The history of INSTOR

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The INterventional Stroke Therapy Outcomes Registry (INSTOR)[1] was commissioned over a decade ago at the specific request of the American Society of Interventional and Therapeutic Neuroradiology (now the Society of NeuroInterventional Surgery (SNIS)) and the American Academy of Neurology (AAN) Interventional Stroke Task Force, in order to answer questions concerning intra-arterial (IA) fibrinolysis. INSTOR is now an automatic error detecting, risk adjusting, HIPAA compliant (Health Insurance Portability and Accountability Act), computerized, web based registry that tracks intra-hospital processes, patient demographic, and procedural risk factors, as well as angiographic and clinical outcomes for both intravenous (IV) tissue plasminogen activator (tPA) and endovascular stroke interventions. This is the story of its birth, evolution, and current goals.

In 1998, Prolyse in Acute Cerebral Thromboembolism II (PROACT II) was reported as the first prospective randomized trial using endovascular techniques for the treatment of acute ischemic stroke.[2] PROACT II was a phase III statistically positive trial that demonstrated 15% absolute and 60% relative benefit in functional outcomes in treated subjects, the greatest absolute benefit in clinical outcomes of any stroke trial ever performed. Indeed, PROACT II was so powerfully positive that the large numbers necessary to show benefit in the National Institute of Neurological Disorders and Stroke (NINDS) IV tPA stroke trial were not needed due to the strength of clinical benefit.[3] It was anticipated that these results would usher in a new era of stroke treatment and growth of our new neurointerventional specialty.

After the publication of PROACT II, I was approached by Mike Morrison, the head of the Abbott Laboratories stroke division, to create a nationwide training program to begin the process of expanding and advancing endovascular stroke care. We decided to create several regional didactic training centers (about 5–7) with the final 1.5 day hands on training to be held at the MERI institute in Memphis (using live dogs and human cadavers). We (SNIS, American Society of Neuroradiology (ASNR), Society of Interventional Radiology (SIR)) wrote an official document stating that, with appropriate skills and training, our members were capable of treating stroke.[4] We were building an entirely new national clinical infrastructure for endovascular stroke treatment across the USA by harnessing the interventional community, recognizing that there were fewer than 50 fellowship trained 'neurointerventionists' in the entire USA, many of whom had never treated a stroke and many who never wanted to.

We anticipated that Prolyse would receive Food and Drug Administration (FDA) approval as the first endovascular stroke drug and treatment. However, due to poor understanding of the rules of the FDA both by Abbott Laboratories (the manufacturers of Prolyse (pro-urokinase)) and the interventional stroke community, this was not to be. Two positive phase III trials are necessary for FDA approval as Prolyse was a 'new' drug whereas drugs already FDA approved require only one new positive trial for a new label indication. Activase (recombinant tPA; Genentech/Roche) had received FDA approval in 1987 after two positive phase III trials for treatment of acute myocardial infarction. Activase then received the additional label indication for stroke after the single NINDS stroke trial.[3] After learning that the FDA would not approve Prolyse, we then learned that Abbott was unwilling to fund a second $30 million trial in order to sell $1 million worth of product.

Shortly thereafter and due to an unfortunate and unanticipated chain of events, our most commonly used IA fibrinolytic drug Abbokinase (urokinase, urokinase-type plasminogen activator) was taken off the market by the FDA. This was a major calamity for both cerebral and peripheral thrombolytic interventions as urokinase was also the active agent in Prolyse, a prodrug. Due to my relationship with Abbott, I was chosen to give the details at the ASNR/SNIS annual meeting. It was proprietary information that Abbokinase was cultured from human renal cells harvested from fetal kidneys of stillborn or deceased premature infants acquired from a single hospital in Columbia, South America. This was early in the age of HIV and hepatitis C, and Abbott was unable to confirm the absence of these viruses from the human cell donors. Further, when Abbott offered to make urokinase by means of recombinant techniques (just as Activase was made), the FDA determined that 'recombinant' urokinase would be a 'new' drug and therefore require two brand new trials!

Thus in a matter of months we did not acquire Prolyse (for stroke) and we lost urokinase. For IA fibrinolysis, all we had left was Activase and reteplase (Retavase, EKR Therapeutics Inc). We did not know the most efficacious and safe methods to give these drugs (preparation, dose, volume, concentration, or infusion rate). Neither drug had FDA approval for IA infusion for any indication, including stroke.

With urokinase off the market, an emergency meeting was held in New York with invited guests from all over the USA to give their experience with IA tPA for peripheral use. I was invited as a representative for the neurointerventional community. The general consensus was that there had been no lower limit of dose efficacy identified for IA Activase. IA doses of Activase as low as 0.01 mg/h delivered intra-arterially for lower extremity fibrinolysis had been used with good results. Indeed, there was never an upper limit established for any IA use, either. But more importantly, there was published evidence that higher doses of Activase worked more slowly than lower doses.[5 6] This fact, still ignored to this day, has major implications for stroke fibrinolysis where speed and efficacy are of the essence in vivo.

After the New York meeting it was apparent that the neurointerventional community needed similar consensus. I obtained funding and then convened an international multidisciplinary 'Consensus conference on current strategies for intracerebral fibrinolysis for acute stroke' in Memphis, Tennessee, on 8–9 January 2000.[i] We had a newly proved treatment for a terrible condition but with no FDA approved drug. We had two off-label fibrinolytics that we had no clue how to use. After 2 days of intensive discussion it was decided that we needed to start from scratch in the study of IA stroke treatment. Our interventional stroke

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[i]Consensus conference on current strategies for intracerebral fibrinolysis for acute stroke. Peabody Hotel, Memphis, TN. 8–9 January 2000. Conference organizer: Connors JJ. Participants: Connors JJ, Barr J, Furlan T, Higashida R, Nesbit G, Sunshine J, Tomsick T, Wechsler L, Wojak J, Yonas H, Zeumer H, *et al*.

community first and foremost needed a dose ranging and safety study for the two fibrinolytic agents we still had, alteplase and reteplase. No company, including Genentech, was willing to sponsor a trial of 'off-label' use of a drug for a minor amount of sales. To this day, no dose ranging or speed of lysis study has been performed for any lytic agent, and minimal research on how to dilute and how to deliver these agents has been performed.

During this Stroke Consensus Conference, and at the specific instruction of SNIS and the AAN Interventional Stroke Task Force and the multidisciplinary stroke consensus group, INSTOR was designed and created. INSTOR was intended to be an observational dose ranging clinical and angiographic outcomes database with a 'pick what you like' menu with predefined dosing regimens. After much discussion, the consensus group designed both low dose and high dose arms with alteplase (1.5 or 15 mg/h), reteplase (0.1 or 1.0 unit/h), and combination lytic/antiplatelet arms (eg, abciximab (ReoPro, Centocor/Eli Lilly Co)). All of these were presented in 'cookbook' format to be chosen as each practitioner wished so that we could easily compare efficacy and speed of lysis as well as clinical outcomes. Our group postulated that if our active SNIS and SIR members participated as we thought they would, that we could get reasonable data within 2–4 years. At the urging of Dr Higashida (SNIS president), SNIS donated $50 000 as a start-up and I recruited additional funding from Centocor, Genentech, Guidant, and others. I formed the non-profit 501c3 NeuroVascular Research Foundation[7] to act as host of INSTOR and bought the website http://www.strokeregistry.org where INSTOR is found to this day.

The interventional stroke community then set about training the few catheter interventionists in the country capable of treating stroke by endovascular means. SIR and SNIS followed the Consensus Conference with the world's first ever dedicated stroke training course in Washington, DC, on 15–16 October 2000.[ii] The course was a striking success with over 100 attendees but, unfortunately, was very much about what we did not know. INSTOR was officially introduced at this course with a plea for people to enter data so that we might learn more about proper dosing, safety, and clinical efficacy of the pharmaceutical agents available for endovascular stroke therapy. Amazingly, even though INSTOR paid $500 per case for data (more than we were paid for actually doing the case), very few people entered any data and the results were far from statistically valid. We still, to this day, do not know the optimal parameters of tPA administration. This fact could have significant implications and might be demonstrated in the results of the recently stopped Interventional Management of Stroke (IMS) 3 trial. Also relevant to IMS 3, INSTOR indicates that by far the best clinical outcomes are achieved in patients with large vessel occlusion and an National Institutes of Health Stroke Scale score of 6–9.

In order to satisfy the need for additional data regarding patient selection and procedural performance, another invitation only SIR/SNIS summit was held in Chicago in 2003.[iii] The additional data points concerning procedural details recommended by the panel were then incorporated into an updated version of INSTOR. As part of the official SNIS annual program, INSTOR was presented year after year but with little response from the neurointerventional community. However, several institutions and conscientious practitioners chose to use INSTOR to track their outcomes for quality assurance and/or institutional review board purposes, and documented good clinical outcomes.[8]

In the recent age of Pay for Performance and Quality of Care initiatives, there have been repeated unanimous recommendations from numerous neuroscience associations and medical societies for tracking outcomes on *every* patient treated. These mandates for tracking clinical outcomes utilizing national registries (rather than local databases) have emanated from the Brain Attack Coalition (Comprehensive Stroke Centers),[9] the American Stroke Association (Metrics of Comprehensive Stroke Centers),[10] and explicitly from SNIS, the Society of Vascular and Interventional Neurology (SVIN), AAN, American Association of Neurological Surgeons,[11] as well as from SIR.[12] Because of these recently published mandatory requirements, INSTOR was completely redesigned to reflect the need for data concerning contemporary stroke therapy and also to track 90 day outcomes for IV tPA (not done in other stroke registries such as Get With The Guidelines/Stroke (GWTG)).[13]

Recently published papers[14 15] bemoan the poor results for IA stroke therapy based on hospital discharge data but without knowing actual 90 day clinical outcomes. The 90 day modified Rankin Scale scores are the benchmark by which stroke revascularization outcomes are evaluated.[2 3 16 17] Much of the clinical benefit from revascularization comes from improvement between 30 and 90 days.[18] Measuring outcomes at 30 days (eg, GWTG) will predictably produce worse results than are traditionally acceptable. An accurate picture of the benefit of IA stroke therapy is not possible with non-specific national databases[15] or GWTG.[13] Neither collect 90 day modified Rankin Scale scores, and both lead to the impression espoused in the editorial that IA therapy is probably harmful.[14]

The success of mechanical devices has recently spurred a renaissance in the world of endovascular therapy. With this heightened attention, there is a new focus on physician training and performance, process improvement, and quality assurance for endovascular treatment of stroke. At the present time, multinational endovascular societies involved in stroke care in the USA, Canada, and Europe (SIR, ASNR, Canadian Interventional Radiology Society, Cardiovascular and Interventional Radiological Society of Europe, European Society of Minimally Invasive Neurological Surgery, Society of Cardiac Angiography and Intervention, SNIS, SVIN) are co-authoring a standards of performance document for endovascular stroke treatment that will again mandate the use of a national registry to document hospital and procedural performance as well as angiographic and clinical outcomes on every patient treated. This document is intended not only to guard quality of care for patients but also to ensure individual practitioner adherence to minimum standards. Further, these performance standards can force institutional adherence to overall hospital processes just as cardiology has done for the acute revascularization of myocardial infarction (eg, door to balloon time).[19] INSTOR has again been reprogrammed to track and report these individual performance and institutional processes of care with real time feedback on items such as mean time to CT, mean time to treatment (IV and IA), as well as real time anonymous comparison of angiographic and clinical

[ii]Emerging therapies: Stroke. Course directors: Connors JJ, Durham J, Latchaw R, Tomsick T. Ritz Carlton, Washington, DC, 15–16 October 2000.

[iii]Interventional stroke therapy consensus conference. Chicago, IL; 21–22 June 2003. SIR/SNIS. Organizers: Connors JJ, Sacks D, Tomsick T, Jauch E, Rymer M, Wojak J, Alberts MJ.

outcomes with risk adjusted analyses based on clot location, age, sex, diabetes, baseline CT or MRI findings, time to IA therapy, and many more variables.

Accurate tracking of clinical outcomes of endovascular stroke treatment would seem to be obligatory in light of the concerns expressed by SNIS/SVIN in the 'Point–Counterpoint' editorials recently published in this journal,[20–22] as well as the 'mandatory' requirements by all neuroscience organizations, as described above. Documenting these clinical outcomes and procedural practices advances our science, assures process improvement, protects the individual practitioners that are doing good work, and also gives a correct picture of the current practice of IA stroke care, both locally and nationally. Results from INSTOR would not only answer many clinical questions but might also serve as arbiter in disagreements regarding patient care across all interventional disciplines. It would thus seem that SNIS would mandate INSTOR to be a requirement for practice of endovascular stroke therapy in all institutions!

Consistent with our societal commitment to quality of care, SNIS/SVIN leadership and members need to document our procedural details and angiographic and clinical outcomes. INSTOR was commissioned by SNIS and has been and continues to be the only tool to measure our success in accomplishing our published goals. As I have said for over a decade, our profession needs to prove that what we do works, uphold our own published standards, and lead by example in the world of training and treatment of stroke.

Acknowledgements This commentary concerning INSTOR was suggested by Josh Hirsch, president of SNIS, due to the fact that it was clear to him that there is lack of institutional memory for the story of urokinase, pro-urokinase, and the genesis and charge (by SNIS) of the INSTOR registry. I (JJC) was at the center of activity in the early days of endovascular stroke care but few people either know or remember many of the important details recounted in this paper. I wrote the paper, and performed the literature search with help from Tricia McClenny (SIR administrative staff present during the entire history of INSTOR) as well as from Joan Wojak. Buddy Connors created the INSTOR registry with the help of Dr Joan Wojak. The NeuroVascular Research Foundation was formed under the laws of the Commonwealth of Virginia (the state of residence of JJC when NVRF was created). The executive director of the foundation from the origin until this day is Jim Robinson. David Sacks, past president of SIR, was involved from the beginning in the early stages of development of stroke training programs and consensus meetings, as indicated in this document. He continues to be so to this day. Dave Sacks and Joan Wojak as well as Jim Robinson have all reviewed this paper in detail and were involved from the inception of INSTOR, and act as guarantors.

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