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REVIEW

A review of NICE appraisals of pharmaceuticals 2000–2016 found variation in establishing comparative clinical effectiveness

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Abstract

Objective: To identify and assess the methods for estimating comparative clinical effectiveness for novel pharmaceutical products licensed on the basis of nonrandomized controlled trial (non-RCT) data and to evaluate the corresponding National Institute for Health and Care Excellence (NICE) recommendations.

Methods: Our identification strategy was twofold. First, we reviewed all NICE appraisals between 2010 and 2016 and identified technologies where comparative clinical effectiveness estimates were calculated using non-RCT data. Second, we checked if NICE appraisals completed from 2000 to 2010 had included pharmaceuticals that were granted European Medicines Agency marketing authorization without RCT data between 1999 and 2014. Information was extracted on the method used to establish comparative clinical effectiveness as well as the corresponding NICE recommendations. We also collected information on the rationale for utilizing non-RCT data in NICE appraisals.

Results: Of 489 individual pharmaceutical technologies assessed by NICE, 22 (4%) used non-RCT data to estimate comparative clinical effectiveness. Methods for establishing external controls in such studies varied: 13 (59%) used published trials, 6 (27%) used observational data, 2 (9%) used expert opinion, and 1 (5%) used a responder vs nonresponder analysis. Only 5 (23%) used a regression model to adjust for covariates. We did not observe a notable difference in the proportion of pharmaceutical technologies that received a positive recommendation from NICE whether the decision was based on RCT or non-RCT data (83% vs 86%).

Conclusions: To date, a small number of appraisals by NICE based on non-RCT data did not result in substantially different treatment decisions. The majority of the technologies appraised on the basis of non-RCT data either received a positive recommendation or a positive recommendation with restrictions. The methods used to calculate comparative clinical effectiveness estimates varied, highlighting the need to establish clear guidance. © 2018 Elsevier Inc. All rights reserved.

Keywords: Single-arm trials; Uncontrolled trial; Drug approval; Nonrandomized studies; Quality of evidence; National Institute of Health and Care Excellence

1. Introduction

The gold standard for establishing the clinical effectiveness and safety of a pharmaceutical technology is to conduct a randomized controlled trial (RCT). RCTs are the mainstay of research and development of new medicines and are used to establish reliable comparative efficacy estimates [1]. The random allocation of patients between an intervention and control arm reduces confounding as compared to other types of study design where there is no randomization [2,3]. This is reflected in the National Institute for Health and Care Excellence (NICE) guidance for technology appraisals, which states that RCTs are "considered to be most appropriate for measures of relative treatment effect" and outlines that the "problems of confounding, lack of blinding, incomplete follow-up, and lack of a clear denominator and endpoint occur more commonly in nonrandomized studies and noncontrolled trials than in RCTs" [4].

Clinical equipoise, defined as the absence of certainty about the superiority of alternative treatment options for a given indication, is a fundamental ethical criterion to randomly allocate participants to different treatment groups

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What is new?

Key findings

- Between 2000 and 2016, 22 of the 489 (4%) individual pharmaceutical technologies assessed by NICE were based on comparative clinical effectiveness estimates calculated using non-RCT data.
- Of these 22, 11 (50%) were included in technology appraisals published in either 2015 or 2016.
- 10 (45%) received a positive recommendation from NICE, 9 (41%) received an optimized recommendation, and a further 3 (14%) received a negative recommendation.
- 14 (64%) appraisals calculated comparative clinical effectiveness estimates using a naive unadjusted indirect comparison against an external control, not utilizing any regression methods. This may reflect the limited availability of individual patient-level data to adjust for covariates.

What this adds to what was known?

- Despite non-RCT data leading to significant uncertainty in quantifying clinical benefit, we only observed a small difference in the proportion of pharmaceutical technologies that received a positive or negative recommendation from NICE when comparing decisions based on RCT or non-RCT data.

What is the implication and what should change now?

- Clear guidance is needed to establish the comparative clinical effectiveness of pharmaceuticals with non-RCT data.
- There is a need to monitor and follow-up the real-world comparative clinical and cost-effectiveness of pharmaceutical technologies recommended on the basis of non-RCT data.

[5]. However, this criterion may not be necessary in the context of precision medicine with targeted therapies, where earlier studies have demonstrated a large magnitude of treatment effect. In such cases, some observers have postulated that RCTs may not be necessary [6–8]. In addition, in the context of small populations, RCTs may be unethical and misleading, as results could be statistically underpowered [9]. As a result, drug licensing agencies such as the European Medicines Agency (EMA) may grant marketing authorizations to pharmaceutical technologies with no RCT data, when there is certainty that the product's benefit outweighs potential harm [10].

Once products are on the market, health technology assessment (HTA) agencies, such as the NICE, are responsible for evaluating not only the relative benefits but also the cost-effectiveness of novel technologies compared to existing alternatives in established use in clinical practice. Reliance on non-RCT data poses significant challenges for HTA agencies that are faced with increased uncertainty regarding the comparative clinical effectiveness and therefore the cost-effectiveness estimates of pharmaceutical products [11,12].

In the absence of a controlled trial, alternative methods are required to generate relative clinical effectiveness estimates against comparator agents. Such estimates are an essential component for economic evaluation analyses conducted to establish the value of new agents. For example, an external control could be considered in an economic evaluation model using either historical data or a self-control [13]. According to technical guidance developed by NICE's Decision Support Unit, use of a regression model is the preferred option to adjust for the effects of covariates when using an external control, although this is only possible when individual patient-level data are available for both the noncontrolled trial and external control [14].

Our objective in this article was to review NICE appraisals between 2000 and 2016 that calculated comparative clinical effectiveness estimates using non-RCT data. We reviewed the methods used and compared the final published committee recommendation for these technologies versus those where comparative clinical effectiveness estimates were calculated using RCT data.

2. Methods

2.1. Identification of pharmaceutical technologies

We adopted a two-pronged approach to identify pharmaceutical technologies whereby comparative clinical effectiveness estimates in NICE technology appraisals were calculated using non-RCT data. First, one researcher systematically reviewed all publicly available guidance documents from NICE single technology appraisal (STA), multiple technology appraisal (MTA), and highly specialized technology (HST) processes published between January 2010 and December 2016. Second, we reviewed all NICE STA, MTA, and HST guidance published between January 2000 and December 2016, which appraised pharmaceutical technologies listed within two previously published systematic reviews of pharmaceutical technologies that were granted EMA marketing authorization without RCT data between 1999 and 2014 [10,15].

For each technology appraisal, the corresponding clinical and economic evidence within NICE committee articles and evidence review group (ERG) reports were reviewed. NICE committee members are selected from the institute itself, the National Health Service (NHS), patient and carer organizations, academia, and the pharmaceutical industry [16]. The ERG reports are produced by a group of independent

experts, in academia, and commissioned by the National Institute for Health Research to review and critique both the clinical and cost-effectiveness evidence available for each technology under appraisal [4].

As the NICE MTA process considers multiple pharmaceutical technologies for the same indication, each individual pharmaceutical technology under MTA with its own corresponding clinical and economic evidence base was reviewed separately.

We excluded all nonpharmaceutical technology appraisals and those which were subsequently updated or terminated due to manufacturer nonsubmission.

2.2. Eligibility criteria

Pharmaceutical interventions reviewed by the NICE STA, MTA, and HST appraisal processes were screened and categorized by one researcher as either a non-RCT–based or an RCT-based technology. A non-RCT–based technology was defined as a pharmaceutical technology whereby the comparative clinical effectiveness estimates used within the economic evaluation model were calculated using non-RCT data. Non-RCT data could either be obtained from uncontrolled studies (i.e., a single-arm trial or a trial without a concurrent comparator group) or the intervention arm of an RCT interpreted as a single-arm trial by NICE. The latter occurred when the original comparator included in the RCT was deemed not to be relevant to the NICE decision scope (as specified in the published appraisal report).

We relied on the ERG's final economic evaluation model. The ERG may choose to alter the economic evaluation model submitted by the manufacturer to correct errors, consider different clinical or cost inputs, or modify the structure of the model. The ERG's final economic evaluation model is therefore the most comprehensive reflection of available evidence that ultimately informs the NICE assessment.

The final sample of technologies was checked and confirmed by a senior member of the research team.

2.3. Data extraction

One researcher reviewed the appraisal guidance and ERG reports and collected data on (1) the methods for establishing comparative clinical effectiveness estimates, (2) NICE recommendations, and (3) NICE committee comments.

2.3.1. Methods to establish comparative clinical effectiveness estimates

For each technology in our sample, within the final ERG's economic evaluation, an unanchored indirect comparison was used to estimate comparative clinical effectiveness. The external control and methods used to estimate comparative clinical effectiveness in the economic model was identified. It was also determined if a meta-analysis or regression model was used in the final economic model to adjust for covariates.

2.3.2. NICE recommendations

One researcher reviewed the NICE committee articles to characterize the corresponding recommendations for all technologies, including both the committee decision outcome and any use of patient access schemes. The committee decision outcome could be "recommended" (approved with no restrictions), "optimized" (approved within a specified patient subgroup), "not recommended" (not approved for routine use in the NHS), or "only in research" (approved within a research setting). Many recommendations by NICE are based on a patient access scheme in which the cost-effectiveness of a technology under appraisal is improved by offering the technology at a discounted price. The NICE recommendations were reviewed for all technology appraisals published by NICE between January 2000 and December 2016.

2.3.3. NICE committee comments

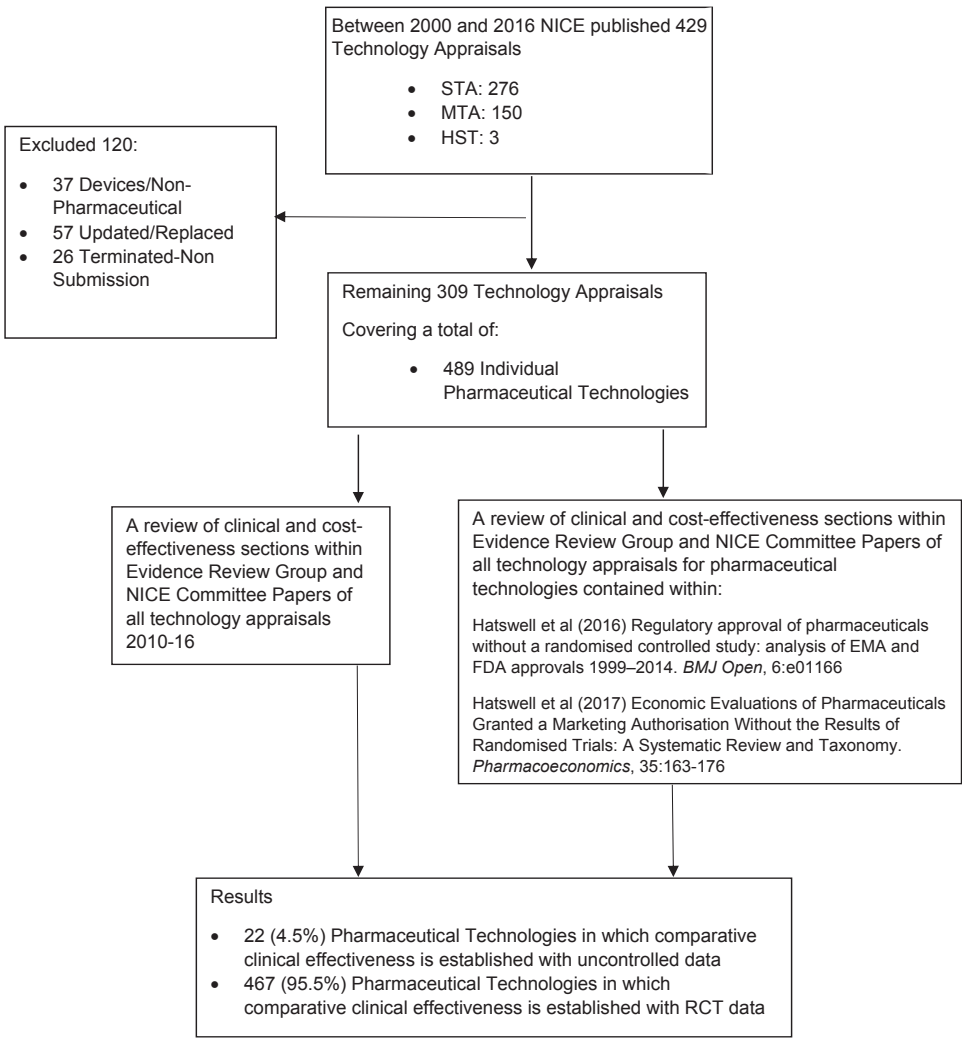
For all technologies in our sample, one researcher reviewed the key conclusions of NICE committee documents to highlight any additional factors considered as well as concerns regarding the clinical evidence base and/or incremental cost-effectiveness ratio (ICER) estimates to gain an insight into the committee's decision-making process.

3. Results

3.1. Identified pharmaceutical technologies

We identified a total of 429 NICE technology appraisals between January 2000 and December 2016 (Fig. 1). Of these, we excluded 120 appraisals because they included nonpharmaceutical technologies (37), they were subsequently updated (57), or they were terminated due to manufacturer nonsubmission (26). In the latter two cases, NICE committee articles were not publicly available. Reviewing the EMA initial marketing authorization documents revealed 4/26 (15%) of these terminated technologies were approved on the basis of a pivotal trial with non-RCT data. All 26 terminated technologies were due to manufacturer nonsubmission.

The remaining 309 technology appraisals included a total of 489 individual pharmaceutical products. Of these 489 pharmaceutical technologies, 22 (4%) individual pharmaceuticals across 20 technology appraisals were based on non-RCT data and therefore met our eligibility criteria; 12 (55%) had an oncology indication, 6 (27%) had a hepatology indication, 3 (14%) had a



NICE: National Institute for Health and Care Excellence; **STA**: single-technology appraisals; **MTA**: multiple-technology appraisals; **HST**: highly-specialised technologies;

Fig. 1. Flow diagram of study selection process for appraisals in the review.

rheumatology indication, and 1 (5%) had an immunology indication.

3.2. Methods used to establish comparative efficacy

When choosing an external control to establish comparative clinical effectiveness estimates in the economic model, 13 (59%) used previously published trials, 6 (27%) used observational data, 2 (9%) used expert opinion, and 1 (5%) used a responder vs nonresponder analysis (Table 1). Only 5 (23%) appraisals used a regression model, and only 6 (27%) appraisals used a meta-analysis to combine results from multiple studies. Comparative clinical effectiveness estimates for 14 pharmaceutical technologies (64%) were calculated using a naive unadjusted indirect comparison against an external control, possibly due to a lack of individual patient-level data.

3.3. NICE recommendations

There was small differences between technologies in our sample (appraised on the basis of non-RCT data) and technologies with RCT data receiving the NICE committee decision outcome of "recommended" 10/22 vs 289/467 (45% vs 62%) or "not recommended" 3/22 vs 81/467 (14% vs 17%) (Table 2). Technologies in our sample were more than twice as likely to receive the NICE committee decision outcome of "optimized" as compared with those with RCT data (9/22 vs 91/467; 41% vs 19%). The "only in research" designation was not used for non-RCT–based pharmaceutical technologies and for 6/467 (1%) of RCT-based pharmaceutical technologies.

Table 1. Methods used for technology appraisals with economic evaluations using non-RCT data to establish comparative clinical efficacy

Number	Year	Name	Intervention efficacy data
NICE recommendation: not recommended			
178	2009	Sunitinib	Two uncontrolled studies
202	2010	Ofatumumab	Single uncontrolled study[a] (responders)
209	2010	Imatinib 600 mg/800 mg	Multiple uncontrolled studies
NICE recommendation: optimized			
195	2010	Adalimumab	Single uncontrolled study
195	2010	Etanercept	Single uncontrolled study
195	2010	Infliximab	Single uncontrolled study
330	2015	Sofosbuvir	Multiple uncontrolled studies
363	2015	Ledipasvir-sofosbuvir	Multiple uncontrolled studies
364	2015	Daclatasvir	Multiple uncontrolled studies
HST1	2015	Eculizumab	Single uncontrolled study
408	2016	Pegaspargase	Pediatric: one uncontrolled study Adult: multiple uncontrolled studies
410	2016	Talimogene laherparepvec	Single-arm of an RCT
NICE recommendation: recommended			
23	2001	Temozolomide	Single-arm of an RCT
86	2004	Imatinib	Single uncontrolled study
185	2010	Intravenous trabectedin	Single uncontrolled study
246	2012	Pharmalgen	Multiple uncontrolled studies
300	2013	Peginterferon alfa	Single uncontrolled study
331	2015	Simeprevir (genotype 4)	Single uncontrolled study
365	2015	Ombitasvir-paritaprevir-ritonavir	Multiple uncontrolled studies
395	2016	Ceritinib	Multiple uncontrolled studies
401	2016	Bosutinib	Single uncontrolled study
416	2016	Osimertinib	Multiple uncontrolled studies

HST1 is the number of the high specialised technology appraisal undertaken. HST is mentioned within the eligibility criteria outlined within Section 2.2, and identification of pharmaceutical technologies in Section 2.1.

Abbreviations: NICE, national institute for health and care excellence; RCT, randomized controlled trial; HST, highly specialized technology.

[a] This was the same study.

Technologies with non-RCT data were more likely to use a patient access scheme as compared with those with RCT data, 7/22 vs 111/467 (32% vs 24%; Table 2). All patient access schemes were financial-based except for one for a non-RCT–based technology. This scheme relied on a combination of a financial- and performance-based patient access scheme, i.e., a managed access agreement [17].

3.4. NICE committee comments

Several factors were considered by NICE committees when evaluating technologies with non-RCT data. The most frequent factors were significant unmet need (11/22, 50%), a small patient population (6/22, 27%), and cases when early trials had shown substantial benefit (2/22, 9%). The small sample size limited the possibility to explore the association between NICE committee recommendations and these factors (Table 3). All committees explicitly highlighted concerns regarding the clinical evidence for all 22 technologies in our sample. These concerns included the immaturity of data, and the uncertainty associated with the lack of a direct comparator. Conversely, issues regarding the cost-effectiveness of each technology seemed to correlate with the NICE committee decision, they were present for the two "not recommended" technologies where an ICER estimate was available (100%, 2/2), the majority of the nine "optimized" technologies (78%, 7/9) and rarely present for the 10 "recommended" technologies (20%, 210) (Table 3). Concerns were typically raised when the associated ICER estimate was above an acceptable threshold.

4. Discussion

4.1. Summary of findings

Our review of NICE appraisals conducted between 2000 and 2016 identified 22 pharmaceutical technologies that relied on non-RCT data when generating comparative efficacy estimates used in the economic model. In these

Comparators efficacy data	Comparison method	Meta-analysis	Regression model
No comparison made	No comparison made	No	No
Single uncontrolled study[a] (nonresponders)	Responder vs nonresponder analysis	No	Yes
Observational study	Naïve unadjusted indirect comparison	No	No
Multiple uncontrolled trials and RCTs	Naïve unadjusted indirect comparison	Yes (comparators)	No
Multiple uncontrolled trials and RCTs	Naïve unadjusted indirect comparison	Yes (comparators)	No
Multiple uncontrolled trials and RCTs	Naïve unadjusted indirect comparison	Yes (comparators)	No
Multiple uncontrolled studies and RCTs	Naïve unadjusted indirect comparison	No	No
Multiple uncontrolled studies and RCTs	Naïve unadjusted indirect comparison	No	No
Multiple uncontrolled studies and RCTs	Naïve unadjusted indirect comparison	No	No
Observational data set	Naïve unadjusted indirect comparison	No	No
Pediatric: Multiple single-arms of RCTs Adult: expert opinion	Pediatrics: Naïve unadjusted indirect comparison Adult: expert opinion	≤25 years—Yes (comparators) >25 years—No	No
Multiple RCTs	Adjusted indirect comparison	No	Yes
Multiple uncontrolled studies	Naïve unadjusted indirect comparison	Yes (comparators)	No
Observational study	Naïve unadjusted indirect comparison	No	No
Observational data set	Adjusted indirect comparison	No	Yes
Observational study	Naïve unadjusted indirect comparison	Yes (intervention)	No
Expert opinion	Expert opinion	No	No
Single-arms of an RCT	Adjusted indirect comparison	No	No
Multiple uncontrolled studies and RCTs	Adjusted indirect comparison	Yes	Yes
Single uncontrolled study	Naïve unadjusted Indirect comparison	No	No
Observational study	Naïve unadjusted indirect comparison	No	No
One RCT	Adjusted indirect comparison	Yes	Yes

instances, we did not identify a consistent methodological approach to compare the technology to its comparators specified in the decision scope. Although existing guidelines recommend the use of statistical methods to adjust for covariates [14,18], a regression model was used in only 5 of 22 appraisals identified in our review. Final recommendations did not differ for technologies with and without RCT data.

Previous research has indicated that the strongest predictor for a NICE recommendation is the ICER estimate [19]. Other factors that may influence NICE recommendations include severity of underlying illness, end-of- life considerations, disadvantaged populations, unmet need, and pediatric indications [20]. Our findings are consistent with the previous literature. We found no notable differences between technologies appraised on the basis of non-RCT or RCT data receiving a positive (86% vs 83%) or negative (14% vs 17%) recommendation from NICE. We found that NICE committees considered several additional factors when appraising technologies on the basis of non-RCT data, including unmet clinical need, small patient populations, and large treatment effects. Among the positive recommendations, there was a higher proportion of technologies with non-RCT data receiving the ''optimized'' decision outcome (41% vs 19%), likely reflecting the fragmented nature of the target patient population. In these circumstances, a patient population may be defined by a disease stage or other subgroup and be limited in numbers; conducting an RCT may therefore be challenging.

Reviewing a recent EMA report, it was found that 6/22 (27%) of these technologies were granted conditional marketing authorization by the EMA [21]. Despite several alternative strategies to mitigate the uncertainty associated with relative clinical effectiveness estimates derived from non-RCT data, they were seldom used by manufacturers or ERGs. First, the ''only in research'' recommendation was not used for any non-RCT–based technologies. Although the ''only in research'' designation may be appropriate in some cases, this must be balanced against delayed access to medicines for

Table 2. Characteristics of technology appraisals with economic evaluations using non-RCT data to establish comparative clinical efficacy

Number	Year	NICE program	Technology	Indication
NICE recommendation: not recommended				
178	2009	MTA	Sunitinib	Advanced and/or metastatic renal cell carcinoma (2nd line)
202	2010	STA	Ofatumumab	Chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab
209	2010	MTA	Imatinib 600 mg/800 mg	Unresectable and/or metastatic gastrointestinal stromal tumors
NICE recommendation: optimized				
195	2010	MTA	Adalimumab	Rheumatoid arthritis after the failure of a TNF inhibitor
195	2010	MTA	Etanercept	Rheumatoid arthritis after the failure of a TNF inhibitor
195	2010	MTA	Infliximab	Rheumatoid arthritis after the failure of a TNF inhibitor
330	2015	STA	Sofosbuvir	Chronic hepatitis C
363	2015	STA	Ledipasvir-sofosbuvir	Chronic hepatitis C
364	2015	STA	Daclatasvir	Chronic hepatitis C
HST1	2015	HST	Eculizumab	Atypical hemolytic uremic syndrome
408	2016	STA	Pegaspargase	Acute lymphoblastic leukemia
410	2016	STA	Talimogene laherparepvec	Unresectable metastatic melanoma
NICE recommendation: recommended				
23	2001	MTA	Temozolomide	Recurrent malignant glioma
86	2004	MTA	Imatinib	Unresectable and/or metastatic gastrointestinal stromal tumors
185	2010	STA	Intravenous trabectedin	Advanced soft tissue sarcoma
246	2012	STA	Pharmalgen	Bee and wasp venom allergy
300	2013	MTA	Peginterferon alfa	Chronic hepatitis C in children and young people
331	2015	STA	Simeprevir	genotype 1 or 4 chronic hepatitis C
365	2015	STA	Ombitasvir-paritaprevir-ritonavir	Chronic hepatitis C
395	2016	STA	Ceritinib	Non–small-cell, anaplastic lymphoma kinase positive, previously treated
401	2016	STA	Bosutinib	Previously treated chronic myeloid leukemia
416	2016	STA	Osimertinib	Metastatic EGFR and T790M mutation-positive non–small-cell lung cancer

HST1 is the number of the high specialised technology appraisal undertaken. HST is mentioned within the eligibility criteria outlined within Section 2.2, and identification of pharmaceutical technologies in Section 2.1.
Abbreviations: EGFR, epidermal growth factor receptor; ERG, evidence review group; HST, highly specialized technology; ICER, incremental cost-effectiveness ratio; MTA, multiple technology appraisal; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; STA, single technology appraisal; TNF, tumour necrosis factor.

patients [22]. Second, patient access schemes offer another option to mitigate uncertainty regarding value of new technologies. Interestingly, there was only a small difference between technologies with and without RCT data utilizing a patient access scheme. Furthermore, only one of these schemes was performance-based. This may reflect the methodological challenges associated with collecting real-world data following market entry [23].

Therapeutic area	PAS	Additional factors considered by NICE committees	NICE committee concerns	
			Efficacy estimate	ICER estimate
Oncology	Yes	Significant unmet need	Yes	N/A
Oncology	Yes	Early trial showed substantial benefit	Yes	Yes
Oncology	No	Small patient population	Yes	Yes
Rheumatology	No	Nil	Yes	Yes
Rheumatology	No	Nil	Yes	Yes
Rheumatology	No	Nil	Yes	Yes
Hepatology	No	Early trial showed substantial benefit	Yes	Yes
Hepatology	No	Significant unmet need	Yes	Yes
Hepatology	No	Significant unmet need	Yes	Yes
Nephrology	No	Small patient population Significant unmet need	Yes	Yes
Oncology	No	Pediatrics: Nil Adults: small population	Yes	No
Oncology	Yes	Small patient population. Significant unmet need	Yes	No
Oncology	No	Small patient population. Significant unmet need	Yes	Yes
Oncology	No	Significant unmet need	Yes	No
Oncology	Yes	Small patient population. Significant unmet need	Yes	No
Immunology	No	Nil	Yes	No
Hepatology	No	Nil	Yes	No
Hepatology	No	Nil	Yes	No
Hepatology	No	Nil	Yes	No
Oncology	Yes	Significant unmet need	Yes	No
Oncology	Yes	Significant unmet need	Yes	No
Oncology	Yes	Significant unmet need	Yes	Yes

4.2. Implications

To combat significant uncertainty associated with approving technologies based on non-RCT data alone, novel risk sharing approaches are needed. For example, NICE, NHS England, and the UK Department of Health have launched a new Cancer Drugs Fund, which fund oncology medications while further data are collected. For drugs recommended within the Cancer Drugs Fund, a managed access agreement is agreed with both a data

Table 3. NICE committee recommendations

NICE decision outcomes	Non-RCT–based technologies	RCT-based technologies
Decision outcome		
Recommended	10/22 (45%)	289/467 (62%)
Not recommended	3/22 (14%)	81/467 (17%)
Optimized	9/22 (41%)	91/467 (19%)
Only in research	0/22 (0%)	6/467 (1%)
Patient access scheme		
Patient access scheme	7/22 (32%)	111/467 (24%)

Abbreviation: RCT, randomized controlled trial.

collection and a commercial agreement [24]. Similar initiatives to address clinical uncertainty are also being considered for nononcology medications. Furthermore, the ADAPT SMART project has begun to explore how adaptive pathways and performance-based managed access schemes could be used [25].

Although only a small number of pharmaceutical technologies were appraised on the basis of non-RCT data during our study period, the majority were in the last few years. Recent research has shown that larger effect sizes in noncontrolled studies are associated with higher rates of EMA licensing approval [7]. Although this offers useful insight, clear criteria are needed to specify the circumstances in which noncontrolled trials are appropriate. Currently, the uncertainty in guidance represents a significant challenge for the pharmaceutical industry, regulatory authorities, and HTA organizations. A collaborative technical advisory group involving both regulatory authorities such as the EMA and HTA organizations could begin efforts toward outlining guidance for a more consistent approach to both assessing the suitability of non-RCT data in evidence submissions and accruing further evidence over time.

4.3. Limitations

This study has a number of limitations. First, although our review comprehensively captures NICE appraisals of technologies that received EMA approvals without RCT data, we may have missed technologies from 2000 to 2009 if NICE considered the comparator arm of some trials to be irrelevant for the decision scope during this period. Second, while one researcher was involved in screening the appraisals extracting data from technology appraisals and associated documents, a senior member of the research team verified the sample. Third, our sample size was small, as technologies appraised on the basis of RCT data constitute the majority of NICE appraisals. However, half of the technologies without RCT data in our sample were appraised in the last 2 years.

5. Conclusion

From 2000 to 2016, 22 technologies were appraised by NICE based on non-RCT data. The methods used to calculate comparative efficacy estimates in the absence of comparative trials varied. Although regression methods can decrease the uncertainty associated with the evidence base of these technologies, this relies on the availability of individual patient-level data for any external control selected. Only a minority of the technologies appraised on the basis of non-RCT data received a negative recommendation.

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References

[1] Bärnighausen T, Røttingen J-A, Rockers P, Shemilt I, Tugwell P. Quasi-experimental study designs series—paper 1: introduction: two historical lineages. J Clin Epidemiol 2017;89:4–11.
[2] Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-based medicine working group. JAMA 1995;274:1800–4.
[3] Akobeng A. Understanding randomised controlled trials. Arch Dis Child 2005;90:840–4.
[4] National Institute of Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Available at https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed October 5, 2018.
5] Clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial. BMJ 2000;321:756–8.
[6] Sharma MR, Schilsky RL. Role of randomized phase III trials in an era of effective targeted therapies. Nat Rev Clin Oncol 2011;9(4):208–14.
[7] Ioannidis JP, Khoury MJ. Are randomized trials obsolete or more important than ever in the genomic era? Genome Med 2013;5(4):32.
[8] Djulbegovic B, Glasziou P, Klocksieben FA, Reljic T, VanDenBergh M, Mhaskar R, et al. Larger effect sizes in nonrandomized studies are associated with higher rates of EMA licensing approval. J Clin Epidemiol 2018;98:24–32.
[9] Halpern SD, Karlawish JHT, Berlin JA. The continuing unethical conduct of underpowered clinical trials. JAMA 2002;288:358–62.
[10] Hatswell AJ, Baio G, Berlin JA, Irs A, Freemantle N. Regulatory approval of pharmaceuticals without a randomised controlled study:

analysis of EMA and FDA approvals 1999−2014. BMJ Open 2016; 6(6):e011666.

[11] Woolacott N, Corbett M, Jones-Diette J, Hodgson R. Methodological challenges for the evaluation of clinical effectiveness in the context of accelerated regulatory approval: an overview. J Clin Epidemiol 2017; 90:108−18.

[12] Wallerstedt SM, Henriksson M. Balancing early access with uncertainties in evidence for drugs authorized by prospective case series - systematic review of reimbursement decisions. Br J Clin Pharmacol 2018;84(6):1146−55.

[13] Xenakis A, Beckerman R. Strategies to overcome hurdles in HTA appraisals amid limitations resulting from single-arm trial data. Value Health 2014;17(7):A729.

[14] Faria R, Hernandez Alava M, Manca A, Wailoo AJ. NICE DSU technical support document 17: The use of observational data to inform estimates of Treatment effectiveness in technology appraisal: methods for comparative individual patient data. Available at http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD17-DSU-Observational-data-FINAL.pdf;. Accessed October 5, 2018.

15] Hatswell AJ, Freemantle N, Baio G. Economic evaluations of pharmaceuticals granted a marketing authorisation without the results of randomised trials: a systematic review and taxonomy. Pharmacoeconomics 2017;35:163−76.

[16] Technology appraisal committee. NICE. Available at https://www.nice.org.uk/get-involved/meetings-in-public/technology-appraisal-committee. Accessed October 5, 2018.

17] NICE. Managed access agreement osimertinib for treating metastatic EGFR and T790M mutation-positive non-small-cell lung cancer. Available at https://www.nice.org.uk/guidance/ta416/documents/committee-papers-3;. Accessed October 5, 2018.

18] Naci H. What to do (or not to do) when randomization is not possible. J Heart Lung Transplant 2017;36(11):1174−7.

[19] Dakin H, Devlin N, Feng Y, Rice N, O'Neill P, Parkin D. The influence of cost-effectiveness and other factors on nice decisions. Health Econ 2015;24:1256−71.

[20] Rawlins M, Barnett D, Stevens A. Pharmacoeconomics: NICE's approach to decision-making. Br J Clin Pharmacol 2010;70(3):346−9.

[21] European Medicines Agency (EMA). Conditional marketing authorisation report on ten years of experience at the European medicines agency 2017. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/01/WC500219991.pdf. Accessed October 5, 2018.

22] Claxton K, Palmer S, Longworth L, Bojke L, Griffin S, Soares M, et al. A comprehensive algorithm for approval of health technologies with, without, or only in research: the key principles for informing coverage decisions. Value Health 2016;19(6):885−91.

[23] Neumann PJ, Chambers JD, Simon F, Meckley LM. Risk-sharing arrangements that link payment for drugs to health outcomes are proving hard to implement. Health Aff (Milwood) 2011;30(12): 2329−37.

[24] National Institute of Health and Care Excellence (NICE). Cancer drugs fund. Available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund. Accessed October 5, 2018.

25] Adaptsmart|adaptsmart. Available at https://www.infographic.adaptsmart.eu/. Accessed October 5, 2018.