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Editorial
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A Theory that will Work not only in Experiments but also in Patients

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Editorial

The upcoming healthcare reforms differ from previous ones in terms of cost, political sensitivity, and the underlying knowledge base. A new theory on how to demonstrate "real-world effectiveness" (suitability for everyday practice) could help resolve this difficult political challenge. It allows an objective distinction between essential and non-essential healthcare services that previously could be made only subjectively.

About 40 years ago, as junior doctors, we noticed that the results published in journals and textbooks were significantly better than the observations we made in our own patients at the university hospital. We could explain this only by distinguishing between "efficacy" (now referred to as "proof of principle") and "effectiveness" (more clearly described as "real-world effectiveness" or the suitability of healthcare services for everyday practice).

Initial insights into this "efficacy-effectiveness conflict (Eff-Eff conflict)" rooted in our city. The legacy of Albert Einstein, an honorary citizen of Ulm (*1879) and the Ulm School of Design (*hochschule für gestaltung* or hfg) provided the crucial impetus for developing a solution. The breakthrough came with the recognition of a fundamental mistake in countries around the world. Experimental data from randomized trials is used (in the absence of suitable alternative methods) to justify decisions across ethical, epidemiological, medical, economic, legal, and political domains. Conservative estimates from practitioners, economists, and scientists suggest that experimental results overestimate the effects achievable in routine clinical practice by approximately 30%. Similar discrepancies were suspected when

comparing laboratory exhaust emission measurements with real-world road measurements.

Evidence-based medicine can be further advanced through one key innovation: Sir Archibald Cochrane and Sir Austin Bradford Hill called for answers to three questions - Can it work? Does it work? Is it worth it? - before an innovation is implemented into routine care [1]. Answering these three questions - a task that is far from simple – to reduce fundamental problems across healthcare systems. Table 1 outlines how these requirements can be translated into a strategy [2].

Table 1: The three-dimensional strategy based on the Cochrane-Hill questions.
Dark and light markings distinguish between objective and subjective - or experimental and pragmatic - assessments of healthcare services. Modified from [2].

Queries	Types of care	Perspectives	Study types	Methods	Answers
Can it work?	Experimental Study Condition (ESC)	Experimental clinical research	Experiment. (interventional) study	Exp. Randomized Contr. Trial (RCT)	Objective Proof of Principle (POP)
Does it work?	Pragm. Real-World Condition (RWC)	Health services research	Pragmatic (observational) study	Pragmatic Controlled Trial (PCT)	Object. (RWE) Real-World Effectiveness
Is it worth it?	Care As Usual (CAU)	Economic research	Complete Economic Analysis	Cost-Effectiveness Analysis (CEA)	Perception of subjective Value (VAL)

The previously missing method for demonstrating real-world effectiveness has now been established in the form of Pragmatic Controlled Trial (PCT) [3,4]. In this approach, all patients receive care according to standard "Care As Usual" (CAU) practice. One challenge is to develop a method that accurately and without bias captures the effects generated under the apparently chaotic conditions of CAU. This is a task for us scientists to resolve. The complex task of documenting the resulting data must be performed by professional data managers (such as experienced nursing staff – particular those in the second half of their professional careers - or part-time physicians and funded through public resources.

Implementing this concept can only succeed if we can convince our fellow citizens and decision-makers of the need for a strategic shift. To date, healthcare reimbursement has largely been based on the production costs of goods and services. In the future, however, financing should be primarily aligned with patients' individual risk profiles. Patients with multiple conditions require the management of more complex problems and higher level of care than a single health issue. Furthermore, the realistically achievable care outcomes differ between these two patient groups and medical teams from various specialties will employ tailored care strategies based on the best knowledge and expertise.

The PCT method makes it possible to identify different care strategies within an ecosystem - characterized by shared values - that entail varying costs yet generate comparable added value in terms of health outcomes. It remains up to each society to decide what conclusions to draw from this data.

Proposed solution: Stratification instead of randomization

Generating Real-World Evidence (RWE) is only possible if every patient receives CAU, with outcomes systematically recorded and analyzed using a non-experimental Bayesian approach could not be put into practice 2,500 years ago.

The necessary separation of professional roles

Physicians should be relieved of virtually all documentation tasks. The time freed up will be needed for patient interaction, an aspect of care that is often undervalued. Scientists must develop the appropriate methodology and analyze the results. Trained data monitors with experience in routine clinical care must collect all necessary data with AI support. This includes Endpoint-Specific Risk Profiles (ESRPs) and Endpoint-Specific Risk Classes (ESRCs) for each individual patient. Both ESRPs and ESRCs need to be calculated separately for every measured endpoint. General endpoints are primary outcome, adverse effects, and total cost of care. In addition, the care strategies employed, any necessary modifications to those strategies, and the study endpoints achieved need to be documented.

Financing Concept

When it comes to financing healthcare, the decisive factor is not the theoretical efficacy (POP) of individual therapies, but the achievable added health value of the entire care strategy employed. This success depends only partly on the interventions themselves; above all it depends on the patient's individual health risk profile. In the first semester of our medical training, we were taught about the significant differences observed when comparing the survival times of patient populations categorized by disease stages I through IV against the survival times of therapy "A" or "B." Survival times across disease stages I through IV show far greater variation than survival times after therapy "A" or "B."

Achievable progress and resulting implications

In almost every area of life, the price we are willing to pay for products or services is ultimately based on the added value achieved, not on production costs. Until now, we have been unable to base our willingness to pay for one of the most valuable assets - our health - on the added value achieved. That opportunity now exists. We should weigh the "costs" - that is, everything we must accept or bear - against the consequences. Shifting our mindset from a model based on input/effort to one based on achievable, risk-dependent added value creates several new perspectives.

"Clinical Economics" (CLINECS) combines economic and health-related perspectives and describes "what must be accepted to achieve a targeted added health value." The foundations of these considerations have been described **[5,6]**. The implementation of the concept will only succeed if the project's ecosystem is large enough (50 to 150 million citizens) to capture existing risk profiles and if its population has sufficiently homogeneous values to define – and implement – shared goals.

The shift in strategy could increase care efficiency to 30% but requires reorganization and individual responsibility for goals, methods, and outcomes across all healthcare professions. For the healthcare industry, this could significantly shorten the time from planning to market authorization and reduce development costs. Fewer Randomized Controlled Trials (RCTs) would be needed to demonstrate Proof of Principle (POP) and safety. At the same time, the health-care system's care mandate could be combined with the demonstration of Real-World Effectiveness (RWE) and financed through a public-private partnership.

General practitioners will take on the new task of maintaining with AI support an electronic record of all health data collected for a patient. The AI will transmit only critical warning signals to the relevant specialists and the generalist to reduce the rare but high-risk coincidence e.g. of life-threatening cardiac arrhythmia occurring alongside hypercalcemia and hypokalemia and the frequently occurring various types of undetected overtreatment.

The distinction between "telecommunication" and "syntopy"

The added value of scientists meeting in person at the same location is arguably one of the most cost-effective forms of research funding [7,8]. Consideration of the logical sequence of political decisions and scientific advice, and the optimal functioning of advisory experts:

The benevolent confirmation of policymakers' preconceived opinions by advisors requires no robust justification. Far more valuable than the benevolent confirmation of preconceived opinions are sound arguments supporting political decisions. "Scientists make decisions;policymakers take decisions" [9].

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