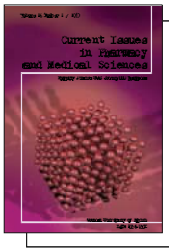

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Tools for a correct design and quality assessment of pragmatic randomized controlled trials: PRECIS, PR-tool and Pragmascope tool

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ABSTRACT

Identification of scientific data in the systematic reviews required for the rational decisions on health policy is an important tool in determining the validity of the financing of treatment from public funds based on the health technology assessment (HTA). The primary source of scientific medical evidence are randomized controlled trials (RCTs), but their features markedly reduce the possibility of the transfer of the results to the routine practice. In this situation an important role begin to play pragmatic randomized controlled trials (pRCTs), providing highly reliable information about drug effectiveness in contrast to observational studies or registries. Here, we described three suitable universal tools, which can be used during the designing or evaluation of reliability of pRCTs: PRECIS, PR-tool and Pragmascope tool.

Keywords: health technology assessment (HTA), PRECIS, PR-tool, Pragmascope tool, quality assessment

INTRODUCTION

Collecting of scientific data in the systematic reviews is required for the rational decisions on financing of treatment from public funds based on the health technology assessment (HTA). The primary source of scientific evidence for health technology assessment are randomized controlled trials (RCTs, explanatory trials), but their standard features, which ensure that their results are more likely to be reliable (e.g. randomization or blindness), markedly reduce the possibility of the transfer of these results to the routine practice [2, 11]. Hence RCTs are better for understanding the mechanisms of treatment effect found and answer the question: "Can this intervention work under ideal conditions?" [7, 8,11].

In fact, an important issue is to answer to the question of the actual comparative effectiveness and costs of interventions in daily medical practice [2]. Even novel/expensive drugs have limitations, which sometimes can be observed only in conditions of routine practice in refractory patients with chronic disease or comorbidities. This maybe contrary to the hypothesis of superiority proven in explanatory trials with the use of placebo-comparator [6]. Frequently data about this unexpected difference between efficacy in clinical and real-world conditions are provided by multicenter observational studies or patients registries – large-scale trials demonstrating the results of the most representative groups of patients for routine medical care. However, these trials, in which exposure to the factor or analyzed intervention is not evaluated using the strict protocol, as in randomized controlled trials, are less credible source of information [2].

An attempt to reach a compromise between obtaining high performance of trials and the possibility of reference their results to the real conditions of the health care are pragmatic randomized controlled trials (pRCTs). Differences between explanatory and pragmatic randomized controlled trials are mostly due to different methodological assumptions. The most important characteristics of randomized controlled trials designed to reflect the standard conditions of medical practice are: the development of broader inclusion criteria, minimizing the exclusion criteria or broadening the scope of patients' evaluation [2].

It should be noted that cases of purely pragmatic or explanatory trials are very rare [8]. The key methodological features distinguishing pRCTs and RCTs are summarized in Table 1. The majority of features of both types of trials seem to be opposing and should be clearly defined for

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each kind of randomized controlled trial [1, 2, 5]. However, in most cases these differences are blurred. For example, in certain explanatory trials some aspect of intervention may be beyond the investigator's control. Similarly, the away of conducting an pragmatic trial may lead to the setting not quite usual [8, 9]. Thus a trial may demonstrate varying levels of pragmatism across different dimensions of methodology, which implicates that in quality assessment of randomized controlled trials much better is multidimensional continuous way instead of dichotomy [8].

Table 1. Summary of the methodological features of explanatory and pragmatic randomized controlled trials (modified for [1, 5])

RCTs	pRCTs
Experimental setting	Routine clinical environment
Evaluation of efficacy	Evaluation of effectiveness
Placebo controlled	Without placebo
Evaluation of acute conditions	Assessment of chronic conditions
Usually blinded	Not blinded
Smaller sample-sizes	Larger sample-sizes
Homogeneous group of patients	Heterogeneous group of patients
High internal consistency	High external consistency
Shorter follow-up	Longer follow-up
Analysis of patients who received at least one dost of study drug	Intention-to-treat analysis
Treatment according to the study protocol	Routine treatment approach
One specific outcome measure	Multiple outcomes reflecting daily concerns of patients

In response to this issue several questionnaires have been developed to help researchers and pharmacoeconomical analysts to locate the position of prepared or analyzed trial on the pragmatic and explanatory continnum [3]. In this paper we present the most common ways to well design and assess the effectiveness of trials.

METHODS

A systematic review in Medline through Pubmed using the following queries: "(pragmatic OR practical OR naturalistic OR real world) AND (quality OR validity)", was performed till June 2013 to gather current information about quality assessment of pragmatic randomized trials.

RESULTS

Using above search strategy nearly 18 000 hits were obtained, which were analyzed and verified to find the most common questionnaires. We found threesuitable universal tools, which can be usedduring the designing or evaluation of reliability of pRCTs: PRECIS, PR-tool and Pragmascope tool.

PRECIS. PRECIS (Pragmatic-Explanatory Continnum Indicator Summary) was developed by international group of interested trialists. PRECIS originally supposed to be used by researchers to determine how the study design corresponds to establish clinical research targets. This tool summarize the methodological characteristics, which defines the nature of a randomized controlled trial. Ten domains have been identified to distinguish pragmatic from explanatory trials – we present them below and describe characteristics of the most ideal pragmatic study:

- The eligibility criteria for trial participants – the extremely pragmatic approach would assume only the identification of study participants with the conditions of interest from as many sources as possible.
- The flexibility with which the experimental intervention is applied – in pragmatic trial we should leave the details of how to implement the experimental intervention to practitioners.
- The degree of practitioner expertise in applying and monitoring the experimental intervention – experimental interventions should be put into the hands of all practitioners treating (educating and others) the study participants.
- The flexibility with which the comparative intervention is applied – see above.
- The degree of practitioner expertise in applying and monitoring the comparative intervention – see above.
- The intensity of follow-up of trial participants – follow-up contact with the study participants should be not more often than in the usual practice; for example a practitioner has no contact with patients and instead obtains outcome data by other means (e.g. administrative databases to determine mortality).
- The nature of the trial's primary outcome – patient-important outcome similar to these from phase 3 or 4 trials.
- The intensity of measuring participants' compliance with the prescribed intervention, and whether compliance-improving strategies are used – pragmatic approach recognizes that noncompliance with intervention is a reality in routine medical practice.
- The intensity of measuring practitioners' adherence to the study protocol, and whether adherence-improving strategies are used – it would not be concerned how practitioners vary and customize a trial protocol to suit their setting.
- The specification and scope of the analysis of the primary outcome – pragmatic approach to the primary analysis would typically be an intention-to-treat analysis of an outcome of direct relevance to the study participants and the population they reflect.

The results of this analysis are presented on the "wheel", which consists of straights corresponding to the above mentioned domains (Figure 1A). In the analysis one selects a point on straight line for a particular domain, whose distance from the center of wheel reflects the fullfillment of the criteria – for RCTs closer to the center, for pRCTs further from the center. Finally one creates a pie chart [7, 8, 9]. Examples of such evaluations reflecting explanatory and pragmatic trials present Figure 1B and 1C.

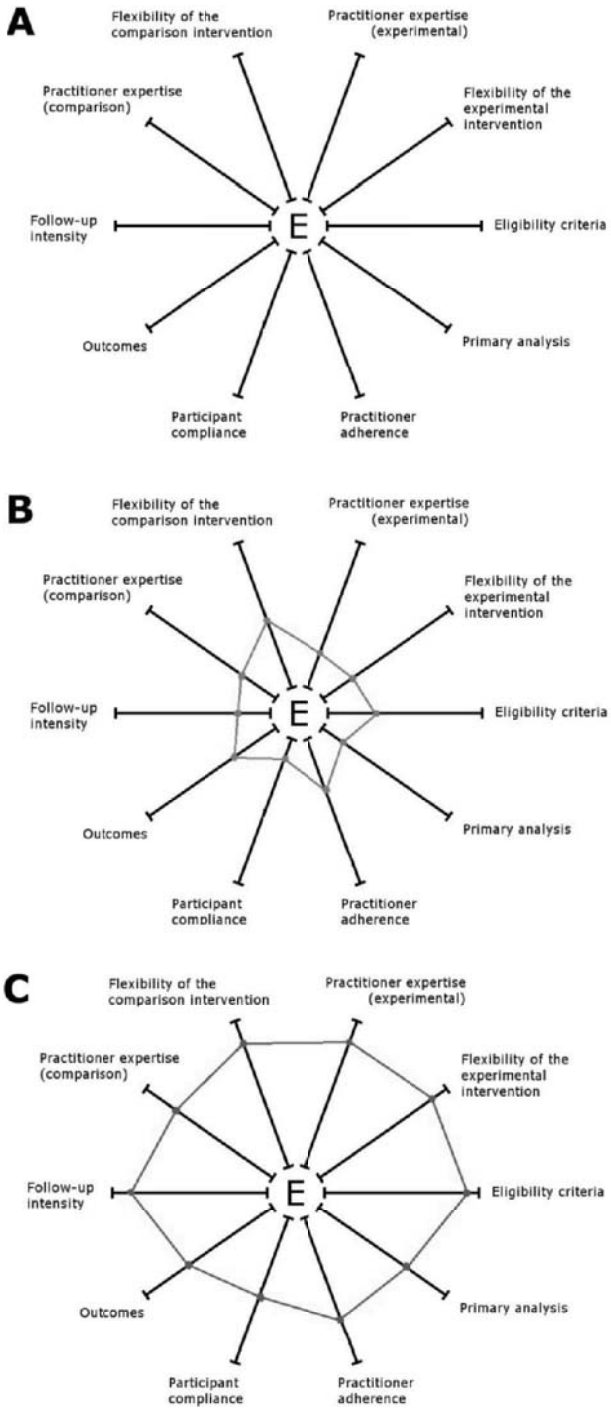

Fig. 1. "Wheel" of the pragmatic–explanatory continuum indicator summary (PRECIS) tool. "E" represents the "explanatory" end of the pragmatic–explanatory continuum: (A) blank; (B) represents explanatory trial; (C) represents pragmatic trial (modified for [9])

PRECIS questionnaire can also be used to assess the pragmatical degree in studies already published, especially in health technology assessment. Such a use of this tool is indicated both for the assessment of systematic reviews [3], as well as single study [2, 10].

It should be noted that currently the work to improve original PRECIS scale is ongoing and it should be completed next year by creating a modified scale called PRECIS-2 [4].

PR-TOOL. There is also a modification of PRECIS tool used to analyze the nature of systematic reviews: PR-tool (PRECIS-Review tool). It involves the use of numerical values – data from randomized clinical trials included in the review are assessed at the 5-point scale, where 1 is the ideal explanatory trial, and 5 great pragmatic study (the results can also be expressed as a percentage). Sometimes the publication describing a clinical trial does not allow for proper assessment of all domains – where there are more than 3, the sample should not be taken into account in calculating the average score for the entire systematic review [3].

PRAGMASCOPE TOOL. A similar type of assessment offers another tool called Pragmascope tool, but in contrast to the PR-tool, is dedicated rather to assess individual RCT than to a comprehensive analysis of the nature of the systematic reviews. Total score for 0-15 mean that intervention will work in ideal circumstances, while 36-50 that intervention has a meaningful effect in routine practice. A total score 16-35 suggest a interim result, where trial design balances pragmatic and eplanatory domains. Figure 2 presents Pragmascope tool "wheel" [10].

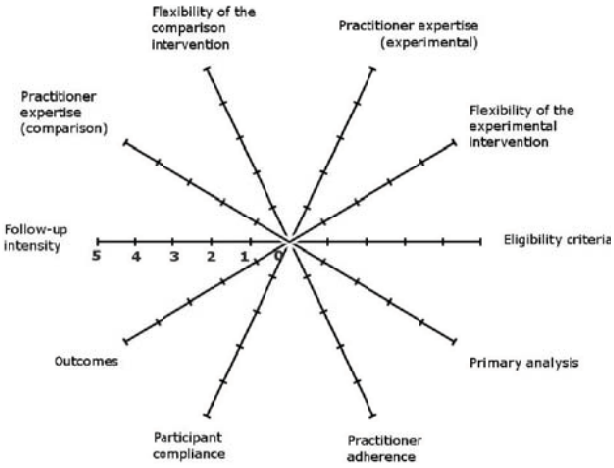

Fig. 2. Blank "wheel" of the Pragmascope tool (modified for [10])

CONCLUSIONS

We found and shortly described three useful tools, which can be valuable for the recognition pragmatical character of randomised controlled trials. PR-tool and Pragmascope tool will be necessary to make a good health technology assessment report of new medical technologies, which will be showing the results and more importantly, the effectiveness of the technology under standard conditions of medical care of the patient. The PRECIS is applicable both in the evaluation of study protocol and the results of the analysis of the effectiveness degree of results from single publication related to the

randomized controlled trials. It should be noted that the presented tools are constantly improving and validating – especially very important is detail the basic version of diagrammatic evaluation of PRECIS. But mentioned ongoing works [4] probably will result in increased reliability of questionnaires included in this publication.

In summary, data from properly designed and assessed pRCTs in conjunction with information about the efficacy from RCTs will serve as a whole to determine effectiveness of investigated drugs or methods in clinical trials. Consequently it will also facilitate business decisions in medical practice and health care organizations as well as rationalization of cost-reimbursement through financing from public founds the use of drugs demonstrating the efficacy both in controlled conditions and in the standard health care setting.

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