SCOPING REVIEW

Developing neuro-oncology clinical trials in low- and middle-income countries: a scoping review of the current literature

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Abstract

Low- and middle-income countries (LMICs) have historically been under-represented in clinical trials, leading to a disparity in evidence-based recommendations for the management of neuro-oncological conditions. To address this knowledge gap, we conducted a scoping review to assess the current literature on clinical trials in neuro-oncology from LMICs. The eligibility criteria for inclusion in this review included clinical trials registered and conducted with human subjects, with available English language text or translation, and focussed on neuro-oncological cases. The literature search strategy captured 408 articles, of which 61 met these criteria, with a significant number of randomised controlled trials from specific LMICs. The review found that LMIC clinical trials have contributed significantly to understanding surgical, chemotherapeutic, and radiation therapy interventions for brain tumours, paediatric cancers, and the repurposing of drugs as new targets in neuro-oncology. These findings highlight the potential for expanding clinical trials research in neuro-oncology in LMICs, which may significantly impact global understanding and management of these conditions, particularly from diverse populations from the global south.

Keywords: neuro-oncology, brain tumour, drug Repositioning

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Introduction

Clinical trials are the foundation for defining new cancer treatment standards; comparing diagnostic or therapeutic approaches can broaden our understanding of the disease process, susceptible patient groups, and the path forward in disease management and remission. Clinical studies from diverse communities have helped highlight the function of genetic composition and distinct populations that can be treated with particular, tailored treatment in many diseases, such as breast and lung illness. Similarly, the history of neuro-oncology clinical trials is littered with examples of big cohorts, multicentre investigations, and discovering innovations in treatment. However, historically, low- and middle-income countries (LMICs) have been under-represented in clinical trials, resulting in disparities in evidence-based recommendations for addressing neuro-oncological disorders in these locations. Clinical trials in neuro-oncology may be less common in LMICs for various reasons, including a lack of resources and infrastructure for conducting clinical trials, as well as cultural and socioeconomic variables that may influence patient recruitment and participation. Furthermore, gaining finance and regulatory permission for clinical studies in LMICs may be difficult.

Despite these limitations, there is a rising acknowledgment of the relevance of adding LMICs in neuro-oncology clinical trials. The molecular and socio-demographic epidemiology of neuro-oncological disorders in (LMICs) may differ from that in high-income countries (HICs), with major implications for therapy and management. For example, certain brain tumours and neurological malignancies may be more frequent in LMICs, and the frequency of certain risk factors may differ. As a result, clinical trials in LMICs may give useful insights into managing neuro-oncological disorders in these areas. Including LMICs in clinical trials can also assist in addressing global health inequities and guarantee that novel medicines are available to everyone. As a result, it is critical to continue emphasizing the inclusion of LMICs in neuro-oncology clinical trials to increase our understanding of these disorders and improve patient outcomes worldwide. The authors conducted a scoping review to capture the present status of neuro-oncological clinical trials and LMICs, highlight important strengths in LMIC clinical trial research, and recommend new paths for extending studies.

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Methods

A systematic search (Appendix 1) of multiple databases, (PubMed, Scopus, Cochrane Library, EBSCO) was conducted on 30.6.2023 using specific keywords related to clinical trials in neuro-oncology in LMICs (Figure 1). The search was limited to studies published in English or with available English translations. Eligibility criteria for inclusion in the review included clinical trials registered and conducted with human subjects, focussing on neuro-oncological cases. Non-trial studies, case reports, case series, systematic reviews, and meta-analyses were excluded. Post-hoc analyses and conference papers/abstracts were excluded. Two reviewers independently screened the titles and abstracts of the identified studies for eligibility, and full-text articles were obtained for those that met the inclusion criteria. Data were extracted from the included studies using a standardised form, including information on the study design, sample size, interventions, outcomes, and conclusions. Any discrepancies between the reviewers were resolved through discussion with a third senior author. The extracted data were analysed and synthesized to identify key themes and gaps in knowledge. The data were categorised into themes and subthemes, and the findings were compared and contrasted across studies.

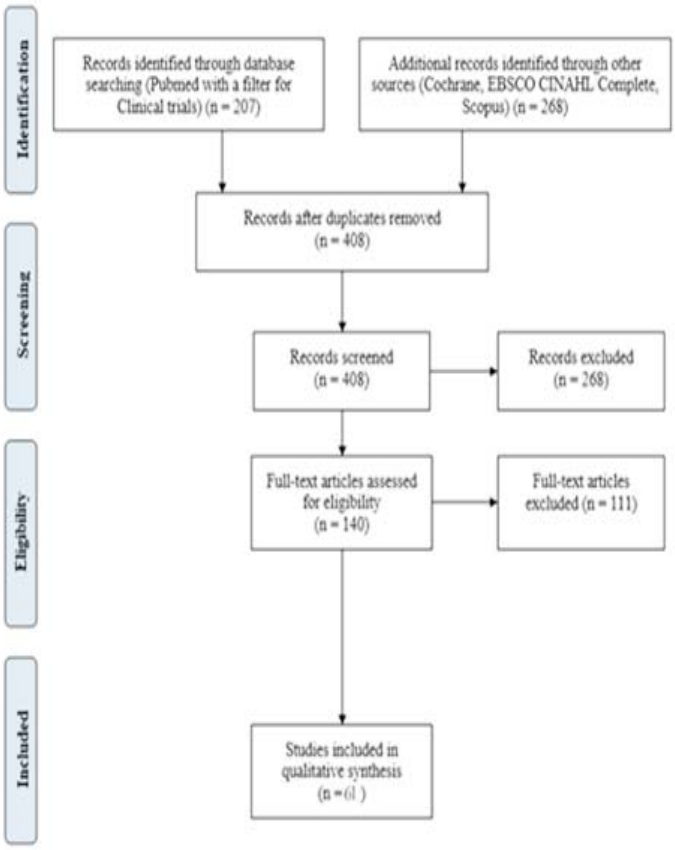

Figure-1: PRIMSA Chart detailing the search methodology and systematic screening of articles.

Results

We conducted an extensive literature review and identified 408 articles pertaining to the use of clinical trials to study and treat different types of brain tumours. Sixtyone articles were shortlisted after the title, abstract and full-text review – the results are detailed in tabulated forms Table 1[1-34], Table 2[35-46], Table 3[47-57] and Table 4[58-61], according to treatment arms assessed and conclusions of the trial.

Discussion

Current state of clinical trials literature

Most clinical trials were conducted within the surgery, anaesthesiology, and critical care section(34 articles) – in comparison, we saw few clinical trials published in radiation and medical oncology. India and Egypt contributed significantly to the literature. Analysing the literature by categories and time points, within surgery and anaesthesiology, before 2010, historically, LMIC clinical trials in neuro-oncology have contributed towards investigating anaesthesia protocols for supratentorial tumour surgery, awake craniotomy, controlling ICP during pituitary surgery, PONV (postoperative nausea vomiting), and one study comparing pituitary surgery with the microscopic endo-nasal approach (Figure 2). A cursory view of this time period shows studies that were easily conducted due to small sample sizes and with varying cohorts – often, these would be mixed cohorts of supratentorial tumours, with no specific tumour subtype investigated. Post-2010, there is more specific diversification, with investigations of tranexamic acid for meningioma surgery, improving clinoidal meningioma resections with mobilisation of the cavernous sinus membrane, and image-guided surgery to compare intra-operative MRI and 2D-fluoroscopy for resection rates in pituitary macroadenoma surgery. There is still a plethora of literature generally investigated ideal postoperative and intraoperative medication regimens.

Twelve distinct trials were published regarding chemotherapy in LMICs. This appears to be mostly recent work, with only 2 publications from before 2010 – one investigating hydrocortisone replacement in DI post-trans-sphenoidal pituitary study, and adjuvant chemotherapy for paediatric high-risk medulloblastoma. A common trend in recent publications (post-2020) is reducing doses to minimize side effects from chemotherapeutic agents: an investigation in 2020

Table-1: Surgery, Anaesthesiology, Critical Care (n = 34)

No.	Year	Author	Country	Type of Tumour (n)	Treatment Arms	Outcomes Assessed/Conclusion
1	2017	Hooda et al. [1]	India	Meningioma (60)	Tranexamic acid group: intravenous bolus of 20 mg/kg over 20 min followed by an infusion of 1 mg/kg/h till conclusion of surgery	Blood loss significantly less in TXA group compared to placebo (830 ml vs 1124 ml; p = 0.03). Transfusion requirement less in tranexamic acid group (p > 0.05), patients fared better on 5-grade surgical haemostasis scale with good haemostasis (p = 0.007)
2	2012	Bansal et al [2]	India	Supratentorial (80)	Cases (Craniotomy) Propofol: 19, Fentanyl and propofol: 21 Controls (Spinal Surgery) Propofol:19, Fentanyl and propofol: 21	Propofol dose for induction of anaesthesia was significantly reduced when administered after fentanyl in patients with supratentorial tumours.
3	2021	Barik et al [3]	India	Supratentorial (90)	Group 1: equimolar 20% mannitol Group 2: 3% hypertonic saline Group 3: 8.4% sodium bicarbonate	8.4% sodium bicarbonate solution infusion is associated with superior intraoperative brain relaxation scores and improved hemodynamic stability compared to equimolar 3% hypertonic saline solution and 20% mannitol.
4	2008	Bhagat et al [4]	India	Supratentorial (150)	Group 1: Low-dose propofol Group 2: Fentanyl Group 3: Isoflurane At the time of dural closure, until the beginning of skin closure	Low-dose fentanyl during craniotomy closure is more advantageous than propofol or isoflurane for early emergence in neurosurgical patients and most effective for preventing early postoperative hypertension
5	2022	Chandra et al [5]	Indonesia	Intracranial -(60)	Group 1: Intravenous bolus of lidocaine (2%) 1.5 mg/kg before induction followed by 2 mg/kg/h continuous infusion up to skin closure Group 2: Placebo	Continuous lidocaine intravenous infusion improves brain relaxation after dura opening, and decreases intraoperative opioid consumption
6	2007	Gupta et al [6]	India	Intrinsic eloquent area lesions	Awake group: 26 General anaesthesia group: 27	Mean operative time and blood loss were found to be less in GA group patients than in awake group. Better tumour cytoreduction, neurological improvement was seen in GA group than in awake group patients
7	2015	Ghoneim et al [7]	Egypt	Supratentorial (60)	Group 1: Isoflurane Group 2: Sevoflurane Group 3: Desflurane	Desflurane and sevoflurane can be used to facilitate early emergence from anaesthesia in neurosurgical paediatric patients. Emergence times are shorter with desflurane or sevoflurane than with isoflurane. Desflurane or sevoflurane had similar intraoperative and postoperative incidence of adverse effects compared with those who received isoflurane
8	2018	Hegazy et al [8]	Egypt	Spheno-clinoidal meningiomas without cavernous sinus involvement -(94)	Mobilization of the outer cavernous sinus membrane as a part of the surgical approach	Amount of blood loss and estimated blood loss were significantly less in the "with mobilization group" - mobilization group patients had a higher rate of radical resection
9	2018	Jonathan et al [9]	India	Pituitary adenomas (60)	30 patients were randomly assigned to undergo trans-sphenoidal surgery with intraoperative	Intraoperative CSF drainage significantly reduced the incidence of CSF leak from 46.7% in the no LSAD group to 3.3% in the LSAD group (P < 0.001).

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					lumbar drain insertion (LSAD group) or no lumbar drain insertion (no LSAD group)	No statistically significant differences in the incidence of postoperative CSF rhinorrhoea between the two groups. No statistically significant difference in the extent of resection between the two groups.
10	2013	Beltagy et al [10]	Egypt	Paediatric fourth ventricular tumours (60)	Conventional micro neurosurgical techniques: 30 Neuro-navigated intraoperative ultrasonography (NIOUS) technique: 30	Total tumour excision was achieved in 96.7 % of NIOUS group versus 80 % in the conventional group. Mean operative time NIOUS group was 150 min versus 140.6 min in the conventional group. The mean operative blood loss was 67.5 ml NIOUS group versus 71 ml in the conventional group.
11	2021	Abdelhaleem [11]	Egypt	Supratentorial brain (52)	Block group (B): 26 received a bilateral trans nasal sphenopalatine ganglion block (SPGB) with 2% lidocaine	SPGB can control factors that increase cerebral blood flow during anaesthesia by the block of parasympathetic vasodilatory fibres to the arterial system in the anterior cerebral circulation, while neither hindering cerebral venous drainage nor impairing cerebral oxygenation
12	2017	Paul et al [12]	India	Supratentorial (60)	Desflurane: 30 Isoflurane: 30	Desflurane significantly reduced emergence times, and was able to facilitate an early neurological examination for patients.
13	2022	Rajkiran et al [13]	India	Supratentorial (110)	Group 1: Intravenous paracetamol Group 2: Intravenous diclofenac sodium 30 minutes before the end of surgery and postoperatively at 12-hour intervals up to 48 hours	Compared with paracetamol, diclofenac sodium provided more effective postoperative analgesia at 24 hours with no evidence of adverse effects on coagulation profiles
14	2022	Mishra et al [14]	India	Supratentorial (40)	Control: fluid regimen based on routine hemodynamic Intervention: stroke volume variation guided therapy	No benefit of intervention over conventional intraoperative fluid therapy in terms of incidence of postoperative complications, hospital and ICU stay, and Glasgow outcome scores at-discharge Use of guided fluids treatment led to better perioperative fluid management and brain relaxation scores.
15	2021	Konay et al [15]	India	Pituitary tumours (48) Transsphenoidal surgery	Group 1: preoperative intranasal packing with 15ml 1.5% lidocaine with ephedrine	Similar hemodynamic stability during surgery, bleeding in field, and postoperative pain
16	2020	Sriganesh et al [16]	India	Supratentorial (24)	Group 1: fentanyl Group 2: dexmetomidine	Stress response to surgery is similar with opioid (fentanyl) and non-opioid (dexmedetomidine) analgesia as assessed by SPI (surgical pleth index) and blood markers such as cortisol, glucose, and pH.
17	2020	Singla et al [17]	India	Supratentorial (30)	Group 1: 5 ml/kg of 20% mannitol Group 2: 3% HTS (hypertonic saline)	Intraoperative brain relaxation was comparable; statistically significant difference in the mean arterial pressures (MAPs) between the two groups after one minutes (min) with a greater degree of decrease in blood pressure recorded in the mannitol group

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						Urine output was significantly higher in the mannitol group MAP with mannitol was significantly lower than the pre-induction value after 75 min of administration Administration of HTS was associated with a transient increase in serum sodium concentrations, which was statistically significant but returned to normal within 48 hours.
18	2019	Sriganesh et al [18]	India	Supratentorial (24)	Group 1: Fentanyl Group 2: Dexmetomidine As primary intraoperative analgesic drug	Dexmedetomidine has the potential to be non-inferior to fentanyl for perioperative analgesia during craniotomies Compared between fentanyl and dexmedetomidine, there was no difference in the intraoperative fentanyl (top-up) and no difference in postoperative pain at 15 and 60 minutes. Adverse events were similar.
19	2017	Tandon et al [19]	India	Pituitary macroadenoma (50)	A: Intraoperative MRI (IOMRI) guided trans-sphenoidal pituitary resection: 25 B: 2Dimensional fluoroscopic guided resection: 25	Extent of resection was similar in both study arms (A, 94.9% vs B, 93.6%; p = 0.78), despite adjusting for experience of operating surgeon and use of microscope/endoscope for surgical resection. IOMRI helped optimize the extent of resection in 5/20 patients (25%) for pituitary tumor resection in-group A. Study failed to observe superiority of IOMRI over conventional 2D-F guided resection.
20	2017	Salimi et al [20]	Iran	Pituitary adenoma (60)	Dexmedetomidine infusion (0.6μg/kg/hour) or normal saline infusion	Propofol maintenance dose (μg/kg/min) and total Fentanyl use (μg) were significantly lower in Dex group compare to control group (P=0.01 and 0.003, respectively). Total bleeding amount during operation in Dex group was significantly lower than control group (P=0.012). Surgeon's satisfaction was significantly higher in Dex group at the end of surgery. MAP and heart rate throughout surgery were significantly lower in Dex group compare to control group
21	2013	Misra et al [21]	India	Adult intracranial tumours (63)	placebo (group D) or gabapentin (600 mg) (group GD) premedication orally, 2 hours before induction of anaesthesia. In addition, all patients received 4 mg of intravenous dexamethasone on the morning of surgery and continued receiving it after every 8 hours	gabapentin plus 4 mg of dexamethasone significantly reduced the 24-hour incidence of nausea and PONV. However, there was no reduction in either the postoperative pain scores or opioid consumption
22	2011	Soliman et al [22]	Egypt	Supratentorial (40)	Group A: —The dexmedetomidine was given as a bolus dose of 1 microg/kg in 20 minutes before induction of anaesthesia, followed by a maintenance infusion of 0.4 microg/kg/hr. The infusion was discontinued when surgery ended.	Continuous intraoperative infusion of dexmedetomidine during craniotomy for supratentorial tumours under general anaesthesia maintained the haemodynamic stability, reduced sevoflurane and fentanyl requirements, decreased intracranial pressure, and improved significantly the outcomes

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					Group B: —The patients received similar volumes of saline.	intraoperative end-tidal sevoflurane (%) in patients of group A less than in patients of group B (P-value <0.05). The intracranial pressure decreased in patients of Group A more than group B (P-value <0.05). The Glasgow coma scale (GCS) improved in patients of group A and deteriorated in patients of Group B with significant statistical difference between the two groups total fentanyl requirements from induction to extubating of patients increased in patients of group B more than in patients of group A (P-value <0.05). The total postoperative patients' requirements for antiemetic drugs within the 2 hours after extubating decreased in patients of group A more than group B (P-value <0.05). The postoperative duration from the end of surgery to extubating decreased significantly in patients of group A more than group B (P-value <0.05). The total urine output during the duration from drug administration to extubating of patients increased in patients of group A more than group B (P-value <0.05)
23	2011	Singh et al [23]	India	Supratentorial (116)	Group I: Nitrous oxide - Isoflurane anaesthesia (Nitrous oxide-based group) Group II - Isoflurane anaesthesia (Nitrous oxide-free group).	avoidance of nitrous oxide in one's practice may not affect the outcome in the neurosurgical patients median duration of ICU stay in the nitrous group and the nitrous-free group was 1 (1 - 11 days) day and 1 (1 - 3 days) day respectively (P = 0.67), whereas the mean duration of hospital stay in the nitrous group was 4 (2 - 16) days and the nitrous free group was 3 (2 - 9) days (P = 0.06). The postoperative complications in the two groups were comparable.
24	2001	Korula et al [24]	India	Pituitary macroadenomas (57)	Study group 29 – controlled hypercarbia, raising end-tidal carbon dioxide levels to a maximum of 50 mm Hg by hypoventilation Control 28 - intrathecal saline	Twenty-seven of 29 patients in the study group and 25 of 28 patients in the control group reached the target pressure of 20 mm Hg Both techniques were equally effective in raising intracranial pressure and in providing descent of the suprasellar component of the tumour. No untoward side effects occurred while using either technique. The authors conclude that controlled hypercapnia is effective in producing descent of the suprasellar portion of a pituitary adenoma.
25	2023	Sarhan et al [25]	Egypt	Posterior fossa tumours (42)	Early hyperventilation group: 23 Early norm ventilation group: 19	Moderate hyperventilation reduced cerebral oxygenation without significant improvement of the surgical brain relaxation or the ICP
26	2009	Ali et al [26]	India	transsphenoidal resection of pituitary tumours (90)	randomly divided to receive propofol, isoflurane, or sevoflurane for maintenance of anaesthesia	After tracheal intubation, the rise in blood pressure was more in sevoflurane group than propofol Emergence and extubating times were significantly shorter with propofol and sevoflurane. Patients who received propofol had better cognition scores. Aldrete scores were better with propofol and sevoflurane than isoflurane. The pressor response after intubation and

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						emergence hypertension was significantly less with propofol. Better recovery profile was seen in sevoflurane and propofol groups and a better cognition in patients receiving propofol. Propofol plus nitrous oxide anaesthesia could be the technique of choice in patients undergoing trans nasal transsphenoidal pituitary surgery.
27	2019	Bhagat et al [27]	India	Intracranial tumours (90)	randomized to receive NS, RL, or a combination of NS and RL	use of NS was associated with hyperchloraemic metabolic acidosis and ionic hypocalcaemia. RL caused significant hyponatremia and increase in serum lactate levels. The combination of NS and RL has least influence on biochemical and metabolic parameters. The effects of three fluids were similar on the hemodynamic, brain relaxation score, as well as on postoperative complications and the duration of postoperative hospital stay.
28	2015	Gopalakrishna et al [28]	India	TNTS for pituitary tumour (46)	continuous infusion of DEX (group D) or 0.9% saline (group C)	Total fentanyl consumption during the study period was significantly lower in group D compared with group C End-tidal isoflurane concentration requirement was found to be significantly reduced in group D compared with group C throughout the surgical period. Fentanyl and end-tidal isoflurane concentration requirement was reduced in group D compared with group C by 40% and 33.3%, respectively. Heart rate and mean arterial pressure were significantly higher in the group C compared with group D after intubation, during various stages of surgery and immediately after extubating. The group D had excellent surgical conditions and lesser bleeding in comparison to group C. Emergence time and extubating time were significantly shorter in group D compared with group C. Conclusions: DEX as an aesthetic adjuvant improved hemodynamic stability and decreased anaesthetic requirements in patients undergoing TNTS resection of pituitary tumour. In addition, DEX provided better surgical field exposure conditions and early recovery from anaesthesia.
29	2014	Bodaghabadi et al [29]	Iran	Recurrent Cushing Disease (52)	Group 1: 26, transsphenoidal micro adenoidectomy Group 2: 26, Gamma Knife radiosurgery	No significant relationship was found between preoperative 24-hour free urine cortisol and disease-free months or tumour volume among both groups. Our statistical analysis showed higher recurrence-free interval in the GKRS group compared with TSA group. With longer recurrence-free interval, GKRS could be considered a good treatment alternative to repeated TSA in recurrent CD.

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30	2012	Daif et al [30]	Egypt	Brain tumours (40)	2 groups (haemodilution and control). In the haemodilution group (HG), 1000 mL of blood was drawn and replaced with the same volume of HES 130/0.4 (6%, Voluven) colloid. control group (CG), no blood was drawn, and hemodynamic were stabilized using normal saline until allogenic blood was needed	ANH and allogenic blood transfusion used in this study design were accompanied by comparable cerebral oxygenation parameters in patients subjected to brain tumour resection
31	2000	Shaheen et al [31]	India	Supratentorial (20)	Group 1 (10): alcuronium Group 2 (10): pipecuronium	The rise in intracranial pressure at intubation was significantly greater in group I (21.10+/-3.97 torr, 122.59%) when compared to group II patients (1.80+/-0.70 torr, 10.04%) (p<0.0 1). Cardiovascular parameters also showed a significantly greater degree of rise in group I when compared to group II patients. Heart rate increased by 29+/-6.32 beats min(-1) (33.52%) and systolic arterial pressure by 11.60+/-7.37 torr (9.47%) in group I. These parameters did not change significantly in group II.
32	2009	Jain et al [32]	India	Supratentorial (90)	3 groups to receive either placebo (saline), ondansetron 4 mg, or granisetron 1 mg intravenously at the time of dural closure	incidence of vomiting in 24 hours, severe emetic episodes, and requirement of rescue antiemetics were less in ondansetron and granisetron groups as compared with placebo (P<0.001). Both the study drugs had comparable effect on vomiting. However, the incidence of nausea was comparable in all 3 groups (P=0.46) ondansetron 4 mg and granisetron 1 mg are comparably effective at preventing emesis after supratentorial craniotomy. However, neither drugs prevented nausea effectively.
33	2007	Jain et al [33]	India	Pituitary adenomas (20)	Ten cases were operated by endoscopic endonasal trans-sphenoidal approach by endoscopic rhinologist (EETSS group) and other 10 cases were excised by microsurgical endonasal trans-sphenoidal approach by a neurosurgeon (SMETSS group)	Endoscopic approach provides a wide surgical field and broad lateral vision making easier distinction of tumour tissue: gland and gland diaphragm interface. Thus, there is less blood loss and nasoseptal complications, whereas there was no statistically significant difference in operative time and complete tumour removal
34	2018	Dey et al [34]	India	Supratentorial tumour (44)	two groups of 22 each to receive either normal saline or BC (Plasmalyte) as the maintenance fluid, intra-operatively	balanced crystalloid maintains metabolic status more favourably than normal saline in neurosurgical patients. Hyperchloremic metabolic acidosis, and the other problems which occur as a consequence of normal saline infusion may be circumvented by choosing a balanced crystalloid electrolyte solution. Neither of the crystalloids appeared to have any adverse effect on brain relaxation.

Table-2: Chemotherapy (n = 12).

No.	Year	Author	Country	Type of Tumour (n)	Treatment Arms	Outcomes Assessed/Conclusion
1.	2020	Khoury et al [35]	Lebanon	Metastasis (117)	Group 1 (84): Dexamethasone doses of 1144 mg/m2)Group 2 (33): (Dexamethasone doses of 618 mg/m2)	Decreasing cumulative dose of dexamethasone for low-risk childhood acute lymphoblastic leukemia patients aiming to avoid serious viral infections led to a significant increase in isolated central nervous system relapse
2.	2013	Gaber et al [36]	Eygpt	Glioblastoma Multiforme (60)	Group 1 (30): Temozolomide at a dose of 75 mg/m2 daily with radiotherapy for 42 days starting 4 weeks after surgery and reaching to a total radiation dose of 60 Gy/30 Fractions/6 weeksGroup 2 (30): Temozolomide at a dose of 75 mg/m2 concomitantly with the same radiotherapy schedule daily in the first and last weeks of the same radiotherapy program	Reduced radiosensitizer dosing of temozolomide concomitant with radiotherapy in glioblastoma multiforme exhibited comparable efficacy with a classic continuous daily schedule, though with better tolerability
3.	2021	Gupta et al [37]	India	High-risk/metastatic medulloblastoma; residual tumour >1.5 cm2 or leptomeningeal metastases (97)	Newly diagnosed patients received concurrent carboplatin (35 mg/m2) for 15 days (day 1 to day 15) during craniospinal irradiation plus posterior fossa/tumour bed boost, followed by six cycles of standard adjuvant chemotherapy	On univariate analysis, leptomeningeal metastases and histological subtype emerged as significant prognostic factors for survival.Addition of concurrent carboplatin to RT as radio sensitizing chemotherapy is a simple and effective way of treatment intensification in high-risk/metastatic medulloblastoma.
4.	2017	Mousa et al [38]	Egypt	CNS tumours (80)	Intervention group received 5 g of Nigella sativa seeds (NS) daily throughout treatment while controls received nothing.	NS seeds showed a decrease in incidence of febrile neutropenia in children with brain tumours with shortening of subsequent length which may improve their outcome and thereby quality of life.
5.	2021	Koundal et al [39]	India	Sellar and suprasellar (50)	Patients in the intervention group received a nurse-led DI bundle (validated by three Delphi rounds) with four dietary components: intake of only water duringthirst and avoidance of the following—added salt, high-protein foods and caffeinated drinks. Treating clinicians and the investigator assessing outcome were blinded about enrolment. Urine output, serum sodium, vasopressin requirement and hospital stay were assessed as primary outcomes. The outcome measures were monitored daily till the 6th postoperative day.	mean daily urine output was significantly lower in the DI bundle group than in control, both overall and among endonasal operated pituitary adenomas [3000.09(462.7) vs. 4095.71(896.4) ml & 2987.14(419.5)vs. 4064.73(1051) ml], with the greatest difference on the second postoperative day.Though hypernatremia in controls became most prominent during days 2–3 and resolved in a week, it was significantly lower in the intervention group (12.7% vs. 30.7%) overall, 11.4% vs. 29.4% endonasal adenomas). The need for vasopressin analogues and hospital stay were also significantly lower with DI bundle ($p < 0.001$).

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6.	2020	Melika et al [40]	Iran	benign brain tumours (60)	The study group (n 1⁄4 30) received intramuscular injection of 300,000 IU vitamin D3 prior to surgery. The control group (n 1⁄4 30) was left without intervention, and both groups underwent routine therapies	On day 5 after craniotomy, the serum 25(OH)D levels increased significantly in the study group (P1⁄4 <0.001). The length of ICU and hospital stay was significantly lower in the study group compared tothe control group (P 1⁄4 0.01 and P 1⁄4 0.008, respectively). It was true when the age, tumour size, tumour type, Karnofsky Performance Scale (KPS) score, and calcium and albumin levels at baseline entered thelogistic regression model (OR 1⁄4 0.17 (95%CI 1⁄4 0.04e0.72, P 1⁄4 0.01), and OR 1⁄4 0.19 (95%CI 1⁄4 0.04e0.82, P 1⁄4 0.02), respectively). With and without the application of logistic regression analysis, there was nosignificant difference in perioperative complications.
7.	2022	Thakur et al [41]	India	Newly Diagnosed Glioblastoma (71)	Short-course radiotherapy (25 Gy in 5 fractions) has been shown to be non-inferior to standard course radiotherapy in elderly and frail patients (60 Gy in 30 fractions). The purpose of this study was to determine the effects of temozolomide combined with short-course radiotherapy on the outcome of elderly and frail patients.	In terms of overall survival and progression-free survival,radiotherapy with concurrent temozolomide and adjuvant temozolomide outperformed short-course radiotherapy alone.The median overall survival in arm 1 was 146 days and 121 days in arm 2 (P=0.146). The median progression-free survival in arm 1 was 109.50 days, while it was 77 days in arm 2 (P=0.028). With a median follow-up time of 6 months, the quality of life at 4 weeks and 12 weeks after treatment was not different between the two arms.adding temozolomide to short-course radiotherapy significantly improved progression-free survival and showed an increasing trend in overall survival without compromising the quality of life.
8.	2022	Patil et al [42]	India	Recurrent GBM not eligible for re-radiation (88)	CCNU-MBZ (CCNU was administered at 110 mg/m2 every 6 weeks with MBZ 800 mg thrice daily): 44TMZ-MBZ (MZ was administered at 200 mg/m2 once daily on days 1-5 of a 28 days cycle with MBZ 1600 mg thrice daily): 44	The 9-month OS was 36.6% (95% CI 22.3-51.0) and 45% (95% CI 29.6-59.2) in the TMZ-MBZ and CCNU-MBZ arms respectively, in the ITT population. ECOG PS was the only independent prognostic factor impacting OS (HR-0.48, 95% CI 0.27-0.85; P = 0.012).The addition of MBZ to TMZ or CCNU failed to achieve the pre-set benchmark of 55% 9-month OS.
9.	2003	Rajaratnam et al [43]	India	Pituitary macroadenoma (114) underwent transsphenoidalsurgery	Thirty-two patients were allotted to Group 1(conventional dose hydrocortisone protocol), 30 toGroup 2 (intermediate dose hydrocortisone protocol) and 52 to Group 3 (low dose hydrocortisoneprotocol)	The incidence of DI with the conventional dose was 52%, intermediate dose,36% and low dose, 24% (p = 0.025). The low dose hydrocortisone protocol reduced the incidence of DI by 46% when compared with theconventional dose hydrocortisone protocol
10.	2015	Hosseini et al [44]	Iran	Brain metastasis (20)	In the first group, patients were treated with WBRT alone (control arm), and in the second group (intervention arm), patients received WBRT with concomitant sodium nitrite.	intravenous infusion of sodium nitrite with this dose and schedule to patients with brain metastases concurrent with radiotherapy did not show any major benefit in terms of radiologic response.

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11.	2005	Abd El-All et al [45]	Egypt	Paediatric high-risk medulloblastoma (48)	First (group I) included 21 patients who received postoperative craniospinal radiation therapy (36Gy+boost 20Gy to the posterior fossa). The second (group II) included 27 cases who received postoperative combination cranio-spinal radiation therapy (with the same dose as the first group) and chemotherapy (vincristine, etoposide, cisplatin).	In-group I, complete remission (CR) was achieved in 71.4% of the cases; partial remission (PR) in 14.3% of the patients; stationary disease (SD) in 14.3% and none of the cases suffered from progressive disease. The three-year OS was 69.5% and the three-year DFS was 61.3%. In-group II, CR was achieved in 59.3% of the cases; PR in 3.7%; SD in 3.7% and PD in 37.3% of the cases. The three-year OS was 48.4% and the 3-year DFS was 48.9%.In group I; 13 patients (62%) suffered a reduction of 8-20% in IQ in comparison to their normal siblings, whereas in Group II; 13 patients (48%) developed a reduction in IQ ranging from 12-21%.poorer outcome in the chemo-radiation group was due to the treatment interruption during radiation therapy caused by myelosuppression since the incidence of myelosuppression was higher in the chemo-radiation group and the recovery time was longer
12.	2016	El-Hamamsy et al [46]	2016	Brain metastases (50)	30-Gy WBRT (control group: 25 patients) or 30 Gy WBRT + simvastatin 80 mg/day for the WBRT period (simvastatin group: 25 patients)	addition of simvastatin was toleratedResponse rates were 60% and 78.6% (p = 0.427), 1-year PFS rates were 5.2% and 17.7% (p = 0.392), and 1-year OS rates were 12% and 8% (p = 0.880) for the control group and simvastatin group, respectively. Nonsignificant differences were found between the two arms regarding HRQL scales. The addition of simvastatin 80 mg/day did not improve the clinical outcomes of patients with BM receiving WBRT.

Table-3: Radiation Therapy (n = 11)

No.	Year	Author	Country	Type of Tumour (n)	Treatment Arms	Outcomes Assessed/Conclusion
1.	2014	Pashaki et al [47]	Iran	Glioblastoma Multiforme (68)	GBM, treated with resection, and given postoperative radiotherapy followed by concurrent and/or adjuvant chemotherapy	Higher radiation doses of (>60Gy) can improve local control and potentially survival
2.	2009	Asghar et al [48]	Pakistan	Brain Metastasis (30)	Whole brain radiotherapy with 20 Gy was given in five consecutive daily fractions. All were followed up for six months for survival.	Significant effect of treatment with 20 Gy radiotherapy as 76% of the patients during and 80% on the last day of therapy showed >50% response (p<0.05).Median survival of the patients after radiotherapy was two months (p<0.05). No serious toxicity was noted during this therapy.
3.	2013	Goda et al [49]	India	Children with diffuse intrin-sic pontine gliomas(20)	Impact of multiparametric MRI and 18 F-FDG-PET on the outcomes	Cumulative RPI was able to classify the patients into different grades and was predictive of overall survival (p = 0.02). MR perfusion also predicted survival (p = 0.039). Sensitivity and specificity of MRI and FDG-PET to detect low-grade gliomas were low to moderate (33–66%), but moderate to high in detecting high-grade

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						gliomas (50–100%). Baseline FDG uptake on PET scan did not correlate with survival (p = 0.7).
4.	2022	Zaghloul et al [50]	Egypt	Paediatric diffuse intrinsic pontine glioma (253)	3 arms of radiation therapy regimens: HF1, receiving 39 Gy in 13fractions; HF2, receiving 45 Gy in 15 fractions; and conventional fractionation (CF), receiving 54 Gy in 30 fractions.	The median overall survival for the HF1, HF2, and CF were 9.6, 8.2, and 8.7 months, respectively. Younger patients (2-5 years of age) had better median OS in the whole cohort (11.6 months), HF1 (13.5), and CF (12.1) but not HF2 (6.2) (P = .003). Furthermore, the OS rates at 1, 1.5, and 2 years for children 2 to 5 years of age in the HF2 arm were lower than those in the HF1 and CF arms.Two hypo fractionated radiation therapy proved to be noninferior to conventional fractionation. The young age superiority was lost with a higher hypo fractionated radiation therapy dose, necessitating more caution in applying 45 Gy in 15 fractions in younger children (2-5 years of age).
5.	2017	Jalali et al [51]	India	Benignand Low-Grade Brain Tumours(200)	High-precision SCRT: 100ConvRT to a dose of 54 Gy in 30 fractions over 6 weeks: 100	In young patients with residual and/or progressive benign orlow-grade brain tumours requiring radiotherapy for long-term tumour control, SCRT compared with ConvRT achieves superior neurocognitive and neuroendocrine functional outcomes over 5 years without compromising survival.
6.	2011	Santra et al [52]	India	GBM (90)	Histopathologically proven glioma who had suspicion of recurrence clinically or imaging were evaluated using Tc-99m GHA SPECT and FDG PET/CT.59 patients were positive and 31 werenegative for tumour recurrence.	On subgroup analysis, GHA SPECT performed better than FDG PET/CT in all grades except for grade II gliomas, where both were equally effective. In all, 15 patients hadintramodality discordance, with GHA SPECT being correct in 13 of them.GHA SPECT appears to be a better imaging modality than FDG PET/CT for detection of recurrent gliomas.
7.	2018	Mallick et al [53]	India	GBM (89)	Hypo fractionated accelerated radiotherapy (HART): 60 Gy in 20 fractions over 4 weeks @ 3 Gy/per fraction to high-risk planning target volume (PTV) and 50 Gy in 20 fractions over 4 weeks @ 2.5 Gy/per fraction to low-risk PTVconventional fractionated radiotherapy (CRT): 60 Gy in 30 fractions over 6 weeks @ 2 Gy/per fraction	Median OS in the CRT and HART arms were 18.07 months (95% CI 14.52-NR) and 25.18 months (95% CI 12.89-NR) respectively, p = 0.3.HART is comparable to CRT in terms of survival outcome. HART arm had no excess treatment interruption and minimal toxicity. Dose escalation, reduction in overall treatment time, is the advantages with use of HART
8.	2010	Kalaghchi et al [54]	Iran	CNS Tumours (4)	two groups (20 patients each), the first receiving GCSF prevention therapy before weekly craniospinal radiotherapy and the control group without this prophylaxis.	No significant differences in platelets and WBC loss between the treatment and control groups. Treatment interruption was lower in weekly GCSF therapy group (35%), compared to the control group (55%), although the difference was not statistically significant (P value 0.2)Weekly GSCF injections among CNS tumour patients receiving craniospinal therapy may decrease treatment interruption.

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9.	2020	Izzuddeen et al [55]	India	DIPG (33)	Patients in arm A received conventional fractionated RT of 60 Gy in 30 fractions over 6 weeks while patients in arm B received hypo-fractionated radiotherapy of 39 Gy in 13 fractions over 2.6 weeks along with concurrent Temozolomide (TMZ) 75 mg/m2 from day 1 to day 17 followed by adjuvant TMZ for six cycles.	93% (n = 14) of patients in the conventional arm completed treatment while only 17% (n = 3) of the children could complete planned course of treatment in the experimental arm. The median overall survival (OS) was 11 months (95% CI - 7.5 to 14.5 months) in the conventional arm and 12 months (95% CI - 10.5 to 13.5 months) in the experimental arm (p = 0.208). 28% (n = 5) patients in the experimental arm developed grade 3 or 4 haematological toxicity.Conclusion: The above study shows that hypo fractionated radiotherapy with concurrent and adjuvant temozolomide does not improve OS and has higher haematological toxicity. Conventional radiotherapy remains the standard of care.
10.	2014	Gantery et al [56]	Egypt	Brain metastases (1-3) (60)	21 patients received WBRT + SRS, 18 patients received SRS alone and 21 patients received WBRT alone	Median local control was significantly better for WBRT + SRS compared to SRS alone & WBRT alone (10 vs 6 vs 5 months, respectively, P = 0.04). There was non-significant survival benefit for WBRT + SRS compared to SRS alone & WBRT alone. Survival was significantly better for patients with controlled primary tumour who received WBRT + SRS compared to SRS alone & WBRT alone (median survival was 12 vs 5.5 vs 8 months, respectively. P = 0.027)
11.	2003	Sharma et al [57]	India	High grade gliomas and glioblastoma multiforme who underwent surgery partial, sub-total or near-total excision as the primary treatment (50)	Study Group A: Localized field external radiotherapy 50 Gy/25#/5 wks followed by Boost 10 Gy/5#/1 wk, Control Group B: Whole brain external radiotherapy 40 Gy/20#/4 wks followed by Boost 20 Gy/10#/2 wks by localized field.	No significant difference in the local response was seen between the two groups after radiotherapy. Six months progression-free survival of the study group was 44% as compared to 26% in the control group. Six months overall survival was 66.67% in the study group and 50.72% in the control group (P<0.01). Maximum recurrences were noticed within 2 cm of the original tumour margin in both the groups. Although local control and survival of the patient in both the groups were same, performance status definitely improved in patients treated with localized field irradiation only.

Table-4: Miscellaneous (n = 4).

No.	Year	Author	Country	Type of Tumour (n)	Treatment Arms	Outcomes Assessed/Conclusion
1.	2019	Thakur et al. [58]	India	Intracranial tumors (80)	Nurse-led intervention was provided in the form of individual counselling, and a pamphlet was given to patients and caregivers in the experimental group at the time of discharge	Patients in the experimental group had significantly fewer behavioural symptoms and less severity of behavioural symptoms as compared to the control group. Caregivers in the experimental group had significantly less severity of distress as compared to the control group.
2.	2018	Patil et al [59]	India	Adult glioma (II-IV)(65)	Compared video follow-up and conventional clinical follow-up	Concurrence in decision of administering TMZ between VF and CF was 100% (p<0.00).Median cost incurred in VF was US$58.15 while that incurred in CF was

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						US$131.23 (p<0.00)VF can substitute CF during adjuvant TMZ administration
3.	2015	Mirrahimi et al 60	Iran	Supratentorial (60)	treatment group (30), 5 g of MgSO4 in normal saline was infused in 6 h 2 days before surgery, and the same dosage was repeated the day before and during surgery. The control group (30) received placebo	Significant change in S100B protein levels before and after surgery ($p < 0.05$), but we could not find similar results for NSE protein and the Barthel index score
4.	2010	Puri et al [61]	India	High-grade glioma (50)(GBM 32/50)	surgery followed by adjuvant radiotherapy and concomitant paclitaxeloral lycopene (Group A) 8 mg daily with radiotherapy or placebo (Group B)	Magnetic resonance imaging (MRI) of brain and Single Photon Emission Computed Tomography (SPECT) were done three-monthly for two visits and six-monthly thereafter. Primary endpoint was response at six months post radiotherapy.Pre- and post-treatment plasma lycopene levels in the patients in Gropu A were 152 ng/ml and 316 ng/ml and in the patients in Group B were 93 ng/ml and 98 ng/ml (P = 0.009). There was non-significant differences in favour of lycopene between Group A and Group B with higher overall response at six months (P = 0.100), response at last follow-up (P = 0.171) and time to progression (40.83 vs. 26.74 weeks, P = 0.089)

optimized steroids for CNS involvement in childhood ALL to reduce viral infections. Similarly, short course radiotherapy with Temozolomide was found to improve survival without compromising QoL in newly diagnosed GBM in frail/elderly patients. Radiation oncology literature was also limited from LMICs (11 papers), with only two recent papers discussing DIPG treatment with conventional fractionated RT vs. hypo fractionated RT.

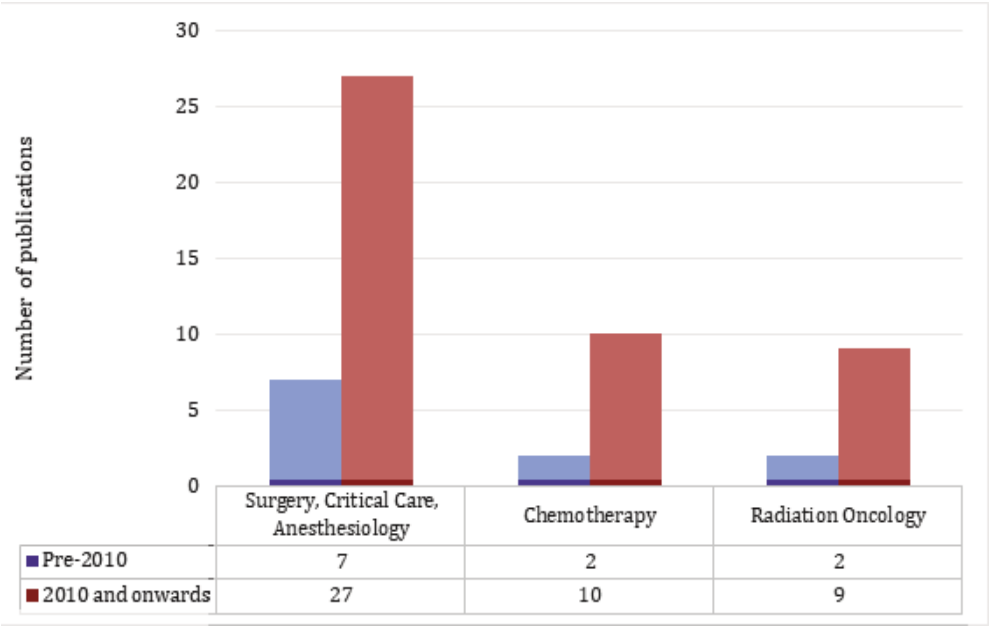

Figure-2: Comparison of clinical trials published before and after 2010 according to categories.

Further avenues for clinical trial development

A subjective assessment of current trends in neuro-oncological clinical trials from LMICs shows great promise in terms of repurposing previous drugs for chemotherapy and radiosensitisation [62], developing new protocols for reducing chemo- and radiation-related toxicities in childhood brain tumours, and novel, low-cost interventions in surgical neuro-oncology. With the advent of new immune-checkpoint inhibitors and CAR T cell therapy, it may be

difficult to determine financial viability of these options in LMIC health economies, considering many patients pay out-of-pocket for treatment and supply-chain demands may affect availability. A recent phase 1 study repurposing mebendazole, a common anti-helminthic drug, for recurrent high-grade glioma was able to determine tolerable dosing in concurrence with adjuvant concurrent chemo and radiotherapy (CCRT); such studies are practicable approaches towards conducting effective trial research in LMICs considering cost demands.

Much work has been published by the SIOP PODC (International Society of Paediatric Oncology (SIOP) committee named Paediatric Oncology in Developing Countries) regarding chemotherapy and radiation regimen recommendations for LMICs in paediatric brain tumours, based on local evidence, experts working within LMICs, and availability of medications.[63] These guidelines have been effective in developing standards of care for these pathologies in resource-limited settings; clinical trials assessing response and treating recurrent tumours with the available resource are needed. Low-cost interventions in neuro-oncological surgery, such as ultra-low-field portable MRI for assessing tumour resection rates, are other possible avenues of trial research.[64]

Developing trials and infrastructure in LMICs

The evidence presented supports the need for greater buy-in from LMIC institutions towards building clinical trial research centres and collaborations, both local and regional, to help generate more well-founded science in the practice of neuro-oncology. The benefits from the perspective of LMIC stakeholders is developing real-world evidence for interventions that are locally sourced, well founded in populations of interest, and lead to LMIC researchers contributing significantly to global scientific efforts. This in turn incentivizes greater collaboration with other centres of excellence across the world – HIC researchers would benefit through understanding clinical trial research in populations distinct from their own, allowing for greater insights into treatment response and tumour behaviour, and help expand the potential pool of participants for ethical trials.

Clinical trial development in LMICs is currently ongoing – in an overview of recent oncology RCTs globally, it was reported that only 8% of oncology trials were lead by either upper-middle income countries (UMICs) or LMICs.[65] Despite greater inclusion of LMIC populations in HIC-led RCTs, LMIC research output does not reflect strong evidence of locally developed trials or infrastructure, as evidenced in further investigations.[66] Resource and logistics-related barriers to clinical trials in LMICs are well-documented[67]; however, academic and industrial partnerships, in line with ethical and local governance standards, can help support clinical cancer care systems and conduct novel, effective clinical trial research. Within neuro-oncology trial research especially, prioritizing cooperative trials can help improve research output from LMICs.

Conclusion

The presented review of LMIC-led clinical trials in neuro-oncology identifies trends in research and insights into new pathways for developing research. The current literature shows steady improvement in research output, with diversification and investigation into specific tumours, improving chemo- and radiation therapy regimens for specific populations, and investigating resource-efficient measures. Overall, there is a dire need for greater participation and collaboration in improving trial research output from these underserved populations.

Appendix 1:
Search strategy:

(((randomized clinical trial) OR (RCT)) AND ((neuro-oncology) OR (neuro oncology) OR (Brain tumour) OR (CNS tumour) OR (Central nervous system tumours) OR (Glioma) OR (Astrocytoma) OR (Oligodendroglioma) OR (GBM) OR (Glioblastoma) OR (Glioblastoma multiforme) OR (Glial tumour) OR (Medulloblastoma) OR (Ependymoma) OR (Pinealoma) OR (Craniopharyngioma) OR (Brain Metastasis)) AND ((LMIC) OR (Low income country) OR (Middle income country) OR (Low to middle income country) OR (Low-to-middle-income country) OR (Afghanistan) OR (Burkina Faso) OR (Burundi) OR (Central African Republic) OR (Chad) OR (Congo, Dem. Rep) OR (Eritrea) OR (Ethiopia) OR (The Gambia) OR (Guinea) OR (Guinea-Bissau) OR (Korea, Dem. People's Rep) OR (Liberia) OR (Madagascar) OR (Malawi) OR (Mali) OR (Mozambique) OR (Niger) OR (Rwanda) OR (Sierra Leone) OR (Somalia) OR (South Sudan) OR (Sudan) OR (Syrian Arab Republic) OR (Togo) OR (Uganda) OR (Yemen) OR (Rep. Zambia) OR (Angola) OR (India) OR (Philippines) OR (Algeria) OR (Indonesia) OR (Samoa) OR (Bangladesh) OR (Iran) OR (São Tomé and Principe) OR (Benin) OR (Kenya) OR (Senegal) OR (Bhutan) OR (Kiribati) OR (Solomon Islands) OR (Bolivia) OR (Kyrgyz Republic) OR (Sri Lanka) OR (Cabo Verde) OR (Lao PDR) OR (Tanzania) OR (Cambodia) OR (Lebanon) OR (Tajikistan) OR (Cameroon) OR (Lesotho) OR (Timor-Leste) OR (Comoros) OR (Mauritania) OR (Tunisia) OR (Congo) OR (Micronesia) OR (Fed. Sts) OR (Ukraine) OR (Côte d'Ivoire) OR (Mongolia) OR (Uzbekistan) OR (Djibouti) OR (Morocco) OR (Vanuatu) OR (Egypt) OR (Myanmar) OR (Vietnam) OR (El Salvador) OR (Nepal) OR (West Bank and Gaza) OR (Eswatini) OR

(Nicaragua) OR (Zimbabwe) OR (Ghana) OR (Nigeria) OR (Haiti) OR (Pakistan) OR (Honduras) OR (Papua New Guinea).

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