Universiteit Leiden
The Netherlands

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Maas, A.I.R.; Ercole, A.; Keyser, V. de; Menon, D.K.; Steyerberg, E.W.

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BIG DATA IN NEUROCRITICAL CARE

Opportunities and Challenges in High-Quality Contemporary Data Collection in Traumatic Brain Injury: The CENTER-TBI Experience

Andrew I. R. Maas[1*], Ari Ercole[2], Veronique De Keyser[1], David K. Menon[2] and Ewout W. Steyerberg[3]

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Abstract

Strong evidence in support of guidelines for traumatic brain injury (TBI) is lacking. Large-scale observational studies may offer a complementary source of evidence to clinical trials to improve the care and outcome for patients with TBI. They are, however, challenging to execute. In this review, we aim to characterize opportunities and challenges of large-scale collaborative research in neurotrauma. We use the setup and conduct of Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) as an illustrative example. We highlight the importance of building a team and of developing a network for younger researchers, thus investing toward the future. We involved investigators early in the design phase and recognized their efforts in a group contributor list on all publications. We found, however, that translation to academic credits often failed, and we suggest that the current system of academic credits be critically appraised. We found substantial variability in consent procedures for participant enrollment within and between countries. Overall, obtaining approvals typically required 4–6 months, with outliers up to 18 months. Research costs varied considerably across Europe and should be defined by center. We substantially underestimated costs of data curation, and we suggest that 15–20% of the budget be reserved for this purpose. Streamlining analyses and accommodating external research proposals demanded a structured approach. We implemented a systematic inventory of study plans and found this effective in maintaining oversight and in promoting collaboration between research groups. Ensuring good use of the data was a prominent feature in the review of external proposals. Multiple interactions occurred with industrial partners, mainly related to biomarkers and neuroimaging, and resulted in various formal collaborations, substantially extending the scope of CENTER-TBI. Overall, CENTER-TBI has been productive, with over 250 international peer-reviewed publications. We have ensured mechanisms to maintain the infrastructure and continued analyses. We see potential for individual patient data meta-analyses in connection to other large-scale projects. Our collaboration with Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) has taught us that although standardized data collection and coding according to common data elements can facilitate such meta-analyses, further data harmonization is required for meaningful results. Both CENTER-TBI and TRACK-TBI have demonstrated the complexity of the conduct of large-scale collaborative studies that produce high-quality science and new insights.

Keywords: Traumatic brain injury, Big data, Data curation, Large-scale observational study, FAIR principles, Review

*Correspondence: andrew.maas@uza.be
[1] Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Drie Eikenstraat 655, 2650 Edegem, Belgium
Full list of author information is available at the end of the article

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Introduction

Traumatic brain injury (TBI) is a global problem with substantial individual, family, societal, and health economic impact. *The Lancet Neurology* Commission on TBI [1] surveyed the landscape of TBI research in 2017 and identified limitations posed by small, fragmented studies, including difficulties in harmonizing and combining data collected in such studies to deliver meaningful and robust conclusions. The availability of an agreed definition and accepted common data elements for TBI research (https://www.commondataelements.ninds.nih.gov/) provided the foundation for harmonized data collection across countries. It led to the funding of large prospective cohort studies that targeted improved disease characterization, comparative effectiveness research, and better prognostic precision. The Collaborative European Neurotrauma Effectiveness Research in TBI (CENTER-TBI) (www.center-tbi.eu) study was one of these cohort studies.

CENTER-TBI was primarily supported by the 7th Framework Program (FP7) funding platform of the European Union (Grant 602150). It was designed as an integrative project to optimize existing knowledge through extensive systematic reviews and merge this with new evidence [2, 3]. This new evidence was generated from a prospective observational core study and a registry collecting data on patients with TBI from 18 countries in Europe and Israel. As the study progressed, we included substantial contributions from Australia, China, and India, which allowed us to examine greater variations in management and exploit these in comparative effectiveness research. The core study collected detailed data from over 4500 patients across all severities of TBI in Europe and from an additional 1200 patients in Australia and India. We established repositories for blood/serum samples, neuroimages, and genomics, thus providing for legacy research after the formal end of CENTER-TBI. The registry collected in-hospital data on 22,782 patients, aiming to assess representativeness of the core study and to analyze effects of structural parameters in a larger cohort. Linked efforts in China and India increased the total number to over 40,000 individual patients. The main aims of CENTER-TBI were to develop precision medicine approaches and to identify best practices by comparative effectiveness research. In this review, we aim to characterize opportunities and challenges of large-scale collaborative research in neurotrauma. We use the setup and conduct of CENTER-TBI as an illustrative example.

Conception and Funding

In October 2009, four leading TBI researchers visited with the European Commission to lobby for European funding for research in TBI. Specifically, we made a strong plea for transatlantic collaboration and support for a combined European–US clinical study on TBI. This led to the formation of the International Initiative for TBI Research (InTBIR) (https://intbir.incf.org/) [4]. InTBIR was initially designed as a collaboration of funding agencies and has recently transitioned to an investigator-driven initiative. The idea for one transatlantic project, however, did not fly. We learned that although both the European Commission and National Institutes of Health have mechanisms to include foreign institutes in grants, no existing mechanisms allowed integrated funding for a project across the two bodies. As a consequence, separate applications were submitted in Europe and in the United States. This resulted in funding of CENTER-TBI in Europe and of Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) (https://tracktbi.ucsf.edu) in the United States. Both projects were aligned and largely harmonized. However, because uncertainty existed on the chances of success at the time of submission, neither project included support for analyses across studies, which subsequently proved to be a key omission.

Building a Team

CENTER-TBI was designed as a collaborative team effort, bringing together over 100 leading experts from 47 scientific institutes worldwide. However, as in sports, a group of highly qualified and talented individuals will not deliver top performance in the absence of team spirit and team effort. We spent substantial efforts in promoting team spirit and developing a great network, especially also for young researchers, across all domains involved in the field of TBI. All scientific participants were actively involved in the design of the project. Multiple smaller preparatory meetings, and a larger general meeting of all participants at the start of the project, were held. The environment of this meeting (Antwerp Zoo) and social activities (tasting of Belgian beer) were instrumental to consolidating the team spirit. We actively involved investigators and research personnel at sites that would be collecting data to provide them with a feeling of "ownership." This was accomplished in two ways. First, investigators were given the opportunity to provide input in the case report form (CRF) development, in which they could also suggest additional data elements to better cover their research interests. This approach might have been successful in promoting involvement, but the downside was perhaps an overly extensive CRF. An iterative process was developed, during which the members of the management committee finalized the CRF. The electronic case report form (e-CRF) was developed on the template used in the pilot TRACK-TBI study, aiming for harmonization with TRACK-TBI, and was further pilot tested at the coordinating center. Second, we felt that investigators

should be able to receive credit for their efforts. We hereto implemented a strategy for including all investigators as group contributors on every substantive publication that made use of CENTER-TBI data. In practice, this proved more challenging than anticipated (see "Credits for investigators" section).

Cost Model for Observational Data Collection

Establishing an appropriate cost model to compensate sites for their efforts in collecting data for the core study was complex, especially within the limits of the available budget. Two main options existed: (1) per-case payment and (2) support for dedicated research personnel. We opted for a system of per-case payments because we felt this would provide an incentive for efficient recruitment and would fit better with the complex rules of the European Commission for reimbursement of costs under an FP7 grant. These rules would not permit payment of dedicated research personnel at investigator sites that were not scientific participants in the project (approximately 70% of sites). The FP7 rules further stipulate that only actual costs can be reimbursed, that reimbursements are limited to 75% of the actual costs, and that no profit can be made. Within a project of this size, we could not incur any financial risk related to an open-ended budget, and a cap for maximum reimbursement of costs was imposed. We were aware that wages (and costs) differed substantially within Europe. We found that the reported monthly salary for a senior resident ranged from a low of between 500 and 800 € in Eastern Europe to a high of 7900 € in Norway. The median salary (3479 €) and differences between countries were consistent with that reported for a researcher in the European Union in 2007 (3562 €; https://cdn1.euraxess.org/sites/default/files/policy_library/final_report.pdf). We used these rankings to differentiate case payments into two groups, in which average calculated costs were reduced for countries ranked in the lower interquartile range (IQR) and increased for those in the middle and upper IQRs. We considered this a fair and pragmatic approach. Clearly, however, this approach led to some leveling of differences in costs. As a consequence, various potential sites in high-income settings decided to withdraw because they considered the payments offered too low to cover actual costs. Of the initially 90+interested sites, the study could be initiated in only 65 centers. Further, the principle that case payments could never exceed actual costs remained, and we were required to provide proof of this for every site. In all cases, actual costs exceeded the case payments, in some sites from high-income countries even by a factor of two or three. The required procedures caused an additional administrative burden to sites. Some of these complexities may be specific to the European setting, but they illustrate that careful attention to the most appropriate cost model is required for any large-scale collaborative clinical study on TBI, balancing considerations of study representativeness, efficiency, fairness, and requirements of funding bodies.

Heterogeneity in Institutional Review Board and Consent Procedures

A basic prerequisite for conducting a clinical study is approval by the country/site-specific institutional review boards (IRBs) and implementing procedures for obtaining consent according to national and local regulations. The European Union aims to optimize patient protection and efficacy of health-care-related research by harmonizing procedures across member states. CENTER-TBI, with its broad representation of many European countries, offered a unique opportunity to explore the extent of harmonization. The CENTER-TBI protocol was evaluated in 18 European countries by IRBs of 66 neurotrauma centers [5]. Fourteen IRBs considered CENTER-TBI an observational study. In contrast, two considered CENTER-TBI an interventional study because the protocol described blood draws. A further two countries considered CENTER-TBI as a combined observational and interventional study. Primary IRB review was conducted centrally in 11 of 18 (61%) countries, with a median time to basic approval of 98 (IQR 94–114) days, and locally in 7 of 18 (39%) of countries, with 50 (IQR 29–102) days to basic approval. Additional local IRB approval was required in 6 of 11 (55%) countries with central procedures and increased the time to final approval by a median of 104 (marginal review) to 189 days (extensive additional review). Although additional local IRB approval is generally considered a feasibility check, in practice a full new review was often conducted. The total median duration across centers from submission of the CENTER-TBI protocol until definitive approval was 114 (IQR 75–224) days, with a range from 1 to 535 days. The driving factor for delays appears to result from extensive local IRB reviews following initial central review. Better streamlining of local procedures to accord with central review processes would have the potential to substantially accelerate IRB approvals. Currently, the substantial variation in IRB procedures across European Union member states poses challenges to research collaborations for what is generally considered an observational study. As a general indication, sponsors of clinical studies on TBI should plan for 4–6 months between IRB submissions and approval, realizing this may take up to 18 months for some centers.

In the European Union, several approaches are used for obtaining consent in situations when patients cannot

provide consent themselves because of acute mental incapacity or because of the emergency situation. These include the following:

- Proxy consent (surrogate consent by close relatives or legal representatives)
- Deferred patient consent
- Deferred proxy consent
- Waiver of consent with consent by an independent physician

In CENTER-TBI, proxy consent was the most frequently used approach for patients admitted to the intensive care unit (1377 of 2137; 64%) [6]. Although deferred consent was considered valid in over 80% of centers, it was only used actively in 26% and employed in practice in 16% (334 of 2137) of patients. Waiver of consent was only reported to have been used in <1% of patients. Although proxy consent is generally accepted and broadly used, proxies are not always available soon after injury, and it should be recognized that they may be too overwhelmed by the stressful event to provide valid proxy consent [7]. We suggest that deferred consent be considered more frequently.

Patient informed consent was used in 95% (805 of 844) of patients recruited to the ER stratum (patients discharged out of hospital from the Emergency room) and in 83% (1266 of 1517) of those recruited to the admission stratum. On the basis of our experience, we suggest that formal testing to confirm that the patient is out of posttraumatic amnesia be considered prior to obtaining consent.

Data Quality and Curation

High-quality data are critical to any clinical study. For large observational clinical studies, a specific challenge is the amount of multimodal data needed for addressing numerous research questions, either alone or in combination with other data sets. We underestimated the effort for data curation. The final clinical data set for CENTER-TBI was rather complex, with over 2400 unique distinct, discrete, and longitudinal variables, with the latter involving both regularly and irregularly sampled time points and a wide variety of data types.

Measures were implemented to ensure high quality of the CENTER-TBI data. First, all efforts were made to standardize data collection as best as possible. We, however, did not wish to interfere with local procedures and therefore chose to document procedures used. For example, investigators were requested to document the zero reference level for monitoring of intracranial pressure. All time-dependent data were time stamped. Time intervals for recording vital parameters, including intracranial pressure data for patients undergoing monitoring, were prespecified. In a subgroup of patients, high-resolution intensive care unit data were continuously recorded (waveform) and captured via a Moberg device (Moberg Research Technologies; www.mobergresearch.com) or the ICM+platform (www.neurosurg.cam.ac.uk/pages/ICM/order.php) provided to investigators. A dedicated event annotation tool was developed and implemented. Second, automated data checks were built into the e-CRF system to alert investigators to impossible or improbable values and to detect inconsistent data entries, providing immediate feedback to investigators. Third, source data verification of major characteristics was performed by ICON (Paris, France). Source data verification was performed in 100% of cases for informed consent and in 28% of patients for major characteristics on a total of 13,448 data points. Fourth, a team of three dedicated personnel was employed full-time to check completeness and accuracy of entered data. Finally, a data curation task force (DCTF) was formed to perform data curation at a structural level.

Incoming CRF data was initially available as a relatively unnormalized relational master database structure. The DCTF necessarily consisted of a multidisciplinary team with both clinical statistical and database programming experience. The DCTF examined data for missingness and across-center plausibility and for multivariate consistency by cross-checking variables with other related concepts in the database. An agile "sprint" project management strategy was employed, and remote working was facilitated using a searchable team-messaging tool so that code generated in the curation process could be archived and referenced. To ensure reproducible analysis, derived variables were introduced in which there might be ambiguity in how investigators might transform the data. For example, once optimal CENTER-TBI-approved imputation strategies had been developed and validated for ordinal outcome [8] and baseline predictors [9], derived variables following these strategies were added to the data set to facilitate and encourage consistent use.

Data quality problems were addressed by the DCTF in three broad ways. First, for a small number of systematic data entry inconsistencies, it was possible to transform data or unify concepts across time points. Documented pipelines were created to automatically populate a second curated database. Secondly, when systematic issues were identified, there was a robust process involving a dedicated team to go back to sites to understand and identify problems and implement solutions. These included process validation at the source and ongoing training/needs analysis. When common but unsystematic errors were identified, e-CRF rules were updated and the subjects reflagged as being incomplete so that sites could go

back and make corrections. Finally, a comprehensive data dictionary with frequency tables was created, including descriptions of any known issues with individual data elements to help researchers understand the complex data (https://www.center-tbi.eu/data/dictionary). This data dictionary also serves as meta-data in the context of findable, accessible, interoperable, and reproducible (FAIR) data principles [10].

To ensure reproducible analysis, data sets were made available as referenceable "release" versions. A "data mart" was created to obviate the need to query the complex curated relational database, which would require database programming skills that investigators were unlikely to have. An initial attempt to use TranSmart [11] failed because the complexity, structure, and volume of the CENTER-TBI data exceeded the capabilities of this platform at the time. A novel data mart (International Neuroinformatics Coordinating Facility (INCF) Neurobot https://www.incf.org/resources/tools/neurobot) was developed in-house, allowing investigators to access data in a reproducible and easy-to-use way through a Web interface. A second data mart based on the Opal platform [12], which additionally allowed programmatic access to the data, was later developed.

Prior to CENTER-TBI, there was little published concerning techniques for data curation at large scale. Consequently, not all curation measures were foreseen at the start of the project: the above systematic approach was developed over the course of the study and required a substantial academic contribution. These experiences triggered the development of consensus-based guidelines for data acquisition in collaboration with InTBIR partners. Data Acquisition Quality and Curation for Observational Research Designs (DAQCORD) was henceforth proposed as a general framework for data curation from study design to implementation [13].

Our data curation efforts have resulted in high-quality and well-documented data. The final data set consists of 2829 data elements in eight versions of data sets, with overall file storage exceeding 2.6 TB. All clinical data are coded according to the standards of the common data elements (https://www.commondataelements.ninds). Our hope was that this would also facilitate meta-analyses across studies involved in InTBIR. We learned, however, that harmonization of data in preparation of meta-analyses goes beyond coding issues. Collaboration between CENTER-TBI and TRACK-TBI made us recognize that issues of interpretation also need to be addressed. For example, we learned that the approach to outcome assignment according to the Glasgow Outcome Scale - extended (GOSE) was performed differently in the United States compared with Europe. In the United States, only TBI-related disabilities are considered, whereas in Europe the focus is more on all-cause disability. Prior to our work, this discordance had not been recognized. The choice for all-cause vs TBI-related scoring of disability is context dependent. Nevertheless, it should be recognized that scoring of all-cause disability according to a structured format is fairly objective, whereas assessment of TBI-related disability entails an element of subjectivity. In discussion with the TRACK-TBI team, we suggest primarily recording all-cause disability as being the most objective measure and additionally documenting TBI-related disability if considered appropriate. Recommendations for scoring the GOSE are provided in a recent joint CENTER-TBI/TRACK-TBI publication [14]. "Deep harmonization" is required to prepare for robust and meaningful meta-analyses. Neither the meta-analyses nor the required deep harmonization was included in the funding application for CENTER-TBI, and we are currently seeking additional funding to support these. We recognize that e-CRF systems, data management platforms, and artificial intelligence applications have greatly evolved since the study start (2013) and may allow nowadays for more efficient monitoring and reduction of systematic errors and data entry inconsistencies. Nevertheless, a major lesson learned is that any clinical study should allocate a substantial sum toward data curation and deep harmonization. We estimate that such costs may amount to 15–20% of the study budget.

Streamlining Analyses and Ensuring Responsible Use of Data

There has been a growing recognition that data obtained through publicly funded research should be widely available for public use, as reflected in the FAIR data principles [10]. The CENTER-TBI data set and repositories provide an important vehicle for ongoing collaboration and represent a valuable legacy resource. We wished to ensure good use of the data, maintain an overview of ongoing work, and prevent redundancy of efforts. To this purpose, we implemented a study and publication proposal platform on the CENTER-TBI website (https://www.center-tbi.eu/data). Study proposals submitted by internal and external researchers are reviewed by the management committee for scientific rigor and feasibility (Fig. 1). Reviewers of publication proposals conduct a final check to ensure that the manuscript includes an appropriate ethics statement, acknowledges all support received, and provides a list of group contributors if using CENTER-TBI data. To date, over 400 study proposals have been submitted, of which approximately 40 originated from external research groups. All accepted proposals are listed on the website. The mechanism proved highly effective. Although research plans of internal researchers were largely specified in the work packages

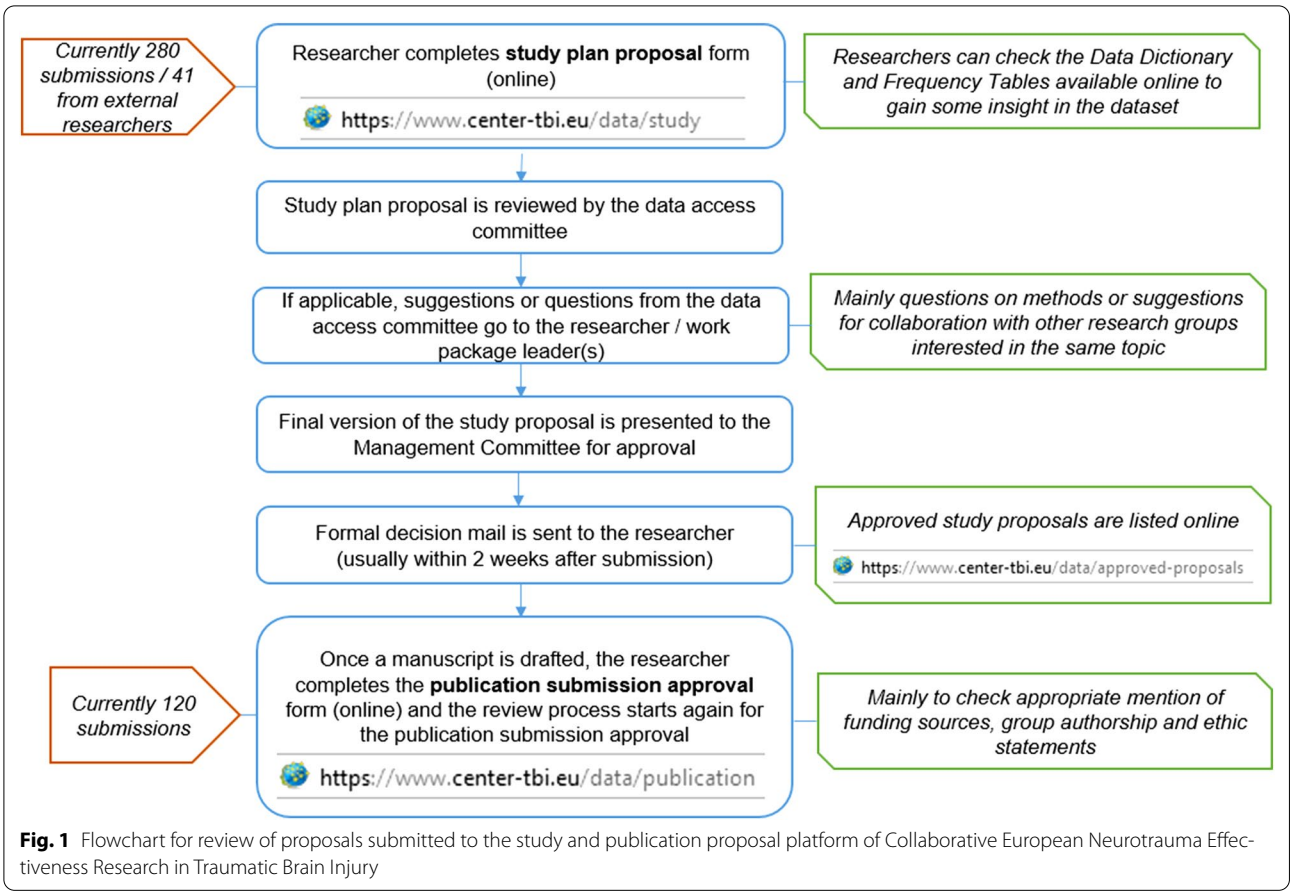

Fig. 1 Flowchart for review of proposals submitted to the study and publication proposal platform of Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury

of CENTER-TBI, these plans did not provide sufficient detail on specific tasks within the work package. As the study progressed, other related study questions arose, often addressing interests spanning different work packages. We found that the platform served an additional important purpose in promoting collaborations between research groups. Ensuring good use of the data was a prominent feature in the review of external proposals. As data controller in the sense of European legislation, the coordinator is obliged to ensure such good use, both in terms of data security and privacy protection and in terms of valid analysis. The latter is particularly relevant to a complex and broad study such as CENTER-TBI, in which some risk of misinterpretation of data is present. For example, uninformed overall analysis of admission rates for patients with mild TBI across centers would yield an erroneous range of 0–100% because some centers enrolled exclusively in the ER stratum (with patients, by definition, being discharged out of hospital from the ER) and others in the admission stratum (with all patients being admitted). Lack of knowledge of study design can therefore lead to misinterpretation. Although over 75% of all proposals were accepted, approximately half of the submitted external proposals were rejected. Of the accepted external proposals, some proposed confirmatory analyses and others addressed new study questions not previously described within the CENTER-TBI framework. The main reasons for rejecting proposals were (1) study question could not be answered from the CENTER-TBI data, (2) insufficient guarantee of data security, and (3) unclear study question.

In some cases, it appeared that the sole intent was to gain nonspecified access to the data rather than address a clear hypothesis. These concerns were articulated in an editorial in the *New England Journal of Medicine* previously [15]. The editorial made a useful distinction between parasitic and symbiotic research collaboration for reuse of data. We are strong advocates of the FAIR principles for data sharing but suggest that, in practical implementation, some mechanism be built in to ensure good and responsible use of the data. The processes needed for FAIR data sharing are not cost free; the Alzheimer's Disease Neuroimaging Initiative (ADNI) investigators were reported to have estimated that ~ 15% of project costs were consumed by data sharing [16]. This is difficult enough when the project is running but becomes

impossible to sustain without additional funding once the study comes to an end. Funders should recognize these costs and find ways to support such activity. For CENTER-TBI, we have ensured additional support that will allow us to continue the study and publication platform for the next three years. This system will serve to ensure good use of data and offer support and advice to external researchers.

Collaborations with External Parties: Opportunities and Pitfalls

Multiple interactions occurred with both academic and industrial partners as we explored possible collaboration. The main interest was on the biomarker and neuroimaging repositories. In most cases, these interactions were mutually perceived as highly stimulating and productive. They resulted in six formal collaborations with the following main themes:

- Validation of biomarker platforms
- Analyses of diagnostic and prognostic value of additional biomarkers
- Metabolomic and lipidomic analyses
- Exploration of lesion progression on computed tomography scans as an early mechanistic end point

Some of these collaborations also provided some limited additional funding to CENTER-TBI as compensation for efforts. Despite this overall positive experience, other interactions with potential commercial partners ended without success. This was often due to a mismatch of expectations and aims, which arose from a lack of detailed communication at the start. We suggest that clear ground rules for establishing collaboration be essential so that resources and time are not wasted.

Overall, the multiple interactions and formalized collaborations illustrate the great value of high-quality clinical, biomarker, and neuroimaging data obtained in an observational study. Such collaborations can serve to further advance science outside the direct scope of the project, thus adding to the efficient use of public funding.

Credits for Investigators

Clinical teams that gather data for large multicenter studies, such as CENTER-TBI, are essential facilitators for successful research and availability of high-quality data. A contribution to data collection alone is traditionally not sufficient for authorship; authorship requires meaningful substantive contributions to the study and to the manuscript [17]. Moreover, a pragmatic argument is that it is impractical for hundreds of authors to take responsibility for the overall study. On the other hand, treating such data collection as a fee-for-service paid for by research funding also neglects the reality that, in academic studies such as CENTER-TBI, the funds provided do not compensate the effort adequately (see "Cost model for observational data collection" section). We felt that all participants and investigator sites should receive credits for the work performed in and for CENTER-TBI and included a list of group contributors on all publications based on data collected during the CENTER-TBI studies.

Although large group contributor lists are common in many fields of science, the inclusion of our lists in the medical domain proved highly challenging because these lists appeared to be irregularly picked up by PubMed. It first appeared that this varied by journal and could be related to the positioning of the group contributor list in the article (e.g., at the end of the article, in the acknowledgment section, or in the supplementary material). It later turned out that PubMed changed their policy for extraction of authorship lists in 2016, when they moved the work involved in producing group contributor lists, which had been undertaken by PubMed, to journal publishers. Some journals have the luxury of in-house production teams, but many do not. As a consequence, visibility of group contributor lists in PubMed is inconsistent. To complicate matters further, it turned out that academic bodies in some European countries (e.g., Norway) do not recognize group contribution as meeting standards for obtaining academic credits. We had recognized the conceptual difference between "group authors" and "group contributors" (http://www.icmje.org/) but had not realized the different interpretation in terms of academic credits. Group contributors do get listed in PubMed, but the primary authorship is not because as the listing is considered as a nonauthor contribution. On analyzing these experiences, we conclude that besides the practicalities for presentation in PubMed and other bibliographies, the main challenge lies in the appropriate translation of group contribution into academic credits. Fully reimbursed commercial contract research has different drivers and economics and is likely to require different ground rules.

Managing a Large-Scale Collaborative Project

Managing a large-scale project such as CENTER-TBI is a complex undertaking requiring assurance of continuity and ongoing team-building through the organization of multiple meetings and trainings. Formally, Antwerp University Hospital was the coordinator of the project, but we established dual leadership provided by Andrew Maas (Antwerp University Hospital) and David Menon (University of Cambridge). The coordinators were supported in their work by a strong multidisciplinary management committee that ratified all major decisions. Despite the strong team spirit of CENTER-TBI, conflicts

can occur in any large-scale collaboration, and the few that occurred were mediated and resolved by the management committee. Ego management remained a main focus throughout the project. We noted, for example, that some proposals submitted to the study and publication platform appeared to primarily claim ownership of the topic. In these instances, we turned the challenge to an asset and stimulated collaboration. Strict follow-up on the delivery of results from submitted study proposals was implemented. Toward the final phase of the project, we recognized some potential tensions between the interests of individual researchers, interests of participating institutions, and the integrated scientific interests of the study. The cessation of funding meant that some individual investigators (and their institutions) were keen to realize academic benefits within the financial resources available at that time. These resulted in relatively restricted publications, which did not always meet our aspiration to generate more substantive integrated outputs with greater depth and impact.

Indeed, it proved challenging to synthesize all separate parts of the output of a large-scale project like CENTER-TBI into one coherent bigger picture. This is impossible to do in conventional publications but is often captured in the final report made to funders. Our final report distinguished between recommendations and conclusions targeted at citizens and patients, policy makers, and health care professionals and researchers and is now publicly accessible on the Cordis website of the European Union (https://cordis.europa.eu/project/id/602150/reporting).

Marketing of Results to Stakeholders and Policy Makers

CENTER-TBI has been highly productive; as of November 2021 there have been over 250 publications in the international peer-reviewed scientific literature and over ten PhD theses. Although publications in the scientific literature serve to improve the knowledge of and care provided by health care professionals, perhaps even greater advances can be obtained by implementing improvements at the policy level. CENTER-TBI developed various initiatives targeting policy makers. The publication of our commissioned issue on TBI in *The Lancet Neurology* (http://www.thelancet.com/commissions/traumatic-brain-injury) had a direct focus to inform policy makers on the huge burden posed by TBI to society and is now viewed as a main reference resource on TBI, having been cited over 900 times. The commission was presented at the European Parliament on November 7, 2017, an occasion attended by a patient and his mother. Substantial advances in creating awareness for TBI at the policy level in the United Kingdom have been realized through interactions with the All-Party Parliamentary Group on Acquired Brain Injury. This input drew heavily on the work undertaken in CENTER-TBI and in particular *The*

Table 1 Lessons learned and recommendations for future studies

Lessons learned and recommendations for future studies
Large-scale collaborative clinical studies have a huge potential but are complex to execute
Funding agencies are open to discussing ideas for large-scale collaborative projects, and these may translate into a call (European Union) or request for applications (National Institutes of Health). Researchers need to be more aware of their potential influence in agenda setting
Funding mechanisms to support global collaborative projects are underdeveloped
Huge differences in salaries of academic and research personnel exist among European countries, making a standard cost model for compensating time and effort spent on patient recruitment difficult to implement
Careful attention to the most appropriate cost model for any large-scale clinical study is essential; this may vary between studies but should attempt to optimize costs models in individual participating centers
Obtaining IRB approvals for an observational study typically requires between 4 and 6 months but may take up to 18 months
Approximately 15–20% of the budget for data collection should be dedicated to data curation and quality control
Standardized data collection and coding according to common data elements can facilitate meta-analyses across studies, but a further deep harmonization is required to permit robust and meaningful meta-analysis
Complementary to general research plans from various stakeholders, a structured inventory of detailed study plans is effective in maintaining an overview of ongoing work and in promoting collaboration between research groups
Collaborations with commercial parties will be most effective if both partners understand their respective aims and drivers and communicate these at an early stage
Mechanisms for ensuring good use of data should be considered equally relevant to data sharing as adherence to the FAIR principles
FAIR use of data needs to be fair to the study that is sharing data, both in terms of financial resources and in terms of return in initial investment of intellectual capital and data collection
The current system of academic credits in the field of medicine should be critically appraised and revised to ensure that investigators who set up local frameworks for data collection and invest substantial time and effort collecting data receive appropriate recognition
Researchers in TBI should actively seek to involve patients and patient organizations in their research

FAIR findable, accessible, interoperable, and reproducible, *IRB* institutional review board, *TBI* traumatic brain injury

Lancet Neurology Commission on TBI, which was provided to all UK members of Parliament in advance of discussions. A full report, published online on October 18, 2019, concluded that the UK government should bring together a task force to address the issues and recommendations as a matter of urgency (https://cdn.ymaws.com/ukabif.org.uk/resource/resmgr/campaigns/appg-abi_report_time-for-cha.pdf). CENTER-TBI attracted media interest across the globe, including Australia, China, Belgium, Germany, Hungary, Italy, the Netherlands, and the United Kingdom. EuroNews broadcasted a special feature on CENTER-TBI in November 2019 (https://www.euronews.com/2019/02/25/i-was-not-who-i-was-researcher-into-new-care-for-traumatic-brain-injury-victims). Social media accounts were maintained and demonstrated broad interest across the world. We developed and implemented an interactive public information platform explaining the impact and future developments of TBI research in lay language within the public section of the CENTER-TBI website (https://www.center-tbi.eu/). This platform aimed to make the public active partners in research, clinical care, and policy development and provided links to patient organizations. The platform generated multiple requests from patients for advice, including many from the United States, indicating a clear need. We recognize that patient organizations and individual patients can have much greater influence on policy makers than health care professionals and researchers. Unfortunately, patients with TBI are not always their own best advocates and seldom seek a public profile. In that respect, much can be learned from the field of spinal cord injury, in which patient advocacy is more prominent and highly successful. Our experience is that if appropriately prompted, patients with TBI are keen to aid in bringing their needs to the public attention. We hence encourage researchers to involve patients and patient organizations in their research.

Recommendations and Lessons Learned

The journey of CENTER-TBI from conception to completion combined science with politics, marketing, and the business of a small enterprise. From this experience, we distill lessons learned and present recommendations for future studies (Table 1).

Author details
[1] Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Drie Eikenstraat 655, 2650 Edegem, Belgium. [2] Division of Anaesthesia, University of Cambridge and Addenbrooke's Hospital, Box 93, Cambridge CB2 0QQ, UK. [3] Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands.

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Author contributions
All authors were involved in the concept, design, and execution of CENTER-TBI and have all contributed to this review. The final manuscript was approved by all authors.

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Declarations

Conflicts of Interest
All authors were involved in the CENTER-TBI study, primarily supported by the FP7 program of the European Union. The authors report no relevant conflicts of interest.

Ethical approval/informed consent
CENTER-TBI adhered to ethical guidelines, IRB approvals were obtained in all participating centers, and consent was obtained from all participants or their proxies according to national and local regulations. The CENTER-TBI study (grant 602150) has been conducted in accordance with all relevant laws of the European Union, if directly applicable or of direct effect, and all relevant laws of the country where the recruiting sites were located, including, but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force, including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects." Informed consent by the patients and/or the legal representative/next of kin was obtained, according to the local legislations, for all patients recruited in the core data set of CENTER-TBI and documented in the e-CRF. Ethical approval was obtained for each recruiting site. The list of sites, ethical committees, approval numbers, and approval dates can be found on the website: https://www.center-tbi.eu/project/ethical-approval. We note, however, that the current review article did not make use of individual patient data.

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