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Federating distributed clinical data for the prediction of adverse hypotensive events

BY ANTHONY STELL^{1,*}, RICHARD SINNOTT¹, JIPU JIANG¹,
ROB DONALD^{2,11}, IAIN CHAMBERS³, GIUSEPPE CITERIO⁴, PER ENBLAD⁵,
BARBARA GREGSON⁶, TIM HOWELLS⁵, KARL KIENING⁷, PELLE NILSSON⁵,
ARMINAS RAGAUSKAS⁸, JUAN SAHUQUILLO⁹ AND IAN PIPER¹⁰

¹*National e-Science Centre, and ¹¹Department of Statistics,
University of Glasgow, Glasgow G12 8QQ, UK*

²*C3 Amulet Ltd, Dingwall IV15 9XL, UK*

³*James Cook University Hospital, Middlesbrough TS4, UK*

⁴*Neuroranimazione, Hospital San Gerardo, 20052 Monza, Italy*

⁵*Department of Neurosurgery, Uppsala University Hospital,
751 85 Uppsala, Sweden*

⁶*Department of Neurosurgery, Newcastle General Hospital,
Newcastle NE4 6BE, UK*

⁷*Neurosurgery, Ruprecht-Karls-Universität Hospital Heidelberg,
69120 Heidelberg, Germany*

⁸*Kaunas University Hospital, 44029 Kaunas, Lithuania*

⁹*Neurosurgery, Vall d'Hebron University Hospital, 08035 Barcelona, Spain*

¹⁰*Clinical Physics, Southern General Hospital, Glasgow G51 4TF, UK*

The ability to predict adverse hypotensive events, where a patient's arterial blood pressure drops to abnormally low (and dangerous) levels, would be of major benefit to the fields of primary and secondary health care, and especially to the traumatic brain injury domain. A wealth of data exist in health care systems providing information on the major health indicators of patients in hospitals (blood pressure, temperature, heart rate, etc.). It is believed that if enough of these data could be drawn together and analysed in a systematic way, then a system could be built that will trigger an alarm predicting the onset of a hypotensive event over a useful time scale, e.g. half an hour in advance. In such circumstances, avoidance measures can be taken to prevent such events arising. This is the basis for the Avert-IT project (<http://www.avert-it.org>), a collaborative EU-funded project involving the construction of a hypotension alarm system exploiting Bayesian neural networks using techniques of data federation to bring together the relevant information for study and system development.

Keywords: data federation; hypotension prediction; clinical grids

* Author for correspondence (a.stell@nesc.gla.ac.uk).

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1. Introduction

Prediction of detrimental changes to the health of a patient is of paramount importance in all clinical care. Hypotension, where a patient's blood pressure is abnormally low, is a condition that commonly occurs in intensive and high-dependency care units. Emergency treatments of hypotension are often highly invasive and carry associated risks of secondary complications including: tachycardia; peripheral vasoconstriction; and cardiac ischaemia. To be able to predict the onset of a hypotensive event would be of clear benefit to a patient's outcome and this, in turn, has been estimated could translate to a reduction in ICU length of stay and thus a cost saving of an average of €1600 per patient per day across the EU25.¹

To enable the prediction of these events through the use of a novel bedside alarm system is the central premise of the Avert-IT project ('Advanced Arterial Hypotension Adverse Event prediction through a Novel Bayesian Neural Network'). There are a number of reactive bedside systems currently in use, which typically sound an alarm as soon as a patient's vital signs indicate that they have entered a hypotensive phase. An example of such a system is the Odin monitor and browser (Howells *et al.* 1995). In the intensive care management of patients with traumatic brain injury (TBI), the actual definition of a clinically significant hypotensive event can vary widely from centre to centre—the partial standardization of which across the participating clinical centres is itself a research outcome of the Avert-IT project (see §2). However, no system currently exists that can predict the onset of an adverse hypotensive event.

There are a variety of commercial systems available, which allow the prediction of forthcoming clinical states. Examples include the BioSign device (Tarassenko *et al.* 2005), which produces an index predicting cardiovascular instability based on several vital signs such as heart rate (HRT), respiration rate (RR), etc., and the Philips Medical Event Surveillance Monitor (<http://www.medical.philips.com/main/products/patient-monitoring/assets/docs/event-surv-4522-982-91371.pdf>), which supports the manual correlation of patient parameters into discrete 'events'. However, none of these systems provide any probabilistic measure of the causative information of the events occurring and therefore cannot be tied to the context.

There are also a number of medical and clinical research groups that are attempting to enumerate the correlation of patient parameters such as blood pressure and HRT to the onset of hypotension, but these are non-automated (Marmarou 1991; Manley *et al.* 2001). Therefore, a gap in the process of patient diagnosis has been identified: the automated prediction of hypotension in a patient. It is this gap that the Avert-IT project is attempting to address, by producing a predictive system, trained through an appropriate decision-support tool, on the data provided by six specialist centres from across Europe.

Section 2 of this paper outlines the clinical context and results obtained from research conducted into the definitions of hypotensive events. This in turn impacts the distribution of cases and data to be used later in the project. Section

¹ Avert-IT project proposal—'Advanced Arterial Hypotension Adverse Event prediction through a Novel Bayesian Neural Network' (see <http://wiki.avert-it.org/wordpress>).

3 details the computational requirements of the project, with §4 discussing the security issues in particular. Section 5 outlines the implementation of the proposed infrastructure and shows the progress to date.

2. Clinical brain trauma context

In order to federate the necessary clinical data and use this to predict future events, the project consortium must first prioritize what those data should be. To do this, the definition of an event and identification of possible causal data must be agreed upon.

(a) *Definition of a hypotensive event*

The generally accepted verbal definition of hypotension can be expressed as ‘an abnormal drop in a patient’s blood pressure’. Although there are guidelines defining hypertension (Mancia 2007) and accepted ranges for what is considered ‘normal’ blood pressure, there is no accepted standard definition for hypotension. In the management of patients with TBI, some guidelines suggest maintaining a patient’s systolic blood pressure (BPs) above 90 (Chesnut *et al.* 1993) or even 120 mm Hg (Piek 1998), but variability in following management guidelines for patients with TBI is considerable (Stochetti 2001; Bulger *et al.* 2002). Thus there appears to be no general numerical consensus on what constitutes a hypotensive event in terms of the various measurements of blood pressure (systolic, diastolic or mean).

A survey conducted between the partners involved in Avert-IT showed a variation in using the systolic and mean blood pressures (BPm) and cerebral perfusion pressure (CPP) values as indicators for a hypotensive event, shown in table 1, with the definition of the event terms used shown in figure 1.

The Avert-IT project has been closely linked to the BrainIT project (<http://www.brainit.org>)—an Internet-based group set up to work collaboratively on standards for the collection and analyses of data from brain-injured patients towards providing a more efficient infrastructure for assessing new health technology (Sinnott & Piper 2008). As such, a study was conducted over the database created by this group to discover the spread of hypotensive events as defined by the different centre thresholds shown in table 1. The spread of these results from the Avert-IT centres (within BrainIT) is shown in figure 2.

Concern over the technical accuracy of measuring BPs led some clinicians to recommend including a blood pressure ‘mean’ component to the definition. Such an approach was adopted by the group in Edinburgh and became standard as published in the Edinburgh University Secondary Insult Grading System (EUSIG; Jones 1994). Therefore, further research was conducted upon the BrainIT database using four definitions of hypotensive events, based upon the EUSIG scoring system, which are shown in table 2.

From these results, and those expanded on in Donald (2008), the EUSIG definition of less than 90 mm Hg over 5 min (90; 5) for a hypotensive event threshold appears to be the most appropriate for training the decision-support tool later in the project. The fact that all four definitions produced similar numbers supports the decision to continue using parameters from a published study that can be justified to colleagues in the medical community.

Table 1. Hypotensive event definitions.

parameter	Uppsala	Glasgow	Kaunas
measure and threshold	BPs < 100	BPm < 70	BPs/BPd < 90/50
event hold down	2	5	5
clear hold down	BPs > 100; 5m	BPm > 70; 5m	BPm > 70; 5m
parameter	Heidelberg	Monza	Barcelona
measure and threshold	CPP < 50	BPs < 90	BPs < 90
event hold down	5	5	5
clear hold down	CPP > 60; 5m	BPs > 90; 10m	BPs > 90; 15m

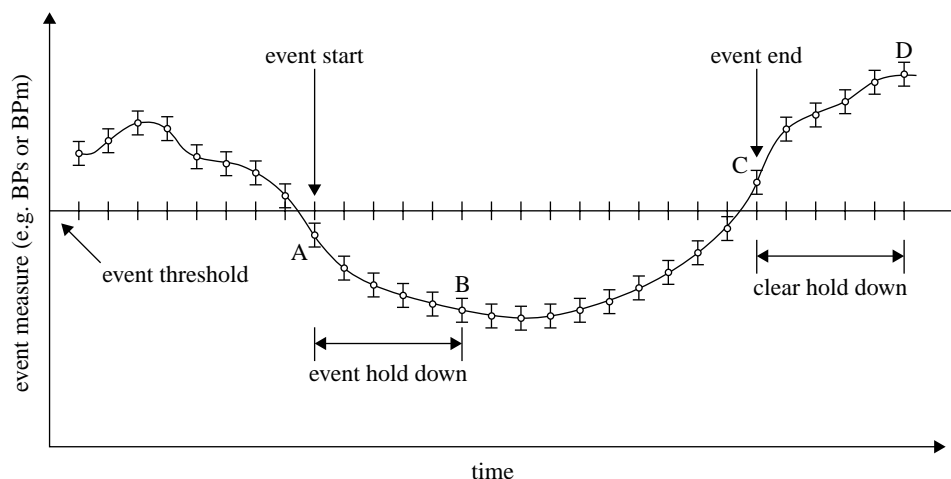


Figure 1. Hypotensive event definition.

(b) Identifying causes of adverse events

The parameters studied so far to produce the hypotension event results above have been the following measures of blood pressure:

- systolic (BPs): the maximum pressure when the heart contracts and blood begins to flow,
- diastolic (BPd): the minimum pressure, occurring between heartbeats, and
- mean (BPm): a combination of the two above, most often calculated as $BPd + (BPs - BPd)/3$.

There are 11 different profiles that characterize the detection of events in the study, which are summarized in [table 3](#). An important result to date has been the large number of type 6 events occurring within this representative dataset, where an event is triggered and held down by BPm only ([figure 3](#)). The implication from this result is that many hypotensive events are being missed by centres that only measure BPs—a common practice, given that this issue of which pressure to measure is still subject to great debate in the clinical community.

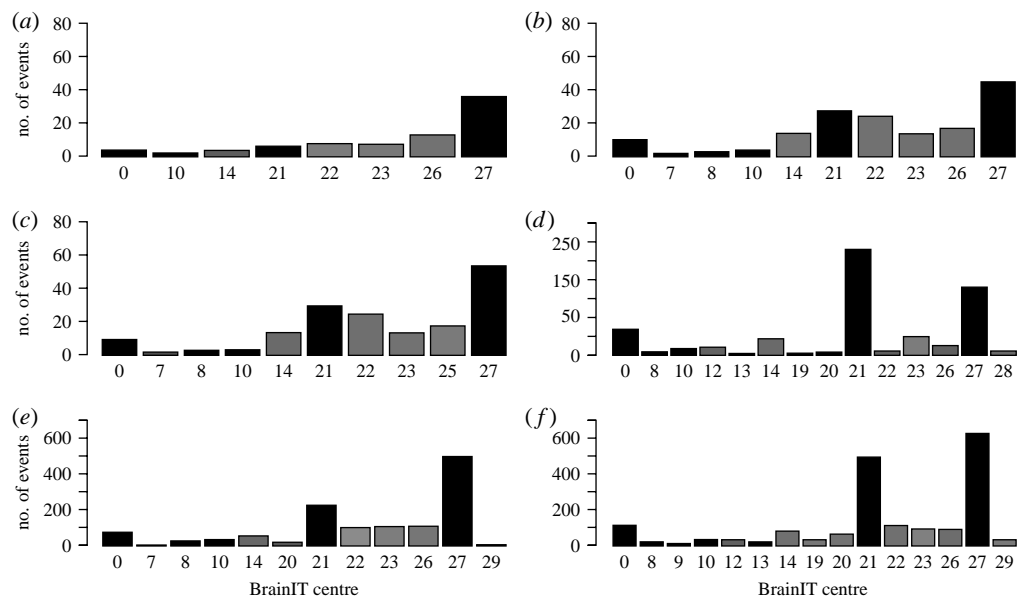


Figure 2. Number of events by BrainIT centre. (a) Kaunas: events=73, patients=26; (b) Barcelona: events=149, patients=59; (c) Monza: events=168, patients=59; (d) Heidelberg: events=607, patients=81; (e) Uppsala: events=1166, patients=100; (f) Glasgow: events=1770, patients=111.

The suggestion that the BPm should be given more weight than previously thought is an important research finding that will be investigated further throughout the project.

3. Computational requirements

There are three key steps to the delivery of the final system proposed in the Avert-IT project:

- (i) the collection of data from the various distributed sources around Europe, contributing to the project,
- (ii) the construction of a system that ‘learns’ to recognize significant patterns in the variable indicator fields and associate them (correctly) with the onset of hypotension, and
- (iii) the implementation of an interface that will trigger an alarm based on the prediction of this event, and provide causative information to aid with the administration of treatment.

Steps (i) and (ii) have fundamental research challenges, which must be addressed for the project to be successfully completed.

(a) Data federation

Figure 4 shows the proposed architecture for the infrastructure to support the Avert-IT project.

Table 2. Event definitions for further analysis.

parameters	BPs event hold down	BPs clear hold down
BPs < 90 OR BP _m < 70	5	5
BPs < 100 OR BP _m < 70	5	5
BPs < 90 OR BP _m < 70	2	2
BPs < 100 OR BP _m < 70	2	2

Table 3. Event classification (T, trigger; C, clear).

BPs	BP _m
T-BPs-C-BPs-BP _m -enclosed (1)	T-BP _m -C-BP _m -BPs-enclosed (5)
T-BPs-C-BPs-BPs-only (2)	T-BP _m -C-BP _m -BP _m -only (6)
T-BPs-C-BP _m (3)	T-BP _m -C-BPs (7)
T-BPs-C-both (4)	T-BP _m -C-both (8)
both	
T-both-C-BPs-enclosed (9)	
T-both-C-BP _m -BPs-enclosed (10)	
T-both-C-both (11)	

The connection between non-clinical centres—the data grid provider and the front-end/prediction-engine developer (grouped together in the lower box)—is relatively well defined and can be achieved using either Web services or direct JDBC calls, and once established to both parties' satisfaction can remain relatively static for the duration of the project.

However, the connection to clinical systems must satisfy the constraints of a variety of health-centre policies, in terms of access to their data and secure transit of those data into the Avert-IT database, and in terms of the security of those data once they have left the perimeters of the centres involved. The most efficient method of establishing such connections is to have a lightweight client—validated to the satisfaction of the centres involved—sitting within the firewall (or a 'de-militarized zone') of the centre, and which pushes data out to a receiving program run by the grid provider, which can then parse and upload to the Avert-IT database.

The first challenge in setting up a data grid over several heterogeneous clinical sources is to ascertain the structure of the data concerned. This takes the format of the data schema used, and also in this case, the nature of the data files themselves (often in the medical field, it is more than simply a case of connecting to a database), which include in this project ASCII text files, semi-structured XML and clinical-specific Health-Level 7 (HL7) format.

As the initial prototype system is developed, the volume of data is relatively low and, as is the nature of prototyping, any development issues can be overcome on a small scale in the first instance. However, when the scale of development increases and a production system is required to support the project, two major issues become evident: the method of securely connecting sources in real time and processing the large amount of data in transit over a feasible time scale.

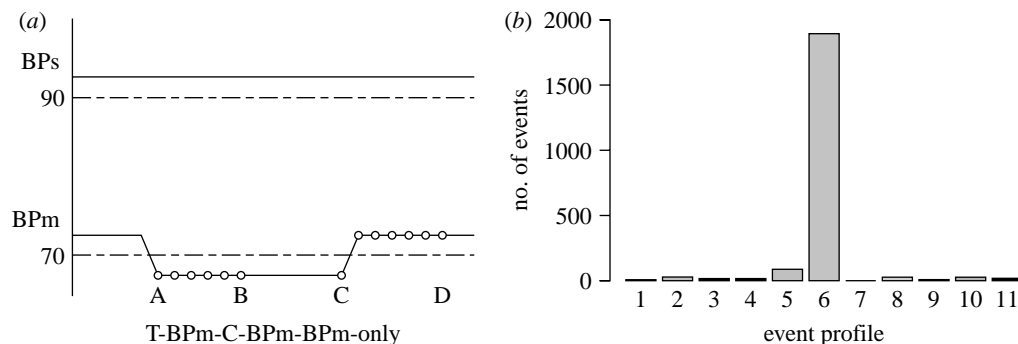


Figure 3. Type 6 event (a) definition and (b) number (90; 5 min, events=2081, patients=100).

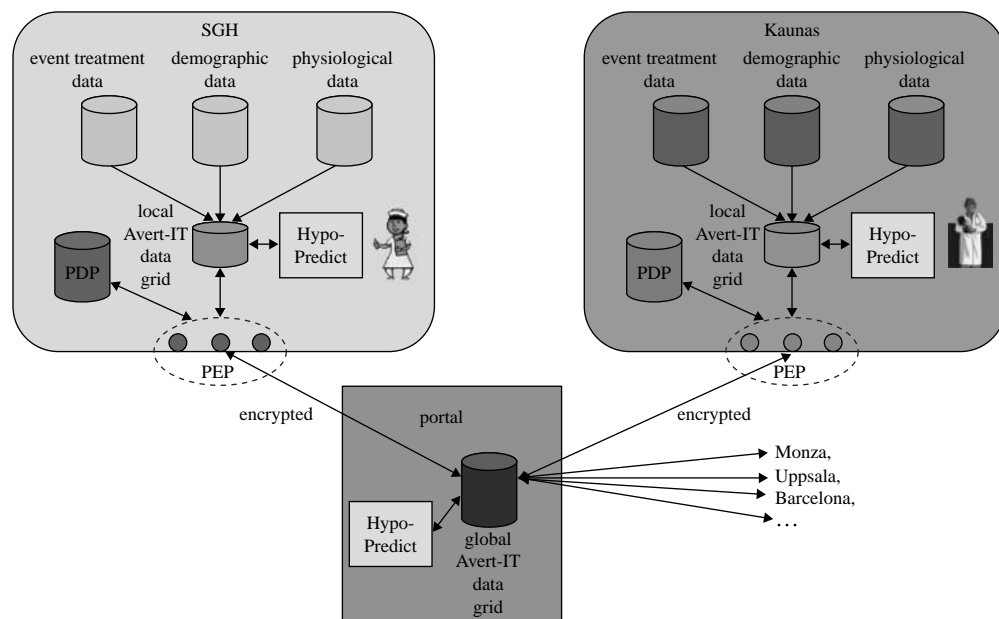


Figure 4. Avert-IT proposed infrastructure.

(b) Decision support for event prediction

To accurately predict events, a decision-support module must be created, which takes account of the data retrieved so far, then makes a decision whether to send an alarm or not. There are a variety of methods of implementing a decision-support system, in addition to simple lookup tables and case-based reasoning, and these are listed below.

- *Genetic algorithms (GA)*. This is a search technique that involves generating a random selection of solutions across the domain, then testing this against a fitness function. The ‘fittest’ solutions are then carried over to the next generation of solutions until a predetermined level of generations has been

completed. Although useful in scheduling and timetabling optimizations, there is some doubt as to whether the GA would be applicable in this system.

- *Bayesian belief networks (BBN)*. This is a probabilistic model that represents a set of variables and their probabilistic dependencies. Inherently capturing probability in its development, training a BBN architecture with data-driven mechanisms has proved difficult.
- *Artificial neural networks (ANN)*. This is a computer-simulated model of the brain, where individual ‘neurons’ are interconnected from an input layer, through one or more hidden layers, to an output layer.

Balancing the project requirements and the various advantages and disadvantages of the different approaches, it has been agreed by the project consortium that a Bayesian approach to training an artificial neural network (BANN) would be the most effective way of ‘training’ the system to detect the onset of a hypotensive event based on the input data of associated parameters. The motivation for considering the BANN is its application to the classification and modelling of highly nonlinear relationships while also considering probabilistic factors, expected to be a major aspect in the clinical inputs involved. Although the investigation of this area through comparison of the different methods would be of great benefit, given the limited time scale of the project, it was decided to choose one method most likely to yield useful results.

4. Avert-IT security

The highly sensitive nature of the information being transferred and analysed in this project means that security is a paramount concern. Without the guaranteed security of the system, the likelihood of any widespread adoption will be remote. This section discusses the main issues that must be addressed to make this a secure and hence viable enterprise.

(a) *Patient anonymity and consent*

Most of the information required for the Avert-IT project does not require the identity of the patient to be known. In the first instance, all that is required are the health indicator measurements, the resultant outcome and the threshold information by which the relevant centre determines what constitutes a hypotensive event. Certain statistical demographic information is also required but nothing that can immediately identify patients.

However, the ethics of the project dictate that, if a patient’s data are to be used, then they must give consent to that use. As such, a feedback loop must exist that allows the researcher to identify what patient data would be most useful to the study, requesting the use of these data back to the providing centre, then obtaining consent for its use. In studies involving patients with TBI, there is the added difficulty that subjects are incapacitated and cannot consent themselves. Instead ‘assent’ being obtained from relatives.

The data used in the first stage of this project are sets of example dummy data that cannot be linked to real patients. In the production stage, it is envisaged that any data leaving the bounds of the clinical centres will only have an identifier that only has meaning to the centre involved (a local ID).

(b) Role-based access control

The delineation of duties and an agreement that outlines what recourse can be taken in place of a security breach is paramount. A necessary part of this agreement is to establish a policy of role-based access control that limits what parties can see what data, based on their role privilege.

In Avert-IT, there is likely to be a coarse-grained hierarchy of roles, based on location within the project itself. The clinical centres should be able to see their own data, but not that of the other partners. The users at the end of the development process should also have a subset hierarchy based on their role within the environment using the system.

As the mediating agent bringing the data together, a pertinent question is whether NeSC, the data grid provider, should be able to view the data. This is a question that is yet to be resolved, but for which the Virtual ANonymisation Grid for Unified Access to Remote Data (VANGUARD) solution exists (Sinnott *et al.* 2008). The VANGUARD system allows data to be joined from two centres and presented to a final user, without having access to the data itself (through the exchange of cryptographic keys between end-user and data provider).

5. Implementation

This section on implementation will provide the details in setting up the local unified grid infrastructure, which brings together the distributed data and makes it accessible to the development of the user interface and the Hypo-Predict engine.

(a) Clinical endpoints

There are six clinical centres involved in the Avert-IT project, each with idiosyncratic methods of recording and outputting patient data relating to hypotensive episodes. In addition, the comprehensive BrainIT database is available for use by the Avert-IT project. These are the primary sources with which NeSC must interact in order to set up the unified data grid.

The results so far from study of the various systems architectures are as follows (the sources at Uppsala and Kaunas have yet to be analysed).

- Philips DocVu (<http://www.medical.philips.com/main/products/patient-monitoring/products/doc-center/>). Data are output from the ICU monitors and written to ASCII text files stored on a single server (per hospital) situated behind the firewall of the UK health service (NHS). Optional DocVu interfaces to the local hospital information system also provide basic patient demographic data and laboratory test results.
- CMA ICU-Pilot (CMA Microdialysis ICU-Pilot—<http://www.icupilot.com>). Generally stored in proprietary format behind the campus firewall, there is an option to export the information to standard XML.
- Dräger Medical (<http://www.draeger.com>). One of the more sophisticated technologies, the output is sent to HL7 files, a standard adopted by the health community at large.
- BrainIT. This is a straightforward Access database, hosted on the BrainIT secure area.

As can be seen, the general format of the various systems is similar in that the same parameters are drawn, but they are stored in very different schemas. Therefore, the data in their raw format must be translated into a standard description.

(b) *Avert-IT data grid*

The output of the data grid takes the form of a simple database that stores selected patient demographic information, centre details (in effect an audit trail of the data history) and the parameters themselves. The required core parameter values as identified in the BrainIT database (which has been published as the predominant standard in the field; Piper 2003) are: HRT; RR; BPM; BPs; diastolic blood pressure (BPd); blood oxygen concentration (SAO₂); temperature (TC); mean intracranial pressure; and CPP.

As the project progresses and the investigation of contextual information develops, other parameters previously unused may become significant (e.g. end-tidal carbon dioxide—EtCO₂). As such, the ability to modify this schema and its data is a requirement.

The processes involved in the parsing of the raw data files do still require separation when the system gets to production stage (and during the test phases). It is envisaged that the parsing described above will take place through a lightweight client application distributed to each centre, validated by their system administrators and held on their side of their own firewall. The parsing will then package the relevant data into ‘WS-friendly’ (Web services) XML ready for communication to NeSC, which will be analysed and uploaded.

The overall automation of this process is a non-trivial task and must take account of three key issues: identifying relevant patient information at the clinical centre; coping with the volume of data to be transported; and maintaining security at all stages in the process.

(c) *Progress to date and next steps*

The progress of the work, as of the date of submission (1 September 2008), is that example file outputs from four sources (the BrainIT database, Glasgow, Heidelberg and Monza clinical data systems) have been parsed and input into the grid database. This comprises a minimal example of the data grid, from which the front-end and BANN developer can draw parameters from. The JDBC connection between these two parties has been established and functions correctly. The interface to the data grid can be viewed through a portal at <http://avert-it.nesc.gla.ac.uk:18080/gridsphere>.

The next steps have been identified as sourcing sample files from the other clinical partners (Barcelona, Uppsala and Kaunas) and following a similar pattern in uploading the relevant data parameters.

Between the clinical sources and the data grid provider, the parsing code that currently exists will need to be decomposed into packaging of Web service XML files and negotiations will need to proceed into allowing this communication between dedicated servers across firewalls. It is likely that business cases will need to be compiled to defend the need for this cross-institution communication, and the focus of such cases will of course be on the security of the system.

6. Conclusions

The Avert-IT project proposes the development of a system architecture that can automatically predict adverse hypotensive events over a useful time scale, without the intervention of a health care professional.

The results of clinical research performed over the BrainIT database in conjunction with various definitions of hypotensive event thresholds have suggested that a value of 90 mm Hg over 5 min (one of the EUSIG definitions) is the optimal hypotension threshold definition to proceed with, and that positive research results have been obtained, which provide evidence of the desirability of uniformly measuring mean and BPs together—a practice still subject to debate in the clinical community.

The computational requirements, along with the implementation so far, of setting up a grid infrastructure and passing this data to a decision-support tool have been discussed, along with the different types of support tools available, the BANN being preferred, due to its probabilistic abilities. The major security issues in unifying and using such data have been discussed, with the identification of static agreements and role-based policies being requirements before the Avert-IT system gets anywhere near production level.

Research to date has already produced useful information in the investigation of the causes and definitions of hypotension in patients. It is hoped that, with the successful completion of the infrastructure outlined here, the Avert-IT project will produce a highly innovative system that will have a great impact on the field of clinical health care.

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