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Public Policy for Regenerative Medicine in Brazil: Changes in State Capacities

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Abstract:
Conclusions of ongoing research projects on regulation frameworks, institutional and State capabilities, innovation, media coverage and patient organizations´ practices are the main context of this paper on regenerative medicine in Brazil, comparative to the sector´s global evolution. The present study´s main purpose is to map historically, in a brief manner, trends in State agencies´ capacities to develop main public policies and normative actions on innovation and regulation in the sector and show controversies and their unresolved gaps and conflicts. It aims at showing the contradictions existing between the high quality of local scientific and medical development, production, distribution and implementation of advanced therapies and the problems faced by State agencies for therapy approval and their full adoption within the public health system, in ways that provide wide public access. The study also considers the incoherence and duplication of efforts found within and between relevant public agencies, the lack of adequate training in the area among key policymakers and their scarce knowledge on strategies directed to media coverage and general public engagement. Their development and the adoption of regenerative medicine by the public health system could become some of the main short-term challenges for the State in Brazil, in the short and medium terms. The paper concludes that the country would benefit from declaring regenerative medicine as a strategic sector for scientific and industrial development in the near future and ends mentioning some policy recommendations that could contribute in that direction.

Keywords: regenerative medicine, cellular therapy, State capacity, health policymaking, molecular genetics, rare disease patient organizations, State agencies, public health system.

INTRODUCTION

Regenerative Medicine (RM), a subsector of stem cell research and molecular genetics, has transformed conventional medical practices (Webster, 2011). RM focuses on the repair and regeneration of cells, tissues and genes, using different kind of stem cells removed from human bodies and generally reproduced *in vitro* (Mason& Dunnil, 2008). Cellular and genetic therapies are often applied jointly and they have been classified as advanced therapies (AT).

They are often described in media coverage in overly optimistic ways and give unrealistic hope of readily available new cures, especially, to treat fatal or rare diseases (Bubela et al., 2012). However, the risks and uncertainties in the manipulation of biological materials that are alive are still a matter of scientific and social concern (Martin et al., 2008). RM has required new forms of regulation of biological materials and products as well as, the updating of some of the State capacities to handle and implement new cellular and genetic therapies, at the public, private, local

and supranational levels (Morrison, 2012; Faulkner, 2016). This new medicine has also led to the inclusion of new social sectors (stakeholders) in the area´s governance.

The present study, summarizes conclusions from previous and ongoing research on RM in Brazil undertaken in comparison to practices in other countries– especially, to the United States of America and the United Kingdom, two world leaders in RM. Among those studies can be mentioned: a) a research project self-coordinated and financed by the Foundation for the Support to Research of the State of Rio de Janeiro (FAPERJ) in the position of Visiting Senior Professor (2009-2010) and by the National Council of Scientific and Technological Development (CNPq – Universal Call for Grants,2009) between 2010 and 2012: 'Development of Governance Capacities: Social Visions and the Debate on Stem Cells in Brazil'; b) the research project: 'Public policies on innovation and regulation in stem cell research: a comparison between the cases of Brazil and the United Kingdom´, developed as Senior Researcher of the CNPq between 2018 and 2019; c) the ongoing research project : 'State and supranational capacities in innovation, governance and regulation in Regenerative Medicine: The experiences of Brazil, Argentina, the USA , the UK and Canada', part of the INCT/PPED/IPEA network since 2020 and, at present, also supported by the a Postdoctoral level scholarship from the CNPq (07/2023-06/2024).

The present study has the aim of:

- Mapping the main public policies and regulations in RM in Brazil since its beginnings till today.
- Discussing the main State capabilities and activities in RM throughout time and showing gaps, incomplete aspects and conflicts between agencies, their capacities and forms of regulation.
- Suggest recommendations on public policy for RM in Brazil for the near future.

RESEARCH METHODS

Methodologically, the study is based on a bibliographical and documental revision, using mainly secondary data and on a qualitative analysis of information, as well as, on limited quantitative analysis of statistical data. More specific information was raised, specially from the websites of the main innovation, regulatory, legislative and ethic review public agencies and institutions that directly or indirectly deal with RM, as will be shown in the text. This data contributed to the construction of the brief historical perspective on the main events in RM in Brazil presented in the next section.

Semi-structured interviews - of approximately one hour duration- were conducted, at intervals, between 2019-2020 to key informants (5) and 15 to Brazilian RM leaders. Thirty interviews had been previously carried out, between 2010 and 2012, with a sample of: local scientists, policy makers and representatives from civil society. Another six interviews were developed more recently with leading policy makers from Brazilian public agencies (2021-2022). Moreover, 28 interviews with representatives of patient and civic society organizations were developed between 2021 and 2022.

These interviews were analysed for context, content, narrative and emotional connotations, as well as, their implicit social values, following what Mulkay (1993, p. 723–724) has defined as "discourse regularities", meaning: the forms and contents that are constructed according to social and cultural beliefs that reveal the interconnections between the basic views of the

interlocutors. Narratives from open-ended questions were analysed looking for convergence, divergence, dissonance and smaller variations in dealing with key topics.

This analysis focused on recurrent themes found in the secondary data previously gathered, upon categories such as:: trends in financial budgets and modalities, levels of coordination between State agencies, training programmes for policymakers, flaws in innovation, regulation and monitoring, design of RM aims and objectives, type of State dynamic capacities (quality and coherence of public policies and actions, partial or wide policy reach, legitimation of public decision making processes, leaderships' strategies, as well as, operational and administrative skills) and the engagement dynamics of different social sectors. Results were reviewed and coded qualitatively following the methods prevailing in grounded theory (e.g., Bonilla-Garcia et.al. (2016); Cutcliffe (2001); Harris (2014)).

BRIEF HISTORICAL ACCOUNT OF THE MAIN PUBLIC POLICIES IN RM

The main events in RM public policy in Brazil, since its beginnings, will be summarized next, showing recent developments and institutions in this field. The section does not intend to present a complete picture of the historical evolution of the local scientific, medical and regulatory progress, though it illustrates its key moments. [For a more complete description see, The author, 2023].

The beginnings of RM could be located around 2001 with the creation of the first public bank of umbilical cord blood and placenta (BPSCUP), based at the National Cancer Institute (INCA). Between 2003 and 2009, the Health Ministry (MS) and the National Council for Scientific and Technological Development (CNPq) – within initiatives located its Department of Science and Technology (DECIT) and its Secretariat for Science, Technology and Innovation and Industrial Complex (SECTICS) - launched a number of calls for research grants, fellowships and scholarships on stem cell research. In 2004, the MS contributed to the establishment of the Public Network Brazil Cord, banks for the transplant of bone-marrow and umbilical cord cells to patients. During the design of the National Agenda of Priorities in Health Research (ANPPS), in that same year, alongside the scientific community, RM was included for the first time.

A big step was taken at the national level with the design and implementation of a large multicentric randomized clinical trial on different types of heart disease using adult stem cells (EMRTCC) and covering clinical phases 2 and 3. It was financed jointly by the Ministry of Science, Technology and Innovation (MCTI) and the MS. This trial included nationally, 1 200 patients and 30 centres and lasted from 2004 to 2012. Though arriving at some interesting results regarding heart conditions provoked by Chagas disease, its Coordinator announced that more basic and clinical stem cell research would be required to meet the necessary standards to develop efficient clinical therapies (Zorzanelli et.al, 2017). However, it became a quite well-known trial at the global level, as only Germany had been previously responsible for performing a similar kind of expanded clinical trial.

The stem cell initiatives where somewhat stalled between 2005 and 2008 due to internal debates on the use of embryonic stem cells for research, a sensitive issue in Brazil. In 2005, the Biosecurity Law (Lei nº 11.105) was approved by Congress. This law considered the use of both genetically modified organisms (GMO) and embryonic stem cell research, under certain conditions. At that time, the Technical National Commission of Biosecurity (CTNBio) was created within the MCTI, as a technical consultation body to the Federal Government, for the implementation of the National

Policy on Biosecurity. It prioritized evaluations on GMO and the environment, but also the protection of human health and living organisms. However, in 2008, a Direct Action of Unconstitutionality (ADI 3.510) was presented to the Federal Supreme Court (STF) against stem cell research with embryonic cells, on moral and religious grounds. This led to an extended public debate and an open public audience. (See, The author, 2011; Cesarino, 2007, for further details). Two groups were central in that debate: those against their use, associated to the Catholic and Evangelic Churches, including also a minority of specialized scientists/medical doctors, and another one, in favour of that type of research and integrated by the majority of the scientific specialists, representatives from organized civil society groups, patient organizations and individual patients. Finally, the controversy was resolved in favour of the continuation of embryonic stem cell research, though only with the use of cells extracted from eggs frozen for over three years since the law was passed.

Once this issue was legally resolved, there was a need for specialized scientists to collaborate more closely between them in the studies being developed. With this aim, in 2008, the National Network of Cellular Therapy (RNTC) was founded to support those data exchanges and also eight new Centres of Cellular Therapy (CTC), to develop research grade stem cell lines. Moreover, new public calls for grants for research centres and laboratories were launched. These initiatives were financed by the MS (DECIT) in collaboration with the MCTI, the CNPq, the National Bank of Economic and Social Development (BNDES) and the Agency for the Funding of Studies and Projects (Finep), i.e. by all the main agencies for funding science and technology at the national level.

The following year the area kept expanding through the signing of a Cooperation Agreement between Brazil and Argentina (PROBITEC), for the exchange of students and professionals and collaboration in joint research projects. The decision was taken jointly between the MS (DECIT) of Brazil and the Ministry of Science, Technology and Industry of Argentina. It became a very successful endeavour that was periodically renewed.

By 2010, the country was ready to launch its first bank of embryonic stem cell lines developed locally and called LanCE- National Laboratory of Embryonic Stem Cells. The bank later on, started to work also with iPS lines (induced pluripotent stem cells). This was an initiative launched between the Federal University of Rio de Janeiro and the University of São Paulo.

That same year there was also the establishment of the National Centre for Structural Biology and Bioimage (CENABIO) supporting preclinic research. It was jointly funded by the Ministry of Education (MEC), the Universal System of Health (SUS) and the Chan Zuckerberg Initiative. The National Bank for Pluripotent Induced Stem Cells (iPS)- Patient Specific, was created in 2011 by the National Agency of Sanitary Vigilance (ANVISA) and the UFRJ. The following year, a new Bank was also established for iPS between the UFRJ and the USP. These cells began to be locally and globally more widely used in research and therapy, as they present less moral controversy, compared to embryonic stem cells and have relatively similar effects.

Since 2012, the MCTI and other public agencies took several new initiatives regarding the protection of animals, such as, the creation of the National Network for Alternative Methods (RENAMA) – for the substitution of animals for experimentation in the laboratories; the approval of the normative resolution (RN) nº 17, 2014, by the National Council for the Control of Experiments with Animals (CONCEA); the RN nº 18, of 2014, that considers seventeen alternative

mandatory methods for the use of animals in research, as well as, the RN n° 31 of 2016 that added seven other methods.

In 2012, given the fast expansion of the area, ANVISA created both, the Technical Chamber of Advanced Therapy (CAT), as its consultative branch for RM, as well as, the Brazilian Registry for Clinical Trials (ReBEC) linked to the United Nations Registry. However, the first lacks adequate representation of organized civil society. Registration became mandatory for the performance of all new clinical trials in Brazil. These had previously only some been registered at the Clinicaltrial.gov USA platform, that does not check for the technical or ethical approval of the trials announced.

A number of Normative Resolutions (RDC) had already been passed by ANVISA, between 2004 and 2013, to prepare for the local consolidation of RM regarding regulatory procedures. These were, for example, the approval of RDC 21 that contributed to the tertiarization of clinical trials by specialized consultants, the RDC 36 21, that simplified the directives on good clinical practices and the RDC 38 for the approval of medicines with "expanded access to patients", compassionate use and use post clinical trials.

In 2014, the MCTI, the MEC, the CNPq and the Coordination for the Improvement of Higher-Level Personnel (CAPES) launched a pioneer training and research programme called 'Science without Borders', to promote the internationalization of local S& T, innovation and competition through scientific exchanges and professional/student international mobility, that positively impacted upon RM.

In order to promote the culture of human tissue in 3D studies, in 2015, the project "Human–on-a-chip" was established at the National Laboratory of Biosciences in Campinas, São Paulo. This facilitated enormously the testing of medicines, generated from biological materials extracted from specific individuals and reproduced three dimensionally. The new technique facilitated the path towards 'personalized medicine'. The programme was jointly supported by the MS, the MCTI and the CNPq.

To further promote the path towards translational medicine in RM, the Federal Brazilian Constitution of 1988, that prohibits the commercialization of the human body or its parts in paragraph 4° of article 199, was reviewed in 2018, by the Federal Attorney´s Office together with Anvisa. Their final Report n° 12/2016 PF-Anvisa/PGF/AGU, then allowed for the use of biological materials in the development of stem cell and genetic therapies.

The expansion of the legislative approach allowed for the further clinical development of advanced therapies (AT). These were only defined as such in Brazil that same year, i.e. each as a Product of Advanced Therapy (PTA) - that comprise cellular, genetic therapies, and tissue engineering. AT were divided into two classes, I e II, those less and those highly manipulated. For each category different norms of production and implementation became mandatory, as the first class (I) – the use of a patient tissue for the culture of stem cells and reintroduction into his own organism or autologous use - presents less risks and more security than the second class (II). The last type is generated from tissue provided by multiple donors and are eventually applied to larger groups of patients, or else, are commercialized 'off-the-shelf', for example, skin to cure burns. This big change of course in local regulation was complemented that same year by the issuing the

RDC 214, that defines good clinical practices in research with human beings (BPF) and the RDC 260 that describes standard protocols for the development of clinical trials in AT.

In 2019, through a joint effort between some of the main public Universities, such as, UFRJ, USP, UERJ, other public institutions – Anvisa, FAPERJ, INCA - and with the support of the PNUD, the mapping of the genetic profile of the immune system of 4 million Brazilians was started. This programme was located at the National Bank of IPs cells. In that same year, with the purpose of aiding specialists in applying the new regulatory framework correctly and also, for the analysis of *dossiers* of clinical trials and/or the registration of new products, the National Network of Specialists (RENETA) was formed by Anvisa integrating 30 reviewers. Given the importance of Big Data in this field and in other health issues, the Action Plan for the Monitoring and Evaluation of the Digital Strategy of Health in Brazil was also set up.

In 2020, a number of different regulatory measures were taken. Two genetic therapies were approved by Anvisa: Luxturna (Novartis Biosciences) for retina hereditary dystrophy and Zolgensma (developed by Novartis Biosciences) for muscular spinal atrophy among children less than 2 years old. The RDC 338 was passed to regulate the adoption of AT in the public health system and its commercialization in Brazil. There were also other new Research Grant Calls for industrial innovation in RM and designed by the Brazilian Enterprise of Industrial Innovation (EMBRAPII). Also, the MS in collaboration with the MCTI, the CNPq, the BNDES and Finep, as well as with the scientific community, announced an important Call for Grants for research projects on AT, of the order of 48 million reais.

Another milestone involved the creation of the National Programme of Genomics and Precision Health ("Genomas Brasil") through the Resolution 1949, that involves two different stages. First, stage 1.0 to sequence the genome of local people with rare, heart, infectious diseases and cancer for diagnoses and prevention and second, the stage 2.0 of AT for therapeutic aims. The programme, financially supported by the MS and the MCTI, was launched at the President´s Office. The investment initially proposed was of 160 million reais and different international partnerships were signed. One of the most important agreements on bilateral scientific cooperation in AT was established between the MS and the United Kingdom, in 2022. In that same year, a new genetic therapy developed by the firm Novartis Biosciences was approved by Anvisa, i.e. Kymriah used for the treatment of refractory or lymphoblastic leukaemia.

The next section will explore, given this type of progress in RM in Brazil, what has been the State´s positioning regarding interaction between agencies, the development of normativity and the spaces that remain open to design further measures and/or for change.

THE EVALUATION OF STATE PERFORMANCE: PROGRESS, LACUNAE AND/OR UNSOLVED TOPICS

A group of State dynamic capacities in Brazil have been gradually evolving, most especially, over the last ten years. Dynamic capacities have been defined as those that target concrete problems, especially, in contexts of risks, uncertainty and permanent transformation (Kattel & Mazzucatto, 2018). At the very beginning of RM in Brazil, during the last decade, there was a synchronized State coordination between the MS, the MCTI, Finep and BNDES, all of them focused on promoting collaborative networks between sectors of the specialized scientific community.

Initially, there was also a strong dependency of the relevant State agencies from the substantive contributions of the emerging public scientific sector, in relation to the definition of strategic priorities in RM within basic and preclinical research topics, for supporting the modernization of equipment and infrastructures, as well as, towards updating regulation. But after that initial stage, RM key policymakers started training activities to specialize in RM, for example, they participated in national level training programmes, established collaboration between representatives of different agencies, undertook visits to key international institutions, as well as, organized internal debates between different agencies relating regulation and organizational experience. Policymakers also promoted international scientific partnerships and participated in the upgrading of the ethical, regulatory and juridical framework in RM, for example, discussing the Law Project (PL 7082), about developing a new System for Ethics in Clinical Research.

At present, operational capabilities among policymakers have substantively improved, in spite of there still being an important deficit in relation to clinical research monitoring, the manufacturing of therapeutic products and the management of the large volume of data commonly generated by this type of research (Big Science). Misinformation and dis-information also contribute to hinder the systematic evaluation of results in the implementation of RM public policies. Lacunae in public action harms the development of State planification based upon evidence and transparent disclosure of new initiatives and results to the general public. As a result, it indirectly reduces useful public engagement.

However, mission-oriented public policy has been scarce in RM. This type of policy entails the resolution of concrete problems creating conditions to access new markets through systemic actions with specific objectives and it is fundamental in the formulation of policies in any frontier sector, such as RM, that presents still a lot of risks and uncertainties and is continually changing. (Mazzucatto,2017; Kattel & Mazzucatto, 2018; Edquist& Zabala- Iturriagagoitiaa, 2012). Thus, RM public policies have had limited reach, are subjected to high experimentation and conducted in quite a disorganized or partial manner and, in some cases, with parallel, contrasting or overlapping initiatives taken by different public agencies, for example, in the case of funding. Moreover, these policies are very far from attaining global standards on RM (The author, 2014). Furthermore, the sector lacks long term financial stability and sufficient finance for basic, pre-clinical and clinical research. This is largely because research projects tend to be funded mainly through the Calls for Grants and/or Scholarships of the CNPq (see, Table 1) or of State-level research agencies, that support every research project approved just for short periods of time, usually one to two years, - too short a time to reach substantive results in RM. The choice of projects lacks a direction towards national strategic priorities on RM.

Table 1: Distribution of funding for RM among agencies and number of projects in stem cells, cellular therapy and regenerative medicine (2002=04/2021)

State Agency	Value (R$)	%	Number of projects	%
Ministério da Saúde (DECIT-SUS)	150.772.638,15	32,24	257	15,52
BNDES	46.135.329,00	9,86	7	0,42
FINEP/MCT	88.410.031,34	18,90	34	2,05
CNPQ	182.354.707,59	38,99	1358	82,00
Total	467.672.706,08	100	1656	100

Source: The research.

State action legitimation has varied throughout time. There was a moment when RM received full support and had an important expansion – during the two periods of President Lula Da Silva´s government and the first period of President Dilma Rousseff´s. Both governments were sustained by similar hegemonic coalitions, i.e., stakeholders´ groups that included sectors of organized civil society (Gaitán & Boschi, 2016). Those coalitions acted following a specific type of convention, based on a 'developmentalist' style, to deal with technological and industrial progress. A convention has been defined as, "a collective cognitive devise, formed by codified and tacit knowledge that allows to hierarchize problems and solutions, as well as, facilitate coordination between social actors" (Erber, 2011, p. 53).

By contrast, since the second government of President Dilma Rousseff, policy actions favourable to RM were reduced. There was a still more systematic weakening of the support system of RM in the following two government periods–those of Presidents Michel Temer and Jair Bolsonaro – whose hegemonic coalition was based on a new set of elite social actors that promoted a neoliberal ideology and literally attacked science and education. This more recent period, is characterized by strong budget cuts in most public agencies, such as, at the MCTI and the MEC. Those cuts included: diminished funding for ongoing projects, a substantive reduction in the number of research calls for new RM projects, substantial cuts in financial aid for students´ and professionals´ training, as well as, for the international exchange of students and professors in associated careers (Interview conducted with Rodrigo Rocha, Innovation Superintendent at Finep, May 5, 2022) (Reis & Macário, 2020).

At present, there is a new wave towards a more effective coordination of public policy between those agencies that support funding and those that develop regulation, even though, policies still present many flaws, as observed, for example, in the fragmentation of sources of funding (Table 1). Lack of a centralized public program on RM, has also contributed towards excessive bureaucratization of the ethical and technical approval of AT projects. Vacuums and discontinuities in policy implementation are mainly found in the definition and follow up of biological materials to start research, the incomplete regulation of clinical trials and of good manufacturing AT practices- even when norms on these issues have been recently passed. In the last years, agencies have tried to improve researcher´s training in new regulatory procedures for grant applications (See, the setting up of the internet-based network RENETA by Anvisa https://www.reneta.org.br/).

Administrative and operational State capacities are out of pace with the fast development of this emerging scientific and medical area. Local scientific breakthroughs in RM are reflected in, for example, the large amount and good quality of Brazilian scientific researchers´ publications or those studies co-authored with foreign professionals and published in internationally prestigious journals (The author, 2013; 2021; Machado, 2021). Moreover, the development of operational capacities within some of the government agencies has taken place only after the shaping and expansion of the institutions that form the main public scientific structure. For example, there is a profound neglect in governmental design of upgraded measures for continuous planning and monitoring within the CTC and the Centres of Excellence in Genetics (Marin & Paganini, 2018). The sector has largely self-evaluated its own activities. There is an absence of effective regulatory measures within State action to support manufacture of nationally generated allogeneic AT (e.g. Silva Junior et.al., 2018; Bizon Carlas et.al., 2018; Valadares Folgueiras-Flatschart et al., 2018; Cavaleiro da Costa et al., 2018; Miranda Parca et al., 2018). In the case of autologous cellular transplants, that have a longer tradition in Brazil, better control measures have been already

implemented by the State. Misinformation and dis-information also contribute to hinder a systematic evaluation of results in the implementation of RM public policies. Lacunae in public action harms the development of State planification based upon evidence and transparent disclosure of new initiatives and results to the general public. As a result, it indirectly harms productive public engagement. The majority of the academics working in RM lack deep involvement with the general public, as well as, with private hospitals and private national or foreign firms, except in a few cases, some associated to multicentric clinical trials. No relevant mechanisms have been designed to offer incentives that would strengthen the relations between hospitals and academia, between academia and firms and between foreign and national partners. Moreover, stage 3 clinical trials are yet not too frequently performed in Brazil and usually, depend upon international sponsors that do not work too closely with local research centres.

In spite of a longstanding programme for the implementation of public/private partnerships, based on the legal norms established by the Technological Innovation Law of 2004 (Lei de Inovação Tecnológica 10.973) and the Law of Goods of 2005 (Lei do Bem 11.196), neither law discusses the specificities needed to adjust to the differential characteristics of AT. Both industrial and technical capacities in RM to attain therapy manufacture, present important gaps when compared with those prevalent in advanced countries – see, for example, the functions of the Gene and Cell Therapy Catapult in the United Kingdom https://ct.catapult.org.uk/ and the studies of authors, such as, Gardner & Webster (2018) and Acero (2019; 2020).

In the present study, BNDES´s interviewees commented that the firms´ demand for refundable credits is almost inexistent, because AT are still considered as 'services' – instead of products- contrary to the last resolutions approved by da Anvisa. Moreover, in the case of clinical trials, national firms show yet no interest to invest. Finep is the agency that tends to finance the whole innovation spectrum of a set product, i.e., until the product reaches the market with technological maturity. It has had an initial role of structuring RM, as well as, recently approved aim-specific project funding for private hospitals. The non-refundable or 'collaborative' funding offered by Finep has also been substantive and mainly bestowed to institutes of science and technology (ICT) in partnership with firms. The institution has also granted refundable economic credits to start-up firms in RM- even though, in this case financial aid has been quite limited.

In spite of these strategies, recent concrete State actions for the promotion of innovation capacity have suffered from the persistent dismounting of the resources for the National Fund for Technological Development (FNDCT), since 2015. (Reis& Macário, 2020) - official policy of President Jair Bolsonaro ´s government. Investments in science and technology have been reduced to the order of 600/700 million reais - an amount that, according some of our interviewees, "would not even pay for the scholarships from CNPq".

One of the weakest spots and a matter of concern and of some urgency relating State capacities in health, consists in the adequate preparation of the public health system (SUS) for the correct implementation of AT. Upgrading of SUS´s functions suitably should include: the specialized training of medical doctors, health technicians and nurses, the reform of infrastructures and transport, the gathering and storage of clinical data and a wider participation of patients and patient organizations as key informants. Moreover, in the case of genetic therapy and bioinformatics associated to RM, the country even lacks the number of specialized professionals required.

However, SUS counts with the capabilities and the institutions to develop the adoption of new therapies, such as: the National Commission for Technology Incorporation (Conitec) with 123 members, created in 2011, and the Brazilian Network for Health Technology Evaluation (Rebrats), which runs 24 Nuclei of Technological Evaluation in Health (NATS), since 2009, within public hospitals to coach management strategies. These instances need only to be upgraded and suited to AT demands. (Uziel,2020; Caetano et al., 2017).

All of the public institutions analysed up to now have recently organized debates and seminars to discuss new models for the adoption of AT in the national level, for example, the viability of different cost reimbursement systems for AT, the potential for the design of public models for cost reimbursement based on shared risks between stakeholders and /or on the results obtained by treatments. But the design of alternatives for the reimbursement of costs by the private health plans and of the fixing of adequate market prices for AT are still unresolved matters. Thus, it is important to further build up the necessary State capacities for the construction of social consensus relative to these topics.

However, the innovation RM pathway adopted in Brazil presents a significant flaw: the limited inclusion of organized civil society - beyond the scientific and medical community and of some representatives from key firms, especially from start-ups. This acts as a big obstacle within the State, as it lacks awareness of the problem, as well as, scarcely trains its policymakers to design public engagement strategies. These are largely restricted to public consultations by internet, announced in the websites of the relevant agencies and scarcely publicized. Inclusion of stakeholders´ opinions becomes extremely selective in those consultations and their participation within assessing bodies and technical chambers of the agencies in charge is very reduced. Given this situation, places for formal discussion and debate with the integration of those different social organizations´ views become an exception. Thus, patient organizations of rare diseases interviewed for the present study, reveal a continuous need to actively verify the implementation of public policies already designed and legalized by government (The author, 2022). These associations have to exert permanent pressure on the State to have their rights to access AT guaranteed, even when some products, e.g. three genetic therapies, have already been approved by Anvisa for local commercialization, though they are to be acquired privately (i.e., out of SUS).

Adequate training of policymakers in public and media engagement, the reduction of the evaluation periods of health therapies and wider public access to medications, could also contribute to reduce the "judicialization" of health associated to RM, in the acquisition, distribution and utilization of AT (Souza Soares & Deprá, 2012). Wider disclosure of information, could also contribute to avoid medical tourism towards foreign countries for patients looking for RM treatments unavailable in Brazil – medical tourism that has expanded globally (Sipp et.al., 2017; ISCT, 2018; Rivas et.al., 2018).

The uncertainties and risks that frequently characterize AT and the real time periods between scientific and medical experimentation and the approval of products and adoption by SUS, are aspects that are practically absent from contemporary Brazilian public debates. In this sense, the State has been unable to accompany the national and global scientific and medical developments in RM. It also requires to focus more actively in the simplification and modernization of the terms of free and informed consent for patients (TCLE) via the ethic evaluation system of the Commission for Ethics in Research (CONEP) - the central headquarter- and the Committees of Ethics in Research (CEPs) – distributed within institutions of education and research throughout the country. It is

evident, for example, that the instruments of TCLE must be better structured and targeted to the needs and levels of comprehension of patients, as well as, to the specificities of RM.

On the other hand, the State could have greater participation in a more transparent disclosure of information on ongoing therapies and clinical results through an adequate access to mass communication tools and services. The role of RM relevant agencies vis-à-vis the media is very limited, in spite of the national efforts taken towards defining a Programme on the Popularization of Science and Technology supported by specific grant calls, fellowships and scholarships and launched by CNPq and the Coordination for the Upgrading of Higher-Level Personnel (CAPES) (See, Tait Lima et al., 2018). Communication with the media has been taken up by specialized professionals and patient organizations committed to the local development of RM.

In summary, some of the advantages and disadvantages of the Brazilian State system in relation to practices in RM have been briefly discussed. The next section presents general conclusions and some recommendations for the future of the sector, at the national level, and its potential projection towards the global arena. They are based on our research results, as well as, on the comments from colleagues and research participants, that were generous enough to review a first draft of the present proposal.

CONCLUSIONS

The study´s results provided some indication towards the implementation and follow up of RM, engaging the wider public at the national level and tried to consider the near future projection of local RM at the global level. Conclusions are intended to contribute to orient, decision making processes at the most relevant State agencies, based upon recent evidence, and most especially, offer reflections on how to promote wider access to AT therapies for patients and their families.

For Brazil to become a global multiplier in RM, at least within Latin America, or else, a key actor among the so-called BRICS (Brazil, Russia, India, China and South Africa) and future BRICS 'enlarged', the sector has to be explicitly declared by the State to be a strategic area for national scientific and public health development. Most especially, as it has been recognized, that RM will become the 'medicine of the future' and Brazil´s contribution cannot lag from this global redefinition of the field.

There is a need for the revision and upgrading of the specificity of the local laws, regulation and norms on clinical trials, in order to standardize them: the development, implementation and follow up of the results of clinical trials, especially of those that are multicentric. This process entails also the design of specific mechanisms for the inclusion of national and foreign capital more systematically and of the expansion of international collaborations and partnerships, of great relevance for the growth of RM.

The gathering, processing and storage of the large amount of data (Big Data) generated during clinical trials and the adoption of AT, requires the development of a new technical and ethical normativity and of innovative ways to monitor and disclose highly sensitive private information in data platforms.

One of the biggest obstacles, at a national and global level, in the present phase of AT regards the reformulation of manufacturing and distribution processes to adapt them to the new medicine. The lack of specialized professionals in Brazil in several new professions, requires substantive new

capacity building and an enlargement of State´s training programmes targeted to specific audiences.

An aspect to be taken into account prior to the stages mentioned, is that all the new public policies are to be based on empirical evidence (quantitative and qualitative information), as well as, be sustained by a periodical evaluation of their impacts and results. Results should also be informed to the general public in a mandatory, transparent, periodic and stable manner and through different communicational channels, e.g., at the national, regional and community-level.

The promotion of wide public debates, to dialogue on the main ethical and technical dilemmas in RM, should initially form part of the State´s responsibilities. The instruments used in overall well-acknowledged systems of public engagement, ensure the inclusion of the perspectives and practices that represent different sectors of organized civil society and they ae not being applied in Brazil (See, for example, Irwin,2001; Irwin et al., 2012).

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