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The death of a neurotrauma trial lessons learned from the prematurely halted randomized evaluation of surgery in elderly with traumatic acute subdural hematoma (RESET-ASDH) trial

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ABSTRACT

Introduction: Acute subdural hematoma (ASDH) due to traumatic brain injury (TBI) constitutes an increasing global health problem, especially in the elderly population. Treatment decisions on surgical versus conservative management pose a neurosurgical dilemma. Large practice variation exists between countries, hospitals, and individual neurosurgeons, illustrating the presence of 'clinical equipoise'. The RESET-ASDH trial aimed to address this dilemma but was terminated prematurely due to insufficient patient recruitment.
Research question: What factors may have contributed to the premature discontinuation of the RESET-ASDH trial?
Materials and methods: The RESET-ASDH was a multicenter randomized controlled trial (RCT) comparing functional outcome at 1 year after early surgery or an initial conservative treatment in elderly patients (≥65 years) with a traumatic ASDH. Logs of registry data, medical-ethical approval timelines and COVID-19 related research documents were analyzed. Furthermore, non-structured interviews with involved clinical research personnel were conducted.
Results: The concept of clinical equipoise was broadly misinterpreted by neurosurgeons as individual uncertainty, hampering patient recruitment. Also, the elderly target population complicated the inclusion process as elderly and their informal caregivers were hesitant to participate in our acute surgical trial. Moreover, the COVID-19 pandemic added additional hurdles like delayed medical-ethical approval, a decline in eligible patients and repeated trial halts during the peaks of the pandemic.
Discussion and conclusion: The premature termination of the RESET-ASDH study may have been related to the trial's methodology and target population with an additional impact of COVID-19. Future acute neurosurgical trials in elderly may consider these challenges to prevent premature trial termination.

1. Introduction

Unfortunately, neurosurgical trials are rare: they constitute less than 1% of published papers in leading neurosurgical journals (GHOGAWALA et al., 2008; Barker, 2016). Trial discontinuation is common with about one-fifth of neurosurgical RCTs being discontinued early, mostly due to inadequate patient recruitment (Jamjoom et al., 2017; Knottnerus and Tugwell, 2016). Some -jocularly- attribute this to *Lasagna's law*, stating that *'the number of patients available to join a trial drop by 90% the day the trial begins and re-appear as soon as the study is over'* (Bogin, 2022). Others believe that the lack of high-quality neurosurgical trials is inherent to the unique nature of neurosurgery, as it mostly encompasses rare diseases and often acutely life-threatening conditions where high-stake decisions have to be made under time pressure. A

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disconcerting idea cynically referred to as '(neuro)surgical exceptionalism' (Martin et al., 2019; Helmy et al., 2009).

Traumatic brain injury (TBI) is a global burden with the highest incidence in relatively young people in low- and middle-income countries, while in the 'ageing' high-income countries elderly people (≥65 years) are the main contributors to this major and ever-increasing global health problem. Prolonged vitality of the elderly prompts a desire to survive disorders and stay mobile which increases their risk of sustaining TBI (Maas et al., 2017; Brazinova et al., 2021; Mak et al., 2012). An acute subdural hematoma (ASDH) is the most common injury encountered in elderly with TBI, frequently presenting with a GCS of 13–15, which is paradoxically defined as 'mild' TBI (Harvey and Close, 2012a).

The operative versus conservative treatment of an ASDH in elderly remains an important neurosurgical dilemma, both from a clinical and ethical perspective (Harvey and Close, 2012b; Maxeiner, 1998; Gavrila et al., 2021; Van Essen et al., 2019). Early hematoma evacuation via craniotomy or decompressive craniectomy may result in good clinical outcome, but comes with relevant (surgical) risks, especially in frail elderly patients (Mak et al., 2012; Howard et al., 1989; Cagetti et al., 1992; Karibe et al., 2014; Raj et al., 2016; Etzioni et al., 2003; van Essen et al., 2023). On the other hand, initial conservative management –possibly followed by burr-hole drainage in second instance if needed after several weeks– will result in less surgical morbidity, but may lead to secondary neurological deterioration or potentially devastating complications related to inactivity and prolonged hospital admission (Borkar et al., 2011; Evans et al., 2019; Gavrila et al., 2023). Definitive evidence on who (not) to operate is not available (Bullock et al., 2006) and as the BTF guidelines are not based on studies in elderly (Carney et al., 2017), not surprisingly, large practice variation exist between countries, medical centers and even between individual neurosurgeons within hospitals (Cnossen et al., 2021; Van Essen et al., 2017; Lingsma et al., 2011; van Essen et al., 2022). This practice variation, i.e. the same elderly patient with a similar ASDH and clinical presentation will be treated differently depending on the location of the accident or the neurosurgeon on call, illustrates the presence of 'clinical equipoise'. This notion was first articulated by Benjamin Freedman in 1987 and described as '*an honest, professional disagreement among expert clinicians about the preferred treatment*' (Freedman, 2017).

The major global healthcare burden, the burning clinical question whether to operate or not, and the existence of clinical equipoise for the treatment of elderly patients with an ASDH, constituted the rationale for our Randomized Evaluation of Surgery in Elderly with Traumatic Acute SubDural Hematoma (RESET-ASDH) trial (Singh et al., 2022). Unfortunately, this trial had to be discontinued early due to the lack of patient recruitment by several causes.

In this manuscript, we aim to delineate the obstacles that ultimately led to premature discontinuation of the RESET-ASDH trial, with the hope that future researchers can learn from this experience and adjust their research strategies. Besides the surgeon-scientists it is important to inform non-surgical disciplines about inherent difficulties of RCT's and to make public and private beneficiaries aware that randomizing a patient between invasive surgery and non-surgical treatment is different from comparing one medical treatment to the other medical treatment in an acutely life-threatening disorder.

2. Materials and Methods

The RESET-ASDH study was a pragmatic, multicenter randomized controlled trial (RCT) set up to compare survival and functional outcome of elderly patients with a traumatic ASDH after early neurosurgical hematoma evacuation versus an initial conservative treatment. The study was led by the Leiden University Medical Center (LUMC) in the Netherlands together with the University Hospital Leuven (UZL) in Belgium. Eligible patients were elderly (≥65 years) patients presenting to one of 16 level-1 trauma centers across the Netherlands and Belgium with a traumatic ASDH for whom clinical equipoise existed regarding the preferred treatment strategy *(see supplementary material 1 for detailed in- and exclusion criteria)* (Singh et al., 2022). The existence of clinical equipoise was explained in the protocol, indicating that, based on available evidence, neither treatment would have superiority for the responsible neurosurgeon caring for that specific patient. Even though equipoise is a prerequisite for clinical trials, we explicitly added this criterium because of the possibility that case-specific factors, not captured by the in- and exclusion criteria, may waive clinical equipoise. In such cases, it was deemed not feasible or ethical to randomize patients against the treating neurosurgeon's best intention of best care for his or her individual patient. Patients were to be randomized at presentation to the neurosurgeon for acute surgery or an initial non-surgical treatment with possible delayed surgery if the patient showed signs of deterioration due to the traumatic ASDH. Patients were preferably included by informed consent or proxy consent, but deferred consent was also possible depending on the urgency of the situation. The primary outcome was functional outcome after one year measured on the Extended Glasgow Outcome Scale (GOS-E). The study was approved by the central medical-ethical boards in the Netherlands and Belgium as well as by all 16 participating centers. The trial was funded by the collaborative Netherlands/Belgium (ZonMw/KCE) BeNeFIT grant [852101065].

Data regarding the factors that may have contributed to the premature discontinuation of the RESET-ASDH trial was gathered from the RESET-ASDH trial registry logs – containing eligible patients who were not included in the trial –, documentation from the Dutch and Belgian Medical Ethical Research Committees (MERC) and regulatory agencies' reports related to the COVID-19 pandemic. Furthermore, non-structured interviews were conducted with clinical research personnel involved in the RESET-ASDH trial.

3. Results

3.1. The complex concept of 'clinical equipoise'

From the RESET-ASDH trial registry database, we found that *'lack of clinical equipoise'* was the most common reason (69% [29/42]) for not including potentially eligible patients (Table 1). (Singh) An illustrative example came from one of our participating centers, where a trainee suggested to the attending neurosurgeon to include the following patient in the RESET-ASDH trial.

3.1.1. Illustrative case 1

76 year-old female patient on anticoagulants who sustained TBI due to a low-energetic fall from standing height. Her GCS (at the time of the decision) was 14 (E3M6V5) and she had a left-sided hemiparesis scored as a Medical Research Council (MRC) grade 4. Computed tomography (CT) scan demonstrated a fairly hyperdense right-sided ASDH with a maximum thickness of 20 mm and an associated midline shift of approximately 10 mm without accompanying cerebral contusions (Fig. 1A).

The senior neurosurgeon answered: *"I have performed [treatment A] on such patients ever since I was a trainee and I have never had any doubt about it. Why should I start doubting myself now?"*. The patient was not

Table 1
Reasons for not including eligible patients in the RESET-ASDH trial.

	Number of patients in NL and BE (n = 42) (%)
Lack of clinical equipoise	29 (69%)
Patient/family refusal to participate	8 (19%)
Neurological deterioration	2 (5%)
Too busy/forgotten to include	3 (7%)

Abbreviations: RESET-ASDH, Randomized Evaluation of Surgery in Elderly with Traumatic Acute SubDural Hematoma; NL, The Netherlands; BE, Belgium.

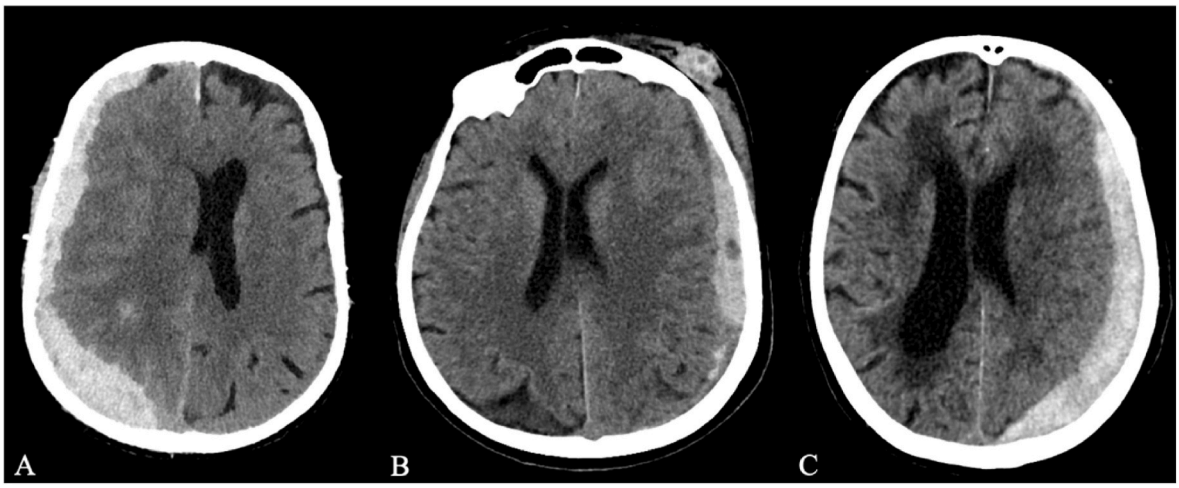

Fig. 1. Brain CT-scans of potentially eligible patients with an ASDH. **A:** ASDH with a maximum thickness of 20 mm and an associated midline shift* of 10 mm, **B:** Subacute SDH with a maximum thickness of 12 mm and an associated midline shift* of 6.5 mm, **C:** ASDH with a maximum thickness of 14 mm and an associated midline shift* of 7 mm. *midline shift was measured as the perpendicular distance between the septum pellucidum and a line designated the midline on axial CT-scan in brain setting. Abbreviations: ASDH, acute subdural hematoma; CT, computed tomography.

included in the trial.

The possibility of recruitment difficulties related to the interpretation of clinical equipoise was acknowledged in the RESET-ASDH trial protocol, which stated: "*Clinical equipoise, caused by scientific uncertainty and lack of evidence, can be a difficult subject for surgically trained medical doctors as they are educated to not let uncertainty influence their acute decision-making*" (Singh et al., 2022).

Despite training all involved clinicians in the methodological concept of clinical equipoise before the start of the RESET-ASDH trial, it seemed to be broadly interpreted as individual uncertainty, which is a related but fundamentally different concept.

3.2. Trial participation of elderly patients

From the RESET-ASDH registry logs, we found that *'patient or family refusal to participate'* was the reason for not including 19% (8/42) of potentially eligible patients. Two cases are presented below:

3.2.1. Illustrative case 2

79 year-old female on antiplatelet therapy who sustained TBI after she tripped over an exposed tree root while working in her garden. Her GCS at admission was 14 (E4M6V4) and neurological examination revealed a non-fluent speech as well as a mild receptive aphasia and a right-sided hemiparesis MRC grade 4. CT brain scan demonstrated a left-sided 'subacute' SDH – consisting of predominantly hyperdense but also hypodense components – measuring 12 mm in thickness with a midline shift of 6.5 mm (Fig. 1B).

After discussing the RESET-ASDH trial with the patient, she decisively stated that undergoing a craniotomy was 'a bridge too far' for her, even in the possible event of neurological deterioration, which could result in severe morbidity and even death without evacuation of the ASDH. Conservative treatment with the possibility of delayed burr-hole drainage was an acceptable option for her. Since her clear treatment preferences conflicted with one of the RESET-ASDH treatment arms (early surgery), she was not included in the trial.

3.2.2. Illustrative case 3

83 year-old male on antiplatelet drugs who presented three days after a fall down the stairs with progressive confusion, gait disturbances and decreased verbal fluency. His admission GCS was 12 (E4M5V3) and neurological examination demonstrated an agitated patient with a no lateralizing symptoms. The CT scan showed a left-sided hyperdense ASDH with a thickness of 14 mm and an accompanying midline shift of 7 mm (Fig. 1C).

Given the patient's condition, participation in the RESET-ASDH trial was discussed with his legal representatives – in this case his children. At that moment, however, these were heavily occupied with a multitude of practical matters requiring their urgent attention, including the care for the patient's elderly partner (their mother). In addition, they were understandably emotional about their father's condition. Therefore, after apologizing for their 'limited space of mind' to properly consider the RESET-ASDH trial, they refused participation.

The above-mentioned difficulties in obtaining informed consent for trial participation were partly anticipated. For instance, dedicated research nurses were appointed to discuss trial participation with eligible patients and their families (during working hours) and to conduct follow-up visits at the patients' place of residence. Despite this, we experienced significant reluctance to participate from both elderly patients and their relatives.

3.3. The impact of COVID-19 on clinical trials

The RESET-ASDH trial was also severely affected on several fronts by the COVID-19 pandemic. To start, the ethical approval process experienced delays in both the Netherlands and Belgium, as medical-ethical committees prioritized expeditious evaluations of COVID-19 studies (Centrale Commissie et al., 2020). While the maximum period for medical-ethical evaluation of clinical trials in the Netherlands and Belgium is typically 8 weeks, the RESET-ASDH ethical approval process took over 6 months (Fig. 2). (Medisch-Ethische Toetsingscommissie Leiden Den Haag) Moreover, after medical-ethical clearance was obtained, the trial – together with all RCTs in participating hospitals at that time – was temporarily suspended by the hospital boards three times for varying durations ranging from several weeks to two months during the peaks of COVID-19. The rationale for repeatedly suspending the RESET-ASDH trial during these COVID-19 peaks was related to the associated scarcity of intensive care unit (ICU) resources which threatened to culminate into a 'code black' scenario during which extraordinarily strict triage protocols would become effective (Broughton et al., 2023). In this context, risk assessments performed by regulatory agencies and hospital boards led to prioritization of necessary patient care over the conduct of clinical trials, especially if trial participation involved utilization of already scarce resources (European Commission - Directorate-General for Health and Food Safety, 2022; Centrale Commissie et al., 2021a; Centrale Commissie et al., 2021b; Inspectie et al., 2020). Therefore, patient inclusion in the RESET-ASDH trial was not an

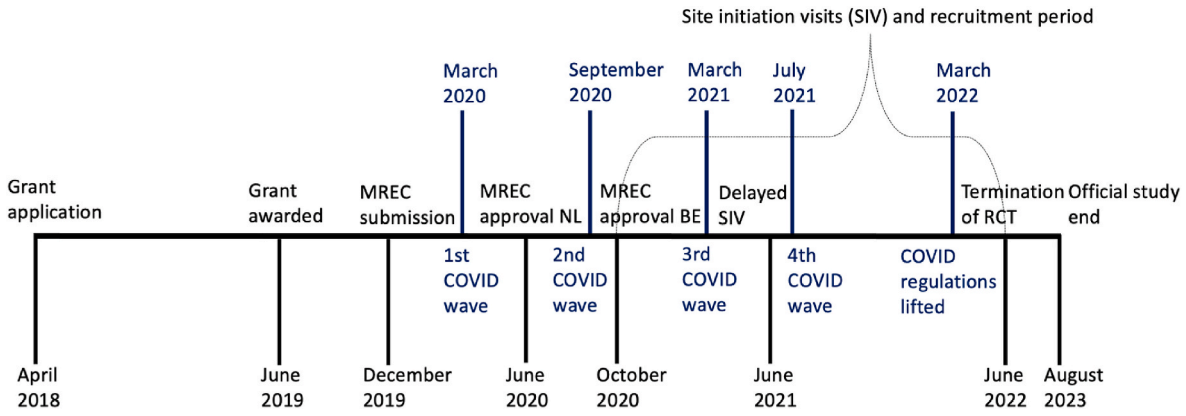

Fig. 2. COVID-19 effects on RESET-ASDH trial timeline. Abbreviations: MREC, Medical Research Ethical Committee; RCT, randomized controlled trial; SIV, site initiation visit.

option for potentially eligible patients in these periods during which the trial was put on hold.

Another effect of the COVID-19 crisis on the RESET-ASDH trial was the decline in TBI incidence observed in our participating centers during the peaks of the virus surge (Santing et al., 2020). Besides regulatory mobility restrictions, including lockdowns, obviously contributing to this decline (Lara-Reyna et al., 2020), reluctance of elderly people to seek medical care for mild symptoms due to COVID-19 concerns may also have played a role (Pinggera et al., 2021; Singhal et al., 2021). In our study, these effects of the pandemic may have been particularly noticeable as the population at risk for severe COVID-19 infection largely overlapped with the target population for the RESET-ASDH trial. Furthermore, ongoing travel restrictions hindered personnel engagement in participating centers. Although periodic online progress meetings were conducted, in-person discussions were found to be more effective, especially regarding complex trial methodology.

Finally, the high demands placed on our neurosurgical clinical and research personnel who were actively engaged in COVID-19 care while also upholding their neurosurgical responsibilities, reasonably reduced their focus on including patients in the RESET-ASDH trial. This was also evident from our registry database which indicated that 7% (3/42) of potentially eligible patients were not included because the resident on call was either too busy or did not think about the trial in the acute moment. In some cases, patients deteriorated neurologically in second instance after which they no longer met the inclusion criteria for trial participation.

4. Discussion

4.1. Clinical or scientific equipoise versus individual uncertainty

The premature discontinuation of the pragmatic, multicenter Dutch-Belgian RESET-ASDH trial may have been caused by multiple factors that are partly related to the study methodology, the specific acute nature of the disease, and the target population with an additional impact of COVID-19. The complex concept of clinical equipoise seemed to be broadly misinterpreted by neurosurgeons in participating centers as individual uncertainty, which has significantly hampered patient recruitment.

At the onset of a clinical trial, genuine uncertainty should exist within the medical community regarding the comparative merits of the treatments under investigation. A true null hypothesis serves as the ethical foundation for many trials. In the above-mentioned report in which Freedman introduced the term 'clinical equipoise', he also described that '*a trial must be designed in such a way as to make it reasonable to expect that, if it is successfully concluded, clinical equipoise will be disturbed*'. Interestingly, a predictable relationship has been reported in literature between the moral principle of clinical equipoise underlying clinical trials and the outcomes of those trials, which were indeed positive in just over 50% (Djulbegovic et al., 2013). In other words, assuming that individual trials based on true equipoise have a pre-trial likelihood of approximately 50% to identify the treatment under investigation as superior to the comparator, one would expect a large number of trials to also yield positive results in around 50%, confirming the theoretical concept of clinical equipoise as a solid trial foundation (Djulbegovic, 2007).

However, the misinterpretation of clinical equipoise as individual uncertainty may be an important reason for inadequate patient recruitment in neurosurgical trials. In contrast to clinical equipoise, the uncertainty principle implies that the individual clinician's uncertainty about the relative merits of the investigated treatments – rather than the collective uncertainty of the medical community – should drive patient enrolment in a trial (Weijer et al., 2000). As neurosurgeons are trained to make rapid decisions, often based on incomplete clinical information, it is understandable that incorporating a sense of individual uncertainty into their decision-making process may feel unnatural. Although this baseline attitude can be understood from an individual moral way of decision-making, it may be undesirable from a societal and future guideline perspective. Previous literature suggests that scientific evidence, clinical training and personal experience contribute in approximately equal measures to neurosurgical decisions (Bogaert et al., 2019). The classically quoted surgical attitude towards clinical decision-making '*sometimes wrong, but never in doubt*' is at odds with the tolerance of uncertainty (McCulloch et al., 2005). In line with this, a previous neurosurgical trial on traumatic intracerebral hematomas (STITCH) also explicitly stating 'clinical equipoise' as an inclusion criterium was prematurely halted by the funding agencies due to lacking patient recruitment in the United Kingdom (Mendelow et al., 2015).

In the RESET-ASDH trial, we aimed to address this issue by training all involved clinicians in the concept of clinical equipoise before start of the trial, as also described in the protocol: "*All neurosurgical-, trauma- and neuro-ICU staff participating in the RESET-ASDH study and involved in the acute care of neurotrauma patients will be trained by the study team on location prior to trial start by means of case-based tutoring sessions*" (Singh et al., 2022).

Although these productive training sessions took place, we feel we have not been able to sufficiently familiarize the Dutch-Belgian neurosurgical communities with the concept of clinical equipoise.

In our view, a prerequisite for successfully conducting a similar trial in the future, provided that the ethical prerequisites for conducting an RCT are met, is ensuring that all participating neurosurgeons are willing to administer their less favored treatment if the evidence of superiority of one treatment over the other is truly lacking. This cognitive process can be stimulated through the knowledge that their less favored

treatment is actually favored by a likeminded, equally competent and similarly trained colleague, and that they together represent the collective uncertainty within the community. This clinical equipoise holds greater scientific value than individual opinions. In this regard, we advise to omit clinical equipoise as a separate inclusion criterium, as its existence is already evident from previous literature and listing it as a requirement for inclusion may cause confusion among neurosurgeons. Whether phrasing the concept of clinical equipoise in a different manner will indeed cause neurosurgeons to transcend their individual uncertainties and recruit more eligible patients into acute neurosurgical trials, remains a matter of speculation.

4.2. Treatment preferences and overcharged informal caregivers

Another factor that has likely impeded patient recruitment in the RESET-ASDH trial was the reduced willingness of elderly patients and their relatives to consider trial participation.

Although many health-care services are predominantly utilized by elderly patients, they have traditionally been excluded from clinical trials (Schwartz, 2023). While an upper age limit may be reasonable for some research questions or study designs, it is unjustified in many other cases and may reduce generalizability of a study's findings (Bayer and Tadd, 2000). In the scarce trials specifically targeted at the elderly population, patient enrollment has been notoriously difficult compared to trials in the adult population (Hutchins et al., 1999). Several reasons for this have been proposed in previous literature. Firstly, elderly patients are considered more likely to feel overburdened by their illness and the accompanying stress, making them less inclined to participate in clinical trials (Hempenius et al., 2013). Moreover, necessary travels to the hospital for additional study-related visits have been reported to discourage elderly patients from participating, partly because of not wanting to burden their relatives by asking them to accompany them (Forsat et al., 2020). Indeed, relatives are recognized to have a major influence on the elderly patient's decision whether or not to participate in a clinical trial (Hempenius et al., 2013).

Treatment preferences of elderly patients have also been mentioned as a reason for not consenting to participate in surgical trials (Keding et al., 2019). In fact, many (elderly) patients may not enroll in surgical trials because of the perceived invasiveness and the irreversible nature of surgery, especially when the comparator is a non-surgical treatment (Sibai et al., 2012). The importance of 'shared decision-making' with elderly patients and their relatives to ensure their wishes and preferences are respected while also providing them with adequate information about -trial related-treatments has been extensively emphasized in surgical literature (Clapp et al., 2022; Millis and Suwanabol, 2022; Lipstein et al., 2021).

Anticipating on patients' preferences regarding the treatments under investigation, for example by conducting a questionnaire study before trial start, could be useful to adequately estimate the appropriate recruitment period for future trials. Also, paying attention to the additional (practical) concerns that typically fall upon the shoulders of often already overcharged networks of informal caregivers – frequently children – may increase their inclination to consider trial participation in the acute moment after trauma.

4.3. RESET-ASDH and COVID-19 – overlapping patient populations

Lastly, the challenges inherent to acute neurosurgical trials in the elderly were likely exacerbated by the COVID-19 pandemic, which introduced additional ethical, organization and logistical hurdles, further negatively impacting patient recruitment. The COVID-19 pandemic has had a major disruptive effect on the conduct of clinical trials around the globe and across various medical disciplines (Margas et al., 2022; Traxler et al., 2022; McDonald et al., 2023). Public safety measures including lockdowns and mandatory closure of research facilities were amongst the most important reasons for trial disturbance (Ledford, 2021). Furthermore, regulatory agencies around the world, including the Netherlands and Belgium, have temporarily or indefinitely suspended clinical studies during the various epidemiological peaks of the virus (Centrale Commissie et al., 2020; Ledford, 2020).

Trials that were permitted to remain open were also adversely impacted by the pandemic in various ways. For example, individuals at high risk for adverse outcomes upon contracting COVID-19, such as elderly or immunocompromised patients, were reportedly more reluctant to seek healthcare, which may have reduced the pool of eligible patients for studies recruiting in clinical settings (Chlan et al., 2023). The internationally reported decrease in patients presenting to emergency departments with stroke and acute coronary syndrome during the pandemic period is a striking example (Dula et al., 2020; Nogueira et al., 2021; Huynh, 2020). For TBI specifically, a steep decline in incidence has been reported around the world during the peaks of the COVID-19 crisis (Petr et al., 2022; Rajalu et al., 2022). Furthermore, research staff availability to enroll patients in clinical studies was considerably reduced since many non-patientcare – including research – departments were designated to assist in front-line COVID-19 care (Rasmussen et al., 2020).

For neurosurgical patients in general, changes in triaging practices have been reported including a 'recalibration of the elective-to-emergent spectrum' with the aim to conserve vital resources for the expected 'waves' of COVID-19 patients (Jean et al., 2020). Whether the pandemic has influenced neurosurgical decision-making for elderly patients with an ASDH cannot be answered based on the current data. Prospective clinical data regarding the decision-making process and subsequent comparisons with (pre-)COVID-19 cohorts are required to this end. Hence, the RESET-ASDH study will be continued as a multicenter, observational cohort comparing early surgery versus initial conservative treatment in elderly ASDH patients with a specific focus on the decision-making process.

It remains to be seen whether an RCT design for this particular research question will be feasible at some point. However, future neurosurgical studies with comparable characteristics may draw insights from our experiences with the RESET-ASDH trial to avoid similar obstacles and reduce the risk of premature trial termination.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2024.102903.

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