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Clinical Article

The *BrainIT* group: concept and core dataset definition

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Summary

Introduction. An open collaborative international network has been established which aims to improve inter-centre standards for collection of high-resolution, neurointensive care data on patients with traumatic brain injury. The group is also working towards the creation of an open access, detailed and validated database that will be useful for post-hoc hypothesis testing. In Part A, the underlying concept, the group coordination structure, membership guidelines and database access and publication criteria are described. Secondly, in part B, we describe a set of meetings funded by the EEC that allowed us to define a "Core Dataset" and we present the results of a feasibility exercise for collection of this core dataset.

Methods. Four group meetings funded by the EEC have enabled definition of a "Core Dataset" to be collected from all centres regardless of specific project aim. A paper based pilot collection of data was conducted to determine the feasibility for collection of the core dataset. Specially designed forms to collect the core dataset demographic and clinical information as well as sample the time-series data elements were distributed by both email and standard mail to 22 *BrainIT* centres. A deadline of two months was set to receive completed forms back from centres. A pilot data collection of minute by minute physiological monitoring data was also performed.

Findings. A core-dataset was defined and can be downloaded from the *BrainIT* web-site (go to "*Core dataset"* link at: www.brainit.org). Eighteen centres (82%) returned completed forms by the set deadline. Overall the feasibility for collection of the core data elements was high with only 10 of the 64 questions (16%) showing missing data. Of those 10 fields with missing data, the average number of centres not responding was 12% and the median 6%. An SQL database to hold the data has been designed and is being tested. Software tools for collection of the core dataset have been developed. Ethics approval has been granted for collection of multi-centre data as part of a pilot data collection study.

Interpretation. The *BrainIT* network provides a more standardised and higher resolution data collection mechanism for research groups, organisations and the device industry to conduct multi-centre trials of new health care technology in patients with traumatic brain injury.

Keywords: Head injury; multi-centre network; health technology assessment.

Part A: *BrainIT* group concept

Head injury has devastating economic and social consequences both to the victim and to the society that supports the victim [1]. The incidence of serious head injury is estimated at 1500 per 100,000 population per annum. On a European dimension this translates into over a million hospital admissions with a head injury per year. Head injury is a leading cause of death in young males and survivors have serious and long term morbidity. The loss of employment to the victim and the stress and increased burden of care to family members have significant social and economic effects upon Europe.

When assessing head injured patients' outcome from new therapies or the application of new monitoring devices, a large number of patients are required [23]. Recruiting patients from multiple centres will significantly reduce the time to assess new therapy and monitoring. However, despite the existence of guidelines for the management of severely head injured patients [3, 9, 13, 18, 24] this group of patients is subject to considerable variability in care [8, 11, 17]. As a first step towards improving management standards in this population, both the inter and intra-centre variability in the management and treatment of these patients needs to be assessed on a multi-national basis, and to do so requires a more standardised and higher resolution methodology for acquiring patient management and monitoring information.

One consequence of the variability in management that probably exists both across and within centres that manage patients with TBI (traumatic brain injury), is its confounding influence upon trials of therapy. There have

been in the last few years several multi-centre clinical trials of potential neuroprotective drugs targeted at patients with brain trauma. However, despite promising pre-clinical results, all have failed to show efficacy in the head-injured population. A number of reasons have been proposed for these failures which include: poor study design, insufficient dose of drug penetrating the blood brain barrier and inter-species differences in brain injury mechanisms.

Another possibility, not as yet systematically examined, is the occurrence of secondary insults which are missed through use of inappropriate monitoring methods. Even in large scale randomised trials, an efficient stratification design cannot be made without a knowledge of the incidence of relevant confounding factors.

Improving the standards and resolution for multicentre data collection will also impact upon the assessment of new medical technology of relevance to the medical device industry. The majority of companies that develop or support devices used to monitor brain injured patients in intensive care are small to medium size enterprises. Unlike the pharmaceutical industry, these small device companies lack the resources to independently assess their devices in multi-centre studies. This severely limits the provision of quality evidence demonstrating the clinical utility of their products.

What is required is an open, collaborative network of centres interested in developing higher resolution and more standardised methods for collection of monitoring and management data from patients with traumatic brain injury. Such an infrastructure will provide a more efficient means for assessing new and developing health care technology, whether it is new drugs, management approaches or new monitoring devices.

Group formation

The idea for the Brain Monitoring with Information Technology (*BrainIT*) group came from discussions arising during the 10th International Symposium on Raised Intracranial Pressure and Neuromonitoring in Brain Injury held in Williamsburg, USA in May 1997. A few participants at this meeting, with a specific interest in neuro-monitoring, agreed that a more open and collaborative approach to the assessment of new monitoring technology would be a more efficient approach then continuing our current practice of conducting small scale, single centre studies.

Collection of minute-by-minute physiological monitoring is now common in many neuro-intensive care units. However, there are no agreed standards for defining the collection, summary and analysis of monitoring data, particularly pertaining to data collected from head injured patients. Cerebral perfusion pressure (CPP = BP–ICP) monitoring is a good example. When we report CPP values, how do we correct for differing policies between centres on the level to which the BP transducer is zeroed? Tracking changes in bed tilt (which affects the size of hydrostatic pressure gradients between the head and heart) is also a significant technical issue without defined standards. As a result of these factors, it is often difficult to compare even the most common forms of monitoring when data are presented at meetings. Development of standards and guidelines in this area is an important step for the future design and conduct of trials of new intensive care monitoring and treatment methods.

From those initial meetings in Williamsburg, a web site was setup (www.brainit.org) and from the interest generated, it became clear that *many* were interested in the concept of an open collaborative approach to developing standards in this area. Currently there are over 150 members from 35 countries who have registered interest in the group via the website. It is possible to summarise the interests of the group into three main aims.

The main aims of the group are:

1. To develop and disseminate improved standards for the collection, analysis and reporting of intensive care monitoring data collected from brain injured patients.
2. To provide an efficient multi-centre infra-structure for generating quality evidence on the utility of new forms of intensive care monitoring and methods for improving the care and outcome of brain-injured patients.
3. To develop and use a standardised database as a tool for post hoc hypothesis testing, hypothesis generation and the development, testing and validation of new data analysis methodologies.

This paper describes the collaborative approach being taken by the group and why we believe it will lead to a more systematic and efficient approach to health care technology assessment in the management of brain injured patients. In part A, we describe the group coordination structure, membership guidelines and database access and publication criteria are also described. In the second part, we describe a set of meetings funded by the EEC which allowed the group to define a "Core Dataset" and in this paper we present the results of a pilot feasibility exercise for collection of this core dataset.

The BrainIT group approach – what are the differences?

The Ethos of the *BrainIT* group is one of fostering open and free collaboration. The approach used, which we believe is novel in this field of medicine involves the following key elements:

1. Only high-resolution minute-by-minute monitoring and detailed management data is collected using computer based data collection tools. A basic set of data collection software tools are provided to all data contributing members free of charge. In addition to the free tools offered, the group is collaborating with industry on the development of more sophisticated data collection technology. A technical sub-group works towards developing tools and methods to assist with standardising data collection, analysis and database tools across centres.
2. A project-by-project based collection of data, where members voluntarily donate their time and effort towards collection of data for specific projects in which they are enrolled. The BrainIT group Internet based facilities (Web page and Forum) allow members either individually or in groups to form their own projects, enlist interest from other members, attract grant funding and manage their own project. Individual project PI's are responsible for project management, funding and publication of their results.
3. The data model used differs from previous collaborative groups working within the field of traumatic brain injury in that data collected as part of individual projects is also donated to a joint database. Data collection tools used in projects collect, as a minimum, a ''Core Dataset'' which once collected and anonymised is added to a common database. The common database will be openly accessible, through the Internet, to all ''Data Contributing'' centres. The database will be able to be queried over the Internet and datasets of interest can be downloaded to any member who has also contributed data to the database.
4. A steering group (including a group statistician), with overall responsibility for group management, does not dictate project selection but can help with project design if required. An important function of the steering group is to track data analyses being performed on the joint database to ensure a high level of analysis is maintained. Only officially registered and planned analyses conducted on ''validated'' data can lead to publication and presentation at meetings. The steering group will ensure that database access, analysis and publication criteria are adhered to.
5. An important element of the BrainIT group approach is to continuously work towards the development of improved ''standards'' for multi-centre collection and analysis of data in this patient population. We have achieved a key first step in this process by defining minimum data validation standards and have developed a mechanism for checking the validity of data against original documentation using regionally hired ''data validation'' staff. The BrainIT network provides an infrastructure supporting data quality control for trials of management or monitoring similar to that required by the Pharmaceutical industry in the conduct of trials of new drugs.

A detailed BrainIT Group ''Operational Strategy'' document can be viewed and downloaded from the group web-page (www.brainit.org → go to Operating Strategy Link). A sub-set of this document is summarised below.

Figure 1 Outlines the Group Concept.

Group membership

There are two forms of BrainIT group membership: **Individual Membership** and **Centre Membership**. Centre membership, in addition to individual membership, is required because it is a centre or institution that is responsible for allowing local patient data to be used in research. Each centre has a local principal investigator responsible for BrainIT database access. *Individual members within centres who are not the centre PI who wish access to the database must apply to the Steering group.* Membership (both individual and centre) is free.

Individual membership

Pre-requisites for Individual membership are:

– Applicants are clinicians, scientists, engineers or researchers employed within institutions or organisations supporting the monitoring or management of brain injured patients.
– Completion of the internet registration form: www.brainit.org

Centre membership

Pre-requisites for centre membership are the same as the criteria for individual membership AND:

– Must be contributing data (at least 5 patients *core data* per year) to a *BrainIT* group project.

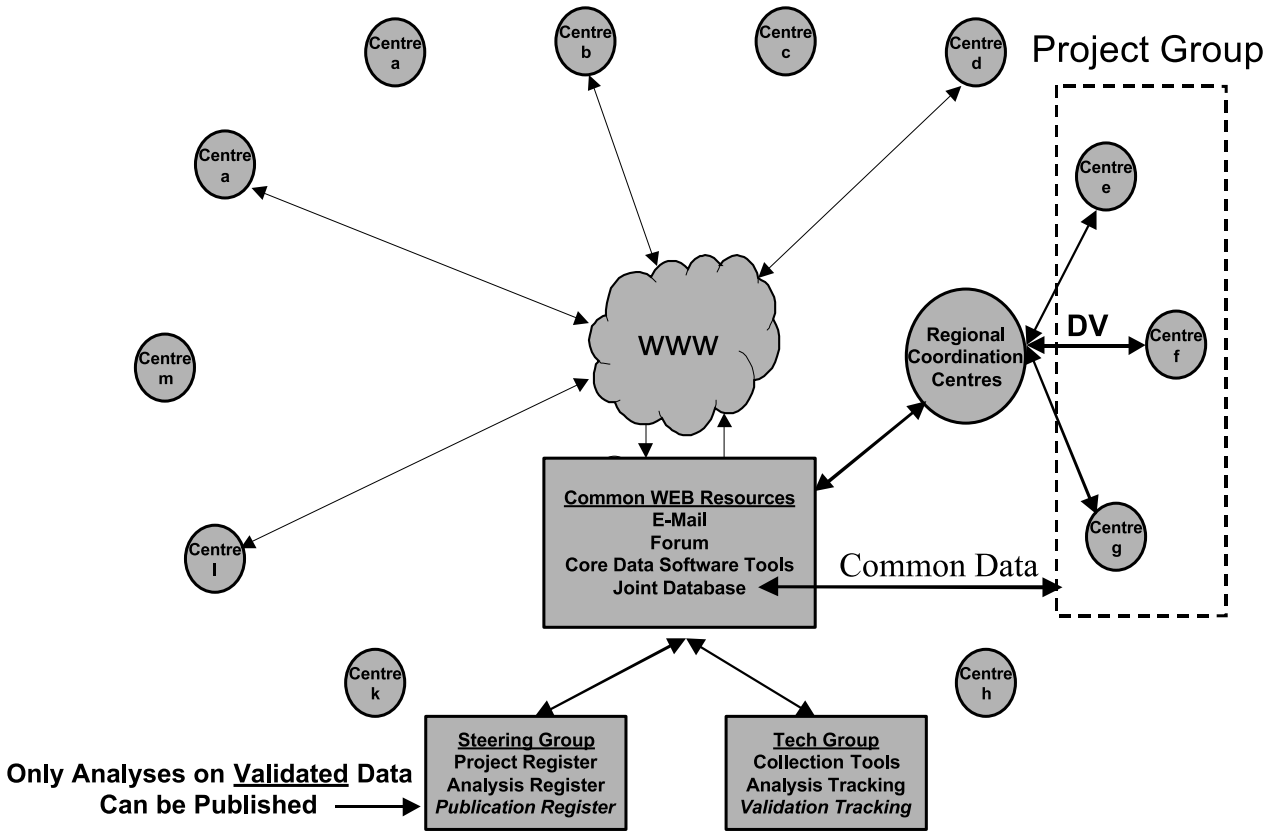

Fig. 1. *Graphical Representation of BrainIT Group Concept*. Using the Internet as a mechanism linking individual investigators, the *BrainIT* group provide web resources (mailbase forum, discussion forum and free access to common data collection tools) to foster formation of project groups. Project groups are responsible for managing, funding and publishing their own work. Collected data is anonymous and donated to a common database for the benefit of the entire network. Any data-contributing centre can access the entire common database useful for post-hoc hypothesis testing and generation. Only "Validated" data can lead to publication and the BrainIT group provides a region-by-region based mechanism for hiring and managing Data Validation *(DV)* staff to validate project group data. Validation costs will be generated from a range of resources, including a contribution from grant funding sourced from individual project group grants. Project and analysis duplication is prevented by a Steering group maintaining and managing a project and analysis register. A technical group helps develop data collection, analysis and database tools

Benefits of individual membership

a) Name and Email Address added to *BrainIT* Web Members on-line address book.
b) Membership Certificate
c) Added to circulation list of information on group events, meetings and newsletters.
d) Access to the Individual Members Section of the BrainIT Forum allowing members to participate in project specific forum discussion topics.

Benefits of centre membership

a) As for Basic Membership plus the designated PI from each centre has automatic access to the common *BrainIT* Database.

The *BrainIT steering group* will be responsible for reviewing applications for new or annually renewed centre membership.

Group management, structure and coordination

With the exception of any fixed contract, project funded, technical or administrative staff, All *BrainIT* steering group, technical group and data contributing members work voluntarily and do not receive any form of fee or stipend for the support they provide.

The full group management, organisational structure and coordination can be viewed from the Operational Strategy Document which can be downloaded from the BrainIT Group Web: (www.brainit.org → go to Operating Strategy Link)

Regional coordination

Each region (usually one but occasionally more than one country sharing a common language) with more than one neuro-intensive care centre contributing data to the *BrainIT* database has a *regional* coordinator

providing coordination support for centres within their region. They also hire, train and support ''Data Validation'' staff (funding dependant), used to travel to local centres to train local centre staff in the use of *BrainIT* data collection and analysis tools, as well as, conducting data validation exercises. *See the Operational Strategy Document for an overview of BrainIT Data Validation Approach.*

Legal status

The *BrainIT* group is a ''not for profit organisation'' and is currently seeking appropriate legal status. Data held within the database will be owned by the *BrainIT* non-profit making organisation and is accessible only to data contributing centres or to those directly collaborating with the principal investigator in the data contributing centre.

Guidelines to database access and publication

- All data is stored on a dedicated research data server at the BrainIT Coordinating Centre.
- Data is anonymous and it will not be possible to tell from which centre the data originated.
- Data will be searchable by the project title which was responsible for the data to be collected.
- As not all projects have funding which will allow data to be validated against original documentation, data will also be searchable upon whether it is ''Validated'' or ''Not Validated''.

Database access/analysis criteria

1. Those wishing to access the database must themselves be from centres that have contributed data to the database.
2. Centres must contribute at least 5 ''Core Dataset'' patients per year to maintain database access in any given year.
3. Only the PI in each centre contributing data will have automatic access to the common database. Other individuals within centres contributing data may be given access to the database at the discretion of the local PI, however, the local PI remains responsible for any analyses performed on the data accessed from their centre. Where there is conflict between the local PI and Individual members within the same centre, the *BrainIT* Steering Group will determine which other individuals may access the joint database.
4. Only ''Validated'' data should be used in analyses intended for publication or submission as an abstract to a local or international meeting. See the ''Operational Strategy'' document for details of the data validation approach: (www.brainit.org → go to Operating Strategy Link)
5. Unvalidated data may be accessed and used in analyses intended for hypothesis generation or post-hoc hypothesis testing, but may not be used in analyses intended for publication.
6. All data sent to the database must have been produced from research studies where the protocols for those studies have been approved by the sending institution's local ethics committee. A copy of the letter of approval must be lodged with the BrainIT coordinating centre.
7. Individual patients must not be identifiable from the data sent to the database and the data collection protocols used must conform to the Helsinki Accords.
8. Should an abstract for presentation at a meeting or a manuscript intended for publication be produced from the joint database – the paper being submitted should first be sent to the steering group who will review the manuscript. This is to ensure that a consistent and high standard of data analysis and interpretation is maintained. The steering group must return comments to the author within 14 days of receipt of the MS or meeting abstract. Failure to comply with these criteria will result in a letter being sent to the organising committee of the meeting or the journal editor from the steering group.
9. It is required that a copy of any processed data and full results of any analyses from data within the database that has resulted in the production of a paper *accepted for publication* should also be made available to all data contributing members. The steering group will ensure that such analyses will be posted to a common ''Results'' folder and will notify members whose data that were used in the analysis that results have been posted.
10. Data downloaded from the database by one centre for a given analysis must not be sent to any other centre.
11. Downloaded data for a specific and declared analysis must not be used for another analysis.
12. The database either whole or in part must not be sold to any organisation.

Guidelines for Non-Profit External Research Organisations or Individual members not from Data Contributing centres wishing to Access the BrainIT Database

Non profit making external research organisations or individuals not from data contributing centres *may not have direct access* to the common database, however, they may gain in-direct access through collaborating with a centre PI provided:

1. They (the non-profit external research organisation) are themselves registered as BrainIT group individual members AND:
2. They (the non-profit external research organisation) have also agreed and signed to the same Database access criteria (Internet Based) presented to the centre PI with whom they are collaborating.

In such a collaboration, the centre PI remains responsible for access to the database and for tracking any analyses resulting from the collaboration with Non profit making external research organisations or individuals not from data contributing centres.

In the event of any conflict between a centre PI and the collaborating non-profit external research organisation, the Steering Group will make the final decision on whether the database can be accessed and whether the intended analyses can be performed.

Joint authorship guidelines

A. If any data from the joint database was used in the analyses which subsequently formed part of a published abstract or manuscript – reference to the "*BrainIT* Group" must be given in the Author's citation. e.g.: A. Author1, A. Author2. . .& *"on behalf of the BrainIT Group"*.
B. As part of the normal *BrainIT* review process, all members from centres contributing data will be invited to both review and to contribute towards any abstract or manuscript produced prior to submission to a meeting or for publication. Those members who made a *significant contribution* to the design, analysis or writing of the abstract/manuscript will also be named co-authors on the abstract or manuscript. Where there is uncertainty over whether a *significant contribution* was made by a given data contributor – a final decision will be made by the steering group**.**

Attempts at publishing analyses of data from the database without adhering to all the above criteria will result in the sending of a letter by the BrainIT steering group to the editor of the journal and prevention of future access to the common database.

Group funding

The major resource cost of the BrainIT group is for the hiring and travel support of Data Validation Staff. These staff are currently grant funded. Grant funding will, for the most part, remain the predominate source of support, however, other sources of support are being considered including by industry and public donation. As the group expands and more project groups form and bring in their own funding, it may be possible to create a central DV staff resource fund based upon a fixed percentage of project funding.

Part B: core data set definition

Defining a core dataset

In December 2000, the *BrainIT* group received EEC research infrastructure support under the Quality of Life and Management of Living Resources Programme. This support enabled the group to meet to discuss the definition of a core dataset and to define and implement a mechanism for determining the feasibility for collection of the core data set from all current *BrainIT* group centres (see Appendix A).

A meeting was held in Glasgow and 25 participants from 9 countries attended. Representatives were also present from the European Brain Injury Consortium and from medical device manufacturers and the pharmaceutical industry.

The aim was to define a minimum or *core dataset* to be collected from all head injured patients which would be common to all future research projects. Individual projects would then either draw from the core-dataset or append new data elements to the core dataset on a project-by-project basis. To facilitate discussion, the core dataset was sub-divided into four logical groups: a) *Demographic and Clinical Information* b) *Minute by Minute monitoring information* c) *Intensive care management information* d) *Secondary insult treatment information.* The meeting participants assigned themselves to one of these four groups and each group was assigned a chairperson responsible for guiding discussion towards a consensus. Each group was given a draft list of data elements which could potentially be included in the core-dataset. At the completion of discussions, the

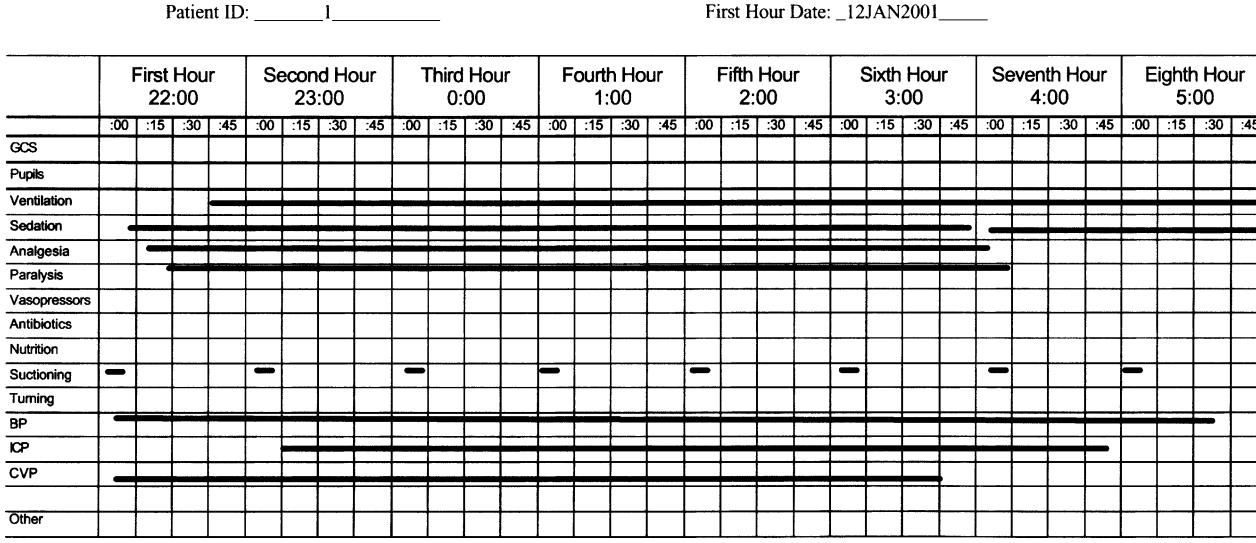

Fig. 2. *Paper based – pilot data collection form*. The form shows the data for patient 1, starting at 22:00 on the evening of January 12, 2001. This patient was on ventilation from 22:40 to end of the time period, was sedated from 22:00 to 03:50, and again from 04:10 to the end of the period. The patient was suctioned every hour at 5 minutes past the hour. Time of BP, ICP and central venous pressure *(CVP)* monitoring is also indicated

chairperson presented the results of their group's consensus on the data elements to be included in the core dataset. The meeting chairman led general discussion towards a consensus on any data element which raised questions as to whether it should be included in the core dataset.

Testing the feasibility of collecting the core dataset

A paper form was designed to test the feasibility for collecting the core dataset from all centres. Although the contents of a core dataset was agreed at a *BrainIT* meeting, it is important to test whether those data *can* be collected. For example, if only 10% of centres regularly collect a given data element – there is little point in collecting that data as a *core data* component.

Centres were asked to fill in the core data elements for one head injured patient with at least arterial blood pressure (BP) and intracranial pressure monitoring in place for 8 hours or more. As this exercise was to test the feasibility for collecting the core data, rather than determining the accuracy of data collection, for the more time consuming minute by minute data collection we designed a graphical form which bed side nursing staff could indicate, by a simple tick, once every 15 minutes, whether the physiological channels were still being monitored. Figure 2 shows an example chart indicating the time-series collection of monitoring data from one centre.

Testing the feasibility of collecting the PC based monitoring data

The collection of the bedside minute-by-minute physiological monitoring data is the most challenging. This is due in part to the large variation in hardware monitoring available between centres. To test the feasibility for collecting the core minute by minute physiological monitoring data from each centre, a request went out to all centres to collect, anonymise and transfer to the *BrainIT* coordinating centre in Glasgow a short sample (at least 10 minutes of minute by minute data) of the typical range of bedside physiological monitoring that is performed in their typical head injured patient. This data was collected and summarised in terms of frequency of channel types.

Results

Core dataset definition

The full core dataset definition is attached as an appendix and can also be downloaded from the *BrainIT* website (go to core dataset link at: www.brainit.org).

For the core dataset, the emphasis was upon collection of data which would normally be collected as part of routine patient management. In the following text, we highlight, within each data collection category, specific examples which either prompted group discussion or we felt required further explanation.

Demographic and clinical data

This group contains data elements which are only collected once per patient and as such are not considered time-series data. Examples being the age and sex of the patient. To ease adherence to national and

international guidelines on patient data anonymity, we chose to record and transfer a patients age as an absolute decimal number: e.g.: 53.4 years. This number is calculated by software from the patient's date of birth and knowing the date of injury.

The usual description of injury variables are collected with users offered a choice from fixed categories. Medical history is focused upon identifying previous neurological injury, substance abuse and associated injuries.

Data elements are then collected describing the clinical status of the patient (e.g.: GCS scores) at both pre-neurosurgical hospital admission and at admission to the hospital with Neurosurgery. Pre-neurosurgical hospital admission encompasses the sources of data from the Emergency Medical Services and the Emergency/Casualty Center of the admitting hospital (if not the hospital with neurosurgery). If data is available from more than one source for the pre-hospital care, the data most indicative of the patient's post-resuscitation/pre-intubation condition at the place of injury is chosen for the pre-neurosurgical hospital admission data.

Group discussion lead to a simplification of the scoring system for recording pupil size and responsiveness. Both eyes are recorded individually and responsiveness classed as reacting or un-reacting. Pupil size is recorded as small, normal or large.

CT-Scan data:

In common with many existing data collection methods, both the first and worst CT-Scan information is collected. Classification is based upon the Traumatic Coma Databank (TCDB) nomenclature. A selection between a "Main Lesion" (none, subdural, extradural, intraparenchymal) is made and using the normal in-house methods an estimate is made as to whether the main lesion (largest hyper-intense lesion) is greater than or less than 25 ml in volume. Cistern state (present, compressed, absent) is also noted. The usual TCDB classification is applied but to avoid interpretation difficulties in the "Evacuated/Non Evacuated Mass lesion" categories – a consensus to record the worst CT abnormality as only a "Mass Lesion of mixed or high density of >25 ml. Although, by definition not part of the core-dataset, an option exists on a project-by-project basis for collection of copies of the main CT scan images for central reading.

Discharge status:

Consensus was achieved to collect from all patients the Extended 8-point Glasgow Outcome Scale (GOSe) at 6 months post discharge from the neurosurgical centre.

A structured questionnaire (downloadable from the Web site: http://www.brainit.org) is used for scoring the GOSe.

Information will also be obtained on the interview method used: in order of preference:

1. Direct (face to face) or telephone interview with patient.
2. Direct (face to face) or telephone interview with relative.
3. Postal questionnaire to Patient/Relative – if no phone number known
4. Telephone interview with GP.

We also will collect information on who was the "*respondent*" to the interview: patient, relative/carer, patient + relative/carer. Also an indication of what the "*most important factor in the patients outcome is due to*": a) head injury, b) illness or injury to other parts of body, c) a mixture of both.

Minute by minute monitoring data

This is the minimum *minute by minute* monitoring data required for inclusion in the *BrainIT* Database and include: Heart Rate (specifying source: ECG or Pulse Oximetry), Respiration Rate (sources: impedance plethmography or ventilator), Mean Arterial Pressure, mean ICP, Pulse Oximetry (SaO2) and Temperature (sources: rectal/oesophageal/ bladder/skin.)

However, additional variables: Central Venous Pressure (CVP), EtCO2, SjO2, TCD, PbrO2, Brain Temperature, Microdialysis... will also be included in the database if they are monitored, in a given patient, as part of their usual clinical management.

Thus the emphasis is to not exclude data which is part of any given centre's *normal monitoring practice* and in so doing build a rich and varied database for post-hoc analysis.

Intensive care management information

This section focuses on the *baseline* medical management and monitoring of clinical status that occurs to patients *more than once* in their stay in ITU. Our intention is to collect this time-series information with a greater frequency and accuracy than has been previously attempted.

To acquire the information with the required frequency, data here will typically be collected by menu driven PC software or in some cases by direct links to hardware (e.g.: infusion pump links). Start times and end times will be given for any change in condition. Data collection methodology varies between centres.

Types of data include: GCS scores, pupil scores, ventilation settings, sedation levels, fluid input and output, nutrition, use of vasopressors, antibiotics.

Coded fields will annotate routine nursing (eye/mouth care, ET tube suction, bed care.), physiotherapy and bedside interventions/ investigations (line insertion/renewal, transducer calibration, x-ray.) and patient transport (to and from Theatre/CT-Scan.).

Routine blood gases and daily laboratory values will also be recorded – Biochemistry (Na, K +, Glucose), Haematology (Haemaglobin, White Cell Count, Haematocrit).

Further detail can be obtained by viewing the core dataset definition or by downloading it from the *BrainIT web-site* (go to core dataset link at: www.brainit.org).

Secondary insult management data

This is medical management/therapy given to patients specifically to treat secondary insults which occur to patients despite their *baseline* intensive care medical management.

To distinguish therapy given to patients to treat secondary insults from those of baseline intensive care, we have devised a coding system which allows specific categories of therapy to be assigned a "therapy target". For example, arterial pressors may be given to treat systemic hypotension or to treat reduced cerebral perfusion pressure (CPP) secondary to raised ICP. By choosing an appropriate target for each secondary insult therapy will enhance the usefulness of the database on medical therapy.

Data here will typically be collected by menu driven PC software. It is to be limited to *non-surgical* management. Start and end times must be given.

Each Therapy *must* be assigned a "Target" chosen from a drop down list. If drugs are given then one can indicate continuous infusion if drugs are delivered by a continuous infusion pump or one can indicate boluses if it is delivered non-continuously.

Figure 3 summarise the minimum choice of therapy categories and associated targets for the BrainIT core dataset.

Paper based feasibility exercise

Having met and defined a core dataset, the group next performed a paper based feasibility exercise. The intention being to determine if the core data elements *can be* collected from the majority of centres. If only

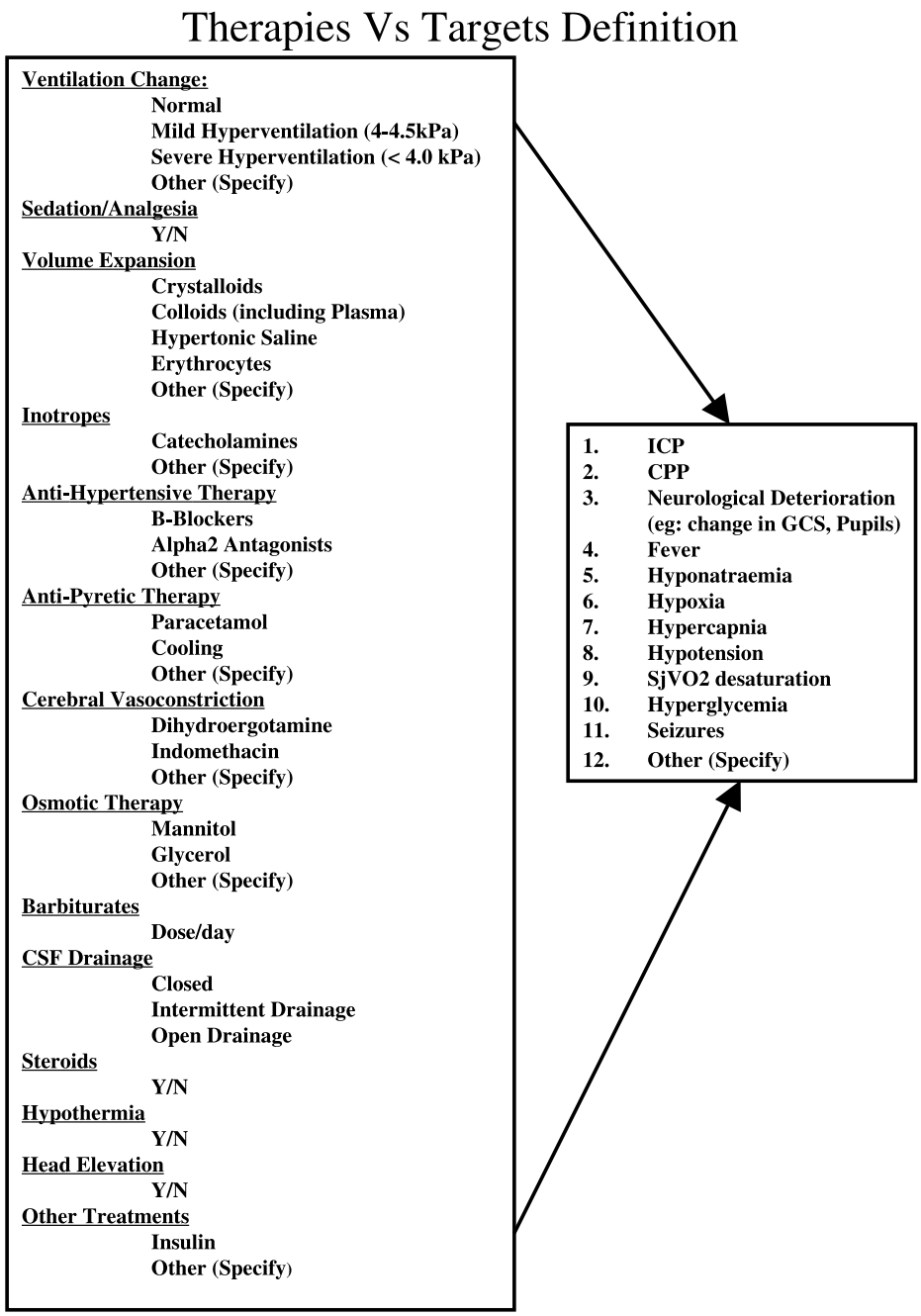

Fig. 3. *Tracking Therapies and Targets*. Lists *BrainIT* core dataset definition therapies and therapy targets. This therapy tracking model has been designed to be easily implemented in software

10% of centres routinely collect a given data element – then it is not feasible to collect that item in all centres.

Specially designed forms to collect the core dataset demographic and clinical information as well as sample the time-series data elements (see Fig. 2) were distributed by both email and standard mail to 22 *BrainIT* centres. A deadline of six weeks was set to receive completed forms back from centres and all results were presented and discussed at the next *BrainIT* group meeting.

Eighteen centres (82%) returned completed forms by the set deadline. Overall the feasibility for collection of the core data elements was high with only 10 of the 64 questions (16%) showed missing data. Of those 10 fields with missing data, the average number of centres not responding to those questions was 12% and the median 6%. The maximum percentage of missing data was associated with the question on "Associated Major Injuries" with a missing error rate of 33%. However, from the group discussion of the data pilot results, it became clear that the question wording was not optimal and a field for responding "none" was omitted. So it was not clear if the field was left blank due to missing data, or there were NO associated major injuries.

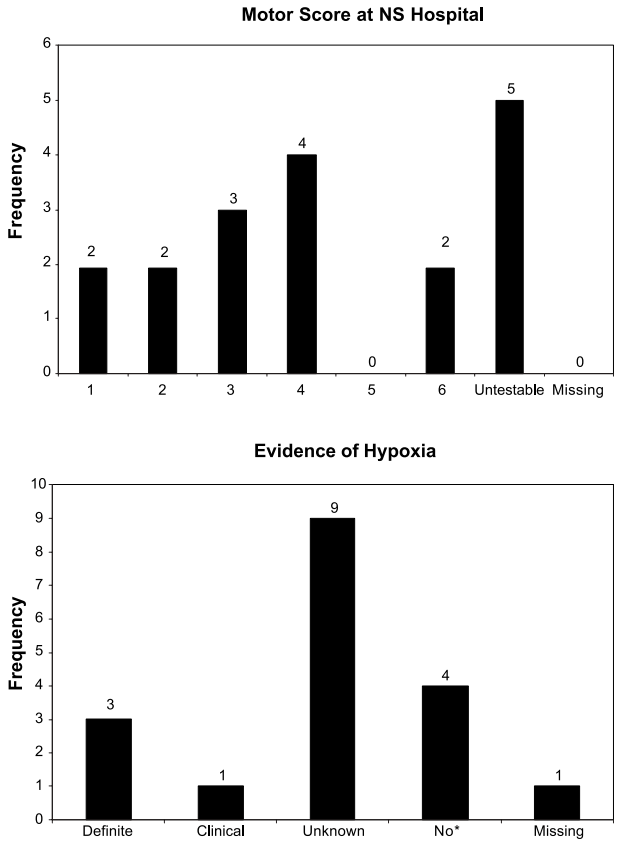

Fig. 4. *Paper based Data Collection Results*. Plot giving example inter-centre responses for two questions from the pilot data collection exercise

Table 1. *Bedside monitoring types found across centres*

System type	Use networked solution	Use RS232/AD solution	Need interface	Total
Phillips medical	3	4	1	8
Marquette	2	3	1	6
Siemens	1	0	1	2
Datex	1	2	0	3
Spacelabs	1	1	0	2
Hellege	1	0	0	1
Totals	*9*	*10*	*3*	*22*

As an example of the type of responses achieved, the bar chart in Fig. 4 gives the distribution of centre responses for two questions: a) Motor score on arrival at the neurosurgical hospital b) Evidence of hypoxia at the accident scene.

Group members were also invited to make comments on the form on data elements which they felt the instructions either needed clarification or the categories required modification. The comments were summarised and any necessary changes to the data elements definition file discussed at a *BrainIT* group meeting. In particular, it was decided that all questions should have fields for "not testable" and "unknown".

Monitoring based feasibility exercise

Table 1 summarises the bedside monitoring types found across centres and Fig. 5 shows which types of monitoring data were collected and summarised in terms of frequency of channel types. Of the 22 BrainIT centres polled: 17 (77%) were able to return example minute by minute bedside monitoring data by the imposed deadline. Of the remaining 5 centres: two centres have either new monitoring systems being installed

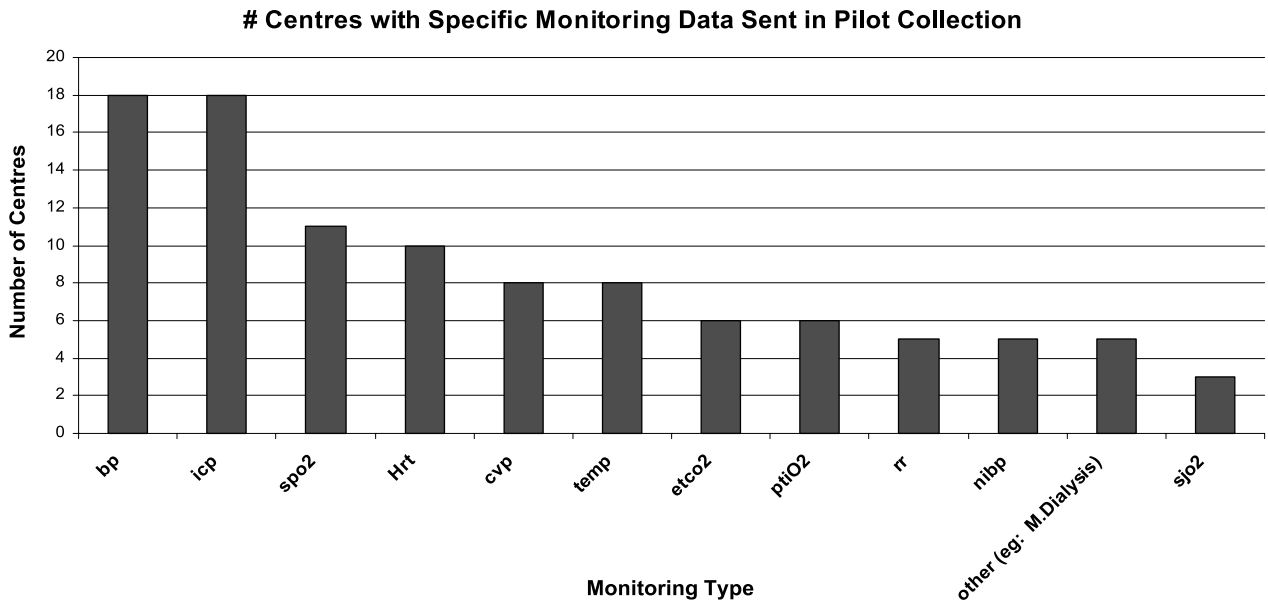

Fig. 5. *Monitoring Pilot Collection results.* Plot showing which types of monitoring data were collected as part of the feasibility exercise. Data is summarised in terms of frequency of channel types

or the PI has recently moved to a different unit and data will be forthcoming. The remaining three centres currently have no PC connection to their bedside monitoring and require assistance with developing a suitable interface. The *BrainIT* group is collaborating with three medical device companies (Philips Medical, CMA Microdialysis and Licox) to develop solutions for these centres. For the purposes of this pilot, the key question was to determine that ''minute by minute'' data is collectable from all centres. The data returned is only a sample and so may not be representative of the full range of monitoring which will be collected in future. This can only be determined from a prospective data collection period with multiple patients data collected per centre.

Discussion

This paper has outlined the concept underlying the *BrainIT* group approach to collaboration and describes the groups efforts to define and test the feasibility for collection of a core-dataset.

BrainIT group concept

The *BrainIT* group approach is to foster free and open collaboration towards raising standards for collection and analysis of data from patients with traumatic brain injury. Data generated as a result of the work of the group is also donated to a common database. The data model used differs from previous collaborative groups working within the field of traumatic brain injury in that data collected as part of individual projects is openly accessible by all who contribute data to the database. Data collection tools used in projects collect, as a minimum, a ''Core Dataset'' which once collected and anonymised is added to a common database. The common database will be openly accessible, through the Internet, to all ''Data Contributing'' centres. The database will be able to be queried over the Internet and datasets of interest can be downloaded to any member who has also contributed data to the database.

The underlying hope is that such openness will lead to a more diverse and innovative range of analysis approaches than would be otherwise possible by any fixed group of investigators with a limited range of skills. Analyses tracking by the Steering group will prevent duplication and may stimulate inter group collaboration. The strength of post-hoc analyses of such a database is in the generation of new hypotheses which can be prospectively tested.

The success of this approach will depend upon the correct balance between openness and control. The concept of an open access database would not have worked in previous years, due to the difficulty of managing and protecting such a resource. However today, the pervasive nature of the Internet and the power and ease of use of discussion forums and remotely administrable and auditable databases makes the implementation of such an approach feasible. However, any such open database can only work if it is based, to some extent, on trust. Criteria have been set and must be met by contributors to the database. Those accessing and analysing data will be audited and those who fail to follow group guidelines will be prevented from future access to the database.

The success or failure of the *BrainIT* group approach will depend upon if the generation and publication of standards, new findings and analyses outweigh any abuse of the open access approach.

Core dataset definition

In contrast to most forms of clinical trial data collection methodologies, the *BrainIT* group data collection requirements are uniquely detailed and require as a minimum some form of PC based collection of patient monitoring data at a collection frequency of no less than 1 sample per minute. The technical aims of the group are to collect both monitoring and non-monitoring core dataset elements from multiple centers using bedside, standardized PC based data collection methods. Towards that end, in this paper, we have outlined the groups efforts towards defining a uniquely detailed core dataset. A feasibility exercise was successfully carried out demonstrating that the core dataset is collectable across centres with an acceptably low frequency of missing data.

However, it is not enough to just set up procedures for collection of multi-centre data – the procedures must be shown to work and estimates of inter and intra centre missing data and data error rates need to be determined. To do so requires a prospective trial of the effectiveness of the BrainIT procedures. EEC funding has recently been obtained to employ data validation staff, organised on a region-by-region basis to conduct a prospective data collection and data validation project. We estimate between 5 and 10 patients per centre need be recruited and Multi-centre Research Ethics Committee (MREC) approval has been obtained. The successful completion of this ''proof of concept'' phase will create a network of centres capable of multi-centre computer based standardised collection of validated, high resolution, well documented management and monitoring data from patients with TBI. The results of the data validation study will provide a baseline measure of inter-centre missing data and data field error rates. In addition, a mechanism for

testing the efficacy of maintaining patient confidentiality will be implemented and tested. Such a network, once tested, will be a valuable resource, not only for academic medicine and the medical device industry, but also for the Pharmaceutical industry as a vehicle for early Phase I/II trials of new pharmacological therapy. In this regard, of particular relevance to trials of therapy, will be the advantage of using the BrainIT ''therapy targets'' (See Figure 3) instead of giving fixed criteria for adverse events and indications for treatment. Some advantages of this approach are: a) There is no need to come to an agreement between centres on standard treatment, thus allowing more centres to participate in any given study, b) Delivers an increased possibility to study the effects of different treatment thresholds and a wider spectrum of treatments.

The case for raising standards

Although most trial designs incorporate data collection methods for quantifying and controlling for secondary insults that may occur during the trial period, these measures will at best identify only major adverse events discernible from the nurses hourly chart records. More frequent shorter duration secondary insults are often missed if sampling periods greater than 1 minute is used [6]. Apart from data sampling rate there is also still uncertainty amongst investigators as to the optimal methodology for identification and definition of these adverse events. In particular the duration and critical threshold that should be used to define a specific type of secondary insult remains unclear. A good example is cerebral perfusion pressure insults. Over the last few years an interest in CPP targeted therapy for head injured patients has developed with a number of observational studies indicating that a CPP of 70 mmHg appears to be a critical value [2, 5, 14–16, 21]. Publication of the American Guidelines for the management of severe head injury by the Brain Trauma Foundation, state that there is not sufficient evidence to establish either a standard or guideline for the management of CPP, although they indicate management of CPP greater than 70 mmHg as a management option. However, as yet, there are no published randomised *multi-centre* trials demonstrating a benefit in patient outcome if CPP is maintained at or beyond this threshold. Conversely, a recently published study from a *single-centre* randomised CPP management trial has shown that aggressive management of CPP >70 mmHg, although reducing the incidence of jugular venous desaturations $<50\%$, increased the incidence of acute respiratory distress syndrome and worsened neurological outcome [20, 21].

Whether it is possible to define if the optimal CPP threshold should be set at 60 mmHg, 70 mmHg or higher is further complicated by a number of technical issues. These include a lack of standardisation between centres on the site of ICP monitoring (intraventricular vs intraparenchymal vs subdural) and the technology used (catheter-tip vs fluid-filled catheter-transducer systems). Most arterial pressure measurement is based on fluid-filled catheter-transducer systems where the degree of system ''damping'' is an important factor. Altering the damping of such a system over typical limits can cause up to a 7 mmHg bias in recorded arterial pressure [7]. In terms of arterial pressure recording such a bias may not be significant, but for CPP measurement, a 7 mmHg error will make the difference to calculated CPP being above or below a treatment threshold. Another important source of error is the inter-centre differences in location of the ''zero'' pressure reference site for the BP transducer. This issue alone can account for up 13 mmHg variance in calculated CPP when combined with the effect of hydrostatic fluid columns which depend upon the degree of angle of head up tilt of the patient [10]. Before we can define thresholds for secondary insults, in a multi-centre study, better standardisation between centres of the type, damping, placement and calibration of physiological monitoring is needed.

Apart from optimising the methods for measuring adverse events, data sampling rate is also important. There are now a number of microcomputer based data-acquisition software systems that can be used to acquire patient physiological data on a frequent basis ($<=1$ sample/minute). These packages provide the means for quantifying, with greater resolution, the degree of secondary injury occurring in head injured patients over specific periods of monitoring [4, 6]. As a result, secondary insults such as intracranial hypertension, and arterial hypotension have been found to occur, in head injured patients, more frequently than previously realised with more than 90 percent of patients exhibiting one or more insults during their management in intensive care [12]. To accurately detect and quantify these events, specialised computer based sampling techniques are required and studies have shown that taking data from the nursing charts alone often miss and frequently underestimate the actual incidence of these events [6]. This is particularly relevant as, to date, all previous clinical drug trials have used paper based clinical

research forms (CRF) for recording data on adverse events with a sampling rate similar to the bedside nurses chart.

For the above mentioned reasons, it is conceivable that large numbers of secondary insults could be missed in a trial. It is also possible that many of these missed events might occur *non-randomly* across centres as the ability to detect short acting secondary insults may vary between centres depending on the type and method of monitoring employed. It is also still unknown to what degree the intensity of patient management and any intra/inter centre management variation influences the incidence of short acting secondary insults. An investigator's choice of participating centre may be more driven by a centres past recruitment rate rather than providing a representative sample of these other factors. For these reasons, it is feasible that missed secondary insults could potentially adversely influence outcome by as much or greater than a potential neuroprotective drug, management or monitoring approach might improve outcome.

By not using appropriate high resolution standardised data collection methods to detect these events, drug companies or research groups cannot control for these factors in their design and analysis and thus the power for detecting an effect of a trial drug or a new management or monitoring approach could be significantly reduced.

Summary

The *BrainIT* group is developing a multi-centre transnational network of intensive care units using standardised computer based methods capable of more detailed collection of admission, monitoring, treatment and outcome data from patients with brain injury. This network will provide a unique mechanism for research groups, pharmaceutical organisations and the medical device industry to more effectively conduct multi-centre trials of new health care technology in the management of patients with brain injury. In future, this network may also aid health authorities to monitor, maintain and raise intra and trans-national standards in the management of patients with brain injury. The creation of an open access, detailed and validated database that will be useful for post-hoc hypothesis testing.

Collectively working towards raising data collection and analysis standards is a critical aim of the BrainIT group and the current work towards defining minimum data validation standards and developing a mechanism for checking the validity of data against original documentation using regionally hired ''data validation'' staff will provide an infrastructure supporting data quality control for trials of management or monitoring similar to that required by the Pharmaceutical industry in the conduct of trials of new drugs.

Appendix A

PI's from BrainIT centres that have participated in the EEC funded Core Dataset study are shown in **Bold** and the additional centres also participating in the new EEC Project in *Italics*. Note, this list is only a subset of the *BrainIT* members registered on the Website, not all of which are eligible for participating in EEC funded projects

Centre Investigator	*BrainIT Centre & Country*
Chambers, Iain	Newcastle General Hospital, Newcastle, UK
Citerio, Guiseppe	Ospedale San Gerardo di Monza, Monza, Italy
Cruickshank, Garth	Neurosurgery, Queen Elizabeth Hospital, Birmingham, UK
Czosnyka, Marek	Neurosurgery, Addenbrookes Hospital, Cambridge, UK
De Jong, Dirk	University Hospital, Rotterdam, Netherlands
Della Corte, Francesco	Cattedra di Anestesiologica Novara, Novara, Italy.
Dunn, Laurence	Southern General Hospital, Glasgow, UK
Enblad, Per	University Hospital, Uppsala, Sweden
Eynon, Andrew	Southampton General Hospital, Southampton, UK
Fadrus, Pavel	Neurosurgery, University Hospital Brno, Brno, Czech Republic.
Gjerris, Flemming	Neurosurgery, Rigshospitalet, Copenhagen, Denmark
Goffin, Jan	Gasthuisberg Hospital, Leuven, Belgium
Iencean, Stefan	Neurosurgery, SF Treime Hospital, Iasi, Romania.
Jarzemaskas, Egidijus	Neurosurgery, Vilnius University Hospital, Vilnius, Lithuania
Kiefer, Michael	Universitatskliniken des Saarlandes, Homburg, Germany
Kiening, Karl	Ruprecht-Karls-Universität-Heidelberg, Germany
Lemaire, Jean-Jacques	Neurosurgery, Hôpital Gabriel Montpied, Clermont-Ferrand, France
Lobato, Ramiro	Neurosurgery, Hospital 12 Octubre, Madrid, Spain
Mascia, Luciana	Ospedale Molinette, Torino, Italy.

Appendix A (*continued*)

Mixenburger, Jurgen	Neurosurgery, University Hospital Leipzig, Leipzig, Germany
Nordstrom Carl-Erick	Neurosurgery, University Hospital Lund, Lund, Sweden
Ragauskas, Arminas	Kaunas Medical University Hospital, Kaunas, Lithuania
Rydenhag, Bertil	University Hospital, Gothenburg, Sweden
Sahuquillo, Juan	Vall d'Hebron University Hospitals Barcelona, Barcelona, Spain
Stochetti, Nino	Terapia Intensiva Neuroscienze, Milan, Italy
Stocker, Reto	Universitatsspital Zurich, Zurich, Switzerland
Vajkoczy, Peter	University Hospital Mannheim, Manheim, Germany
Watkins, Lawrence	Neurosurgery, National Hospital, Queen Square, London, UK
Whittle, Ian	Clinical Neurosciences, Western General Hospital, Edinburgh, UK
Zavala, Elizabeth	UCI Quirurgica, Hospital Clinic Barcelona, Barcelona, Spain

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Comments

In this important manuscript, the authors have documented the first efforts of the "BrainIT Group" to collece online physiological data, from a large cohort of severe head injured patients in intensive care units around Europe.

As such, this is extremely important data.

The manuscript is well written and the assumptions are justified by the data.

R. Bullock
Richmond

This paper provides an introduction to the origins of the BrainIT Group, how it arose and what its aims are both now and for the future. It describes the need to define a core data set in a number of areas

important in evaluating various aspects of head injury care. The potential of the group to develop methods to overcome of the major criticisms of previous multi-centre trials in looking at efficacy is important.

The paper sets out the terms of reference of the core data set and the ability to obtain it in an accurate way, and addresses some of the difficult issues posed by such collaborative activities, such as ownership of data and accessibility to the data. Who could obtain access to this data and how might it be used in the future? How would someone become involved in the BrainIT Group and would membership be a necessary component for access to data? These issues are extremely important because, if the BrainIT Group is to integrate in future research projects with the pharmaceutical industry, clear lines of delineation over these areas will need to be established.

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