Project Management for Healthcare: The Case of the Translational Research [1]

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INTRODUCTION

The translational research "translates" research results in clinical results – mainly via the knowledge transfer and the adoption of appropriate protocols – and vice versa – mainly via the acquisition of patient information and feedback. This approach enables the setup, the maintenance, and the optimization of a harmonic flow that maximizes the synergies between the basic research, the laboratory tests, and the medical assistance, by performing clinical trials that are oriented to the generation of value and of benefits for the community in a large variety of healthcare-related basic issues, including medicines, specialized equipment, diagnoses, therapies and vaccines.

Since the translational research is based on evidences, which arise both from research and from clinical practice, it can be considered, in all respects, an application of evidence-based medicine. As we saw in a previous paper (Pirozzi and Strigari, 2020), in today's world, both the extent and the complexity of healthcare projects need special approaches to reach efficacy and efficiency respecting ethical and other constraints, preserving the care to the person by achieving the satisfaction of stakeholders, and minimizing negative risks. The Evidence Based Medicine (EBM) takes into account the above factors by integrating best scientific evidence with both clinical expertise and patient values and expectations, while Project Management discipline can effectively support EBM projects in facing complexity with efficacy and efficiency. This paper briefly gives an overview about translational research, examines the peculiar characteristics of translational research projects, and proposes project management as an effective support to face complexity, to realize efficacy and efficiency, to satisfy stakeholder requirements and expectations, to target project success, and to reduce drastically the threats and the uncertainties.

THE TRANSLATIONAL RESEARCH

In general, the research is based on the researchers' knowledge, enriched by the input of sources of evidence such as the Cochrane Library, PubMed, Medline, EMBASE, etc. For the purposes of formulating an appropriate question in the EBM process, the PICOT approach (Stillwell et al., 2010) is generally used to framing the clinical question of trial trough five components: P that corresponds to the population of interest, I that corresponds to the type of intervention or clinical action, C that corresponds to the comparison represented by "usual treatment" (or "nothing"), O that corresponds to all

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possible outcomes to be explored, T that corresponds to the time duration for intervention or to the outcome ascertainment time. Once the PICOT question is formulated, the search for evidence can start and then proceed step by step in generating value.

The Translational Research Value Chain (Fig.1) may be often characterized by a long way; indeed, several steps are mandatory to demonstrate the proof-of-principal (based on experiments conducted on cells and indicated as *in vitro* study) and the proof of concept (based on animal models that represent the first step of complexity), and, therefore, to verify these hypotheses into human-based clinical trials (phase I, II, and III).

Fig.1 – The Translational Research Value Chain

Specifically, above iterative sequence moves from simple observational methods (which correspond to the steps T0, T1 and T2) to increasingly rigorous and systematic methodologies (which correspond to the steps T3 andT4). While the proof-of-principal – often indicated as *in vitro* study – is based on experiments conducted on cells, the proof of concept is based on animal models, and, then, it represents the first step of complexity to overcome in order to replicating the *in vitro* results also taking into consideration, for example, the immunity factors. The above approaches, which are indicated as T0 (preclinical & animal studies), focus on studying/defining pathobiology, mechanisms, targets, lead molecules, and also on an initial regulatory interaction, represent the first attempt of the translation from basic science to human studies, and are intrinsically subject to the risk of possible failure due to a “valley of death” (Seyhan et al. 2019) devoid of significant results.

The sequential – but potentially iterative – following steps are planned, implemented, and controlled to verify in clinical trials the hypotheses that were assessed in the preclinical

models. The step indicated as T1 (Phase 1 of Clinical Trials, targeting safety, proof of mechanism and proof of concept, dose selection, …) includes the studies of new methods of diagnosis, treatment or prevention, and regards just a limited cohort of selected patients that could benefit from the relevant scientific discoveries, and who generally are not candidate to other treatments or strategies. The step indicated as T2 (Phases 2 and 3 of Clinical Trials, targeting proof of efficacy, safety) is conducted as a controlled study to provide the effective care, the benefit/risk profile, and the healthcare economic data improvement. Then, translation of new data into the clinical and health decision making are generally based on the subsequent steps indicated as T3 and T4. The T3 step (Phase 4 of Clinical Trials and Clinical Outcomes Research) aims to deliver recommended and timely care to right patients, post marketing safety, and new indications, while the step T4 (Population Level Outcomes Research) represents the final step, and aims to demonstrate the real benefits for the society by engaging in the trials a larger population.

Going into a further detail, the crucial step T3 is based on the randomization, which refers to the process of assigning the study participants to experimental or controlled groups at random, in order to eliminate both selection bias and balance known. In particular, the block randomization and the stratification ensure a balance in the number of patients with different prognostic factors (e.g., such that patients can be considered at low, medium or high risk of recurrence) in each treatment arm.

The Randomized Controlled Trial usually provides the most reliable evidence on the effectiveness of the interventions and/or the treatments because the processes that are used for its conduct minimize the risk of confounding factors, which could potentially influence the results. Indeed, the validity of the trial methodology, the magnitude and the precision of the treatment effect, and the number of enrolled patients are all factors that may affect the accuracy of the results and, in general, the applicability of the research results. Ultimately, these phases are mandatory to implement a specific research into the clinical standard through both the evidence-based medicine and the biology-driven therapy, taking properly into consideration the ‘‘hierarchy of evidence’’ (Akobeng et al., 2005), which provides a framework for ranking evidence, i.e. for evaluating which research propositions are more powerful than others. The utility of a hierarchy of evidence is that it indicates which studies should be considered prioritized for their ability to answer to research questions that are based on an evident effectiveness of the interventions and/or of the treatments.

As the evidence grows and, therefore, moves towards the standardization of the cares and/or of the interventions, new methodologies and/or operations are introduced in the clinical world. At this stage, the application of the trial results in the clinical practice is limited both by the patient’s heterogeneity in the real world – which is evidently characterized by a high level of complexity –, and by the delivery of techniques that correspond to a situation in which a real world staff uses a heterogeneous available technology in a real world environment. Therefore, there is a consequent risk of making

evaluations that are affected by real, but possibly incomplete or missing, data, and an important possible consequence of this situation might be that the results of controlled clinical trials could not be confirmed in the real world due to an inappropriate collection of clinical data and information. Moreover, the introduction of the new interventions may encounter numerous obstacles or limitations, which are related to the heterogeneity of equipment, or to the availability of a limited number of departments that are able to support the introduction of above novel technologies in the clinical practice.

Definitively, the clinical information, the laboratory data and patient imaging, and the stakeholders' values and expectations that are collected in the real word may suggest the need to refine the research question or to identify a novel interventional procedure, and, then, to proceed iteratively. For instance, a "refined" question could represent the need of better investigating the concomitant introduction of new technologies or drugs, or of better taking into consideration the clinical needs and/or the stakeholder values and expectations. Ultimately, in order to assess the impact of the biomedical research on the clinical practice and the healthcare policy, all the above aspects have to be considered for an efficient allocation of the research resources – which are in any case subject to limitations – and for providing accountability to the different stakeholders that are involved. In all clinical trials phases, therefore, the patient's perception takes on a great value, as well as the stakeholder education and training. In this scenario, the availability of websites dedicated to patient information and interactions, so that they can collaborate and participate directly and actively in the process through dedicated apps that may be interfaced with the treatment system databases (Pirozzi and Strigari, 2020) could be extremely important. Basically, the highest complexity of above context, and the need of reaching results effectively, efficiently and minimizing risks, but always targeting the centrality of the people, require a modern, specific, and stakeholder-centered project management approach in order to increase the translational research projects' delivered value to the community.

TRANSLATIONAL RESEARCH PROJECTS AND PROJECT MANAGEMENT

Although healthcare projects include a large variety of projects, which may be very different in typology, in size, and in complexity, they all share some peculiar characteristics; in fact, since focus is always on human life, aspects like the management of risks, the constraints due to ethics, the availability of lessons learned, and the attention to stakeholder satisfaction, take on an extreme importance. Specifically, all Evidence Based Medicine projects, of which the translational research projects are part, are characterized by a high level of complexity; indeed, since evidences emerge retrospectively only, the most appropriate action path is necessarily probe – sense – respond, the collection of evidences/ lessons learned arises to be also a fundamental part of the deliverables, the satisfaction of both the project requirements and the stakeholder expectations becomes the critical success factor, and the discipline of project management becomes essential.

Definitely, translational research are projects that have peculiar characteristics:

- ✓ they reduce threats and uncertainties by concentrating on objective and validated information;
- ✓ their triad bench side – bedside – community requires specific focuses on lessons learned, on competences, and on available resources;
- ✓ they are stakeholder- centered because their target is satisfying both stakeholder requirements and expectations (Pirozzi, 2019),
- ✓ the patients' perceived value gives a fundamental contribute to the project delivered value (Pirozzi, 2021);
- ✓ the importance of the research teams (that could be also different in the diverse phases) is evidently extraordinary, and their engagement is generally complex, i.e. it needs high competences;
- ✓ good economic competences are crucial also for effective relationship management with investors/funders, who are evidently essential for the very existence and continuation of the projects;
- ✓ effective communication with stakeholder network (Pirozzi, 2017) is essential, and, specifically, Web X.0 technologies can be a great support (Pirozzi and Strigari, 2020) in the interactions among the team(s) and with both the patients and the external influencers (Stretton, 2019);
- ✓ they are multiphase, adaptive/incremental/iterative;
- ✓ since they are intrinsically featured by a high level of complexity, their effective and efficient management requires to integrate the management of their process with the project management discipline, which, on turn, should be preferably enhanced by the use of appropriate Key Performance Indicators (KPIs) – e.g. research and healthcare KPIs – in order to increase both delivered and perceived value.

In fact, the selection and the management, during the whole investment and project lifecycles, of proper KPIs is very helpful in all projects, and it is foundational to target the efficacy, the efficiency, and, ultimately, the success in all projects that are characterized by a high level of complexity (Pirozzi 2019), as the translational research projects evidently are. The KPIs that are useful to translational research project setup, implementation, and optimization have to be properly selected among these following groups:

- ✓ quantitative and qualitative measures of the evidences relevant to each translational research project phase; nowadays, available web X.0 (i.e. 1.0, 2.0, 3.0, and 4.0) technologies can greatly enhance project management in supporting the collection and validation of qualified evidences, and their integration with clinical expertise and patient values and expectations (Pirozzi and Strigari, 2020).
- ✓ Functional and/or quantitative measures and the relevant percentages of completion/deviation from budget/schedule, which are specific for each project,

and which have to be defined and handled starting from the initial proposition phase.

- ✓ Measures and percentages of the stakeholder satisfaction (in terms of their both requirements and expectations), measures and percentages of the stakeholder (positive) engagement (Pirozzi, 2019).
- ✓ Measures of the perceived value (Pirozzi, 2021), as the perceived research value, clinical value, social value, and personal value, and of the perceived quality, reputation, environment climate, innovation, sustainability, and social responsibility (Pells, 2021).
- ✓ Measures of Research Infrastructures (ESFRI, 2018): indicators relevant to scientific excellence outcomes, output and delivery of talent, reference role in the disciplinary field (uniqueness in capabilities, in capacity) at International level, progress in achieving the Research Infrastructures' milestones along its life cycle, impact, innovation, entrepreneurship, establishment and development of the Research Infrastructures' user community, scientific data management policy, metadata catalogue interfacing, open science initiatives, advanced data services for scientific analysis and for innovation developments, enforcement of quality control of access (peer review), data, and services to research and innovation.

The multiphase, adaptive/incremental/iterative nature of the translational research projects (Fig.1) harmoniously addresses a hybrid approach to project management, which can integrate properly the five adaptive translational phases with the two predictive phases of the initial proposition and of the final phase of the effective dissemination to community. Definitively, a modern project management approach that provides for the use of proper KPIs can then greatly support to face complexity, to realize efficacy and efficiency, to satisfy stakeholder requirements and expectations, to target project success, and, specifically in translational research projects, to reduce drastically the risk of falling in a "valley of death" when translating from basic science to human studies.

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Massimo Pirozzi, MSc cum laude, Electronic Engineering, University of Rome "La Sapienza", Principal Consultant, Project Manager, and Educator. He is a Member of the Executive Board and of the Scientific Committee, and an Accredited Master Teacher, of the Istituto Italiano di Project Management (Italian Institute of Project Management). He is certified as a Professional Project Manager, as an Information Security Management Systems Lead Auditor, and as an International Mediator. He is a Researcher, a Lecturer, and an Author about Stakeholder Management, Relationship Management, and Complex Projects Management, and his papers have been published in U.S.A., in Italy, and also in Russia; in particular, he is the Author of the innovative Book "*The Stakeholder Perspective: Relationship Management to enhance Project value and Success*", CRC Press, Taylor & Francis Group, Boca Raton (FL), U.S.A., October 2019. Due to the acknowledgement of his comments on stakeholder-related issues contained in Exposure Draft of The Standard for Project Management - 7th Edition, he will be also included in the list of *Contributors and Reviewers of The PMBOK® Guide - Seventh Edition*.

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