Commentary

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

Franz Porzsolt[1]

1. Private Research Institute Clinical Economics, Germany

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. Four strategies were used to solve these tasks. We use the questions of Cochrane and 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 "Form Follows Function (FFF)" rule supported both the definition of three care conditions (RCT, PCT, Care as usual, CAU) and four steps that support the construction of precise study questions. Fourth, specific objective criteria such as form, function, and thresholds were discussed to replace the assigned levels of scientific evidence.

The 3-dimensional strategy describes the proof of principle (RCTs), real-world effectiveness (PCTs) and subjective benefits by means of Complete Economic Analyses (CEAs). The FFF rule identifies scientific inconsistencies, e.g. the conflict between "efficacy" and "efficacy", the loss of information in the step-by-step development of scientific questions and replaces missing criteria to confirm the validity of the hierarchy of levels of evidence.

Conclusions. Scientists need to uncover hidden forms of bias that cause avoidable societal burdens. The examples in this review include suggestions for possible corrections that provide a new ethical and moral basis for medical, economic, legal, and policy decisions. A "Living Review" can initiate the transformation of the healthcare system, increase its efficiency and develop new concepts for the necessary cooperation between the healthcare industry and health care.

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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 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 journals reported data 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 it 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 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 products 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 considered 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 Phippen'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 of all studies use two-sided statistical tests to answer one-sided questions. This decision is based on scientific recommendation. From an ethical point of view, more patients than are required for a one-sided test are exposed to an experiment –

and also incur additional costs. 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, unless 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 a 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 Phippen's project confirms that individual effects that were investigated independently of each other are not sufficient to identify the causes of incorrect answers.

After 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 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), (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 Phippen's thesis [19]. More sophisticated prospective projects may be useful to confirm the significance of both the congruence of form and function and of the contents in multistep strategies.

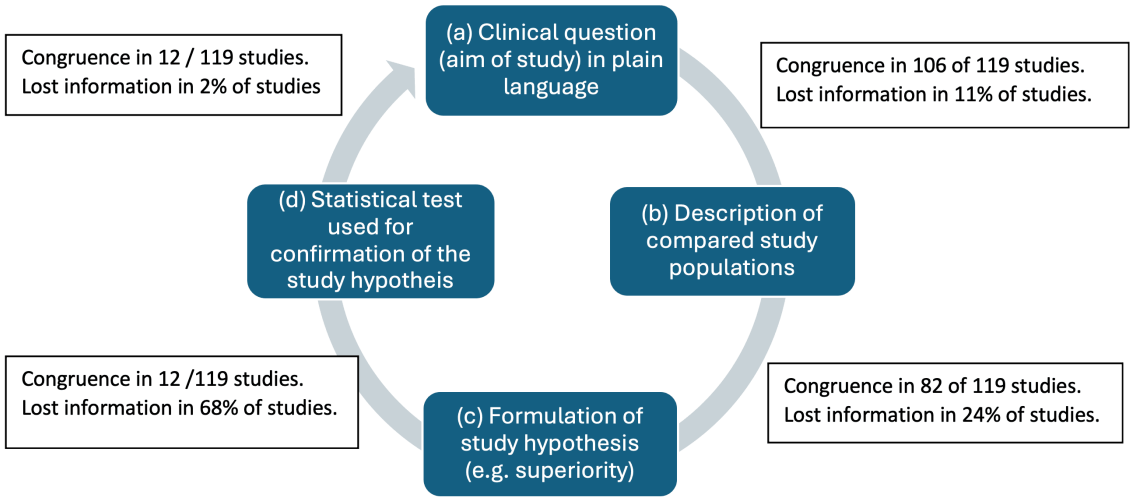

Figure 1. The way from the study question in plain language (a) to the description of the applied statistical test in clinical studies (d). In 11% of the studies, information was lost during the transition (a/b)., 20% in step (b/c), 62% in step c/d), and 25 in step (d/a) [18].

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 derived hierarchy assumes that results of randomized trials and their meta-analyses are the best available basis for decision-making in the healthcare sector. However, the analysis of this assumption shows that results of randomized trials can be used under ideal conditions to provide a proof of principle (PoP; effectiveness). 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 is intended to distinguish between the two functions PoP and RWE, define two additional threshold values in order to achieve the best possible ethically justifiable result and also include subjective assessments in the discussion. Without setting thresholds – initially based on experience – it

will be almost impossible to avoid oversupply. The two thresholds define the limit of the minimum requirement and the minimum success of the supply that justifies the offer. The supply results achieved make it possible to successively adjust the initial thresholds, which are based on RWE's result and the subjectively perceived value (VAL). Thresholds are already used in recommendations for the treatment of elevated blood pressure or increased metabolic indicators. However, compliance with these thresholds in experimental studies does not confirm the expected reduction in health risks. Without a threshold that defines the expected clinical success, the observed results can only be interpreted to a limited extent.

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 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.

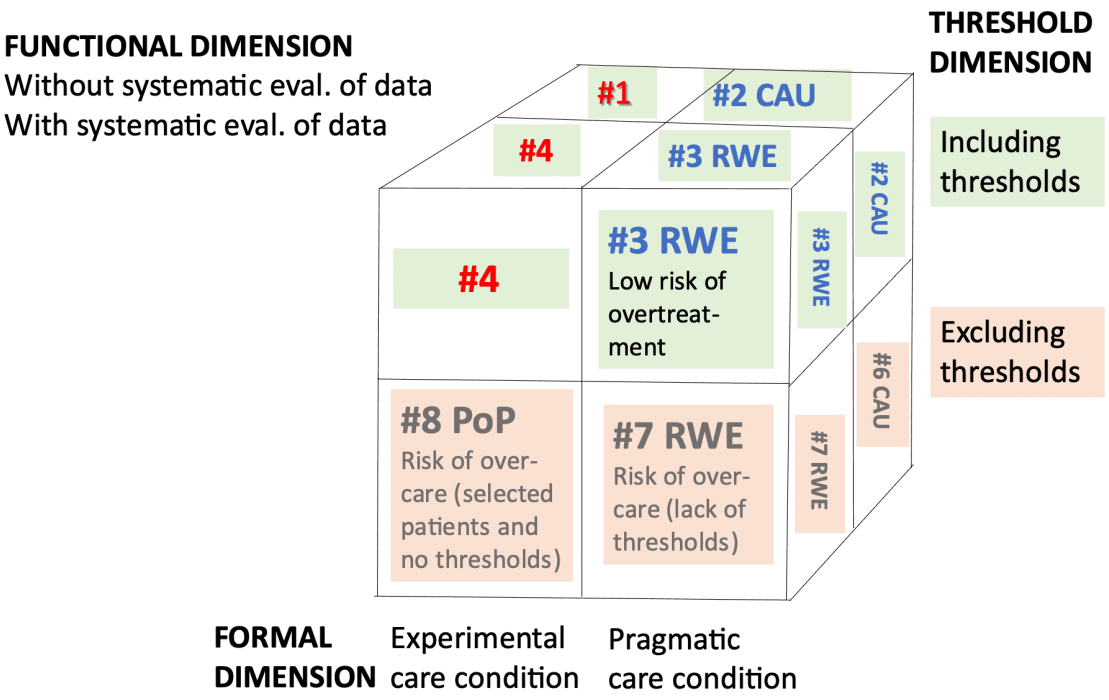

Figure 2. Cube of Clinical Care (CCC). The numbers (#1- #8) mark the eight small cubes that represent five different forms of health care delivery. These five forms of care can be distinguished from each other by three criteria: experimental or pragmatic care conditions, without or with systematic evaluation 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 completed (red letters). Care setting #5 an experimental treatment without systematic evaluation of data is not 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 resuts when compared with 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 definition of thresholds (#8).

Discussion

The aim of this review is to propose scientific contributions to reduce 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

CAU due to a lack of established instruments for assessment of the RWE. The identification of these methodological problems is possible by using different strategies.

In line with Cochrane and Hill's request, it is shown that the experimental proof of health care services is not sufficient to make decisions in everyday care. The objective proof of RWE and the subjective assessment of the values achieved under the conditions of everyday care are equally important (Table 1).

The results in Table 2 describe the consequences that could be derived from the application of the designers' FFF rule. This rule can distinguish correct from incorrect study designs. Unsuitable study designs emerge when the requested sequences of development steps will be disregarded. "Form Follows Function" means that the function of a product or concept needs to be defined first, followed by the selection of the appropriate form that corresponds to the expected function.

The FFF-rule can also be used to analyze the precision of study questions. The significance of the perfect and complete study question is one of the limiting factors in all research projects. The precision of a study question may be supported by demonstrating the congruence of four consecutive steps in the development of a complete study question. These steps start with a study question in plain language followed by the precise description of the compared study populations, followed by the description of the planned statistical hypothesis, the mathematical confirmation of the hypothesis, and finally the derived interpretations of results. Our results in Fig. 1, extracted from 119 publications [19][18], confirm the loss of information due to a lack of congruence between the four consecutive steps in the development of the study question.

Any question of a scientific study should also note that the risk profile of the population studied is one of the most powerful factors influencing the outcome of the study. Without analyzing the risk profiles of all patients in a study, it is not possible to identify treatment-sensitive and resistant subgroups. Likewise, it is impossible to distinguish between different effects, e.g. physical/chemical or psychological effects, unless appropriate control groups have been studied.

The application of the FFF rule to the pyramids of scientific evidence confirms that the various forms (structures) of knowledge gain are hierarchically ordered, but without justifying the chosen hierarchy with data. We are all aware of the problems resulting from the derived hierarchy. So far, however, there are no proposals for solutions. The application of the FFF rule confirms that the necessary data are available to describe the chosen form of care (RCT or PCT or CAU), the expected functions of these forms of care and the consideration of threshold values (Fig. 2). The expected goals of each care project can thus be defined and evaluated.

Additional details such as the function and form of inclusion and exclusion criteria in clinical trials are not addressed here. 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 CAU as 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 discussed 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) cause the doubts. Consequently, the interpretation of the results of an RCT is only valid if it considers the effects caused by the framework conditions. Otherwise, the effects that can be achieved will be misinterpreted. RCTs allow us to name the interventions that work, but not the risk profiles of the target populations that benefit from the interventions. Detailed data to derive new care concepts require the description of the endpoint-specific risk profiles (ESRPs) 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.

If the objective 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 patents with different risk profiles.

Progress in health care can be achieved step by step. The supplied patents 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 basis 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 IT 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 as 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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References

1. ^*Bowman L, Weidinger F, Albert MA, Fry ETA, Pinto FJ. Randomized Trials Fit for the 21st Century. A Joint Opi nion from the European Society of Cardiology, American Heart Association, American College of Cardiology, a nd the World Heart Federation. Global Heart. 2022; 17(1): 85. DOI: https://doi.org/10.5334/gh.1178*
2. ^*Park JJH, Detry MA, Murthy S, Guyatt G, Mills EJ. How to use and interpret the results of a plat-form trial: user s' guide to the medical literature. JAMA. 2022;327(1):67-74. doi:10.1001/jama.2021.22507*
3. ^*Gordon AC, Angus DC, Derde LPG. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. Reply. N Engl J Med. 2021 Sep 16;385(12):1147-1149. doi: 10.1056/NEJMc2108482. Epub 2021 Aug 18. PMID: 34407 335.*
4. ^*Writing Committee for the REMAP-CAP Investigators; Higgins AM, Berry LR, Lorenzi E, Murthy S, McQuilten Z, Mouncey PR, Al-Beidh F, Annane D, Arabi YM, Beane A, van Bentum-Puijk W, Bhimani Z, Bonten MJM, Brad bury CA, Brunkhorst FM, Burrell A, Buzgau A, Buxton M, Charles WN, Cove M, Detry MA, Estcourt LJ, Fagbodu n EO, Fitzgerald M, Girard TD, Goligher EC, Goossens H, Haniffa R, Hills T, Horvat CM, Huang DT, Ichihara N, La montagne F, Marshall JC, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Neal MD, Nichol AD, Parke R L, Parker JC, Parry-Billings K, Peters SEC, Reyes LF, Rowan KM, Saito H, Santos MS, Saunders CT, Serpa-Neto A, Seymour CW, Shankar-Hari M, Stronach LM, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Gre en C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Derde LPG, Gordon AC, Webb SA, Lawler PR. Long-term (180-D ay) Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial. JAMA. 20 23 Jan 3;329(1):39-51. doi: 10.1001/jama.2022.23257. PMID: 36525245; PMCID: PMC9857594.*
5. ^*Barnett ML, Sax PE. Long-term Follow-up After Critical COVID-19: REMAP-CAP Revisited. JAMA. 2023 Jan 3; 329(1):25-27. doi: 10.1001/jama.2022.23700. PMID: 36525259.*

6. ^Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. J. Chron. Dis 1967;20: 637-648 (1967).

7. ^Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. Lancet 2002:359; 57-61.

8. ^Thiese MS. Observational and interventional study design types; an overview. Biochem Med 2014: 24(2); 199-210 (2014). http://dx.doi.org/10.11613/BM.2014.022.

9. ^Wiedemann F, Porzsolt F. Measuring Health-Related Quality of Life in Randomised Controlled Trials: Expected and Reported Results Do Not Match. Pragmat. Obs. Res. 2022 Apr. 11;13:9-16. Doi 10.2147/POR.S350165. PMID: 35431592; PMCID9012498.

10. ^Haynes B. Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving. BMJ. 1999 Sep 11;319(7211):652-3. doi: 10.1136/bmj.319.7211.652. PMID: 10480802; PMCID: PMC1116525.

11. a, bSullivan, L.H. The tall office building artistically considered. Lippincott's Magazine 1896;57: 403-409. Reprinted in Inland Architect and News Record 27 (May 1896), pp. 32-34; Western Architect 31 (January 1922), pp. 3-11; published as "Form and Function Artistically Considered" The Crafts-man 8 (July 1905), pp. 453-58. https://www.giarts.org/article/tall-office-building-artistically-considered-excerpt. Last access oct 22, 2019

12. a, b, cPorzsolt F, Eisemann M, Habs M, Wyer P. Form Follows Function: Pragmatic Controlled Trials (PCTs) have to answer different questions and require different designs than Randomized Con-trolled Trials (RCTs). J Publ Health 2013;21:307-313. DOI 10.1007/s10389. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3655212/

13. a, bPorzsolt F, Rocha NG, Toledo-Arruda AC, Thomaz TG, Moraes C, Bessa-Guerra TR, Leão M, Migowski A, Araujo de Silva AR, Weiss C. Efficacy and Effectiveness Trials Have Different Goals, Use Different Tools, and Generate Different Messages. Pragmatic and Observational Research 2015;6:47-54. DOI http://dx.doi.org/10.2147/POR.S89946

14. a, b, cPorzsolt F, Wiedemann F, Phlippen M, Weiss C, Weiss M, Schmaling K, Kaplan RM. The terminolo-gy conflict on efficacy and effectiveness in healthcare. J Comp Eff Res. 2020;9:1171-1178. doi: 10.2217/cer-2020-0149.

15. a, b, cPorzsolt F, Weiss Ch, Weiss M. Covid-19: Hybridmethode zum Nachweis der Real-World Effective-ness unter Alltagsbedingungen [Covid-19: Twin method for demonstration of real-world effective-ness (RWE) under the conditions of day-to-day care]. Das Gesundheitswesen 2022;84:1-4. DOI: 10.1055/a-1819-6237. ISSN 0941-3790.

16. a, b, c, d, ePorzsolt F, Weiss Ch, Weiss M. An Evidence-Based Hypothesis: Doctors Do Not Make Decisions Randomly but Based on Individual Patient's Risk Profiles. Preprint from Qeios, 21 May 2024 https://doi.org/10.32388/n02184 PPR: PPR856245

17. a, bPorzsolt F, Weiss M, Weiss Ch. Applying the Rule of Designers and Architects "Form Follows Func-tion (FFF)" Can Reduce Misinterpretations and Methodical Shortcomings in Healthcare. Trends Gen Med. 2024; 2(1): 1-

7. ISSN: 2996-3893

18. a, b, c, d, e, f, g, h Porzsolt F, Phlippen MS, Legrum P, Weiss M. The Front-End Processor Developed by Engineers — A Useful Tool for Describing the Quality and Quantity of Progress in Healthcare. Qeios ID: 8PWWZD · https://doi.org/10.32388/8PWWZD

19. a, b, c, d Phlippen MS. Progress in evidence-based medicine by critical appraisal of evidence-based medi-cine: the HOST catalogue: concordance of study hypothesis, objective, statistics and translation (Doctoral dissertation, Universität Ulm). https://oparu.uni-ulm.de/items/0b086662-3c9a-44f2-84e2-e150bf27b361.

20. ^ Porzsolt F, Wiedemann F, Becker SI, Rhoads CJ. Inclusion and exclusion criteria and the problem of describing homogeneity of study populations in clinical trials. BMJ Evidence-Based Medicine 2019; doi:10.1136/bmjebm-2018-111115

21. ^ Porzsolt F, Pfuhl G, Kaplan RM, Eisemann M. Covid-19 pandemic lessons: Uncritical communica-tion of test results can induce more harm than benefit and raises questions on standardized quali-ty criteria for communication and liability. Health Psychology and Behavioral Medicine 2021;9:818-829. DOI 10.1080/21642850.2021.1979407

22. ^ Krauss A. Why all randomised controlled trials produce biased results. Annals of Medicine 2018;50:312-322. https://doi.org/10.1080/07853890.2018.1453233

23. ^ Jureidini J, McHenry LB. The illusion of evidence based medicine. BMJ. 2022 Mar 16;376:o702. doi: 10.1136/bmj.o702. PMID: 35296456.

24. ^ Orlowski JP. Ethical principles in critical care medicine. Crit Care Clin. 1986;2:13-25. PMID: 3331304.

25. ^ Chen NL, Sng BL. Ethical Principles of Clinical and Translational Research. Anesthesiol Clin. 2024;42:581-592. doi: 10.1016/j.anclin.2024.01.003.

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