

Medicines and translational research: steps, actors, and health policies in the Brazilian context

Medicamentos e pesquisa translacional: etapas, atores e políticas de saúde no contexto brasileiro

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ABSTRACT Translational research has come up with the purpose of reducing the time gap between basic research and its clinical application. As for what concerns medicines, this time can reach decades, demanding the evaluation of barriers through translational research. Our aim was to review the literature in order to identify the steps of translational research, as well as normative acts, public health policies, and the key agents in the Brazilian context. For the identification of translational research framework, a systematic search was carried out on PubMed, Embase, and Lilacs databases, with 23 publications selected. Official websites were consulted to gather information on policies and actors. As a result, the literature initially pointed to one step (from bench to bedside), recently incorporating the additional steps of research synthesis and the public health impact assessment. Several actors are transversally involved in translational research, such as universities, research institutions, and funding agencies. It is observed that Brazil has implemented important policies in the fields of pharmaceutical services, research, science, technology, and innovation in health, which may potentially integrate resources, actors, and efforts aimed to the practical application of research results in clinical practice, improving the health and life condition of the population.

KEYWORDS Translational medical research. Health systems. Health policy. Pharmaceutical services. Pharmaceutical preparations.

RESUMO A pesquisa translacional surgiu com o objetivo de reduzir o tempo entre a pesquisa básica e a sua aplicação clínica. Para os medicamentos, esse tempo pode chegar a décadas, o que denota a necessidade de se avaliarem possíveis barreiras por meio da pesquisa translacional. Objetivou-se revisar a literatura para identificar as etapas da pesquisa translacional, bem como os atos normativos, as políticas públicas de saúde e os principais atores no contexto brasileiro. Para a identificação de modelos da pesquisa translacional, realizou-se revisão com busca sistemática nas bases PubMed, Embase e Lilacs, sendo selecionadas 23 publicações. Sítios eletrônicos oficiais foram consultados para o levantamento das políticas e dos atores. Como resultados, a literatura inicialmente apontava uma etapa (da bancada ao leito), incorporando recentemente a síntese de pesquisas e a avaliação de impacto na saúde pública como etapas adicionais. Diversos atores são transversais na pesquisa translacional, como universidades, instituições de pesquisa

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e agências de fomento. Observa-se que o Brasil instituiu políticas importantes nas áreas de assistência farmacêutica, pesquisa, ciência, tecnologia e inovação em saúde, o que pode potencialmente integrar recursos, atores e esforços visando à aplicação prática de resultados para melhorar as condições de saúde e de vida da população.

PALAVRAS-CHAVE *Pesquisa médica translacional. Sistemas de saúde. Política de saúde. Assistência farmacêutica. Medicamentos.*

Introduction

The search for time optimization between basic research and clinical application of its results has been a subject of growing interest in the specialized literature¹. From this perspective, translational research has emerged as a new strand for knowledge integration, aimed at promoting the access of products, policies and practices to potential users and enabling the practical application of the knowledge generated by research^{2,3}.

Different definition patterns can be found for translational research. According to the literature^{2,4,5}, the most used meaning alludes to a 'bridge' between basic research (biomedical or laboratory bench) and applied research (classically clinical trials), being the expression 'bench to bedside' referred to quite frequently in the literature and which gained prominence with the article 'Crossing the valley of death', published in 2008 in the journal *Nature*⁶. Such a perspective would involve, therefore, the discovery of an idea until its materialization in a product (medicines, diagnostic tests, devices, etc.).

However, there is also an interpretation that goes beyond the availability of the product in the market, encompassing the access of the population to these medicines, changes in health behavior with the adoption of clinical practice guides and the evaluation of the true impact on people's health²⁻⁴.

Thus, translational research can be generically understood as the processes involved in

the creation of knowledge and its application to produce benefits for society. Specifically in public health, translational research seeks to reduce the gaps between the knowledge produced and its application, in order to maximize the benefits of health actions and services and improve the health conditions of the population^{3,7}.

Although other definitions can be found in the literature^{8,9}, they converge on the need to apply knowledge to produce benefits for society. Despite this convergence, there is no consensus regarding the definition of the stages of translational research, with both overlaps and subdivisions between them. Moreover, the literature on the time lag between the stages is still poorly developed, as well as how 'reasonable' or necessary the time spent in each stage would be, ensuring good technical and ethical practices^{1,10,11}.

As an essential input in the health field, medicines are the subject of study in various sciences, methods and approaches, and could not be different in the context of translational research. It can even be said that such technologies are a great example for understanding translational research models, since there are the basic research phases that investigate the activity of drug candidate molecules, with very complex models and methodological approaches.

The journey before society's availability and access to medicines is long. In general terms, it starts with the need to change the course of a pathology, goes through research and in vitro

testing on laboratory models, advances to the preclinical and clinical study steps to demonstrate safety and efficacy, and in the end, submits the registration application for review and approval by a regulatory health authority¹.

A recent review points out that at least 14 years are needed for Research and Development (R&D) of medicines, ranging from preclinical to health registration, at an estimated cost of between US\$ 1.3 billion and 1.8 billion per medicine¹².

Along the same line, Pharmaceutical Research and Manufacturers of America (a business group representing the pharmaceutical industries in the United States) estimates that it takes an average of 10 years to 15 years from R&D to Food and Drug Administration (FDA) approval, and only 12% of experimental medicines entering clinical trials are approved by the FDA¹³. It is noteworthy that many factors interfere with the estimation of such times, such as, for example, the type of medicine (synthetic, biological, among others) and the clinical indication in question (oncology, endocrinology, infectology, etc.)¹².

In addition to the time previously described, there is, also, the deadline for research evidence to be effectively applied in the daily practice of clinical practice, which is estimated in the literature at 17 years¹⁰. This period depends on an estimated time interval and the markers or tracers, that is, dates on which the relevant events occurred.

In order to optimize such processes, it is important to know the average deadlines used in each step, as well as to identify the so-called 'time lags'. On this subject, the literature is still underdeveloped and points to dissent in gauging the elapsed time, since the studies use different measures of different objects and technologies (medicines, medical devices, health promotion interventions), at different times or phases, which makes comparisons difficult^{10,11}.

From the perspective of the Unified Health System (SUS), a series of processes

and instruments are associated with effective access to technologies by the population, such as the judgment on the cost-effectiveness of a treatment and the elaboration of a clinical practice guide. In this sense, translational research would seek the interface and development of a *continuum* between researches, practices and actions of interest to public health, considering the needs of the population and the epidemiological indicators.

Thus, it refers to the need to produce evidence in this recent field, in order to contribute to the identification of the stages and actors involved in each of the macroprocesses, aiming at generating knowledge that can be applied in the fields of management and clinic, besides subsidizing future research.

Given this context, this article aims to review the literature to identify the stages of translational research related to medicines, as well as normative acts, public health policies and the main actors in the Brazilian context.

Methods

The methodological approach adopted in this review consisted of two steps. In the first one, a systematic literature search to identify the models and markers of each stage of the translational research was carried out. The Medline databases (via PubMed), Embase and Lilacs were consulted on February 27, 2019, adopting the structured combination of the following descriptors: PubMed: (('model'[Title/Abstract]) OR 'framework'[Title/Abstract])) AND (('Translational Medical Research'[MeSH]) OR 'Translational Research'[Title/Abstract])) AND 'drug\$'[Title/Abstract]; Embase: (framework':ab,ti OR model':ab,ti) AND 'Translational Research' AND drug:ab,ti; Lilacs: ('Investigación en Medicina Traslacional' OR 'Pesquisa Translacional'). Additional publications were also collected manually, especially through references to retrieved articles and previous research for preliminary investigation of the topic.

Inclusion criteria were reviews, descriptive or exploratory studies that addressed the conceptual models and stages of translational research, in the Portuguese, English and Spanish languages, with no publication date limit. Studies with results from *in vitro* experiments or animal models, translational research models applied to specific diseases (mostly related to preclinical and clinical research phases, with descriptive content restricted to *in vivo* or *in vitro* models) or full text publications not available were excluded.

In the second stage, from searches in sources not necessarily indexed (government sites and public repositories), the main actors involved in the translational research process in the Brazilian context were raised, as well as normative acts and established policies on pharmaceutical assistance, research, science, technology and innovation in health, regarding research, development, production and access to medicines. For this, the official websites Portal da Legislação Brasileira, Sistema Saúde Legis of the Ministry of Health (MH), website of the National Health Surveillance Agency (Anvisa) and Official Journal were consulted for the location of normative acts. Additionally, the repository of the Observatory of Political Analysis in Health – Oaps (<http://www.analisepoliticaemsaude.org>) was also consulted, in order to collect

normative acts and policies. Oaps consists of ‘a network of researchers in various health education and research institutions and others involved in the production of critical knowledge in health policy’.

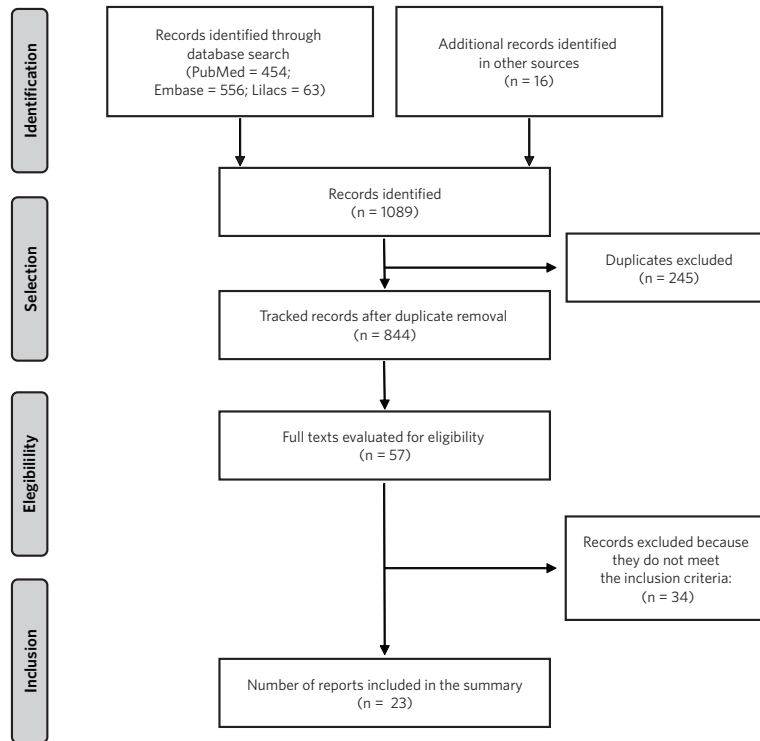
It is worth emphasizing that certain actors are transversal throughout the process, such as universities and research institutions, government (especially, MH and Anvisa), among others. However, for schematic representation, the most relevant actors for each stage of translational research were presented, whose activities and competences are concentrated in certain stages.

The scope, objectives, guidelines and principles of the health policies instituted at SUS were also analyzed, aiming to schematically relate them to the stages of translational research.

Results

Altogether, 1.089 publications were identified from the database search and manual search. After removing duplicates, in the selection process, title and abstract of 844 publications were evaluated. Based on the application of the eligibility criteria, the full text of 57 publications was evaluated and a total of 23 studies were included for this first stage of the study. *Figure 1* presents the study selection flowchart.

Figure 1. Flowchart for selection of studies



Fonte: Own elaboration.

The 23 studies used to identify the stages and markers of translational research are summarized in *chart 1*.

Chart 1. Main characteristics of the studies included in the review

Author	Year	Type of study	Origin	Context	Main conclusions
Sung et al. ¹⁴	2003	Narrative Review	Unites States	Research and Innovation	The core challenges facing clinical research can be listed in public participation, information systems, workforce training and funding.
Davis D ¹⁵	2003	Narrative Review	Canada	General practitioner	Further research is needed to discuss and test knowledge translation models, determining which domains and clinical contexts are most appropriate and which interventions produce results from medical care.
Hörig et al. ¹⁶	2005	Opinion Article	Unites States	General practitioner	A new model of healthcare practices is paramount and should seek better communication between basic scientists, general practitioners, health professionals and patients.
Graham et al. ¹⁷	2006	Narrative Review	Canada	Health education	The implications of translating knowledge for continuing education in health professions include the need to be based on the best available knowledge, the use of proven and effective educational strategies, and the value of learning about planning theories for change in practice.
Khoury et al. ¹⁸	2007	Narrative Review	Unites States	Genomics	The complete <i>continuum</i> of translational research needs adequate support in genetics, since a maximum of 3% of research published in this field so far focuses on T2 onwards and evidence-based guidelines and research on T3 and T4 are very rare.

Chart 1. (cont.)

Westfall et al. ¹⁹	2007	Opinion Article	Unites States	General practitioner	Practice-based research is a crucial scientific step for the major medical advances of the next 25 years.
Woolf SH ²	2008	Opinion Article	Unites States	Research and Innovation	The appropriate investment in T2 research is vital to recover the investments in T1 research, because bringing a medicine to the market without knowing how to bring it to the patients impairs its major objective.
Contopoulos-loannidis et al. ²⁰	2008	Systematic review	Greece	Medicines	Successful translation takes a lot of effort and time, even under the best of circumstances. However, making unrealistic promises for breakthroughs and quick cures can undermine the credibility of science in the public eye.
Dougherty et al. ²¹	2008	Opinion Article	Unites States	Collective Health	Starting a national discussion involving all participants in the translational research phases is a first step in improving health outcomes and transforming the health system of the USA.
Rubio et al. ⁸	2010	Narrative Review	Unites States	Health education	Translational research moves in a bidirectional manner from one type of research to another, from basic research to population-based research and vice versa, involving collaboration between scientists from various disciplines.
McClain DA ²²	2010	Opinion Article	Unites States	General practitioner	As mechanisms for promoting translational research, it stands out, among others, the training of individuals across the whole spectrum of translations, the simplification of the process of knowledge translation, the application of advances in computer science, image generation and data analysis to translational research and career development of translational researchers.
Morris et al. ¹⁰	2011	Narrative Review	England	General practitioner	Although little is yet known about the timing of delays and how they should be managed, translating scientific findings to benefit patients faster is a political priority of many health research systems.
Trochim et al. ¹¹	2011	Narrative Review	Unites States	General practitioner	Although there is still no consensus on translational phase models, there is little doubt that evaluation will be essential to manage translational research effectively.
Cabieses et al. ²³	2011	Systematic review	Chile	Collective Health	The incorporation of a translational perspective can become a priority for any country seeking to define what should be investigated, who should finance and how much resources should be invested in each stage of the research, in favor of the health of the population.
Guimarães R ⁴	2013	Opinion Article	Brazil	Research and Innovation	The universal health system as a fundamental part of the ecosystem of the demands of innovation by society.
Fishburn CS ⁵	2013	Opinion Article	Unites States	Medicines	Translational research represents a dominant strategy in the field of medicine discovery and will be paramount in defining the relationships between its actors in the coming decades.
Montoya HAC ²⁴	2013	Narrative Review	Colombia	Health education	The integration of basic sciences with clinical areas will provide an educational context of greater applicability to future professionals.
Silva et al. ³	2014	Narrative Review	Brazil	Telehealth	Telehealth is close to translational research by allowing people to connect science and benefit those in health services.
Hanney et al. ¹	2015	Narrative Review	England	General practitioner	It is necessary to distinguish between time elapsed and undesirable delays, as certain periods of time in the translation of research are necessary to ensure the safety, efficacy and cost-benefit of treatments.
Cohrs et al. ⁹	2015	Consensus	Europe	General practitioner	Translational Medicine is defined as "an interdisciplinary branch of the biomedical field, supported by three main pillars: bench, bedside and community". Its objective is to "combine disciplines, resources, knowledge and techniques within these pillars to promote improvements in prevention, diagnosis and therapies".
NIH ²⁵	2015	Fact Sheet	Unites States	General practitioner	The spectrum of translational science is not linear or unidirectional and each stage is based on and informs the others.
Vivas et al. ²⁶	2016	Systematic review	Brazil	Research and Innovation	The translational approach presents the interaction between the translation phases in a dynamic and non-linear way, with activities occurring in parallel and requiring constant feedback.
Luz PL ²⁷	2018	Narrative Review	Brazil	General practitioner	Among other points, it is essential to change culture within universities seeking the integration of basic and clinical research and multidisciplinary.

Source: Own elaboration.

The analyzed literature provides consensus that a shorter time is desirable in translating basic research into clinical practice, although it considers different standards of methods and definitions^{1,2,5,10,11,15,20,22,26}. Trochim, et al.¹¹ and Woolf² examined the most prominent conceptual models of translational research. Models have as their prerogative the explanation of a complex and multifaceted reality, based on empirical data. Especially in translational research, by identifying and characterizing the stages, as well as estimating the average time spent in each of them, one can better know reality with the aim of reducing the time between knowledge generation and its practical application, bringing more benefits to the population in a shorter time.

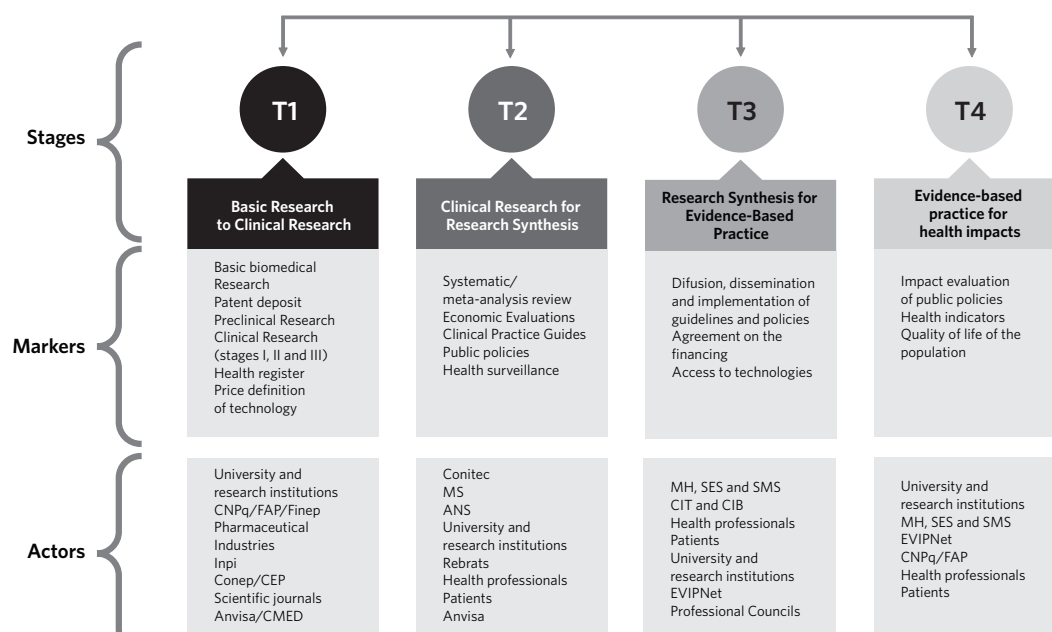
These stages are commonly referred to as time periods (T – time), in which

studies refer to two^{9,14}, three^{19,21} or four^{18,25} T periods. In examining and synthesizing various models, Trochim et al.¹¹ found five main macroprocesses of translational research, namely: i) basic research, ii) clinical research, iii) research synthesis (meta-analysis, systematic reviews and clinical practice guides), iv) evidence-based practice and v) health impacts.

Of course, because they are macroprocesses, there are numerous subprocesses with considerable specificities. It should also be noted that such processes do not necessarily occur linearly and sequentially, but, roughly, follow this pattern over time.

Based on the macroprocesses described by Trochim et al.¹¹, the steps and markers of translational drug research are described in *figure 2*, as well as the actors in the Brazilian perspective and in the context of the SUS.

Figure 2. Stages, markers and actors of translational research from the Brazilian perspective and the SUS context.



Source: Own elaboration. Stages and markers adapted from Trochim et al.¹¹.

T1 - From Basic Research to Clinical Research

Stage T1 covers the processes of basic research and clinical research, since discovery, development and registration of the medicine to a regulatory body. Basic research includes biomedical research, non-human experimental research and other non-clinical research^{3,4,9,24,28}. In the case of drug candidate molecules, preclinical studies are required for physicochemical characterization, demonstration of the safety profile and evaluation of various parameters by laboratory models (cell culture, tissue etc.) and testing in animals^{5,29}.

For research and testing involving human beings, prior evaluation and approval by the Research Ethics Committees/National Research Ethics Committee (CEP/Conep system) are required to protect research participants.

After approval by the CEP/Conep System, the clinical research of medicines, commonly classified into four phases (I to IV), begins. Briefly, in phase I, the medicine is tested in groups of healthy individuals, aiming to preliminarily evaluate the safety, pharmacokinetics and tolerability of the drug. In phase II, the drug is tested on patients to evaluate safety and efficacy, but still with few participants. In phase III, the number of patients increases substantially, usually involving other research centers, characterizing the so-called multicenter studies, seeking to confirm the efficacy and safety of these medicines. Such results are published in specialized scientific journals^{3,5}.

From a set of information and fulfilled all the requirements of the competent bodies, Anvisa evaluates and grants the health record of the medicine. The price of the medicine is also defined by the Brazilian Drugs Market Regulation Chamber (CMED), making it, therefore, available for marketing and wide use in the market. Finally, phase IV (pharmacovigilance) comprises monitoring of the medicine in daily practice^{29,30}.

The patent of the invention can be claimed, submitting the process for the proper evaluation of the National Institute of Intellectual Property (Inpi). In the case of pharmaceutical products and processes, the granting of patent will depend on prior consent of Anvisa.

The main actors at this stage are researchers from universities and research institutions, public or not, including the pharmaceutical industries and research participants. Funds for research funding may come from their own budgets or, where applicable, through agencies and institutions that foster science, innovation and technological development, such as the National Council for Scientific and Technological Development (CNPq), Research Support Foundations (FAP), the Financier of Studies and Projects (Finep) and the Department of Science and Technology (Decit) of the MH. It may also be mentioned the Department of Industrial Complex and Innovation in Health (Deciis/MH) and its activities regarding the promotion, development and innovation for industrial inputs in health.

T2 - Clinical research for research synthesis

In stage T2, phase IV studies of clinical research are carried out, as well as publications that compared the efficacy and safety of the new medicine in question with those available on the market for the same clinical condition. Economic evaluations of the cost dimensions and health outcomes of the drug before the payers are also carried out, whether they are the patient himself with payment from his/her own pocket, health systems through the financing of public programs and policies and the private market, from a national or international perspective^{2,4,16,27}.

With the plain production of these evidences, systematic reviews (with or without meta-analysis) are elaborated aiming at gathering and thickening the knowledge. This structured knowledge supports the evaluation of drug incorporation in the SUS, the elaboration of

clinical practice guides and public policies, guiding health decisions in clinical, administrative and political spheres^{8,17,30}.

As main actors, the National Commission for Incorporation of Technologies in SUS (Conitec) can be mentioned, as well as the National Supplementary Health Agency (ANS), universities and research institutions that have experience in Health Technology Assessment (HTA), linked to or not to the Brazilian Health Technology Assessment Network (Rebrats), as well as the technical areas of the MH, with emphasis on Decit, the Department of Management and Incorporation of Health Technologies (DGITS) and the Department of Health Economics, Investments and Development (Desid).

Similar structures may exist at the state, municipal and hospital levels, respecting the autonomy of subnational entities conferred by the Federal Constitution of 1988, with emphasis on the Pharmacy and Therapeutics Commissions (CFT), Drug Information Centers and Services (CIM/SIM) and Committees to promote the rational use of medicines.

T3 - From synthesis of research to evidence-based practice

Stage T3 comprises the processes and instruments involved in implementing guidelines and technologies. It incorporates a broader research scope than traditional clinical research, focusing not only on the patient level, but also on the provider, service organization and health policy level. Thus, in compliance with the norms, flows and recommended practices and from the implementation of policies and clinical practice guides, the medicine becomes available at the population level^{1,2,19,23}.

The Pharmaceutical Services and Strategic Health Supplies (DAF) may be cited in the MH, a key actor that has the competence to provide access to medicines incorporated into the SUS, as well as to implement and realize the continuous improvement of national

policies of pharmaceutical assistance and drugs. Regarding surveillance and health care, the actions developed by the Health Surveillance Secretariats and the Health Care Secretariat, respectively, as well as Anvisa, are essential.

As foreseen in the SUS regulation, effective integration and communication must take place between the three management spheres, since it is in the territory in which policies, programs and actions are effectively operationalized. The importance of the Bipartite (CIB) and Tripartite (CIT) Intergovernmental Committees is emphasized for policy discussion and agreement, including defining the responsibility for financing incorporated drugs.

Furthermore, this stage includes Decit, DGITS, Conitec and the Health Technology Assessment Centers, linked or not to Rebrats, responsible for the elaboration of HTA studies as well as for the elaboration and implementation of clinical practice guides. In addition, the Evidence-Informed Policy Network (EVIPNet) can be mentioned, an initiative to promote the systematic and transparent use of scientific evidence in the decision-making process for the formulation, implementation and evaluation of health policies, as well as providing greater interaction between managers, researchers and representatives of civil society^{31,32}.

T4 - Evidence-based practice for health Impacts

The last stage of translational research involves the comprehensive measurement of the benefits generated by the use of technologies. For example, health-related indicators such as quality and life expectancy of the population, morbidity and mortality rates can be measured, among others^{11,18,23,25}.

The impact evaluation of public policies would also be one of the markers that identify how much it was possible to advance and change a given health reality, through a

political action or choice. For example, there is no doubt that expanding access to vaccines and other essential medicines has completely changed the health history of countries.

As also in the other stages, a systemic evaluation of the health sector presupposes the integration and joint work among the actors of this stage, among which stand out managers from the three management spheres, researchers linked to universities and research institutions, civil society and the community itself. Development agencies and institutions play a relevant role in supporting and funding such evaluations.

Translational research related to medicines in the context of SUS: policies and normative acts

With the promulgation of the Citizen Constitution in 1988, the Brazilian State made possible the development of a universal and free public health system, based on important doctrinal principles, such as universality, integrality and equity. Since then, the SUS has been materializing through economic and social policies for its expansion and consolidation, in order to guarantee health actions and services that aim to promote, protect, cure and rehabilitate the health of the population³³.

Comprehensive therapeutic care, including pharmaceutical, is the field of action of the SUS that has been undergoing several designs since the publication of the Organic Health Law (1990). In this field, it is worth highlighting two National Policies: Medicines (1998), which aims to guarantee the necessary safety, efficacy and quality of medicines, the promotion of rational use and the population's access to those medicines considered essential; and Pharmaceutical Assistance (2004), which involves a set of actions aimed at health promotion, protection and recovery,

including pharmaceutical care as an intersectoral policy and guiding other policies, such as medicines, science and technology and industrial development.

Regarding the vectors that can contribute to the foregoing in the Federal Constitution as for the increase of scientific and technological development and innovation as one of the attributions of the SUS, the following are the normative policies and acts for the improvement of the regulatory capacity of the State, the technological domain aiming at SUS sustainability and the strategic use of the purchasing power of the State, especially of the federal entity.

The creation of the Secretariat of Science, Technology and Strategic Inputs in the MH, in 2003, made the Science & Technology (S&T) and Pharmaceutical Assistance guidelines more organic, in compliance with the Federal Constitution, and reinforced through the reports of several National Health Conferences and the I National Conference on Science and Technology in Health (CNCTS), held in 1994³⁴.

In 2004, from discussions held at II CNCTS, the National Policy for Science, Technology and Innovation in Health (PNCTIS) was launched. Among the strategies of this policy, the creation of the national health innovation system and the construction of the national agenda of health research priorities stand out^{30,34}.

The guidelines of this policy could be responsible for the intensification of the articulated actions between the translational research actors, aiming at the materialization of intersectoral policies, the availability of health products and services in a timely and costly manner to society. In the pharmaceutical supply chain, for example, such actions were important to foster public laboratories, institute programs (such as the Program to Support the Development of the Pharmaceutical Industrial Chain – Profarma) and enable research and development³⁴.

Formulated in accordance with PNCTIS

principles, the National Policy for the Management of Technologies in Health (PNGTS) was established in 2009, with the overall objective of ‘maximizing the health benefits to be derived from available resources, ensuring people’s access to effective and safe technologies under fair conditions’. Its guidelines orient the implementation and institutionalization of the processes of evaluation, incorporation, diffusion, management of the use and withdrawal of technologies³⁰.

It is worth noting that the procedures and deadlines for health technology assessment, preparation of clinical practice guides and availability of technologies in the SUS are regulated by normative acts (Law n° 12.401/2011 and Decree n° 7.646/2011).

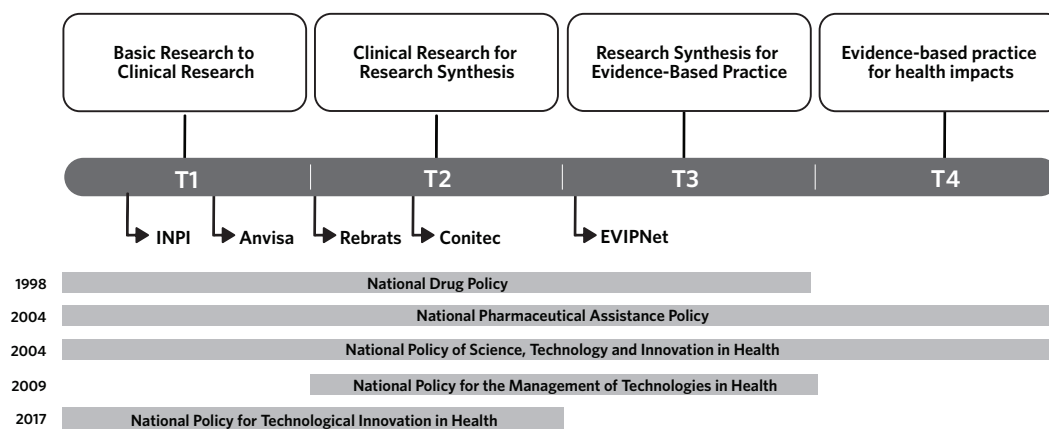
The strategy of the Productive Development Partnerships (PDP) is characterized as partnerships between public institutions and private entities, with the objective of transferring innovative and essential technologies to the public, reducing SUS vulnerability and reducing prices

charged. In 2014, the strategy had its regulatory framework redefined, establishing process steps and their respective deadlines, in addition to the annual publication of the list of products considered strategic for SUS³⁵.

Thus, the PDP resulted from the operationalization of the Productive Development Policy, launched in 2008 by Decree DSN of 05/12/2008, currently repealed by Decree n° 9.245, of 12/20/17, which established the National Policy for Science, Technology, and Innovation in Health. (PNITS).

In *figure 3*, the stages of translational research are schematically related to the instituted health policies on pharmaceutical assistance, research, science, technology and innovation. As cross-cutting policies to the four stages of translational research, the National Policy of Pharmaceutical Assistance (PNAF) and the PNCTIS are mentioned. The National Drug Policy (PNM) covers the stages from T1 to T3, the PNGTS focuses on T2 and T3, while the PNITS privileges T1 and T2.

Figure 3. Relationship between translational research stages and health policies imposed in SUS on pharmaceutical care, research, science, technology and innovation



Source: Own elaboration.

Discussions

Stages of translational research

Interest in translational research has been growing in recent years. Because it is considered a recent topic by many authors, there are numerous opportunities for scientific research. Only in 2010, a specific descriptor was introduced in Medical Subject Headings (MeSH), the Translational Medical Research. Until March 23, 2019, a PubMed/Medline search with that descriptor reported 9.192 results and for Translational Research [Title/Abstract], 8.906 results. In both cases, there has been an exponential increase from the last few years.

According to Woolf², translational research tends to assume different meanings for different people and contexts, but is considered important by all. Added to this are a range of specialist journals that have come up in recent years to communicate the subject: 'American Journal of Translational Research', 'Clinical and Translational Science', 'Science Translational Medicine', 'Journal of Translational Medicine', among numerous others of great prestige.

According to Hanney et al.¹ and Horig et al.¹⁶, the identification of the stages, markers and actors involved in translational research can contribute to the knowledge of the flows and times elapsed in each stage.

The methods for measuring the time of research and development of medicines included in T1 are not consensual among the authors who investigated the subject. This is due to several factors, among which stand out especially: i) the arbitrary choice of markers used to account for the beginning and end of the time period; ii) data and information that have not gone through peer review scrutiny of specialized literature or even data found in grey literature; and iii) data reliability problems^{1,10,11}.

Nevertheless, the process marker model

approach has been used with some reasonableness by authors, once the process events or markers are established, thus, allowing comparisons between the time used in research^{1,11}.

Moris et al.¹⁰ and Hanney et al.¹ emphasize the heterogeneity of the methods used in the studies that proposed to estimate the times of each stage of translational research, which makes the process of generalization and comparison of results difficult.

By knowing the biggest bottlenecks of time and process markers that tend to have the most variation, it is possible to invest efforts and resources into interventions to optimize processes that take more time than needed. In this last aspect, Hanney et al.¹ propose the use of the term 'time elapsed' to describe the total time required, reserving 'time lag' to describe the undesirable delays that occur in the translational search process.

Notwithstanding, ethical issues permeate translational research, especially with regard to clinical research, so that the desirable reduction of time between basic research and clinical research is ensured by good ethical and technical practices³⁶. In Brazil, the debate on clinical research is also in the Legislative power, where the Bill n° 7.082/2017 is pending, whose origin is PLS n° 200/2015, and divides opinions from many sectors of society due to the discussions involving the ethical, regulatory, clinical, social and economic dimensions.

The federal executive, based on a joint action, in 2005, between the Ministries of Health and Science and Technology, cites the creation of the National Clinical Research Network to integrate research centers and increase scientific and technological production²⁹. More recently, the Ministry of Health established, through Ordinance GM/MS n° 599/2018, the Action Plan on Clinical Research in Brazil, which aims to increase the capacity of the Country to develop and attract clinical trials. It is noteworthy that the translation and diffusion of knowledge in clinical research are presented as objectives of the referred Plan.

A recent study analyzing new medicines

registered in Brazil from 2003 to 2013 showed a disproportionate relationship between the percentage of new drugs and the burden of disease. Underrepresentation of drugs for infectious, heart and digestive respiratory diseases was found³⁷. Another study that evaluated clinical trials with drugs conducted in Brazil between 2012 and 2015 found that only 4% of them focused on poverty-related diseases³⁸. Both studies reinforced the prioritization and incentive strategies for the research and development of innovative medicines needed for the health situation of the Country.

Another time that adds up to T1 refers to that accounted for publishing research results in scientific journals. Yokote and Utterback (1974)³⁹, over 45 years ago, had already expressed concern about the substantial time lag between the completion of research and the dissemination of information, a problem often reported at the time by researchers and clinicians in impact journals, such as 'Nature', 'British Medical Journal' and 'American Journal of Psychiatry'.

The approach used by Contopoulos-Ioannidis et al.²⁰ to estimate the time lag (average of 24 years) in research draws attention to the aspects involving T2 and T3. The authors used as initial marker of the process the first scientific publication or patent filing describing the discovery of technology and, as final markers, the most cited articles (according to the authors, those with more than one thousand citations) and partial or total refutation of technology.

The limitation, in this case, is due to the fact that not necessarily practices and behaviors will be changed due to the existence of high impact articles or frequently mentioned in the literature. It is known, therefore, that the formulation of a public policy or clinical practice guide should be able to select, evaluate and adapt research evidence for health scenarios, taking into account social, cultural and economic aspects, among others^{23,31,32}.

In this sense, discussions about HTA have been gaining centrality in health agendas and

have their origins in the trends of Evidence-Based Medicine and health (SBE). The HTA process should address the health needs of the population, ethical, technical and political aspects such as budget, social control, responsibilities of the three spheres of government, as well as the principles of universality, completeness and equity of the SUS.

Regarding the prioritization of health technologies, a study³⁰ points out some strategies adopted by the MH in HTA processes. These are: epidemiological relevance (magnitude of the problem and burden of disease), relevance to services and policies (cost reduction and increased access by the population), knowledge phase (sufficient availability of scientific evidence and quality studies), operational feasibility (structure and resources available for technology implementation) and social/judicial demand (political pressure, lobbying and lawsuits).

The activities of stage T3 are subsidized by the culture of SBE. There is a consensus in the literature that the processes of formulation, implementation and evaluation of public policies should take into account the best available scientific evidence, aiming to rationally use resources and obtain effective policies. Thus, under the newer term Evidence-Informed Policies, such a process presupposes the need to use scientific knowledge in decision-making in order to reduce the gap between 'theory and practice'^{32,40}.

The translation of knowledge has the potential to reduce the distance between the generation of evidence and its application to produce impacts on health. Some continuing education strategies, such as academic detailing, the involvement of opinion-forming specialists and campaigns in congresses and specialized media, may be employed to increase the adherence of professionals to clinical practice guides^{15,17}.

Studies point out that the notion of translational research has been gaining steps beyond the bi-directional flow of basic research to clinical research by including in the models,

for example, aspects of productive processes and health care practices^{4,23}. This reveals the greater need for integration of research results when defining the impacts on population health in stage T4 of the translational research cited in some models^{18,25}.

Because they are even more complex and depend on a number of other steps and constraints, T4 evaluation studies are still incipient, which requires intersectoral efforts to conduct them. Future prospects, artificial intelligence, and big data methodologies may be required to process a huge volume of information from multiple sources to accelerate decision-making, bring competitive advantage, and sustain the healthcare system.

Translational research and pharmaceutical care, science, technology and innovation policies of the SUS

As a universal health system, SUS presupposes access to medicines as a fundamental human right to health. For this, public policies must guarantee these rights and generate benefits for the population. Moreover, such policies should be articulated and synergistic, considering the dimensions of research and innovation, technological internalization for public production of essential medicines, as well as the development of the economic and industrial health complex⁴¹.

With the creation of SCTIE, the agenda of S&T and health innovation gained strength and political space in the State agenda. It can be said that the legal-normative framework created through these policies induced a series of other programs and positive measures for health, namely: periodic institution of national agenda of research priorities, formation of critical mass of professionals and researchers, creation and promotion of National Institutes of Science and Technology, institution of generic

medicine (Law n° 8.787/1999), definition of mechanisms of drug price regulation by CMED (Law n° 10.742/2003), expansion of population access to medicines⁴², induction of the Brazilian national technology park³⁵, actions to promote the rational use of medicines, definition of the criteria for comprehensive therapeutic care and the deadlines and criteria for the evaluation of health technologies under the SUS (Law n° 12.401/2011), among others.

In an analytical essay on policies to promote science, technology and innovation in health in Brazil and the situation of clinical research, the authors conclude that Brazil has advanced in regulatory frameworks aimed at strengthening research and development activities²⁹. On the other hand, studies^{41,43-45} indicate that there are important agendas that need to be improved in the fields of health research, intellectual property, productive innovation and health technology assessment.

There is a situation of tension between the private interest in proposing the incorporation of registered medicines, even if these do not present as options for collective health, either by SUS already offer treatments with a better cost-effectiveness profile, or in accordance with health priorities⁴⁵.

Even with the regulated deadlines, there are cases in which the effective availability of medicines in the public network can reach 2 years⁴⁶, exceeding the 180-day deadline set in the legal provision. Moreover, it is known that there is a delay for it to be, in fact, widely used. Several factors influence the rate of diffusion of technology, such as availability and access to technology, training of health professionals, acceptability and preference of patients and professionals, organizational culture, media pressure and lobbying, presence or prioritization of the topic on the agenda health, judicialization, aspects of the clinical condition, availability of other medicines, among others^{47,48}.

Present on national and international agendas, access to medicines is not only a problem for developing countries, but also affects developed countries. Proof of this is

that the theme has gained space in the United Nations Organization, which convened a High-Level Panel to deal with the issue. In addition to the report⁴⁹ prepared by this Panel in 2016, another important publication⁵⁰ is added to the Lancet's Commission on Essential Medicines, in 2017.

As Bermudez⁴¹ reveals about patents and intellectual agreements and the state-market-society relationship, there are inconsistencies and tensions between the right to health and the rights to intellectual property and trade, once current prices for various medicines are beyond the reach of governments and patients.

Limitations of the study

As for the limitations of the study, the unpaired selection of first stage articles can be cited, as well as the difficulties inherent in locating articles. In this last aspect, the example of the recent descriptor incorporated in the MeSH, the heterogeneity of the keywords and descriptors used in the publications, which directly impacts the way of indexing the articles are mentioned. It is also mentioned the disagreement between the published studies regarding the definitions of translational research stages, which, depending on the adoption of one or another model, can directly influence the arrangement and organization of stages, markers and actors.

It is worth emphasizing that stage 1 (From Basic Research to Clinical Research) must necessarily occur so that the other steps unfold from the availability of a drug in the market. However, from T2 onwards, the stages do not necessarily take place chronologically or sequentially. Public policies that could be related to certain medications may never be instituted (T2), clinical guidelines may never be developed or published, and the impact on the living conditions of the population may not be measurable. Therefore, the schematic representation of *figure 1* seeks to approach a situation that takes into account

a 'rational' that, often, does not materialize in real-world scenarios.

Perspectives and challenges for translational health research in Brazil

In the publication 'Health in Brazil in 2030: guidelines for strategic prospecting of the Brazilian health system', translational research is cited as a niche of competence to be explored within the Health Economic-Industrial Complex⁵¹. This denotes the importance of translational research as a theme that should be present in the agenda of the State for the induction and articulation of economic and social policies, aiming at development with equity and supported on a sustainable and solid basis for the provision of social rights to the population, including access to health goods and services.

As a challenge to translational research and the advancement of science, technology, and pharmaceutical assistance, it refers to the scenario of the federal government spending ceiling, established through Constitutional Amendment (CA) n° 95/2016.

Leite et al.⁵² emphasize the need to increase the budget for health funding and the repeal of CA n° 95/2016. Coupled with this, the uncertain future scenario for the funding of research, whether basic or applied, the promotion of public production of medicines and the induction of the Economic-Industrial Health Care Complex, as well as the impact on the capacity of the State to incorporate or not new technologies and the continuous provision of those already incorporated^{35,41,53}.

Thus, it is increasingly necessary to improve the efficiency of the State to design, implement and evaluate public policies informed by the best available evidence, integrating what is necessary, rational and cost-effective to improve the health and living conditions of the population.

In conclusion, there are high expectations in translational research regarding a gradual and consistent change of culture in the health system, as it proposes to approach and systematically integrate the steps, processes and key actors to reduce the distances between knowledge generated and its application to produce more benefits for society.

Collaborators

Lupatini EO (0000-0001-6231-891X)* contributed to the conception, planning, collection,

analysis and interpretation of data, preparation of content and approval of the final version of the text. Barreto JOM (0000-0002-7648-0472)* contributed to the conception and planning of the study; critical revision of the content and approval of the final version of the text. Zimmermann IR (0000-0001-7757-7519)* contributed to the interpretation of the data and critical revision of the text. Silva EN (0000-0001-8747-4185)* contributed to the development of the study design, data analysis and interpretation, review and approval of the final version of the text. ■

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