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How real-world data compensate for scarce evidence in HTA

Wie Real-World-Daten spärliche Evidenz im Rahmen von HTA-Bewertungen wettmachen können

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Value assessment;
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NHS-based observational studies

Summary Most guidance developed by NICE is based on a value assessment using clearly articulated and published clinical and cost effectiveness criteria. In order to enable consistency and fairness across all decisions, NICE uses as a unit of health benefit the quality-adjusted life year (QALY). Both QALYs and costs for a technology are estimated by long-term disease modelling. This requires a variety of clinical input parameters, and often extrapolation beyond the trial period, and of intermediate or surrogate to final outcomes. RCT data will remain the main data source for the majority of appraisals, but because the data necessary for disease modelling is often not available from RCTs, particularly for the UK context, the use of non-RCT data is the norm in NICE technology appraisals. This does not only apply to data on resource use, service provision and HRQL data, but also to efficacy data. In some situations non-RCT data are more relevant to a decision context than the RCT data, and in some situations, as illustrated by 3 examples, it would be unreasonable, not to take account of existing non-RCT data.

The use of non-RCT clinical evidence is most common for devices, interventions where RCTs are difficult, and in conditions with poor prognosis where single arm studies are often carried out. Therefore, a pragmatic approach to the available evidence is needed for many decision made by the NICE Appraisal Committees to come to a reasonable and defendable decision.

SCHLÜSSELWÖRTER
Nutzenbewertung;
Langzeitkrankheits-modelle;
Extrapolation von Studiendaten;
NHS-basierte Beobachtungsstudien

Zusammenfassung Die meisten der vom *National Institute for Health and Care Excellence* (NICE) entwickelten Leitlinien stützen sich auf Nutzenbewertungen, für die eindeutig definierte und publizierte klinische sowie Kosteneffektivitätskriterien herangezogen wurden. Um eine entscheidungsübergreifende Einheitlichkeit und Fairness zu gewährleisten, verwendet das NICE als Messgröße für die Bewertung des gesundheitlichen Nutzens das qualitätskorrigierte Lebensjahr *(quality-adjusted life year*, QALY). Sowohl die QALYs als auch die Kosten einer medizinischen Technologie werden mithilfe von Langzeitkrankheitsmodellen geschätzt. Als Inputdaten werden die verschiedensten klinischen Parameter benötigt, und oftmals ist auch die Extrapolation über den Studienzeitraum hinaus sowie die Extrapolation von Zwischenergebnissen bzw. Surrogatparametern auf die endgültigen Ergebnisse erforderlich. Für die Mehrzahl

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der Bewertungen werden Daten aus randomisierten kontrollierten Studien (RCTs) zwar auch weiterhin die wichtigste Datenquelle bleiben, doch weil die für die Modellbildung benötigten Daten aus RCTs häufig nicht zur Verfügung stehen (vor allem in Großbritannien nicht), stellt die Verwendung von Daten aus nichtrandomisierten Studien für die Technologiebewertungen des NICE die Norm dar. Dies gilt nicht nur für Daten zur Ressourcenverwendung, zu Versorgungsleistungen und für HRQL-Daten, sondern auch für Wirksamkeitsdaten. In manchen Fällen sind Daten aus nichtrandomisierten Studien für die Entscheidungsfindung von höherer Relevanz als solche aus RCTs, und in bestimmten Situationen wäre es, wie an drei Beispielen gezeigt werden soll, sogar unvernünftig, vorhandene Daten nicht zu berücksichtigen, nur weil sie nicht aus RCTs stammen.

Aus nichtrandomisierten Studien stammende klinische Evidenz wird am häufigsten für Medizinprodukte und Interventionen herangezogen, bei denen die Durchführung von RCTs schwierig ist, sowie bei Krankheitsbildern mit einer ungünstigen Prognose, bei denen oftmals nur einarmige Studien durchgeführt werden. Aus diesem Grund bedarf es bei vielen der von den NICE-Bewertungsgremien zu treffenden Entscheidungen eines pragmatischen Umgangs mit der verfügbaren Evidenz, um zu einer vernünftigen und belastbaren Entscheidung zu gelangen.

This article sets out to explain in what way the National Institute for Health and Care Excellence (NICE) considers evidence from sources other than randomised controlled trials (RCTs). NICE is an English Non-Departmental Public Body which provides national guidance to the NHS in England on the promotion of good health and the prevention and treatment of ill-health in line with the best available evidence of clinical-effectiveness and cost-effectiveness. Since 2000, NICE has published guidance on health technologies (drugs, medical devices and diagnostics, interventional procedures), clinical practice (clinical guidelines), public health interventions (since 2005), and since 2013 is also developing social care guidance. In addition to publishing guidance, NICE also develops quality standards and performance metrics for those providing and commissioning health, public health and social care services, and provides a range of informational services for commissioners, practitioners and managers across the spectrum of health and social care. The guidance produced by one of the NICE programmes, Technology Appraisals, carries a funding direction, which means that any technology recommended in a published Technology Appraisal has to be funded by the NHS within 3 months of guidance publication. As such, NICE recommendations are the primary source of guidance for new medicines and new licence indications for existing medicines within the NHS. NICE also provides implementation and adoption support for its other guidance programmes.

Guidance published by NICE, with the exception of interventional procedure guidance, is based on a value assessment using clearly articulated and published clinical and cost effectiveness criteria for decision making. For NICE, this value assessment applies the perspective of the whole NHS system, and is defined through an assumed opportunity cost, which is the health benefit displaced elsewhere in the NHS if a new technology is adopted, or in other words, what the NHS pays on average to generate a unit health benefit. In order to enable consistency and fairness across all decisions for all therapeutic areas, NICE uses as a unit of health benefit the quality-adjusted life year (QALY). QALYs are estimated by multiplying length of life with an index measuring quality of life. Cost effectiveness of a new technology is therefore expressed as cost per QALY gained compared with standard care. The opportunity cost is clearly articulated in the Guide to the Methods of Technology Appraisal [1] as the maximum acceptable cost per QALY gained (£20,000-30,000 per QALY gained).

The health gain provided by a technology is estimated by, mainly long-term, disease modelling. Then resources use and costs are added to create cost effectiveness modelling. The aim is to answer the simple question of how well the new technology works in relation to how much it costs, compared with standard practice in the NHS.

Therefore, cost effectiveness modelling requires a variety of clinical input parameters, such as clinical effect sizes, adverse events and complications, baseline clinical data (epidemiology/ natural history of disease), health related quality of life (HRQL) data, and compliance/ adherence data. Because in most cases long term modelling is necessary, there is also a need for extrapolation beyond trial period, and also extrapolation of intermediate/ surrogate to final outcomes, and of trial results to relevant settings, for example by incorporating country-specific data to provide meaningful modelling of the NHS context.

As far as HRQL data are concerned, NICE prefers the use of the EQ-5D as the measure of HRQL in adults, and specifies in its Methods guide [1] that changes in HRQL should be described directly by patients, but that the value of changes in patients' HRQL should be based on preferences expressed by the public. Importantly, this means that the utility data resulting from the EQ5D reflect what the public would trade off to avoid a certain health state. Data on HRQL is often collected in clinical trials, but not often used in modelling approaches submitted to NICE. Instead many models use HRQL data from sources other than RCTs.

Resource use and cost parameters required for modelling should reflect the health system's service delivery patterns and routine setting, and it is therefore not always appropriate to include resource use from RCTs because the latter are protocol-driven (e.g. regular CT scans or clinical appointments) and not reflective of routine clinical practice. Also, because it is important for NICE to use UK specific costs, sources for resource data are often from NHS-based observational studies, administrative data, chart reviews, listing published by the Department of Health, national data based on healthcare resource groups, such as the Payment by