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MOVING FORWARD FROM DRUG-CENTERED TO PATIENT-CENTERED RESEARCH

A White Paper initiated by EORTC and developed together with the BioMed Alliance members

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Take-home message: This paper discusses how to restructure the process of clinical research to maximize the potential of precision medicine.

Plain language summary: European bodies need to be proactive if precision medicine is to become a reality. This paper proposes changing the architecture of clinical research to maximize the benefit of scientific advances for patients and provide economic benefit to health care services.

ABSTRACT

Maximizing the potential of precision medicine for patients and health care services is a major societal challenge. It requires a holistic approach to the development of therapeutic strategies and a re-thinking of the entire process, including the role of the respective stakeholders and the way they interact, from the early steps of drug development to access in real life. First, the new technologies that inform us about the biology of the disease and enable better treatments plead for a reversal of the "protocols search patients" approach, to "patients searching (the best possible) treatments and protocols". Second, new drugs reaching the market is not an end but a start. Information that is critical for the integration of new treatments in daily practice needs to be collected and analyzed to optimize the use of resources and maximize patient benefits. Optimal dose, sequence, combination and duration of treatments as well as cut-off values of biomarkers and their clinical utility all represent crucial pieces of information not only for patients and doctors, but also for health care systems facing complex decisions on reimbursement and access. The gap that currently exists between market approval and real-life clinical practice, and that is not addressed by the commercial sector, requires a new infrastructure for applied clinical research which needs to be fully integrated into the cycle of drug development, market approval and clinical application. This process needs to be re-engineered in a such a way that it truly serves the needs of patients and generates the data needed to inform clinical practice.

Abstract word count: 254 words

1. Rationale for change

An unprecedented speed in the growth of knowledge, combined with the availability of large prospective cohorts and the emergence of new technologies, is enabling effective validation of therapeutic targets and pharmacogenomics [1]. Over the last few years, empiric drug development in a single clinically and pathologically defined disease has been challenged by the identification of molecularly or genetically defined subsets of patients amenable to targeted treatments. In the cancer field, "histology agnostic trials" testing new drugs aimed at molecular targets rather than at the same tumor are already part of the clinical research landscape, leading to registration of new agents based on molecular features [2, 3].

Taking the full regulatory and scientific environment into account is critical. The first necessity is to develop a different framework, where more refined patient stratification and individualized effective care, rather than drug development, are at the center of the process [4].

Patients must remain the focus throughout the discovery process, whilst the regulatory framework for testing new interventions in a robust and meaningful way is revisited.

Patients' needs are multiple; most commonly they do not depend on a single intervention and are likely to change with the natural history of the disease. Therefore, the concept that therapeutic interventions are developed with the sole purpose of market access – not anticipating any questions beyond registration / market authorization – needs to be revisited. This new approach should cover not only pharmaceuticals, but also other modalities, such as surgery, diagnostics and screening. Similarly, questions surrounding the sequence and combinations of multiple therapeutic interventions need to be addressed to rationalize implementation of agents and better understand their value in the therapeutic armamentarium. Typically, all these questions are addressed by the non-commercial sector through applied clinical research. After market authorization, long-term safety and effectiveness in broader patient populations need to be monitored [5]. Regulatory agencies are already beginning to require such information [6].

Taken together, these considerations highlight the need for a profound transformation in the development cycle of any therapeutic intervention and for a departure from the comfort zone within which many stakeholders now operate [7].

The current regulatory framework has resulted in a dramatic increase in the cost of conducting randomized clinical trials, without increasing patients' safety [8]. Investigator-led trials are increasingly difficult to conduct and the number of new interventions as well as of optimized therapeutic strategies that can be tested has decreased dramatically. This development represents a major threat to our health care system. At present, research protocols are written to fit existing rules for drug development rather than in the interest of finding the best solution for stakeholders. This must change and change soon. There is robust evidence supporting the implementation of streamlined applied clinical research, but still much uncertainty as to whether it will be embraced by all stakeholders. Thus, it is vital that Regulatory Authorities but also Health Technology Assessment (HTA) bodies engage with the non-commercial sector over the disruptive knowledge that accompanies the advent of precision medicine.

The following principles underpin the strategy proposed by the BioMed Alliance:

- Patients have the right to benefit from the latest scientific discoveries and to be treated according to the highest level of clinical evidence. Technologies allowing the stratification of patients according to biological/genetic features should lead us to change our models: from "drug protocols looking for patients" to (fully biologically/genetically characterized) "patients looking for matching protocols" [9]. Thus truly placing patients at the center of the research and development (R&D) process.
- Patients should also be informed better about the value of clinical trials and be more involved in trial design and the choice of primary outcomes.

- New solutions are needed for optimal benchmarking of emerging technologies across and within a class of agents. The concept of "one intervention, one target, one protocol" is no longer the way forward [10].
- Key questions anticipating real-life implementation of new interventions need to be addressed early on, i.e. combinations, duration of treatments, long-term safety in patients with multi-morbidity and/or polypharmacy etc [11, 12]. These types of questions are crucial not only for patients, but also for HTA bodies and payers [13].
- Long-term toxicity monitoring of mechanism-based therapies needs to extend beyond registration into real life for a prolonged period. There should be a continuum between drug development, regulatory assessment, clinical research, and applied clinical research.
- Trial endpoints should take into consideration outcomes that reflect the needs and priorities of patients (not just of regulators) [14].

2. Infrastructural gaps

There is much room for improvement in the process of bringing the latest science to patients, while taking into account their priorities such as quality of life. Too often, regulatory agencies, governments and funding agencies do not encourage the integration of research into care and vice versa. Similarly, the pharmaceutical drug development process remains protected during the competitive phase, placing drug development priorities before public health issues when the continuum of care would require early consideration of these issues, a broader view and a more comprehensive approach. While continuing to preserve the interest and needs of all stakeholders, a substantial waste of knowledge and resources must be avoided.

The following principles underpin the strategy proposed by the BioMed Alliance:

- There needs to be an integrated pan-European infrastructure to support the use of patient data for health research. Such a system circumvents the expense of active long-term follow up (and thus, allows adequate assessment of safety and cost-effectiveness of interventions) and provides information that is accessible for independent assessment by health authorities and the public. Independent data capture (e.g., via electronic patient records) for all types of clinical, biological and imaging data, alongside biomarker test results, all therapies received, and outcomes are critical for the affordable implementation and validation of state-of-the-art precision medicine.
- Traditionally HTA bodies and payers base their decisions on drug development research, which remains relatively artificial (often studying highly selected patient populations and providing only short-term safety and efficacy data). We argue that infrastructures such as a clinical population-based registry would allow the recruitment of patients into clinical trials directly from clinical services, better reflecting real life and providing long-term safety data and comparative effectiveness data [15].

3. Conceptual changes are needed

Drug development protocols are usually written with the aim of bringing a new agent to the market for a very specific clinical situation. They do not test the optimal integration of a new drug into existing therapeutic strategies, such as how to combine treatment, in which sequence, and for how long. While short-term regulatory trials are needed to demonstrate therapeutic benefit, they may not address real-life issues (such as those arising from disease progression) and may fail to capture rare or delayed safety outcomes arising from drug exposure.

There is, thus, a missing link between regulatory trials and health care systems. Implementing applied clinical research to address this missing link must be considered [16]. An example can be the advent of immuno-oncology, as no information is available on the optimal duration of treatment with so called "check-point inhibitors", despite their costs and potential long-term side effects. These solutions will help place the continuum of drug development for optimal patient access at the forefront of clinical trials and will enable applied clinical research in real life. Tailor-made solutions could open doors to integration with population-based registries, reducing costs and allowing investigator-initiated and patient-centered assessment of relevant therapeutic interventions.

4. Defined objectives

Two major issues that need to be addressed at European level in order to achieve a successful transition to precision medicine are:

- The establishment of Europe-wide clinical population-based registries, which will provide the infrastructure for patient-centered, affordable, real-life testing of new and repositioned treatment strategies.
- Optimizing treatment in real life based on robust evidence, taking into account key patient-centered questions for real-life implementation such as optimal dose, duration, sequence, combination, and quality of life.

For any transition to succeed, a balance must be found between the interests and needs of all stakeholders:

a) Patient triage (molecular/genetic screening) and trial access: academia in partnership with pharma, biotech, diagnostics etc.
b) Drug development: industry in partnership with researchers, medical societies, patient organizations and relevant agencies.

c) Therapeutic optimization led by the non-commercial sector: academia in partnership with HTA and payers.

d) Real-life implementation and long-term monitoring of treatments led by the non-commercial sector: academia in partnership with registries, HTA and payers.

A major transformation of clinical research, building on the strengths and complementarity of stakeholders working alongside new business models, must be tackled in order to make the above possible, notably developing strategies for chronic diseases.

5. A vision for the future

We strongly advocate that both R&D in health care and its regulatory framework need to involve all stakeholders.

Widespread availability of imaging, molecular, genetic and biochemical biomarkers derived from prospective cohorts and patients' medical records is necessary to refine patient selection to clinical trials. A European-wide infrastructure that allows patient identification and affordable long-term follow up, for instance via their electronic medical records, is essential to the practice of "intelligent" and sustainable health care.

The model we propose would be patient-centered (as patients would gain access to the most suitable treatment) and would optimize the understanding of patterns of recurrence or failure, informing investment in new R&D strategies.

It is critical that patient information for health research be obtained from databases that are curated and constantly updated. The existence of such infrastructure would allow not only optimal selection of patients in clinical trials, but also enable long-term follow-up of all patients as well as benchmarking of clinical research in real life with no loss to follow-up [17].

It is urgent that European bodies that have the capacity to stimulate such changes get their acts together if we want to make precision medicine a viable option, rather than a chance happening that generates false hope for patients and the scientific community.

We propose to re-discuss the architecture of the process of clinical research and explore the design and maintenance of clinical outcome-focused systems, which have anticipated real-life questions early on in their development. Such a change in architecture is needed, not only for maximizing the potential of scientific advances for individual patients, but also for bringing economic benefit to health care services through the ability to target new and established treatment to those who are certain to benefit from it.

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