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Clinical Trials in Portugal: Past and Future. Position Paper from the Colleges of Clinical Pharmacology and Pharmaceutical Medicine

Ensaios Clínicos em Portugal: Passado e Futuro. Posicionamento dos Colégios de Farmacologia Clínica e de Medicina Farmacêutica

Filipa BORGES-CARNEIRO✉*[1], Miguel TORRE SOUTO*[1], Isabel SILVA[1], Paula LEÃO MOREIRA[1], Paula FERRAZ DE OLIVEIRA[1], Diogo José LOPES[1], Luís FIGUEIRA[1,2,3], Marta REINA-COUTO[1,4,5], Luís CUNHA-MIRANDA[6,7], Diogo PONCES BENTO[7,8], Fernando MAGRO[1,9]

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In recent decades, clinical research, especially clinical trials, has been shown to improve: i) access to new health technologies and frontline scientific knowledge; ii) adoption of better clinical practices; iii) quality of generated data and analysis; iv) education level of the workforce; and v) creation of new jobs and alternative sources of funding for institutions and countries.[1] The massive amounts of data produced by clinical research have become a valuable asset, which is expected to impact economic policies in the coming decades.[2]

Constraints related to clinical research in Portugal were previously acknowledged and remain topical: lack of funding, financial incentives, adequate policies, and a solid strategy for clinical research.[3]

In this article, we aim to evaluate the clinical trials panorama in Portugal regarding structures, procedures, and outcomes (Table 1) and describe possible solutions to the identified problems (Table 2).

Clinical research in Portugal faces intricate challenges rooted in organizational structures, resource limitations, and regulatory complexities. These challenges, spanning the spectrum from clinical trial initiation to patient recruitment, demand a holistic approach for substantial improvement in the Portuguese clinical research landscape.

Structures orchestrating clinical studies encompass pivotal elements such as trial registration, data management infrastructures, and support for engaged researchers. However, the Portuguese clinical investigation scenario reveals constraints in both physical infrastructure and human resources, hampering the development of a robust clinical research ecosystem.

A stark reality emerges from the reduced number of approved clinical trials in Portugal, standing at 152 in 2022,[4] which is indicative of a substantial gap in comparison to European standards. Moreover, the inadequate investment in research and development, with the government allocating only €75.6 per person in 2021 (70% less than the European average),[5] amplifies the challenges. The scarcity of national funding programs for non-commercial clinical research and limited funding for the Portuguese Clinical Research Infrastructure Network (PtCRIN) further hampers progress.[6]

While Portuguese patents and scientific publications show gradual improvement, they remain below the European Union (EU) average.[2] The low level of involvement of primary care physicians in research and challenges in patient recruitment comprise the systemic issues.[3]

Based on the experience of countries like the Netherlands, which are at the forefront of clinical research, we believe that key strategies for enhancing the Portuguese clinical research landscape include educational initiatives, national and international networking, high standards of care, improvement of infrastructure, new recruitment strategies, scientific production, and high quality of data collection and reporting.[7]

Essential to this transformation is the capacitation of qualified human resources dedicated to clinical research,

* Co-first authors.
1. Clinical Pharmacology Unit. Unidade Local de Saúde São João. Porto. Portugal.
2. Center for Drug Discovery and Innovative Medicines (MedInUP). Faculty of Medicine. Universidade do Porto. Porto. Portugal.
3. Department of Ophthalmology. Unidade Local de Saúde São João. Porto. Portugal.
4. Intensive Care Medicine Department. Unidade Local de Saúde São João. Porto. Portugal.
5. College of Clinical Pharmacology. Ordem dos Médicos. Lisbon. Portugal.
6. Portuguese Institute of Rheumatology. Lisbon. Portugal.
7. College of Pharmaceutical Medicine. Ordem dos Médicos. Lisbon. Portugal.
8. Department of Infectious Diseases. Unidade Local de Saúde de São José. Lisbon. Portugal.
9. CINTESIS@RISE. Faculty of Medicine. Universidade do Porto. Porto. Portugal.
✉ **Autor correspondente:** Filipa Borges-Carneiro. filipa.joao.carneiro@chsj.min-saude.pt

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Table 1 – Definitions and examples of structures, procedures, and outcomes for clinical trials in Portugal

	Definitions and examples
Structures	Encompass the deliberate organization and interplay of the various elements involved in the establishment and execution of a clinical study. This can include critical components such as platforms for the registration of clinical trials, infrastructures necessary for data collection and management, as well as the provision of training and support for researchers engaged in the study.
Procedures	Denote the systematic sequence or methodology employed in conducting a study. This includes various aspects such as legislation and the standardization of documents like informed consent and contracts across different study sites, the systematic collection of data, and the pivotal roles played by governing bodies responsible for the assessment and oversight of the study.
Outcomes	Defined as the conclusive results or effects that constitute a vital component of the study findings, influencing various stakeholders. These effects can include improvements in patient health and well-being, enhancing the quality of care and services offered by healthcare institutions, and providing valuable insights and guidance to healthcare professionals. For instance, outcomes may entail better patient recovery rates, streamlined healthcare processes within institutions, and evidence-based recommendations that aid healthcare professionals in making informed decisions.

a factor hindered by insufficient support from hospitals. The crucial role of physicians in patient enrollment underscores the need for incentives, rigorous feasibility analyses, and enhanced knowledge of ongoing trials.[8] Regulatory amendments, fiscal incentives for private companies supporting university education, business-friendly tax and labor laws, and health and science literacy programs are essential components for a comprehensive solution. Leveraging EU funding through the Recovery and Resilience Plan becomes crucial in counteracting the brain drain phenomenon and boosting work opportunities in knowledge-intensive activities.[2]

Piloting multidisciplinary investigation centers emerges as a tangible solution, incorporating accountability, financial autonomy, protected resources, systematic trial registration, effective leadership, and integration into national and international networks. This approach seeks to test and validate proposed solutions in a controlled environment.[9] Recommendations for performance indicators, such as recruitment metrics and contract timelines, provide a structured approach.

The procedural aspect of clinical research requires a comprehensive evaluation of limitations in Portugal. Achieving better performance requires a convergence of stakeholders' visions, including the Ministry of Health, to shape a governmental agenda and strategic plan.[1,9] Harmonizing documentation and collaboration among regulatory bodies, healthcare providers, pharmaceutical companies, academic institutions, and patient organizations is pivotal. The new clinical trials regulation (CTR) provides a foundation, but additional streamlining and standardization through initiatives like the European Clinical Research Infrastructure Network are vital.[3,9]

Addressing challenges related to sample size, time intervals for trial initiation, and recruitment processes is crucial, as in Portugal the time elapsed between study approval and the recruitment of the first participant is, on average, one year.[3] Urgent steps include reviewing recommendations on advertising clinical trials and standardizing documents like informed consent and contracts across different study sites.

New clinical study models, like collaborative and decentralized trials, are crucial for advancing medical research, improving patient access to trials, and accelerating the development of new treatments. However, they face challenges in compliance, data management, patient engagement, and logistics. Also, increasing capacity to conduct investigator initiated clinical studies could help advance scientific understanding, improve patient care, and spark new treatment research ideas, elevating the country's clinical research environment.

Prominent entities like the Portuguese Pharmaceutical Industry Association (APIFARMA) and the Agency of Clinical Investigation and Biomedical Innovation spearhead training and awareness projects, intending to uplift clinical trial practices in Portugal. Quality improvement in integrity plans gains momentum through initiatives like SOPs4RI, while platforms such as 'The Embassy of Good Science' provide valuable resources and information on responsible and ethical scientific activity.[3]

Horizon Europe is the EU's key funding program for research and innovation, aiming to tackle global challenges, achieve United Nations sustainable development goals, and boost the EU's competitiveness and growth. Participation in Horizon Europe projects can enhance clinical research diversity, broaden research scope, and boost innovation in the Portuguese healthcare sector.

Table 2 – Outcomes and limitations and suggestions regarding the structures and procedures associated with clinical research in Portugal

Structures	
Limitations	**Suggestions**
Lack of platforms for clinical trials dissemination	Systematic registration of trials and recruitable patients
Hospital management not inclined to clinical research	Portuguese National Health Service reform with clinical research as a priority
Lack of funding/incentives	Incentives for healthcare worker involvement in clinical trials (dedicated time, monetary compensation, and education, among others)
Low level of national funding for non-commercial clinical research	Partnerships between government, university hospitals and industry
Scarce professional recognition of investigators	Motivation and support of researchers, promoting their professionalisation
Limited logistical support	Implementation of multidisciplinary research units in hospitals and better collaboration with Contract Research Organisations and pharmaceutical companies
Lack of human resources totally dedicated to clinical trial activities	Multidisciplinary investigation centres with accountability and financial autonomy
Fragmented training and lack of experience in clinical trials	National integration with respect to training requirements
Difficulty in recruiting significant sample sizes	Strategies to improve recruitment and retention of participants (i.e., attractive monetary compensation for healthy volunteers, rigorous feasibility analysis, healthcare worker´s knowledge of ongoing clinical trials)
Limited participation of the private sector in Research & Development	Business-friendly tax and labour laws, Regulatory reforms and fiscal incentives to private companies that fund research
Lack of professional opportunities in business	Collaboration between stakeholders
Need to standardize and strengthen regulatory activities	Long-term national agenda for clinical research
Industry-led investigation is disregarded and is seen as resource consuming	Public education about the contribution of the pharmaceutical industry in improving healthcare
Deficient local infrastructures	Units with management and infrastructures capable of supporting the conduct of clinical trials
Portuguese brain drain	Funding to address Portugal's lack of job opportunities in knowledge-intensive activities
Precarious work conditions for most researchers	Protected and incentivized human resources
Procedures	
Limitations	**Suggestions**
Lack of adequate policies and strategy for clinical research	Convergent vision between the various stakeholders in the definition of a national agenda and a strategic plan for the sector
Inefficient and complex legislative and regulatory framework	Thorough examination of existing laws to ensure consistent documentation and stronger collaboration among key players
Difficulty in effectively collecting data	Implement integrated information systems where patient data can be collected, anonymized, and used to drive innovation
Long time between study submission and first patient recruitment	Develop specific legislation about advertising clinical trials and standardizing documents
Outcomes	
On December 2022, the European Medicines Agency reported an increase of 16% in clinical trial applications under evaluation and a 22% increase in clinical trial applications in the clinical trials information system compared with the previous reporting period.	
In Portugal, the number of clinical trial applications increased from 175 to 230, between 2021 and 2022.	
Data from the second trimester of 2023 seems to suggest that the growing trend persists, with 129 authorized trials until June 2023.	
Regarding therapeutic area, the greatest representation in clinical trials in 2021, 2022 and 2023 (2nd trimester data), were antineoplastics and immunomodulators (with 42%, 40%, and 25% of the total of submitted trials, respectively) followed by central nervous system (with 11%, 15%, and 19% of the total of submitted trials, respectively).	
Portugal has been showing a residual value of trials initiated by the investigator (8% of the total in 2022 and 6.7% of the total as of June 2023).	
Concerning the year of 2022, the medium decision time for clinical trial applications was of 60 days.	

Harnessing the full potential of data demands innovative approaches, including integrated information systems for anonymized patient data. Overcoming time-consuming local feasibility assessments requires defined regulatory limits and pragmatic inspections. Additionally, addressing issues related to reimbursement of medicines and reluctance to prescribe new drugs is crucial for fostering a conducive research environment.

The pivotal outcomes of clinical trials resonate across patient health, healthcare quality, and professional insights. Recognizing this, a 2016 report by APIFARMA and the National School of Public Health outlined a consensus and recommendations, emphasizing the need for government involvement in mapping areas of excellence, defining investment priorities, establishing minimum criteria for research centers, and promoting patient literacy.[9] In this setting, the digital platform 'Portugal Clinical Trials', which was created under the motto "union for cutting-edge health", intends to be the largest aggregator of information regarding clinical research in Portugal.[10]

In the context of recent changes introduced by the new CTR, Portugal is well positioned to undergo a paradigm shift. The implementation of the CTR, with obligations for clinical trial authorization through the clinical trials information system, aims to streamline processes, albeit facing initial challenges for smaller companies.

Empowering patients and involving them in health innovation is a key aspect of the future. The 'Patient Innovation' platform stands as a testament to the innovative capabilities of patients and caregivers, underscoring the need for continued support and dissemination. This digital platform emerges as a beacon, showcasing patient learnings and innovative solutions they have come up with in their daily lives.[2] As part of the future of health innovation, it not only disseminates solutions but also offers mentoring and training programs to empower patients and caregivers.

In conclusion, the multifaceted challenges within the Portuguese clinical research landscape demand a comprehensive and collaborative approach. The proposed strategies, spanning structures, procedures, and outcomes, aim to reshape the narrative by fostering an environment conducive to robust clinical research in Portugal.

AUTHOR CONTRIBUTIONS

FBC, MTS: Study design, literature review, writing and critical review of the manuscript.

IS, PLM, PFO: Study design, literature review, writing of the manuscript.

DJL, LF, MRC, LCM, FM: Study design, critical review of the manuscript.

DPB: Study design, literature review, critical review of the manuscript.

All authors approved the final version to be published.

COMPETING INTERESTS

FM served as a speaker and received honoraria from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratórios Vitória, Ferring, Hospira, and Biogen; is a board member of the Portuguese IBD Study Group and President-Elect of ECCO.

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