Dear Professor Tracey Wade,
Manuscript # IJED-17-0314

The Modelled Cost-Effectiveness of Family-Based and Adolescent-Focused Treatment for Anorexia Nervosa.

Thank you for allowing us to resubmit our manuscript for your consideration in light of the three reviewers' helpful comments below are details regarding how we have addressed each comment. The reviewers' comments appear in the left column and each comment is in the right column (with new text or changes to the manuscript in red text).

We appreciated the constructive comments made by the reviewers, and believe the manuscript is stronger for this.

Kind regards,

Long Le, on behalf of the study authors.

Comment from Reviewer 1	Addressed in the manuscript
<p>1. The aim of the current study was to evaluate the cost-effectiveness of family-based treatment (FBT) compared to adolescent focused individual therapy (AFT) or treatment as usual (TAU) within the Australian healthcare system. Authors found that the FBT is the best choice among treatment arms and AFT was not cost-effective compared to TAU. The manuscript is well written and the findings</p>	<p>We would like to thank the reviewers for their helpful comments. There is a lack of evidence to support the cost-effectiveness of treatment, we believe that our study, for the first time, provides a significant contribution to the literature as well as critical information to decision makers. For more detailed evaluation, it is critical to clearly define the comparison</p>

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version record](https://doi.org/10.1002/eat.22786). Please cite this article as [doi:10.1002/eat.22786](https://doi.org/10.1002/eat.22786).

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<p>are clearly presented, however I have many doubts that its findings might have important clinical implications on a global scale, since it deals with a specific topic in Australia. Hence it may be more suitable to publish this paper in a local journal.</p>	<p>study was conducted within Australia and its health care system, it is likely that this result is relevant to the cost of delivering the intervention in many other high income settings. This is because, as noted in the discussion, eating disorders are similar in distribution and determinants between countries, and the intervention pathway, intervention effect size and program training information is based on data from countries of similar high income settings (<i>line 5 - 8, page 14</i>).</p>
<p>2. The study is based on several assumptions often confirmed by only one study (i.e., lines 5-7 p. 7; line 6 p.9) or by no study (i.e., lines 6-8, p.9). Thus, we could hypothesize that with different assumptions the results could change. The evaluation of the cost-effectiveness of different interventions could be very useful if applied to a real RCT. For these reasons, the title and the discussion, should be moderated, and clearly refer to assumptions and no to real data. For example the first sentence of the discussion: “In the current study, FBT was shown</p>	<p>We agree with the reviewer that our study is based on several assumptions and with different assumptions, the results would be changed. This is a feature of ‘model based economic analyses’ and not unique to our study. However we must also stress that when assumptions were required, which was not always the case, we tried to use plausible assumptions which would not bias towards the intervention. The model was built on actual evidence of efficacy (so this was not an assumption but evidence from a RCT). However we</p>

to be more effective at a cheaper cost than either AFT or TAU” is correct if applied to an RCT.

did have to employ some assumptions with respect to costing the intervention and potential cost-offsets in particular. As per good modelling guidelines (e.g. Briggs, A., Sculpher, and Buxton (1994) or Briggs, A. H. et al. (2012)), we did include two approaches to test the robustness of the results (as described in method section, *line 6, page 9 to line 5, page 10*). The first approach is known as “uncertainty analysis” which was conducted by using Monte Carlo simulation. We ran the model 5000 times in which, each time the model was re-run, the input parameters’ values were randomly chosen from range of values of the parameter (or 95% uncertainty interval of the parameter’s value). This process produced 5000 iterations of the incremental cost-effectiveness ratio (ICER). The proportion of iterations of ICER under the willingness-to-pay threshold indicates the probability of the intervention to be cost-effective. The second approach was via a series of sensitivity analyses in which each time we re-ran the model, one input parameter was changed to test whether

the conclusion of the study changed. For example, for testing the proportion of people receiving the intervention, we first re-ran the model at 0% receiving the intervention, then re-ran the model with 90% receiving the intervention. As stated above, the majority of assumptions were based on the review of the literature, in addition to the clinical expert opinions (study authors PH, SS and EH). Some assumptions might be based on limited supporting evidence such as one study or the expert opinions. Having said that, to address this limitation, all assumptions were tested in the uncertainty and sensitivity analyses. More generally, limitations associated with the model assumptions is a known characteristic of modelled economic evaluations, which we have noted in the discussion (*line 9, page 14 to line 6, page 15*).

However, to be clearer to readers that this study is a modelled economic evaluation, we have now add the word “modelled” in the title as “The **Modelled** Cost-Effectiveness of Family-Based and

	Adolescent-Focused Treatment for Anorexia Nervosa”
3. The method section is too long, and the authors are invited to shorten.	We have condensed the method section as suggested by reviewer. In particular, we have now transferred much of the details of the sensitivity analyses into Table 3 and some redundant sentences have been removed.
4. The tables are dispersive, moreover the quality of figures are poor	We have revised the table to meet the Journal’s criteria but the information contained in the tables has been retained within the manuscript. This is because according to the Guidelines for reporting an economic evaluation, all assumptions, value of input parameters and details of sensitivity analysis need to be presented clearly (Husereau et al., 2013). In our study, this information was presented in Table 1, Table 2 and Table 3, respectively. Table 4 represent the overall result of primary and secondary analysis. We have also now increased the quality of figures as suggested by reviewer. We have re-drawn Figure 2 to make it more precise and eliminated Figure 3 to prevent the duplication with the literature.

Comment from reviewer 2	Addressed in the manuscript
<p>The study compared the cost effectiveness of FBT to AFT and TAU in the Australian healthcare system, finding that FBT is less costly than the other treatments.</p> <p>1. Pg. 3: “Included within the evaluation were family therapies that utilized the FBT manual, as well as those that adhered to the same core principles (i.e., Maudsley family therapy or behavioural family system therapy).” It seems, based on the cited reference, that Maudsley family therapy in this context refers to multiple family day therapy. This form of treatment does adhere to some of the same core principles as FBT but differs in some significant ways. For example, the authors state that for FBT “the intervention is delivered by a psychologist in a face-to-face format, with 24 sessions of 60 minutes” but this is not true for the Eisler multiple family day therapy. In addition, the evidence base for it is less robust than for manualized</p>	<p>We agree with the reviewer that there are differences across family-based therapy although they adhere to similar core principles. It is for this reason that we refer to the intervention as family-based ‘treatment’ rather than ‘therapy’. We also agree with the reviewer regarding including analyses that look at just manualized FBT compared to AFT and TAU (or no intervention in the revised version). In fact, we did just that in the sensitivity analysis – scenarios 8, in which we excluded Eisler’s study of multiple family day therapy and just included two studies (Lock et al., 2010; Robin et al., 1999) of manualized FBT. Reassuringly, in this sensitivity analysis the conclusion of the cost-effectiveness of FBT was not changed.</p>

FBT. Is it possible to include analyses looking at just manualized FBT compared to AFT and TAU, as well as the analyses currently included in the paper?	
2. Pg. 4, description of AFT: “Parents are required to attend together with adolescents in 8 sessions.” Parents actually attend these sessions alone without the adolescent.	Thank you for detecting this. We have now replaced ‘together’ with ‘separately’. <i>(line 1, page 5)</i>
3. Pg. 5: What was the rationale for including patients up to age 20? FBT looks somewhat different for young adults who are not living with their parents. Were all patients living with parents?	Thank you for pointing out an important issue. We included patients up to age 20 because it was the age range reported in the study from Robin et al. 1999. However, we agree with reviewer, and also from this study, that only young adults who are living with their parents are eligible. Therefore, in the revised version, we now include only patients aged 11 to 18, and have excluded those aged over 18 to ensure the correct target population for FBT.
4. Pg. 5: “We made the assumption that 90% of adolescents diagnosed with AN have a duration of less than 3 years...” The cited study states that the peak age of onset is 19-20 for AN, although other	We agree with the reviewer about this point. We now use the lower assumption of 71% of adolescents diagnosed with AN who have a duration of less than 3 years that is based on the mean proportion

<p>studies have found that the average age of onset is closer to 12 (Swanson et al., 2011). Either way, given that the sample includes patients between the ages of 11 and 20, it is somewhat unclear why the assumption would be made that 90% of patients in the sample would have a duration of illness of less than 3 years?</p>	<p>retrieved from two studies (Morgan, Purgold, & Welbourne, 1983; Morgan & Russell, 1975). In addition, this assumption was tested in the sensitivity analysis where the proportion varied from 50% to 100%. <i>(line 10-11, page 5)</i></p>
<p>5. Table 1: Why was there supervision for only the parent sessions of AFT?</p>	<p>Thank you for detecting this typo error that has now been corrected.</p>
<p>6. Overall this is a worthwhile study to conduct, but it is somewhat difficult to understand. Could the authors describe some of the terms and findings in more layperson-friendly language?</p>	<p>We appreciate that there is a fair bit of necessary technical language in this paper. We have now provided further information in the method to explain the disability-adjusted life year outcome, the incremental cost-effectiveness ratio and how to interpret the result in more accessible language.</p> <p>“DALY is a measure reflecting burden of disease that captures the impact of premature deaths and years of healthy life lost due to ill-health or disability (Vos et al. 2015). In the other words, total DALYs averted were estimated as the difference between total DALYs within</p>

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	<p>each arm, which accounts for the years of life lived with a disability (YLDs) and number of life years lived via a reduction in excess deaths attributable to AN. To calculate the prevalent YLD, the prevalence rate was multiplied by the most recent Global Burden of Disease (GBD) disability weight (Salomon et al., 2015).” (<i>Line 4-8, Page 3</i>)</p> <p>“Results of this study were presented as incremental cost-effectiveness ratios (ICERs) which are calculated as the difference in total costs between alternative interventions divided by the difference in DALYs averted. In the other words, the ICER refers to the cost to generate an additional averted DALY by the intervention relative to the comparator. In order to determine whether the ICER is acceptable, it is compared to a cost-effectiveness willingness-to-pay threshold that represents the highest acceptable cost per additional averted DALY. This study used a cost-effectiveness willingness-to-pay threshold of AU\$50,000 per DALY averted which has been used in</p>
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	previous Australian economic evaluation studies (Carter et al., 2008; Vos et al., 2010).” (<i>Line 23-25, page 3 to line 1-7, Page 4</i>)
Comment from reviewer 3	
<p>This paper presents the results of a rather extensive modeling study of the cost-effectiveness of family-based treatment, adolescent-focused individual therapy, and essentially no treatment, which the authors refer to as “treatment as usual.” The results of the paper, in brief, argue fairly convincingly for the cost-effectiveness of FBT in particular.</p> <p>This is, in general, a very well-written and clear paper that was a pleasure to read. To the authors’ credit, they have followed closely current reporting guidelines for cost-effectiveness trials in the medical literature. In addition, they have made decisions about a wide variety of sensitivity analyses which are generally well supported (although, see a few notes below). Furthermore, appropriate measures for</p>	<p>Thank you for your favourable comments about the contribution of our manuscript.</p>

assessing error variance are used.	
1. I have several relatively minor, technical points for the authors to consider or review. First, on page 2, in the Abstract the conclusion is, “FBT is the best choice among treatment arms.” I would like the authors to consider rewording the term “best choice.” Perhaps this should be “most cost-effective?”	We agree with the reviewer and have now replaced the term ‘best choice’ with ‘ most cost-effective ’ in the abstract.
2. Second, the Introduction references an Agras, at al. analysis that “suggested that the average treatment cost per individual was US \$10,000 less than systemic family therapy.” I would carefully review that to make sure that that was a total of \$10,000 less for every single treated participant, as opposed to per successfully treated participant. Perhaps the reference is correct as provided, but it seems a large difference.	We have carefully reviewed this article, which reported “the mean treatment costs per individual (family therapy plus hospitalizations until the EOT) was \$8963 for FBT and \$18,005 for SyFT”. We have now revised the sentence as: “suggested that the average treatment cost of FBT plus hospitalisation at the end of treatment per individual was US\$10,000 less than systemic family therapy” (line 5-6, page 2)
3. Third, the treatment as usual model that they’ve used is, I think, a little bit questionable. It is really essentially no treatment at all, and the authors should consider at least two things. First, perhaps	We agree with the reviewer about this point and have replaced the term “treatment-as-usual” with the term “no intervention” to reflect the true comparator. As a result, we also eliminated a single, 40-

<p>sensitivity analysis could try to examine something that would replicate less sophisticated and less thorough treatment? Second, at a bare minimum, it seems unlikely to me that a primary care provider or GP would see a person with anorexia nervosa for a single, 40-minute visit, ever. If nothing else, this does not afford much of an opportunity to trigger hospitalization, which is assumed in the model. This perhaps could either be changed for the base case, or handled in sensitivity analyses.</p>	<p>minute visit cost out of this comparator but kept hospitalisation costs in this group as the cost-offsets. This assumption was tested in the sensitivity analysis where the hospitalisation costs were excluded.</p>
<p>4. A decision was made to include training costs for FBT and AFT in every case. Do the authors really anticipate a model where, every time that someone receives FBT or AFT, training is undertaken? That is, do they assume that in every case there would be a new and inexperienced therapist? This seems unlikely. I like the inclusion of supervision time, but I question the training time decision.</p>	<p>We agree with the reviewer about this point. However, it is unclear how many therapists receive training for FBT or AFT. Given that, we applied the ‘most conservative’ situation that all therapists required training. In fact, if the training costs are reduced, the impact of this is to make the intervention even more cost-effective.</p> <p>We have now added a short sentence in the discussion as follow:</p> <p>“...our study might overestimate that all therapists required training for FBT and AFT. However, if the training costs are reduced in the</p>

	real world (i.e. less therapists receiving intervention training), the impact of this would be to make the intervention even more cost-effective” (Line 21-24, page 14)
5. The model is done from a health care system perspective and I think that’s appropriate, but it also includes a limited societal perspective in that parent travel costs are included. I would argue that it does give this a partial societal perspective, and later in the discussion the authors note both the difficulties and the desirability of doing a real societal perspective analysis, but even here their comments which would support the idea that they have taken a slightly societal perspective. This could be changed or it simply could be acknowledged.	We agree with the reviewer and have now revised the discussion as: ‘Firstly, only health-sector related costs were included in the primary evaluation. Given that there is insufficient evidence to model any incremental differences relating to productivity impacts between the different interventions, the partial societal perspective that included parents’ time and travel costs was examined in the secondary analysis. It was noteworthy that including productivity costs (should there be any such impacts) is likely to make the active interventions even more cost-effective.’ (line 12-13, page 14)
6. It appears that a single YLD value was assumed, but this should be made a little bit clearer.	We agree with the reviewer and have now revised the sentence as: ‘Through the model, total DALYs averted were estimated as the difference between total DALYs within each arm, which account for the years of life lived with a disability (YLDs) and number of life

	<p>years lived <i>via</i> a reduction in excess deaths attributable to AN. To calculate the prevalent YLDs, the prevalence rate was multiplied by the most recent GBD disability weight (Salomon et al., 2015).’ (line 6-8, page 3)</p>
<p>7. Finally, a decision was made to exclude psychiatry and medication costs. This could be argued either way, I think. My read of the literature with regard to medication is that there’s really not much evidence of benefit for pharmacologic treatment of anorexia nervosa at the moment, but it is frequently undertaken; but if the authors were conducting an observational study using “real” data in AN treatment, they undoubtedly would encounter both psychiatry visits and medication costs. I think it’s OK to proceed as they do here (since they are largely confining themselves to treatments which have been shown to be beneficial, and that doesn’t describe medications in AN very well) but this decision should be addressed in the Discussion.</p>	<p>We agree with the reviewer and have now included the following discussion point: ‘Finally, as with similar simulation models, the current model used many assumptions that might limit conclusions. For example, although this study took into account the additional health services of GPs during the treatment phase, other costs associated with psychiatrist visits and/or medication usage were not captured in the model. However, including medication costs is unlikely to change the conclusion of this study given that these costs accounted for a very small proportion (e.g. 3%) of total treatment costs for AN (Lock et al., 2008). Future effectiveness studies that include an economic dimension are needed to more accurately determine an estimation of cost-effectiveness in the treatment of AN.’</p>

	(line 24-25, page 14; line 1-6, page 15)
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The Cost-Effectiveness of Family-based and Adolescent-Focused Treatment for Anorexia Nervosa

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TITLE: The Modelled Cost-Effectiveness of Family-Based and Adolescent-Focused Treatment for Anorexia Nervosa

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Abstract

Background: Anorexia Nervosa (AN) is a prevalent, serious mental disorder. We aimed to evaluate the cost-effectiveness of family-based treatment (FBT) compared to adolescent-focused individual therapy (AFT) or no intervention within the Australian healthcare system.

Method: A Markov model was developed to estimate the cost and disability-adjusted life-year (DALY) averted of FBT relative to comparators over six years from the health system perspective. The target population was 11-18 year olds with AN of relatively short duration. Uncertainty and sensitivity analyses were conducted to test model assumptions. Results are reported as incremental cost-effectiveness ratios (ICER) in 2013 Australian dollars per DALY averted.

Results: FBT was less costly than AFT. Relative to no intervention, the mean ICER of FBT and AFT was \$5,089 (95% uncertainty interval (UI): dominant to \$16,659) and \$51,897 (\$21,591 to \$1,712,491) per DALY averted. FBT and AFT are 100% and 45% likely to be cost-effective, respectively, at a threshold of AUD\$50,000 per DALY averted. Sensitivity analyses indicated that excluding hospital costs led to increases in the ICERs but the conclusion of the study did not change.

Conclusion: FBT is the most cost-effective among treatment arms whereas AFT was not cost-effective compared to no intervention. Further research is required to verify this result.

Keywords: Health economics, Eating Disorder, Family-based therapy, Anorexia Nervosa, Adolescent-focused treatment.

Title: The Modelled Cost-Effectiveness of Family-Based and Adolescent-Focused Treatment for Anorexia Nervosa**INTRODUCTION**

Anorexia Nervosa (AN) is a serious mental disorder with substantial impairment in health-related-quality of life, medical morbidity and the highest mortality of any psychiatric disorder (Arcelus, Mitchell, Wales, & Nielsen, 2011; Jenkins, Hoste, Meyer, & Blissett, 2011; Zipfel, Giel, Bulik, Hay, & Schmidt, 2015). In comparison to other types of eating disorders (EDs), patients with AN have significantly elevated healthcare utilization and higher healthcare costs (Ágh et al., 2016), primarily due to the extent that individuals with AN require hospitalization (Agras et al., 2014; Madden et al., 2015; Striegel-Moore, Leslie, Petrill, Garvin, & Rosenheck, 2000).

Family-based treatment (FBT) is the most evidence-based treatment for adolescents with AN (Watson & Bulik, 2013) supported by national treatment guidelines in the USA, UK and Australia (Hay et al., 2014; Watson & Bulik, 2013). The most recent meta-analysis found that FBT was superior to individual treatment in achieving remission at 6-12 month follow-up (Couturier, Kimber, & Szatmari, 2013), with individual treatment consisting of adolescent-focused treatment (AFT). Although FBT has been compared to other forms of family interventions (Agras et al., 2014; Eisler et al., 2000; Le Grange et al., 2016), and different durations of FBT have been compared (Lock, Agras, Bryson, & Kraemer, 2005), it is noteworthy that no significant differences in outcomes have been found. Importantly, there is limited evidence regarding direct head-to-head comparisons between other types or versions of FBT and individual treatment (Couturier et al., 2013).

Whether FBT or AFT is cost-effective when it is implemented at a population level is of relevance to decision-makers including health providers and their funders. To our knowledge, such information is rarely reported, although some studies have undertaken economic

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evaluations of psychotherapy for AN alongside clinical trials. In particular, a recent study from Agras et al. (2014) suggested that the average treatment cost of FBT plus hospitalisation at the end of treatment per individual was US\$10,000 less than systemic family therapy. Byford et al. (2007) demonstrated that specialist out-patient treatment was more effective and less costly than both psychiatric inpatient and treatment as usual (TAU) for AN treatment. However, both studies' results did not reach statistical significance.

The objective of the current study was to represent the modelled population cost-effectiveness analysis of FBT for adolescents with AN relative to individual treatment (in this case, AFT) or no intervention within the Australian healthcare system. This study aims to provide a comprehensive economic evaluation to address whether FBT provides value-for-money when implemented at the population level.

METHODS

The analytical methods used in the current study are based on a standardised technical methods developed as part of the Assessing Cost-Effectiveness approach that has been developed to help improve the comparability of cost-effectiveness of different interventions across different mental disorders in Australia (Carter et al., 2008; Mihalopoulos, Carter, Pirkis, & Vos, 2013; Whiteford, Harris, & Diminic, 2013). This study also adheres to the guidelines reported in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al., 2013). The main objective of this study was to evaluate the cost-effectiveness of different interventions that could be used to reduce the burden of mental disorders as measured by the most recent burden of disease studies (Whiteford, Ferrari, & Degenhardt, 2016). Thus, a cost-utility analysis framework was used, expressing outcomes as disability-adjusted life-years (DALYs). DALY is a measure reflecting burden of disease that captures the impact of premature deaths and years of healthy life lost due to ill-health or

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disability (Vos et al., 2015). In the other words, total DALYs averted were estimated as the difference between total DALYs within each arm, which accounts for the years of life lived with a disability (YLDs) and number of life years lived via a reduction in excess deaths attributable to AN. To calculate the prevalent YLD, the prevalence rate was multiplied by the most recent Global Burden of Disease (GBD) disability weight (Salomon et al., 2015).

● This study adopted the perspective of the health system, and included costs and benefits accruing to individual patients, health care providers and third-party payers. Productivity costs (i.e., costs of decreased productivity at the workplace) were excluded since they fall beyond the health system and there is also limited evidence regarding how these costs are incurred by patients and families of adolescents with AN. The costs of unrelated diseases resulting from increased life expectancy were also excluded. Parents' time and travel costs to attend treatment sessions were excluded in the base case but reported as a secondary analysis. In order to adjust the time preference for the costs and benefits of a decision, by providing present value, all costs and benefits were discounted at 3% per annum, as recommended by Husereau et al. (2013). All costs were measured in Australian dollars and expressed in 2013 dollar values using published health price deflators from the Australian Institute of Health and Welfare (AIHW) when appropriate (Australian Institute of Health and Welfare, 2015).

Results of this study were presented as incremental cost-effectiveness ratios (ICERs) which are calculated as the difference in total costs between alternative interventions divided by the difference in DALYs averted. In the other words, the ICER refers to the cost to generate an additional averted DALY by the intervention relative to the comparator. In order to determine whether the ICER is acceptable, it is compared to a cost-effectiveness willingness-to-pay threshold that represents the highest acceptable cost per additional averted DALY. This study used a cost-effectiveness willingness-to-pay threshold of AU\$50,000 per DALY averted

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which has been used in previous Australian economic evaluation studies (Carter et al., 2008; Vos et al., 2010).

Intervention descriptions

FBT was chosen for this economic evaluation given the strongest evidence of efficacy and effectiveness for adolescents with AN (Couturier et al., 2013). Included within the evaluation were family therapies that utilised the FBT manual (Lock & Le Grange, 2013), as well as those that adhered to the same core principles (i.e., Maudsley family therapy (Eisler, 2005) or behavioural family system therapy (Robin et al., 1999)). Hereafter these are collectively referred to as FBT. In brief, the intervention promotes parental control of weight restoration while enhancing family functioning as it relates to adolescent development (Lock et al., 2010). The intervention is delivered by a psychologist in a face-to-face format, with 24 sessions of 60 minutes (Lock et al., 2010; Russell, Szmukler, Dare, & Eisler, 1987). Parents are required to attend all sessions together with their adolescent.

AFT is the most frequently comparator to FBT in the literature. Briefly, this is a psychodynamically informed individual psychotherapy focusing on enhancing autonomy, self-efficacy, individuation, and assertiveness while also including collateral parent meetings to support individual treatment (Lock et al., 2010; Robin et al., 1999; Russell et al., 1987). In this study, AFT included individual therapies that followed the same core principles, referred to as ego-orientated individual therapy (Robin et al., 1999). Similar to FBT, this intervention is also delivered by a psychologist, in a face-to-face format but with 32 sessions of 45 minutes. Parents are required to attend separately with adolescents in 8 sessions (Lock et al., 2010).

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Another comparator arm included in this study was no intervention. We defined no intervention as adolescents with AN who did not receive any treatment except hospitalisation if needed.

Eligible population for the intervention.

The target population for the interventions in the model was the 2013 Australian population of adolescents aged 11 to 18 years and diagnosed with AN. According to the literature, FBT is most effective in adolescents with less than three-year duration of disease (Couturier et al., 2013). Approximately 71% of adolescents diagnosed with AN were assumed to meet this criteria. This proportion was sourced from the literature (Morgan, Purgold, & Welbourne, 1983; Morgan & Russell, 1975). Given that individuals with diagnosable ED have low levels of help seeking for an ED-specific treatment, 50% of those were assumed to receive the interventions (Hart, Granillo, Jorm, & Paxton, 2011; Kirk et al., 2017).

Outcome of interventions

We updated the most recent meta-analysis of FBT for AN treatment (Couturier et al., 2013). Although a number of RCTs related to FBT were found from 2010 (the cut-off year of the previous review), these were all trials which compared different types of FBT (Dimitropoulos, Farquhar, Freeman, Colton, & Olmsted, 2015; Le Grange et al., 2016), compared FBT to systemic family therapy (Agras et al., 2014) or different duration of inpatient stays prior to FBT (Madden et al., 2015). Therefore, only three trials from the previous meta-analysis were used to calculate the effect-size of efficacy of FBT versus AFT. Recovery was chosen for this economic evaluation since this study sought to model burden reduction which required health outcome data to be expressed as a change in the discrete number of prevalent AN cases. It is noteworthy that there is significant inconsistency in how recovery is defined across studies (Couturier & Lock, 2006; Lock, Couturier, & Agras, 2008). Effect sizes for this outcome (expressed as a relative risk) for FBT vs. AFT were calculated

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post-treatment and at one-year follow-up using available data. Given the lack of intervention effect size beyond one-year follow up, it was assumed that intervention effects are reduced by 50% annually for the next 4 years (Mihalopoulos, Vos, Pirkis, & Carter, 2011). After that, the efficacy of FBT was assumed to be equal to AFT. This assumption was tested in the sensitivity analysis in which the decay rate was varied.

● Costing Analysis

In the base case, the interventions were assumed to operate in a “steady state”, meaning that trained staff and the necessary infrastructure are available to implement the interventions (Carter et al., 2005). However, the specific training costs for FBT and AFT were added to the intervention costs. The interventions’ costs also included the cost of Psychologist sessions (sourced from the Medicare Benefits Schedule (Australian Government Department of Health and Aging, 2013)) and Psychologist supervision. The time costs for psychologists to attend training and weekly supervision were sourced from Payscale 2015 (PayScale, 2015).

Costs of clinical investigations were included for both FBT and AFT interventions. Dual energy x-ray absorptiometry for bone density was assumed to be undertaken twice: at the beginning of treatment and one year later. Other routine investigation costs were assumed to be conducted at the beginning of treatment. We also included the cost of an initial GP visits to examine the adolescent and refer them to a psychologist as the first step towards specialist treatment, and assumed three GP visits (one 40-minute visit plus two 20-minute or less visits) for FBT or AFT. In addition to the specialist service, GP visits (at least 40 minutes per visit) were assumed to occur monthly during the treatment duration for active interventions.

Hospitalization costs were also included. The assumption that 36% of adolescents requiring hospitalisation in the treatment phase (early hospitalization), was made regardless of treatment arm (Lock et al., 2010; Madden et al., 2015). However, the length of stay was

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assumed to vary across treatment arms (Hughes et al., 2014). In particular, we assumed that each adolescent who received FBT had an average of 30 days hospitalization per year compared to 40 days per year for each adolescent who received AFT or no intervention. These data were retrieved from an Australian FBT implementation study which showed that the average annual bed days per person declined by 10 days when comparing two time points: 2 years prior to the introduction of FBT and 2 years after the introduction of FBT (Hughes et al., 2014). The hospitalization costs were estimated based on National Activity Based Funding (The Independent Hospital Pricing Authority, 2014) using Australian Refined Diagnosis Related Groups for EDs.

Parents' time and travel costs were also included in the current analysis. For FBT, we allocated one and a half hours of parent time to attend a psychologist visit with their child. For AFT, only one hour was allocated of the parent's time to attend a psychologist visit. Regardless of intervention type, parents were assumed to incur one-hour of travel. Travel costs were based on a standardised weighted average cost of a trip to a health professional, similar to that reported in other mental health economic evaluations (Lee et al., 2016; Vos et al., 2010).

The key assumptions that were made in costing the intervention pathway are detailed in Table 1.

[INSERT TABLE 1]

Modelling health outcomes

A decision-analytic multiple-cohort Markov model (known as illness-death model) was developed in Microsoft Excel to estimate the benefits and costs across the included interventions. A time horizon of 6 years was chosen as that was the length of follow-up in the studies evaluating the efficacy of FBT (Eisler et al., 1997; Eisler, Simic, Russell, & Dare,

2007). The revised DisMod-II model was used to simulate how a population cohort moves between three health states over time (being diagnosed with AN, recovered and dead) (Supplementary figure S1) (Barendregt, Van Oortmarssen, Vos, & Murray, 2003; Le et al., 2017). As there is limited evidence of individual heterogeneity of intervention outcomes, more complicated models (e.g. microsimulations) were considered unsuitable (Le et al., 2017). Transitions between health states were governed by remission rates, relapse rates and adjusted mortality rates.

Recovery for FBT was calculated from eight studies. Recovery for no intervention was calculated from five natural disease or controlled studies published from 2000 (i.e. this cut-off was selected since more recent studies would represent more recent disease epidemiology). The linear regression function in Excel was used to impute the remission values if these were not available from the literature. Recovery for AFT was calculated by dividing the recovery rates of FBT by the effect size of FBT vs. AFT as listed in Table 2. Further details are presented in Supplementary Tables S2 & S3.

Relapse rates were also retrieved from the literature. Given limited evidence about the relapse of AN in adolescents, the pooled relapse probabilities post-treatment (42%, 95% CI: 30% to 57%) and at one-year follow up (33%, 95% CI: 24% to 41%) were calculated from natural history of disease or controlled studies published from 2000 (see Supplementary Table S4). Relapse rates for the following year were assumed to be equal to relapse rates at one-year follow up.

Mortality rates were retrieved from the GBD 2013 study (Vos et al., 2015). These were adjusted by the standardized mortality ratio of 5.86 as reported in the previous meta-analysis of AN mortality rates (Arcelus et al., 2011).

Uncertainty and sensitivity analysis

In order to test the robustness of the results to the assumptions made in the analysis, a probabilistic multivariate uncertainty analysis was undertaken using Monte Carlo simulation. For the Monte Carlo simulation, probability distributions related to all input parameters (e.g. remission rates, relapse rates), disability weight and costs were incorporated into the analysis. The incremental costs and QALYs were estimated by re-running the model 5000 times, whereby each time a different draw was undertaken from the pre-specified distributions. Results of uncertainty simulations are presented on a cost-effectiveness plane that is a quadrant of cost differences plotted against benefit differences (Briggs, A., 1999) in which compass direction is used to indicate the area as north, south, east and west. The area above the horizontal axis (i.e. north west and north east) indicates that the intervention is more costly while the area to the right of the vertical axis (i.e. north east and south east) indicates that the intervention is more effective (than the comparator). The proportion of iterations of the ICER under the willingness-to-pay threshold of \$50,000 per DALY averted was deemed as the probability of the intervention being cost-effective. The details of the parameters that were varied within the uncertainty analysis are shown in Table 2.

[INSERT TABLE 2]

Further to multivariate probabilistic uncertainty analysis, a series of one-way sensitivity analyses were conducted to explore how different input parameters (e.g. hospitalization, and participant rates) impacted the analysis. Two-way sensitivity analyses were also conducted to test the impact of two parameters varying at the same time. These analyses included equivalent effect of AFT versus no intervention combined with population remission rates from GBD 2013 study or equivalent effect of AFT versus no intervention with decay rate on the results. (Further details of different sensitivity analyses are reported in Table 3)

[INSERT TABLE 3]

RESULTS

Table 4 contains a detailed breakdown of the baseline cost-effectiveness results. In the primary analysis in which patients’ time and travel costs were excluded, the largest total costs were \$13,383,861 (95% uncertainty interval (UI): \$11,225,374 to \$15,700,089) for AFT, followed by \$10,600,559 (95% UI: \$8,798,924 to \$12,527,236) for FBT and \$9,878,893 (95% UI: \$8,481,095 to \$11,293,603) for no intervention. In terms of DALYs averted, relative to no intervention, FBT and AFT accounted for 142 (95% UI: 74 to 225) and 65 (95% UI: 2 to 146) DALYs averted respectively. FBT averted 74 (95% UI: 26 to 130) DALYs compared to AFT.

[INSERT TABLE 4]

Base case analysis indicated that FBT was dominant (i.e. more effective and less costly) compared to AFT with none of the uncertainty iterations above the threshold of \$50,000 per DALY averted. As opposed to no intervention, FBT and AFT were more effective and more costly in both primary and secondary analysis. The ICER of FBT and AFT relative to no intervention were, respectively, \$5,089 (95% UI: dominant to \$16,659) and \$51,897 (95% UI: \$21,591 to \$1,712,491) per DALY averted. With a willingness-to-pay threshold of \$50,000 per DALY, FBT is 100% cost-effective whereas AFT had a 45% chance of being cost effective compared to no intervention. Figure 1 shows that the uncertainty iterations mainly fell in the north-east corner of the cost-effectiveness plane, which represents health gain at a cost for both active interventions in the primary analysis.

[INSERT FIGURE 1]

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In the secondary analysis, the inclusion of patients' time and travel costs did not change the conclusion of cost-effectiveness of FBT and AFT compared to no intervention (i.e. 99% uncertainty iteration of ICER fell well below threshold of \$50,000 per DALY averted) but led to AFT having lower probability (i.e. 21%) of being cost-effective (Table 3).

Sensitivity analyses

The results of the sensitivity analyses are presented in Figure 3. In brief, the sensitivity analyses demonstrated some changes in the ICER results, however, the overall conclusion still remained that FBT was a cost-effective choice when compared to AFT or no intervention and that AFT was not likely to be cost effective as opposed to no intervention when the willingness-to-pay threshold of \$50,000 per DALY averted was considered.

One-way sensitivity analyses found that the current evaluation was most sensitive to hospitalization costs (scenarios 1a, 1b or 1c). In scenario 1a, in which hospitalization costs were excluded or deemed similar across treatment arms, the ICER of FBT vs. no intervention increased to \$24,829 per DALY averted yet remained well below the willingness-to-pay threshold of \$50,000 per DALY averted. Similarly, the ICER of FBT vs. no intervention was increased to \$23,108 per DALY averted and half of uncertainty iteration fell below the threshold of \$50,000 per DALY averted when the differences in number of hospitalized days per year per person varied to one day. Other sensitivity analyses including similar effect on remission between AFT and no intervention (scenario 2), variation in time horizon (scenario 3), changes in the proportion of adolescents who were diagnosed with AN within three years (scenario 4), the proportion who agreed to receive the interventions (scenario 5), and use of an alternative method to predict remission rates (scenario 6) did not or only slightly altered the results of the ICER of FBT vs. no intervention (Figure 3). Similarly, changes in the decay rate of the effect size or estimated effect size after excluding the Russell et al. (Russell et al., 1987) study did not change the conclusion that FBT was less costly than AFT.

[INSERT FIGURE 2]

Two-way analysis indicated that the ICER of FBT versus no intervention was significantly increased to \$47,168 per DALY averted with 56% uncertainty iterations under the stated threshold willingness-to-pay in the worst case scenario 11, suggesting that FBT was still cost-effective (Fig. 2). In scenario 12 where FBT reduced hospitalisation rates but not length of hospital stay (sourced from Lock et al. 2010) compared to no intervention, the ICER was increased to \$17,669, with 99% of iterations of ICER falling below the threshold of \$50,000 per DALY averted. Other two-way analysis did not change the conclusion of the study.

DISCUSSION

In the current study, FBT was shown to be more effective at a lower cost than AFT. On the other hand, FBT and AFT was found to be more costly than no intervention and 100% and 41% of uncertainty iterations fell below the value-for-money threshold of \$50,000 per DALY, respectively. While this threshold is somewhat arbitrary, it appears to be an acceptable threshold for Australian decision-makers that has been used in a number of previous health economic evaluations, including mental health interventions (Carter et al., 2008; Le et al., 2017; Mihalopoulos et al., 2011). Importantly, the conclusion that FBT was cost-effective is robust in the sensitivity analyses, even with three worst case scenarios: (a) when the cost offsets (i.e., hospitalization costs) were excluded; (b) when people who did not receive intervention achieved similar recovery-rates to AFT, with or without a decay of the effect-size beyond the first year; and (c) when a short-term effect (i.e., 2-year time horizon) was adopted. Furthermore, regardless of the benefit of FBT on reduction of hospital rates or length of stay, the conclusion that FBT remained cost effective compared to AFT or no intervention remained. Compared to AFT, in only one scenario (excluding cost offsets), FBT

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had an ICER of \$31 per DALY averted or \$2,370 per DALY averted (when including time and travel costs); otherwise, FBT was the more effective and less costly choice.

Findings from the current study are difficult to compare with other economic evaluations for AN as to our knowledge, this is the first cost-effectiveness analysis of FBT relative to AFT or no intervention using a population-based model. Three economic evaluations have investigated the cost-effectiveness of psychotherapy for AN. Byford et al. (2007) used the Morgan-Russell Average Outcome Scale score as a primary outcome and found that specialised outpatient treatment for adolescents with AN (not limited to less than three-years duration) including individual CBT and parental counselling was more effective and less costly than inpatient treatment and TAU. Similarly, Egger et al. (2016) showed that outpatient psychotherapies for adults with AN, including focal psychodynamic therapy and enhanced CBT, were found to be less costly than optimised TAU in all outcomes examined (i.e., recovery, QALYs, BMI) from a societal economic perspective. It is noteworthy that both of these studies were economic evaluations conducted alongside clinical trials and that while the results supported the cost-effectiveness of the active interventions, the differences between groups on both costs and outcomes were not statistically significant. Another modelled evaluation from Crow and Nyman (2004) which examined adequate care (treatment approach involving inpatient weight restoration to close 100% of ideal body weight) compared to usual care, indicated that adequate care yielded an incremental cost of US\$30,180 per year of life saved. All things considered, our study compares favourably to other studies in terms of supporting the cost-effectiveness of psychotherapies for AN treatment.

This study has several strengths. First, we used plausible assumptions which were sourced from the latest available literature, augmented by expert opinion. This study also made an effort to design an intervention pathway which was as similar as possible to routine care.

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Using both uncertainty and (one-way and two-way) sensitivity analyses helped to ascertain which variables had the largest impact on the conclusions. Despite the Australian context, the methods and results of this study can be applied internationally. For instance, the intervention pathway, intervention effect size and program training information was based on data from high income settings such as the United States, Europe and Australia.

● However, this study also has some limitations. Firstly, only health-sector related costs were included in the primary evaluation. Given that there is insufficient evidence to model any incremental differences relating to productivity impacts between the different interventions, the partial societal perspective that included parents' time and travel costs was examined in the secondary analysis. It was noteworthy that including productivity costs (should there be any such impacts) is likely to make FBT even more cost-effective. Secondly, the definition of recovery (and relapse) were not equivalent across studies, and recovery rates were retrieved from individual studies instead of from head-to-head comparison studies. This led to uncertainty in the effect size of FBT or AFT compared to no intervention. However, in the very conservative scenario that 'no intervention' had a similar effect to AFT, the ICER of FBT remained well below the threshold of \$50,000 per DALYs averted. It is appropriate for future research to directly test the effectiveness and cost-effectiveness of FBT vs either AFT or no intervention. Thirdly, our study might overestimate that all therapists required training for FBT and AFT. However, if the training costs are reduced in the real world (i.e. less therapists receiving intervention training), the impact of this would be to make FBT even more cost-effective. Finally, as with similar simulation models, the current model used many assumptions that might limit conclusions. For example, although this study took into account the additional health services of GPs during the treatment phase, other costs associated with psychiatrist visits and/or medication usage were not captured in the model. However, including medication costs is unlikely to change the conclusion of this study given that these

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costs accounted for a very small proportion (e.g. 3%) of total treatment costs for AN (Lock et al., 2008). Future effectiveness studies that include an economic dimension are needed to more accurately determine an estimation of cost-effectiveness in the treatment of AN.

CONCLUSION

In conclusion, this economic evaluation suggests that FBT is a cost-effective treatment for adolescents with AN of relatively short duration compared to either AFT or no intervention in Australia. These results therefore support the implementation of FBT as a very cost-effective first line family therapy for adolescents with AN.

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Table 1: Assumptions and cost items for the interventions.

Parameters	Unit cost (range, if applicable)	Sourced / Assumption
General Practitioner visit (adolescent)	\$39 per visit	MBS items 3, 23, 36 (weighted average annual costs of combined services by age group) for 20-minute or less visit (Australian Government Department of Health and Aging, 2013)
	\$104 per visit	MBS item 44 for 40-minute or more visit (Australian Government Department of Health and Aging, 2013)
Psychologist visit (adolescent)	\$120 per visit	MBS items 80010 and 80110 ((weighted average annual costs of combined services by age group) (Australian Government Department of Health and Aging, 2013).
Psychologist salary	\$37.6 (\$25.9 to \$62.4) per hour	Clinician Psychologist PayScale 2016

Investigation costs

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DEXA bone density	\$102.40	MBS – item 12306, 12309, 12312, 12315 (Australian Government Department of Health and Aging, 2013)
Electrocardiography	\$31.25	MBS – item 11700 (Australian Government Department of Health and Aging, 2013)
Full Blood Test	\$16.95	MBS – item 65070 (Australian Government Department of Health and Aging, 2013)
Liver Function Tests, Urea and Electrolytes including Creatinine, Calcium, Magnesium, Potassium, Acid Phosphate, Phosphate	\$17.70	MBS – item 66500 (Australian Government Department of Health and Aging, 2013)
B12 & Folate	\$23.60	MBS– item 66599, 66602 (Australian Government Department of Health and Aging, 2013)
Thyroid function tests	\$34.80	MBS – item 66719 (Australian Government

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		Department of Health and Aging, 2013)
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Training costs

Workshop costs	\$888	Training Institute for Child and Adolescent Eating Disorders (Training Institute for Child and Adolescent Eating Disorders, 2016) (using purchasing power parity to convert USD to AUD) (OECD, 2013)
Duration of workshop	2 days equivalent to 15 working-hours of Psychologists	Training Institute for Child and Adolescent Eating Disorders (Training Institute for Child and Adolescent Eating Disorders, 2016)

Supervision costs

Senior psychologist salary	\$75.9 (\$28.4 to \$312.2) per hour	Assumption that senior psychologist have 1.1 to 5.0 times psychologist salary.
Duration of session	75 (60 to 90) minutes	Expert opinion
Number of sessions	24 sessions for FBT	Expert opinion

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32 sessions for AFT

Parent costs		
Time	\$23.49 per hour	Mihalopoulos et al. (2015)
Travel	\$8.9 per trip	Mihalopoulos et al. (2015)

Notes. MBS: Medicare Benefit Schedule; DEXA: Dual energy x-ray absorptiometry

Table 2: Input parameters and uncertainty ranges used in the simulation analysis

Parameters	Values	Statistical distributions [#]	Source
Efficacy (FBT vs. AFT) RRs		Lognormal	Own meta-analysis of three RCTs (Lock et al., 2010; Robin et al., 1999; Russell et al., 1987).
- Post intervention	1.69 (1.02, 2.80)		
- One-year follow up	1.75 (1.13, 2.70)		
- Two-year follow up	1.37 (1.06, 1.85)		
- Three-year follow up	1.19 (1.03, 1.42)		
- Four year follow-up	1.09 (1.01, 1.21)		
AN remission for FBT		Gamma	Own meta-analysis of nine studies. Non-available data was predicted by linear regression.
- Post intervention	0.49 (0.36, 0.66)		
- One-year follow up	0.28 (0.19, 0.41)		
- Two-year follow up	0.27 (0.16, 0.38)*		
- Three-year follow up	0.26 (0.14, 0.38)*		
- Four year follow up	0.26 (0.13, 0.43)*		
- Five-year follow up	0.28 (0.20, 0.66)		
AN remission for no intervention	0.09 (0.04, 0.22)	Gamma	Own meta-analysis of four studies. Non-

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- Post intervention	0.15 (0.10, 0.24)*	available data was
- One-year follow up	0.17 (0.11, 0.25)	predicted by linear
- Two-year follow up	0.20 (0.11, 0.29)*	regression.
- Three-year follow up	0.23 (0.12, 0.32)	
- Four year follow up	0.28 (0.12, 0.66)*	
- Five-year follow up		
AN relapse		Gamma Own meta-analysis of
- Post intervention	0.55 (0.36, 0.84)	five studies (post
- Follow up	0.20 (0.14, 0.26)	intervention) and one
		studies (follow up)
Standardized mortality ratios		Lognormal Arcelus et al. (2011)
- Anorexia Nervosa	5.86 (4.17, 8.26)	
Disability weight of AN	0.22 (0.15, 0.31)	Beta GBD 2013 study
		(Salomon et al., 2015)
Number of FBT/AFT sessions	24 (16.0, 46.8)	Pert From 5 RCTs
Proportion of attended sessions	88% (53%, 98%)	Pert From 5 RCTs
Psychologist salary	\$37.6 (\$25.9, \$62.4)	Pert Payscale 2016
Senior psychologist salary	\$75.9 (\$28.4, \$312.2)	Pert Expert Opinion
Private costs	±20%	Pert Own assumption

Notes. FBT: Family-based treatment; AFT: Adolescent-focused treatment; RR: relative risk; RCTs: randomized controlled trials; AN: anorexia nervosa; GBD: Global Burden of Disease. * predicted value by linear regression. # The statistical distribution was chosen based on guidance from Briggs, A. H. and Gray (1999) and Barendregt (2009).

Table 3: Details of Sensitivity Analysis

Scenarios	Values (range)
1a. The hospitalization costs were excluded or they were similar across arms.	
1b. Hospitalization rates	0% to 90%
1c. FBT had fewer days in hospital than those treated with AFT & no treatment	1 to 20 days
2. The effect of AFT and no treatment on remission rate were assumed to be equivalent.	
3. The time horizon of the model.	2 to 10 years
4. The proportion of participants who had AN for less than three years	50% to 100%
5. The participant rates of receiving the intervention	10% to 90%
6. The remission rates were predicted by exponential regression.	
For effect size between FBT vs. AFT, two scenarios were proposed:	
7. The decay rate.	0% to 100%
8. Excluding the Russell et al. (Russell et al., 1987) study in the effect size calculation since this study used less stringent criteria for remission and the version of FBT and AFT were somewhat different compared to those in the Robin et al. (Robin et al., 1999) and the Lock et al. (Lock et al., 2010) studies.	

Two-way sensitivity analysis included

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9. The effect of AFT and no intervention on remission rate was (Vos et al., 2015) assumed to be equivalent and the remission rate from GBD 2013 study was used.

10. The effect of AFT and no intervention on remission rate was assumed to be equivalent and the decay rate of effect size varied 0% to 100%.

11. The effect of AFT and no intervention on remission rate was assumed to be equivalent and the hospitalization costs were excluded.

12. Hospitalization rates and length of hospital stay were sourced from Lock et al. 2010 FBT: 15% vs AFT = No treatment: 37% 10 days of hospital stay were applied for all treatment arms.

Notes. FBT: Family-based treatment; AFT: Adolescence-focused treatment, GBD: Global Burden of Disease.

Table 4: Results of cost-effectiveness at primary and secondary analysis.

	Without patients' time and travel costs		With patients' time and travel costs	
	Primary analysis		Secondary analysis	
	Mean	95% Uncertainty Interval	Mean	95% Uncertainty Interval
Total costs				
FBT	\$10,600,559	\$8,798,924 to \$12,527,236	\$12,209,523	\$9,849,833 to \$14,876,457
AFT	\$13,383,861	\$11,225,374 to \$15,700,089	\$14,816,404	\$12,238,856 to \$17,740,492
No intervention	\$9,878,893	\$8,481,095 to \$11,293,603	\$9,878,893	\$8,481,095 to \$11,293,603
DALYs averted				
FBT vs. AFT	74	26 to 130		
FBT vs. No intervention	142	74 to 225		
AFT vs. No intervention	65	2 to 146		
Incremental cost-effectiveness ratio				
FBT vs. AFT	Dominant*	Dominant - Dominant	Dominant	Dominant – Dominant
FBT vs. No intervention	5,089	Dominant to \$16,659	\$16,436	5,374 to \$40,452
AFT vs. No intervention	\$51,897	21,591 to \$1,712,491	\$73,109	\$29,907 to 2,418,113
Probability of being cost-effective at \$50,000 per DALY averted				
FBT vs. AFT	100%		100%	
FBT vs. no intervention	100%		99%	

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AFT vs. no 45%

21%

intervention

Notes. *Dominant means the FBT was 'cost-saving' or 'more effective and less costly' than the comparators. FBT: Family-based therapy; AFT: Adolescent-focused therapy; DALYs: Disability adjusted life years.

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Figure 1: Cost-effectiveness plane of primary analysis with a willingness to pay threshold of \$50,000 per DALY averted.

DALYs: Disability Adjusted Life Years; FBT: family-based therapy, AFT: Adolescent-focused based therapy.

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Figure 2 – One-way and two-way sensitivity analyses of the potential cost-effectiveness of FBT intervention compared to no intervention.

ICER = incremental cost-effectiveness ratio; DALY = disability-adjusted life-year; AFT:

Adolescent-focused treatment; No.I: no intervention.

AUTHOR DISCLOSURE

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CONFLICT OF INTEREST

J. J. B. owned Epigear International, which sells the Ersatz software used in the analysis.

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Figure S1: State transition diagram used to estimate health benefit of treatment intervention for Anorexia Nervosa.

Table S2: Included studies for estimating Recovery/Remission of Family-Based Therapy								
Study name	FBT Duration (months)	Follow-up duration (months)	Total time at-risk (months)	Total time at-risk (years)	Remission Cases (FBT)	Total (FBT)	Remission probability (FBT)	Remission/recovery defined
Russell et al. 1987 (1)	12	0	12.0	1.0	6	10	60%	Good outcome of the Morgan and Russell Scales
Lock et al. 2010 (2)	12	0	12.0	1.0	21	61	34%	Combination of a minimum of 95% of expected IBW + scores within 1 SD from global mean EDE published norms
Robin 1999 (3)	15.9	0	15.9	1.3	10	19	53%	Achieved 50 th percentile BMI
Agras 2014 (4)	9	0	9.0	0.8	27	78	35%	Achieve a minimum of 95% of expected IBW

Eisler et al. 2000 (5)	12.6	0	12.6	1.0	5	19	26%	Good outcome of the Morgan and Russell Scales
Rhodes et al. 2008 (6)	12	0	12.0	1.0	5	10	50%	Combination of a minimum of 95% of expected IBW + scores within 1 SD from global mean EDE published norms
Madden 2015 (7)	13	0	13	1.08	10	41	24%	Combination of a minimum of 95% of expected IBW + scores within 1 SD from global mean EDE published norms
Pooled remission probability at post treatment (equivalent to 12 months).							36%	
Lock et al. 2010 (2)	12	12	24.0	2.0	22	61	36%	Combination of a minimum of 95% of expected IBW + scores within 1 SD from global mean EDE published norms

Robin 1999 (3)	15.9	12	27.9	2.3	13	19	68%	Achieved 50 th percentile BMI
Agras 2014 (4)	9	12	21.0	1.8	32	78	41%	Achieve a minimum of 95% of expected IBW
Madden 2015 (7)	13	12	25.0	2.08	12	41	29%	Combination of a minimum of 95% of expected IBW + scores within 1 SD from global mean EDE published norms
Pooled remission probability at 1 year follow up (equivalent to 24 months)							39%	
Eisler et al.1997 (8)	12	62.4	74.4	6.2	9	10	90%	Good outcome of the Morgan and Russell Scales
Eisler et al.2007 (9)	12.6	62.4	75.0	6.2	13	19	68%	Good outcome of the Morgan and Russell Scales
Pooled remission probability at 5-year follow up (equivalent to 72 months)							82%

IBW: Ideal Body Weight; BMI: Body Mass Index; EDE: Eating Disorder Examination; SD: Standard Deviation.

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Table S3: Included studies for estimating Recovery/Remission of Treatment As Usual.							
Study	Durations (months)	Total time at- risk (years)	Remission cases	Total cases	Recovery/ Remission probability	Recovery/remission definition	Treatment
Salbach-Andrae et al. 2009 (10)	12	1	5	57	9%	Good outcome of the Morgan and Russell Scales AND (1) eating attitudes and weight concerns had to be less than one standard deviation above the mean of a comparison group without AN AND (2) absent binge eating or purging behaviors.	Inpatient treatment (12 weeks)

Claussen et al. 2008 (11)	30	2.5	38	78	49%	The Psychiatric Status Rating Scale <2	100% Dietary counselling, individual integrated psychotherapy, 20% family therapy, 40% group therapy
Herpertz- Dahlmann et al. 2001 (12)	36	3	16	39	41%	Not meet DSM-IV for AN during last 6 month + Good outcome	Dietary counselling, individual integrated psychotherapy, supplementary family therapy
Pooled recovery remission at 3 year					47%		

Keski-Rahkonen et al. 2007 (13)	60	5	37	55	67%	Restoration of weight and menstruation and the absence of bingeing and purging for at least 1 year prior to assessment	A combination of individual and group psychotherapy, family therapy, and behavioural programs for weight restoration
AN: Anorexia Nervosa; DSM-IV: Diagnostic and Statistical Manual 4 th edition.							

Table S4: Included studies for estimating Relapse of Anorexia Nervosa.

Study	Durations (months)	Total time at- risk (years)	Relapse cases	Total cases	Recovery/ Remission probability	Relapse criteria	Treatment
Pike, Walsh et al. 2003 (14)	12	1	8	15	53%	The Eating Disorder Examination	Nutritional counseling
Carter, Blackmore, et al. 2004 (15)	15.6	1.3	18	51	35%	BMI<17.5 for at least 3 consecutive months	Some forms of specialized treatment for their eating disorder.
Carter, Mercer-Lynn, et al. 2012 (16)	12	1	41	100	41%	BMI $\leq$ 17.5 for 3 consecutive months or at least one episode of binge-purge behaviour per week for 3 consecutive months during the 1-year follow-up period	Unclear

Carter, McFarlane, et al. 2009 (17)	12	1	20	30	66.6%	BMI $\leq$ 17.5 for 3 months or the resumption of regular binge eating and/or purging behavior for 3 months.	Three 90-min group therapy sessions per week for up to 12 weeks (if patients needed)
Richard, Bauer and Kordy 2005 (18)	12	1	40	135	30%	Returning to full symptomatic status at least 1 month.	Hospitalization.
Richard, Bauer and Kordy 2005 (18)	24	1	44	135	33%	Returning to full symptomatic status at least 1 month.	Hospitalization.

AN: Anorexia Nervosa; DSM-IV: Diagnostic and Statistical Manual 4th edition.

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