Uncovering the Blind Spot: A Targeted Search of Placebo Effect Adjustments in Submissions to the National Institute for Health and Care Excellence

EE692

Anathea Cristea,[1] Anna Grootendorst,[1] Nils-Peter Ipland,[2] Jamshaed Siddiqui[3]

[1] NHTA Sweden AB, Stockholm, Sweden; [2]Jazz Pharmaceuticals, Denmark ApS, Copenhagen, Denmark; [3]Jazz Pharmaceuticals, UK Ltd., London, UK.

Introduction

- Placebo effects in clinical trials may occur for various reasons, including:
  1. The Hawthorne effect, where patients report better outcomes due to being observed within the setting of a clinical trial[1,2]
  2. Regression to the mean, where patients get better over time[3,4]
  3. The true placebo effect, which is the response to placebo if other non-specific effects are removed[5,6]
- Adjusting for placebo effects is a post-trial modification and may introduce structural uncertainty in economic models in the absence of clear guidance.
- Oftentimes in reimbursement applications globally, the National Institute for Health and Care Excellence (NICE) guidance is referenced and considered best-practice with regards to the technical aspects of health economic models.
- However, NICE has no methodological guidance on how to account for significant observed placebo effects within cost-effectiveness analyses, making it a blind spot in the development of economic models that are fit-for-purpose.

Objective

- This study aimed to identify which placebo effect adjustment methods have been used in previous NICE submissions to determine potential best practices.

Methods

- A targeted search of the NICE website was conducted using the terms: 'placebo effect adjustment', 'Hawthorne effect', and 'true placebo'. There was no date restriction applied to the search. Company method, NICE committee preferred method, and External Assessment Group (EAG) comments were subsequently collected with the aim of identifying best practices.
- Submission documents were screened for any mention of placebo effect adjustments.
- The disease area, NICE recommendation, inclusion of placebo effect adjustments in the base case, and submission dates were collected to assess trends and frequency.
- The different implementations of the placebo effect were analysed to assess whether any best practice could be identified.

Theoretical framework

Hawthorne effect: Effect occurring when participants change their behaviour simply because they know they are being observed. This can lead to inaccurate observations of efficacy in both the treatment and comparator arms, as any changes may be due to increased attention rather than the treatment itself.[1,2]

Regression to the mean: Statistical phenomenon occurring when patients with extreme baseline measurements show improvement or deterioration towards an average disease state on subsequent observations, that is unrelated to treatment. In the context of placebo effects, this can mislead the perceived effectiveness of a treatment if not properly accounted for.[3,4]

True placebo effect: The psychological and physiological responses triggered by receiving a placebo. Patients' expectations and beliefs about the treatment can activate neurobiological mechanisms, leading to real health improvements despite the absence of an active therapeutic agent.[5,6]

Results

Figure 1. Flow diagram of search results

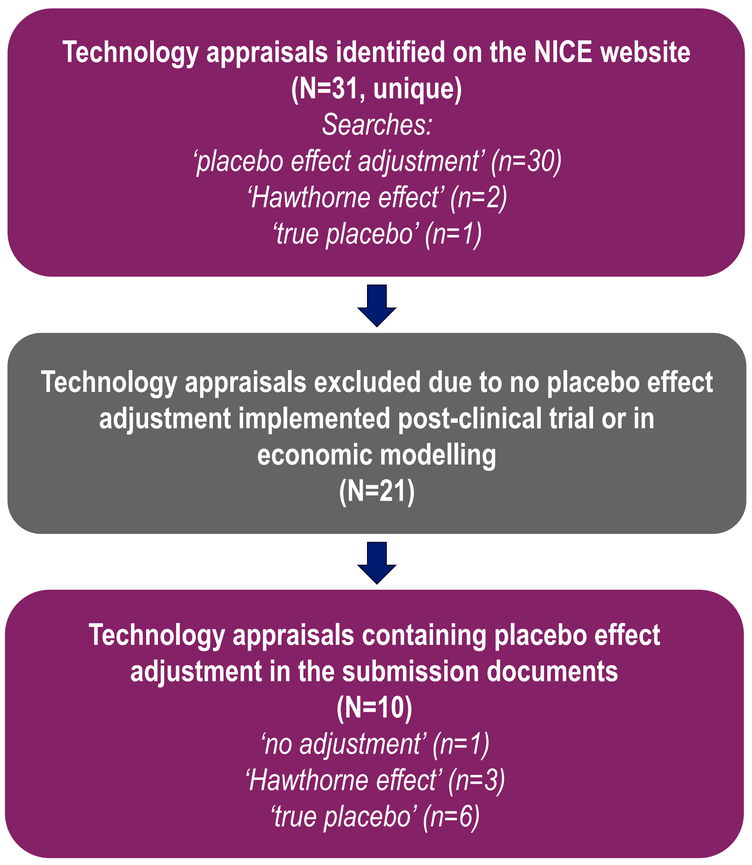


Figure 2. Technology appraisals with placebo effect adjustments grouped by indication

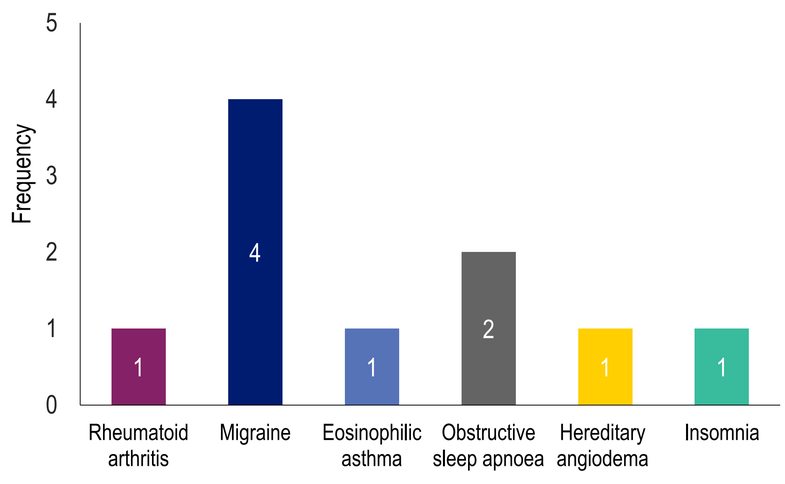


Figure 3. Inclusion of placebo effect adjustment mention in cost-effectiveness analyses

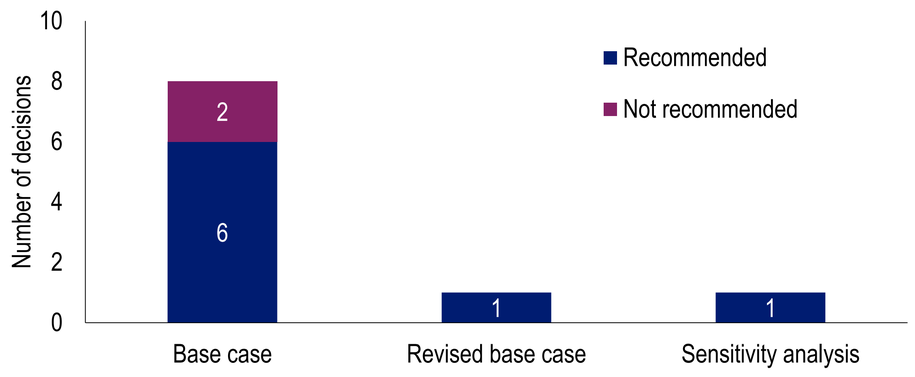


Figure 4. Method of placebo effect adjustment and NICE recommendation

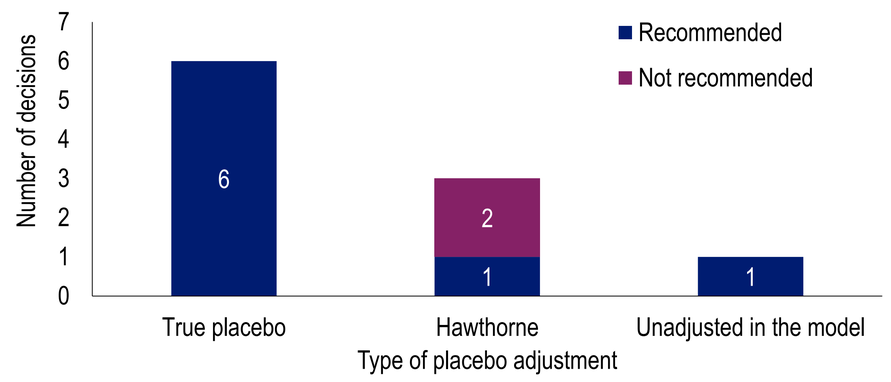
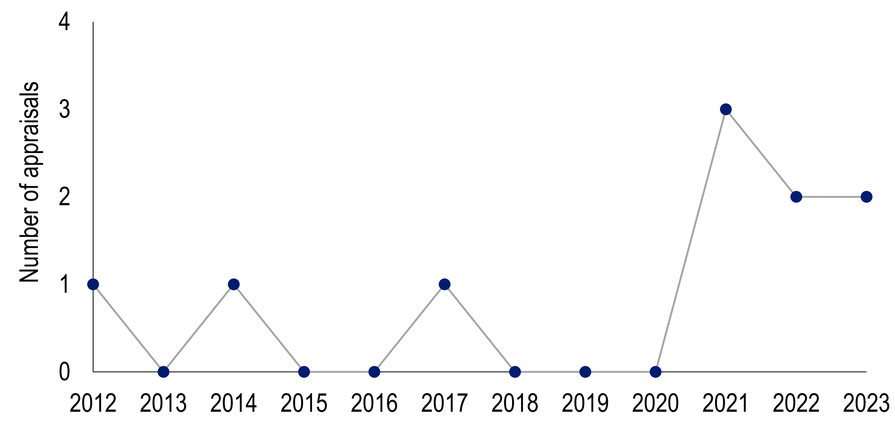


Figure 5. Technology appraisals with placebo effect adjustments over time



- Searches yielded a total of 31 unique results: 30 for 'placebo effect adjustment'; two for 'Hawthorne effect' (both also within the first search); one for 'true placebo' (**Figure 1**).
- Following full-text screening, ten of the appraisals across varying indications (**Figure 2**) contained mentions of placebo effect adjustment in their cost-effectiveness analyses (**Figure 3**).
- True placebo effect adjustment and Hawthorne effect were considered in six and three final appraisal documents, respectively (**Figure 4**).
- One appraisal had no adjustment for placebo effect implemented in the model, this adjustment was instead applied to the clinical data (**Figure 4**).
- In the NICE submission documents reviewed, the EAG frequently observed that there was no standardised approach for incorporating placebo effect adjustments into health economic models. This led to a process that required several, extensive rounds of comments from all parties involved.
- The impact of placebo effect adjustments on the incremental cost-effectiveness ratio (ICER) was found to be inconsistent; in some cases, it reduced the ICER (n=3), while in others, it increased it (n=3); others did not report the effect (n=4).
- **Figure 5** illustrates the distribution over time of submissions that include adjustments for placebo effects. Due to a limited number of relevant submissions, it is difficult to identify any clear trend from the data.

Conclusions

- Here we show that a variety of placebo effect adjustment methods have been used in cost-effectiveness analyses within NICE submissions. There does not appear to be a consensus by NICE nor the EAG for one method over another.
  - This variability highlights the absence of a clear mechanism to predict the direction and magnitude of the placebo effect's influence on cost-effectiveness outcomes
  - Despite ongoing research for more than a decade, there is still a lack of guidance on adjusting for placebo effects
  - This lack of standardisation and the inherent uncertainty in adjusting for placebo effects may have led to recommendations being made, despite potential inaccuracies in the placebo adjustments within the models
- Further work is needed to determine if best practice can be established.
- In the meantime, marketing authorisation holders and health technology appraisal agencies should continue to align on the most appropriate method on a case-by-case basis.

References: 1. McCambridge J, et al. *J Clin Epidemiol.* 2014;67(3):267–277. **2.** Davis SA, Feldman SR. *JAMA Dermatol.* 2013;149(4):490–491. **3.** Adrian G Barnett, et al. *Int J Epidemiol.* 2005;34(1):215–220. **4.** Linden, A. *BMC Med Res Methodol.* 2013;13:119. **5.** Hafliðadóttir SH, et al. *Trials*. 2021;22(1):493. **6.** Benedetti F, et al. *Neuropsychopharmacology*. 2011;36(1):339–354.

Acknowledgements: Editorial assistance was provided to the authors by Syneos Health, UK, and funded by Jazz Pharmaceuticals, Inc.
Support: This study was sponsored by Jazz Pharmaceuticals, Inc.
Disclosures: All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. **AC** and **AG** have consulted for, conducted a study funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc.; **JS** is an employee of Jazz Pharmaceuticals, UK Ltd., **NP** is an employee of Jazz Pharmaceuticals, Denmark Aps.

Scan this code to access this poster online. This code is not for promotional purposes.

The International Society for Pharmacoeconomics and Outcomes Research Europe Conference 2024; 17–20 November 2024; Barcelona, Spain