatives of multiple stakeholders including the government (TİTCK specifically), investigators, hospital management, ethics committees, patient associations, site coordinators and CRO and sponsor companies. The purpose of these interviews conducted between May and September 2019 was to gather insight into the clinical research environment, infrastructure and processes in Turkey.

In November and December 2019, 11 follow-up interviews were conducted with 17 representatives of government institutions (TİTCK, TÜSEB, the Directorate General for R&D Incentives and the Department of Chemical and Pharmaceutical Industry at the Ministry of Industry and Technology, the Ministry of Treasury and Finance, the Parliament, the Directorate General of Plans and Programs at the Presidency of Republic of Turkey Strategy and Budget Office, Board of Health and Food Policies at the Presidency of Republic of Turkey , YÖK, and SSI) and additional feedback was received from 11 key opinion leaders representing investigators, hospital management and ethics committees.

Input received from all these key stakeholders was used in multiple chapters throughout this report.

KEY STAKEHOLDER WORKSHOP

With the purpose of evaluating the improvement opportunities for Turkey and developing a detailed list of action recommendations to address such opportunities, a workshop was carried out with participation of 55 attendees representing all critical clinical research stakeholders on October 2nd, 2019. The stakeholders represented were the government (TİTCK, TÜSEB, the Ministry of Trade and the Ministry of Industry and Technology), investigators, hospital management, ethics committees, patient associations, site coordinators, CRO and sponsor companies, molecule inventors and pharmaceutical start-ups.

Following a plenary session and a presentation of findings-to-date was a break-out session where 9 opportunity areas were evaluated in 7 roundtable discussions. As a result of these discussions, 32 unique recommendations were developed and presented to the attendees. Each recommendation was evaluated in terms of its level of potential impact on the related opportunity area and its level of difficulty of implementation. The overall list was then refined by IQVIA for a broader-scale analysis.

In addition to the workshop output, a set of potential recommendations was also developed by IQVIA based on a detailed analysis of all the opportunity areas. In the final analysis, the two sets of recommendations were combined and refined by IQVIA and a shortlist was created by selecting the recommendations of the highest impact from a range of difficulty levels. These recommendations are detailed in Chapter 8 of this report.

INFLATION AND EXCHANGE RATE ASSUMPTIONS

Actual TRL inflation rates have been used for 2018 and before. Inflation rate assumptions in the New Economic Program have been used for 2019 to 2022. For 2023 and beyond, the inflation rate has been assumed to remain constant at its 2022 level.

Actual annual average TRL/USD exchange rates have been used for 2019 and before. TRL/USD exchange rate assumptions in the New Economic Program have been used for 2020 to 2022. For 2023 and beyond, TRL/USD exchange rate has been assumed to increase at the same rate as the TRL inflation rate.

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