

Applying the Rule of Designers and Architects “Form Follows Function (FFF)” Can Reduce Misinterpretations and Methodical Shortcomings in Healthcare

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ABSTRACT

Sir Archibald Cochrane requested about 100 years ago answers to three questions before implementation of innovations in health care. These answers request the confirmation of efficacy, i.e. the “Proof of Principle (PoP)”, of the objective “Real-World Effectiveness (RWE)” and of the subjectively perceived value (VAL) of health care services. At the same time, Sir Ronald A. Fisher developed the concept of the Randomized Controlled Trial (RCT) for research in agriculture. This concept has become the accepted gold standard for demonstration of effects in health care research in the past 50 years.

RCTs are a useful study design to answer the first of the three Cochrane questions “Can it work?”. A wide range of different tools is available to answer the third (subjective) Cochrane question “Is it worth it?”, but none of these tools can answer the second question “Does it work?” in an unselected sample of patients of day-to-day care who present a variety of different comorbidities. We need to consider that the patient individual baseline risk profile may have a stronger effect on the assessed outcomes than our interventions. Without knowledge of the individual patient risk profile, we may probably disregard the strongest effect on the assessed outcomes.

Our comment substantiates and justifies the need of a new method than the RCT for demonstration of RWE. For that, we propose the Pragmatic Controlled Trial (PCT) and describe 1) the methods we used for analysis of data and the emerging strategy recommended for the three-dimensional assessment of outcomes, 2) the identification of the terminology conflict, 3) example to illustrate the evaluation using a PCT, 4) limitations of a PCT, 5) potential impact of the PCT, 6) literature on similar studies.

In summary, The PCT enables the answer to the second Cochrane question. This answer is based on the important effects of the “Endpoint-Specific Risk Profiles (ESRPs) of individual patients on the explored endpoints. In addition, the PCT facilitates the standardized analysis of revenue and expenses. The time and costs of documentation for approval of drugs and medical devices can be effectively reduced due to considerable reduction of necessary experimental RCTs for demonstration of PoP. The results of PCTs also enable new justifications of ethical, medical, economic, and political decisions.

"To explain the complexity of the concept some of the important remarks were repeated or expressed in simple language"

Keywords

Healthcare, Randomized controlled trial, Pragmatic controlled trial.

Introduction

Two historic events in Ulm supported the reduction of misinterpretations and methodical shortcomings in healthcare: the preservation of Albert Einstein’s legacy (born in 1879 in Ulm) and that of the Academy of Design in Ulm (Hochschule für Gestaltung,

1953-1968). Albert Einstein left us his Theories of Relativity and helpful advice that, “A problem cannot be solved by the way of thinking that caused the problem.” The Academy’s legacy entails tenets for design and architecture, such as “Form Follows Function” (the FFF rule) and the requirement to develop not only individual but generally valid solutions with social relevance.

Applying these Ulm legacies to healthcare services has succeeded in identifying two scientific conflicts to reduce their undesired results. The first conflict concerns the misinterpretation of the results of randomized controlled trials (RCTs). The second conflict describes the methodical shortcomings in evaluating the need for healthcare provision and the efficiency of all provided healthcare services.

The results of RCTs are internationally accepted to justify ethical, epidemiologic, medical, judicial, and political decisions without taking into consideration that the conditions under which an RCT is performed and evaluated differ in formal and functional criteria from the ‘natural chaos’ prevailing in everyday medical practice. Examples of these differences are the selection of subjects, the required focus on a primary endpoint, the analysis of risk profiles, and the assessment of dropouts. Accordingly, the results of an experimental RCT can verify the “efficacy”, i.e. the proof of a principle (PoP) under ideal study conditions, but not the ‘real-world’ effectiveness (RWE) of interventions performed under the non-structured conditions prevailing in the provision of everyday healthcare. Evidence of the suitability of measures provided under everyday conditions is required to optimize healthcare provision. The proof of this evidence lies in the analysis of factors that cause the natural chaos of everyday healthcare provision. For that, we suggest a design of a non-experimental but structured pragmatic controlled trial (PCT) that meets this challenge. In a PCT all subjects are evaluated according to stratified endpoint-specific risk profiles (ESRPs).

The aim of our comment is to investigate the appropriateness of the FFF-rule for confirmation of the concordance of formal and functional criteria of epidemiological rules in health services research. This comment is structured according to the helpful recommendations of expert reviewers.

Results

The principle of the FFF-rule and its application to healthcare evaluation

The FFF-rule was published by the American architect and designer Louis H. Sullivan in the end of the 19th century [1]. Sullivan concluded in his publication a “natural law”, the general concordance of form and function of all natural phenomena. He transmitted the validity of this conclusion to architecture. According to his understanding, the form of a building should be congruent with its function i.e., the building should support the users of this building in the performance of their duties. This demand defines the necessary sequence. The form of a building should be geared to the expected function of the building but not the function to the form. This rule may apply as well to products and rules developed for daily life including those in science. If this assumption is correct, lacking concordance of form and function may indicate a limitation of the expected function. Consequently, the application of the FFF-rule may also be useful to check the functionality of products and concepts in health services research.

The cooperation with a designer group of the “Hochschule der Künste (academy of arts) Berlin” and the former “hochschule für gestaltung (hfg) ulm” acquainted us with the concepts of designers that are not part of the medical education. The application of the FFF-rule enabled the detection and correction of the terminology conflict between “efficacy” and “effectiveness” in health services research. This conflict emerged by using the same method (form of study), i.e. the Randomized Controlled Trial (RCT), for description of two different functions, i.e. the PoP and the RWE. The details of the terminology conflict and its solution have been described [2]. Table 1 shows the details of the strategy we propose for implementation of the three-dimensional outcomes as suggested by Sir Archibald Cochrane [3].

Two facts may explain the reason of the terminology conflict. First, there was a lack of an established method for description of effects that are generated in the unstructured conditions of everyday care. Second, almost all representatives of scientific research decided in the first two decades of this century to use the same form of study (the experimental RCT) for conformation of two rather different outcomes i.e. efficacy and effectiveness

Table 1: Three-dimensional strategy for description of Proof of Principle, Real-World Effectiveness, and Value. A possible answer to the three questions of Sir Archibald Cochrane. Non-exp. RWC: Non-experimental Real-World Condition. Preliminary versions of this table have been published [4-6].

Cochrane questions	Can it work?	Does it work?	Is it worth it?
Outcome dimensions	Efficacy or Proof of Principle (objective PoP)	Real-World Effective-ness (objective RWE)	Value individual or societal (subjective)
Study conditions	Experimental study condition (ESC)	Non-exp., RWC with systematic evaluation of data	Non-exp., RWC without systematic but individual evaluation of data
Perspectives	Clinical research	Health services research	Economic research
Forms (structures)	Explanatory or interventional study	Pragmatic or observational study	Complete economic analysis
Functions	Demonstration of Proof of Principle	Confirmation of Real-Word Effectiveness	Comparison of costs and consequences
Tool	Randomized Controlled Trial (RCT)	Pragmatic Con-trolled Trial (PCT)	Cost Effectiveness Analysis

[2]. This decision contradicted Cochrane's requests as well as the statements of Schwartz & Lellouch [7] and Grimes & Schulz [8]. About 20 years later, we worked up the courage to denote the Real-World condition a "natural chaos" because the risk profile of almost any patient is unique and the doctors realign their treatment strategy on the implicit perception of the patient individual risk profile and on their individual convictions and ideals in case of patients consent [9]. The gold standard of the comparative methods in medicine, the RCT is an appropriate method for confirmation of the experimental efficacy but not of the pragmatic effectiveness. The potential of the FFF-rule becomes evident by confirmation of the differences of efficacy and effectiveness [2-11].

The Identification of the Terminology Conflict. Differences of Experimental & Pragmatic Studies and Validity of Pragmatic Controlled Trials for Analysis of Real-world Data

The detection of a terminology conflict requires the knowledge of the expected function of the investigated product or concept and the capability of the investigator to differentiate proper from improper forms (structures) for completion of the expected functions. This capability includes detailed knowledge on all components and factors that influence the assessed endpoints. Most users of clinical trials benefit from a cooperation with experts of other fields such as statistics and computer science.

The confirmation of efficacy (PoP) can be expected as function of a correctly performed Randomized Controlled Trial (RCT). A precisely defined study design can confirm the dimension of either efficacy (PoP) or effectiveness (RWE). The confirmation of RWE in the unstructured conditions of daily care is limited by two components. The risk profiles of individual patients are different, and the attending physicians will select the appropriate strategy according to his perception of the patient individual risk profile and his convictions on available tools and methods.

Examples for Illustration of the Structured, Pragmatic Healthcare Evaluation

The subjective assumption, medical decisions are arbitrary unless based on scientific evidence, was induced in the end of the 90th when Evidence-based Medicine (EbM) was reactivated by David L Sackett and his team. This indentation should be avoided as doctors make decisions only to some degree "arbitrarily". They are very likely using a consistent concept. The suspicion of arbitrary decisions may be induced by the observation that almost all complex decisions are influenced by subjective values of the decision maker. Hence, we consider it important to describe the sequence of physician's considerations that lead to their final decisions. Without concrete plan for decision making, it may be impossible to develop an unknown decision process further to a strategy that can be used in health services research. We hypothesize five necessary steps for future development of medical decision principles into a strategy, the PCT. This strategy is expected to compare without bias the effects of different interventions in cohorts of patients with similar ESRPs. The necessary steps for confirmation of a therapeutic success in a malignant disease may be used as example.

Definition of the Target Effect

A study in health services research usually expects answers to three outcome dimensions, the main outcome, the side effects, and the costs. In cases where the successful prevention of a relapse of the disease by a preventive treatment following the primary surgical intervention is expected, the standardized confirmation of a relapse (main outcome), side effects (such as thrombosis, bleeding complications), and costs may be defined as endpoints of a PCT. These definitions require the description of the point in time and of methods for gain of information. Standardized imaging methods, histopathological confirmation and/or results of bio-molecular analyses may be reliable indicators.

1. Identification of factors that form the ESRPs of individual patients for all assessed endpoints.

For description of the ESRP the existing comorbidity and co-treatments that may influence one of the assessed endpoints need to be listed. Violations of the protocol of a PCT, e.g. additional diagnostic information not mentioned in the protocol need also to be reported. Lacking or additional information to the protocol may influence the time of detection of a relapse and distort the correct interpretation of the study effects.

2. Development of an algorithm for allocation of patients to endpoint-specific risk groups.

The algorithm (different for each of the assessed endpoints) is based on all risk factors that influence the endpoint of interest. Each patient needs to be allocated to a high or intermediate or low risk group related to each of the endpoints assessed in a PCT. The necessary algorithm provides the standardized method of allocation in a particular PCT. There are two reasons to ask professional societies to define these algorithms and the characteristics of different risk groups. The necessary information may initially be missing in some situations.

Assumptions need to be used initially for construction of the study design but need to be replaced by information gained in successfully conducted PCTs. Second, the professional societies may contribute to guaranty the high quality of data reporting as the completeness and quality of the reported data will be limiting the progress in improving health care.

Different PCTs that investigate the same study question may develop different algorithms for risk classification and may observe different results. The congruence of the results of these potentially different algorithms with RWE can be compared and will identify the best fit.

3. Defining comparable cohorts of patients.

Cohorts of patients are comparable when their ESRPs are identical. This means, the classification of a patient as low risk related to one endpoint does not necessarily mean the same patients will also be classified "low risk" to another endpoint (Figure 1). This conclusion may be extrapolated to the challenging statement:

"Cohorts that include patients of different risk groups generate only "average" results that may or may not apply to patients with a specific risk profile."

The results of RCTs apply to a cohort of patients who represent the identical distribution of risk groups like the patients included in the RCT and were randomized to either the experimental or control group. RCTs generate “average results” related to the “average risk profile” that will be identical in the total group and in the randomized subgroups of an RCT. However, these “average results” generated in experimental conditions of the RCT may not be applicable to individual patients who expect the optimal care adapted to their individual risk profile.

The significance of these differences in the individual risk profiles of patients is formally considered only rarely. However published data confirm that the stage of disease, i.e. one of the important components of the individual risk profile, has a considerably stronger impact on many outcomes than any intervention. This observation underlines the importance to consider the risk profiles of individual patients. The number of different forms (structures) of risk profiles will be immense especially in multimorbid patients.

When comparing the single risk factors of individual patients, we may identify patients with predominantly low risk factors related to a particular endpoint and other patients who present with several high-risk factors. Using this information, we will be able to construct an algorithm that describes the criteria that classify a patient as high-risk patient for a particular endpoint. A group of other criteria characterize low risk patients for this particular endpoint. Patients who belong neither to the high risk nor to the low-risk group may be classified as intermediate risk patients for this endpoint.

The function of the ESRPs is to predict the outcomes that may be expected in one specified endpoint. For that an “endpoint-specific algorithm” needs to be defined that describes the rule, which

classifies an individual patient as high- or intermediate- or low-risk patient related to that specific endpoint. The form (structure) of the ESRP—that is expected to match its function—is expressed by the risk factors of an individual patient that are related to at least one of the assessed endpoints. This explanation confirms the usefulness of the FFF-designer rule. The function predicts the outcome while the form, which follows the function according to the designer’s rule, needs to fit the expected function of a perfect product or concept.

4. Effects of different interventions in cohorts of patients of the same risk class.

The description of RWE presumes a realistic image of the patient risk profiles and of the interventions used by individual physicians in individual patients. The spectrum of different interventions used in Real-World Conditions (RWC) will be too big as to report any details of all possible forms of care. In other words, an algorithm needs to be developed to categorize the applied interventions in analogy to the algorithm that was developed for categorization of risk groups based on the individual risk profiles.

A possible starting point in the categorization of interventions is a distinction according to different strategies, which is used in many experimental studies, e.g. surgery + adjuvant hormonal treatment. Large variations of outcomes within the same risk group and the same intervention group suggest strong effects of not specifically considered factors. This example demonstrates the additional information that may be derived from outcomes that consider interventions and risk profiles. A graphic that describes the forms and functions of RCTs and PCTs may help to clarify the differences of the two concepts for assessment of PoP and RWE (Figure 1).

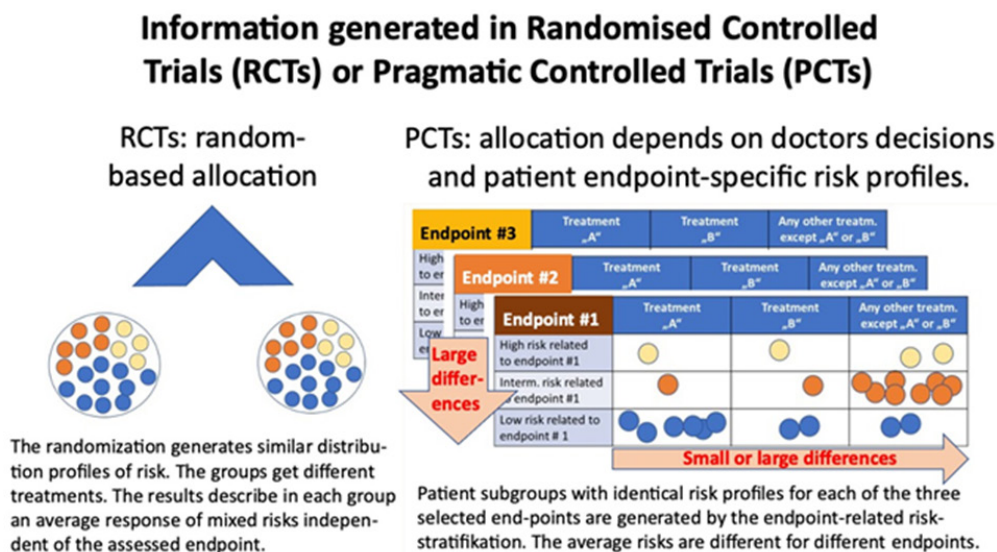


Figure 1: Forms and functions of experimental RCTs and pragmatic PCTs. The PCT identifies the individual patients that received a defined treatment “A” or “B” or are listed in the group “any other treatment” when the differences in outcomes of type “A” or type “B” treatment should be compared to the range of outcomes observed in patients of the same risk group who received any other treatment. “A” and “B” may include a single type of treatment or a group of similar treatments. In addition to the treatment the ESRP were used in all patients for stratification in a high-risk (yellow) or intermediate-risk (red) or a low-risk group (blue) patient separately for each of the endpoints. The same patient may be classified to different risk groups depending on the assessed endpoint. Modified from [5].

Figure 1 visualizes the main difference of patient allocation in RCTs and PCTs. In RCTs the patients are allocated by randomization. In PCTs the patients are allocated according to three criteria, the selected endpoint, the ESRPs, and to the type of intervention. The investigator defines the groups of patients e.g. “A” or “B” in each “risk level” that are compared with either any patients who received neither treatment “A” nor “B” or a specific treatment “C” (not shown in Figure 1). All comparisons need to be limited to patients from the same endpoint specific risk level. The functions of RCTs and PCTs are not shown in Figure 1.

The function of RCTs is to compare the result of the experimental group with the result of the control group. The difference of these two results may confirm the superiority “on average” of the experimental group to the control group related to the investigated endpoint. No information can be derived on the effects on the different risk subgroups of an RCT.

The function of PCTs is to compare the outcomes in patients of the same risk group that received different treatments. For interpretation of the results the observed differences it is important to note that large differences are expected between different risk groups. The differences between different treatments in patients with the same risk group are usually smaller than the differences between the risk groups. Clinically important treatment effects will be seen if large difference are observed between different treatment groups within the same risk group.

Limitations of the PCT related to methodology, data sources, or generalizability of the findings

The core message of our comment is the assessment of the “Endpoint-Specific Risk Profile (ESRP)”. The difficult assessment of the ESRP may be limiting the acceptance of the entire concept due to the required new way of thinking and the required initial assumptions due to potentially lacking information on risks. The knowledge in health services research can be increased by the formal integration of the already existing but so far not yet standardized documentation of information. If the professional medical associations can elaborate a consensus on the needed risk profiles, the data management can be provided by experts in information technology. A considerable part of the administrative work of the physicians and their teams that consumes up to 30% of working time can be reduced.

The PCT method should be applicable to any form of health care. The precise definition of the goals of health care is one of the essential requirements. For that, four steps from an informal question to the statistical confirmation of a mathematical hypothesis may be considered (the description of the aim of study in plain language, the translation into an exact hypothesis, the selection of the corresponding statistical test, and finally, the confirmation or rejection of the hypothesis). An initial resistance against these necessary modifications may be expected like the reservation we observed 30 years ago when the new strategy of EbM was discussed.

Potential Impact and Significance of the Principle of PCT on Patient Outcomes, Resource Allocation, and Decision-Making Processes

- a. The RCT is an experimental study design based on the hypothesis to generate subgroups with comparable risk profiles by random allocation.
- b. This hypothesis can be confirmed in large but not in small samples when a similar distribution of all important confounding factors cannot be achieved (internal validity of RCTs).
- c. This hypothesis of random allocation concerns the internal but not the external validity of RCTs. The internal validity of an RCT depends on the perfect function of the randomization while the external validity depends on the characteristics of the study population recruited in a RCT.
- d. The function of the randomization can be confirmed by various tools e.g. the propensity score matching. In RCTs the exact function of the recruitment of study patients is defined only by the definition of inclusion and exclusion criteria but not by risk profiles.
- e. In PCTs, the standardized description of ESRPs of all recruited patients is essential, otherwise it will be impossible to consider the effects of existing risks on the assessed endpoints.
- f. This statement on the significance of existing risks to the interpretation of assessed results applies to all types of studies, not only to PCT.
- g. RCTs need to record and use risk profiles when the effects of interventions are compared in subpopulations with different risk profiles. It is important to identify the subpopulations before randomization and to randomize each subpopulation separately. As most RCTs are not considering the risk profiles of the included patients, the results of different RCTs may be only comparable when the quantity and quality of risk profiles of the compared studies are similar (limited external validity).
- h. The different results of RCTs with similar endpoints and similar interventions is a known but unsolved challenge in the interpretation of the results of reviews, Health Technology Assessments, and Metanalyses [12].

The PCT is a non-experimental observational trial that relies on the Bayes’ principle. This principle considers the probability of an expected or apprehended event to depend not only on an intervention but also on the preexisting risk related to the assessed endpoint. The key message of our comment addresses two types of information that are needed for precise interpretation of assessed endpoints: the effects of the ESRPs and of the interventions.

Our group has access to clinical data to confirm that the same intervention may show the expected result in the group with high ESRPs, while other interventions are more useful in groups with low ESRPs.

The only limitation of PCTs is the small sample size. The validity of PCTs and the reliability of decisions will rise the more exactly the ESRPs of individual patients can be described. The implementation of PCTs will consume resources but will also increase the value of health care in general.

Literature Review Section on Similar Studies

A search in PubMed using the term „Pragmatic Controlled Trial“ was found in 8660 documents, in 787 reviews, but not in systematic reviews. The term was included in the title of 32 documents [13]. The analysis of these 32 documents confirmed that the term “Pragmatic Controlled Trials” is used for the analysis of data that were collected either in unstructured conditions of usual daily care or in structured conditions of an RCT or in mixed, structured, and unstructured conditions. We refrained from reporting details in the absence of solid evidence.

The lack of a systematic review on “Pragmatic Controlled Trials” seems to confirm our observations. A consensus is missing for definition of the form (structure) of conditions that need to be provided for unbiased description of the RWE. A reliable analysis will hardly be possible without consensus.

Conclusion

The second question of Sir Archibald Cochrane confirms the justified need of a method for demonstration of the RWE. The FFF-rule of the American designers was used to analyze the congruence of the forms and the expected functions in health services research. For that, we translated the sequence of considerations that doctors use for medical decision making into the protocol of a PCT.

The PCT protocol is different from the protocol of an experimental RCT. RCTs are providing a *monocausal* explanation of the observed result. This monocausal approach in RCTs is possible due to the (experimental) random distribution of any other effects that may influence the assessed outcome. In contrast, the PCT cannot use experimental tools for assessment of RWE. Therefore, it was necessary to develop a *multicausal* concept that considers not only the intervention but also the ESRPs of individual patients that will influence the observed outcomes.

The implementation of PCTs will increase the perception and the experience of the important difference of risk profiles and risk groups. Risk profiles are individual patient characteristics. Risk groups combine patients with different risk profiles that could be classified as either high risk or intermediate risk or low risk related to one specific endpoint. In a more detailed discussion, the ways can be discussed that allow the recognition of potentially wrong risk classifications and their corrections.

When initially only few reliable criteria are available for risk classification, e.g. for classification of the risk of costs, additional criteria that reduce the variance of assessed results may be tested for an expanded risk classification. Robust evaluations are impossible without additional information to side effects and costs of care strategies.

The workload for designing a PCT protocol is certainly higher than for designing a RCT protocol due to the necessary consensus on the risk classification. The additional societal value that can be achieved by the description of the RWE will justify the necessary expenditures and reform. As a next step, the robustness of the

scientific concept needs to be challenged. If confirmed, the support of experts in communication will be needed to also include the users of health services in the discussion on future care.

Contributions

FP detected about 40 year ago junior doctor in hematology / oncology the difference of results published in journals and textbooks and the results observed in the own university hospital. A reasonable hypothesis on different risk profiles of the investigated patients could be developed only several decades later. However, the initial impression was strong enough to keep the motivation until a possible solution could be offered.

Without support of a huge number of doctoral fellows and colleagues from different countries, it was not possible to arrive at the described conclusions.

MW (MD and PhD of anesthesiology and intensive care medicine) and CW (PhD, mathematics, biostatistics, and data management) are cooperating colleagues since 20 years and contributed essential parts through the perspectives from their professional fields.

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