Neurosurgical Review (2019) 42:133–137
https://doi.org/10.1007/s10143-018-0967-8

ORIGINAL ARTICLE

Impact of randomized controlled trials on neurosurgical practice in decompressive craniectomy for ischemic stroke

Thomas Beez[1] · Hans-Jakob Steiger[1]

Received: 3 February 2018 / Revised: 3 March 2018 / Accepted: 12 March 2018 / Published online: 19 March 2018

Abstract

Randomized controlled trials (RCTs) are gold standard for comparing treatment modalities. Recently, RCTs transformed ischemic stroke care by first proving benefit of decompressive craniectomy (DC) and later of interventional mechanical thrombectomy. Aim of this study was to explore the impact of RCTs on neurosurgical practice. RCTs investigating DC and thrombectomy were identified. Annual numbers of DCs for ischemic stroke between 2000 and 2017 were determined and correlated with publication dates of RCTs. The initial RCTs demonstrating efficacy of DC were published in 2007, followed by an increase in DC numbers between 2008 and 2009. The first RCTs on mechanical thrombectomy were published in 2014 and 2015, with a decline in DCs observed between 2015 and 2016. There is a close temporal relationship between publication of these RCTs and changes in neurosurgical practice. Dynamics of annual DCs appear to correlate with the publication of RCTs. Significantly positive results of surgical and interventional RCTs were translated into clinical practice with a latency of 1 year, as reflected by shifts in annual DC numbers.

Keywords Cerebral infarction · Ischemic stroke · Decompressive craniectomy · Interventional mechanical thrombectomy · Randomized controlled trial

Introduction

Randomized controlled trials (RCTs) are considered the gold standard for investigating the relationships between medical or surgical interventions and outcomes as well as comparing different treatment modalities [21]. The main hallmark of a RCT is the randomization process, which is, if successfully accomplished, the most reliable and efficient way of forming groups without systematic differences in their baselines characteristics, i.e. free from selection bias. Another important step to reduce bias is to implement blinding of patients, medical personnel and outcome assessors. These measures can reduce performance and detection biases, although especially in surgical RCTs effective blinding may not be possible [9]. Additionally, modern RCTs have to be registered in publicly available databases, such as ClinicalTrials.gov, to meet law and publication requirements. Registration before beginning of a RCT assures transparency to participants and the research community, provides reliable information to potential participants and referring clinicians and helps reduce publication bias [29].

However, despite their inherently higher risk of bias, other forms of study (such as observational studies) are considered to have certain advantages over RCTs, such as lower cost, greater timeliness and a broader and thus more realistic range of patients [1]. Comparisons of results from RCTs and preceding non-randomized trials suggest consistency in at least 60% [22].

With the propagation of evidence based medicine, the available published data acquired through RCTs increased significantly [16]. Of note, the risk of study discontinuation and presumably also the non-publication rates of such results are reported to be substantial in surgical RCT compared to medical RCTs [28]. While this certainly indicates higher obstacles when exploring surgical treatments with RCT methodology, these findings also reveal a significant publication bias in surgery.

Despite these intricacies, medical, surgical, and interventional RCTs have significantly influenced the treatment of

✉ Thomas Beez
thomas.beez@med.uni–duesseldorf.de

[1] Department of Neurosurgery, Medical Faculty, Heinrich-Heine-University, Moorenstr. 5, 40225 Düsseldorf, Germany

patients with ischemic stroke: While recanalization with intravenous, intraarterial or mechanical thrombolysis is strongly associated with improved functional outcomes and reduced mortality, decompressive craniectomy (DC) has been shown to reduce mortality in those patients who still suffer a space-occupying territorial cerebral infarction [5, 23]. Aim of the present study was to explore the extent and timeline of the translation from RCTs to routine patient care and the subsequent impact on neurosurgical practice.

Materials and methods

We have hypothesized that publication of a RCT would influence routine patient care, and that significant shifts in major ischemic stroke outcomes would ultimately be reflected in the number of patients requiring DC for space-occupying territorial cerebral infarction, as we assume the majority of those patients to represent failures of preceding recanalization attempts.

Since RCTs for intravenous and intraarterial thrombolysis were mainly published before the widespread implementation of DC and an association is thus undetectable, the present study focused on RCT investigating DC and mechanical interventional thrombolysis. The PubMed database (https://www.ncbi.nlm.nih.gov/pubmed, accessed on 22nd October 2017) was searched for "ischemic stroke" and "cerebral infarction" and search results were automatically filtered to include only "randomized controlled trials" published between January 2000 and October 2017. The search results were then manually screened for RCTs investigating DC and mechanical interventional thrombolysis. The reference lists of relevant meta-analyses and systematic reviews were searched for additional RCTs.

The annual number of decompressive craniectomies for ischemic stroke performed between January 2000 and October 2017 at our institution, which is a tertiary referral hospital delivering neurosurgical care to a large urban catchment area with approximately seven certified stroke units and ten to fifteen general neurological departments, was calculated in an anonymous, retrospective fashion. The electronic hospital reporting is based on the German version of the *International* Statistical *C*lassification of *D*iseases and Related Health Problems (ICD-10; https://www.dimdi.de/static/de/klassi/icd-10-gm/kodesuche) and on the German version of the *I*nternational *C*lassification of *P*rocedures in *M*edicine (ICPM; https://www.dimdi.de/static/de/klassi/ops/kodesuche/onlinefassungen/opshtml2018/index.htm). Employing these classification systems, annual patient numbers undergoing DC for ischemic stroke were retrieved by using the ICD-10 codes I63.0 to I63.9 and the ICPM codes 5-012.0, 5-010.1× and 5-010.10 to 14.

Results

Between 2008 and 2009, we have observed a sharp increase in annual decompressive craniectomies for stroke from 26 to 43, respectively (Fig. 1). The numbers remained relatively stable between 2008 and 2015, with a median annual number of 45 operations. Between 2015 and 2016, a sharp decline was evident from 45 to 33 operations per year.

We have identified three RCTs investigating the role of DC in space occupying cerebral infarction [10, 15, 31]. A previously published meta-analysis of the data from these trials suggested that in patients with malignant cerebral infarction, DC reduces mortality with a number needed to treat of two for survival irrespective of functional outcome [30]. The results were deemed highly consistent across these RCTs. We have identified nine RCTs investigating the role of mechanical thrombectomy in acute ischemic stroke [2–4, 7, 14, 18, 24, 25, 27]. These RCTs uniformly reported positive results and demonstrated superiority of endovascular clot retrieval over the previous standard of care. Mechanical thrombectomy is a highly effective treatment modality for ischemic stroke with a number needed to treat of less than three for improved functional outcome [8]. It has therefore been quickly implemented and made widely available as a new standard of care for acute stroke patients in several countries, including Germany [19].

The dynamics of annual decompressive craniectomies for stroke correlate with the publication of RCTs, with a presumed impact on neurosurgical practice detectable with a latency of approximately 1 year (Fig. 1): The first two RCTs demonstrating efficacy of DC for space occupying cerebral infarction were published in 2007, followed by a sharp increase in annual operation numbers between 2008 and 2009 [15, 31]. The first RCT on mechanical thrombectomy was published in December 2014, with four further RCTs being published in 2015 [2, 4, 7, 14, 27]. Subsequently, we observed a decline in annual decompressive craniectomies for stroke in 2016.

Discussion

The present study demonstrates an increase in annual numbers of decompressive craniectomies for ischemic cerebral infarction in temporal relationship with the publication of the first two RCTs suggesting a reduction in mortality, with a latency of approximately one year. Conversely, the publication of the initial five RCTs revealing superiority of mechanical thrombectomy over previous recanalization approaches was followed by a decline in annual decompressive craniectomies for stroke, suggesting a reduction of space occupying cerebral infarctions after implementation of mechanical clot retrieval. Similar time trends can also be observed in the data on DC published by Lammy and co-authors [20].

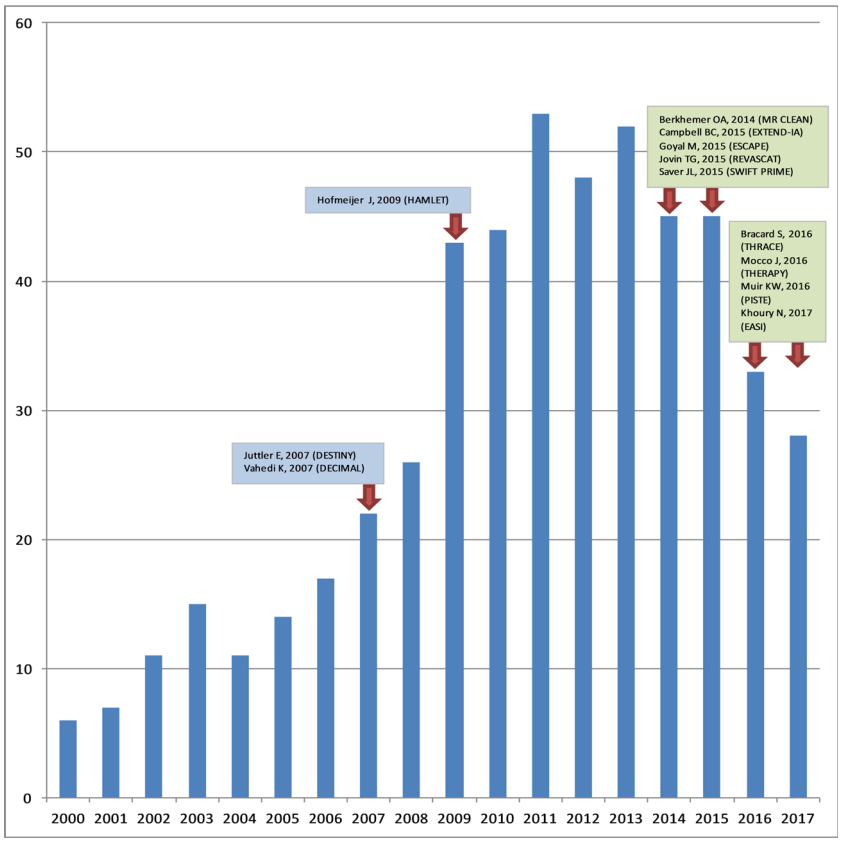

Fig. 1 Annual numbers of decompressive craniectomies for stroke at our institution, correlated with publication years of RCTs on DC and thrombectomy, blue boxes indicate publication of RCTs on DC and yellow boxes indicate publication of RCTs on mechanical thrombectomy

Our analysis suggests that results from positive or partially positive RCTs are quickly translated into clinical practice, similar to previous reports in different medical fields [6, 11, 26]. However, the latency of implantation into clinical routine appears to vary between few years, as reported by us as well as Hudgins et al., and several years, as described by Ketley and Woods [11, 17]. This variation might be related to the extent of change in outcomes ascribed to the "new" treatment, or in other words, whether the results of the RCT are truly "groundbreaking" advances. Other factors might be the increased promotion of products with proven benefit by manufacturers and the degree of doctors' willingness to adopt a new treatment as opposed to abandon an "established" treatment in response to positive or negative RCT results, respectively [11]. Of note, negative results are less likely to be translated directly into clinical practice, in addition to the well-established publication bias regarding negative findings [12, 13]. Concerns have been raised for surgical RCTs in particular, with higher discontinuation and non-publication rates compared to medical trials [28]. Another factor could be the limited generalizability of RCT findings, which can be related to differences between patients enrolled in an RCT and those encountered in day-to-day practice as well as to limited availability of certain treatment options in the clinical routine setting [32]. However, our results suggest that these obstacles were overcome for both the DC RCTs as well as the mechanical thrombectomy RCTs.

A limitation of the present study is related to potential bias within the retrospective patient cohort undergoing DC: We assume that some patients presented too late for mechanical thrombectomy or other forms of thrombolysis or were not eligible for an interventional approach. This subgroup would not be affected by RCT results. However, presumably the proportion of patients presenting too late with already demarcated, unsalvageable cerebral infarction remains stable over time. Intravenous and intraarterial thrombolysis were implemented before DC became wide spread practice and thus no assumptions were possible concerning impact of these RCTs on operation numbers.

In summary, the present study demonstrates a close temporal relationship between publication of RCTs in acute ischemic stroke and neurosurgical practice at a tertiary referral hospital. The publication of surgical and interventional RCTs with significant positive or partially positive results was translated into clinical practice with a latency of 1 year, as reflected by annual numbers of decompressive craniectomies for cerebral infarction. These results suggest that neurosurgery, neurology, and neuroradiology in Germany offer a dynamic, evidence-based and up to date patient care with fast implementation of the latest study results into routine clinical practice.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Ethics statement This study was performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was not required, as this study did not directly involve patients, but was based on anonymous data, which is in similar form publicly available in legally required annual hospital quality reports.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Benson K, Hartz AJ (2000) A comparison of observational studies and randomized, controlled trials. N Engl J Med 342:1878–1886. https://doi.org/10.1056/NEJM200006223422506
2. Berkhemer OA, Fransen PSS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJH, van Walderveen MAA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PLM, van Rooij WJJ, van den Berg JSP, van Hasselt BAAM, Aerden LAM, Dallinga RJ, Visser MC, Bot JCJ, Vroomen PC, Eshghi O, Schreuder THCML, Heijboer RJJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, MES S, SFM J, LFM B, van den Berg R, Koudstaal PJ, van Zwam WH, YBWEM R, van der Lugt A, van Oostenbrugge RJ, CBLM M, DWJ D, MR CLEAN Investigators (2015) A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 372:11–20. https://doi.org/10.1056/NEJMoa1411587
3. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, Guillemin F, investigators THRACE (2016) Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 15:1138–1147. https://doi.org/10.1016/S1474-4422(16)30177-6
4. Campbell BCV, Mitchell PJ, EXTEND-IA Investigators (2015) Endovascular therapy for ischemic stroke. N Engl J Med 372:2365–2366. https://doi.org/10.1056/NEJMc1504715
5. Evans MRB, White P, Cowley P, Werring DJ (2017) Revolution in acute ischaemic stroke care: a practical guide to mechanical thrombectomy. Pract Neurol 17:252–265. https://doi.org/10.1136/practneurol-2017-001685
6. Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE (2003) Anticoagulation therapy for stroke prevention in atrial fibrillation. JAMA 290:2685–2692. https://doi.org/10.1001/jama.290.20.2685
7. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo J-H, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn S-I, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD, Trial Investigators ESCAPE (2015) Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 372:1019–1030. https://doi.org/10.1056/NEJMoa1414905
8. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, Donnan GA, Roos YBWEM, Bonafe A, Jahan R, Diener H-C, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BCV, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG, collaborators HERMES (2016) Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet (London, England) 387:1723–1731. https://doi.org/10.1016/S0140-6736(16)00163-X
9. Higgins J, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. In: Cochrane Collab. www.cochrane-handbook.org (accessed September 2014)
10. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, HAMLET investigators (2009) Surgical decompression for space-occupying cerebral infarction (the hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurol 8:326–333. https://doi.org/10.1016/S1474-4422(09)70047-X
11. Hudgins JD, Fine AM, Bourgeois FT (2016) Effect of randomized clinical trial findings on emergency management. Acad Emerg Med 23:36–47. https://doi.org/10.1111/acem.12840
12. Ioannidis JPA (1998) Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 279:281–286. https://doi.org/10.1001/jama.279.4.281
13. Johnson RT, Dickersin K (2007) Publication bias against negative results from clinical trials: three of the seven deadly sins. Nat Clin Pract Neurol 3:590–591. https://doi.org/10.1038/ncpneuro0618
14. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Pérez M, Goyal M, Demchuk AM, von Kummer R, Gallofré M, Dávalos A, REVASCAT Trial Investigators (2015) Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 372:2296–2306. https://doi.org/10.1056/NEJMoa1503780
15. Jüttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, Witte S, Jenetzky E, Hacke W, DESTINY Study Group (2007) Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY): a randomized, controlled trial. Stroke 38:2518–2525. https://doi.org/10.1161/STROKEAHA.107.485649
16. Kennedy HL (1999) The importance of randomized clinical trials and evidence-based medicine: a clinician's perspective. Clin Cardiol 22:6–12
17. Ketley D, Woods KL (1993) Impact of clinical trials on clinical practice: example of thrombolysis for acute myocardial infarction. Lancet (London, England) 342:891–894
18. Khoury NN, Darsaut TE, Ghostine J, Deschaintre Y, Daneault N, Durocher A, Lanthier S, Pope AY, Odier C, Lebrun L-H, Guilbert F, Gentric J-C, Batista A, Weill A, Roy D, Bracard S, Raymond J, trial collaborators EASI (2017) Endovascular thrombectomy and medical therapy versus medical therapy alone in acute stroke: a randomized care trial. J Neuroradiol 44:198–202. https://doi.org/10.1016/j.neurad.2017.01.126
19. Krogias C, Bartig D, Kitzrow M, Brassel F, Busch EW, Nolden-Koch M, Reimann G, Weimar C, Weber R, Eyding J (2017) [Availability of mechanical thrombectomy for acute stroke : analysis of the health care reality in Germany]. Nervenarzt. https://doi.org/10.1007/s00115-017-0324-0
20. Lammy S, Al-Romhain B, Osborne L, St George EJ (2016) 10-year institutional retrospective case series of decompressive craniectomy

for malignant middle cerebral artery infarction (mMCAI). World Neurosurg 96:383–389. https://doi.org/10.1016/j.wneu.2016.09.004

21. Lange S, Sauerland S, Lauterberg J, Windeler J (2017) The range and scientific value of randomized trials. Dtsch Arztebl Int 114: 635–640. https://doi.org/10.3238/arztebl.2017.0635
22. LeLorier J, Grégoire G, Benhaddad A, Lapierre J, Derderian F (1997) Discrepancies between meta-analyses and subsequent large randomized, controlled trials. N Engl J Med 337:536–542. https://doi.org/10.1056/NEJM199708213370806
23. Lu X, Huang B, Zheng J, Tao Y, Yu W, Tang L, Zhu R, Li S, Li L (2015) Decompressive craniectomy for the treatment of malignant infarction of the middle cerebral artery. Sci Rep 4:7070. https://doi.org/10.1038/srep07070
24. Mocco J, Zaidat OO, von Kummer R, Yoo AJ, Gupta R, Lopes D, Frei D, Shownkeen H, Budzik R, Ajani ZA, Grossman A, Altschul D, McDougall C, Blake L, Fitzsimmons B-F, Yavagal D, Terry J, Farkas J, Lee SK, Baxter B, Wiesmann M, Knauth M, Heck D, Hussain S, Chiu D, Alexander MJ, Malisch T, Kirmani J, Miskolczi L, Khatri P, Trial Investigators* THERAPY (2016) Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. Stroke 47:2331–2338. https://doi.org/10.1161/STROKEAHA.116.013372
25. Muir KW, Ford GA, Messow C-M, Ford I, Murray A, Clifton A, Brown MM, Madigan J, Lenthall R, Robertson F, Dixit A, Cloud GC, Wardlaw J, Freeman J, White P, PISTE Investigators (2017) Endovascular therapy for acute ischaemic stroke: the pragmatic ischaemic stroke thrombectomy evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry 88:38–44. https://doi.org/10.1136/jnnp-2016-314117
26. Rapp M, Sadat H, Slotty PJ, Steiger HJ, Budach W, Sabel M (2015) Feasibility of the EORTC/NCIC trial protocol in a neurosurgical outpatient unit: the case for neurosurgical neuro-oncology. J Neurol Surg A Cent Eur Neurosurg 76:298–302. https://doi.org/10.1055/s-0034-1396437
27. Saver JL, Goyal M, Bonafe A, Diener H-C, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R, SWIFT PRIME Investigators (2015) Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 372:2285–2295. https://doi.org/10.1056/NEJMoa1415061
28. Shah HM, Chung KC (2009) Archie Cochrane and his vision for evidence-based medicine. Plast Reconstr Surg 124:982–988. https://doi.org/10.1097/PRS.0b013e3181b03928
29. US National Library of Medicine ClinicalTrials.gov. https://clinicaltrials.gov/ct2/manage-recs/background. Accessed 3 Mar 2018
30. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser M-G, van der Worp HB, Hacke W, DECIMAL, DESTINY and H investigators (2007) Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol 6:215–222. https://doi.org/10.1016/S1474-4422(07)70036-4
31. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard J-P, Boutron C, Couvreur G, Rouanet F, Touzé E, Guillon B, Carpentier A, Yelnik A, George B, Payen D, Bousser M-G, DECIMAL Investigators (2007) Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL trial). Stroke 38:2506–2517. https://doi.org/10.1161/STROKEAHA.107.485235
32. Zarin DA, Young JL, West JC (2005) Challenges to evidence-based medicine: a comparison of patients and treatments in randomized controlled trials with patients and treatments in a practice research network. Soc Psychiatry Psychiatr Epidemiol 40:27–35. https://doi.org/10.1007/s00127-005-0838-9