Key Opinion Leaders in Deep Brain Stimulation (Mid Atlantic region)
A Consensus Meeting Hosted by The Parkinson Alliance

February 20-21, 2015

Hooman Azmi MD, Matthew Boyce MD, Danielle Englert MD, Stephen Grill MD PhD, Kathryn Halloway MD, Ihtsham ul Haq MD, Martin Henegar MD, Patrick Hickey DO, Nandan Lad MD PhD, Adrian Laxton MD, K. Singh Sahni MD, Joseph Savitt MD PhD, Mustafa Siddiqi MD, Stephen Tatter MD PhD, Jeffery Wertheimer PhD, Zachary Levine MD

* Dr. Zachary Levine was the moderator of the consensus meeting and is the principal author of this report.

The following document is a summary and distillation of discussions concerning deep brain stimulation (DBS) for Parkinson's disease (PD) that occurred in Richmond Virginia on February 20th - 21st 2015. In attendance were neurologists, neurosurgeons, neurophysiologists, industry and the Chief Executive Officer of The Parkinson Alliance who hosted the event.

The focus of this discussion was to develop guidelines for best practice of DBS for PD. This document does not represent all of the opinions in regard to treatment of Parkinson's disease with deep brain stimulation but was a result of exchange among experienced physicians and surgeons. Although many of the topics discussed were verified in the literature, some of the discussion was based on experience as well as tested evidence.

Gathering experienced people to engage in an unfettered discussion, we hoped to arrive at guidelines that help patients understand DBS, its benefits and limitations and help physicians and surgeons improve their practice.

This report was intended for two audiences, health care professionals and individuals with PD and their families. Given the robust content of the discussion, we decided to have an integrated, comprehensive report for all of its readers.

Background of Deep Brain Stimulation:

Deep brain stimulation was approved for treatment of PD by the FDA in 2002. Since that time, DBS is now considered an acceptable treatment for motor symptoms of PD: tremor, bradykinesia, freezing, rigidity, dystonia and dyskinesia, a frequent side effect from medication. Evidence points to DBS as better than best medical treatment (optimal management of symptoms with medications) for advanced PD. However, not all motor symptoms improve and there are risks associated with the procedure. The technological and surgical techniques associated with DBS have evolved. These changes have helped mitigate the risks, increased the comfort and success of the surgery and given us insights into the limitations. We still have an incomplete understanding of the mechanism of DBS, but we are constantly refining the practice of surgical implantation and postsurgical programming. Through this iterative process we gain understanding and improve success. In addition, by exchanging ideas in the literature and in open discussion we can also do the same. In our exchange we sought to refine the practice by discussing techniques, challenges and the processes concerning DBS. This comprehensive discourse

started a conversation that we hope continues. These conversations augment the medical investigation and research, which is very important for moving forward.

Conference Structure*:*

The conference was broken down into sections. We first discussed challenges that we all have had as individual practitioners. In a logical fashion we moved forward with preoperative screening, surgical planning, surgical techniques and postsurgical programming. Although these topics are quite broad, we approached them in a detailed and structured fashion. The goal of each section was to come up with acceptable or best practice. In addition, industry representatives were in attendance to give us some insight to their technology and thought process. We were also graciously supported by the Parkinson Alliance who has been a concerned and thoughtful advocate for DBS for PD for many years. Furthermore, Lee Silverman Voice Treatment (LSVT) offered a presentation on DBS and speech. LSVT is an intensive and effective speech treatment for individuals with PD requiring 16 sessions of therapy in 4 weeks. Speech disturbance is a significant challenge for individuals with PD, and longitudinal studies have identified speech disturbance as a potential side effect of STN-DBS with a high incidence rate. The benefits of LSVT on speech disturbance following DBS were presented. The participants concluded that the time discussing these important matters was productive, and they look forward to continuing this forum.

Although individual challenges were discussed in a broader sense, the respective challenges set a tone rather than elucidating specific issues that need to be addressed. Broadly, the challenges of DBS for PD include: Who are candidates for surgery, what techniques or targets are best, how do we maximize benefit and mitigate risk as well as side effect from stimulation and lastly, how do we make the surgery better. As physicians and surgeons, these are our goals. For patients, these are key questions and concerns. We hope that this meeting and its summary document can help practitioners and patients expand choices, and improve decision-making as well as outcomes.

Patient Selection:

Determination of candidacy for DBS is the first and many would argue the most important step in the process. Many variables are considered during the selection process. Diagnosis (idiopathic PD), co-morbidities, and cognitive state are among the most important determining factors in patient selection for DBS. Age, anatomy and support network are also considered. Age is a relative contraindication to DBS. Some published reports excluded patients greater than 72 years of age. As more evidence emerges, however, it has been concluded that clinical condition and general health should be considered over chronological age. Poorly selected candidates will not get sufficient benefit from the surgery. For example, DBS for Parkinsonism due to a different medical condition (i.e., Multiple System Atrophy; MSA) will not yield the best results. A poorly selected candidate that receives little to no benefit diminishes the statistical success and ultimately utilization of a proven treatment.

The clinical confirmation of the diagnosis is essential. DaT scanning, a new imaging technique that uses small amounts of a radioactive drug to help determine how much dopamine is available in a person's brain, may help accurately diagnosis patients with tremor. PD, however, can present with bradykinesia and rigidity without tremor. DaT scanning can help differentiate essential tremor from PD, but a movement disorder trained neurologist does as well, if not better than imaging. Experience, training and clinical acumen trump "testing" in making the diagnosis of PD. It is our recommendation that a movement disorders trained neurologist evaluate all patients prior to surgical intervention.

In general, patients with idiopathic PD who have shown benefit from levodopa therapy make up the majority of PD patients benefitting from DBS. However, those that receive less benefit but suffer significant side effect from the medications: hallucinations, gastrointestinal upset, and significant dyskinesias may be considered good candidates. Initially, DBS was reserved for those patients who had significant motor fluctuations throughout the day despite alterations in medication doses and schedules. These patients were thought to have reached an "end point" in medical therapy. Surgery was the next option.

There are studies that have compared best medical therapy to DBS for patients with "advanced stage" PD (Hoen-Yahr III). These studies have shown that DBS is superior to best medical therapy in these patients (Weaver, et al., 2009; Williams, et al., 2010). Surgery is not saved for those who have failed medical therapy. Some would argue that those who are not responding to medication will not respond well to DBS. DBS should be considered for all patients with idiopathic PD who are receiving no further benefit from medication despite alterations, or have significant side effects from the medications. Multiple attempts at altering medications may not yield any addition "on time" or improve quality of life. Waiting for a patient to reach an advanced disease state may not be beneficial. Advanced PD patients may have other significant issues that may make surgery difficult and may not meet expectations.

Early surgery has been investigated and may offer more benefit than late stage surgery in some individuals (Kahn, et al., 2012). Patients with tremor as the predominant symptom may benefit more from early surgery. There are some who believe that DBS is neuroprotective (prevents further cell loss) but this has not been proven. If true, early surgery would be further beneficial by slowing the disease. Neither patient age, nor the time of diagnosis should be considered absolute indications or contraindications for DBS.

In general, selection criteria must include: confirmation of diagnosis, response to and side effect from medication, co-morbidities, anatomical considerations, cognitive state and psychological/psychiatric status. The age and disease stage are not as essential. We recommend preoperative evaluation by a movement disorder neurologist, experienced surgeon, and neuropsychological testing. Preoperative imaging should also be done to determine anatomic considerations for targeting.

There are some cognitive and psychological states that place patients at risk of experiencing changes in cognition (i.e., memory and other thinking skills) and/or psychological disturbance (i.e., exacerbation of a mood disorder). For this reason, neuropsychological testing, conducted by a neuropsychologist, is necessary to assess cognitive and psychological profiles to assist in determining candidacy for DBS therapy. Importantly, for good candidates, changes in cognition and psychological status are not to be expected. For individuals who are more vulnerable to cognitive or psychological changes, however, confusion, depression, anxiety, hallucinations, or developing an overly excited mood may be experienced following surgery. These cognitive and psychiatric symptoms usually lessen within days or weeks of the surgery, and typically disappear completely. If these symptoms persist, medication or stimulation adjustments may remedy them.

Furthermore, and as it relates to cognitive status, dementia is the most frequent exclusion criterion for DBS surgery (Bronstein, et al., 2011). Some clinicians believe that individuals with major cognitive dysfunction may have difficulty tolerating surgery, may have irreversible worsening of cognitive function postoperatively, may have significant difficulty with the management of DBS therapy, and may perceive little overall functional gain even if motor performance is improved. Notably, defining unacceptable level of cognitive dysfunction (i.e., resulting in declaration of a contraindication to DBS therapy) can be a controversial aspect of patient selection, especially since many PD patients suffer from executive dysfunction (i.e., difficulties with concentrated attention, mental flexibility, planning, organizing, initiating, problem solving, etc.) and memory deficits, but are functional in their daily lives. A general rule is that PD patients with major memory or cognitive problems suggestive of pronounced dementia, and those who get disoriented frequently are poor candidates for DBS therapy.

In the context of psychological well-being, unstable moderate to severe depression is commonly considered a risk factor for adverse outcomes following DBS surgery. Surgery is generally deferred in patients with unstable psychiatric conditions until their symptoms have been adequately managed. Moreover, psychopharmacological intervention (i.e., antidepressants and/or anti-anxiety medications) and psychotherapy (ideally rendered by mental health professionals familiar with PD) may assist in stabilizing psychological well-being, which can help facilitate more appropriate candidacy fro DBS therapy. Furthermore, it has also been recognized that DBS can exacerbate impulse control disorders (e.g. inappropriate shopping, gambling, eating, and/or sexual behaviors). Additionally, there are several reported cases where these types of behavioral side effects have occurred following DBS surgery. If an individual were to encounter any of these behaviors, formal assessment by their movement disorder specialist is indicated, and treatment can be provided to address these symptoms.

Obstacles to Surgery:

We believe that more patients could benefit from DBS. Fewer patients are being referred due to some obstacles. Patient and physician education are two of the barriers to DBS. Patients are often unaware of the surgery and are frightened by the

prospect of "brain surgery." In addition, many physicians are not properly educated on the outcomes, risks and timing of the surgery. There is a perception that surgery is a "last resort" treatment. The diagnosis of idiopathic PD can be difficult. The diagnostic challenge can delay surgical referral or lead to improper referral; both can be problematic.

Surgery, specifically brain surgery is a daunting prospect for any patient. The risks of brain surgery can be great, but the risks associated with DBS are not as great as perceived. When compared to best medical therapy, DBS is superior in outcomes in regard to motor scores on the UPDRS (Unified Parkinson's Disease Rating Scale), and over all quality of life measures (Deuschl, et al., 2006; Weaver, et al., 2009; Williams, et al. 2010). Even with this information many patients are not referred for surgery or opt out when presented with the choice.

Many neurologists are not trained in DBS programming. This lack of expertise often prevents referrals for fear of losing the patient to a neurologist with DBS experience. Often patients are referred only after multiple attempts at adjusting medications and mutual patient and physician frustration. These patients are often more tenuous candidates for the surgery as they may have progressed beyond the therapeutic window for benefit. A poor outcome in this population may then prevent future referrals. This cycle of late referrals and potentially less beneficial outcomes might be prevented with more physician/patient education.

Misdiagnosis is also a barrier to surgery. Some patients are not diagnosed in a timely fashion and are never referred. These numbers are difficult to estimate but we believe this occurs. In addition, a number of patients who have received DBS did not have PD but parkinsonism. This population does not receive the same benefit from DBS. These poor outcomes might discourage future referrals for surgery.

When reviewing surveys of patients who have had DBS, 95% said they should have done it earlier and only 5% regret having had the surgery. Based on brain bank data a movement disorders trained neurologist has 1% margin of error in regard to PD diagnosis. Although there is an expected initial fear of surgery, the overwhelming majority of patients are not only satisfied by the results, also wished they had it earlier. With a movement disordered trained neurologist, the difficulty of diagnosis is overcome. Obstacles to surgery can be overcome with patient/physician education and early referral to a movement disorder trained neurologist with DBS experience.

The Surgery:

After patient selection is complete, DBS can be broken down into processes: Planning, implantation (stage I and II) and programming. We discussed planning focusing on target selection. Implantation of the DBS lead(s) varies from center to center. Some surgeons prefer stereotactic frames (three-dimensional coordinate system to locate small targets inside the brain) and others use so called "frameless" techniques. Traditional "frames" in DBS procedures use a metal frame bolted to the operating table, requiring patients to lie still. Frameless DBS, in contrast, uses a lightweight, less-restrictive platform that gives patients a bit more freedom to move.

The lighter-weight, less-restrictive platform is the only difference between the traditional and frameless DBS procedures.

Surgery can be done awake with or without microelectrode recording (a high-precision technique used in functional neurosurgery to assess neural signals or response to electrical stimulation of nervous tissue) and usually with test stimulation (to see how the patient's symptoms are responding to the stimulation). DBS is also done under general anesthesia. While under general anesthesia the surgeon either confirms electrode placement radiographically (brain imaging that helps view brain structures and electrode placement) and/or with electrophysiology (studying the electrical properties of specific cells).

Our consensus was that any of these methods are acceptable and have literature to support their use in the hands of an experienced team. Programming is done after implantation. There is often a recovery period of 3 weeks or more after surgery before effective programming begins. (Lungu C. et al., 2014) This time period allows for recovery and stabilization of the local tissue impedance. Electrical current delivery to the intended tissues is opposed by impedance, which is the resistance to current flow in an alternating current circuit. Allowing stabilization of the tissue impedance is crucial for understanding current transfer from electrode to tissue, which is a key step in the mechanism of DBS. Once stabilization of tissue impedance occurs, stimulation parameters (voltage or current, frequency, pulse width, specific contact(s), and polarity of stimulation) are then selected in order to optimize therapeutic benefit in the individual patient. The value of impedance depends in turn on the stimulation parameters selected. Programming is further discussed below.

Target Selection:

Once the patient is referred for DBS, the goal is to optimize outcome and minimize risk and side effect. Just as medication has benefit and side effect, so does DBS. The surgery should be tailored to the needs of the patient. The three main targets for PD include the ventral intermediate nucleus of the thalamus (Vim), internal segment of the globus pallidus (GPi) and the Subthalamic nucleus (STN). Vim is used predominately to treat tremor. Both GPi and STN treat tremor, bradykinesia, rigidity, freezing and dyskinesia can be reduced with both of these targets. The non-motor symptoms of PD are not well treated with DBS and gait and balance symptoms are

still somewhat ellusive. The pedunculo-pontine nucleus (PPN; a structure in the brainstem) has also been used as a DBS target for gait and balance issue with varied success (Khan, et al., 2011). The symptom profile of the patient and the results of the preoperative evaluation including neuropsychological testing are used to help tailor the surgery.

The majority of patients with DBS are most likely being targeted at the STN. This target has been shown to be effective for a wide range of motor symptoms. It is the "smallest" of the three main targets. The electrophysiology is quite distinct and test stimulation outside the target yield predictable symptoms. These factors make the target easier to define, but its size makes it harder to hit.

From an imaging standpoint the STN is visible on certain FLAIR sequences (a technique used in brain imaging to suppress fluid effects on the image). It is also found indirectly based on other brain structure locations, such as the mid-commissural point (MCP) and adjacent structures such as the red nucleus. The STN is roughly 12mm lateral, 4mm posterior and 4mm inferior to the MCP. It is about 5mm in length, oblong in shape and is oriented about 8 to 12 degrees (superior lateral, inferior more medial) in coronal plane and 55 to 65 degrees (superior anterior, inferior more posterior) in the sagittal plane. (SW atlas).

The benefits of STN stimulation include tremor control, diminished freezing, rigidity, bradykinesia, and dystonia, and often the patients can decrease medications. A reduction in medication can result in decreased dyskinesias. Side effects of stimulation include speech issues, blepharospasm and in some circumstances mood and behavior changes. Leads that are off target can lead to diplopia (double vision), significant muscle contractions/spasms and dysesthesias (unpleasant sensation such as tingling, burning, pain, etc.). Also side effect might predominate over benefit in an off target lead.

The GPi is a commonly used target for PD, as well. Stimulation of GPi also treats tremor, freezing, rigidity, bradykinesia, dystonia but also seems to primarily treat dyskinesia. This effect seems independent of medication reduction. With GPi stimulation there is not the same reduction in medication, but the dyskinesias resolve. This is a comparatively larger target than the STN. The targeted portion of the GPi lies approximately 20mm lateral, 2mm anterior and 4mm inferior to the MCP. Typically the trajectory through this target is steeper in the sagittal plane: 65-70 degrees and less steep in the coronal plane: 12-20 degrees. The GPi is bounded inferiorly (at the base/bottom) by the optic tract, which allows for confirmation of the target.

Studies comparing these two targets have been done. There does not seem to be a significant difference in outcome in regard to symptoms with either target. There maybe some advantage to GPi stimulation in regard to cognitive issues. Side effect profiles are different and the reduction in medication is quite different. Both of

these targets are seen as acceptable for the treatment of a diversity of motor symptoms in PD.

The use of thalamic targeting is reserved for tremor predominant PD and alone it does not have the same effect on other symptoms such as rigidity, freezing, bradykinesia (slowness of movement) and dyskinesia (abnormal movements ranging from a slight tremor of the hands to an uncontrollable movement of the upper body or lower extremities). Some centers, however, are using co-stimulation of the thalamus and the GPi or STN to achieve more symptomatic relief. The ventral intermediate (Vim) nucleus of the thalamus is located 11-13mm lateral to wall of the third ventricle and the bottom of the nucleus is at the AC-PC plane. The anterior-posterior position is approximately one quarter the distance of the AC-PC line behind its midpoint. Side effect of stimulation is often associated with transient parasthesia (an uncomfortable sensation on the skin commonly manifesting in burning, prickling, itching, and/or tingling). Unlike the other targets, the electrophysiology of this target and trajectory is not as variable as the others. Microelectrode recording (MER) for this target is often not done. It does not add significant amounts of data for target confirmation. However, test stimulation is very reliable for the Vim. With current imaging techniques, we cannot visualize the Vim as a distinct target in the thalamus. It is not as well defined radiographically (brain imaging to help view brain structures) as GPi and STN. The current recommendation is perform Vim DBS with an awake patient with or without MER. Test stimulation is used to screen for benefit and side effect. Lead placement may be changed based on test stimulation.

Stereotactic techniques and Lead Placement:

There are many ways to accurately place DBS leads. Frameless and stereotactic frames are common and acceptable approaches. Stereotactic frames have been in use for almost a century and have evolved. Although not originally designed to place DBS leads, stereotactic frames do this with proven accuracy. The vast majority of DBS leads have been placed using one of the various frames that are available. In the last 12 years new devices have been specifically developed to place DBS leads. These too have been carefully tested and their accuracy has been confirmed. Leveraging new imaging techniques, optical tracking and rapid-prototyping or 3-D printing these newer methods have been labeled "frameless." This is merely a way to differentiate these devices from stereotactic frames. Both frame-based and frameless techniques use volumetric, high-resolution imaging to localize targets. MRI and CT "3-D" or volumetric scans are used. The images are fused and planning is done using the anatomic definition of MRI and the precision of CT.

In addition to the development of novel devices to place leads accurately, new methods using image guidance to confirm placement have developed. Intraoperative imaging using MRI or CT has been reported. These methods often allow the patient to be under general anesthesia. This approach may eliminate discomfort and may speed the surgery, but with some of these techniques there is no physiologic confirmation of the target. There is only anatomic confirmation. However

without intraoperative imaging converse is true: physiologic confirmation without anatomic confirmation. Using image guided placement in an MRI scanner, under general anesthesia does not allow for electrophysiologic confirmation or test stimulation.

The magnetic fields of the scanner can prevent the use of MER and test stimulation. However, precise imaging does allow for anatomic confirmation and compensation in real time for brain shift due to cerebral spinal fluid (CSF) loss. Using microelectrode recording and test stimulation while the patient is awake allows for realization of side effect and some idea of benefit in the operating room. Some centers are using stereotactic robots to place leads as well. The experience with robotic placement is interesting and needs to be considered. Intraoperative imaging with anatomical targeting and physiologic confirmation techniques are both acceptable for DBS placement in experienced hands with one exception. This group felt that there was not enough anatomic delineation of the Vim to allow for intraoperative imaging to determine placement alone. Physiologic confirmation needed to be done. It is also recommended that postoperative imaging should be performed and matched to the preoperative plan when intraoperative imaging is not used. This information is important for programming as well as refining targeting in the future.

In summary, the stage I procedure - placement of the DBS leads - can be done in various ways. Frame-based and frameless techniques, or DBS lead delivery devices are all accurate. Intraoperative imaging and intraoperative physiology both provide confirmation of placement. The FDA has approved DBS implantation for PD using either microelectrode recording and/or test stimulation, but that does not mean this is required for successful surgery.

Unilateral/Bilateral Surgery:

Although the FDA has approved DBS for PD for bilateral placement, not every patient will get bilateral surgery. Most centers place both leads simultaneously. Unilateral placement is useful when one side has predominant symptoms or when there are significant cognitive issues preventing cooperation for a more lengthy operation. Bilateral simultaneous surgery can also cause cognitive issues. There are some centers in the United States that routinely do staged bilateral procedures. They plan to implant both sides, but they complete one side at a time staging them 6-8 weeks apart. The pulse generator is then placed after the second stage is done. This too is an acceptable method of implanting the electrodes.

Placement of the IPG:

The second stage of the DBS procedure is the placement of the IPG and connection to DBS leads. This surgery is less variable than lead placement. Typically, the IPG is placed beneath the skin in the infraclavicular region (in the upper chest wall below the clavicle bone). Tunneling under the skin from the head to the chest is done to place the extension cable that connects the DBS lead to the IPG. Most centers place

the IPG at a separate surgery due to insurance reimbursement structure. When placed at the same surgery, there is a significant financial burden on the hospital. There is no disadvantage to this method. The IPG can be placed in the abdominal region as well. Some surgeons prefer to place one IPG for each lead. This separation of pulse generators is advantageous should one side get infected, the other side is not compromised. In addition, with the placement of 2 extension cables on one side of the neck leading to a common pulse generator, some patients may experience extensive scar tissue and pulling along the side of the neck with the extensions. This has been called "bow stringing".

There are many pulse generators available on the market. Some will power two leads and others only one. Rechargeable and non-rechargeable, “primary cell” models are also available. Currently, there are no rechargeable devices that will accommodate only one lead. There are advantages and disadvantages to each of these devices.

The rechargeable pulse generator offers an advantage in its size and longevity. With appropriate recharging the device lasts 9-10 years. Current FDA guidelines require the device be replaced at 9 years. However, this device does require a certain amount of maintenance. Charging has to be done on a regular basis and failure to do so has consequences. Patients with cognitive issues will often need assistance with the charging.

The primary cell devices, which include the single-channel and dual channel devices do not require charging but their longevity is diminished. With higher voltage and energy settings on the device there is diminished battery life. Frequent reoperation for battery replacement may lead to infection and certainly increases the risks associated with infection. However, there is no day-to-day maintenance on these devices as is required with the rechargeable cell.

As mentioned previously, the single channel device is used in those patients who have only one lead implanted, or may be a surgeon preference to isolate the two systems for cosmetic or other reasons. Some surgeons also believe the single channel offers the neurologist more programming options. The dual channel devices do not allow for independent frequency setting for each side. The single channel device is smaller than the dual channel primary cell. In patients who have bilateral stimulation with a single-channel device infection on one side will not immediately put the second side at risk. In addition, the risk of "bow stringing" is diminished with only one extension on either side of the neck.

In general, whether one has a rechargeable device or a primary cell device, the stimulation is the same. The outcomes are the same. It is the decision of the team to move forward with the appropriate stage II procedure for each patient. This group did not feel it necessary to indicate a best practice in regard to stage II placement. All of the devices on the market have an advantage and disadvantage. Again, the technique and choice should be tailored to the patient and his/her needs.

Complications:

Complications from DBS can be either from surgical issues or hardware issues. Surgical complications are often seen immediately or very soon after implantation. The device related complications may occur later in the course following the procedure. Intra-operative or immediate post-operative hematoma is the most common complication, but this outcome is rare (2% or less), and even when it occurs, it is often incidental without inducing neurologic symptoms. Post-operative infection is another complication. It often leads to hardware removal. This is most commonly seen at the pulse generator implantation site or the lead connector site. Cerebritis or brain infection is extremely uncommon. Venous air embolus, when air is entrained in to the venous system and then travels to the heart, can be very serious, though such a complication is very rare. Even though it is rare, it needs to be recognized and adequately treated, as it is potentially fatal. End tidal CO_2 monitoring should be done to help aid in the diagnosis of such an event. The first clinical sign of a venous air embolus in the awake patient without an endotracheal tube is coughing.

Overall complications are infrequent and are rarely fatal or cause permanent disability. Device related complications include hardware failures such as fractured leads and damaged pulse generators. Late erosions or ulcerations over the battery or connectors, or bur hole covers may also be considered hardware failures. These are also rare but in some reports are as high as 10%. These issues are problematic as it may result in hardware ex-plantation or cessation of therapy for some time. However, they often result in cessation of therapy and re-implantation at a later time. This can be disconcerting to the patient. The patient needs to understand that their safety is paramount and long term benefits are best with careful and meticulous attention to detail.

Programming:

General Overview:

The final process in DBS is programing the system. Along with selecting the appropriate candidate and accurately placing the electrode, programming of the DBS system is the third pillar of a good outcome. The programmer must be experienced in programming in order to ensure good results. Programming should be done by an experienced, movement disorders specialist or other qualified clinician (i.e., formally trained nurse, nurse practitioner, physician assistant, physician, etc.). Programming may require multiple visits initially, but only periodic adjustments are needed subsequently. Medication adjustments and stimulator changes are made in concert. This allows the patient to obtain the most benefit from each therapy. Medication and DBS are not independent nor mutual exclusive therapies.

Programming includes establishing the effective contacts and minimizing potential side effects. Information from the implantation procedure (if test stimulation was performed during the surgical procedure) can assist the programming neurologist in localizing the most effective contacts. In some circumstances a postoperative neuroimaging procedure is used to guide programming. Once the initial parameters are established subsequent adjustments are easier. A well-placed lead should offer multiple contacts that yield benefit. The goal of the programming neurologist is to design a program or series of programs that maximize benefit and minimize side effects with least amount of total energy drain on the battery. It was the consensus of the group that programming should not be done until the brain has adequately recovered from the surgery. Data have shown that impedance changes equilibrate and return to normal about 14-21 days after implantation (Stage I). After this period the impedance, as measured through the device, does not significantly change, allowing for long-term predictable results of programming. Programming sooner may require more frequent visits as the settings may have to be altered to adjust in the impedance changes during this initial, recovery period.

Initial Programming:

Initial programming should be done in the "off" state (off medications) so that medication effects do not interfere with stimulation results. An "off" then "on" state programming ("off" medications then "on" medications) can be done in one prolonged visit. This approach allows for adjusting of the medication to compensate for the stimulation effects. Once this initial program has been established, medication adjustments will need to be made over a period of time. Often subsequent visits are needed to "fine tune" the stimulator or add additional programs so that the patient can get the most benefit.

The initial parameters can be established a number of ways. The parameters include amplitude (*V*, voltage or *Amp*, current), pulse width (PW) measured in microseconds (μs), frequency measured in cycles/second or *Hz* and contact configuration (bipolar vs. monopolar). Information from the surgery is very important to establish a starting point for programming. Some groups actually use brain atlas overlays on postoperative images of the brain to assist in programming. A brain atlas provides a map of the brain to help the neurologist with programming, like detailed driving maps produced from satellite images that help an individual visualize different routes. The DBS lead has multiple contacts, and each contact has the ability to stimulate. Multiple contacts can be activated simultaneously. In order to establish the integrity of the system and each contact, impedance testing should be performed. The impedance of each circuit for each contact should be within a normal range or it will not be effective at delivering stimulation. A high impedance circuit will not yield any stimulation and a low impedance circuit will drain the battery and also not yield effective stimulation. In most cases all circuits have normal impedances. At the IPG implantation, surgery impedance measurements are taken and should be available for the programming neurologists. The initial part of the programming session is to screen each contact at

increasing amplitudes, observing for benefit and side effect. The pulse width and frequency are kept constant. Useful contacts yield benefit without side effects in a wide range of amplitudes. The higher the amplitude the more likely one can experience side effect.

Once each contact has been "screened," programming can begin on the most beneficial contacts. Records are kept on each contact so that less effective contacts are not used. The process can be lengthy for this initial visit, but proper attention on the first visit will make subsequent adjustments easier.

Programming - Additional Details:

The algorithm for programming varies depending on the target: STN, GPi, or VIM. As mentioned, due to the complicated nature of programming, oversight from a movement disorder specialist is indicated.

VIM programming is the most straightforward, as the only symptom that is being addressed is the tremor. Programming can increase in complexity if medications need to be adjusted in concordance with programming. This complexity in programming is more of a concern with STN stimulation, which can have an additive effect to medication. In that instance, increasing the stimulation will result in the patient developing more dyskinesia unless medication is reduced. Thus there is a long term benefit of medication reduction with a short term negative of added complexity. On the other hand, GPi stimulation can suppress dyskinesia in addition to treating symptoms. The data show that medication reduction occurs less often with GPi stimulation. It is unclear if this is because patients require more medication or there is less motivation to reduce medication.

The exact location of the electrodes within the target structure is very important. Information learned in the operating room can be very helpful with regards to programming. This includes the results of microelectrode recording and test stimulation. While post-operative MRI can be helpful with programming, it becomes more useful in the context of a poor clinical response to stimulation.

Each DBS lead consists of four contacts or electrodes. Generally one or two of these will be located within the "sweet spot," – the area where stimulation leads to the greatest benefit. The programmer can select one or a combination of contacts to use for stimulation.

Aside from choosing which of the contacts to use, the programmer will also adjust the pulse width, frequency, and voltage or amplitude. The current iteration of generators allows the programmer to choose between setting a constant voltage or a constant current. While there is some debate about which is better (consistent with a separate DBS consensus meeting in 2014; Bronstein, et al., 2015), the group agreed that they are both similar, but that constant current will use more battery power.

Programming is typically scheduled as an initial office visit for mapping, which can last between one and three hours depending on the complexity of the patient and the programmer's experience. Patients are usually in the "off" state for this visit if tolerated. This initial visit is followed by several visits over the next few months for additional programming during which the patients may be "on" or "off" depending on the clinical scenario. Because of the need to make medication changes with STN leads, these patients may require more frequent programming sessions early on.

The basic algorithm for an initial programming session is very similar between the various targets. Generally it is recommended to start with the pulse width at 60 microseconds and the frequency anywhere between 130 and 185 Hertz. The group felt that higher frequency generally adds more efficacy, especially with tremor, but that the difference is miniscule compared to the effects of changing the voltage or pulse width.

Next, the programmer will select one contact to represent the cathode (a cathode is the electrode from which an electrical current leaves a polarized electrical device) and the generator itself will serve as the anode (where current flows into an electrical device) (monopolar stimulation). Amplitude will begin at zero and gradually increase. The patient is examined at various intervals to assess efficacy and look for side effects. Tremor and rigidity (muscle stiffness) are felt to respond almost immediately to stimulation, so these symptoms are most important to observe. Bradykinesia and gait changes may respond quickly as well but are subject to variable effort and delayed effects of stimulation. The benefits of stimulation may last for a minute or longer after turning off the stimulator. Prior to moving to the next electrode, it's important to turn the amplitude back to zero until the patient's symptoms resume. This sequence prevents falsely attributing efficacy to the current electrode. Once each of the four contacts has been assessed to determine the thresholds for efficacy and side effects, the contact with the lowest threshold for efficacy and/or the highest threshold for side effects is selected.

For subsequent programming sessions, the algorithms differ a little more. For STN programming, if the patient develops significant issues with dyskinesia, medication will need to be reduced. Reducing the amplitude will also help, and then it can be increased at future visits as the medication is slowly weaned. It is important not to wean dopaminergic medication too quickly as this can cause withdrawal symptoms that are very unpleasant. Sometimes stimulating at a more posterior contact can help reduce or suppress dyskinesia. This can be done by using a bipolar setting or with interleaving. Interleaving consists of utilizing separate contacts in alternating individual monopolar configurations.

For GPi or VIM programming, you may be able to select adequate amplitude more quickly. Reduction in medication can be done as tolerated. Also consider dyskinesia as a symptom that can be improved with more stimulation. For all targets, if symptoms persist, gradually increase amplitude or pulse width. If side effects limit

further increases, try an adjacent contact or bipolar configuration (using another contact as the anode). If efficacy requires high amplitude (more than 4 V and which may occur more with GPi leads), consider setting two adjacent electrodes as the cathode with the case still the anode. This will create a larger monopolar field. While gait freezing can respond to deep brain stimulation, the group felt that this is true only if the freezing occurs in the "off" medication state. For some patients, despite having DBS, freezing continues to be an issue. Studies have suggested that lower frequencies (60 Hz, for example) can reduce freezing. The experience of the group was heterogeneous and it was felt that it may help and merits a trial. An additional strategy was to lower the amplitude on the less affected side and to consider adding back more medication.

Two features of the currently available generators were discussed as well; "interleaving" and "groups." As previously mentioned, interleaving consists of utilizing separate contacts in alternating individual monopolar configurations. While one contact is in the stimulation portion of the high frequency square wave pulse, the other is in the "off" portion of the square wave pulse. This allows for two monopolar fields to be superimposed over the extent of the lead. The individuals at this meeting felt that interleaving was useful in terms of providing more capability with current shaping. New technology is under investigation to further improve our ability to shape and steer current to the target tissue. Moreover, advances in neural engineering research are improving DBS systems. One such advance is the concept of current steering, or the use of multiple stimulation sources to direct current flow through targeted regions of brain tissue. DBS advancements are resulting in improved customization to individual patients, potentially enhancing therapeutic efficacy.

Groups is a setting that allows for multiple (up to four) separate programs to be stored within the generator. This allows the programmer to use completely different contacts and settings for each program and then allows the patient to switch between them to determine which one is the most effective. This tool is used more regularly. One benefit is allowing patients to switch back to a previous program without having to return back to the clinic. Another would be setting up a low frequency program to test its effect on freezing.

Concluding Comments:

The aforementioned overview of DBS for individuals with PD provides informative perspectives about the current status of DBS, patient selection/candidacy for DBS therapy, the surgical procedure, and programming. There is unequivocal evidence that DBS is an intervention that can help improve quality of life for people living with PD; in addition to medication management for PD, DBS is considered a gold standard intervention for appropriate candidates. That said, clinicians and scientists are continuously studying DBS to figure out ways to make it better and safer for people to manage their disease. Moreover, while various advances—such as better DBS devices and batteries and better targeting and programming —have led to life changing intervention for individuals with PD, scientists, scientist-practitioners, and

clinicians continue to work together with the PD community as a whole to help improve DBS therapy. Furthermore, meetings such as this one – a consensus meeting among interdisciplinary experts in DBS – are necessary to strengthen our understanding about and approach to DBS therapy to improve quality of care and intervention for individuals with PD.

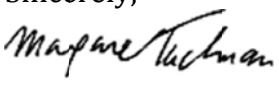
Disclaimer:

The document produced from this meeting ensued from discussions concerning deep brain stimulation (DBS) for Parkinson's disease (PD) that occurred in Richmond Virginia on February 20th - 21st 2015. In attendance were neurologists, neurosurgeons, neurophysiologist's, industry and the chief executive officer of The Parkinson Alliance who hosted the event. This document does not represent all of the opinions in regard to treatment of Parkinson's disease with deep brain stimulation but was a result of exchange among experienced physicians and surgeons. Although many of the topics discussed were verified in the literature and supported by scientific evidence, some of the discussion was based on personal experience by clinicians who attended the meeting.

Contact Information:

As a sponsor of this event and contributor to the write-up of this report, if you have any questions or comments, you can email your questions or comments to The Parkinson Alliance at info@DBS4PD.org, or you can call us toll free at 1-800-579-8440.

Sincerely,



Margaret Tuchman
Bilateral DBS-STN, 2000
President, The Parkinson Alliance
Encl.

Carol Walton, CEO
The Parkinson Alliance

Bronstein J, Tagliati M, Alterman R, Lozano A, Volkmann J, et al. Deep Brain Stimulation for Parkinson Disease: An expert consensus and review of key issues. *Arch Neurol. 2011*;68(2):165-171.

Bronstein J, Tagliati, M, McIntyre C, Chen R, Cheung T, Hargreaves E, Israel Z, Moffit, M, Montgomery E, Stypulkowski P, Shils J, Denison T, Vitek J, Volkman J, Wertheimer J, Okun M. The Rationale Driving the Evolution of Deep Brain Stimulation to Constant-Current Devices. *Neuromodulation: Technology at the Neural Interface*, 2015; 18 (2): 85-89.

Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson'sdisease. N Engl J Med. 2001 Sep 27;345(13):956-63.

Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep brain stimulation for Parkinson's Disease. N Engl J Med. 2006 Aug 31;355(9):896-908. Erratum in: N Engl J Med. 2006 Sep 21;355(12):1289.

Fasano A, Romito LM, Daniele A, Piano C, Zinno M, Bentivoglio AR, Albanese A. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. Brain 2010; 133: 2664-76.

Fenoy AJ, Simpson RK. Risks of common complications in deep brain stimulation surgery: management and avoidance. J Neurosurg. 2014; 132-139

Follett KA, Weaver FM, Stern M et al. Pallidal versus Subthalamic deep brain stimulation for Parkinson's Disease. N Engl J Med. 2010 Jun 3;362(22):2077-91

Khan E, D'Haese PF, Dawant B, Allen L, Kao C, Charles PD, Konrad P. Deep brain stimulation in early stage Parkinson's disease: operative experience from a prospective randomised clinical trial. J Neurol Neurosurg Psychiatry. 2012 Feb;83(2):164-70

Khan S, Mooney L, Plaha P, Javed S, White P, Whone AL, Gill SS
Outcomes from stimulation of the caudal zona incerta and pedunculopontine nucleus in patients with Parkinson's disease. Br J Neurosurg. 2011 Apr;25(2):273-80

Kumar R. Methods of Programming and Patient Management with Deep Brain Stimulation of the Globus Pallidus for the Treatment of Advanced Parkinson's Disease and Dystonia. Movement Disorders Vol 17, Suppl 3, 2002, pp S198-207.

Lungu C, Malone P, Wu T, et al. Temporal Macro- and MicroDynamics of the Post-Operative Impedance at the Tissue-Electrode Interface in Deep Brain Stimulation

Patients. J of Neurol Neurosurg Psychiatry 2013;0:1-4

Odekerken VJ, van Laar T, Staal MJ, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease(NSTAPS study): a randomised controlled trial. Lancet Neurol. 2013 Jan;12(1):37-44.

Piboolnurak P, Lang AE, Lozano AM, Miyasaki JM, Sait-Cyr JA, Poon YY, Hutchison WD, Dostrovsky JO, Moro E. Levodopa response in long-term bilateral subthalamic stimulation for Parkinson's disease. Mov Disord 2007; 22: 990-7.

Priker W., Correlation of dopamine transporter imaging with parkinsonian motor handicap: how close is it? Mov. Disorder 2003 Oct;18 Suppl 7:S43-51

Schaltenbrand G and Wahren W. Atlas for Human Stereotaxy. Thieme 2nd Edition 1977

Spielman J, Mahler L, Halpern A, Gilley P, Klepitskaya O, Ramig L. Intensive voice treatment (LSVT LOUD) for Parkinson's disease following deep brain stimulation of the subthalamic nucleus. J Commun Disord. 2011; 44: 688-700.

Vercruysse S, Vandengerghe W, Munks L et al. Effects of deep brain stimulation of the subthalamic nucleus on freezing of gait in Parkinson's disease: a prospective controlled study. J Neurol Neurosurg Psychiatry 2014; 85:871-877.

Verhagen Metman L, Slavin KV. Advances in Functional Neurosurgery for Parkinson's Disease. Movement Disorders, Vol 30, No. 11, 2015, pp 1461-1470.

Voges J, Waerzeggers Y, Maarouf M, et al. Deep Brain Stimulation: Long term analysis of complications caused by hardware and surgery- experiences from a single centre. J of Neurol Neurosurg Psychiatry 2006; 77:868-872

Volkmann J, Moro E, and Pahwa R. Basic Algorithms for the Programming of Deep Brain Stimulation in Parkinson's Disease. Movement Disorders Vol 21, Suppl 14, 2006, pp S284-289.

Weaver FM, Follett K, Stern M, et al. Parkinson disease: a randomized controlled trial. JAMA. 2009 Jan 7;301(1):63-73.

Wertheimer J, Gottuso A, Nuno M, Walton C, Duboille A, Tuchman M, Ramig L. The impact of STN deep brain stimulation on speech in individuals with Parkinson's disease: The patient's perspective, Parkinsonism and Related Disorders. *2014; 20(10):*1065-70

Williams A, Gill S, Varma T, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol. 2010 Jun;9(6):581-91

Xie T, Vigil J, MacCracken E et al. Low-frequency stimulation of STN-DBS reduces aspiration and freezing of gait in patients with PD. Neurology 2015; 84: 415-420.