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BMJ Open

Positron emission tomography (PET) for prediction of glioma histology: Protocol for an individual-level data meta-analysis of test performance.

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Manuscripts

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6 1 **Title:** Positron emission tomography (PET) for prediction of glioma histology: Protocol
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8 2 for an individual-level data meta-analysis of test performance.
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44
45 33 **Keywords:** Glioma, Positron-Emission Tomography, Network Meta-Analysis

46
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6 **Abstract:**
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8 **Introduction:** Gliomas, the most commonly diagnosed primary brain tumors, are
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11 associated with varied survivals based, in part, on their histological subtype. Therefore,
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14 accurate pretreatment tumor grading is essential for patient care and clinical trial design.
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16
17 **Methods and Analysis:** We will perform an individual-level data meta-analysis of
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20 published studies to evaluate the ability of different types of PET to differentiate high
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23 from low grade gliomas. **Ethics and Dissemination:** Ethics approval was not
24
25
26 applicable, as this is a meta-analytic study. Results of the analysis will be submitted for
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29 publication in a peer-reviewed journal.
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31 Review PROSPERO registration number: 78649
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47 **Article Summary:**

48 Strengths of this study

- 49 • This is a first of its kind network meta-analysis aiming to establish the
50 diagnostic accuracy of PET with various tracers for grading of glioma.
51 Individual treatment meta-analysis with pooling of data can provide more
52 statistical power to determine differences between imaging modalities.

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6 53 Limitations
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9 54 • Variability of data obtained from external sources and limited number of
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11 55 patients.

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14 56 • Inherent limitations of MTM and IPD-MA for data interpretation / findings
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17 57 might be speculative
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6 **71 Background**

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9 72 Gliomas are among the most commonly diagnosed primary brain tumors with an
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11 73 estimated annual incidence of over 20,000 in the United States (SEER projection for
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14 74 2017). Based on clinical, histological and molecular characteristics, gliomas can be
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17 75 broadly divided into two major clinical subcategories: low-grade and high-grade.
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20 76 High-grade gliomas (also called malignant gliomas) are rapidly growing tumors and
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23 77 include glioblastomas (grade IV), anaplastic astrocytomas (grade III), mixed anaplastic
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26 78 oligoastrocytomas (grade III), and anaplastic oligodendrogliomas (grade III). Despite
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29 79 recent advances in multimodality therapies including temozolomide, high-grade gliomas
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32 80 remain incurable with a median survival of less than 3 years for glioblastomas and less
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35 81 than 5 years for anaplastic gliomas (NCCN & ESMO Clinical Practice Guidelines).
36
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38 82 In contrast, the low-grade gliomas include astrocytomas (grade II), oligodendrogliomas
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41 83 (grade II), and oligoastrocytomas (grade II), and are indolent, with a median survival
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44 84 over 5 years[1]. Treatment of low grade gliomas is evolving and includes maximal
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47 85 tumor resection with the option of radiation and chemotherapy[2].
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50 86 From the above it is evident that accurate pre-therapy histological grading is of
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53 87 paramount importance. In the usual clinical setting, histology is clarified with
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56 88 conventional computed tomography (CT) or magnetic resonance imaging (MRI),
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6 89 image-guided biopsy /subtotal surgical resection or near total resection. Unfortunately,
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9 90 apart from complete resection, other approaches are error-prone: Imaging does not
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11 91 provide usable tissue for final diagnosis. Biopsies and partial resections can misguide,
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14 92 as gliomas can demonstrate histological heterogeneity due to histopathological
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17 93 progression; a tumor often has both low- and high-grade components. Unless total
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20 94 surgical resection is performed, histological results depend on which part of the tumor is
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23 95 sampled.

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25 96 As much as it is desirable, extensive tumor resection is not always feasible in
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28 97 frail patients or those with tumors located adjacent to critical structures. Therefore, in
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31 98 order to improve tumor grading either noninvasively, or by better, targeted biopsies, one
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34 99 needs to be able to supplement morphological information obtained from conventional
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37 100 imaging with tumor-specific functional information.

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39 101 PET is a useful imaging modality that provides additional metabolic
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42 102 information to CT- or MRI-based morphologic characterization of tumors. Its usefulness
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45 103 has been proven in lung cancer[3] and aggressive lymphomas[4]. Several studies have
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48 104 evaluated PET using various tracers such as 18F-FDG, 11C-MET, 18F-FET, and
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51 105 18F-FLT for pre-therapy histological prediction to differentiate high-grade from
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54 106 low-grade glioma, and reported promising results[5-7]. The sample sizes of these

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6 107 studies, however, are typically small, resulting in imprecise estimates of diagnostic
7
8 108 accuracy and use heterogeneous designs / protocols for PET assessment, making
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11 109 interpretation of the published data difficult. Often, the positivity cutoff criteria are
12
13
14 110 defined *post-hoc* to calculate the best pairs of sensitivity and specificity for each study
15
16
17 111 and lack generalizability. In this situation, aggregate-level data meta-analysis
18
19
20 112 (ALD-MA) typically calculates overestimated summary statistics.
21
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23 113 A useful approach to the above problem to perform a meta-analysis based on
24
25
26 114 individual-level data (Individual-level data meta-analysis; ILD-MA). This technique
27
28
29 115 employs a predefined uniform cutoff value to estimate test performance measures for all
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31
32 116 included studies and combines their results. IPD-LD can also evaluate the effect of
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35 117 specific factors on test performance at the level of individual, simultaneously
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38 118 accounting for between-study variations. We therefore planned an ILD-MA to provide a
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41 119 comprehensive overview and quantitative synthesis of information on the test
42
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44 120 performance of PET for this purpose.
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122 **Methods**

123 This meta-analysis is an extension of a part of a series of systematic reviews on PET in
124 clinical management of patients with glioma[8][9]. Although these reviews share a

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6 125 common literature search until June 2011, each project employs an independent
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8 126 prespecified research protocol with standard systematic review methodologies, and
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11 127 assesses mutually exclusive research objectives. Interim results of an earlier related
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14 128 study of this research project have been presented at an international meeting[10] but
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17 129 never published as full-text.
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21 22 23 131 *Literature search*

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25 132 We will use our literature database of publications on PET assessed for patients with
26
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28 133 glioma. We established the database based on the searches of PubMed and Scopus from
29
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31 134 inception through June 30, 2011 with no language restriction and full-text evaluation of
32
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34 135 potentially relevant articles found through abstract screening. The complete search
35
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37 136 strategy and full list of the database is reported elsewhere[9]. We will update the
38
39
40 137 searches until July 30, 2017, and examine the reference lists of eligible studies and
41
42
43 138 relevant review articles.

44
45 139 One reviewer (TN or NAT) will screen abstracts and at least two of three investigators
46
47
48 140 (TT, NAT, and TT) examine full-text articles of potentially eligible citations.
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51 141 Discrepancies will be resolved by consensus.

52 53 54 142 *Inclusion and exclusion criteria*

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8 144 We will select studies that assess PET using 18F-FDG, 11C-MET, 18F-FET, or 18F-FLT
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10
11 145 for predicting glioma grading, verified with histologic confirmation by surgery or
12
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14 146 biopsy to be eligible. We have selected these four particular tracers before conducting
15
16
17 147 this research on the basis of an empirical evaluation of published studies of PET on
18
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20 148 glioma[9] and recently published narrative reviews[11][12]. We will include both
21
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23 149 prospective and retrospective studies. We will define pathologic confirmation (either by
24
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26 150 biopsy or surgical resection) as the acceptable reference standard and explicitly exclude
27
28
29 151 studies (or individual patients in a study), in which (or for whom, respectively),
30
31
32 152 pathological confirmation is not performed. We will consider the total surgical resection
33
34
35 153 as the (nearly) perfect reference standard, whereas, (stereotactic) biopsy will be deemed
36
37
38 154 to be the imperfect reference standard. We will include only English language
39
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41 155 publications that evaluated at least 10 patients for whom PET scanning and
42
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44 156 histopathological confirmation is successfully performed. We will also exclude
45
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47 157 editorials, comments, letters to the editor, and review articles. When multiple
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50 158 publications with potentially overlapping patient populations are available, we will only
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53 159 include a publication with the largest sample size.

54 160 We will contact study authors by email if studies do not report adequate
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6 161 information on PET and histological results in the participant-level. We will consider
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9 162 our request to be rejected if two email request reminders separately sent q 14 days after
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12 163 the initial contact attempt are rejected. Even in this case, we will allow for the inclusion
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15 164 of a study report in which quantitative data is not reported but the digital extraction (i.e.,
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17 165 data extraction by using a digitizer from its published graphical presentations) is
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20 166 feasible. Otherwise we will exclude these studies. Data will be kept in a shared secure
21
22
23 167 folder accessible by all co-authors.

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26 168 ***Data extraction***

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28 169 One reviewer (TN or NAT) will extract descriptive data from each eligible study.
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30
31 170 Another one non-overlapping investigator (TN, NAT, or TT) will verify all the extracted
32
33
34 171 data. We will extract the following published descriptive information from eligible
35
36
37 172 studies: first author, year of publication, journal, patient demographics and clinical
38
39
40 173 characteristics, therapeutic interventions in the case of post-therapy or recurrence
41
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43 174 assessment, technical specifications of PET, and interpretation of PET results.

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48 176 One reviewer (TN, or NAT) will extract published quantitative data regarding imaging
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51 177 results (i.e., visual assessment and quantitative assessment such as standard uptake
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54 178 values (SUVs) or tumor-to-normal uptake ratio (T/N ratio)) and final diagnoses (i.e.,

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6 179 histopathologic subtype and grading) at the individual level. Another one reviewer (TT)
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9 180 will verify all the data. We will exclude any cases in which PET scanning is
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11 181 unsuccessful (and thus results are arbitrary imputed *post-hoc*). We will also exclude any
12
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14 182 cases in which alternative reference standards such as clinical follow-up instead of
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17 183 pathological confirmation is used to determine histologic grading.
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20 184 If reported, we will also extract the following individual-level variables as the candidate
21
22 185 effect-modifiers to be evaluated in meta-regression: age, sex, clinical scenario (i.e.,
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25 186 primary diagnosis vs. post-therapy/recurrence assessment), and tissue sampling methods
26
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28 187 (i.e, how the pathological specimens are obtained, either biopsy, partial or total
29
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31 188 resection)

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37 190 ***Assessment of risk of bias.***

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40 191 To assess the risk of bias and applicability of each study, two reviewers (TN, NAT) will
41
42 192 independently assess patient selection, index test, reference standard, and their flow and
43
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45 193 timing based on the revised Quality Assessment of Diagnostic Accuracy Studies
46
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48 194 (QUADAS-2). Discrepant ratings will be resolved by consensus. The complete list of
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51 195 operational definitions to rate each item is available from the authors upon request.

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6 197 ***Data synthesis***
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9 198 We will use a bivariate model to obtain an estimate of the summary sensitivity and
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11 199 specificity with their corresponding confidence intervals (CIs). We will fit a two-level a
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13
14 200 generalized mixed regression model conditional on the sensitivity and specificity of
15
16
17 201 each study and a bivariate normal model for the sensitivity and specificity between
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20 202 studies [13](Reitsma et al, 2005 Journal of Clinical Epidemiology; Chu H and Cole SR,
21
22 203 2006, Journal of Clinical Epidemiology). We will calculate summary positive and
23
24
25 204 negative likelihood ratios based on the summary sensitivity and specificity estimates.
26
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28 205 Positive likelihood ratio (LR+) is the ratio of sensitivity over (1-specificity) whereas
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31 206 negative likelihood ratio (LR-) is defined as the ratio of (1-sensitivity) over specificity.
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33
34 207 The discriminating ability of a diagnostic test is better with higher LR+ and lower LR-.
35
36
37 208 A good diagnostic test typically has LR+ >5.0 and LR- <0.2. We will also construct a
38
39
40 209 hierarchical summary receiver operating characteristic curve (HSROC) based on the
41
42
43 210 parameters of the fitted model (Rutter Cm and Gatsonis CA, 2001; Statistics in
44
45
46 211 Medicine; Macaskill P, 2004; Journal of Clinical Epidemiology). We will assess
47
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49 212 between-study heterogeneity visually using forest plots, and also by plotting sensitivity
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52 213 and specificity in the ROC space. We will construct 95% credible regions for summary
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55 214 sensitivity and specificity from the estimated parameters as proposed[14].
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9 216 ***Subgroup analysis and meta-regression***

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11 217 To explore heterogeneity, we will perform subgroup analyses and if feasible, the
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14 218 statistical differences among mutually exclusive subgroups will be assessed by
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17 219 univariable meta-regression. We will add a candidate modifier (as either 0 [absence] or
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20 220 1 [presence]) to the test performance parameters (i.e., sensitivity and specificity
21
22
23 221 parameters, or diagnostic odds ratio and threshold parameters, respectively) jointly in
24
25
26 222 the bivariate random-effects model or binormal random-effects model, respectively.
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28 223 We will record: publication year, study design (i.e., prospective versus retrospective) as
29
30
31 224 the study-level covariates, age, sex, clinical scenario (i.e., primary diagnosis vs.
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34 225 post-therapy/recurrence assessment) and tissue sampling methods (i.e., biopsy vs.
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37 226 partial or subtotal resection vs. total resection).

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42 228 ***Comparisons among different PET methodologies***

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45 229 We will compare the test performance among alternative PET tracers, and also those
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48 230 based on different imaging assessment protocols (i.e., visual assessment vs. quantitative
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51 231 assessment, either T/N ratios or SUVs). Regarding the T/N ratios, we will operationally
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54 232 define three categories based on the specified referent tissues: mean or median uptakes
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6 233 in the gray matter (GM), those in the white matter (WM), and other miscellaneous
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9 234 methods (MISC) including mean or median uptakes in the contra-lateral corresponding
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11 235 anatomical sites or those in the adjacent normal tissue regardless of GM or WM.
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14 236 For indirect comparisons, we will visually compare the constructed summary
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17 237 ROC curves and the credible regions of sensitivity and specificity. We will also
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20 238 statistically assess the differences by univariable meta-regression using the tracers or
21
22 239 assessment methods as the covariate being incorporated into the meta-analytic model.
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25 240 These results however, need to be interpreted carefully because findings from the
26
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28 241 indirect comparisons may be only speculative[15]. To tackle this issue, we will also
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31 242 perform these analyses limiting only to comparative studies that assess multiple tracers
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34 243 or methods for the same participants, from which direct comparisons can be performed.
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37 244 We will conduct all analyses using STATA, version 14/SE (Stata Corp, College
38
39 245 Station, TX), and OpenBUGS, version 3.2.3 (members of OpenBUGS Project
40
41
42 246 Management Group; see www.openbugs.net). All tests will be two-sided and statistical
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45 247 significance will be defined as a p -value $< .05$.
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48 248 **Discussion**

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51 249 Differentiating high from low grade malignancies has significant prognostic
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54 250 information for a variety of tumors; gliomas are not an exception. While an optimally
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6 251 resected biopsy specimen is always preferable to indirect evidence, imaging can provide
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9 252 helpful adjunct information. Moreover, functional imaging, such as positron emission
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12 253 tomography with select biotracers has the potential to become a powerful tool in
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15 254 assessment of patients and influence treatment decisions. By conducting a multiple
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18 255 treatment meta- analysis and IPD meta-analysis, this study hopes to clarify the
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21 256 diagnostic accuracy of PET/CT with various tracers in differentiating glioma histology
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24 257 and establish thresholds, upon which further studies can be performed.

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26 258 **Contributorship statement:** Abstract screening: TN and NAT. Full-text article
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29 259 examination: TT, NAT, and TT. Data extraction: TN, TT and NAT. Assessment of the
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32 260 risk of bias and applicability of each study: TN and NAT. Statistical analysis: TT and
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35 261 EE. All authors (TN,TT,EE,NAT) have equally contributed to the final version of the
36
37
38 262 protocol, have reviewed and have approved of it.

39
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42
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44
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46 265 commercial or not-for-profit sectors.

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52 267 freely upon request.

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54 268 **Provenance and peer review:** Not commissioned; externally peer reviewed.
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46 319 **of comparative studies of diagnostic test accuracy.** *Ann Intern Med* 2013,
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48 320 **158**(7):544-554.
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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a Line1	Identify the report as a protocol of a systematic review.
Update	1b Line 123	If the protocol is for an update of a previous systematic review, identify as such
Registration	2 Line 44	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a Line 23	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b Line 258	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4 Not applicable	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a Line 264	Indicate sources of financial or other support for the review
Sponsor	5b N/A	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c N/A	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6 Line 72	Describe the rationale for the review in the context of what is already known
Objectives	7 Line 118	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8 Line 132	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9 Line 133	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10 Line 135	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		

Data management	11a Line 166	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b Line 144	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c Line 169	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12 Line 171	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13 Line 176	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14 Line 190	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a Line 205 15b Line 198 15c Line 216 15d	Describe criteria under which study data will be quantitatively synthesised If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ) Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16 Line 191	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17 Line 211 and 217	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Positron emission tomography (PET) for prediction of glioma histology: Protocol for an individual-level data meta-analysis of test performance.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-020187.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Dec-2017
Complete List of Authors:	Trikalinos, Nikolaos; Washington University in St Louis, Internal Medicine Nihashi, Takashi ; Komaki Shimin Byoin, Department of Radiology Evangelou, Evangelos; Dept of Hygiene and Epidemiology Terasawa, Teruhiko; Fujita Hoken Eisei Daigaku Igakubu Daigakuin Igaku Kenkyuka, Department of Emergency and General Internal Medicine
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Diagnostics
Keywords:	glioma, PET, meta-analysis

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Manuscripts

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6 1 **Title:** Positron emission tomography (PET) for prediction of glioma histology: Protocol
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8 2 for an individual-level data meta-analysis of test performance.
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43 44 33 **Keywords:** Glioma, Positron-Emission Tomography, Network Meta-Analysis

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46 47 34 Word count: 2072 (excluding title page, abstract, references, figures and tables)

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6 35 **Abstract:**

7
8 36 **Introduction:** Gliomas, the most commonly diagnosed primary brain tumors, are
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11 37 associated with varied survivals based, in part, on their histological subtype. Therefore,
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14 38 accurate pretreatment tumor grading is essential for patient care and clinical trial design.
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17 39 **Methods and Analysis:** We will perform an individual-level data meta-analysis of
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19
20 40 published studies to evaluate the ability of different types of PET to differentiate high
21
22
23 41 from low grade gliomas. We will search PubMed and Scopus from inception through
24
25
26 42 July 30, 2017 with no language restriction and full-text evaluation of potentially
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28
29 43 relevant articles. We will choose studies that assess PET using 18F-FDG, 11C-MET,
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31 44 18F-FET, or 18F-FLT for grading, verified with histologic confirmation. We will
32
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34 45 include both prospective and retrospective studies. Bias will be assessed by two
35
36
37 46 reviewers with the QUADAS-2 tool and as per method described by Deeks et al. **Ethics**
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39
40 47 **and Dissemination:** Ethics approval was not applicable, as this is a meta-analytic study.
41
42
43 48 Results of the analysis will be submitted for publication in a peer-reviewed journal.
44

45 49 PROSPERO registration number: CRD42017078649
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6 **53 Article Summary:**
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9 **54 Strengths of this study**

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11 • 55 This is a first of its kind network meta-analysis aiming to establish the
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14 56 diagnostic accuracy of PET with various tracers for grading of glioma.
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17 57 Individual treatment meta-analysis with pooling of data can provide more
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20 58 statistical power to determine differences between imaging modalities.
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22
23 **59 Limitations**

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25 • 60 Variability of data obtained from external sources and limited number of
26
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28 61 patients.
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31 • 62 Inherent limitations of MTM and IPD-MA for data interpretation / findings
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34 63 might be speculative
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6 **71 Background**

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9 72 Gliomas are among the most commonly diagnosed primary brain tumors with an
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11 73 estimated annual incidence of over 20,000 in the United States (SEER projection for
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14 74 2017). Based on clinical, histological and molecular characteristics, gliomas can be
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16
17 75 broadly divided into two major clinical subcategories: low-grade and high-grade.
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20 76 High-grade gliomas (also called malignant gliomas) are rapidly growing tumors and
21
22
23 77 include glioblastomas (grade IV), anaplastic astrocytomas (grade III), mixed anaplastic
24
25
26 78 oligoastrocytomas (grade III), and anaplastic oligodendrogliomas (grade III). Despite
27
28
29 79 recent advances in multimodality therapies including temozolomide, high-grade gliomas
30
31
32 80 remain incurable with a median survival of less than 3 years for glioblastomas and less
33
34
35 81 than 5 years for anaplastic gliomas (NCCN & ESMO Clinical Practice Guidelines).
36
37
38 82 In contrast, the low-grade gliomas include astrocytomas (grade II), oligodendrogliomas
39
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41 83 (grade II), and oligoastrocytomas (grade II), and are indolent, with a median survival
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43
44 84 over 5 years[1]. Treatment of low grade gliomas is evolving and includes maximal
45
46
47 85 tumor resection with the option of radiation and chemotherapy[2].
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50 86 From the above it is evident that accurate pre-therapy histological grading is of
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53 87 paramount importance. In the usual clinical setting, histology is clarified with
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56 88 conventional computed tomography (CT) or magnetic resonance imaging (MRI),
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6 89 image-guided biopsy /subtotal surgical resection or near total resection. Unfortunately,
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9 90 apart from complete resection, other approaches are error-prone: Imaging does not
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11 91 provide usable tissue for final diagnosis. Biopsies and partial resections can misguide,
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14 92 as gliomas can demonstrate histological heterogeneity due to histopathological
15
16
17 93 progression; a tumor often has both low- and high-grade components. Unless total
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20 94 surgical resection is performed, histological results depend on which part of the tumor is
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23 95 sampled.

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25 96 As much as it is desirable, extensive tumor resection is not always feasible in
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28 97 frail patients or those with tumors located adjacent to critical structures. Therefore, in
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31 98 order to improve tumor grading either noninvasively, or by better, targeted biopsies, one
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34 99 needs to be able to supplement morphological information obtained from conventional
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37 100 imaging with tumor-specific functional information.

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39 101 PET is a useful imaging modality that provides additional metabolic
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42 102 information to CT- or MRI-based morphologic characterization of tumors. Its usefulness
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45 103 has been proven in lung cancer[3] and aggressive lymphomas[4]. Several studies have
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48 104 evaluated PET using various tracers such as 18F-FDG, 11C-MET, 18F-FET, and
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51 105 18F-FLT for pre-therapy histological prediction to differentiate high-grade from
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54 106 low-grade glioma, and reported promising results[5-7]. The sample sizes of these

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6 107 studies, however, are typically small, resulting in imprecise estimates of diagnostic
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9 108 accuracy and use heterogeneous designs / protocols for PET assessment, making
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12 109 interpretation of the published data difficult. Often, the positivity cutoff criteria are
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15 110 defined *post-hoc* to calculate the best pairs of sensitivity and specificity for each study
16
17
18 111 and lack generalizability. In this situation, aggregate-level data meta-analysis
19
20 112 (ALD-MA) typically calculates overestimated summary statistics.
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23 113 A useful approach to the above problem to perform a meta-analysis based on
24
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26 114 individual-level data (Individual-level data meta-analysis; ILD-MA). This technique
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28
29 115 employs a predefined uniform cutoff value to estimate test performance measures for all
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32 116 included studies and combines their results. IPD-LD can also evaluate the effect of
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35 117 specific factors on test performance at the level of individual, simultaneously
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38 118 accounting for between-study variations. We therefore planned an ILD-MA to provide a
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41 119 comprehensive overview and quantitative synthesis of information on the test
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44 120 performance of PET for this purpose.
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122 **Methods**

123 This meta-analysis is an extension of a part of a series of systematic reviews on PET in
124 clinical management of patients with glioma[8][9]. Although these reviews share a

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6 125 common literature search until June 2011, each project employs an independent
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8 126 prespecified research protocol with standard systematic review methodologies, and
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11 127 assesses mutually exclusive research objectives. Interim results of an earlier related
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14 128 study of this research project have been presented at an international meeting[10] but
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17 129 never published as full-text.
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21 22 131 *Literature search*

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25 132 We will use our literature database of publications on PET assessed for patients with
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28 133 glioma. We established the database based on the searches of PubMed and Scopus from
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31 134 inception through June 30, 2011 with no language restriction and full-text evaluation of
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34 135 potentially relevant articles found through abstract screening. The complete search
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37 136 strategy and full list of the database is reported elsewhere[9] and also available as a
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40 137 supplementary file. We will update the searches until July 30, 2017, and examine the
41
42
43 138 reference lists of eligible studies and relevant review articles.

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45 139 One reviewer (TN or NAT) will screen abstracts and at least two of three investigators
46
47
48 140 (TT, NAT, and TT) examine full-text articles of potentially eligible citations.
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51 141 Discrepancies will be resolved by consensus.

52 53 142 *Inclusion and exclusion criteria*

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6 143 We will select studies that assess PET using 18F-FDG, 11C-MET, 18F-FET, or 18F-FLT
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9 144 for predicting glioma grading, verified with histologic confirmation by surgery or
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11 145 biopsy to be eligible. We have selected these four particular tracers before conducting
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14 146 this research on the basis of an empirical evaluation of published studies of PET on
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17 147 glioma[9] and recently published narrative reviews[11][12]. We will include both
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20 148 prospective and retrospective studies. We will define pathologic confirmation (either by
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23 149 biopsy or surgical resection) as the acceptable reference standard and explicitly exclude
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26 150 studies (or individual patients in a study), in which (or for whom, respectively),
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29 151 pathological confirmation is not performed. We will consider the total surgical resection
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31 152 as the (nearly) perfect reference standard, whereas, (stereotactic) biopsy will be deemed
32
33
34 153 to be the imperfect reference standard. We will include any language publications that
35
36
37 154 evaluated at least 10 patients for whom PET scanning and histopathological
38
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40 155 confirmation is successfully performed. We will exclude editorials, comments, letters to
41
42
43 156 the editor, and review articles. When multiple publications with potentially overlapping
44
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46 157 patient populations are available, we will only include the publication with the largest
47
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49 158 sample size.

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51 159 We will contact study authors by email if studies do not report adequate
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54 160 information on PET and histological results in the participant-level, or if IPD data are
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6 161 not presented in the paper. We will consider our request to be rejected if two email
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9 162 request reminders separately sent q 14 days after the initial contact attempt are rejected.
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11 163 Even in this case, we will allow for the inclusion of a study report in which quantitative
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14 164 data is not reported but the digital extraction (i.e., data extraction by using a digitizer
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17 165 from its published graphical presentations) is feasible. Otherwise we will exclude these
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20 166 studies. Data will be kept in a shared secure folder accessible by all co-authors.

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23 167 ***Data extraction***

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25 168 One reviewer (TN or NAT) will extract descriptive data from each eligible study.
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28 169 Another one non-overlapping investigator (TN, NAT, or TT) will verify all the extracted
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31 170 data. We will extract the following published descriptive information from eligible
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34 171 studies: first author, year of publication, journal, patient demographics and clinical
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36
37 172 characteristics, therapeutic interventions in the case of post-therapy or recurrence
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40 173 assessment, technical specifications of PET, and interpretation of PET results.
41
42
43 174 One reviewer (TN, or NAT) will extract published quantitative data regarding imaging
44
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46 175 results (i.e., visual assessment and quantitative assessment such as standard uptake
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48
49 176 values (SUVs) or tumor-to-normal uptake ratio (T/N ratio)) and final diagnoses (i.e.,
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52 177 histopathologic subtype and grading) at the individual level. Another one reviewer (TT)
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55 178 will verify all the data. We will exclude any cases in which PET scanning is
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6 179 unsuccessful (and thus results are arbitrary imputed *post-hoc*). We will also exclude any
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9 180 cases in which alternative reference standards such as clinical follow-up instead of
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11 181 pathological confirmation is used to determine histologic grading.

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14 182 If reported, we will also extract the following individual-level variables as the candidate
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17 183 effect-modifiers to be evaluated in meta-regression: age, sex, clinical scenario (i.e.,
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20 184 primary diagnosis vs. post-therapy/recurrence assessment), and tissue sampling methods
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23 185 (i.e, how the pathological specimens are obtained, either biopsy, partial or total
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26 186 resection)

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31 188 ***Assessment of risk of bias.***

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34 189 To assess the risk of bias and applicability of each study, two reviewers (TN, NAT) will
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37 190 independently assess patient selection, index test, reference standard, and their flow and
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40 191 timing based on the revised Quality Assessment of Diagnostic Accuracy Studies
41
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43 192 (QUADAS-2). Methods to detect publication bias are not very reliable when used in
44
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46 193 diagnostic accuracy data, especially in case of heterogeneity, but we will use the method
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49 194 of Deeks et al[13] that has been shown to be the least biased. Discrepant ratings will be
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52 195 resolved by consensus. The complete list of operational definitions to rate each item is
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55 196 available from the authors upon request.

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9 198 ***Data synthesis***

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11 199 We will use a bivariate model to obtain an estimate of the summary sensitivity and
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14 200 specificity with their corresponding confidence intervals (CIs). We will fit a two-level a
15
16
17 201 generalized mixed regression model conditional on the sensitivity and specificity of
18
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20 202 each study and a bivariate normal model for the sensitivity and specificity between
21
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23 203 studies [14](Reitsma et al, 2005 Journal of Clinical Epidemiology; Chu H and Cole SR,
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26 204 2006, Journal of Clinical Epidemiology). We will calculate summary positive and
27
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29 205 negative likelihood ratios based on the summary sensitivity and specificity estimates.
30
31 206 Positive likelihood ratio (LR+) is the ratio of sensitivity over (1-specificity) whereas
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34 207 negative likelihood ratio (LR-) is defined as the ratio of (1-sensitivity) over specificity.
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37 208 The discriminating ability of a diagnostic test is better with higher LR+ and lower LR-.
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40 209 A good diagnostic test typically has LR+ >5.0 and LR- <0.2. We will also construct a
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43 210 hierarchical summary receiver operating characteristic curve (HSROC) based on the
44
45
46 211 parameters of the fitted model (Rutter Cm and Gatsonis CA, 2001; Statistics in
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49 212 Medicine; Macaskill P, 2004; Journal of Clinical Epidemiology). We will assess
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52 213 between-study heterogeneity visually using forest plots, and also by plotting sensitivity
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55 214 and specificity in the ROC space. We will construct 95% credible regions for summary
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6 215 sensitivity and specificity from the estimated parameters as proposed[15].
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11 217 ***Subgroup analysis and meta-regression***
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14 218 To explore heterogeneity, we will perform subgroup analyses and if feasible, the
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17 219 statistical differences among mutually exclusive subgroups will be assessed by
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20 220 univariable meta-regression. We will add a candidate modifier (as either 0 [absence] or
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22
23 221 1 [presence]) to the test performance parameters (i.e., sensitivity and specificity
24

25
26 222 parameters, or diagnostic odds ratio and threshold parameters, respectively) jointly in
27

28
29 223 the bivariate random-effects model or binormal random-effects model, respectively.
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31 224 We will record: publication year, study design (i.e., prospective versus retrospective) as
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33
34 225 the study-level covariates, age, sex, clinical scenario (i.e., primary diagnosis vs.
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37 226 post-therapy/recurrence assessment) and tissue sampling methods (i.e., biopsy vs.
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40 227 partial or subtotal resection vs. total resection).
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45 229 ***Comparisons among different PET methodologies***
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48 230 We will compare the test performance among alternative PET tracers, and also those
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51 231 based on different imaging assessment protocols (i.e., visual assessment vs. quantitative
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54 232 assessment, either T/N ratios or SUVs). Regarding the T/N ratios, we will operationally
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6 233 define three categories based on the specified referent tissues: mean or median uptakes
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9 234 in the gray matter (GM), those in the white matter (WM), and other miscellaneous
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12 235 methods (MISC) including mean or median uptakes in the contra-lateral corresponding
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15 236 anatomical sites or those in the adjacent normal tissue regardless of GM or WM.

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17 237 For indirect comparisons, we will visually compare the constructed summary
18
19
20 238 ROC curves and the credible regions of sensitivity and specificity. We will also
21
22
23 239 statistically assess the differences by univariable meta-regression using the tracers or
24
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26 240 assessment methods as the covariate being incorporated into the meta-analytic model.
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29 241 These results however, need to be interpreted carefully because findings from the
30
31
32 242 indirect comparisons may be only speculative[16]. To tackle this issue, we will also
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35 243 perform these analyses limiting only to comparative studies that assess multiple tracers
36
37
38 244 or methods for the same participants, from which direct comparisons can be performed.

39
40 245 We will conduct all analyses using STATA, version 14/SE (Stata Corp, College
41
42
43 246 Station, TX), and OpenBUGS, version 3.2.3 (members of OpenBUGS Project
44
45
46 247 Management Group; see www.openbugs.net). All tests will be two-sided and statistical
47
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49 248 significance will be defined as a p -value $< .05$.

50 51 249 **Discussion**

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54 250 Differentiating high from low grade malignancies has significant prognostic
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6 251 information for a variety of tumors; gliomas are not an exception. While an optimally
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9 252 resected biopsy specimen is always preferable to indirect evidence, imaging can provide
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12 253 helpful adjunct information. Moreover, functional imaging, such as positron emission
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15 254 tomography with select biotracers has the potential to become a powerful tool in
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18 255 assessment of patients and influence treatment decisions. By conducting a multiple
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21 256 treatment meta- analysis and IPD meta-analysis, this study hopes to clarify the
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24 257 diagnostic accuracy of PET/CT with various tracers in differentiating glioma histology
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27 258 and establish thresholds, upon which further studies can be performed.

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29 259 **Contributorship statement:** Abstract screening: TN and NAT. Full-text article
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31
32 260 examination: TT, NAT, and TT. Data extraction: TN, TT and NAT. Assessment of the
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34
35 261 risk of bias and applicability of each study: TN and NAT. Statistical analysis: TT and
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37
38 262 EE. All authors (TN,TT,EE,NAT) have equally contributed to the final version of the
39
40
41 263 protocol, have reviewed and have approved of it.

42
43 264 **Competing interests:** None declared.

44
45
46 265 **Funding:** This research received no specific grant from any funding agency in the
47
48
49 266 public, commercial or not-for-profit sectors.

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52 267 **Data sharing statement:** Supplementary and raw data can be provided by the authors
53
54
55 268 freely upon request.

269 **Provenance and peer review:** Not commissioned; externally peer reviewed.

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273 **References:**

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278 Ricci P, Bullard D, Brown PD *et al*: **Radiation plus Procarbazine, CCNU, and**
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Literature search strategies

PubMed

((("Brain Neoplasms"[Mesh] OR "Glioma"[Mesh] OR glioma* OR (glioblastoma* OR "glioblastoma multiforme") OR (astrocytoma* OR "anaplastic astrocytoma") OR (oligodendrocytoma* OR "anaplastic oligodendrocytoma") OR (brain AND (tumor* OR tumour*)) OR (neuroectodermal AND (tumor* OR tumour*)) OR ependymoma* OR oligodendroglioma*)) AND ("Tomography, Emission-Computed"[Mesh] OR (positron AND emission AND tomograph*) OR pet) AND "humans"[MeSH Terms])

SCOPUS

(TITLE-ABS-KEY(glioma*) OR TITLE-ABS-KEY(glioblastoma*) OR TITLE-ABS-KEY(glioblastoma PRE/0 multiforme) OR TITLE-ABS-KEY(astrocytoma*) OR TITLE-ABS-KEY(anaplastic PRE/0 astrocytoma) OR TITLE-ABS-KEY(oligodendrocytoma*) OR TITLE-ABS-KEY(anaplastic PRE/0 oligodendrocytoma) OR TITLE-ABS-KEY(brain tumo*r*) OR TITLE-ABS-KEY(neuroectodermal PRE/0 tumo*r*) OR TITLE-ABS-KEY(ependymoma*) OR TITLE-ABS-KEY(oligodendroglioma*)) AND (TITLE-ABS-KEY(positron PRE/0 emission PRE/0 tomograph*) OR TITLE-ABS-KEY(pet))

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a Line 1	Identify the report as a protocol of a systematic review.
Update	1b Line 131	If the protocol is for an update of a previous systematic review, identify as such
Registration	2 Line 49	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a Line 23	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b Line 259	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4 Not applicable	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a Line 265	Indicate sources of financial or other support for the review
Sponsor	5b N/A	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c N/A	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6 Line 72	Describe the rationale for the review in the context of what is already known
Objectives	7 Line 118	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8 Line 132	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9 Line 133	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10 Line 137	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		

Data management	11a Line 168	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b Line 143	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c Line 168	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12 Line 171	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13 Line 174	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14 Line 189	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a Line 199	Describe criteria under which study data will be quantitatively synthesised
	15b Line 204	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)
	15c Line 218	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d N/A	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16 Line 194	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17 Line 218	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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