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Research-on-research studies or methodological studies are primary research

Journal of Clinical Epidemiology has recently published a study of Faggion and Diaz Cavero [1], in which the authors presented types of primary and secondary research. According to the article, secondary research includes two categories—overviews and systematic reviews, whereas primary research includes three categories: human research (e.g., clinical trials, cohort, case series, and so on), animal research, and in vitro research [1]. Although the aim of the study was obviously not to classify all types of research conducted nowadays, this figure glaringly omits classifying the exact type of study that the Faggion and Diaz Cavero [1] have reported in their article. These kinds of studies have been called ''research-on-research'' studies or methodological studies [2], and their purpose is not to collate and summarize existing evidence that is presented in primary study reports; that is, these types of studies are not systematic reviews [2]. Instead, research-on-research or methodological studies use existing evidence, including (but not limited) to published articles or protocol registries, to analyze and create new data that are not related to the original aim of reports that are subject to analysis.

As Gene V. Glass put it in 1976: ''*Primary analysis is the original analysis of data in a research study. Secondary analysis is the re-analysis of data for the purpose of answering the original research question with better statistical techniques, or answering new questions with old data*.'' The data analyzed in methodological studies would not exist without researchers creating them *de novo* from reports that are units of analysis. Therefore, methodological studies about evidence (i.e., research on research) should also be considered primary research and included in classifications of primary research types.

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How can metaresearch be classified?

We would like to thank Dr Puljak for her interest in our article and for providing an interesting point for discussion regarding the classification of the types of primary and secondary research reported in our study.

Dr Puljak suggests that metaresearch (or research on research) should be considered primary research, instead of secondary research [1]. However, the interpretation of the definitions of primary and secondary research may be challenging. For example, some authors suggest that secondary research uses existing data for analysis and/or synthesis, and primary research is an ''activity that generates new, primary data.'' [2]. However, metaresearch generates new data using existing data in the form of published materials (in most cases), resulting in a gray area. For example, a hypothetical metaresearch question on the evaluation of the association between risk of bias and the size of the treatment effect estimates in studies published in systematic reviews might be viewed as a source of new data (primary research), but it uses existing data (secondary research). Cochrane [3] defines ''secondary study'' as ''a study of studies: a review of individual studies (each of which is called a primary study).'' Again, a meta-research study may be considered a ''study of studies'' because it also extracts and evaluates information from primary studies. Thus, metaresearch may be seen as secondary analysis, as the definition ''answering new questions with old data'' [4] suggests.

A figure on primary and secondary research was presented in our article [5] to provide the reader with a chronological scenario about how the data are published (without any hierarchical differences regarding the importance of this research). Primary research is the first published, and secondary research is published posteriorly.

Although the issue on the classification of metaresearch is outside the main scope of our published article, it provides an interesting topic for further discussion within the research methodology community. One could argue that an easier classification for secondary research based on the assessment of what already exists is a more pragmatic approach. We also agree that a metaresearch study is not a classic systematic review on effectiveness or harm of interventions. However, metaresearch is also sensitive to biases; therefore, this type of research should provide a systematic approach to addressing the existing data used to generate new data.

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In the end, what matters most is not the metaresearch classification as primary or secondary research but the characteristics of this research that should be reliable, reproducible, and trustworthy.

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Measuring clinical uncertainty as a preliminary step to randomized controlled trials

Reproducibility is a fundamental scientific property required of any instrument, diagnostic test, or prognostic score [1]. Treatment decisions or management recommendations made by clinicians are authoritative judgments with real-life impact on patients. Shouldn't we verify that they are reliable? How can this be done? Here we propose to study the reliability of clinical management decisions to measure uncertainty before the conduct of a randomized trial.

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It seems natural to think that recommendations made by doctors are inevitably variable and ungeneralizable, for working on a case-by-case basis and with a complex and ineffable reasoning process, they must take into account the unique histories, characteristics, and circumstances of the particular patient [2]. However, this in itself does not make clinicians' recommendations fundamentally different from other clinical judgments such as diagnosis which equally concerns unique individuals: the clinician's verdict (the output of the process) often comes down to allocating the patient to one of a few categories, whether the judgment concerns diagnosis (disease present/absent) or management options (i.e., do not treat/treat medically/treat surgically). No matter the process behind the clinical decision, if it results in contradictory judgments or courses of action when the same patient is presented to different or to the same clinicians more than once, then the process is unreliable and the verdict uncertain.

The similarities in allocating a particular patient a diagnostic or management category are such that we naturally saw that the methodology typically used to study the reliability of imaging diagnoses could be concretely applied to clinical decision-making (Table 1).

In practice, a portfolio of diverse individual patients, all who share a similar clinical problem, and which cover a wide spectrum of clinical presentations, are independently submitted to a variety of clinicians who manage that problem. Clinicians are asked to choose one of the predefined management options to generate interobserver kappa statistics, whereas intrarater agreement can be assessed by a second independent evaluation at a later time. Variability and inconsistency in clinical decision-making need not be resolved through consensus sessions. The studies we propose are designed to transparently identify and measure the clinical uncertainty involved in the management of specific clinical problems, not to provide the a ''truth'' based on expert opinion. Such studies can be informative: the uncertainty can reveal gaps in medical knowledge or identify suboptimal practices that could be improved. The identification and estimation of such uncertainties can serve many purposes: i) clinicians and patients should be made aware that diverse options are actually proposed for the management of similar patients, if only to make alternative options available; ii) clinicians may be reassured when they realize they are not alone in being uncertain. This step may encourage members of the community to proceed with the clinical research that will addresses that uncertainty; iii) when a reliability study is designed with a randomized trial in view [7−10], it can provide empirical evidence of Freidman's notion of ''clinical equipoise'', that ''an honest professional disagreement among expert clinicians about the preferred treatment'' exists [11].

The methodology we propose here is inspired from diagnostic agreement studies, and its application to management decisions permits the demonstration of