**Supplementary Content:**

**Review Protocol: The Cost-Effectiveness of 5-ALA in High Grade Glioma Surgery: A Quality-Based Systematic Review**

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**Background:**

High grade gliomas (HGG) are the most common primary malignant brain tumors in adults. While increased extent of resection (EOR) is associated with improved survival, the infiltrative nature of HGG makes curative treatment a significant challenge. Introduction of the intra-operative adjunct, 5-aminolevulonic acid (5-ALA) in HGG surgery has been shown to increase EOR when compared to standard white light surgery. 5-ALA has therefore been increasingly used in European nations over the years and most recently has been approved for clinical use by the US Food and Drug Administration (FDA), though it remains under review by Health Canada. Currently, no large trials have addressed the impact of increased EOR on post-operative morbidity and quality of life; it is therefore unclear whether the increase in survival may be offset by lower quality of life. Health economic evaluations, which consider costs to patient and society in terms of clinical benefit and quality of life, are essential to guide policy and practice by health providers, insurance companies, and within the Canadian context where 5-ALA has not yet been approved. We therefore aim to conduct the first systematic review on the cost-effectiveness of 5-ALA for HGG surgery.

**Review Questions:**

This review aims to establish, through the existing literature, whether 5-ALA can be a cost-effective adjunct in HGG surgery. Specifically, our questions are:

1. Is 5-ALA a cost-effective adjunct in HGG surgery?
2. What information and lessons can be learned to guide the potential adoption of this technology in the Canadian healthcare system?

**Inclusion Criteria:**

*Types of Participants:*

This review will consider all studies that involve a comparison of human subjects of any age undergoing either traditional white-light surgery or 5-ALA guided surgery for HGG resection. HGG are defined as WHO Grade III or Grade IV glial neoplasms. Although pathological confirmation of diagnosis would be preferred, it will not be a requirement for inclusion in this review.

*Types of intervention:*

Only those studies comparing traditional white-light surgery with 5-ALA guided resection will be included.

*Types of outcome measure:*

The primary outcome of interest is cost effectiveness. This may be measured as cost relative to benefit with a variety of denominators such as progression-free survival, overall survival, quality-adjusted life years gained, overall life years gained, disability, functional status, or other such variables. Studies utilizing incremental cost ratios, which examine the difference in cost of two interventions divided by the difference in their effects, will also be considered.

*Types of studies:*

Our review will consider all health-economic analyses of 5-ALA in HGG surgery. Given that we are focused on assessing the *value* provided by 5-ALA and not simply its monetary cost, simple cost analyses that do not assess cost relative to a specified outcome measure will be excluded. No limits will be placed on date of publication. Only English-language manuscripts will be considered for inclusion.

**Search Strategy:**

The search strategy will be designed to encompass as many relevant papers within the medical and health-economic literature as possible. The search will include Medline, EMBASE, Centre for Reviews and Dissemination (CRD), EconPapers, and the Cochrane databases.

An example of the search strategy utilized for the Medline database is outlined as follows:

Database: Ovid MEDLINE(R) <1946 to March Week 4 2019>

Search Strategy:

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1 exp glioma/ (82048)

2 exp glioblastoma/ (24713)

3 anaplastic astrocytoma.mp/ (1940)

4 glioma/ or astrocytoma/ or gliosarcoma/ (50892)

5 exp Aminolevulinic Acid/ or 5-ALA.mp. (5854)

6 exp Costs and Cost Analysis (233953)

7 1 or 2 or 3 or 4 (82383)

8 5 and 6 and 7 (6)

Full copies of articles identified by the search meeting inclusion criteria based on title and abstract will be obtained. Two independent reviewers will then screen full texts against the specified inclusion criteria (NW, RZ). Discrepancies will be resolved by a discussion between the two reviewers and review by a third independent investigator (AM) in the case an agreement cannot be met.

**Data Collection:**

Data extraction will then proceed on all of the included papers based on the attached data collection form. Two reviewers will independently perform the data extraction (NW, RZ). Quality of each study will also be assessed utilizing the BMJ quality assessment tool for health-economic reports. Two independent reviewers will complete the quality assessment individually (BK, NP) and any discrepancies will be resolved by review by a third reviewer (AM).

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| **Study** | **Country** | **Data Source** | **Inclusion Criteria** | **Sample Size** | **Time frame** | **Modelling Used** | **Quality Rating** | **Cost-effectiveness measures** | **Cost-Effectiveness Results** |
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