

Section VIII

Re-Implantation Guidelines

Background

Harvesting and subsequent implantation (re-implantation) of stem cells has been practiced for more than 50 years. The first successful hematopoietic stem cell re-implant was performed by E. Donnall Thomas in Cooperstown, N.Y. in the late 1950s. The procedure involved the use of donor cells from one identical twin to treat the other twin for leukemia. Because identical twins share the same genetic make-up, the re-implant avoided the potentially life-threatening complication of graft-vs.-host disease (GVHD) which occurs when the re-implanted cells (the graft) attack the patient (the host) as the latter would be recognized a foreign object by the immune cells of the graft. In 1975, Thomas moved his research to Fred Hutchinson Cancer Research Center, where much of the subsequent developmental work on bone-marrow and blood stem-cell re-implantation has been done. Inspired by Dr. Thomas' pioneering accomplishments, the National Marrow Donor Program® (NMDP) was established in 1986 as the result of a Federal contract that was awarded to create and maintain a registry of volunteer hematopoietic stem cell (HSC) donors to serve the tens of thousands of patients in the United States in need of bone marrow transplants, Physicians can search the NMDP Registry on behalf of patients in need of an HSC re-implant when there is no readily available matching donor (such as a relative). In 1999 the NMDP added a Cord Blood Registry to provide more donor source options for patients in need of an HSC re-implant. In order to track and monitor bone marrow re-implantation outcomes the International Bone Marrow Transplantation Registry (IBMTR), located within the Department of Medicine of the Medical College of Wisconsin, was established in 1972. In 2004 the NMDP and IBMTR collaboratively established the Center for International Blood and Marrow Transplant Research (CIBMTR).

In contrast with hematopoietic stem cell re-implants, adult autologous stem cell (A-ASC) re-implants are a relatively recent medical practice, with clinical applications beginning only a few years ago. Because the practice consists of re-implantation of a patient's own stem cells from one part of the body to another (e.g. from the marrow of the hip to the knee) in order to regenerate diseased or injured tissue, there is no issue with GVHD and patient safety is greatly enhanced, relative to allogeneic re-implants. The greater concern with A-ASC re-implants is the potential for tumorigenesis, in which the re-implanted stem cells would possibly form a neoplasm. However, as the A-ASC practice is still at early stage, there are no reports in the medical literature of tumorigenesis or other significant complications with A-ASC re-implants, and also there is no formal system or database for tracking such complications, such as the CIBMTR.

In order to adequately monitor the rapidly expanding practice of A-ASC re-implantation, a unique data collection protocol is required. While allogeneic

hematopoietic stem cell re-implants are focused on donor-recipient matches to avoid rejection and the risks of disease transmission, these risks aren't present in A-ASC re-implants. Rather, A-ASC re-implants face a different set of variables that may dictate outcome and risk of complication. For example, ASC re-implants involve the replication and minimal manipulation of stem cells prior to re-implantation, and thus various cell "lines" result from the harvesting and expansion of different types of stem cells. Other variables include from whence the cells are harvested - although bone marrow and adipose tissues are rich sources, A-ASCs may be harvested and/or introduced from a variety of tissue types where the cells are re-implanted, the condition the re-implant is intended to treat, preparation of the re-implantation site, patient age, gender, and comorbidity, and others. In order to monitor the safety and more rapidly advance the efficacy of therapies involving A-ASCs, it is necessary to track complication and success rates for all cell lines. It is for this reason that the International Cellular Medicine Society (ICMS) has proposed to implement an A-ASC re-implant database and registry.

The purpose of the ICMS A-ASC Re-implant Database and Registry is to rapidly populate an observational databank with information regarding the safety and efficacy of all A-ASC re-implantation procedures. The data contained in database is based on the voluntary reporting of outcomes and complications of various A-ASC procedures by the patients receiving the treatments and the physicians who perform the procedures. The primary goal is the rapid surveillance, analysis, and dissemination of information pertaining to A-ASC complications of all kinds. A secondary goal of the database is to provide information regarding outcomes and efficacy associated with various A-ASC re-implant procedures. The overarching purpose of the Database and Registry is to maintain consistent communication with ICMS physicians and medical professionals so that they are always up to date regarding the safest and most effective A-ASC procedures in clinical practice.

Entry into the Database

All patients presenting to an ICMS physician's office for treatment will be entered into the ICMS registry by a unique identifier that maintains the anonymity of the patient in order to ensure privacy and compliance with Health Insurance Portability and Accountability Act (HIPAA) guidelines. The identifier will include the name of the physician, the birth date of the patient, patient's signs/symptoms, and the date of first presentation. This format will allow for the use of the data concerning the A-ASC procedure and outcome while maintaining patient privacy, and at the same time allow for the ability of the physician to identify the patient in the future should the need arise.

A-ASC Recipient Eligibility Criteria

All recipients of an A-ASC re-implant performed in an ICMS registered center will be recruited for enrollment in the database. This includes adults with and without decision making capacity as well as children.

Informed Consent

All participants will be provided information about participation in the database and must sign an ICMS approved informed consent document indicating their consent for their data to be entered into the database. Documentation of assent and of parent or legal guardian permission of minor participants, and consent for adult participants, must be maintained at the center where the participant, or their parent or legal guardian provided consent to participate. To confirm that participants have given consent to participate in the database, the first form submitted for a participant includes confirmation that the participant signed the informed consent document.

Collection of Data

Each distinct cell line based on the parameters outlined in the ICMS Clinical Guidelines will receive an ICMS registry identifier, which is comprised of the cell type, and the registry number. That identifier will be assigned by the registry. For simple tissue isolates (i.e. bone marrow nucleated cell concentrates, cosmetic fat grafts with stromal vascular fraction isolated through collagenase and centrifugation), the unique registry identifier will be based on the processing of the of the isolate and the method used to implant.

To apply for a new cell line identifier, the clinic or practice must submit a letter to the registry with the following information:

- Why its cell line is unique relative to other cell lines already in the registry. This should include a full description of the cell line as described in the ICMS Clinical Guidelines.
- Intellectual property information such as patent numbers associated with the cell line, if any
- The tissue source
- The tissue target The methods or procedures to produce the cell line (SOP's)
- POC for Q & A regarding this cell line

The Cell Line Registry committee will meet in person or electronically to determine if the new cell line request is in fact a unique line that is eligible to be tracked by the registry. If the new cell line does meet the criteria outlined, an acceptance letter will be sent to the clinic or practice with a unique ICMS registry identifier for the cell line. As an example, an MSC line might be known as ICMS Registry MSC134. An HSC line might be known as ICMS Registry HPC021. Ten exemplar samples, eight taken from unique patients and two the result of two culture expansions of the same patient, will be stored on a permanent basis in -150 C cryo-storage. These will be used to further identify the cell line if complications arise or for further research study if one cell line proves superior to others in treating certain diseases. The registry may subcontract with cryogenic

storage contractors for storage of these samples, but it is the clinic or practice's responsibility to get valid and clean samples in the appropriate format to that cryo storage facility.

The ICMS Re-implantation Registry will track all outcomes and complications related to each stem cell line by its ICMS registry identifier.

A physician may have a clinical rationale for using more than one cell line at a time. To determine if ICMS considers these cell lines distinct, please consult the ICMS Clinical guidelines. If the cell lines are unique, they should be tracked separately, if not, they can be tracked as one re-implant event. In addition, the outcomes and complications tracking should be under all distinct cell lines being used. For example, the use of ICMS Registry #MSC134 and HPC021 in the same patient would raise the following issues:

The clinical translational staging of each line must be considered. For example, this may be EICL for MSC134 and LCCL for HPC021.

The cell lines would be entered into the ICMS registry as entries for each cell line as well as the combination of the two cell lines. For example, the patient would be tracked under MSC134 and HPC0021. A separate entry in the registry would be for MSC134/HPC021.

Collection of Recipient Data

Recipient data is collected at the time of patient registration or re-implant. The data is also collected at 3 months, 6 months, 12 months, and annually for the first 5 years, then at a 10 year time point, and at a 20 year time point.

Initial Data Collected at Registration

At time of re-implant:

- Stem Cell Line Registry Identifier(s)
- Treatment center
- Signed informed consent document
- First, Middle, and Last Name
- E-mail address
- Mailing address
- Home or cell phone number
- Alternate phone number (such as work or cell, or nearest relative)
- City
- State
- Country of birth
- Race and ethnicity
- Gender

- Procedure specific International Classification of Diseases (ICD) -9 or ICD-10 codes (what is being treated?)
- More specific identifier (meniscus tear, tendonitis of the elbow, angina)
- Birth date
- Occupation
- Pre-re-implant target disease(s) or symptoms/signs being treated by A-ASC's
- All co-existing disease at the time of re-implant
- Other Disease: SF-36

On Follow-up (at time points listed above)

All of the above listed data.

- Any new re-implants since the first treatment.
 - Each re-implant should have a Stem Cell Line Registry Identifier(s).
 - Any symptoms/signs or new disease diagnosed since the last contact noted by the physician.

Complications reporting data to elicit:

- Any new diseases (including death) or malignancies that may be related to the A-ASC re-implant
- Any new diseases (including death) related to direct procedural complications (not related to A-ASC re-implant).

The registry will utilize a standard, simple complications tracking questionnaire. The decision to use either a more detailed and comprehensive questionnaire which would have lower compliance or a simpler questionnaire which would have higher compliance is one that was considered by the registry committee. Since high compliance was a priority, the registry chose a simplified questionnaire with the addition of a physician follow-up methodology. The following is the simplified questionnaire:

Did you experience any complications you believe may be due to the procedure (i.e. infection, illness, etc.)? If yes or maybe, please explain. _____Yes
 _____No _____Maybe

Comments: _____

Have you been diagnosed with any new illness since the procedure? If yes, please explain. _____Yes _____No _____Maybe

Comments: _____

¿Ha experimentado alguna complicación que usted crea puede haber sido causada por el procedimiento? (ej. infecciones, enfermedades, etc.) Si responde sí o tal vez, por favor explique. _____ Sí _____ No _____ Tal vez

Comentarios: _____

¿Ha sido diagnosticado con alguna nueva enfermedad desde el procedimiento? Si responde sí, por favor explique. _____ Sí _____ No _____ Tal vez

Comentarios: _____

If either question is answered “Yes” or “Maybe”, then the patient file is flagged for more detailed physician surveillance. This is considered a complaint that must be adjudicated. The registry coordinator must collect as much additional medical data as feasible. This additional information is then sent back to the clinical site by ICMS personnel to be reviewed by the treating physician who will classify the complication report as one of the following:

Relationship to Treatment: The relationship of the complaint to the treatment, broken down into procedural or stem cell related complications. This grading scale was adapted from the Adverse Event Reporting system used by the Department of Health and Human Services Office of Human Research Protections (OHRP)-<http://www.hhs.gov/ohrp/>.

Unlikely: Little or no chance that the complaint is related. More likely attributed to another condition (concurrent illness, progression of disease, medication related, etc...)

Possible: Association between treatment and complaint unknown, but complaint can't readily be attributed to another condition.

Probable: Reasonable temporal sequence between complaint and treatment, association seems likely based on physician's experience/medical knowledge.

If the complaint was felt to represent a probable complication, then that complaint was assigned an Intensity grade by the physician who adjudicated the complaint. If additional data is needed such as exam, the patient should be brought back for examination or diagnostic testing and that information obtained.

Intensity of Condition: This grading scale was adapted from the Adverse Event Reporting system used by the Department of Health and Human Services Office OHRP.

Mild: Requires no treatment, does not interfere with Activities of Daily Living(ADL's)

Moderate: Low level of inconvenience, may interfere with ADL's, treated with simple measures

Severe: Interrupts patient's ADL's, requires ongoing systemic drug therapy or other invasive surgical measures to treat condition.

Significant complications are defined as an impairment of health or a condition of abnormal functioning that is directly caused by stem cell re-implantation. This does not include direct procedural complications such as infection, inflammation, tissue damage physically caused by the re-implantation, or manipulation of tissue. While these procedural complications should be recorded and could be used in the overall assessment of procedure safety, they are not considered directly related to the stem cell line.

If there is a possible significant complication, after the physician contact, the physician will grade the complication as described in the section above (as a likely significant complication, side effect, or unlikely significant complication). If the likely significant complication is reported, this report must be brought to the attention of the registry medical director who will present this data to the Re-implant Registry Safety Committee. The committee will decide using a 2/3's vote super-majority methodology if the stem cell line should be placed into "Watched for Further Complications", "Restrict Use", or "Stop Clinical Use". If a 2/3'rd super-majority is not reached, then the stem cell line will remain in its current status.

The "Re-implant Registry Safety Committee" will consist of the registry medical director, and 5 other active members of ICMS chosen by the medical director to serve 2 year terms. These members must represent the major specialties represented by the registry use. For example, if the registry has cell lines being used for cardiology, orthopedics, plastics, and endocrine uses, specialists in each of these areas must populate the committee.

Registry Medical Director and Possible Actions

The registry will maintain the services of a medical director who is qualified to oversee all activities of the registry. If the treating physician determines that a likely significant complication has occurred, then the medical director will be notified to review the case. The registry medical director can take the following actions:

"Watch for Further Complications": The likely significant complication is determined to be a minor issue that is unlikely to cause significant patient harm if the stem cell line use continues. An example of where this action would be appropriate would include a patient who reports a possible angina which may or may not be related to the A-ASC re-implant. The angina has not lead to any significant permanent harm to the patient. Other examples include the worsening of a degenerative condition that would be expected to worsen over time.

If a stem cell line is placed into this category, it is flagged in the registry as having been placed in the "Watch for Further Complications" status. In this category, there are no restrictions on the stem cell line's use.

“Restrict Use”: The likely significant complication is determined to be consistent with a significant medical condition, but it is unknown if the complication represents an isolated incident and it is unknown if continued use of the stem cell line will lead to significant harm to other patients. As an example of when a stem cell line should be placed into the “Restrict Use” category, an A-ASC treatment is associated with a possible myocardial infarction (MI), however the patient was at high risk for MI prior to the treatment.

The stem cell line’s use may be restricted if a possible pattern of like significant complications is demonstrated. This determination is made by the Re-implant Registry Safety Committee. The committee will consider the risk versus benefit of the treatment. The committee will compare the risk versus benefit of the procedure versus the benefits/risks of other commonly acceptable treatments currently available. The stem cells related risk/benefit must be the same as or better than other comparable treatments being utilized for the disease.

The restriction will involve movement of the cell line grading to the prior clinical staging status. As an example, if the stem cell line was at “Clinical Grade” status, it will be moved back to LCCL status.

The cell line can be moved out of this status if there is no statistically significant association between the cell line use and the significant complication. The best practices for statistical association will be chosen by the Re-implant Registry Safety Committee.

“Stop Clinical Use”: The likely significant complication is determined by the Re-implant Registry Safety Committee to have a consistent statistical association with the cell line and continued use of the stem cell line is considered likely to lead to significant harm to patients. As an example of when a stem cell line should be placed into the “Stop Use” category, a stem cell line is clearly associated with multiple incidences of myocardial infarction in patients not usually considered at high risk for such events. Another example would be a stem cell line clearly associated with a much higher than expected prevalence of cancer diagnosis.

Use of the stem cell line is stopped through the registry until further notice.

To allow the stem cell line’s use through the registry, the appeals process described in detail below must be followed.

Normal Tracking Cohort

A goal of the ICMS registry will be to maintain a normal tracking cohort of untreated patients to allow comparison between this group and A-ASC treated patients. The goal is to compare A-ASC patient events (appearance of disease, death) to an untreated tracking cohort. The tracking cohort will be captured as follows:

For every five consecutive A-ASC treated by the same cell line and for the same disease, an untreated patient will be entered into the registry matched for age, sex, disease status. Co-existing disease information will also be collected.

The untreated patient tracked in the normal tracking cohort will be followed-up in the identical manner described above for patients treated with A-ASC's.

If a concern arises regarding the likelihood of a significant complication being related to the A-ASC treatment, comparison to the Normal Tracking Cohort is one method to determine relatedness. For example, if the annual prevalence of heart disease requiring hospitalization is 1% in the matched stem line/treated disease cohort and the A-ASC treated group shows a statistically significant 5% rate, the stem cell line may be causing the significant complication. A second example is the normal tracking cohort showing a rate of 0.5% for the annual reporting rate of a new cancer while a specific stem cell line shows a similar rate or a rate that is not statistically different from the normal cohort. As in any comparison of groups, valid statistical methods should be used to compare against the normal cohort. If the sample sizes prevent statistically significant comparisons from being used, then the medical director is instructed to show deference toward patient safety.

Epidemiologic approach to Inferring causal association between treatment and adverse outcome

While statistical comparison to a normal tracking cohort can assist in looking for complications that may be rarely occurring in large groups, it is not helpful in determining if individual cases may show significant complications. If the either the treating physician or the medical director has difficulty in determining the causation between the reported complication and the stem cell re-implant, modified Hill criteria of causation should be used, as follows:

Temporal Association: There must be a clear association between the timing of the stem cell re-implantation and the complication. For example, the significant complication should occur within a few hours to a few days after an A-ASC treatment. If the significant complication would need time to become clinically apparent, then there may be a temporal association if the complication is noted later.

Biologic plausibility: It must be determined that the complication could have been caused by the procedure. For example, if the patient fell ill with headaches one week following and A-ASC procedure and was found to have a cerebral glioblastoma the condition could not be attributed to the procedure. In contrast, an A-ASC treatment to the pancreas in a non-insulin dependent, type II diabetes patient that results in the immediate need for insulin management and evidence on MRI of tissue destruction in the pancreas would be a biologically plausible adverse outcome of the treatment.

Lack of Likely Alternative Explanations: There is no medically credible alternative explanation for the complication. As an example of lack of likely alternative explanations, an A-ASC treatment is suspected of causing new onset peripheral mono-neuropathy in an otherwise, young, healthy male. An example of a likely alternative explanation would be a degenerative disc patient with slow onset of increased pain after an A-ASC treatment to the disc that could be attributed to normal progression of the degenerative disease. Such cases would have to be evaluated on a case-by-case basis.

Challenge/Dechallenge: In some cases of multiple A-ASC treatment there will be complications that arise with each treatment and at no other time. The complication may be mild, e.g. urticaria, but should be noted regardless.

If all three of these criteria are met, then there is a likely association between the complication and the stem cell re-implant.

Appeals

If any interested party disagrees with the medical director's decision to change the use status of a stem cell line based on significant reported complications, the party can appeal in writing to the registry. The interested party and the registry will agree on three board certified specialists in the same specialty that typically manages the complication to determine (using the above criteria) if the significant complications are likely related to the stem cell line. If a majority of the specialists find that the complications are unrelated to the stem cell line, then the full use status will be restored in the registry. If the majority of the specialists determine that the stem cell line is the likely cause, the decision of the medical director stands and the use of the stem cell line remains restricted. The three specialists can also choose by majority vote to take the other actions as described above. The decision of the three specialists is considered final.

Multiple A-ASC Treatments

Many A-ASC therapies require multiple applications of stem cells. As a result, for multiple A-ASC re-implants, if the re-implant involves the use of the same stem cell line or lines in the same target tissue, the date for contacts will be the first re-implant date. If the re-implant involves a different stem cell line or a different target tissue (including the opposite side in the same tissue), a new series of follow-up contacts should be started. For example, if the first re-implant involved MSC003 for knee on 1/1/2010 with subsequent re-implants on 2/10/2010, and 3/1/2010, then the date used for contacting the patient for follow-up data would be 1/1/2010. However, if the same patient received a re-implant with HSC126 for cardiac on 4/1/2010, then a new registry entry would be made and a new complications tracking cycle begun. The same would hold true if the patient was re-implanted with MSC003 in the opposite knee or comes back later for a new treatment cycle in the same area. To be determined to be a new treatment cycle, there must be completion of the existing treatment cycle as described in the registry. For example, if the knee treatment discussed above was described in

the registry as occurring once a month for three months, then any additional treatment of that knee after that three month cycle would initiate a new contact cycle based on the first treatment in the second cycle.

Rules Regarding Patient Contacts and Clinic Reporting

The patient should be contacted a minimum of three times by phone, mail, or e-mail before the follow-up data is considered lost for that time point. If at the next consecutive time point, the patient does not respond to three additional, consecutive contacts, he or she can be considered lost to follow-up and subsequent contacts with that patient are not required.

All physicians and clinics participating in the registry must report any occurrence of new disease or complications to the registry. Patients will be informed by the treating clinic staff that they can contact the registry with any reports of complications between specified time points for data collection.

Importation of Existing Data into the Registry Eligibility

ICMS recognizes that stem cell lines may have developed outside of its re-implant registry and that making this cell line available to the registry may allow valuable treatments to be utilized by ICMS members. To be eligible for importation, the stem cell line must meet the criteria in the ICMS Clinical Guidelines (adult, autologous, minimal culture expansion, mononuclear cells without culture expansion, etc.).

To import cases, the number of cases treated to date will be accepted without clinical staging, as long as no significant stem cell related complications have been reported in the cases imported. This is further defined as no cases that would meet the definition as described above as a “Likely Significant Complication” related to stem cells. Cases must represent consecutively treated patients treated for that cell line definition as described in the ICMS clinical guidelines.

Procedures for Importation

To ensure that the registry has internal consistency, the ICMS approved complications tracking questionnaire needs to be answered by all patients being imported. The complications methodology as discussed in “Collection of Recipient Data” must be followed with all imported cases. The stem cell line will then be graded according to the clinical guidelines based on number of cases and duration of follow-up.

Collection of Study Specific Data

In addition to the standard data collected at specified time points, additional participant data may be collected as needed for a specific study. In these cases, any of the required additional data would be data that are available in the participant’s medical records. Examples of additional data that may be requested

for a specific study are more detailed clinical data at time of diagnosis or more detailed disease status data post re-implant.

Collaboration with Other Registries

ICMS will establish collaborative relationships with other re-implant registries. The goal of these collaborative relationships is to allow other registries to determine if clinical relationships exist between A-ASC re-implants and other types of treatment.

Studies Involving Data in the Research Database

Who May Request Access to Data

The data in the Research Database are available to researchers both within the ICMS and outside the organization. The ICMS defines the policies and procedures for release of data.

How Requests Are Reviewed/Approved

Any legitimate investigator may propose observational research studies to the ICMS. Research proposals are reviewed and approved by the scientific committee to ensure that the study is scientifically sound. If the study is scientifically sound, the committee Chair will perform an administrative review of the study protocol to ensure that it is within the limits defined in the database protocol and is covered by the participant's informed consent document for the database. Studies that fall outside the limits defined in the Research Database Protocol will be reviewed by the ICMS. In these cases, additional consent may be required from the participant. Once the study has been approved, the ICMS is informed of new studies that are added to the overall research portfolio. A data extract plan is prepared and the data necessary to conduct the study are extracted from the database into a study-specific research dataset. The data extract never includes individually identifiable data beyond treatment center and treatment and death dates. At no time is an individual investigator given the names of participants, or the identity of the center where the participant was treated. All relevant dates pertaining to a study are replaced with calculated time interval values.

Data Confidentiality

Access to all information in the database is tightly controlled with passwords and logins at multiple levels. Access to the database is limited to those employees who have specific job responsibilities related to the database. All paper forms containing participant information are filed in a locked area. Only those employees who have specific job responsibilities related to the files have access to the files. Patients are assigned an identification number (PIN) when they join the ICMS registry. The PIN contains no identifying information and is used to track all donor information in the database.

Identifying data is stored in a secure database that is totally separated from the database. These identifying data are never used for research purposes. The PIN

contains no identifying information within it. This number is used to track all information about the participant in the database. The identity of participants in the database is kept confidential at all times. Data released to investigators does not include identifying data such as birth date and location of treatment.

Issuance of Clinical Staging Letters

The Registry will be the final arbiter of clinical translation for staging cell lines as defined in the ICMS Clinical Guidelines. To review, these stages are defined as:

Pre-investigational Cell Line (PICL): No animal data is available. These cell lines should not be used in humans until animal data is available.

Early Investigational Cell Line (EICL): This is an un-established stem cell line being used in a new tissue where several animal models exist and do show efficacy and safety, but no human data exists. An un-established cell line can be used in early stage human studies where 5-10 patients are treated and followed for a minimum of 6-12 months. The physician should be able to document subjective and objective outcome measures. Once these criteria are met and no significant complications have been reported, the cell line moves to the next grade. Note that before LICL patients can be seen, a minimum of 6 months follow-up is required at EICL.

Late Investigational Cell Line (LICL): This is an un-established stem cell line being used in a new tissue and is being tested in humans in larger numbers, typically 20-50 patients who are followed for a minimum of 6 months. By the end of the LICL process, EICL patients for an un-established cell line have been followed for at least 12 months. The physician should be able to document subjective and objective outcome measures. Once these LICL criteria are met and no significant complications have been reported, the cell line moves to the next grade. To move onto treating ECCL patients, at least 20 of the LICL patients should be at the 6 month follow-up stage and have no complications.

Early Clinical Cell Line (ECCL): This is an un-established stem cell line being used in a new tissue and is being used for early stage clinical treatments in 50-200 patients. By the end of the ECCL process, EICL patients are in the 12-24 month follow-up range, LICL patients are in the greater than 12 month follow-up range.

Note an established cell line being used in a new tissue does not have to pass the PICL/EICL/LICL process and starts the staging here. The rationale is that for a homologous use, autologous cell line that has shown durable safety in one homologous tissue type, it is likely to show similar safety characteristics in other tissue types as well. As always, all cases are still entered into the re-implantation registry.

The physician should be able to document subjective and objective outcome measures. Once these criteria are met and no significant complications have been reported, the cell line moves to the next grade. To move onto treating LCCL patients, at least 50 of the EICL patients should be at the 6 month follow-up stage and have no complications.

Late Clinical Cell Line (LCCL): This is a stem cell line being used in a new tissue. By the end of the LCCL process, follow-up on EICL patients are in the 24-36 month range, LICL patients are in the 12-24 month range, ECCL patients are in the minimum 12 month range. A minimum of 100-250 patients have been treated in total, in various stages. Note an established cell line being used in a new tissue would have LICL patients in the 12 month plus follow-up status as well as ECCL patients in the 6 month plus follow-up status. The physician should be able to document subjective and objective outcome measures. Once these criteria are met and no significant complications have been reported, the cell line is considered “Clinical Grade” (CG), meaning that patients must still be entered into the re-implantation registry, but that there are no further restrictions on its use. To meet the standards of CG or an established cell line, all patients treated in the LCCL phase must be followed for at least 12 months and no significant stem cell related complications noted.

Note that small culture changes made in an ECCL/LCCL or “Established” stage cell line that has shown no complications and are in accordance with these guidelines (mimicking normal physiology) would allow the “new cell line” to begin in the ECCL stage. As an example, this might include a change of basal media from A-MEM to D-MEM, a change in oxygen tension in culture, or a change from serum free media to a documented, non-inductive FBS.

Mechanism for Cell Line Staging

Note that the ICMS Re-implantation Registry will be the final arbiter of the number of cases followed in each stage and if those cases have shown significant complications. When the clinic or practice believes it has the appropriate number of re-implant cases to move from one stage to the next, a letter will be sent to the ICMS registry requesting a review of the cases in the registry filed under that cell line as defined. The letter must include the registry cell line identifier, the existing clinical staging that the clinic has been operating under, and the requested new staging. The registry will review cases for significant stem cell line complications. If no significant direct cell line complications are detected and the appropriate number of cases has been performed with the specified follow-up, a letter will be sent to the practice or clinic indicating that the next stage for that cell line has been reached.

By way of examples of clinical staging, a stem cell line with 50 patients in 12-24 month follow-up and 10 patients in 24-36 month follow-up that has shown no complications would enter at ECCL status.