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Towards an alternative framework for the evaluation of translational research initiatives

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Abstract: This paper will propose a framework for evaluating translational research by identifying the way in which translational research occurs in practice (rather than the formal linear stages in which the results of such process are typically presented). Following previous work on methods to evaluation science-society interactions, our approach will focus on the processes of TR and the ways in which public initiatives to support new ways of conducting research succeed or fail. Our starting point is that TR is expressed through complex cycles where knowledge is moving back and forth through the bedside-to-bench continuum across various channels, giving rise to complex interactions between research performers and the user of the results of such research. The approach is rooted on empirical context of IDIBAPS, a university-hospital joint institute in Barcelona, one of the European centre of excellence for TR, and a study on social networks and knowledge flows in the Spanish Biomedical Research Networking Centres (CIBERs). Further, we suggest that interactions between biomedical actors are less than optimal because the distances that separate these different groups make the interactions difficult. We end up by stating that learning processes and knowledge exchange interactions are facilitated and strengthened by five forms of proximity: cognitive, social, organisational, institutional and spatial.

Keywords: translational research, evaluation, knowledge flows, distances, clinical research, medical innovation
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1 Introduction

The pathways between basic science and clinical practice and health outcomes are multifaceted and complex. The analysis of these pathways has become of interest to the biomedical research community and public health agencies. Researchers and funding agencies are concerned with the ways in which scientific breakthroughs and evidence-based clinical findings are converted into practices with beneficial health impacts, including, but not limited to, therapies and medical guidelines. This interest is largely driven by the perception that many promising results from basic science in biomedicine have not systematically contributed to medical treatments and, ultimately, health care improvements.[5] In response, a wide range of publicly-funded initiatives have been set up with the aim to address this problem. As the main aim of these initiatives is to facilitate the "translation" of scientific discoveries into beneficial applications and practices, many of these initiatives have been branded as "Translational Research" (TR).

Translational Research has become a very popular term applied for instance, to large research programmes, research activities and, even, academic journals. Consequently, it has been the subject of fast growing interest, mainly from biomedical scholars and institutions (e.g. Marincola, 2003; Woolf, 2008; Zerhouni, 2007). The origins of the concept can be traced back to the 90s, when the U.S. National Cancer Institute (NCI) developed the Specialized Programs of Research Excellence (SPORE) (Lander & Atkinson-Grosjean, 2011). Starting in 1992, this program explicitly supported efforts to facilitate the "translation" of basic discoveries generated at academic centres into new interventions aimed to prevent and treat various types of cancer. Since then, many policy initiatives have given special attention to the transformation of basic knowledge into

[5] Some analysts have gone as far as estimating that less than 10% of the most promising biomedical discoveries had resulted in any benefit to clinical practice two decades later (Contopoulos-Ioannidis, Ntzani, & Ioannidis, 2003; Ioannidis, 2004).

health benefits. In the US, the National Institute of Health (NIH) launched the Roadmap Initiative (Zerhouni, 2003), the Clinical and Translational Science Awards (Heller & de Melo-Martín, 2009), and, in December 2011, a $575 million National Center for Advancing Translational Sciences (NCATS[6]). TR initiatives have also been launched in the European Union (European Science Foundation, 2012) and its Member Countries. Some of them may be explicitly labelled as TR programmes, while others will have similar objectives and use the TR terminology as an element of the programme's rationale. For example, in 2006 the Spanish Ministry of Health launched the Networked Centres of Biomedical Research (CIBER[7]) together with other research initiatives to facilitate the relationship between basic scientists and healthcare practitioners (Rey-Rocha & Martín-Sempere, 2012).

Often the more popular a policy concept, the more ambiguous it becomes. This has clearly been the case with Translational Research. A debate has emerged about the models of research that are to be considered "translational" and the nature and characteristics of a putative TR discipline (Littman et al., 2007). Consequently, the ways in which TR should be analysed, and more specifically the approaches to the evaluation of TR programmes are also the subject of debate. Given the substantial investments in TR programmes the definition of TR evaluation strategies and approaches has become an important element of the policy process.

In a context of ambiguity about the type of activities to be considered as TR, evaluation approaches and practices can play an important role in determining what actions and outcomes are conceived in practice to be relevant and significant, and in so doing shaping

[6] www.ncats.nih.gov

[7] CIBER is the Spanish acronym for "Centro de Investigación Biomédica en Red". http://www.isciii.es/ISCIII/es/contenidos/fd-investigacion/fd-ejecucion/fd-centros-participados/fd-consorcios2/cibers.shtml

the future nature of TR initiatives. This paper discusses the dominant approaches to TR evaluation and proposes an alternative evaluation framework, which would have implications both for TR evaluation processes and for the future shaping of TR programmes.

We first provide an overview of the different ways in which TR is conceptualised. Many approaches see TR as activities that bridge gaps that occur in a continuum that stretches from basic research to the development and application of solutions and their health outcomes, while other views emphasize the research processes and how different groups interact and their role may be redefined under a TR initiative.

Second, we discuss evaluation approaches associated with these different views of TR. A dominant approach is to focus on outputs generated at different points of the "translational research continuum" and when they are achieved. A focus on the "what" and "when" implies a TR evaluation approach that attempts to identify results and how these differ from what would have been achieved in the absence of the initiatives under assessment. It needs to be emphasized that this focus on outputs may be derived from an explicit view of TR that sees it as addressing "translational gaps" along a "translational research continuum", or may emerge without an explicit "theory" of the processes and objectives of TR. Research is measured against success criteria revolving around the generation of outputs that are no different from those that may have been generated in a traditional research context, and this may be occurring in the absence of an explicit programme theory. Note that, in this case, the TR objectives may be defined by the evaluation strategy chosen.

Our alternative is to focus, instead, on the "how", on the processes of collaboration and exchange that can be attributed to TR initiatives. To this end we develop an alternative TR evaluation framework that focuses on understanding the processes of change and

their outputs across the divides that hinder the application of the capabilities and knowledge generated by basic biomedicine to health care. The extant literature attributes the low level of practical application of biomedical research to a variety of causes, including the divide between the interests and skills of basic scientists on the one hand and clinical scientists on the other, the growing difficulties of communication among both fields as biomedical research becomes more complex and specialized (Littman, Di Mario, Plebani, & Marincola, 2007), and the existence of institutional barriers (Lander & Atkinson-Grosjean, 2011).

Following the conceptual framework proposed by Boschma (2005) we propose that TR initiatives can operate by generating "proximities" five different dimensions: cognitive, social, organisational, institutional and geographical. We define these dimensions and then illustrate how different TR initiatives can focus on a subset of dimensions and have effects across all of them.

We conclude by exploring the implications of using our alternative approach to evaluation. TR addresses a problem that has organisational, social and cognitive roots: different communities, with different practices and values are involved in a process that is complex and difficult. Research organisations are generally described in terms of the outputs they produce: mainly publications, sometimes also patents and, in the case of medical research, clinical guidelines and practices. However, in order to understand what is different about TR programmes, one needs to investigate how research objectives and projects are designed, how research is conducted, and how the application of research results is conceived and carried out. In other words, we need to understand in detail, the variety of *processes* involved in TR initiatives. Focusing on outputs does not tell us anything about the reasons why such this output has or has not been generated according to the initial, implicit or explicit, expectations of stakeholders. Further, existing practices

may easily be relabelled as "transitional" if TR policies and their evaluation are just concerned about the generation of specific outputs and their identification. If TR initiatives are to become transformative, they need to implement changes in the way research and the development of clinical practices and therapies are carried out. This calls for an evaluation approach that focuses on these processes.

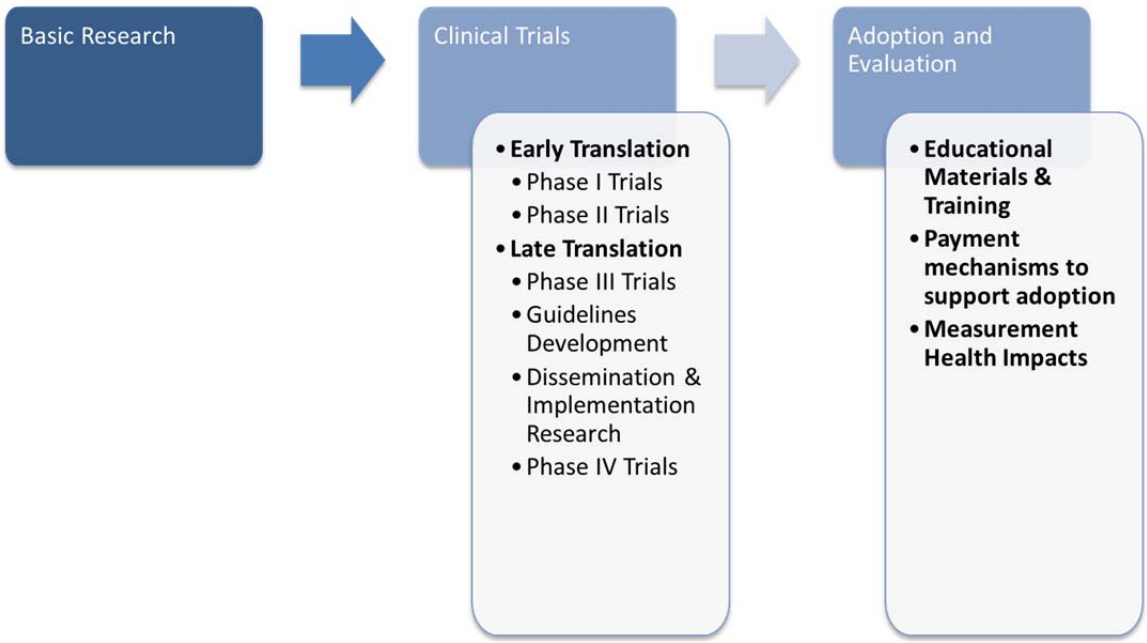
2 Translational Research: a variety of approaches

TR reflects the perceived need to increase the chances that scientific discoveries will lead to benefits for patients, and emerged at a time when other initiatives flourished with the aim of facilitating the "valorisation" or uptake of research by socio-economic actors (Bozeman and Boardman, 2004). TR has become part of the policy discourse justifying many current research funding programmes. The inclusion of the TR discourse in the policy agenda has been accompanied by an intense academic discussion among biomedical scholars. What are the measures that need to be taken to speed up the process of application of biomedical research advances to clinical practice? How should we then characterise TR and evaluate TR initiatives? The development of a conceptual framework to describe the TR process and evaluate TR initiatives has become a theme of academic research (for a review of the discussion see Drolet & Lorenzi, 2011).

The most popular representations of TR assume a linear model of innovation (Rogers, 2003), prioritising basic research as the primary source of new discoveries that are subsequently developed into therapeutic solutions which are finally diffused to patients and the wider society. In the biomedical field, the adoption of this approach sees basic scientists at the origin of the innovation process, producing a large amount of fundamental knowledge on the molecular or cell level, some of which will be relevant for the development of new drugs or therapies. The fundamental knowledge generated by

basic scientists moves forward through the stages of a "translational continuum" until it is eventually translated into specific benefits for patients or the general population in the form of new drugs, devices and new treatment options. Every step in this linear progression addresses a specific problem and is undertaken by a specialised group of researchers. In this view, the successful application of new knowledge is dependent on the successful completion of each and every one of the stages in which the "translational continuum is divided (van der Laan & Boenink, 2012).

Figure 1 A Model of Translational Research Continuum



Indeed, the idea of moving forwards through stages -often coined as "bench to bedside"- is well ingrained in most of the existing conceptualizations of TR, both in academia and among practitioners (e.g.: Khoury et al., 2007; Sung et al., 2003). This approach to TR is not substantially different from the classic linear staged process that characterizes all clinical research. What makes TR approaches different is the explicit search for an eventual identification of the steps within these processes that become problematic and slow down the progression towards application and health benefits. The TR models thus

identify a series of translational chasms, gaps or blocks that need to be bridged (Woolf, 2008). These chasms are viewed as obstacles and are typically described using what has come to be known as a "T-terminology" (Dougherty & Conway, 2008): a structured list of (T)ranslation gaps to be bridged. According to these models, the main objective of TR should be to bridge these gaps so as to facilitate a fast movement of knowledge forward along the successive steps from basic research to application.

One of the first models adopting a T-terminology was developed by the US Institute of Medicine's Clinical Research Roundtable, which identified two main gaps: T1 and T2. The first chasm (T1) is related to the transfer of basic discoveries into human clinical testing, while T2 refers to the dissemination and adoption of successful clinical discoveries into daily clinical practices. As the TR research developed, other scholars proposed more detailed models, adding more T-phases to include more chasms to be bridged. Westfall et al. (2007) proposed a TR model beginning at T1, where knowledge coming from basic science[8] moves to human clinical research through the development of Phase I and Phase II clinical trials. The T2 chasm comprises the activities related to the translation of initial human testing results into clinical practice. Activities such as Phase III and Phase IV clinical trials as well as observational studies and survey research are considered to occur at this stage. The final gap (T3) deals with the translation into practice and dissemination of the new clinical treatment (e.g.: by developing guidelines for clinical practice, patients and the general population). More recent models have broken down the translational continuum even further by proposing an additional final gap (T4) that emerges when trying to advance towards real-world health outcomes by

[8] Therefore, the process starts in the "bench" with fundamental discoveries in molecular biology, genetics and other basic sciences that may be of interest for understanding human health.

promoting the adoption of evidence-based recommendations by health practitioners (Khoury et al., 2007).

Proponents of these linear TR models often recognize that knowledge can also flow from the "bedside to the bench." Marincola (2011), for instance, stresses that hypotheses tested in basic research experiments can be based on observational evidence by practitioners. Research based on clinical evidence is particularly important because it provides factual knowledge collected by practitioners' observation (e.g.: through direct contact with patients) that can be translated into specific hypotheses to be tested in the lab. Yet, although the bidirectional nature of TR is frequently acknowledged in most of the TR models, the majority of the TR policy initiatives pursue or are implicitly based on a unidirectional "bench to bedside" understanding of knowledge generation and application, as reflected by the same terminology of consecutive gaps (T1, T2, T3,…) that need to be bridged.

This focus on the identification of T-gaps has posed a series of challenges that have framed much research on TR analysis and evaluation and some problems. When looking at TR as seeking solutions to tackle different translational gaps, the identification of these gaps and the different views of stakeholders on how to address them can lead to different understandings of what TR is about (van der Laan & Boenink, 2012) and what specific skills translational scientists should develop (Rubio et al., 2010). Littman et al. (2007) point out that, for academics, TR represents a channel to test whether novel ideas generated on the basic side have the potential to be turned onto practical applications, an opportunity to gain observational insights to develop novel scientific hypotheses to be tested at the lab, and a means to gain legitimacy and with it obtain improved access to research funding. However, for clinical practitioners such as physicians or clinical staff, TR is viewed primarily as a response to the need to shorten the path between scientific

evidence and actual practice (Davis et al., 2003). Business organizations view TR as a process to accelerate the development of a new drug or therapy as well as an opportunity to make go/no go decisions at an early stage of the biomedical innovation process – potentially resulting in major savings by avoiding failed investments. Also, the fact that public organisations conduct TR is seen by industry as an opportunity to save investments in research where returns are very uncertain.

Although different communities may hold different views on the objectives of TR, they are typically concerned about specific "gaps" among a succession of translational gaps that hinder the progression from fundamental knowledge to socially beneficial solutions. In doing so, they implicitly or explicitly accept a view that sees knowledge accumulating through different stages from fundamental to applied research. Yet, some scholars have expressed deep concerns about the adequacy of a linear TR model as a way to frame analysis and develop policy strategies (Graham et al., 2006; Littman et al., 2007; Marincola, 2011). A linear TR model implicitly builds over a theoretical separation between basic and applied research. Although this separation is widely used in the practice and analysis of science and technology policy, fundamental knowledge can also be sought with a view to solve an applied problem, *à la* Pasteur. This arguably creates a different form of research, "use-inspired basic research" (Stokes, 1997), which fits well with the TR goal of generating knowledge with an explicit focus on patient applications and public health benefits. However, a TR model based on a linear progression from basic science to health applications cannot account for the existence of "user-inspired basic research".

The idea that knowledge moves forwards and backwards across the unidimensional line of the TR continuum partially captures the view of a dynamic relation between basic and applied research, but cannot account for the existence of a different type of research

where scientists who carry out fundamental research systematically consider potential health applications. The TR continuum is understood as a cognitive dimension, but empirical observations challenge the very existence of such a continuum. Rather one observes a discontinued cognitive line and further dimensions of discontinuation; for example, the physical separation between basic and clinical labs, and the different legal frameworks and organizational affiliations under which scientists operate.

"User inspired basic research" is only one example of how the different groups involved in the R&D process can interact in complex ways, simultaneously playing different roles, and compressing some of the spaces in the different dimensions of discontinuity. For instance, some scientists have claimed that the progress of biomedical research increasingly depends on a close collaboration between researchers, practitioners, medical institutions, patient communities and research sponsors throughout the research lifecycle (Meslin, Blasimme, & Cambon-Thomsen, 2013). Collaboration often occurs through informal and non-structured channels (Sibbald, Wathen, Kothari, & Day, 2013) and hence, it may be particularly challenging to develop and implement policy instruments for the governance and evaluation of such interactions. The role of "boundary spanners", actors who facilitate communication across different communities, is particularly important here (Lander & Atkinson-Grosjean, 2011; Swan et al., 2007). Boundary spanners are individuals who engage in significant transactions with out-group members, facilitate knowledge exchange between groups and manage intergroup conflicts (Richter, West, Van Dick, & Dawson, 2006). From this perspective, clinical scientists working at the interface between basic scientists and health practitioners could play a crucial "boundary spanning" role, intermediating between the needs and objectives of the different actors, and conveying knowledge across them in a fast and timely manner (Kelley et al., 2012). To do so, effective clinical scientists have to develop management

and coordination skills and need to be fluent in the different "languages" used by the diverse "epistemic cultures" of basic scientists and clinicians (Roberts, Fischhoff, Sakowski, & Feldman, 2012). Further, it has been suggested that clinicians working at the interface between basic scientists and the final beneficiaries of the research (e.g.: patients) may help establish new partnering mechanisms with patients with the objective of assessing more effective therapies or performing observational studies (Kelley et al., 2012).

All these studies share a concern about the relationship among the diverse groups of actors that participate in processes leading to the development of new drugs or therapies. For a variety of reasons, which these literatures explore, the links among these communities along a variety of dimensions are seen as problematic. Under these perspectives the main challenge of TR can be conceptualised differently. Instead of focusing on bridging the gaps between successive stages without addressing the traditional specialised role of the different actors working in each of the stages, the **emphasis of TR becomes a redefinition of the interactions among these actors and, consequently, a redefinition of their roles**. So, for instance, fundamental scientists could be involved in TR by conducting "user-inspired research" in close contact with, among others, clinicians and patients. Another avenue for TR could be for patient organisations to play a role transcending that of a beneficiary, collaborating with researchers at all levels in the identification of research problems. Further, clinicians could operate as "boundary spanning" actors helping develop these interactions. There are many different ways through which a TR approach can establish a much closer working interaction among the different actors in the process. Instead of seeing TR as addressing the challenges that appear at specific points in a traditional staged linear

research system, this approach widens its definition to include the ways in which research takes place, and the actors it involves.

3 Implications for TR evaluation

The different ways of understanding the notion of TR give way to a variety of policies and initiatives with differing objectives and logics which are all branded as translational. These different notions are associated with different ways in which TR initiatives and policies can be evaluated according to the TR concept that the evaluators, implicitly or explicitly, hold. In the preceding section we have defined two main, contrasting, views of TR; these views naturally lead to different approaches to the evaluation of TR. We now discuss the evaluation approaches that would fit with these views.

3.1 Gaps and lags: evaluating the translational continuum

When TR is viewed as an attempt to bridge a series of sequential gaps that hamper the translation of research results into socially beneficial applications, evaluation proposals focus on the specific gaps that TR is supposed to address rather than the whole research and development processes. The success of a program can then be defined by the extent to which it has reduced or bridged these gaps. The diversity of evaluation techniques proposed emerges because these gaps are defined differently, and the indicators used to identify whether a gap has been addressed successfully can also vary. Morris et al have reviewed 23 different evaluation papers and concluded that “different studies use different measures, of different things, at different time points.” The authors “argue that understanding lags first requires agreeing models, definitions and measures, which can be applied in practice” (Morris, Wooding, & Grant, 2011).

This perspective assumes that the key indicator to assess TR initiatives is the time it takes for the different translational gaps to be bridged and, therefore, for research to be translated into treatments and other measures improving health. Such time lag is also the indicator taken by Trochim and his colleagues (2011) when developing a generic evaluation model that could provide the basis for a shared approach to TR evaluation. They propose a flexible solution focusing on what they view as the final TR objective: the reduction of the time it takes to develop new clinical practices and drugs that reach patients. Following a generic linear TR model, they propose to identify "markers" in the translation process and assess the time that it takes for outputs to move across markers. There is flexibility in the identification of such markers, and therefore there is no need to adopt beforehand one model of translational research instead of another. There is also flexibility in the direction of the activity across markers, allowing for both "bench to bed", and "bed to bench" directions. Yet, the approach focuses on the outputs of TR and on the time it takes for the output of a specific activity to be translated into a different type of output identified in another marker. In other words, this form of evaluation is concerned by TR outputs rather than the way in which such outputs are achieved.

Many TR evaluations have followed this route. Even when the programs themselves are unclear in the definition of their goals, time lag studies have become an increasingly dominant approach. In these studies, the gap between different research phases and the outputs they generate ceases to be an indicator of success and is converted into the objective of translational research: shortening the time elapsed between different research stages becomes what translational research is about. One could argue that there is a risk here of the tail of evaluation wagging the dog of translational research: the way in which success is measured may define the nature of the research objectives being pursued.

Setting aside this problem, focusing on outputs rather than processes has advantages and limitations. It can, for instance, draw on traditional indicators, like scientific publications, by linking them to a "marker".[9] This can prove convenient as traditional indicators are more easily available, but its application is likely to reinforce some of the processes and practices that TR is supposed, at least in some of its definitions, to combat. For instance, basic scientists can be assessed against their published outputs and in particular the time it takes for publication to take place; but the method is unconcerned about the way in which such outputs have been generated, how the different research steps are defined and the roles of the different actors within these processes. This is problematic if we understand TR to be aimed at changing how participants interact. An understanding of TR that focuses on the way the research and innovation processes are organized will call for different evaluation approaches. Next section outlines an evaluation framework that we argue is better suited to address the way in which TR initiatives affect research and application processes.TR as an interactive process in multiple dimensions: a proximities approach

The main problem that TR initiatives attempt to address is the difficulty to turn the results of basic and applied research into socially beneficial applications. As we have seen in the previous sections, a possible indicator to assess whether a TR initiative has been successful is to measure the time that research results take to be transformed into outputs that bring them closer to final application and social benefits. One potential

[9] The notion of translational research has been applied to specific activities designed to cover one of the "translational gaps". For instance, O'Hara and colleagues apply quasi-experimental techniques to the evaluation of the implementation and effectiveness of a telephone-delivered information system aimed at supporting individuals to make "life-style changes". This is defined as representing "the translation of research evidence applied in the real world (T4 or Phase 4 translation)", and therefore as providing a framework for the evaluation of translational research (O'Hara et al., 2013). From this perspective there is nothing peculiar about translational research. An activity to provide information to the public is defined as translational and analysed using standard evaluation techniques that are fit for this purpose, but may not be adequate to assess the results of other translational activities.

problem that this approach can generate, if it spreads as a common approach to TR evaluation, is common to all evaluation practices that revolve around a narrow set of performance indicators linked to specific outputs: hitting the indicator target may inadvertently become the main objective of policies and practices, losing sight of the ultimate objective of the investments (in this case, to increase the social benefits of research through improved health outcomes). In principle, we do not know *how* this overriding, final goal is to be achieved in each and every specific research context. We know, however, that there is a variety of potential ways to achieve it: through the development of improved diagnostics, of new drugs, or through primary health improvement or prevention in living habits. Each of these different ways involves different sets of actors and different socio-technical configurations, and the way these actors interact will vary across different organisational and institutional settings. Therefore setting up a narrow set of indicators to conduct a "gaps and lags" study is appropriate if one is interested in the interaction rather than the outputs..

The alternative is to focus on how TR programmes affect the way in which research objectives are defined, research is conducted, and its results applied in practice. We can assert that TR initiatives attempt to address problems in the organization and management of biomedical research by bridging the divide between different actors involved in the development of new drugs, therapies, diagnostics or public health practices. The different groups include, for instance, doctors and patients involved in the identification and definition of therapeutic and health problems, researchers defining and addressing relevant fundamental research challenges, and clinicians and doctors developing and testing solutions. The separation among these actors takes various forms: the different groups belong to different organizations, follow different implicit and explicit rules, and respond to different sets of incentives and performance criteria. These

conflicting logics (Sauermann & Stephan, 2013) and epistemic cultures (Knorr-Cetina, 1999) can make it difficult to align the objectives among the parties, and to establish clear and fluid lines of communication. This type of separation results in a difficulty to communicate needs and results across communities separated by institutional and organisational boundaries.

TR initiatives can then seek to reduce some of the divides among biomedical innovation actors. TR would then take place in networks of diverse actors, such a basic research, clinical doctors, general practitioners, regulators, etcetera. It is important to emphasise the networked nature of the social interactions: basic research, for instance, can be influenced by insights from general practitioners and from regulators, without the mediation of clinical doctors.

We propose that these interactions are less than optimal because the distances that separate these different groups make the interactions difficult. Following Boschma (2005), we can state that learning processes and knowledge exchange interactions are facilitated and strengthened by five forms of proximity: **cognitive, social, organisational, institutional and spatial**.

A degree of c*ognitive* proximity - i.e. the extent to which actors share a similar knowledge base - is a prerequisite for interactive learning, as it facilitates effective communication and a common reference space to process and transfer complex information and knowledge. However, as pointed out by Nooteboom (2000) and Boschma (2005), both too much and too little cognitive proximity can be detrimental to innovation and learning processes. A high degree of cognitive proximity between actors may lead to the exchange of irrelevant, redundant information due to a lack of variety of the knowledge sources; while too little cognitive diversity may lead to information

exchange that cannot be adequately understood by the interacting actors, rendering communication ineffective.

Social proximity refers to relations between actors generally built on common experience, friendship and kinship and which can improve communication. *Organisational* proximity refers to the governance structure shaping interactions between actors. High organisational proximity is often associated with a hierarchical structure governing the interactions between actors, while low organisational proximity is generally associated with flat governance structures or arms' length interactions between actors. *Institutional* proximity refers to the norms, rules and values that influence how actors behave; a large institutional distance may impose serious impediments to fruitful learning interactions if the behaviour of interacting actors responds to different, potentially conflicting, sets of incentives or values. For example, universities and firms have considerable institutional distance because their incentives and norms differ significantly. Finally, *geographical* proximity refers to the spatial or physical distance between actors. This matters in knowledge dynamics because spatial co-location favours the exchange of knowledge that is complex or difficult to transfer (i.e. tacit knowledge).

All these types of proximity are inter-related. Some may complement each other, while others may act as substitutes. For instance, Harrison (1992) and Howells (2002) argue that geographical proximity facilitates face-to-face interactions, favouring trust-based relationships and knowledge exchange, suggesting a reinforcing effect of spatial proximity on social proximity. In contrast, some proximity dimensions may substitute each other: barriers for knowledge exchange through large geographical distances (spatial distance) might be overcome if interacting partners share a well-defined and honed division of labour (i.e. organisational proximity) (Rallet & Torre, 1999).

Coming back to TR initiatives, these can explicitly or implicitly address perceived distance problems along one or more of these analytical dimensions. They can for instance establish ways to improve communication and understanding between patients, clinicians and researchers (addressing cognitive distance), they may try to establish better coordination across different organisations involved in the research and application process (addressing organisational distance), align their incentives rules and norms (addressing institutional distance), or improve trust (addressing social distance). In other words, TR initiatives can be described as aiming to bridge the gaps among the actors involved in biomedical research and the application of its results by directly reducing the distance among the actors in one or more of the five analytical dimensions.

4 TR Evaluation: Increasing proximities and "programme theories"

We argue that we can interpret policy initiatives fostering TR as aiming to have an impact in one or various proximity dimensions. In this way we can interpret their "programme theory" (their goals and the processes through which these goals are to be achieved) as revolving around the attempt to develop proximities. This would be the first step in a TR evaluation strategy that could be presented as an alternative to the dominant "gaps and lags" approach. Different TR policies and initiatives have different goals and targets. The section below shows how the dimensions of proximity proposed by Boschma can be used to describe the "programme theory" of TR initiatives drawing on two contrasting examples: the centre IDIBAPS and the CIBER networks initiative.

4.1 Collaborative Centres pursuing spatial proximity: the case of IDIBAPS

IDIBAPS is a translational research centre located right across the street from the Clinic Hospital of Barcelona. It houses some 460 researchers with diverse institutional affiliations: the hospital itself, the University of Barcelona, Spanish and Catalan research establishments (CSIC and ICREA), and its own staff. It is thus organized as a space providing common facilities where researchers with different affiliations and expertise work together. IDIBAPS can be described as a TR initiative aiming primarily to increase spatial proximity. Spatial proximity is necessary to allow shared access to research facilities thus increasing efficiency. IDIBAPS researchers have access to bioinformatics and medical imaging facilities as well as the hospital biobank. In addition, and equally important, spatial proximity is expected to generate other forms of proximity; for instance, IDIBAPS working practices are expected to a spirit of trust and collaboration among different actors (thus increasing social proximity). Further IDIBAPS researchers work within the rules and incentive systems of the Institute (often overlapping with those of their parent organisations); the objective here is to align such incentive systems and norms and thus generate institutional proximity. Ultimately, these proximities should facilitate knowledge flows (increasing cognitive proximity) among different epistemic cultures. An evaluation of an organisation like IDIBAPS should therefore seek to determine whether and how these expectations take place.

4.2 Collaboration networks seeking organisational proximity: the CIBERs

The Biomedical Research Networking Centres (henceforth, CIBERs) were established in 2006 by the Spanish Government to promote excellence in biomedical research through

the establishment of stable structures of cooperative research. The CIBERs were selected through an open call to biomedical research groups. Applicants had to establish a broad network of research groups, which could be placed at Universities, Public Research Organizations, Hospitals, Clinics and research foundations. Nine CIBER research networks were founded between 2006 and 2007, each focused on a specific pathology or disease of strategic interest to the Spanish National Health System[10] and were expected to carry out TR. Each CIBER "platform" is an independent legal entity formed by the association of various research groups geographically dispersed.

Members of the CIBERs continue to work in their own organizations and, therefore, we can state that increasing spatial proximity is not an objective of the initiative. While, the diverse biomedical groups within a CIBER remain part of different institutional and organizational contexts such as universities, hospitals or public research entities, the objective is to coordinate their work, connecting them through the common legal and economic framework provided by the CIBER platform. As far as the work to be conducted under the initiative is concerned, the CIBER platform provides a hierarchical governance structure to catalyze coordinated action among the actors involved in the TR process. By connecting these research groups through hierarchical mechanisms and common practices and decision making processes, the CIBER platform aims to increase organizational proximity among a group of heterogeneous research actors.

Furthermore, although the groups belonging to a CIBER are only "loosely coupled"[11] we can expect that, by setting some basic conditions for the creation of common rules and

[10] Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Epidemiology and Public Health (CIBER-ESP), Obesity and Nutrition (CIBER-OBN), Hepatic and Digestive Diseases (CIBER-EHD), Neurodegenerative Diseases (CIBER-NED), Respiratory Diseases (CIBER-ES), Rare Diseases (CIBER-ER), Mental Health (CIBER-SAM) and Diabetes and Metabolic Associated Diseases (CIBER-DEM).

[11] Loosely coupled networks are organisational structures that may help coordinate transactions among highly heterogeneous partners, providing a balance between mechanisms of control and flexibility. Loosely

shared expectations, the CIBERs may provide the means to generate social proximity, and through it increase cognitive proximity. In other words, we understand the network as an organisational arrangement, which aims, primarily, to increase organisational proximity among all actors (basic researchers, doctors, patient groups), who tend to be distant in all dimensions. This organisational proximity improves, in turn, the proximities in the social sphere which may facilitate flows in the cognitive dimension.

5 Analysing proximities and their effects: the need for diverse techniques and the difficulties of comparability

The focus on processes that underpins the evaluation approach we suggest here is based on the postulate that to understand the effect of TR initiatives we need to learn about how they affect the ways in which research, its objectives and the application of its results are designed and conducted. An evaluation strategy that focuses only on measuring outputs cannot offer information on how the initiative under evaluation has contributed to the observed outputs. When, as it is the case with TR, there is ambiguity about what differentiates this from of research from other forms of research, the need to understand how interventions operate in practice and what processes they trigger is particularly important. We have explored in this paper an avenue to develop a process-based approach to the evaluation of TR initiatives.

Evaluation frameworks are not neutral in relation to the objectives of an initiative. The way in which a project is evaluated will affect how it is conducted and, at least, part of the objectives that the performers will be aiming at. Focusing on specific outputs can implicitly suggest an intervention rationale that is not concerned about the organisation

coupled networks are somewhere in between highly hierarchical organisational structures that may impose too strong a degree of control and bureaucracy for learning-related activities, and weakly articulated governance structures that provide a fragile setting for building trust-based and sustainable relationships.

of research, and the way in which specific "translational gaps" are addressed. The proximities framework we are proposing can help focus attention on the way research is conducted and the specific aspects that an initiative is intended to address. These aspects may be explicit in the definition of the intervention, but they can also be implicit in the way the initiative is implemented. In the latter case, the framework can also be used to explore and develop a "programme theory" for a TR; that is to explore its rationale. The cases above show how we can use the framework to describe both the goals of TR initiatives and the way such goals are expected to be attained.

By adopting this approach we are proposing that the immediate goal of TR initiatives is to address a problem of distance separating different groups involved in the TR process. The "translational gaps" appear because of excessive distance in one or more significant dimensions. The groups involve in the translational process have cognitive differences, are institutionally separated and, therefore, follow different rules, face different types of incentives, and they are often geographically dispersed. Yet, some flexibility must be built into the definition of an initiative and its evaluation to reflect the fact that increased proximity will not always be desirable. For instance, cognitive distance can pose a problem but the same can be said of the overlaps generated by excessive cognitive overlap; cognitive proximity will be positive only up to a certain extent. A specific programme theory will need to reflect this problem and the interpretation of evaluation results will have to be sensitive to this potential problem if there is a possibility that it may become relevant.

The programme theory of a TR initiative will define the expectations about whether and how changes in proximity in one or more dimensions caused by the intervention will trigger shifts in the other dimensions, and the effects of these changes on the development and application of beneficial goods and services. These effects will be

mediated by changes in the way in which research is carried out. Increased proximity can result in increased collaboration among groups involved in the different tasks that constitute the TR process (the definition of fundamental and clinical research objectives, research, and the application of its results). We can expect changes in proximity to generate new interactions across groups, like for instance, between research performers and the diverse users and beneficiaries of the research results, where knowledge is moving back and forth through various channels, not in the linear bedside to bench continuum but within networks.

We can thus define further building blocks of a TR programme theory. An intermediate outcome of increased proximities can be the generation of complex interactions among different groups that become partners in a single TR process. An analysis of intermediate outcomes in terms of interactions among the participants in the TR process needs to consider the variety of actors directly involved and affected by a TR initiative. Although this may vary across initiatives, it is important to take into account that there is a broad variety of potential stakeholders: basic researchers, clinical researchers, technologists, practitioners (doctors, nurses,…), public health and private industry managers, patients. The ways in which stakeholder groups interact can be traced and analysed using instruments developed for the evaluation of the socio-economic impact of research, like for instance those developed by the EU-funded SIAMPI project (Molas-Gallart & Tang, 2011; Spaapen & van Drooge, 2011), which focus on the processes of collaboration that can be linked to an initiative.

Our framework does not determine the research techniques to be employed; these will need to fit the specific circumstances of each initiative under assessment. The activities supported by a TR initiative will be different, implemented against different contexts and having different targets and objectives. For instance, the research techniques applied to

an initiative that focuses mainly on cognitive issues, will be different from those applied to one that addresses institutional differences.

Finally, as the adequacy of a specific research technique will depend on the specific TR evaluation problem confronted and its context, it follows that the outputs of TR evaluations will not, and should not, be directly comparable. Calls for an approach that will be based on a single set of research techniques yielding measurable and comparable indicators of TR "output" are, from the perspective we are developing, out of place. An evaluation approach that focuses on processes will aim at providing detailed information of the effects of an initiative starting at the level of those groups directly involved in it. But the way in which this information is shaped, and the indicators on which it is based will depend on the type of initiative, its objectives and the types of proximities the programme is designed to address.

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