Physicians Should Bring Up Discussion of Advance Directives

Lessons From the Terri Schiavo Case.

Joseph J. Fins, MD

-Special Presentation:

It is important that advance directives are timely and that we, as physicians, have conversations with our patients about their wishes.

The Terri Schiavo case brought to public attention some tough issues that practicing doctors face at the end of life. This was a tragic case of a young woman who, back in the early 1990s, had a cardiac arrest that left her in a permanent vegetative state following anoxic brain injury. It was a case that gripped the nation and led to the involvement of the Florida legislature in 2003 and the United States Congress and President Bush in 2005. There was a dispute between her husband and her parents about whether to remove her feeding tube. It was a case that divided the nation and brought up the tension between the right to die and the sanctity of life. What lessons can we learn from this case? The most important lesson is to communicate preferences and make sure everyone is on board with what you, as the patient, want at the end of your life, which can be hard to do. We never think this type of situation can happen to us or to our patients. It is a defense mechanism that we must break down and grapple with. The idea of advance care planning, having an advance directive, and having a durable power of attorney for health care or a living will (depending on where you live) is a way to articulate your preferences and prevent the kind of conflict that occurred in the Schiavo case. However, even if you have an advance directive but do not talk to those left in charge, they’re often left with a moral quandary about the right thing to do, but the directive is a vehicle that can prompt and encourage the conversation. Doctors sometimes abdicate their role in fostering these discussions with patients, and we need to see this discussion as part of a preventive ethic. In my own practice, I bring this discussion up with patients and then revisit it during flu season. When I give a flu shot, it is a yearly reminder and is also an opportunity to see if the person that you’ve designated to be your health care agent/proxy is still the right person. These directives must be timely and we must have these conversations with our patients. Several studies going back to the early 1990s found that patients want to have these conversations, but if their doctor doesn’t bring it up, they don’t think it’s important, and it’s rare that a patient will come into the office saying, “I’d like to have an advance directive.” This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.

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print tag: ()
Distinguishing Between Advance Directive, Living Will, and DNR

Distinguishing Between an Advance Directive, Living Will, and DNR Order.

Joseph J. Fins, MD

-Special Presentation-

A DNR order is decided upon with a family member when the patient is close to death; however, advance care planning, an advance directive, living will, or health care proxy is done further in advance.

An advance directive is a mechanism by which you express preferences while you have the capacity. It is called decision-making capacity—the law might call it competence—to articulate a preference before you are unconscious or otherwise unable because of dementia to express a preference. Advance directives may include different kinds of documents. There are living wills in which you write down your preferences or you complete a form and no other person is involved. That simply articulates preferences without another individual, and that is good if you have no one to name. However, the preferable vehicle is when you actually name someone to represent you. It is called a durable power of attorney for health care. In most states, it is called a health care agent, and this person is authorized by completing a health care proxy form. This person can actually speak for you when you are no longer able to speak for yourself. Interestingly, this person is also compliant with the Health Insurance Portability and Accountability Act (HIPAA). Therefore, if you actually name a health care agent to represent you, there are no HIPAA concerns because this person has been authorized to receive all your medical information when you lose capacity, and, increasingly, that is becoming an issue. A do-not-resuscitate (DNR) order, in a way, can be an advance directive if patients make their own DNR and then lose capacity. Those wishes would then be ensconced and be important for family members and clinicians to respect. However, advance directives are a little more “upstream” because they are done before the eminent death. The timing of when people usually fill out DNR orders is usually very close to the dying process. Most of the time the order is not filled out by the patient but agreed to by a surrogate, that is, a family member or close friend who sees the patient’s loss of capacity, falling into unconsciousness, etc. The patient may have end stage renal disease or cancer as a marker of a dire prognosis, which triggers the DNR order. Advance care planning, an advance directive, a living will, or naming a health care proxy is done further in advance. It is something we all should have, not just as we face a terminal illness but also as we face life. This is a way to articulate your preferences in advance so that someone can represent you down the road. Because you can designate the advance directive, the health care proxy, or the agent ahead of time, it is important to follow up and revisit the timeliness and appropriateness of the designation on a yearly basis. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Role of Physicians With Dying Patients

The Role of Physicians With Dying Patients.
   - Special Presentation:

Sometimes saving lives is not possible, and the physician has an obligation to ensure a good death and to help patients make that passage in a comfortable and humane fashion.

Physicians want to preserve and save lives, but we also have to embrace the reality that we are all going to die. Sometimes saving lives is not going to be possible, and the physician has an obligation to ensure a good death and to help patients make that passage in a comfortable and humane fashion. We do not train physicians to think of palliative care, end-of-life care, and advance care planning as important obligations. That has improved in the last decade or so, but we are still death avoidant. We like to control, and we like to have sovereignty over things. It is hard to acknowledge that we sometimes fail. There was a classic article in the 1980s called "Death is Medical Failure," and we take death personally. Although it is hard to discuss these types of issues with our patients, it is important to appreciate the calm and the assistance you can provide—the reassurance to families and patients—by having these discussions. Another important issue is not just offering this reassurance to the patient but also to the family. In hospice care, we talk about the patient, but the unit of care is really the family. It is extremely hard for families who have not had conversations ahead of time. It is hard to know what people wanted if they had not been included in the conversation.

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Establishing Relationship With Patient's Family Important

Establishing Relationship With Patient's Family Is Important.

Joseph J. Fins, MD
-Special Presentation; ()-

It is a good risk management strategy to have established a relationship the patient's family member or health care representative prospectively, before the patient is in a critical or life-threatening condition.

What things are helpful in having end-of-life conversations with patients given the inherent difficulties? This discussion should be a part of routine care. Back in the early 1990s, there was a law passed called “The Patient Self-Determination Act.” I will often use this law as an excuse and say, “I’ve got to ask you about whether you have an advance directive.” Patients are uniformly grateful. When patients are hospitalized, we ask them about their next of kin in the event they will need someone to talk for them or, in fact, if they should die. Therefore, it is also important to bring in the people who have been designated to represent the patient to make sure they are the right people. Consider this “the audition” to make sure they are cast properly for the role. You want to make sure that, if the patient is a therapeutic nihilist and never wanted to receive aggressive treatment, the designated surrogate or health care agent is not someone who is going to have a hard time removing life-sustaining therapy. It is also important for the physician to establish a relationship with the surrogate ahead of time. If you have never met these individuals before, the first time you will meet them is when the patients are unable to speak for themselves. Even if the patients love you because you are their doctor, the family members or surrogates may view you as the doctor who couldn't take care of them, and suddenly they find that their loved ones are unconscious in the hospital on a ventilator. The family may wonder what you did wrong. If you have established the relationship ahead of time by showing your concern and meeting them in your office under less stressful situations, they have some confidence in you. It is a good risk management strategy as well to have established a relationship prospectively. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.

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Withdrawing Life Support

Joseph J. Fins, MD

When physicians must remove a patient from a ventilator, causing the patient's death, there is a difference between being responsible and being culpable.

Many physicians still believe that when they remove a ventilator, they are causing someone to die versus letting the dying process occur unimpeded. Let us do a thought experiment with two patients on ventilators. One has acute respiratory distress syndrome (ARDS) because of an underlying fatal condition. The other is on a ventilator because he had surgery. If the ventilator is removed in both cases, the patient with ARDS is going to die; the other is not. Removal of the ventilator is necessary but not sufficient for death to occur. Although we feel responsible, as we should, and although we should be concerned about physician obligation and responsibility, we are not causal in the simple act of removing the ventilator. Physicians must remind themselves of that every time they remove a ventilator, because they often believe they have actually caused the death. While they are responsible, they are not culpable. This is an important point. Other devices, such as automatic implantable cardioverter defibrillators, are more complicated, and the line about ongoing treatment and withdrawal may be a little blurry. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Mechanics of Withdrawal & Associated Treatments

Mechanics of Withdrawal and the Associated Treatments.

Joseph J. Fins, MD
- Special Presentation:

When patients must be removed from the ventilator, it may be necessary to sedate them and make them comfortable so they do not experience the distress in an anticipatory fashion.

The mechanics of withdrawal of treatment and some of the associated treatments that may be considered at the time of withdrawal blur the line between responsibility and culpability because many physicians do not want patients to suffer as the ventilator is removed. They do not want patients to have air hunger during their final moments, so they will sedate them or administer an opioid analgesia and an anxiolytic to make them more comfortable. People might criticize that practice and say that the physicians are hastening death. My sense of my moral obligation to patients is to protect them from harm (the old Latin saying, *primum non nocere*). In this situation, the harm is air hunger and distress. I prefer to sedate patients and make them comfortable so they do not experience the distress in an anticipatory fashion.

Another strategy that might help when family members are uncomfortable about the situation is to make sure there is a basal rate of opioid analgesia and anxiolytics. If the patients are in distress, you can add medication as you would for incident pain. However, if you start with a basal rate, you are taking the edge off. You are not hastening death, and you are guarding against distress. Physicians must understand that they are dealing with an inevitable death, and it should be a "good death." You are not causing the person to die. The underlying disease process makes it necessary for the ventilator, which must be removed, and for the pain medication. The physicians may feel more culpable, but the real sense of responsibility is dealing with palliative care issues and treating a potential and very real distress. This review is an abstract of an audio presentation from *Practical Reviews*. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Allow the patient's family to learn by doing and observing the condition of their loved one.

Experts on ethical issues such as Professor Nancy Dubler have written about mediation in a very nonjudgmental way. In her book co-written with Professor Carol Liebman entitled *Bioethics Mediation: A Guide to Shaping Shared Solutions*, they provide "the theory, practice, and hands-on tools needed to resolve the medical care disputes that regularly entangle patients, family members, physicians, and other health care professionals." For example, you can ask open-ended questions such as, "What do you understand your mom's situation to be?" When asking questions, in order to meet the families halfway, you can use time trials. What I like to do with families is not to come in and impose any type of an assessment but, rather, say something like, "Let's give it time." Time is a great elixir. For example, if we're talking about PEEP on a ventilator, I'll point out that the dial is on 15, which is a high number. I tell the family, "If your mom (or whomever) is going to start getting better over the next couple of days, that number is going to come down, and the oxygen levels are going to come down. Watch that dial over the weekend and then we can kind of meet again on Monday and we'll see how she is." On Monday, the family members may say, "Dr Fins, I was watching the monitor and it's still 15, so I don't think mom is getting better." What you have done is allowed the family to learn by doing and observing, and they may have come to the realization over a very hard 48 hours that the situation may not be remediable, in which case you have been able to align reality and expectations. Then you can shift the goals of care from things that are futile to things that have great utility, such as pain management and palliative care. This review is an abstract of an audio presentation from *Practical Reviews*. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.

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Coma is a self-limited state usually lasting a couple of weeks, but it is an "eyes closed" state of unresponsiveness. From coma, patients can move into complete recovery or can become brain dead. Patients are tested for this with a neurologic exam as well as an apnea test to see if they can breathe on their own. If not, it indicates loss of brain stem function, and they are declared brain dead. From coma, patients can also move into a vegetative state, which represents the recovery of the brain stem in the absence of higher cortical function. These patients have the ability to breathe on their own, have a functioning brain stem, and have sleep/wake cycles, and their eyes are open. This is described as a state of wakeful unresponsiveness. Although the eyes are open, there is no awareness of self, others, or the environment. The vegetative state is not described as persistent or permanent for the first 30 days after the event, after which the patients are considered persistently vegetative for up to 3 months after anoxic brain injury (eg, after a cardiac arrest), and persistent for up to a year after traumatic brain injury. At this point, 3 months for anoxia and a year for traumatic injury, patients are considered permanently vegetative. During that window of opportunity, before the vegetative state becomes permanent, patients can move into a minimally conscious state. This is a state of definite but episodic evidence of consciousness. Patients may follow something in a visual field or may say a word. The real challenge is that they do not always exhibit these behaviors; therefore, in between exhibitions of these behavioral manifestations of consciousness, they are hard to distinguish from patients who are vegetative. This review is an abstract of an audio presentation from *Practical Reviews*. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Vegetative States Represent Diagnostic Challenge

Vegetative States Represent a Diagnostic Challenge.
Joseph J. Fins, MD
-Special Presentation: ()-

There is a real risk of diagnostic error with patients in a vegetative state because patients who may be thought of as vegetative are, in fact, minimally conscious.

(Card 2 of 2) There is a real risk of diagnostic error with patients in a vegetative state because patients who may be thought of as vegetative are, in fact, minimally conscious. This is compounded by the fact that patients often move from an academic medical center after their event to a nursing home and are labeled as vegetative even though they are in a period of transition into a minimally conscious state. Once patients reach this state, there is an open-ended possibility for what is called emergence from the minimally conscious state in which patients actually have reliable, functional communication and are able to demonstrate these behaviors, not episodically but more consistently. A notable case recently reported was that of Terry Wallis, an Arkansas man who started speaking after 19 years in a minimally conscious state. He had been described as vegetative, but he continues to improve. There is also the case of a fireman, Donny Herbert, and a book was recently written about him, The Day Donny Herbert Woke Up. He awoke 9 years after being in a fire, probably with mostly traumatic brain injury with a degree of anoxia, and started speaking fluently. The real challenge is that once someone gets to the minimally conscious state, there is an open-ended possibility of recovery, although it decreases with time, and we do not know all the variables. It is important for clinicians to be aware that this is an emerging diagnostic nosology, and the error rates in assessment would be unacceptable in other domains of medicine. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Embryonic Stem Cells Can Provide Important Answers

Embryonic stem cells are of importance to scientists who are interested in studying not only development of the human body but also diseases that influence and attack the human body and diseases that have a genetic source.

Over the last several years, there has been an incredible amount of attention focused on human embryonic stem cell research and ethical issues that are related to it. Human embryonic stem cells have 2 interesting capacities: (1) they have the ability to self-renew in their undifferentiated state and make mass copies of themselves, and (2) they have the capacity to differentiate into various cell types such as blood, muscle, and nerve cells. Because of these unique capacities, stem cells are essential for understanding human development and human health. Embryonic stem cells first appear in 5-day-old embryos. At this stage, the embryo is called a blastocyst. Eventually, these stem cells will give rise to every cell type and every organ system in the embryo. Embryonic stem cells are interesting because they are capable of differentiating along each of the 3 germ layers (ectoderm, endoderm, and mesoderm), in addition to producing the germ cells (sperm and eggs). They are of interest to scientists because they are useful in helping to understand and answer questions. For example, for the developmental biologist who is interested in how a single-cell zygote forms a complex human being, embryonic stem cells may be used to answer fundamental questions of developmental biology regarding what happens postimplantation to the embryo in terms of development of these 3 lineages. They are also of great interest to scientists who are interested in studying not only development of the human body but also diseases that influence and attack the human body and diseases that have a genetic source. The proposal is to get stem cells that are genetically matched to people who carry some of these genetic diseases to see how their development progresses, and to see how differently development progresses for people who are afflicted with these diseases compared to people who don't have these diseases. This could answer some fundamental questions about developmental biology and root causes of certain diseases. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Moral Issues of Stem Cell Research Vary Worldwide

Insoo Hyun, PhD
Special Presentation:

The U.S. government policy states that there will be no federal funds spent toward stem cell research using stem cell lines derived from embryos after August 9, 2001.

In the United States, many ethical issues relate to the moral standing of preimplantation embryos from which scientists obtain stem cells. To date, the most common source of these pluripotent embryonic stem cells has been from remaining embryos donated through fertility clinics. There is controversy among the public and policymakers as to the moral status of 5-day-old embryos. In the U.S., the government policy favors one particular view on that question: 5-day-old embryos have a pretty serious moral standing, at least to the extent that they should not be used for research. On August 9, 2001, President Bush announced that there would be no federal funds, including National Institutes of Health (NIH) money, spent toward stem cell research using stem cell lines derived from embryos after that date. Every stem cell line that was created up to that point is eligible for NIH funding (or, the so-called “presidential lines”). Currently, there are about 15 lines in the world that qualify for NIH funding. From President Bush’s view, the life or death decision, so to speak, about these embryos has already been made, at least during the time of his pronouncement. He thought that it would be prudent to go ahead and use NIH money for those stem cell lines, but to not further support the destruction of any more embryos using government dollars. However, this is not the view in other parts of the world. There are other countries where the moral standing issue of the preimplantation embryo is not quite as fiery as in the United States. For example, in Israel, the preimplantation embryo has no protected moral or legal status; it gets its culturally protected status about 40 days after implantation. In South Korea, the same thing is true; it is only after implantation that the embryo is thought to have any kind of moral standing. The controversy in the United States seems to stem basically around a rather Judeo-Christian traditional view of the moral status of these research embryos, and it is not a view that is shared everywhere else in the world. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.

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Scientists Prefer New, "Healthy" Stem Cell Lines

Scientists Prefer New, "Healthy" Stem Cell Lines.
Insoo Hyun, PhD
-Special Presentation: ()-

Stem cell lines that are disease-specific can be created using donated embryos from fertility clinics where couples are undergoing embryo screening with preimplantation genetic diagnosis.

Many scientists will want to use recently derived stem cell lines, which are different from those derived prior to August 9, 2001, when federal funding for research of embryonic stem cell lines was stopped. All prior lines must be kept alive on mouse feeder cells, because at that time, it was not known how to keep them alive outside the human body. Since then, human feeder systems and feeder-free systems have been developed, and it is these latter systems that are more likely to be of possible future clinical use. Over time, the older stem cell lines could deteriorate and gain mutations. Scientists want to have a constant, steady new supply of fresh stem cells to be sure that current, cutting-edge research is being conducted on stem cells that are, from the genetic point of view, as healthy as possible. There has been a series of initiatives by different states to bring forward research funding in the absence of federal funding. New stem cell lines have been created recently that are disease-specific, which is another reason scientists want to use new stem cell lines. These lines come from fertility clinics where couples undergoing treatment are having their embryos screened for certain genetic diseases. Embryos determined to be affected by certain genetic diseases are donated to stem cell scientists. Recently, scientists in Israel attempted to derive a stem cell line that was genetically matched to fragile X syndrome, which is the most common known genetic cause of mental retardation. A couple participating in the study had a previous child with fragile X syndrome; they wanted to avoid having any future children with this disease. They underwent preimplantation genetic diagnosis through a fertility clinic to screen for affected embryos. One affected embryo was found and sent to a laboratory. The lab was able to successfully derive a stem cell line that was genetically matched to fragile X syndrome, allowing the lab to study the progression of this disease through various tissue systems in the human body in a way that had not been done before. The scientists realized that the genes responsible for fragile X syndrome were actually activated much earlier in the developmental process than anyone thought. In addition, researchers from Harvard were able to derive a stem cell line that was affected with spinal muscular atrophy disease. New animal models for this disease can now be set up to study progression and possible treatments. None of these disease-specific stem cell lines were available in 2001. When screening for a disease-specific stem cell line, new lines will need to be used; however, federal funds cannot be used. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Alternatives to Using Embryonic Stem Cells in Research

Insoo Hyun, PhD
-Special Presentation; ()-

Stem cells derived from skin is a new, exciting area of research because embryos are not involved in the creation of these stem cell lines.

Recently, much attention has been focused on stem cells derived from skin, which is exciting because embryos aren't involved in the creation of these stem cell lines. This new area of stem cell research is called induced pluripotent stem (IPS) cell research. In 2001, researchers from Harvard fused together embryonic stem cells and human skin cells. This enormous fused cell, with double the number of chromosomes, started to behave like an embryonic stem cell. Although this information is useless for therapeutic purposes, it is an interesting new look at the power of embryonic stem cells. Scientists from Kyoto, Japan, saw these findings and hypothesized there must be something about human embryonic stem cells, maybe some characteristics, that could induce pluripotency in normal skin cells (the ability to turn into any kind of cell type). Instead of fusing the cells together, if viruses could be used to insert genes that are very active in embryonic stem cells into normal skin cells, one at a time, you could possibly get the same effect as the fusion study but without the fusion. The Japanese researchers spent about 4 years painstakingly going through a number of genes that are extremely active in embryonic stem cells and inserting them, one at a time, and using a process of elimination to "whittle down" the essential ingredient needed to transform normal skin cells, such as in the fusion study, to behave like pluripotent embryonic stem cells. They succeeded in the mouse model a few years ago, then greatly improved upon that about 1.5 years ago. Last fall, the same team from Japan and the team from Wisconsin that initially derived and preserved embryonic stem cells in culture, the Thomson Lab, simultaneously published the human IPS cell studies in Science and in Cell. It was this huge advancement from the mouse model to the human model that initiated the interest in this new area of research. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.

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In the minds of many opponents of stem cell research, the need for embryonic stem cell research is pretty much now obviated by the discovery of human induced pluripotent stem (IPS) cells. But researchers, including those who conducted mouse IPS cell studies and human IPS cell studies, do not endorse that point of view. Reasons for having to do both IPS cell research and human embryonic stem cell research side by side are many. For one, IPS cell researchers argue that you have to use human embryonic stem cell research as a control group for IPS cell research to determine exactly what IPS cells can do. IPS cells and human embryonic cells, although very similar, are not identical. There are already >10,000 genetic differences identified between IPS cells and human embryonic stem cells. Human embryonic stem cells are an important comparison group, because they are the only stem cells that are not genetically manipulated to behave like stem cells. These pluripotent embryonic stem cells can give rise to complete human beings and all the various organ and tissue systems. So we know what they can do, just given the role in basic human biology. A pure case must be used to test what the substitute or the artificial version is capable of doing and how closely it can actually get to the embryonic case. Embryonic stem cells, of course, are still being understood. There is still a lot to learn. Our understanding of embryonic stem cells is by no means complete. Knowledge of both cell types has to proceed simultaneously to know exactly how closely IPS cells can get to human embryonic stem cells. IPS cells may never actually pan out in terms of being very beneficial for clinical purposes, so there are enormous opportunity costs if you don’t also keep alive the research program in human embryonic stem cell research. No one knows at this point which avenue of the science is actually going to have the most benefit for clinical applications later. Prudence says you must leave no stone unturned and proceed at the same time as much as you can in an ethical manner. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.

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Don't Disguise Research as Regular Clinical Care

Insoo Hyun, PhD

- Special Presentation: ()

It is crucial for clinicians participating with research teams to be absolutely clear as to whether they are wearing their clinician hat or their investigator hat.

There are several types of ethical issues that have been associated with human embryonic stem cell research that are unrelated to the embryo. Several interesting issues don't get the attention they should, including the requirements for ethical procurement of human materials to obtain stem cells. To obtain stem cells, embryos or gametes from fertility clinics are used. However, there is another way of getting stem cells, such as with induced pluripotent stem (IPS) cells, where you obtain body cells or skin samples from patients who have various diseases, some of which you may want to study. The majority of potential human materials donors for research are going to be patients in one way or another, who are seeking either fertility treatment or treatment for Parkinson's or some other disease. There is a great potential for confusion in the minds of people who are donating these human materials, whether or not they are being interacted with in the capacity of being a patient or as a research participant. It is absolutely crucial for clinicians participating with research teams to be absolutely clear as to whether they are wearing their clinician hat or their investigator hat. Consent issues are complex and are typically not given as much attention as that given to the preimplantation embryo. In other words, a clinician who is involved in procuring materials to be used in stem cell research would not inadvertently make research activities appear as if they are part of someone's clinical care. The clinician should not ask the patient to allow harvesting of additional oocytes during her in vitro fertilization treatment, because the patient might feel compelled to be involved in that research, even when she didn't want to be. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
When Is the Best Time to Ask for Embryo Donations?

When Is the Best Time to Ask for Embryo Donations?
Insoo Hyun, PhD

-Special Presentation:

Some people think there would not be much undue pressure on couples seeking fertility treatment for treating physicians to suggest the idea of donating remaining embryos to research, but others are skeptical of that idea.

If a fertility doctor is part of a research team that is trying to obtain embryos for research, possible pressure to allow harvesting of remaining oocytes may occur during the first informed consent encounter with the person seeking fertility treatment. Some would argue that the best time to bring up the idea of possibly donating embryos for research would be after the couple has made a decision that they would discard remaining embryos. However, the field of bioethics is divided on this issue. Some people think there really wouldn't be very much undue pressure on couples for the treating physician to suggest the idea of donating remaining embryos to researchers, but others are a little more skeptical of that idea. It has been the general consensus, at least according to guidelines in Canada, that you have to have a 2-step consent process. One is to ask couples what they might want to do with remaining embryos before they create the embryos, then ask again after the embryos have been created. Empirical data have shown that people sometimes change their attitudes about the embryos once they have them. So having a 2-step procedure might help maximize clear thinking about the issue in terms of the patient's own values and what they want to do. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Blanket Consent May Not Be Best Choice

Insoo Hyun, PhD

With stem cell research, there is going to have to be animal testing before human testing.

During the consent process, subjects who are donating human materials should be made aware of possible uses of stem cells. Researchers can't do too much in terms of disclosing what could happen, because it is really unclear what could happen. There are several possible future uses of stem cells, which nobody anticipates at the current time. This could be a major issue with having blanket consent for general, open-ended uses of stem cells derived through human materials, albeit a partial or a full genetic match, as in the case of induced pluripotent stem (IPS) cells. The best that can be said is there could be other researchers who use these stem cells for their own research, for which their purposes are not known at this time. All we do know is that they have to be approved through local research-approving bodies. They could even be used for commercial purposes. There are some interesting issues about whether a couple or a person gives blanket consent for all possible future uses of human materials. Is this kind of consent meaningful? There is division in the field of bioethics on that point. One likely use for stem cells will be in laboratory animals. To classify stem cells as being truly pluripotent (truly capable of forming along all 3 germ layer lineages), stem cells will be placed into immunodeficient mice to determine, about 2 or 3 months after transplantation, whether or not they will form teratomas. If they can do that in vivo, then it is a pretty good indication that stem cells have the capacity biologically to form along the lines of all 3 germ lineages in the human being. Therefore, in the very beginning, there is going to have to be an animal test using human stem cells, and some may not be very happy with that idea, but this needs to be disclosed. Prior to any kind of testing in humans for stem cell-based therapies, the Food & Drug Administration (FDA) requires that the stem cell-based therapy be tested by transferring stem cell-derived cells into 2 different animal models to test for safety and efficacy. If stem cells are to be used for eventual clinical research, the teratoma assay must be done first in an animal model very early on to assess whether or not they have pluripotency. Then a second and third test should be done (the Proof of Principle test and the safety and efficacy test for the FDA). These involve transferring stem cell products that are being developed for clinical trials into an animal model, most likely a rodent, and then into something a lot closer to a human, perhaps a nonhuman primate. Therefore, if using the stem cell line eventually for some kind of clinical research, there are at least 3 animal tests that should be done, and some people may not be comfortable with that idea, especially the latter kind, which involves higher-order animals. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Headlines Announce Stem Cell Tx Soon Available

Insoo Hyun, PhD

- Special Presentation: 

If a stem cell-based treatment using embryonic stem cells is approved by the Food & Drug Administration, there will also be the issue of off-label uses.

Headlines seem to announce that stem cell therapies are going to be available in really short order. Practicing clinicians should be concerned about being able to counsel patients who are desperate. The worst of this may be stem cell tourism, although this term doesn't really quite capture all the concerns that people have. One concern is that desperate patients may seek out unproven therapies using stem cells claimed by people who may or may not know what they're doing and who will charge patients a lot of money to travel to their clinic to get their stem cells. Most likely, they are bone marrow stem cells that are injected right back into the patient at various injury sites. One way in which clinicians might be impacted by stem cell research, at least this kind of activity claiming to be stem cell research and stem cell therapy, would be to counsel patients as best as possible about other, more proven alternatives for treatment. There are other ways in which clinicians might be brought into the stem cell research arena. Maybe the researchers' specialty is with a particular disease, so they want to get cells from Parkinson's patients or diabetes patients who are under the clinician's care. These patients will then be asked to donate cells for an induced pluripotent stem (IPS) cell study. Maybe the clinician is working in a fertility clinic, and his patients are approached by a stem cell team that wants to use remaining embryos for their own research, or the clinician himself may be approached by a stem cell team and is asked for his cooperation. The clinician may need to be involved by having to counsel patients about alternatives when they interested in the issue of outside stem cell treatments. If a stem cell-based treatment using embryonic stem cells is approved by the Food & Drug Administration (FDA), there will also be the issue of off-label uses. If the FDA approves a certain drug or device for a particular use, it is typically understood that clinicians can exercise their own judgment and may decide to use the FDA-approved drug or device for that purpose or for some other off-label purpose, if they think it might do the patient some good. In the imaginary scenario of a stem cell-based product approved by the FDA, one concern that some bioethicists have is that clinicians may then be approached, either by patients or peers, with the possibility of providing an off-label use of that stem cell therapy. From the point of view of stem cell researchers, this may not be the safest or wisest move, but it is really up to the clinician to decide what is best in that circumstance. A database about what is safe and effective will be emerging over time, as we gain more and more experience with cell-based interventions. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Getting Info on Stem Cell Research and Its Oversight

The National Academy of Sciences has recommended that Embryonic Stem Cell Research Oversight (ESCRO) committees be in place to help advise on the acceptability and permissibility of certain research protocols in using embryonic stem cells.

There is currently a great push for good adverse event reporting in clinical translational research involving stem cells and their byproducts. Clinicians will be called in to be a part of this reporting system. They will see patients, whether under their care or through the care of another clinician, who received a stem cell-based treatment and are having an adverse event. They will be called upon to report these adverse events, so that people on the research committee can get a better idea of what is happening and what possible consequences there could be for this research. The Food & Drug Administration is one type of oversight for this research, but the National Academy of Sciences in the United States has recommended institutional oversight at the level of all institutions in which this kind of research is occurring. This could be basic research with embryonic stem cell derivation, or it could be animal testing with stem cell research. For any institution in the United States, whether privately or publicly funded, the National Academy has recommended that embryonic stem cell research oversight (ESCRO) committees be in place to have special expertise on board scientifically, ethically, policy-wise, and legally, to help advise on the acceptability and permissibility of certain research protocols in using embryonic stem cells. It is not a law, it's not a requirement, but it is a general recommendation by the National Academy of Sciences. To date, most major institutions conducting this research have taken that recommendation very seriously and have set up their own ESCRO committees alongside the normal institutional review boards and animal care groups, to have oversight over this new area of research. There are web sites affiliated with various patient advocacy groups, such as the Juvenile Diabetes Research Foundation, the Alzheimer's Association, the Michael J. Fox Foundation, the Christopher Reeve Foundation, and various patient advocacy groups that put out well-balanced and informative background information about stem cells and their applicability to diseases in question. There are scientific organizations such as the American Association for the Advancement of Science, the International Society for Stem Cell Research, and the National Academy of Sciences, each of which have nice summaries of stem cell state of the science, current status in research, limitations, and background information about stem cells. This review is an abstract of an audio presentation from Practical Reviews. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.
Failure to Diagnose Minimally Conscious State

Affirming the Right to Care, Preserving the Right to Die: Disorders of Consciousness and Neuroethics After Schiavo.

Fins JJ:
Palliat Support Care; 4 (June): 169-178

Manifestations of minimally conscious state can be episodic and require longitudinal appraisal.

The epic life and death of Terri Schiavo was characterized by rhetoric, uninformed or marginally informed opinions, political machinations, and power struggles. It and comparable antecedent cases have revealed some urgent needs in our profession's understanding and care of patients with the complex diagnoses of disorders of consciousness. If we ignore developments in neurological science appertaining to the nature of these disorders, and if we fail to increase our comprehension of the problems--and opportunities--in the care of these patients, we will fail to save patients who might improve. We should strive both to preserve the right to die for those who are beyond rational hope, while affirming the right to care to those who may yet benefit from neuroscience. We can begin articulation of a palliative neuroethics of care. There are definitive medical criteria for what constitutes the vegetative state, and the differentiation of a persistent vegetative state from a permanent one. It is not a choice based on values but on specific criteria. In contrast with the vegetative state, the minimally conscious state (MCS) is a state of severely altered consciousness in which there is minimal but definite behavioral evidence of self or environmental awareness. MCS patients may say words or phrases, gesture to get attention, and may show evidence of memory, attention, and intention. MCS patients also may track with their eyes. These evidences may be episodic, inconstant, and inconsistent; therefore, longitudinal observation is critical. Ms Schiavo exhibited none of the criteria of MCS. Her diagnosis was, clearly, permanent vegetative state. The risk of misdiagnosis is obvious, and unacceptably high, but crucial. Insufficient periods of observation of episodic behavior may predispose to misdiagnosis. There may even be subtle pressure by organ procurement personnel to urge evaluation of patients by the Glasgow Coma Scale, fixing on low scores as indicators of eligibility for organ harvest. Economic pressures are real and are complicated by nosologic ambiguities. Lack of continuity of informed care after discharge may contribute to missed recognition of MCS rather than persistent vegetative state. These structural barriers to diagnosis can be overcome only by a change in the mindset about the needs of patients and families whose lives have been changed by severe brain injury.

Reviewer's Comments: The author delineates, clarifies, and examines the importance of differentiating the vegetative state (persistent vs permanent) from MCS.

Additional Keywords: Misdiagnosis

print tag: (Joseph J. Fins, MD) Division of Medical Ethics New York Presbyterian-Weill Cornell Medical Center 435 E 70th St, Ste 4-J New York, NY 10021
**Morally Complex Patient-Proxy Relationship**

*Contracts, Covenants and Advance Care Planning: An Empirical Study of the Moral Obligations of Patient and Proxy.*

Fins JJ, Maltby BS, et al:

*J Pain Symptom Manage;* 29 (January): 55-68

"Do everything" instructions are met with more discretionary moral judgment than "do nothing" instructions.

The authors of this article develop the thesis that the patient-proxy relationship exists along a continuum, from **contractual**, in which the proxies follow explicit instructions, to **covenantal**, wherein the proxies accept more discretionary responsibility in making decisions. Ancillary considerations include the "valence" of initial patient instructions, eg, "to do nothing" or "to do everything," and, additionally, the quality of information available to the proxy. Prior speculation by these authors had begun the exploration of this relationship. They surveyed 50 patient-proxy pairs and 50 individuals who had been proxies for patients who had died. With the use of structured vignettes representing 3 separate disease states, the authors assessed whether the participants believed that the proxies should follow instructions explicitly--contractual relationship--or a discretionary, covenantal relationship. Responses were graded on a modified Likert scale. When making moral judgments, patients and proxies think inductively and in context. Neither patients nor proxies considered deviation from prior instructions to be a violation of the patient's autonomy. Rather than adhering to narrow concepts of self-determination by the patients, the participants made nuanced and contextually informed moral judgments. Instructional valence was likewise assessed. "Do nothing," the "negative right to be left alone," was more likely to be explicitly followed if the prognosis was grim or even equivocal. In contrast, "Do everything" instructions were met with discretionary moral judgments. In such cases, patients and proxies might have decided to go against initial instructions, to act covenantally, and even perhaps to choose to withdraw life support. In decision making, it became clear that there are significant contributions to be made in consideration of such variables as disease trajectory (cancer, stroke, and congestive heart failure), the clarity of prognosis, instructional valence, and the quality of patient instructions. Clarity in communication emerged importantly.

**Reviewer's Comments:** The data from this study imply that the delegation of patient self-determination is morally complex. Advance directives should take the exercise of patient autonomy into account, as well as the interpretative burden assumed by the proxy. The findings have implications for patient directives as well as the legal norms that guide advance planning.

(print tag: (Joseph J. Fins, MD) Division of Medical Ethics Weill Medical College of Cornell University 525 E 68th St, F-173 New York, NY 10021)
Criteria for Minimally Conscious State

The Minimally Conscious State: Definition and Diagnostic Criteria.
Giacino JT, Ashwal S, et al:
Neurology; 58 (February 12): 349-353

Patients in a minimally conscious state show behavioral evidence of consciousness but are unable to reproduce such behavior consistently.

There is a subgroup of patients with severe alteration of consciousness who do not meet accepted diagnostic criteria either for coma or vegetative state (VS). Such patients demonstrate inconsistent but discernible evidence of conscious awareness of environs or self. It is important to differentiate these patients (for whom the term minimally conscious state [MCS] is evident) for diagnosis, prognosis, treatment decisions, and medicolegal considerations. This article reflects the results of a series of multidisciplinary meetings held by the Aspen Neurobehavioral Conference. The intent was to establish evidence-based guidelines for the diagnosis, prognosis, and management of MCS, but there were insufficient data to establish evidence-based guidelines. However, the conference was able, by review of the literature, to formulate a consensus-based case definition with behaviorally referenced diagnostic criteria in order to establish a foundation of current knowledge and facilitate future empirical investigation. There were 9 meetings of the workgroup, representing the fields of bioethics, neurology, neurosurgery, physiatry, nursing, and allied health. Coma patients have complete failure of the arousal system with no spontaneous eye openings and are unable to be roused by application of vigorous stimuli. VS is characterized by the complete absence of behavioral evidence for awareness of self or environment. There is preservation of the capacity for spontaneous or stimulus-induced arousal, evidenced by sleep-wake cycles. Some patients, however, have severe alteration in consciousness yet have neurologic manifestations that do not meet established criteria for VS (or coma). Such patients show behavioral evidence of consciousness but are unable to reproduce such behavior consistently. This is MCS, which is differentiated from VS by the preservation of conscious awareness. To make a diagnosis of MCS, limited but discernible evidence of self or environmental awareness must be demonstrated on a reproducible or sustained basis by one or more of the following: following simple commands; giving a yes/no response by gesture or word; intelligible verbalization; purposeful behavior such as smiling, vocalization or gestures in response to questions; reaching for objects and demonstrating a clear relationship between the object located and the reach; touching or holding objects in a manner that accommodates the size and shape of the object; and/or paired eye movements or sustained fixation occurring in direct response to moving or salient stimuli. Emergence is characterized by functional interactive communication and/or functional use of 2 different objects.

Reviewer's Comments: MCS needs to be diagnosed accurately. The Aspen Neurobehavioral Conference was unable to find adequate evidence-based guidelines. This article reflects a consensus-based case definition.

print tag: (Joseph T. Giacino, PhD) JFK Johnson Rehabilitation Institute 2048 Oak Tree Rd Edison, NJ 08820
A Palliative Ethic of Care

Medical Futility.
S. Donald Palmer, MD
-Special Presentation:

Palliative care is a form of active care, using appropriate modalities.

Dr Joseph J. Fins, bioethicist at Cornell, has written Palliative Ethic of Care: Clinical Wisdom at Life's End. This book is reviewed by Dr Miller Davis at the Cleveland Clinic. If there were a silver lining about the physician-assisted suicide debate, it was that this tension helped catalyze the palliative care movement," writes Dr Fins. People on opposing sides of the issue of physician-assisted suicide in the case of the terminally ill, as well as the Supreme Court, agree that palliative care is a reasonable alternative. A first section on "Death and Dying in Context" is followed by a section entitled "Goal Setting: A Strategy for Effective Palliative Care," which addresses ethical issues at the end of life. Included in the book is a useful tool for Goals of Care Assessment. Barriers to effective palliative care are both patient-centered and physician-centered, reflecting the fact that we have had little experience, though lots of opportunity, to consider these goals. We still think in the framework of attempting to return the patient to his or her premorbid state, and we are insufficiently cognizant or experienced in establishing a changed focus of care; we allow it to remain unaddressed. This situation may culminate in a "conflict over futility...the antithesis of palliative care." Transitioning toward appropriate goals of palliative care requires good communication between patient, family, and physician. Goal setting overcomes the routinization of decision-making regarding care, which contributes to inappropriate (not wished for) escalation of care that was not desired.

Reviewer's Comments: The book discusses, in detail, 8 areas for consideration: advance directives, proxy and surrogate decision making, prognostication, breaking bad news, use of opioids, the ethics of double effect, family dynamics, and effective communication. The Goals of Care Assessment Tool can minimize miscommunication and facilitate articulation of preferences and goals for end-of-life care. Palliative care is properly considered and practiced as a form of active care, using appropriate modalities and not simply abandonment. Dr Miller Davis (book review: N Engl J Med 2006; 354 [April 13]: 1653-1654) suggests that the term "palliative medicine" may more accurately reflect the focus.

Reference: Medical Futility. In Fins JJ. A Palliative Ethic of Care: Clinical Wisdom at Life's End. Sudbury, MA: Jones & Bartlett Publishers, 2006. pp 77-90. This review is an abstract of this publication.
Is Deactivating an ICD Ethically Acceptable?

Within You/Without You: Biotechnology, Ontology, and Ethics.
Sulmasy DP:
J Gen Intern Med; 23 (January, Suppl 1): 69-72

Implantable cardioverter defibrillators are regulative interventions and never become "self."

Is the deactivation of an implantable cardioverter defibrillator (ICD) in a fatally ill patient, in severe pain, participating in the killing of the patient, or does it come under the scope of withholding or withdrawing treatment? The author examines several representations on each side of this current question. Cardiologists and patients alike appear to consider the use of an implantable cardiac defibrillator (ICD) to be a "bridge" that one crosses with no possibility of return. Some consider deactivating an ICD to be ethically different from discontinuing other forms of treatment. It is internal, is continuous, and may be of long duration. These proponents suggest, for example, that an external defibrillator can be more acceptably deactivated than an ICD. The term "biofixture" has been coined to describe technologies that have become part of a person. An ICD is not a biofixture. It does not become part of the body in the same sense as a transplanted kidney. No one opposed to euthanasia should think, on this basis, that it is impermissible to deactivate an ICD, since it has not become part of the body. Or is there something intrinsic to the nature and function of ICDs that causes some to consider them differently? Suppose, however, that a patient with an ICD (which he or she has had for many years) now is cachectic with a painful, terminal malignancy, along with recurrent attacks of ventricular fibrillation requiring innumerable jolts. Surely it would be permissible to deactivate the disruptive and ultimately pointless ICD under those circumstances. Thus, deactivating the ICD would appear to be comparable to withholding it. Does the fact that it operates intermittently rather than continuously pose any different consideration? It would appear not. May a patient, in great pain and with death imminent, who has had an ICD for several years, have the ICD inactivated despite its long history? Compare the patient who has been ventilator-dependent for 30 years, who after so many years feels that enough is enough. Duration is not a cogent consideration. Some therapies are regulative, ie, they coax the body back toward homeostasis; some are constitutive and take over a function that the body can no longer provide. ICDs are regulative. Regulative interventions never become "self." Some interventions are replacements, and others are substitutive. The closer an intervention comes to being replacement, the less morally appropriate it would be to withdraw it.

Reviewer's Comments: The author clarifies the reasoning vis a vis the ethics of deactivating an implantable cardiac defibrillator. The ethical issues, though weighty, appear to be clear.

Additional Keywords: Ethics

print tag: (Daniel P. Sulmasy) Dept of Ethics St Vincent's Hospital-Manhattan 153 W 11th St New York, NY
Stem Cell FAQs

_Frequently Asked Questions About Stem Cell Research._

S. Donald Palmer, MD

-Special Article Review; ()-

Embryonic stem cells make up the inner cell layer of the blastocyst.

Stem cells, the primordial cells for all body tissue, are as yet undifferentiated but subsequently will specialize under proper conditions. They are self-sustaining and will replicate themselves for long periods. This constitutes a stem cell line. Embryonic stem cells make up the inner cell layer of the blastocyst, the embryonic hollow sphere occurring about 5 days after conception. They are totipotent, capable of making any specialized cell. Pluripotent cells can make a large number of different types of body cells. Stem cells occurring in various adult tissues, e.g., bone marrow, are multipotent; they have the potential to form many cell types. Stem cells also can be obtained from newborn umbilical cords, baby teeth, and in amniotic fluid. Stem cells have the potential to generate healthy and functioning specialized cells to replace diseased or dysfunctional cells. They thus possibly can function as micro-transplants, conceivably even relieving the shortage of donors for organs, if such problems as tissue rejection and integration of function can be overcome. Stem cells currently commonly used in therapy include only hematopoietic stem cells in the marrow, precursors of all blood cells. The clinical potential for stem cells has been demonstrated in the treatment of diabetes and advanced renal cancer, but only in a very limited number of patients. New treatment applications are being tested in liver disease, coronary disease, autoimmune disease, lupus, and others. Therapeutic cloning is to be distinguished from reproductive cloning. In the former, the embryonic development is allowed to go only to the blastocyst. There is a fair consensus opposed to reproductive cloning, in which a new individual is developed. Experiments have been done in transplanting hematopoietic stem cells into fetuses with hematopoietic genetic problems, including immunodeficiency, thalassemia, and inborn errors of metabolism. Fetal neural stem cell derivatives have been transplanted to replace damaged cells in Parkinson's disease. Only 22 cell lines are currently available that are eligible for federal funding. Under current law, any scientist receiving federal funds is precluded from generating additional human embryonic stem cell lines. Further information can be obtained from the International Society for Stem Cell Research web site, www.isscr.org, and the National Institutes of Health web site, stemcells.nih.gov.info.basics.

**Reviewer's Comments:** This article is a comprehensive, multidisciplinary review of stem cell research, the relevant ethical considerations, and the potential.

**Article Reviewed:** The International Society for Stem Cell Research (ISSCR). Frequently asked questions about stem cell research. Available at http://isscr.org/public/faq.htm. This review is an abstract of an audio presentation from *Practical Reviews*. If you do not have access to this presentation and would like to purchase a copy, please call 1-800-633-4743, email service@oakstonepub.com, or write Oakstone Medical Publishing, 100 Corporate Parkway, Suite 600, Birmingham, Alabama 35242.

**print tag:** ()
ISSCR Guidelines Call for Specialized Oversight Process

The ISSCR Guidelines for Human Embryonic Stem Cell Research.

Daley GQ, Ahrlund-Richter L, et al:
Science; 315 (February 2): 603-604

In vitro culture of human embryos beyond 14 days or formation of the primitive embryonic streak is proscribed.

Research on human embryonic stem cells can be complicated by differing cultural, political, legal, and religious perspectives. The International Society for Stem Cell Research (ISSCR) is the principal scientific society for stem cell scientists. It transcends institutional, regional, and national boundaries. In recognition of the need for scientists to act transparently, to serve the public interest, and to preserve the public trust, the ISSCR convened a task force to formulate guidelines for human embryonic stem cell (ES) research. The guidelines were written by an international team of scientists, ethicists, and legal experts. The guidelines are related to derivation and use of pluripotent human ES lines and do not encompass adult somatic cell research or research on human embryo or fetus. The ISSCR calls for a specialized oversight process to complement existing institutional review boards. The key elements are to eliminate redundancy and allow flexibility for various oversight mechanisms in differing countries. It differs somewhat from the ES cell research oversight committees proposed by the U.S. National Academy of Sciences. The ISSCR guidelines prohibit the following: (1) all experiments lacking compelling scientific rationale, or that raise shared ethical concerns, in particular, human reproductive cloning; (2) in vitro cultures of human embryos beyond 14 days, or formation of the primitive embryonic streak; (3) and interbreeding of animals likely to harbor human gametes. The ISSCR Task Force reasoned that experiments with sound scientific rationale that respect the 14-day limit are permissible if they pass a thorough stem cell research oversight review. There must be contemporaneous and explicit consent from all somatic cell donors. For embryos generated with donated gametes, ISSCR guidelines require explicit consent from both gamete donors. There were varied opinions relevant to compensation to the donor, but all agreed that direct expenses should be covered. Donors of oocytes are compensated up to $5000 in some places; others believe that the sense of altruism should prevail, with no consensus reached even for provision of a modest honorarium. Agreed upon, though, is the principle that compensation of direct expenses and/or other financial conditions could not constitute undue inducement. It was agreed, also, that researchers must make their materials readily accessible to the biomedical research community.

Reviewer's Comments: The guidelines call for journal editors and granting agencies, as a stipulation for publication or funding, to require researchers to attest to compliance with the ISSCR guidelines, or an equivalent set of regulations. To facilitate use of these guidelines, sample documents can be obtained.

Additional Keywords: ISSCR Guidelines

print tag: () Not available.
Pure Altruism Cannot Be Required as Sole Motivation

Fair Payment or Undue Inducement?

Hyun I:

*Nature*; 442 (August): 629-630

The Institutional Review Board Guidebook of the Department of Health and Human Services states that compensation is permitted as long as local review boards ensure that volunteers are fairly recruited and paid according to community standards for this activity.

The U.S. National Academy of Sciences and others take the position that women who undergo hormonal hyperstimulation for production of oocytes to be used in embryonic stem cell research may be compensated for direct expenses only. The author proposes that this position is ethically unwarranted and is unfair to oocyte donors. Women who donate oocytes for embryonic stem cell research should also be compensated for their time, effort, inconvenience, and discomfort. The International Society for Stem Cell Research (ISSCR) recently released draft international guidelines that do not expressly limit remuneration to women's direct expenses. Comments are being sought on their web site (www.isscr.org/scientists/guidelines.cfm). Oocyte providers are healthy research volunteers. It is common practice for healthy volunteers to be compensated for the inconvenience of participating in medical research at such places as the National Institutes of Health. The Institutional Review Board Guidebook of the Department of Health and Human Services states that compensation is permitted as long as local review boards ensure that volunteers are fairly recruited and paid according to community standards for this activity. These common practices belie the assumption that a ban on compensation is ethically indicated. There are several considerations, but the crux of the issue is that if it is ethically and legally permissible for women to offer their oocytes for stem cell research, and if it is also ethical to offer compensation to other, comparable healthy volunteers for research involving procedures such as bronchoscopy or bone marrow donation, then there is strong presumptive reason to extend the same ethical principles to oocyte donors. Oocyte procurement is demanding of women's time and energy, especially when done in an ethically strict and reasonably safe manner. Women may have to devote as many as 40 cumulative hours to provide their oocytes for research.

Reviewer's Comments: There are no convincing negative consequences to remuneration. Undue inducement is unlikely, and it can be prevented. The health and appropriateness of volunteers can be scrutinized. It has not been shown to take advantage of the vulnerable. The commodification argument is unconvincing for 2 reasons: the doctrine of informed consent requires the decision to ultimately reside with the volunteer, and compensation levels would be set by review boards and not by the free market. Pure altruism cannot be required as sole motivation.
Use of products that are banked, transported, or processed in facilities with other cellular or tissue-based products increases the rate of contamination.

The Food and Drug Administration (FDA) has jurisdiction over the production and marketing of any stem cell-based therapy involving the transplantation of human cells into patients. The FDA recently issued regulations providing an appropriate structure for a wide range of stem cell-based products. Scientists need an increased awareness of questions that must be answered before clinical use of stem cell-based products can occur. The authors outline current applicable concerns. Although stem cell treatment actually occurred with the first bone marrow transplantation, this focus is on a subgroup: use of embryonic pluripotent or adult multipotent stem cells in order to create human tissue ex vivo for transplantation into patients with medical conditions caused by degeneration or injury of cells, tissues, and organs. In some cases, there may be no stem cells in the final product. In certain cases, multipotent cells may be transplanted to generate terminally differentiated cells. The term "stem cell-based products" encompasses these germane activities. An FDA category defined as "articles containing or consisting of human cells or tissues intended for implantation, transplantation, infusion, or transfer into a human recipient" encompasses these regulations. Any stem cell-based product that contains cells or tissues that are "highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes" would also be subject to regulation. Before filling out a New Drug Application, the applicant should be able to adequately address the following: (1) Is there a risk of donor transmission of infection or genetic disease? (2) Does the cell or tissue processing pose a risk of contamination or damage? (3) What are the types of cells and what are the purity and potency of cells in the final product? (4) Will the product be safe and effective in vivo? There must be additional screening for infection or genetic disease transmission for tissues that pose a particular risk, such as viable leukocyte-rich or reproductive cells. In all cases of stem cell or embryo donation, donor blood samples should be archived for potential subsequent use. Use of products that are banked, transported, or processed in facilities with other cellular or tissue-bank products increases the rate of contamination. Another safety concern is the potential alteration in the genetic makeup of cells. It is essential to determine where the cells will go after transplantation and what their functions will be. Concern must be exercised regarding tumorigenesis. As scientists conduct research on stem cells, they must be aware of relevant regulations.

**Reviewer's Comments:** The authors clearly outline relevant questions pertaining to regulation of stem cell-based therapies. They stress the necessity for archiving donor samples.

**Additional Keywords:** FDA Regulation

**print tag:** ( ) Not available.
IPS Cells Do Not Replace Human Embryonic Stem Cells

New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells.

Hyun I, Hochedlinger K, et al:

Cell Stem Cell; 1 (October): 367-368

There are many important reasons why induced pluripotent stem cell research must be conducted hand in hand with human embryonic stem cell research.

Recent reports of reprogramming mouse fibroblast (skin) cells to act like human embryonic stem (hES) cells deserve scrutiny and assessment. In 2007, 3 separate groups of researchers demonstrated successful reprogramming. A quartet of genes was discovered to induce pluripotency in mouse cells, albeit incompletely. Now, a second generation of these induced pluripotent stem (IPS) cells has been induced to do almost everything that mouse embryonic stem cells can do. One research team produced fetal mice derived entirely from IPS cells, a criterion for embryonic stem (ES) cells. Reception by the media and governmental levels has been, in part, misguided. Some policy makers and citizens may erroneously be tempted to the assumption that research on hES cells is no longer necessary. This should not be taken as a reason to oppose hES cell research. It would be a serious mistake to conclude that recent IPS cell research obviates the need for continuing, ongoing research on hES cells. There are many important reasons why IPS cell research must be conducted hand in hand with hES cell research. First, progress toward socially beneficial application of stem cell research might be unacceptably delayed if IPS cells are pursued at the expense (literally) of hES. Research on IPS cells is in its infancy. Nothing is known about its tumorigenicity and safety. In that connection, it should be noted that 1 of the 4 genes that induce pluripotency in mice, c-Myc, seems to contribute to induction of cancer in chimeric mice. Retroviruses used to insert these genes might themselves lead to cancer and deleterious malformations. It could take several years to identify what IPS cells are capable of doing. There is no certainty that IPS cell research will translate to human cells. At the present time, ES cells derived from embryos are the only pluripotent cells that are genetically unmodified, a significant consideration.

Reviewer's Comments: Even if human IPS cells are derived, there are yet invaluable areas of research that may not readily be pursued using reprogrammed skin cells (eg, early development of the human embryo). We cannot support the notion that IPS cell research can advance without hES cell research.