LETTERA

First Italian guidelines for the economic evaluation of health technologies: how do they compare to NICE standards?

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In the past decades, in most developed countries, growing public debt and demographic transition (low fertility rate and high life-expectancy) are raising concerns regarding the sustainability of the welfare system in the long term. In 2019, in Italy, healthcare public financing represented 6.4% of GDP, with pharmaceutical expenditure contributing to 15.2% [1]. Traditionally, Italy implemented different cost-containment measures to control pharmaceutical expenditure such as: 1) discounts or agreements at the product level negotiated by national, regional, or local payers [2]; 2) rebates at the industry level, with manufacturers paying back money to national payers when total pharmaceutical expenditure exceeds an expenditure ceiling decided at a national level by law [3] and 3) managed entry agreements among which emerge performance-based agreements [4,5]. Still, public pharmaceutical expenditure rose by 4.6% between 2014 and 2018, passing from 11,848 to 12,913 million [6], while overall healthcare public financing in percentage of GDP decreased in the same period [7]. The shift towards specialty care, including advanced therapy medicinal products and personalized care, requiring higher investment in research and development, is reflected in higher prices, putting public finances under additional pressure.

Within the health technology Aassessment (HTA) framework, economic evaluation is a useful tool for supporting decision making and priority setting in a context of limited resources.

When it comes to new technologies in Italy, the marketing authorization holders (MAH) must submit the price and reimbursement (P&R) dossier to the Italian Medicine Agency (Agenzia Italiana del Farmaco- AIFA), which then establishes the coverage and prices of medicines reimbursed by the National Health System (NHS) with the support of two committees: technical scientific committee (commissione tecnico scientifica - CTS) and prices and reimbursement committee (comitato prezzi e rimborso - CPR). Between 2013 and 2017, 84% of reimbursement decisions were positive [4], while only 51 out of 299 P&R dossiers submitted between October 2016 and December 2018 did present a cost-effectiveness analysis [8].

In Italy, in May 2020 the first official Italian guidelines for economic evaluation were published on the AIFA website [9] followed, in December 2020, by legislative changes aimed at regulating the negotiation and reimbursement process [10].

Meanwhile, in England, the National Institute of Health and Care Excellence (NICE) has established itself as a global leader in HTA [11] over the past twenty years, especially in regard to the technology appraisal (TA) programme carried out by the Centre for Health Technology Evaluation (CHTE).

Given the novelty of the Italian guidelines and the pivotal role of NICE in setting the methodological standards for the economic evaluation of new health technologies [12], it was deemed relevant to assess differences and similarities between the Italian and English guidelines. In particular, the AIFA guidelines relative to economic assessment published in May 2020 [9] are compared to the latest version of NICE's guidelines of single TA programme published in April 2013 [13]. With the objective of allowing a straightforward comparison between the well-known NICE's standard and the first Italian official guidelines, we compared the methodology and requirements for economic evaluation published by AIFA and NICE, identifying parallelism and dissimilarities between the recommended methods of evaluation concerning: the legislative framework, application, study population, time horizon, discounting, comparators to be considered, perspective of the analysis, measurement and collection of the data concerning health effects and types of sensitivity analyses to present.

The first Italian guidelines for the economic evaluation of health technologies aim to provide applicants with detailed information on how to complete the economic chapter of the P&R dossier. They were initially presented with reference

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Table 1. Resume of the legislative framework of Italian guidelines for economic assessment

Date	Event	Notes
May 2020	AIFA publishes on its website the new guidelines for or the economic evaluation of health technologies in Italian [9]	Guidelines are framed within the Inter-ministerial CIPE decision dated 1 February 2001 [14]
July 2020	AIFA publishes on its website the new guidelines for the economic evaluation of health technologies in English [9]	Guidelines are framed within the Inter-ministerial CIPE decision dated 1 February 2001* [14]
2nd August 2020	Decree law abrogating CIPE 2001 [15]	The decree lists the information that should be included in the request of P&R dossier
16th of September 2020	AIFA publishes on its website provisional guidelines and template for the completion of P&R dossier for public consultation [16]	In the new provisional template, the economic evaluation in terms of cost-effectiveness analysis is not identified as a compulsory element to be submitted
30th of December 2020	AIFA publishes on its website final guidelines and template for the completion of P&R dossier [17]	Guidelines are framed within the decree law of 2nd of August 2020 [15]

AIFA : Agenzia Italiana del Farmaco; CIPE: Committee for Economic Planning; P&R : price and reimbursement.
*Please note that in the English version of the document the decision is referred to be occurred in 2020, this was a typo.

to the Inter-ministerial Committee for Economic Planning (CIPE) decision dated 1 February 2001[1][14].

Afterwards, on the 2nd of August 2020, a decree presenting general indication on new requirements of P&R dossier abrogated the 2001 legislative framework [15]. The new detailed guidelines for the completion of P&R dossier were first made available for public consultation on the 16th of September 2020 [16], being published in their final version on the 30th of December 2020 [17]. In this version, guidelines indicate that, for new technologies, an economic analysis is expected or its absence should be properly justified. Nonetheless, if this is missing, AIFA retains the right of requiring it, leading to the suspension of the negotiation process. The economic analysis should be presented in section E and Appendix 2.2 of the P&R dossier [17] and should be filled following May's guidelines [9]. A summary of the recent relevant changes in the Italian HTA process is presented in **Table 1**, while other comparison elements are resumed in **Table 2**.

Currently, in Italy, the financing decision and price setting is based on a multi-criteria approach where the cost-effectiveness of the concerned interventions is considered, when available, together with the therapeutic value and other factors (e.g. equity, affordability, added therapeutic value) [4,18,19]. If a positive appraisal is given, the assessed technology will be included in the clinical commissioning groups' formularies enabling practitioners to prescribe it to patients.

On the other side, NICE is a non-department public body whose current scope was legislated by the Health and Social Care Act 2012. Its appraisal is based on a review of clinical and economic evidence, primarily provided by the MAH, supported by testimonies from patients, healthcare professionals and commissioners [20]. MAHs must present an economic evaluation when the NICE TA is initiated. NICE's main decision criterion is the incremental cost-effectiveness ratio (ICER) expressed as incremental cost per quality adjusted life-year gained [21]. When the appraisal is closed, NICE determines whether the use of the assessed technologies should be recommended for the NHS or not. If a positive recommendation is given, the assessed technology will be included in the national formulary, legally obliging clinical commissioning groups to provide it to patients within 3 months.

AIFA suggests that MAHs should present a cost-effectiveness analysis for: a) orphan medicines, including any related extension of indications; b) new active substances, including reclassification of active substances that have already been negotiated but not reimbursed, as well as combinations containing at least one new active substance; c) new therapeutic indications of established products, except when they concern a mere extension of the population already reimbursed. A cost-minimization analysis is suggested when there is robust evidence of substantial comparability between the medicine of interest and the best available comparator, both in terms of efficacy and safety.

NICE produces technology appraisals for interventions that are likely to have: a) a significant health benefit; b) a significant impact on other health-related government policies; c) a significant impact on NHS resources; d) significant variations in the use of the technology and e) national guidance is likely to add value. Most of the new technologies (new drugs or drugs indication extensions) are assessed. Differently from Italy, NICE's appraisal process also applies to medical devices, diagnostic techniques and surgical procedures.

According to NICE, the time horizon should be long enough to capture the whole impact that interventions have on the health and associated costs of the population assessed. Therefore, a lifetime horizon should be considered when new technologies affect the natural history of the

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Table 2. Resume of differences and similarities between Italian and English guidelines

	Italy	England
Application	• MAH should present a cost-effectiveness analysis for: a) orphan medicines; b) new active substances; c) new therapeutic indications of established products	• TA are produced for interventions that are likely to have: a) significant health benefit; b) significant impact on other health-related government policies; c) significant impact on NHS resources; d) significant variations in the use of the technology; e) national guidance is likely to add value
Time horizon	• AIFA suggests considering three time horizons (5 years, 10 years and lifetime) • No preferred one is stated, it should anyway be a period long enough to capture all the differences between the compared alternatives	• It should be long enough to capture the whole impact that interventions have on the health and associated costs of the population assessed
Discounting	• Both costs and health effects at an annual rate of 3.0% Sensitivity analysis discount rates of 0.0% and 5.0%	• Both costs and health effects at an annual rate of 3.5% • Sensitivity analysis discount rate of 1.5%
Population	• As specified in marketing authorization	• As specified in marketing authorization
Comparators	• MAH should justify the selection of the comparator based on the national or international guidelines, the national clinical practice or the lack of valid alternative	• NICE identifies all potentially relevant comparators during the scoping process, at the beginning of the appraisal process, by taking into account the natural history of the disease, NICE guidance, cost-effectiveness analyses, and available comparators
Perspective of the analysis	• NHS perspective is recommended for the base case analysis • Societal perspective may be presented	• Perspective of the NHS and PSS
Health effects	• RCTs as preferred evidence • Other sources of evidence not excluded but should be accurately described in terms of study methods, assumptions and results • No methodologic requirements for evidence synthesis	• RCTs as preferred evidence • If other sources of information are used, biases should be quantified and adjusted for • Data should be presented in network meta analyses if evidence available in non head-to-head RCTs
Benefit and measurement valuation	• Use referring to the Italian context if possible • If multiple alternative data sources are available, the resulting uncertainty should be assessed in a sensitivity analysis	• Preferably expressed in QALYs and measured with the EQ-5D • When possible, HRQoL associated to health states should be measured in patients while general population should be engaged to elicit preferences
Sensitivity analyses	• Probabilistic sensitivity analyses results should be graphically represented in scatter plots and acceptability curves	• Probabilistic sensitivity analyses are preferred • graphically represented in scatter plots and acceptability curves and tabulated report on correlation/independence between parameters should be examined

AIFA: Agenzia Italiana del Farmaco; EQ-5D: EuroQol-5D (EQ-5D); HRQoL: Health-Related Quality of Life; MAH: Marketing Authorization Holders; NHS: National Health System; NICE: National Institute of Health and Care Excellence ; QALYs: Quality-Adjusted Life Years; TA: Technology appraisal; PSS: Personal Social Services; RCTs: Randomized Clinical Trials.

disease in terms of survival, or impact lifelong costs or health outcomes.

AIFA suggests considering three time horizons (5 years, 10 years and lifetime), without defining the preferred one for the base-case scenario. On the final version of the guidelines for the completion of P&R dossier [17], it was added that the *"time horizon should anyway be a period long enough to capture all the differences between the compared alternatives"*.

Annual discounted rate considered to reflect present value of both costs and health effects should be 3.5% in England and 3.0% in Italy. Both organizations ask presenting sensitivity analyses using different discount rates (1.5% in England, 0.0% and 5.0% in Italy). NICE allows for lower rates (i.e., 1.5%) to be applied in special circumstances with therapies bringing substantial long-term health benefits. Discounting is similar in the two countries, reflecting either similar opportunity costs (i.e. the opportunity that the resources required for healthcare could also have been invested in another sector of the economy) or similar time preferences (i.e. level of impatience) [22].

For both agencies, the population of the economic assessment and the population in the marketing authorization should overlap.

In England, it is given the possibility to account also for the impact of the treatment on the caregivers whenever deemed appropriate.

In both countries, analysis by subgroups should be presented when health outcomes or cost-effectiveness results are heterogenous among subpopulations or special considerations arise.

In terms of comparators, all potentially relevant interventions should be evaluated. In Italy, the MAH should justify the selection of the comparator based on the national or international guidelines, the national clinical practice or the lack of valid alternative. In England, NICE identifies all potentially relevant comparators during the scoping process, at the beginning of the appraisal process, by taking into account the natural history of the disease, NICE guidance, cost-effectiveness analyses, and available comparators.

In England, the perspective to be adopted should be only that of the NHS and personal social services (PSS), while AIFA allows you to assume either the NHS or the societal perspective, although *"in the base case, the analysis should be ideally carried out from the perspective of the Italian NHS"*. When the societal perspective is adopted, indirect costs related to patients' and caregivers' (including informal caregivers) loss of productivity should be considered.

In England, resource consumption is valued based on a drugs' public list of prices, considering available patient access schemes and price reductions. Inpatient care costs may be based on diagnostic-related-groups tariffs, micro-costing, or literature reviews, where appropriate.

In Italy, drug acquisition costs should be the ex-factory price published in the Italian Official Journal, net of statutory reductions (when applicable). Direct costs can be estimated by referring to national tariffs, where available, or cost studies conducted in Italian centers. No indication is provided regarding the method to estimate productivity loss.

In order to determine the impact of an intervention on patients' health, NICE recommends performing a systematic literature review to comparatively describe its effects. Both agencies favor randomized controlled trials (RCT) where interventions are directly compared. If other sources of information are used, NICE requires potential biases to be identified, ideally quantified and adjusted for. When the selected comparator is not included in the RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis, if appropriate. AIFA does not exclude the use of other sources to inform effectiveness, while recommending to accurately describe the study methods, alongside the assumptions and related results. No specific method for synthesizing evidence is suggested. Both agencies require the assessment of the model's external validity. In Italy, the non-interventional scenario is expected to lead to epidemiologically consistent results in terms of national prevalence, incidence and mortality of the disease.

For NICE, health gains are preferably expressed in terms of Quality Adjusted Life Years (QALY). EQ-5D is the preferred tool for measuring Health Related Quality of Life (HRQoL) in adults. When possible, HRQoL associated to health states should be measured in patients while general population should be engaged to elicit preferences. When EQ-5D data are not available, NICE authorizes mapping other HRQoL measures to EQ-5D, mapping functions must be validated, and sensitivity analyses performed.

AIFA does not state any specific measure for quantifying health outcomes or estimating HRQoL. It requires, when possible, to use data referring to the Italian context. In both countries, the deliberative process may also consider other benefits not reflected in QALYs, for instance, the severity of the disease, the availability of other effective therapies and clinical novelty [17]. These considerations appear to have a limited impact on NICE's recommendations [11], while their relative weight is unclear in AIFA's appraisal process.

In order to assess any uncertainty around the results, both agencies require sensitivity analyses. NICE requires to present probabilistic sensitivity analysis (PSA) unless its unfeasibility is specified and justified. Still, model structure and programming should not impede assessing uncertainty. In Italy, PSA results should be graphically represented in scatter plots and acceptability curves, while in England a tabulated report is also possible and correlation/independence between parameters should be examined.

In England, deterministic sensitivity analyses (DSA) can be performed while in Italy they are strongly suggested.

AIFA and NICE documents present a different level of detail and are framed in diverse legislative contexts. The non-definitive character of AIFA's guidelines leaves researchers with higher flexibility to conduct economic evaluations and thus the application of these different guidelines may lead to heterogeneous methodologies and results. Overall, NICE is more prescriptive and specific in its requirements. Namely, NICE's requirements in terms of data identification, production, and validation are more exhaustive, recommending systematic literature review and meta-analysis to synthetize evidence, while no explicit approach is suggested by AIFA. It is interesting to notice that both agencies favor the production of country-specific health outcomes, economic and quality of life data. It follows that there is a high need for model adaptation and external validation considering national data and clinical practice.

The less stringent methodological requirements and relatively lower complexity of the first Italian guidelines reflect an historically more marginal role of economic evaluation within the HTA framework, where cost-effectiveness analysis rarely integrated the P&R dossier [8]. The publication of this first national guidance is particularly relevant, when considering that the role of economic evaluation in the field of health care is still consolidating. The availability of official Italian guidelines has the major merit of establishing a common ground for the evaluation of new health technologies by clarifying reporting requirements and are thus expected to enhance higher comparability among different

studies. They are likely to assume a relevant role in reinforcing economic evaluation weight within the Italian multidimensional decision-making process. Considering the P&R dossier published in December 2020, it is expected that, in order to minimize the risk of AIFA suspending the negotiation process delaying access, most MAH will present an economic evaluation although not strictly compulsory.

Italy's finances are under great pressure and the need to control public spending while ensuring access to healthcare is a major challenge. In a context of cost-containment, healthcare priority-setting is an essential element and should be transparent and well-justified in order to be considered ethically, socially and politically acceptable [19,23]. A sound methodological approach and clear evaluation criteria will lead to more evidence-based decisions enhancing higher efficiency in healthcare resource allocation, while augmenting legitimacy and acceptability. In England, since the TA programme was established in 1999, the technological appraisal progressively became more standardized, specific and detailed over time [24]. A similar evolution is desirable and plausible for Italy as well. Nevertheless, a certain degree of heterogeneity is expected to persist over time reflecting different culture, history, and societal preferences.

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Conflict of interests

At the time of the realisation of this project and the manuscript writing, Francesca Fiorentino and Duccio Urbinati were employees of IQVIA Italy, which receives fees for professional services from several pharmaceutical companies.

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