Inclusion of health-related externalities in cost-effectiveness analysis: an illustration with parents of adolescents who self-harm

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Abstract

Objective - This paper presents alternative health externalities quantification methods in the context of a randomised controlled trial comparing family therapy with treatment as usual as an intervention for self-harming adolescents, and discusses the practical limitations of those methods.

Methods - The trial followed a sample of 754 participants aged 11 to 17 years. Health utilities are measured using answers to EQ-5D-3L for the adolescent and to HUI2 for one parent at baseline, 6 and 12 months. We use regression analyses to evaluate the association between parent's and adolescent's health utilities, controlling for additional health assessment for the adolescent, type and number of self-harm events as well as variables for both the adolescent and the parent. Cost-effectiveness over a 12-month period is presented using mean incremental cost-effectiveness ratios.

Results - We find that the parent's health utility increased over the duration of the trial and is significantly and positively associated with adolescent's health utility at 6 and 12 months only. When considering adolescents' health gain only, the ICER is £45,330 per QALY. When including health externalities to one parent, the ICERs estimates range from £33,690 per QALY to £45,330 per QALY and can also be a dominated option depending on the quantification method used.

Conclusion - We argue that the use of a single disutility value for any parent denies the heterogeneity observed in parents of self-harming adolescents and ignores the QALY gain of parents over the duration of the trial. We demonstrate how adding QALY gains for both the adolescent and the parent might also lead to a dilemma of judging an intervention cost-effective when it benefits the rest of the family but not the patient. We finally propose the use of a household welfare function along with an equivalence scale to measure health externalities for cost-effectiveness analysis.

Keywords: economic evaluation; self-harm; adolescent; EQ-5D-3L; externalities; HUI2.

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1. Introduction

Self-harm is commonly defined in the UK and Europe as any form of non-fatal self-poisoning or self-injury (such as cutting, taking an overdose, hanging, self-strangulation, jumping from a height, and running into traffic), regardless of the motivation or degree of intention to die. This definition would include US definitions of non-suicidal self-injury and suicidal behaviour. Self-harm in adolescents is a major public health issue with one in ten adolescents self-harming each year [1]. Individuals with mental disorders are heavy users of public health services and require emotional support and care from their family [2, 3]. Their disorders are likely to affect other family members' health and own health care needs, especially because individuals with mental health conditions face elevated rates of all-cause mortality and this places a huge burden of costs and life years lost on the family and the community [4].

It appears that the magnitude of externalities on the health of other family members is the greatest in parents of ill children [5, 6]. Beyond the effect of caring for an ill child on parents' health [7], treatments that are provided to a self-harming child may have externalities for the family. Indeed, psychotherapeutic treatments such as family-based therapies are often used with self-harming adolescents; they rely on individuals' relational network, involve parents, caregivers, brothers and sisters or other close relatives and friends in the therapies to improve clinical outcomes [8], and typically aim at maximizing cohesion, attachment and support while moderating parental control [9]. Therapy sessions do not necessarily include all family members but it is expected that they will have an impact beyond the identified patient.

Some prior economic evaluations of psychotherapeutic interventions in young people have looked at the impact of the therapy on the adolescent/child patient and on relatives participating in the therapy. These studies collected parents or carers' outcomes and used them as additional outcomes of interest in a cost-effectiveness analysis [10-12] whilst only two studies combined child and parents' outcomes. Bodden et al. [13] used a compound summary of anxiety specific scores of the child, mother and father, as part of the sensitivity analyses. Their analysis measured the cost-effectiveness per anxiety-free family by including the costs related to the child and other family members' anxiety as self-reported in cost diaries. Cottrell et al. [14] used the same data as this paper over an 18-months follow-up and considered an aggregate QALY of the adolescent and parent's QALYs as a sensitivity analysis. Their application relied on the strong assumption that QALYs can be summed across individuals. This assumption has been used in other studies in child health [15] and is consistent with research showing benefits to other family members involved in mental health family treatment [16, 17]. However, such considerations require a more thorough discussion of the interdependence between the utility functions of the adolescent and the parent, and the most appropriate method to include the overall health benefits.

The NICE reference case underlines that the perspective on outcomes considers "all direct health effects, whether for patients or, when relevant, carers" [18] however, there is no consensus on how these health effects should be measured and valued. Wittenberg and Posser [19] offered a summary of the evidence on the measurement and incorporation of spillover health effects of illness on family members or caregivers across health conditions, as a disutility. In their review, externalities were of three different types: (i) a direct measure of disutility of family members; (ii) a relative measure of family members' utility with a comparison to a control group; or (iii) an estimation of the utility of family members in a hypothetical scenario in which the patient is healthy or does not require caregiving.

In empirical economic evaluation studies, health-related externalities have been included either as accrued health benefits [20-22] or as an estimated multiplier parameter which adjusts the patient's health gain with a spillover for the rest of a wider network (including parents, carers, spouses and other relevant individuals) [23, 24]. Whilst the first method uses a health-related quality of life (HRQoL) questionnaire and directly elicited utilities, the multiplier effect is based on a regression model using observational or primary data collection and consists of two multiplier effects.

In this paper, we use data from a multi-centre, individually randomised controlled trial comparing family therapy with treatment as usual as an intervention for self-harming adolescents aged 11 to 17 [25] as a case study. Both the adolescent and one parent[1] reported their HRQoL as part of the trial across repeated follow-up points. We undertake a within-trial cost-effectiveness analysis (CEA) incorporating health-related externalities using alternative spillover quantification methods. We add to the growing literature in three ways. First, we investigate the correlation between the health utility of the parent and a self-harming adolescent as part of an explanatory regression model using the preference-based HRQoL scores of both self-harming adolescents and their parent. Second, we lead a comparative analysis of different spillover quantification methods as part of an economic evaluation, bringing together the dyadic and the regression-based perspectives. Finally, we discuss how an equivalence scale could be used to adjust health-related externalities.

The outline of the paper is as follows. Section 2 presents the trial study and data. Section 3 investigates the relationship between parent and adolescent's HRQoL using regression models. In Section 4 we discuss alternative quantifications of health-related externalities and present the corresponding incremental cost-effectiveness ratios (ICER). Section 5 discusses the limitations of the additive approach for externalities quantification and proposes a new framework. Section 6 concludes.

[1] The study collected data on the main caregiver, who was either the mother (86%) or the father (11%), so we will loosely use the term parent in this paper.

2. The SHIFT trial case study

The SHIFT study was the first randomised controlled trial (RCT) conducted in local child and adolescent mental health services (CAMHS) in Yorkshire, Greater Manchester and London for adolescents aged 11 to 17 years who had self-harmed twice, and their families. Participants were randomly allocated to receive family therapy (FT) or treatment as usual (TAU). The main objective of the trial was to assess whether or not FT would reduce the number of times the adolescents attended hospital with further self-harm. The main results for the trial are reported elsewhere [14].

Personal characteristics of the adolescent and their parent such as adolescent's gender and age group, type of self-harm episode, total number of self-harm episodes, relationship to the adolescent, and gender and age of their parent were collected at baseline. Information on adolescent's mental health was also collected using the Hopelessness scale for Children[2] [26]. Parent's emotion toward the adolescent was collected through the Family Questionnaire[3] (FQ) [27] and their viewpoint on the family atmosphere through the McMaster Family Assessment Device[4] [28]. Parents completed the General Health Questionnaire[5] (GHQ-12) [29] for their own health. Adolescent's health-related quality of life was measured by the EQ-5D-3L [30], whilst the parent's by HUI2[6] [32, 33] at baseline, 6, 12 and 18 months.

Adolescent's responses to the EQ-5D-3L were converted into health state utility scores using national tariff values [34]. Similarly, parent's responses to HUI2 were converted into health state utility values [33]. The area under the curve approach was used to calculate quality-adjusted life-years (QALYs) for the adolescent and the parent; average QALYs between adjacent time points were calculated to generate smoothed estimates between time points.

Resource use of health services was self-reported by the adolescent and/or their parent at 6, 12 and 18 months. Accident and Emergency visits and inpatient stays of the adolescent were available from NHS Digital records. Resource use was combined with national unit costs distinguishing, where possible, by self-harm and not self-harm-related event leading to hospitalisation [35]. Psychotropic medication costs were calculated using trial medication records. The intervention costs were calculated separately for each treatment arm including the frequency of sessions run by CAMHS and

[2] The Hopelessness scale measures the degree to which adolescents have negative expectancies about themselves and the future. It consists of 17 items with true or false responses, providing a single overall score with higher scores reflecting greater negative expectations towards the future.

[3] The Family Questionnaire is a 20-item self-report questionnaire relating to the different ways in which families try to cope with everyday problems. It consists of a single overall score with higher scores indicating greater levels of expressed emotion directed at the adolescent by the parent.

[4] The McMaster FAD measures family functioning across 60-items on six different dimensions: Problem Solving, Communication, Roles, Affective Responsiveness, Affective Involvement, and Behaviour Control. Higher total score is indicative of poorer family functioning.

[5] The GHQ-12 is a measure of current mental health focusing on two major areas: the inability to carry out normal functions and the appearance of new and distressing experiences. High total scores are indicative of greater psychological distress.

[6] The original research proposal considered HUI2 as HRQoL measure for both the parent and the adolescent. However, EQ-5D-3L was eventually included for adolescents following a pilot study [31].

their duration, number of therapists involved, type of session, attendance, telephone contact with the family between sessions, and therapists' supervision sessions. The median number of CAMHS sessions per young person was five in the TAU arm compared with six in the FT arm.

Eighty hundred and thirty two adolescents and their parent were recruited in the trial (417 in TAU and 415 in FT). This paper focuses on the first 12-month follow-up so discounting is not required, and only adolescents whose parent completed HUI2 questionnaire, are considered. Missing data are not imputed and complete cases are used; the sample is 754 adolescents and their parent at baseline, and reduces to 206 for the 12-month CEA.

Descriptive statistics of adolescent characteristics are presented in Table 1. At baseline, more than two thirds of the adolescents were females with about three self-harm episodes over the duration of the trial. Self-harm was caused by self-injury for over 70% of the adolescents with more than 50% reporting some problems with anxiety/depression. For parents, 86% were mothers of the self-harmed adolescent with average age of 42 years (see Table 2 for more details). Parent's average GHQ-12 is within the distressed range (4-12) but it is lower than the level of psychological distress observed in a sample of caregivers of a dependent relative (8.52, SD=5.38) [36].

Table 3 shows the mean utility scores for adolescents and their parent at baseline, 6 and 12 months overall and by treatment arm. For the adolescents, utility scores increase monotonically over the 12 months and regardless of the treatment arm. Differences in utility scores from baseline for the adolescents are strongly significant at 6 and 12 months showing an increase of about 0.12 in the EQ-5D-3L score; the difference from baseline appears to be slightly larger in FT than in TAU (on average 0.145 versus 0.095). Parent's utility also shows a positive and significant increase in the overall HUI2 score at 6 and 12 months from baseline; this increase however is much smaller than for the adolescent (on average 0.045 versus 0.12) and is not always significant when distinguished by treatment arm.

3. The association between parent's and self-harming adolescent's health

3.1 Methods

We firstly modelled the utility of the parent as a function of the adolescent's HRQoL (EQ-5D-3L items or utility) in the same period controlling for a number of adolescent and parent's characteristics. Our approach was similar to prior research [7, 23] however, as we had multiple time points in our data, we studied whether the relationship between parent's and adolescent's quality of life was consistent across these time points. We investigated this association separately by each time point as follows:

$$H_{it} = a_0 + \beta_{1t} H_{jt} + \beta_{2t} Z_{j0} + \beta_{3t} C_{i0} + \varepsilon_{it} \quad (1)$$

where H_{it} denotes the parent's i health-related quality of life at time t ($t = 0,1,2$); H_{jt} denotes the adolescent's j HRQoL at time t measured by the responses to each of the five items of the EQ-5D-3L and overall EQ-5D-3L index score; Z_{j0} is a vector of characteristics of the adolescent observed at baseline such as age, gender, type of self-harm event, total number of self-harm events; C_{i0} is a vector of characteristics of the parent also observed at baseline such as gender and mental health measured by the GHQ-12; α_0 is the intercept, $\beta_1, \dots, \beta_3$ are the slope parameters and ε_{it} is the error term with $\varepsilon_{it} \sim N(0,1)$.

We estimated all regression models using Ordinary Least Squares (OLS) regression. We initially ran regressions (Model 1) including demographic controls for both the adolescent (age, gender) and the parent (age). To account for the heterogeneity observed in adolescents' parents, we subsequently ran regressions (Model 2) controlling for other characteristics of the adolescent (Hopelessness scale score, type of self-harm) and of the family from the parent's perspective (Family questionnaire, McMaster Family Assessment Device) as well as the parent's GHQ-12.

The same set of estimations was run using the adolescent's responses to each of the five EQ-5D-3L items and the overall EQ-5D-3L utility score.

We supplemented this simplistic association analysis with a more causal understanding of the impact of a positive change in the adolescent's health over time on parent's HRQoL in line with Bhadhuri et al. [37]. We included a binary variable taking the value 1 if the adolescent's EQ-5D-3L score improved between baseline and follow-up but this parameter was not significant and did not impact on the results[7].

3.2 Results

Table 4 presents the regression results controlling for the five EQ-5D-3L items of the adolescent; the association between parent's and adolescent's health varies across time points and model specifications. Results of Model 1 must be considered with caution as the model specification leads to a low rho-squared however, Model 2 with additional controls exhibits a better model fit.

According to Model 1, parent's health is negatively associated with an adolescent reporting extreme pain or discomfort at baseline, moderate and extreme pain or discomfort and extreme anxiety or depression at 6 months, and some mobility problems at 12 months. The largest decrease in parent's health utility is observed when the adolescent reported extreme pain and discomfort and extreme anxiety. This is in line with prior studies on the experience of parents' caregiving for an ill child [5, 7, 38], and carers of people with mental health disorders [3]. When we control for other determinants of health (Model 2), the same associations remain and sometimes strengthen.

[7] Results available upon request.

On the other hand, parent's health becomes positively and significantly associated with adolescent's inability to perform usual activities at 12 months. It has long been known that 'invisible' handicaps can cause more distress to children and their families than handicaps that are more obvious [40]. Clinically, parents find being unable to help their child very upsetting and it may be that when a child is asking for more caregiving this gives the parent a role and reduces their distress by allowing them to feel useful and caring.

Parent's HRQoL at every time point also appears to be negatively associated with a higher score of emotion within the family, of poor family functioning and of psychological distress as measured by GHQ-12, all three measured at baseline. The strong association between parent's utility and GHQ-12 has also been shown in other studies [39]. While at baseline a higher score of hopelessness for the adolescent is associated with better parental health utility, this unexpected association is not observed at the other time points.

When we consider the utility score instead of the individual EQ-D-3L items as a control variable (see Table 5), we find a strongly significant and positive association with parent's health at 6 months in both models 1 and 2 while the other controls show the same associations.

4. Accounting for health-related externalities in cost-effectiveness analyses: five alternative quantifications

We are interested in quantifying the health externalities for the parent in the comparative cost-effectiveness of FT as an intervention for self-harming adolescents.

4.1 Methods

Using as a starting point the regression model presented in Eq. (1), we consider a number of spillover quantifications for our case study.

4.1.1 Relative global health spillover

The estimated parameter $\widehat{\beta_{1,t}}$ in Eq. (1) where $t = 0, 1, 2$ for baseline, 6, and 12 months can be used to extract a spillover coefficient of adolescent's health utility on parents. Assuming policy makers are interested in accounting for broad health benefits independently of the treatment arm, $\widehat{\beta_{1,0}}$, $\widehat{\beta_{1,1}}$, and $\widehat{\beta_{1,2}}$, when controlling for confounders (Model 2), represent a longitudinal utility gain for the parent, which can be transformed into a QALY gain using the area under the curve approach (Quantification 1 – see Table 5). This first quantification is similar to what Al-Janabi et al. (2016) name *relative*

spillover however, here we account for the inconsistency in the relationship between parent and adolescent's HRQoL across the different time points.

4.1.2 Relative global health spillover per treatment arm

One might suggest that we should also account for the heterogeneity in the health spillover according to the treatment received, especially because parents are directly involved in the FT arm but not systematically involved in TAU[8]. Let us consider the estimated parameter $\widehat{\beta_{1,t}^{FT}}$ where $FT = 0$ when Eq. (1) is run on the sample of adolescents receiving TAU and $FT = 1$ when it is run on those receiving FT. Three estimated health spillover coefficients within each treatment arm are then used to quantify a utility gain for the parent, and then transformed into a QALY gain using the area under the curve approach (Quantification 2 – see Table 6).

4.1.3 Absolute global health spillover

Considering the primary outcome of the study was reducing repetitions of self-harm over 12 months one could argue that measuring spillover coefficients according to the final primary outcome provides an *absolute* spillover for the parent. Let us consider $\widehat{\beta_{1,t}^{SH}}$ with $SH = 0$ when Eq. (1) is run on the sub-sample of adolescents who did not have a repeated self-harm at 12 months and $SH = 1$ when the adolescent self-harmed before the 12-month follow-up. The two sets of estimated health spillover coefficients according to repeated self-harm or not, are used to generate an absolute QALY gain for the parent (Quantification 3 – see Table 7).

4.1.4 Absolute global health spillover per treatment arm

The absolute QALY gain for the parent could additionally account for the heterogeneity in health spillover according to treatment. The health spillover is measured using the estimated coefficient $\widehat{\beta_{1,t}^{SH,FT}}$ with $SH = 0{,}1$ and $FT = 0{,}1$ and Eq. (1) being run on the four different sub-samples of adolescents (Quantification 4 – see Table 8).

[8] TAU included supportive therapy/counselling (25.1%), cognitive–behavioural therapy (17.4%), family work (11.5%), formal systemic FT (10.7%), and various other therapies (psychodynamic, communication skills/problem-solving, interpersonal, dialectical behaviour, psychoeducational).

4.1.5 Additive accrued health benefits

Using prior empirical studies [20-22], health spillover could also be measured using an additive approach where the QALY gain of each individual in the dyad adolescent/parent is independently calculated and summed up.

4.2 Results

Table 9 presents the ICERs using the five alternative spillover quantifications along with the base-case analysis when only the adolescent's QALY gain is considered. Since we did not collect health care costs for the parent we note that the costs for each ICER are strictly identical and it is only the level of QALY gain that varies.

Results from the base-case analysis indicate that adolescents in FT incurred £1,080.66 (SE £450.20) higher costs on average and gained 0.024 extra QALYs than the adolescents in TAU, which is equivalent to an extra 8.8 days of perfect health. The ICER from this analysis (£45,330.30 per QALY) is above the recommended threshold range specified for NICE decision-making in England and Wales (£20,000-£30,000 per QALY gain), indicating that FT is unlikely to be cost-effective. The ICER reduces to £33,690 when we simply sum adolescent's and parent's QALYs, demonstrating a potential for FT to bring 11.7 extra days at full health for both the adolescent and the parent but it remains unlikely that FT is cost-effective. When considering relative health spillovers for the parent independently of the treatment arm using Quantification 1, the ICER is almost identical to the one obtained from the base-case analysis. However, when accounting for the direct involvement of the parents in the FT arm, parents and adolescents continue to incur higher costs on average but with 64.6 fewer days of perfect health (loss of 0.177 QALYs) than those in TAU and therefore indicating that FT is dominated by TAU. The ICER remains above the nationally recommended threshold when we control for absolute health spillovers for the parent, using the number of repeated self-harm events at 12 months (£41,995.90) implying that FT is not cost-effective. If we further control for any heterogeneity in the absolute health spillovers for the parent, FT is dominated by TAU with adolescents and parents in the FT arm incurring 35.4 fewer days of perfect health (loss of 0.097 QALYs) than those in the TAU arm. It is important to note that with any quantification method, cost differences between FT and TAU are highly significant whilst QALY differences are never significant, and this was a result already underlined in the trial paper [14].

5. Health-related externalities in CEA

The ICERs appear to be sensitive to the method of calculation of the spillover effects that we have considered here. Ideally one would like to establish which of the quantification methods is preferred.

5.1 Health-related externalities in CEA: limitations of the current framework

While in the context of the economic evaluation of meningitis vaccination, Al-Janabi et al. [23] proposed a unique spillover estimate that was applied to each family member affected or a spillover estimate according to their proximity to the patient (e.g. parents, siblings, other relatives), we believe a single disutility value for all parents would not be appropriate in our case study.

Three arguments motivate our viewpoint. First, a single disutility value would deny the heterogeneity observed in parents' characteristics at baseline and their potential to benefit over the duration of the study according to their level of engagement in the treatment, whether this is FT or TAU. From a clinical viewpoint, it would be expected that FT has an impact on other members of the family and household irrespective of whether those members attended the therapy sessions, and of any change in the self-harming adolescent. If therapy leads to, those attending, behaving or communicating differently this will inevitably have impacts on others they relate to. The magnitude and even the direction of such impacts will vary from one family member to another but cannot be ignored. Second, the treatment arm itself might impact on the parent's health independently from the adolescent's health improvement; in the SHIFT trial for a number of secondary outcomes caregivers reported significantly better outcomes than the adolescents [14]. Third, as part of a trial several repeated observations of health utilities are available and it appears important to account for all the available repeated information when quantifying health-related extermalities.

These arguments would lead us to consider the additive approach, where the QALY gain of each individual in the dyad adolescent/parent is independently calculated, appealing. However, a simple addition of the QALY gain for both the adolescent and the parent, or in a more general case of the patient and one or several other family members is inappropriate. There are clear value judgements about the priority assigned to the identified patient, who is judged the most important individual to benefit from a treatment while the inclusion of social externalities such as health spillover effects for other individuals are of secondary purpose. One would agree that it is important to ensure that the aggregation does not lead to a decision that deteriorates the health of the patient in the first place. Our first proposition is therefore to aggregate health gains at the household level if and only if the QALY gain for the patient is positive or equal to zero and we outline a second proposition for the aggregation hereafter.

5.2 Health-related externalities in CEA: new perspective

The aggregate utility of people is denoted by the term "welfare" and the inclusion of health spillover for the rest of the family could be considered as an aggregation of individual health utilities to obtain a measure of household social welfare. Equivalence scales are typically used to measure social welfare and adjust the incomes of all household members. A wide range of equivalence scales have been used in economics and they provide a homogeneous household income using standardised weights, often accounting for the size of the household and the age of its members [41]. The main objective of the equivalence scale (ES) is related to economies of scale in consumption, as growth in a household does not follow a proportional pattern. In our context, it would offer a standard way to adjust overall health spillovers for the rest of the household as an additional individual equivalent QALY or utility gain (or disutility loss) divided by a defined ES where all the household members (including the patient) are accounted for.

Following Buhmann et al. [41], let us consider that Q measures the adjusted health spillover as follows:

$$Q = \frac{\sum_{r=1}^{R} h_r}{s^a} \quad (2)$$

where h_r equals the health spillover for one family relative r (measured as QALY gains or by an estimated utility coefficient), s is the number of family relatives with an observed utility or QALY gains (including the patient), and a is the elasticity of the scale rate which varies between 0 and 1. The value of a could be defined according to the importance given to family members beyond the patient. The most straightforward ES would be the square root of the whole household ($a = 0.5$).

The ES leads to convert a distribution of observed (dis-)utility or QALY gains across heterogeneous households members (except the patient) into an individualised health gain across homogenous individuals. This adjusted value could then simply be summed to the QALY gain of the patient.

There are several advantages of this proposition. First, ES have been widely used to measure household social welfare. Second, health spillover measured either as a (dis-)utility parameter generated from a regression model or QALY gains measured with an area under the curve can be used. Third, every relative with observed health outcomes could be included and the parameter s adapted to data availability. Finally, we assumed that every relative would count equally although one could adapt the ES to account for family members' proximity to the patient.

6. Conclusion

We showed that parent's HRQoL is strongly associated with the health of a self-harming adolescent, especially when the adolescent reports high level of anxiety and pain. We investigated how health-

related externalities to the parent could be included in CEA using alternative quantification based on estimated coefficients and QALY evaluation. Sensitivity analyses revealed that the valuation technique had a considerable impact on the magnitude of QALY and could change the inference about the most cost-effective alternative in a trial study. We made two propositions in this paper. Proposition 1 suggests that health-related externalities are only aggregated when the QALY gain for the patient is positive or equal to zero. Proposition 2 suggests the use of an ES to convert a distribution of observed health-related externalities across other households members into an equivalent health gain to be added to the patient's QALY gain. This second proposition will require further scrutiny in future research.

There are avenues for improvement of this research work.

Methodologically, the reverse correlation with a focus on the impact of parent's health on adolescent's health could have been of interest to study. Secondly, parent's health utility could be modelled using non-linear regressions since the distribution of health utilities usually follows a bi-modal distribution. Thirdly, we aimed at evaluating the true observed effect of adolescent's health on parent's health by adopting a complete case approach however, a standard practice when undertaking economic evaluation alongside clinical trials is to impute missing variables using chained equations to maximise sample size. Finally, several authors [13, 17, 42] have argued that potential health care cost savings are transferred to others when treating one family member using family-based psychotherapy; it would be ideal to include the health care resource use of the parent had they been available in the data.

Conceptually, we investigated how social externalities such as the health effects on other individuals could be introduced into the framework of CEA; to some extent, this questions whether cost-utility analysis is appropriate or whether cost-benefit analysis with distributional weights should be considered. We did not enter into this debate and assumed that cost-utility analysis would remain the preferred method for the health-related externalities quantification [43].

Admittedly, our proposition to rely on an ES is a pragmatic choice. The adoption of a *unique* scale that would be identical for any CEA would have the advantage to facilitate the generation of evidence that is comparable between individuals and between cost-utility analyses.

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Table 1: Adolescents' characteristics

		Baseline (N=754)
Gender	Males	n=93 (12%)
	Females	n=661 (88%)
Age	11-14 years old	n=396 (53%)
	15-17 years old	n=358 (47%)
Centre	Yorkshire	n=272 (36%)
	Manchester	n=267 (35%)
	London	n=215 (29%)
Total number of self- harm episodes	Mean (SD)	2.92 (21.51)
Type of index episode	Self-poisoning	n=170 (23%)
	Self-injury	n=533 (71%)
	Combined	n=51 (7%)
Source of referral (from hospital)	Yes	n=274 (36%)
	No	n=480 (64%)

EQ-5D-3L score (overall)	Mean (SD)	0.68 (0.27)
EQ-5D-3L Mobility	No problems	n=679 (90%)
	Some problems	n=69 (9%)
	Unable	n=6 (1%)
EQ-5D-3L Self-care	No problems	n=734 (97%)
	Some problems	n=19 (3%)
	Unable	n=1(0%)
EQ-5D-3L Usual activities	No problems	n=510 (68%)
	Some problems	n=227 (30%)
	Unable	n=17 (2%)
EQ-5D-3L Pain/Discomfort	No problems	n=435 (58%)
	Some problems	n=289 (38%)
	Unable	n=30 (4%)
EQ-5D-3L Anxiety/Depression	No problems	n=139 (18%)
	Some problems	n=448 (59%)
	Unable	n=167 (22%)
Hopelessness scale score^	Mean (SD)	7.39 (4.26)

^Hopelessness scale score was not available for 11 adolescents.
EQ-5D-3L: EuroQoL 5 Dimensions 3 Levels
SD: Standard Deviation

Table 2: Parents' characteristics

		Baseline (N=754)
Gender	Males	n=89 (12%)
	Females	n=665 (88%)
Relationship to adolescent	Father	n=85 (11%)
	Foster parent	n=2 (0.3%)
	Guardian	n=11 (1%)
	Mother	n=649 (86%)
	Step-father	n=2 (0.3%)
	Step-mother	n=5 (1%)
Age^	Mean (SD)	42.38 (6.42)
HUI score (overall)	Mean (SD)	0.71 (0.28)
McMaster Family Assessment Device^^	Mean (SD)	2.20 (0.37)
Family Questionnaire*	Mean (SD)	52.86 (10.75)
Parent GHQ**	Mean (SD)	5.70 (4.07)

^Age was not available for 81 caregivers.
^^McMaster Family Assessment Device was not available for 9 parents.
*Family Questionnaire was not available for 1 parent.
**Parent GHQ score was not available for 3 parents.
HUI: Health Utility Index
GHQ: General Health Questionnaire
SD: Standard Deviation

Table 3 – Adolescent's and parent's health-related quality of life by time period

		Baseline (N=754)	**6 months (N=278)**	**Diff. from baseline (N=278)**	**12 months (N=379)**	**Diff. from baseline (N=379)**
Adolescent's EQ-5D-3L score (overall)	Mean (SD)	0.68 (0.27)	0.79 (0.23)	0.12***	0.80 (0.24)	0.12***
Parent's HUI score (overall)	Mean (SD)	0.71 (0.28)	0.79 (0.24)	0.04**	0.78 (0.27)	0.05***
		Baseline (N=371)	**6 months (N=106)**	**Diff. from baseline (N=106)**	**12 months (N=160)**	**Diff. from baseline (N=160)**
Treatment as usual						
Adolescent's EQ-5D-3L score (overall)	Mean (SD)	0.68 (0.26)	0.76 (0.24)	0.10***	0.78 (0.24)	0.09**
Parent's HUI score (overall)	Mean (SD)	0.70 (0.28)	0.77 (0.26)	0.02	0.76 (0.28)	0.06***
		Baseline (N=383)	**6 months (N=172)**	**Diff. from baseline (N=172)**	**12 months (N=219)**	**Diff. from baseline (N=219)**
Family therapy						
Adolescent's EQ-5D-3L score (overall)	Mean (SD)	0.68 (0.28)	0.80 (0.22)	0.14***	0.81 (0.23)	0.15***
Parent's HUI score (overall)	Mean (SD)	0.72 (0.27)	0.80 (0.23)	0.05*	0.79 (0.26)	0.04*

Significance of the t-test of the difference: ***p<0.001, **p<0.01, *p<0.05
HUI: Health Utility Index
EQ-5D-3L: EuroQoL 5 Dimensions 3 Levels
SD: Standard Deviation
Diff.: difference

Table 4 – Regression model of the parent's health-related quality of life with adolescent's EQ-5D-3L items

Variables		**Model 1**			**Model 2**	
	Baseline	6 months	12 months	Baseline	6 months	12 months
Adolescent						
Mobility (ref. no problem)						
Some problems	-0.0204	0.0733	-0.1395*	-0.0098	0.0513	-0.1051*
Confined to bed	0.0709	0.0364	0.0550	0.1628	0.0440	0.0983
Self-care (ref. no problem)						
Some problems	-0.0250	-0.0016	-0.0948	-0.0721	0.0886	-0.1515
Unable to wash or dress	0.2587	.	-0.0365	0.0515	.	-0.2013
Usual activities (ref. no problem)						
Some problems	0.0094	0.0062	-0.0643	0.0061	0.0052	-0.0614
Unable to perform	0.0506	-0.1564	0.2602	0.0985	-0.1809	0.2944*
Pain and discomfort (ref. no problem)						
Moderate pain or discomfort	0.0065	-0.1119**	0.0464	-0.0068	-0.0842*	0.0449
Extreme pain or discomfort	-0.1164*	-0.3149**	-0.0126	-0.1474**	-0.4162**	0.0400
Anxiety and Depression (ref. no problem)						
Moderately anxious or depressed	0.0573*	-0.0509	-0.0102	0.0399	-0.0492	-0.0085
Extremely anxious or depressed	0.0574	-0.1483**	-0.0535	0.0284	-0.1799***	-0.0964
Female	0.0577	0.0864	0.0914*	0.0308	0.0623	0.0739
15-17yo vs. 11-14yo	-0.0268	0.0213	0.0281	0.0054	0.0370	0.0532
Type of index episode (ref. self-poisoning)						
Self-injury				0.0234	0.0400	0.0080
Combined				0.0217	0.0168	-0.0089
Repeated SH episodes (ref. <3 events)				-0.0485	0.0098	0.0446
Hopelessness scale score				0.0077***	0.0018	0.0049
Parent						
McMaster Family Assessment				-0.0653*	-0.1110*	-0.0763
Family Questionnaire				-0.0024*	-0.0030	-0.0039**
Parent GHQ				-0.0310***	-0.0080*	-0.0122***
Female	-0.0743*	-0.0043	-0.0101	-0.0121	0.0051	0.0319
Centre (ref. Yorkshire)						
Manchester				-0.0655***	-0.0292	-0.0051
London				-0.0636**	0.0139	-0.0089
Constant	0.7327***	0.6787***	0.6038***	1.1493***	1.0491***	0.8299***
Observations	754	278	379	731	271	371
Rho-squared (R^2)	0.032	0.118	0.053	0.345	0.251	0.171

***p<0.001, **p<0.01, *p<0.05
HUI: Health Utility Index
GHQ: General Health Questionnaire
y.o: years old
ref. reference
SH: Self-harm

Table 5 – Regression model of the parent's health-related quality of life with adolescent's EQ-5D-3L score (full sample)

Variables		**Model 1**			**Model 2**	
	Baseline	6 months	12 months	Baseline	6 months	12 months
Adolescent						
EQ-5D-3L	-0.0002	0.3237***	0.0881	0.0370	0.3274***	0.1054
Female	0.0718*	0.0736	0.0858*	0.0380	0.0491	0.0683
15-17yo vs. 11-14yo	-0.0230	0.0175	0.0278	0.0061	0.0326	0.0549*
Type of index episode (ref. self-poisoning)						
Self-injury				0.0192	0.0485	0.0033
Combined				0.0257	0.0299	-0.0128
Repeated SH episodes (ref. >3 events)				-0.0369	0.0031	0.0642
Hopelessness scale score				0.0089***	0.0028	0.0037
Parent						
McMaster Family Assessment				-0.0702**	-0.1022*	-0.0710
Family Questionnaire				-0.0027**	-0.0028	-0.0033*
Parent GHQ				-0.0299***	-0.0085*	-0.0132***
Female	-0.0731*	-0.0041	-0.0090	-0.0125	0.0073	0.0370
Centre						
Manchester				-0.0668**	-0.0363	-0.0097
London				-0.0576*	0.01225	0.0045
Constant	0.7456***	0.3813**	0.5071***	1.1243***	0.7277***	0.6585***
Observations	754	278	379	731	271	371
Rho-squared (R^2)	0.015	0.099	0.017	0.328	0.228	0.136

***p<0.001, **p<0.01, *p<0.05; SH: Self Harm
HUI: Health Utility Index
GHQ: General Health Questionnaire
EQ-5D-3L: EuroQoL 5 Dimensions 3 Levels
y.o: years old
ref. reference
SH: Self-harm

Table 6 – Regression model of the parent's health-related quality of life with adolescent's EQ-5D-3L score (per treatment arm)

Variables		**Model 1**			**Model 2**	
	Baseline	6 months	12 months	Baseline	6 months	12 months
Treatment as usual						
Adolescent						
EQ-5D-3L	0.0076	0.4196***	0.2058*	0.0404	0.4418***	0.2914***
Female	0.0503	-0.0173	0.0033	0.0294	-0.0215	0.0001
15-17yo vs. 11-14yo	-0.0480	0.0460	-0.0343	-0.0084	0.0429	0.0030
Type of index episode (ref. self-poisoning)						
Self-injury				0.0054	0.0846	0.0314
Combined				0.0535	0.0879	0.0140
Repeated SH episodes (ref. >3 events)				-0.0262	0.0211	0.1036
Hopelessness scale score				0.0102**	0.0041	0.0057
Parent						
McMaster Family Assessment				-0.0033	-0.0664	0.0245
Family Questionnaire				-0.0042**	-0.0034	-0.0031
Parent GHQ				-0.0301***	-0.0117*	-0.0177**
Female	-0.1027**	0.0099	0.0188	-0.0164	-0.0019	0.0748
Centre						
Manchester				-0.0574	-0.0936	-0.0585
London				-0.0681*	-0.0215	-0.0184
Constant	0.8631***	0.4042	0.6121**	1.0796***	0.6809	0.3573
Observations	371	106	150	359	104	156
R^2	0.023	0.160	0.036	0.311	0.345	0.205
Family Therapy						
Adolescent						
EQ-5D-3L	-0.0057	0.2409**	-0.0106	0.0409	0.2088*	-0.0466
Female	0.0960*	0.1226*	0.1384*	0.0544	0.0864	0.1130*
15-17yo vs. 11-14yo	-0.0014	0.0033	0.6923*	0.0196	0.0229	0.0904**
Type of index episode (ref. self-poisoning)						
Self-injury				0.0433	0.0412	0.0015
Combined				0.0053	0.0236	-0.0107
Repeated SH episodes (ref. >3 events)				-0.0488	-0.0021	0.0443
Hopelessness scale score				0.0065*	0.0013	-0.0006
Parent						
McMaster Family Assessment				-0.1417***	-0.1010	-0.1342*
Family Questionnaire				-0.0011	-0.0036	-0.0036
Parent GHQ				-0.0285***	-0.0053	-0.0076
Female	-0.0457	-0.0125	0.0042	-0.0223	0.0200	0.0291
Centre						
Manchester				-0.0873***	0.0028	0.0015
London				-0.0501	0.0380	-0.0107
Constant	0.6297***	0.4004*	0.4251*	1.1860***	0.7829**	0.8559***
Observations	383	172	219	372	167	215
Rho-squared (R^2)	0.016	0.082	0.045	0.365	0.179	0.155

***p<0.001, **p<0.01, *p<0.05
HUI: Health Utility Index
GHQ: General Health Questionnaire
EQ-5D-3L: EuroQoL 5 Dimensions 3 Levels
y.o: years old
ref. reference
SH: Self-harm

Table 7 – Regression model of the parent's health-related quality of life with adolescent's EQ-5D-3L score (per repeated SH event at 12 months)

Variables		**Model 1**			**Model 2**	
	Baseline	6 months	12 months	Baseline	6 months	12 months
No repeated self-harm						
Adolescent						
EQ-5D-3L	0.0157	0.2934***	0.1304*	0.0230	0.3074***	0.1417*
Female	0.0827*	0.0813	0.0513	0.0306	0.4142	0.0337
15-17yo vs. 11-14yo	-0.0352	0.0274	0.0148	-0.0079	0.0360	0.0424
Type of index episode (ref. self-poisoning)						
Self-injury				-0.0098	0.0280	-0.0559
Combined				-0.0025	0.0390	-0.1105
Repeated SH episodes (ref. >3 events)				0.0005	-0.0078	0.0811*
Hopelessness scale score				0.0070**	-0.0005	0.0017
Parent						
McMaster Family Assessment				-0.0666*	-0.1015**	-0.0902*
Family Questionnaire				-0.0024*	-0.0034*	-0.0021
Parent GHQ				-0.0281***	-0.0069	-0.0129**
Female	-0.0790*	0.0420	-0.0143	-0.0160	0.0488	0.0318
Centre						
Manchester				-0.0640**	-0.0158	0.0145
London				-0.0532*	0.0237	0.0416
Constant	0.7641***	0.2900*	0.5891***	1.1192***	0.7436***	0.7164***
Observations	554	214	287	536	208	279
R^2	0.024	0.085	0.018	0.308	0.234	0.148
Repeated self-harm						
Adolescent						
EQ-5D-3L	-0.0696	0.4245**	-0.056	0.0686	0.4354**	-0.0475
Female	0.0783	0.0601	0.3375**	0.0852	0.0864	0.3021*
15-17yo vs. 11-14yo	-0.0021	-0.0264	0.0944	0.0461	0.0255	0.1316
Type of index episode (ref. self-poisoning)						
Self-injury				0.0981*	0.1283	0.1526*
Combined				0.1185	0.0434	0.2141
Repeated SH episodes (ref. >3 events)				-0.1670*	0.1072	0.0262
Hopelessness scale score				0.0157***	0.0230*	0.0096
Parent						
McMaster Family Assessment				-0.0961	-0.2332	-0.0656
Family Questionnaire				-0.0040	-0.0016	-0.0085*
Parent GHQ				-0.031***	-0.0067	-0.0026
Female	-0.0511	-0.2073	0.0697	-0.0099	-0.2373	0.0554
Centre						
Manchester				-0.0496	-0.0800	-0.0117
London				-0.0652	0.0340	-0.0887
Constant	0.6500**	0.7893*	-0.1222	1.1835***	0.8491	0.2915
Observations	200	64	92	195	63	92
Rho-squared (R^2)	0.011	0.165	0.087	0.395	0.327	0.298

***p<0.001, **p<0.01, *p<0.05
HUI: Health Utility Index
GHQ: General Health Questionnaire
EQ-5D-3L: EuroQoL 5 Dimensions 3 Levels
y.o: years old
ref. reference
SH: Self-harm

Table 8 – Regression model of the parent's health-related quality of life with adolescent's EQ-5D-3L score (per repeated SH event at 12 months and per treatment arm)

Variables		**Model 1**			**Model 2**	
	Baseline	6 months	12 months	Baseline	6 months	12 months
Treatment as Usual - No repeated self-harm						
Adolescent						
EQ-5D-3L	0.0243	0.1856	0.1987*	0.0420	0.1684	0.2788**
Female	0.0668	-0.0364	-0.0416	0.0375	-0.0424	-0.0411
15-17yo vs. 11-14yo	-0.0564	0.0298	-0.0291	-0.0360	0.0258	0.0143
Type of index episode (ref. self-poisoning)						
Self-injury				0.0010	0.0627	0.0127
Combined				0.0865	0.1064	-0.0657
Repeated SH episodes (ref. >3 events)				0.0272	-0.0402	0.0101
YP hopelessness scale score				0.0099**	-0.0027	0.0088
Parent						
McMaster Family Assessment				0.0029	-0.0794	0.0323
Family Questionnaire				-0.0036**	-0.0025	-0.0026
Parent GHQ				-0.0284***	-0.0092	-0.0168**
Female	-0.1072*	0.0932	-0.0280	-0.0399	0.0759	0.0235
Centre						
Manchester				-0.0540	-0.0513	-0.0252
London				-0.0688*	-0.0224	0.0133
Constant	0.8673***	0.5064*	0.7928***	1.013***	0.9689**	0.4702
Observations	280	87	126	270	85	122
R^2	0.031	0.059	0.043	0.308	0.255	0.201
Treatment as Usual - Repeated self-harm						
Adolescent						
EQ-5D-3L	-0.0909	0.9669**	0.1862	0.0249	1.4087**	0.4205
Female	0.0359	#	0.2066	0.0433	#	0.0499
15-17yo vs. 11-14yo	-0.0412	0.1981	-0.1139	0.0655	0.5528	-0.2049
Type of index episode (ref. self-poisoning)						
Self-injury				-0.0006	-0.3142	0.2629
Combined				0.0843	-0.2239	0.5284
Repeated SH episodes (ref. >3 events)				-0.2205*	-0.0751	0.3148
Hopelessness scale score				0.0124	0.0350	-0.0123
Parent						
McMaster Family Assessment				0.0084	-0.5550	0.0076
Family Questionnaire				-0.0070*	-0.0015	-0.0003
Parent GHQ				-0.0332***	0.0178	-0.0224
Female	-0.1000	-0.2824	0.2511	0.0291	-0.4968	0.4080
Centre						
Manchester				0.0083	-0.3630	-0.3032*
London				-0.0413	-0.0718	-0.1341
Constant	0.8593**	0.3808	-0.1426	1.2901**	1.5005	-0.6594
Observations	91	19	34	89	19	34
Rho-squared (R^2)	0.029	0.439	0.151	0.371	0.817	0.513

Continued

Continued

Family therapy - No repeated self-harm						
Adolescent						
EQ-5D-3L	0.0098	0.3509***	0.0592	0.0224	0.3435**	-0.0306
Female	0.1032*	0.132*	0.1197*	0.0276	0.0687	0.0819
15-17yo vs. 11-14yo	-0.0166	0.0221	0.0388	0.0142	0.0357	0.0516
Type of index episode (ref. self-poisoning)						
Self-injury				-0.0083	0.0191	-0.0843
Combined				-0.0800	0.0170	-0.1161
Repeated SH episodes (ref. >3 events)				-0.0187	0.0132	0.0696
YP hopelessness scale				0.0042	-0.0008	-0.0044
Parent						
McMaster Family				-0.1337***	-0.1109*	-0.1872***
Family Questionnaire				-0.0011	-0.0044*	-0.0020
Parent GHQ				-0.0275***	-0.0056	-0.0062
Female	-0.0526	0.0046	0.0170	-0.0088	0.0294	0.0570
Centre						
Manchester				-0.0801**	0.0028	0.0361
London				-0.0412	0.0374	0.0577
Constant	0.6576***	0.2230	0.4314*	1.2103***	0.7291**	0.9716***
Observations	274	127	161	266	123	157
R^2	0.176	0.131	0.036	0.348	0.253	0.208
Family therapy - Repeated self-harm						
Adolescent						
EQ-5D-3L	-0.0567	0.1401	-0.2816	0.0928	0.1438	-0.2314
Female	0.1087	0.0441	0.4236*	0.1413	0.0529	0.2705
15-17yo vs. 11-14yo	0.0274	-0.0393	0.2167**	0.0484	0.0199	0.2164*
Type of index episode (ref. self-poisoning)						
Self-injury				0.1706**	0.1874	0.1578
Combined				0.1456	0.1338	0.1441
Repeated SH episodes (ref. >3 events)				-0.1723*	-0.0752	0.0007
YP hopelessness scale				0.0139*	0.0155	0.0136
Parent						
McMaster Family				-0.1883*	-0.0810	-0.0413
Family Questionnaire				-0.0010	-0.0027	-0.0105*
Parent GHQ				-0.030***	-0.0037	-0.0016
Female	-0.0072	-0.1385	-0.366	-0.1193	-0.3135	-0.4149
Centre						
Manchester				-0.0835	0.0557	-0.0010
London				-0.0737	0.0541	-0.0550
Constant	0.4837	0.9532**	0.5835	1.3097***	1.3775	1.3884
Observations	109	45	58	106	44	58
R^2	0.012	0.040	0.203	0.460	0.190	0.401

***p<0.001, **p<0.01, *p<0.05; # Omitted because of collinearity
HUI: Health Utility Index
GHQ: General Health Questionnaire
EQ-5D-3L: EuroQoL 5 Dimensions 3 Levels
y.o: years old
ref. reference
SH: Self-harm

Table 9 – Incremental cost-effectiveness ratios with alternative spillover quantifications

Scenario	Costs (SE)	QALY (SE)	ICER
Base-case analysis			
TAU (n=73)	£3,484.06 (382.68)	0.756 (0.021)	
FT (n=133)	£4,564.71 (259.15)	0.779 (0.016)	
	Incremental Costs	*Incremental QALY*	
FT vs. TAU	£1,080.66*** (450.20)	0.024 (0.027)	£45,330.30
Relative health spillover – with control			
TAU (n=73)	£3,484.06 (382.68)	0.955 (0.021)	
FT (n=133)	£4,564.71 (259.15)	0.979 (0.016)	
	Incremental Costs	*Incremental QALY*	
FT vs. TAU	£1,080.66*** (450.20)	0.024 (0.027)	£45,330.29
Relative health spillover per treatment arm – with control			
TAU (n=73)	£3,484.06 (382.68)	1.059 (0.021)	
FT (n=133)	£4,564.71 (259.15)	0.882 (0.016)	
	Incremental Costs	*Incremental QALY*	
FT vs. TAU	£1,080.66*** (450.20)	-0.177 (0.027)	Dominated
Absolute health spillover – with control			
TAU (n=73)	£3,484.06 (382.68)	0.955 (0.021)	
FT (n=133)	£4,564.71 (259.15)	0.980 (0.016)	
	Incremental Costs	*Incremental QALY*	
FT vs. TAU	£1,080.66*** (450.20)	0.026 (0.026)	£41,995.90
Absolute health spillover per treatment arm – with control			
TAU (n=73)	£3,484.06 (382.68)	1.018 (0.028)	
FT (n=133)	£4,564.71 (259.15)	0.920 (0.017)	
	Incremental Costs	*Incremental QALY*	
FT vs. TAU	£1,080.66*** (450.20)	-0.097 (0.031)	Dominated
Additive spillover[#]			
TAU (n=73)	£3,484.06 (382.68)	1.537 (0.041)	
FT (n=133)	£4,564.71 (259.15)	1.569 (0.027)	
	Incremental Costs	*Incremental QALY*	
FT vs. TAU	£1,080.66*** (450.20)	0.032 (0.047)	£33,690.35

***p<0.001, **p<0.01, *p<0.05; [#]The adolescent's and parent's QALYs are summed
TAU: Treatment As Usual
FT: Family Therapy
vs. : versus
SE: standard error
QALY: Quality-Adjusted Life Years
ICER: Incremental Cost-Effectiveness Ratio