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A Comparison of National Guidelines for Network Meta-Analysis

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ABSTRACT

Objectives: Within technology appraisals, it is necessary to compare the complete set of treatments that may be used in the patient group under consideration. Randomized controlled trials are a key source of evidence for these comparisons. The techniques of network meta-analysis allow the networks of trial evidence to be evaluated to obtain estimates of comparative efficacy between sets of treatments. These techniques may be the only source of estimates of comparative effectiveness if trials directly comparing the treatments of interest have not been conducted, and may provide useful additional evidence if both direct and indirect comparisons exist. **Methods:** We examined both published and draft guidelines from reimbursement and health technology appraisal bodies, and considered their recommendations using appropriate methodology for the conduct of indirect comparisons and the assessments of their validity. **Results:** Guidelines from 33 countries were reviewed. Of these, guidelines from 9 countries—Australia, Belgium, Canada, France, Germany, Scotland, Spain, South Africa, and the United Kingdom (England and Wales)—included detailed recommendations on the conduct of network meta-analysis. The recommendations were summarized. **Conclusions:** No two recommendations from the multiple national guidelines are mutually exclusive. It is possible to perform one network meta-analysis for submission to multiple national jurisdictions.

Keywords: guidelines, meta-analysis, policy, reimbursement.

Introduction

The development of meaningful clinical treatment guidelines and reimbursement policies entails comparisons of all competing treatment interventions. Some commentators consider systematic reviews of randomized controlled trials (RCTs) to provide the highest level of evidence for evidence-based decision making [1]. RCTs that simultaneously compare all interventions, however, are rarely available in therapeutic areas with multiple treatment options [2].

Standard pairwise meta-analyses include studies that compare the same two treatments. A network meta-analysis (NMA) extends the analysis to include a network of pairwise comparisons across a range of different interventions and provides estimates of comparative effectiveness for multiple treatments. NMAs are often performed if direct comparisons are unavailable; however, they can also make valuable contributions to the overall body of evidence even when direct comparisons are available by providing estimates based on a combination of direct and indirect evidence [3–7]. National regulatory and reimbursement agencies around the world increasingly regard NMA as a key part of the health care decision-making process. Several countries have released guidelines describing their requirements for such an assessment, or developed review documents highlighting the current best practice to inform organizations preparing submissions.

There is currently a lack of literature comparing national submission requirements for NMA. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has devised an online tool for comparing submission guidelines [8]; however, at present it does not include information comparing the conduct of NMAs. Given the transnational nature of therapeutic interventions, and the need for pharmaceutical manufacturers to apply to multiple national jurisdictions to gain regulatory and market access for their products, there is a clear need for the development of a "super set" of requirements that would facilitate the conduct of NMAs acceptable in multiple jurisdictions. The ability to create a single analysis that is acceptable in multiple jurisdictions has the potential to reduce costs for manufacturers and time-to-market for new interventions.

Methods

Identification of Relevant Documents

The sampling frame for the search of national guidelines compared in this review was the countries listed in the Web-based repository of country-specific pharmacoeconomic guidelines maintained by ISPOR [8]. As of July 22, 2013, this comprised guidelines from 33 countries: Australia, Austria, Baltic states

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(Latvia, Lithuania, and Estonia), Belgium, Canada, China, Cuba, Denmark, England and Wales, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Mexico, New Zealand, The Netherlands, Norway, Poland, Portugal, the Russian Federation, Scotland, Slovak Republic, South Africa, South Korea, Sweden, Thailand, Taiwan, and the United States.

The ISPOR repository separates guidelines into three categories: Published Pharmacoeconomic Recommendations (economic evaluation guidelines or recommendations published by experts in the field but not officially recognized or required by health care decision-making bodies); Pharmacoeconomic Guidelines (official guidelines or policies concerning economic evaluation that are recognized or required by health care decision-making bodies); and Submission Guidelines (official guidelines or policies concerning drug submission requirements with an economic evaluation component). Documents from all three categories were considered in this review. In addition, working papers and other methodological reports (including the ISPOR task force report on the conduct of indirect comparisons because this was referenced by a number of guidelines) [9], Web sites, and other listed sources were checked to ensure that the most recent versions of documents were reviewed. To this end, documents in draft were also included in this review. For the purposes of this review, documents were classified as either guidelines or methods reviews.

Guidelines or methods reviews were screened for references to indirect comparisons or NMA, with documents from 14 of the 33 countries included in the review containing references to the use, conduct, or reporting of NMA. Of these, guidelines from five countries (Ireland, Norway, Poland, Sweden, and the United States) made reference to the potential use of indirect comparisons in technology appraisals but did not provide any further detailed guidance as to their conduct and reporting. For example, the Irish guidelines stated that "In the event of limited head-to-head RCT data, mixed treatment comparisons can be used" [10], the United States' Academy of Managed Care Pharmacy guidance mentions indirect comparisons under the heading of "Other Supporting Evidence" and noted that "Today, network meta-analyses are becoming more relied on and accepted as valid means to compare interventions" [11], and the Swedish guidelines issued by Tandvårds-och läkemedelsförmånsverkets föreskrifter contained very few requirements, and instead referenced the ISPOR task force report [12]. Documents from the remaining nine countries (Australia, Belgium, Canada, England and Wales, France, Germany, Scotland, Spain, and South Africa) provided more detailed guidance, which is summarized in this article. These documents are summarized in Table 1.

Comparison of National Guidelines

The national guidelines were initially reviewed, and checklists were developed to summarize their recommendations. These checklists were completed for each of the guidelines by two separate reviewers. A final review of the guidelines was conducted and any additional items required were added to the checklists. Finally, the checklists were compared across reviewers and any discrepancies were resolved.

Results

The recommendations made in the guidelines are described under the following headings: clinical trial search, selection of databases, study selection, bias assessment, and conduct of NMA. Each heading comprises a number of potential recommendations. For each recommendation, we have noted whether it is referred to in the corresponding national guideline; we make no distinction between a "recommendation" and a "requirement."

Clinical Trial Search

The first step in carrying out an NMA is to identify the clinical trials that may potentially form the network of comparisons. Table 2 details recommendations regarding the design, conduct, and reporting of the trial search. These recommendations can be divided into four categories: 1) Definition of search time frame; this allows regulators to assess whether the time frame is adequate; 2) Predefinition of search parameters; typically the population(s), intervention(s), comparator(s), outcome(s), study design approach to reporting studies [13]. This improves transparency and increases confidence in the study findings; 3) Clear description of search conduct; most of the national guidelines require that the search strategy be presented in full with all the terms and relationships documented, and many guidelines require a flow diagram with "n" returns at each step; and 4) Manually checking reference lists in identified articles to increase the sensitivity of the search.

There is an overall focus on the transparency and repeatability of the search. Canada and England and Wales require that the search complies with best-practice guidelines issued by the Centre for Reviews and Dissemination [14,15]. Germany requires that keywords, MeSH identifiers, and other terms used to search electronic databases be grouped into related blocks in the presentation of the search strategy [16].

Selection of Databases

Most of the national pharmacoeconomic guidelines specify which databases should be searched. Table 3 lists the various databases listed in the national guidelines. MEDLINE, EMBASE, and the Cochrane (CENTRAL) databases form a core specified by almost all the national guidelines. Outside of this core there is variation, with some jurisdictions requiring that the search be conducted in databases with a local focus and others requiring more emphasis on clinical trial databases. Four of the nine national guidelines require that the search be conducted in an international registry of clinical trials, either clinicaltrials.gov or the International Clinical Trials Registry Platform, but typically both [14–17]. The German guideline references the industry-maintained clinicalstudyresults.org database, which has been closed since the publication of the German guidelines [16]. The national guideline document issued by the Australian Pharmaceutical Benefits Advisory Committee requires that the Australia New Zealand Clinical Trials Registry form part of the search strategy [17]. The Australia New Zealand Clinical Trials Registry forms part of the International Clinical Trials Registry Platform search portal that is required by other national guidelines; however, the Pharmaceutical Benefits Advisory Committee specifically differentiates between the two. German and Australian guidelines require that company-specific databases be searched and results presented, although the national guidelines contain no indication how the transparency and repeatability of such a search would be enforced [16,17].

The French, Scottish, and Spanish guideline documents do not contain recommendations or requirements regarding the search strategy to be implemented or databases searched [18–20] (A. Ortega, M. Fraga, E. Alegre, et al., personal communication, 2013). The French methods review document does provide details of the search strategy used in the review document itself, but not for identifying trials as part of an NMA.

Study Selection

Following the completion of the search, it is necessary to determine which studies should be included in the NMA. The requirements for the study selection process are listed in Table 4. In many cases, they are less rigorous than the methods