Commentary

Hidden Ethical Conflicts: The Need for Progress in Evidence-Based Medicine - A Living Review

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Background and Introduction. Randomized Controlled Trials (RCTs) are fundamental in Evidence-based Medicine. However, their importance is limited by the experimental design, patient selection, and the lack of real-world effectiveness. This commentary supports these statements and highlights the scientific and ethical contributions of Pragmatic Controlled Trials (PCTs) as a method of assessing Real-World Effectiveness (RWE).

Methods and Results. Three strategies were used to solve three tasks. We use the questions of Sir A. Cochrane and Sir A. Bredford-Hill "Can it work? Does it work? Is it worth it?" to design a three-dimensional strategy for the evaluation of health services. The rule "Form Follows Function (FFF)" was used to take into account the sequence and congruence of formal and functional criteria of epidemiological tools. Finally, the criteria of information that is suitable for confirming the validity of scientific statements, e.g., the levels of evidence, were discussed. The three-dimensional strategy includes the Proof of Principle using RCTs, Real-World Effectiveness using Pragmatic Controlled Trials, and the subjective benefit using Complete Economic Analyses. The FFF rule identifies scientific inconsistencies, such as the terminology conflict of “efficacy” and “effectiveness”. Scientific questions and statements (e.g., the hierarchy of evidence levels) require the description of congruent functions (importance for care) and forms (type of confirmatory data).

Conclusions. It is the task of scientists to uncover hidden forms of bias that lead to avoidable disadvantages for societies. The examples described contain suggestions for possible corrections that provide a new ethical and moral basis for medical, economic, legal, and political decisions. A "Living Review" can initiate the transformation of the healthcare system, increase its efficiency, and contribute ideas to consensus-building from a scientific perspective.

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Background and Introduction

Four international cardiology societies (European Society of Cardiology, American Heart Association, American College of Cardiology, World Heart Federation) issued a joint statement proposing a modification of randomized controlled trials (RCT)[1]. This modification is justified due to increased administrative requirements and financial burdens, as well as a disproportionately low information gain from conventional RCTs. In a 'joint opinion', the design of an adaptive platform study is proposed instead of traditional RCTs[2] because promising results could be achieved by this study design in different studies[3][4][5].

We agree with the Joint Opinion Group's call for a necessary optimization of the standards for gaining knowledge in the healthcare system and contribute our experience that we gained while developing the pragmatic controlled trial (PCT).

The need to develop a specific method for the detection of non-experimental care effects arose in the late 1980s. One of us, a young oncologist, noticed that treatment successes in patients at our university hospital were inferior compared to published oncology reports. Nearly a decade passed before a simple idea could plausibly explain the difference. We observed effects in our hospital that occur in everyday care (real-world effectiveness), whereas the data reported in journals were almost exclusively generated in experimental studies under strictly controlled conditions. A method to distinguish efficacy and effectiveness was missing, although the difference between efficacy and effectiveness was described very early on[6][7][8]. We did not succeed in formally describing the difference between expected and observed results until much later[9].

Evidence-based Medicine taught us Sir Archibald Cochrane's and Sir Austin Bradford Hill's three essential questions to ask before implementing an innovation in the healthcare system: "Can it work? Does it work? Is it worth it?"[10]. Cooperation with teachers and students in the "hochschule für gestaltung (hfg)" (Ulm school of design) taught us the rule "Form Follows Function (FFF)" generated by American designers and architects[11]. As citizens of Ulm, we are familiar with many of Albert Einstein's (born in 1879 in Ulm) statements. One of them points out that problems cannot be solved by the mindset that caused them. We also took note of this plausible indication for years without understanding the significance of this demand. Only after the attempt to leave the traditional way of thinking in favor of an alternative solution did the considerable hurdle of one's thinking become recognizable, which had to be overcome. The recommendations of the British epidemiologists, supplemented by the input of American

designers and a German physicist, made it possible to discuss three issues. A three-dimensional strategy for the evaluation of health services, the importance of both the sequence and congruence of formal and functional criteria when used for the development and evaluation of epidemiological tools, and the need to support any evidence-based statement by the description of both function (relevance to health outcomes) and form (supporting methods and data).

Methods and Results

The three-dimensional strategy for the evaluation of health services

The concept of the three-dimensional strategy is based on the three Cochrane-Hill questions. The answer to the first question, "Can it work?", requires proof of the effective principle (proof of principle, PoP). The second question, "Does it work?" can be answered by demonstrating real-world effectiveness (RWE). The third answer describes the perceived value (Val) of healthcare services from an individual and a societal perspective. Efficacy and effectiveness depend on objective judgments, whereas the description of value is based on subjective but essential judgments (Table 1).

Perspective	Question	Answer	Health care condition	Type of study	Method
Clinical research	Can it work?	Objective confirmation of proof of principle (PoP) or efficacy	Experimental study condition (ESC)	Interventional study	Randomized controlled trial (RCT)
Health services research	Does it work?	Objective confirmation of real-world effectiveness (RWE)	Real-world condition including with systematic evaluation of outcomes	Pragmatic / observational study	Pragmatic controlled trial (PCT)
Economic research	Is it worth it?	Subjective confirmation of value (Val)	Real-world condition without systematic evaluation of outcomes	Complete economic analysis	Cost-effectiveness analysis (CEA)

Table 1. Answering the three Cochrane-Hill questions from the perspectives of clinical research, health services research, and economic research (modified from[12]).

Confirmation of adequate health care requires two assessments: the objective assessment provided by confirmation of RWE and the subjective assessment of an acceptable balance of all types of “costs and

consequences." The objective detection of RWE is influenced by two effects: the sum of all external conditions (interventions) and the patient's existing risk profiles. The risk profiles of individual patients need to be described separately for each measured endpoint, as almost all patients differ from each other in terms of individual risk profiles, and the risk profiles of individual patients are not identical for all care endpoints considered. This task of concise data collection can be supported by information technology (IT) to ensure the completeness of the required data. The affected patients and decision-makers involved take the final subjective decisions. This note describes the complexity of the decisions made. Methodological details for the discussion were mainly described in pre-publication media[12][13][14][15][16][17][18].

The Required Sequence and Congruence of Formal and Functional Criteria.

We have received valuable information from other disciplines on the development and subsequent quality testing of epidemiological tools (methods). Formal (structural) and functional criteria need to be considered for each tool. The order in which these criteria are applied is important in the development of tools and should follow the FFF rule. In other words, the first step is to define the expected function of the tool or method. In the second step, the appropriate form (structure) should be found that enables the expected function to be implemented. In clinical epidemiology, we have made a mistake by recommending that the form of an RCT be used to generate two different responses under experimental conditions: the description of the PoP and the RWE. Today, we understand that the proof of PoP requires experimental study conditions, while the proof of RWE is only possible under (pragmatic) everyday conditions. Both detections require different supply conditions and different measurement methods (RCTs or PCTs). The PCT records all necessary risk profiles and considers all the risks of the individual patient that may influence the expected effects of the care in addition to the effects of our medical measures.

These considerations led to the unexpected result that three forms of care will be needed in the future instead of the two established forms. So far, we have distinguished between structured experimental care in RCTs and non-structured pragmatic care as usual (CAU) under everyday conditions. The third form of supply, the Pragmatic Controlled Trial (PCT), describes a hybrid form of the first two forms. On the one hand, it offers the unstructured CAU – which is necessary to describe the effects of everyday care. This condition requires that the data of all patients treated by the institutions participating in a PCT be collected and reported. Without taking this condition into account, the CAU cannot be mapped. On the

other hand, the PCT uses a non-experimental method, Bayes' Principle, to map all interventions applied and the complete risk profile of each patient. The methodological details are described as graphic and text[16][18]. The detailed differentiation of the three healthcare conditions based on functional and formal (structural) criteria is shown in Table 2. Background colors highlight the functions and forms that are different in all three conditions of care (yellow) or are identical in two of these conditions (blue).

Conditions	**1) Experimental study.** Structured care & structured analysis in RCTs*	**2) Pragmatic study.** Unstructured care + structured analysis in PCTs*	**3) Care as usual (CAU).** Analysis limited to pre-post comparisons.
Criterion of primary function			
(a) Knowledge gain or provision of healthcare	Description of experimental **Efficacy** called **Proof of Principle (PoP)**	Description of pragmatic, non-experim. **Real-World Effectiveness (RWE)**	Description of **Care as usual (CAU)** limited to "pre-post" comparisons
Formal (structural) criteria			
(b) Type of care	Experimental care	Pragmatic care	Pragmatic care (CAU)
(c) Impact of patient risks	Random distribution	ESRC*	Implicit consideration
(d) Recording of interventions	Accord. study protocol	Accord. study protocol	Defined in CGMT*
(e) Study protocol	Required	Required	Defined in CGMT*
(f) Approval by IRB*	Required	Required	Defined in CGMT*
(g) Collection personal data	Consent required	Consent required	Defined in CGMT*
(h) Defined inclusion criteria	Study protocol	Study protocol	Defined in CGMT*
(i) Justified protocol violation	Exclusion criterion	Needs to be recorded	Needs to be recorded
(j) Defined exclusion criteria	Study protocol	None	None
(k) Patient health problems	Single and specified	Multiple problems	Multiple problems
(l) Selection of intervention	Study protocol	Doctor/patient	Doctor/patient
(m) Research liabil. insurance	Required	None	None
(n) Experience with trials	Required	None	None

Table 2. One functional criterion (lane a) and 13 formal criteria (lanes b through n) define three different conditions of care. 1) an experimental study to describe the Proof of Principle (PoP) or Efficacy in Randomized Controlled Trials (RCTs). 2) an observational (called pragmatic) study to describe the outcomes of Care As Usual (CAU), i.e. the Real-World Effectiveness (RWE) in Pragmatic Controlled Trials (PCTs). 3) a description of Care As Usual (CAU) that is used to provide healthcare without systematic evaluation of outcomes. The yellow background marks functions and forms that are different in the three conditions of care. Formal criteria that are identical in two of the three conditions of care are marked by a blue background. CGMT: Contract governing medical treatment. ESRC: Endpoint-Specific Risk Classes. IRB: Institutional Review Board. *PCT: Pragmatic Controlled Trial. *RCT: Randomized Controlled Trial. Previous version published as preprints[16][18]

The FFF rule can be used not only to develop a new product but also to control the quality of an existing product. However, it should be noted that the design of a new product and the evaluation of the quality of an existing product are based on different perspectives. To create a new product, the designer must

describe the expected function of the product. According to the original FFF rule, designers will try to design the optimal shape of the product in such a way that the expected function can be achieved. This procedure corresponds exactly to the recommendation of the FFF rule.

To ensure the quality of an existing product, the user of the product can evaluate its form and function and thus assess its suitability. The reversal of the FFF rule in "Function Follows Form" makes it possible to check the correspondence of form and function. However, the reversal of the rule does not consider the fact that purposeful considerations about the form of a product or concept are not possible without a concrete definition of the product's or concept's function. The principles of cause and effect of the FFF rule are not interchangeable.

The validity of the FFF rule is not generally accepted in the literature. The doubters find the reversal of the rule in "Function Follows Form" just as correct because, in many products, the observable function can be derived from their form. However, it is not taken into account that the "alternative form" excludes the possibility of deriving the ideal form of the product from the expected function. The lack of derivation of the ideal form justifies the rejection of the "alternative form" of the FFF rule as a law of nature. As indicated by Sullivan, his version meets the requirements of a natural law[11]. This statement may become more important as the FFF rule is considered to avoid over-regulation in different areas of society.

The validity of the FFF-Designer rule in clinical epidemiology and healthcare.

Our assumption that doctors make arbitrary decisions in health care is probably wrong. It is more likely that they make an implicit effort to adapt their strategies to the individual risk profiles of patients. However, the process of adaptation has hitherto not yet been structured[16]. The challenge of designing the best possible strategy does not only depend on the current state of science but on the clinical successes that can be achieved by applying the scientific results in practice.

One of the significant but frequently ignored risks of deriving incorrect answers from scientific analyses is the formulation of incorrect questions. Since imprecise questions almost always lead to wrong answers, we have carried out an international project on questions and answers in clinical trials as Meret Phlippen's dissertation. The aim of her thesis was to test the correspondence of form and function of three indicators that characterize the aims and outcomes of clinical studies. In cooperation with six international working groups from Brazil, Germany, Italy, and the USA, three indicators were selected: the hypothesis of the study, the translation of the hypothesis into a concrete study protocol, and the

statistical method used to test the hypothesis. The data were extracted from 119 publications, 20 each from six selected scientific journals[19]. Three conclusions could be derived from her thesis.

First, the form and function of the methods used do not agree in many studies, mainly because experimental methods (RCTs) are used to confirm expected everyday effects. This disagreement confirms the terminology conflict described[14]. Second, it could be shown that most studies use two-sided statistical tests to answer one-sided questions. This decision is based on scientific recommendation. From an ethical perspective, more patients than are required for a one-sided test are exposed to an experiment that can only detect the PoP. At this point, it is to be expected that the information obtained through the experimental detection of the PoP is rather limited. This evidence only confirms that the intervention studied is effective in a selected target group. The detection of PoP can characterize neither the sensitive nor the resistant sub-groups of the treated patients. Likewise, it is not possible to distinguish between different causes, e.g., physical/chemical or psychological effects, if no corresponding control groups have been investigated. Consequently, it could be discussed to generally use one-sided statistical tests to answer one-sided questions. In the future, the risk of misinterpreted experiments will be controlled by the additional requirement to prove suitability for everyday use. In PCTs, the application of one-sided statistical methods for one-sided questions will be unproblematic because the large number of cases required in PCTs should sufficiently control the risk of incorrect assessment. The third effect of Phlippen's project confirms that individual effects that were investigated independently of each other are not sufficient to identify the causes of incorrect answers.

After the completion of the data collection in her project, the idea arose to use the collected data also to quantify the loss of information that can be expected in each multi-step process at the transition from one system to the next. Using the title "Front-end-processor", we present data suggesting that scientific questions may be developed in four steps[18]. The data confirm that the risk of answering the scientific question incorrectly increases if the contents of these four steps do not match. Outcomes cannot be reproduced unless the risk profiles of the investigated patients or the used interventions were comparable[20]. These essential conditions were not considered in all analyzed publications. The results shown in Fig. 1 quantify the congruence of each of the four consecutive steps in the construction of a scientific study question. These steps are (a) the study hypotheses in simple language, (b) the study populations examined, (c) the scientific study hypotheses (e.g., superiority test), and (d) the statistical tests to confirm the study hypothesis[18]. The results of this analysis suggest that a step-by-step development of scientific questions may increase its precision. However, the same data justify the

hypothesis that any multi-stage strategy can significantly distort the outcomes. The analysis shown in Fig. 1 was not planned prospectively. It used the data that were generated in Phlippen's thesis[19]. Similar prospective projects may be useful to confirm the significance of both the congruence of form and function and of the contents in multistep strategies.

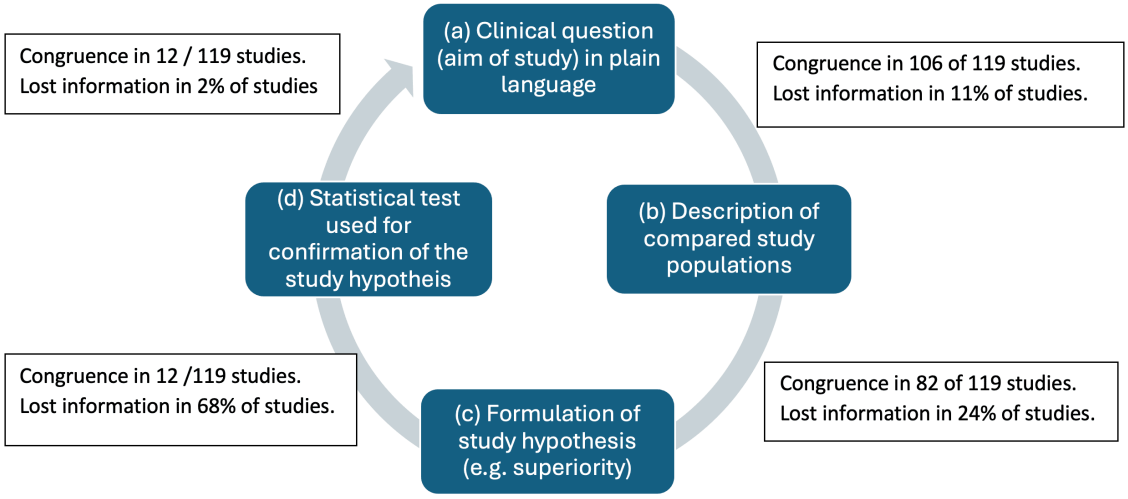

Figure 1. The way from (a) the study question in plain language to (d) the description of the applied statistical test in clinical studies. The total numbers of compared studies (n = 119) and the numbers of studies with congruent contents and relative loss of information in the steps (a and b, b and c, c and d, and d and a) are shown[18]

Another example of clinical epidemiology confirms the necessary description of both criteria, form, and function. The hierarchy of different levels of evidence is intentionally regarded as a measure of the validity of scientific statements. The classification used assumes that the results of randomized trials and their meta-analyses are the best available basis for making decisions in health care. However, the analysis of this assumption shows that the results of randomized trials can provide proof of principle (PoP; efficacy) under ideal conditions. This proof is not sufficient to assume effectiveness in everyday care. In everyday care, patients are treated with complex risk profiles. Most of these patients cannot be included in RCTs. Most RCTs lack an exact description of the complete risk profiles of the included patients. As a result, it has been difficult to identify collectives in which the risk profiles of the patients studied match. Similar considerations are required when comparing different interventions or when combining results from different studies in meta-analyses without knowing the risk profiles of the patients studied. The considerable variance of these risk profiles and the derived therapeutic strategies

cannot be depicted in experimental studies.

In summary, experimental studies can only provide part of the information needed to make healthcare decisions. The new concept should distinguish two functions: PoP and RWE, and define two additional thresholds to achieve the best possible ethically justifiable result. Without setting thresholds – initially based on experience – it will be almost impossible to avoid oversupply. The two thresholds define the limit of minimum need and minimum success that justifies supply. The care results achieved make it possible to successively adjust the initial thresholds, which are based on the result of RWE and the subjectively perceived value (VAL). Thresholds are already used in the recommendations for care in the event of elevated blood pressure or metabolic indicators and are suitable as a necessary condition. However, compliance with these experimental thresholds does not confirm the expected reduction of health risks. Without a threshold that defines the desired achievements, the expected results cannot be confirmed.

These considerations gave rise to the concept of a Cube of Clinical Care (CCC). In this concept, three dimensions of health care are distinguished: the form, the function, and the consideration of threshold values. The form describes experimental or pragmatic care for patients (Fig. 2). The function distinguishes between forms of care with or without systematic analysis of the results. Thresholds make suggestions for distinguishing between health conditions in need of treatment and those that do not, as well as between patients who are successfully cared for and those who are not. This "threshold quartet" makes it possible to identify an oversupply. The comparison of care without or with the application of the threshold values is possible in the unstructured CAU or also in a structured PCT. Both forms of care are suitable for confirming the expected increase in care efficiency by taking thresholds into account from different perspectives.

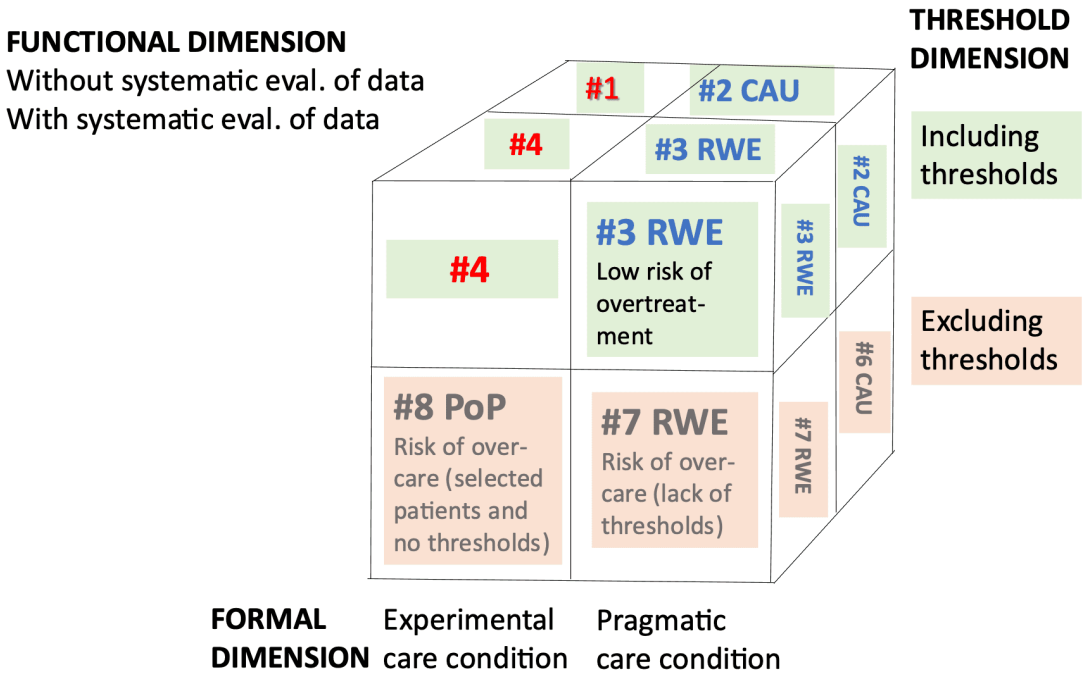

Figure 2. Cube of Clinical Care (CCC). The numbers (#1- #8) mark the eight small cubes that represent five different forms of health care delivery. These five forms of care can be distinguished from each other by three criteria: experimental or pragmatic care conditions, without or with systematic evaluation of care outcomes, and care with or without consideration of the thresholds. Two of the five care settings (blue letters) describe care as usual (CAU) considering thresholds (#2) and real-world effectiveness (RWE) considering thresholds (#3). Three other forms of care, i.e., the experimental treatments without systematic evaluation of outcomes (#1 and #5), are not acceptable. Experimental treatments that consider thresholds (#4) will only rarely be completed (red letters). Care setting #5, an experimental treatment without systematic evaluation of data, is not acceptable. This cube (below #1) is not visible in this graph. The two pragmatic settings of care (#6 and #7) are usually applied without considering thresholds. The results obtained in these two conditions not considering thresholds (black letters) may generate valuable results when compared with the results of the two corresponding conditions (#2 and #3 in blue letters) that do consider thresholds. The experimental treatments for the proof of principle (PoP) are evaluated without the definition of thresholds (#8).

Discussion

The aim of this review is the detection of epidemiological biases in RCTs. These biases lead to misinterpretations, unjustified conclusions, inefficient healthcare, rising care costs, and finally

undetected ethical conflicts. Changes in the quality of care can be quantified neither in well-structured experimental studies nor under unstructured care as usual due to a lack of established instruments for the assessment of the RWE. The identification of these systematic mistakes is possible by using different strategies.

a. In line with Cochrane and Hill's request, it was confirmed that the experimental proof of health care services is not sufficient to make decisions in everyday care. This requires the objective proof of RWE and the subjective assessment of the values achieved under the conditions of everyday care.
b. Applying the designers' FFF rule to analyze RCTs identifies the incorrect sequence in the design of the RCT and the mismatch of form and function. "Form Follows Function" means that the function of a product or concept needs first to be defined, followed by the selection of the appropriate form that corresponds to the expected function. c) The FFF rule can also analyze the congruence of the goals and results of clinical trials, the agreement of the four steps from the study question to the mathematically confirmed result, and finally the results and the derived interpretations of results. The latter emphasize the importance of the risk profiles of the target groups studied. Without analyzing the risk profiles of individual patients, it is not possible to identify treatment-sensitive and resistant subgroups. Likewise, it is impossible to distinguish between different causes of outcomes, e.g., physical/chemical or psychological effects, unless corresponding control groups have been investigated. The application of the FFF rule to the pyramids of scientific evidence confirms that their forms (structures) are hierarchically ordered. The description of the scientifically validated gain in knowledge is missing. The information gained could be substantiated by describing the forms of care, the functions of the detectable effects, and the consideration of thresholds.

Additional aspects such as the understanding of the function and form of inclusion and exclusion criteria in clinical trials or the powerful effects of communication are not addressed here, but are important for distinguishing experimental and pragmatic studies. The exclusion criteria protect the evidence of PoP from bias, but compromise the evidence of RWE because the risk profiles of patients investigated in experimental studies will barely meet the conditions of care as usual. The effects of communicating the results of everyday care have not yet been sufficiently investigated. Theoretical analyses do not confirm all assumptions[18][21].

Several scientists doubted the validity of results of RCTs[22][23]. However, it is quite possible that it is not the method of randomization itself but the necessary framework conditions of the RCT (e.g., the exclusion of certain risks or other influencing factors) that cause the doubts. Consequently, the interpretation of the results of an RCT is only valid if it actually considers the effects caused by the framework conditions. Otherwise, the effects that can be achieved will be misinterpreted. From this, it can be deduced that RCTs allow us to name the interventions that work, but not the target populations that benefit from the interventions. Detailed data to derive new care concepts require the description of the endpoint-specific risk profiles of individual patients separately for all assessed endpoints. This assumption also suggests that PCTs should not be carried out regionally, but at the national level.

This commentary cannot explain all the details needed to evaluate and implement health services. If the objectifiable increase in efficient health care were to be discussed as a new ethical and moral principle, each society would be able to assess the importance and urgency of efficient health care itself. Similar considerations have been discussed for 40 years[24][25]. They concern central aspects of health care and should consider the perspectives of all groups involved.

Appendix

Evidence of fitness for daily use should be demonstrated for all interventions applied in healthcare. The shift of focus from PoP to RWE can be justified:

- RCT studies only involve a highly selected patient population in which the major risk factors affecting the measured primary endpoint have been eliminated by exclusion criteria. Exclusion criteria are not applied in a PCT because they exclude the population that poses the greatest challenge to the care team in everyday care: to design a care strategy whose effects and interactions ultimately meet the expectations of multimorbid patients.
- An RCT limits the choice of healthcare options to the few interventions that can be compared and interpreted in an RCT. The PCT does not limit the choice of healthcare options. Each participating physician chooses the intervention(s) expected to produce the optimal outcomes for the individual patient.
- An RCT is expected to ensure the equal distribution of all risk factors not excluded in the study population(s). This, however, can hardly be confirmed because the size of the studied population depends on many variables, like the number of risk factors, their effect sizes, and their

interrelationships. The smaller the study population of an RCT examined, the greater the risk of comparing patients with different risk profiles.

Progress in health care can be achieved step by step. The supplied patients will only notice that considerably more data is collected than before, but that the supply will remain unchanged for the time being. The advanced data collection will require several basic steps.

1. Selection of the clinical health problem to be analyzed.
2. Definition of the targeted endpoints of care in advance.
3. Definition of the potential risk factors of the patients that may impair the achievement of these endpoints, i.e., the "endpoint-specific risk lists (ESRLs)".
4. Based on these ESRLs, clinical expert teams can form different endpoint-specific risk classes (ESRCs; high, intermediate, low).
5. To evaluate the care outcomes, each patient treated is assigned to a defined ESRC (high, intermediate, low) for each measured endpoint. The methods of AI enable this complex data assessment and collection, which includes not only the risk profile of the patient but also a classification of the therapeutic measures. Usually, multiple health problems require multiple therapies in parallel in most patients[12][13][14][15][16][17][19].

The necessary increase in data collection may be perceived by doctors as a similar burden to the demand for randomization 30 years ago. Nevertheless, there will be a significant difference because the assessment of the risk profile will seem plausible for patients and physicians and, unlike randomization, will not affect the relationship between physician and patient.

A change in our traditional way of thinking is necessary to accept that the proof of everyday suitability of healthcare services, i.e., the new field of healthcare-services research, requires two different healthcare conditions (twin method)[15]: Care must be provided under the non-structured everyday conditions of ‘natural chaos’ prevailing in patient care, while the evaluation of healthcare outcomes requires precisely structured tools, like Bayesian statistics, with no reciprocal influence between these two methods, the care as usual and the method used for the analysis of the data. This comment should appeal to colleagues who share our concern that the uncritical interpretation of the results of experimental RCTs could affect the financial viability of our health systems.

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