REFERENCE GUIDE

Connecting our Stakeholders
Communicating Knowledge
Translating the Proven
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ON UNPROVEN CELLULAR THERAPIES 2015

Talking About Unproven Cell-Based Interventions
A Project by the ISCT Presidential Task Force on the Use of Unproven Cellular Therapies

First Edition

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Printed in the United States of America
First Printing, 2015

ISBN 0-xxxxxxxx-0-0

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The International Society for Cellular Therapy (ISCT; www.celltherapysociety.org), with a strategy adopted more than 5 years ago (Gunter KC et al. *Cytotherapy* 2010), wishes to continue raising awareness about unproven cellular therapies. All over the world, there is a legitimate effort to introduce cellular therapies into the clinic; however, at the same time, a large number of clinics have begun offering cell-based interventions for a variety of diseases with questionable safety or efficacy data or an unclear scientific rationale. This has led to many vulnerable patients subjecting themselves to unproven cellular therapies with no adequate regulatory oversight or reliable information about risks or benefit.

For this reason, ISCT feels the need to provide a new source of information: an open document that represents a sharing of knowledge by leaders in the field. Building upon ISCT’s growing expertise in employing cells as therapeutic tools, we want to identify key aspects of unproven cellular interventions in order to promote effective communication strategies for health-care stakeholders, patient associations, and individuals, highlighting the role of rigorous research prior to treatment.

As our past President Kurt C. Gunter, MD has stated, this is not the end of a process. Rather, this is the beginning of a new multilingual project that foresees the participation of other organizations, bioethicists, and patient associations at a global level. The goal of ISCT will be to stimulate collaboration in generating opportunities to progressively integrate these essential parts, according to new needs and in an online encyclopedic format that is updated yearly. While looking forward to future contributions, I can certainly state that we are all in debt to the current coauthors for their incredible support that enriched all the following sections and tremendously inspired me.

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Prologue

In the following sections, the International Society for Cellular Therapy (ISCT; www.celltherapysociety.org) addresses the multiple facets of unproven cellular therapies that violate the principles and processes required for the proper development of cell therapies. The various parts of this paper 1) define the term “unproven cellular therapy”, 2) dissect several key aspects and parameters involved in cell manufacturing within unproven cellular therapy approaches, 3) investigate the globally diverse and sometimes contradictory regulatory landscape that challenge suitable cell-based product manufacturing, 4) demonstrate how unproven treatments negatively influence the marketing and commercialization of cell-based products, 5) propose intervening action against the administration of unproven cellular therapy by way of improved communication among international monitoring organizations, and 6) conclusively introduce an ISCT initiative to promote “proven cellular therapy”. ISCT is convinced that the entire cell therapy community can benefit from being properly informed, and for this reason the present work represents the beginning of an actively shared, web-based document composed of contributions from cell therapy professionals, scientific organizations, and patient associations. ISCT wants to identify key features of unproven cellular interventions and promote effective and pro-active communication strategies among interested parties, calling attention to the importance of conducting proper research prior to treatment and marketing.
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Part 1
Defining Unproven Cellular Therapies

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TECHNOLOGICAL ADVANCES BETWEEN THE PROVEN AND THE UNPROVEN

Given the potential of cell-based products, including stem/progenitor cells and immune cells, there is a global effort to introduce these therapies into the clinic to correct organ dysfunctions, treat cancer, and to abrogate autoimmune diseases and a wide variety of pathological conditions.\(^1\)\(^-\)\(^3\) Relatively easy access to these cells, obtained from marrow, adipose, cord blood, and other human tissues, provides tremendous opportunity for translational research, particularly for indications with no satisfactory medical solution for patients with “unmet medical needs”. Prenatal and adult stem cells (including induced pluripotent stem cells [iPS]) possess significant potential to rebuild tissues and correct dysfunctional organs in human diseases. In parallel, certain populations of adult stem cells—notably mesenchymal stromal cells (MSC)—can also have modulatory actions in the absence of participating in structural tissue repair.\(^4\) MSCs offer additional therapeutic benefits of which the precise mechanisms of action are still under investigation. Similarly, the ability to isolate, modify, and stimulate immune cells prompted their use within adoptive immunotherapy to treat cancer.\(^5\) In the last two decades technological advances have provided commercially available cell manufacturing devices, reagents, and delivery tools that enable processing, selection, expansion, and storage of cells at a relatively low cost. While these attributes form the basis for progressive acceleration in the field, they have also been associated with an increased early use of these therapies before being vetted within appropriate and adequate risk-benefit analyses. The use of cell-based interventions masquerading as “proven therapies” outside of approved clinical trials is a matter of even greater concern, as better understanding of several biological functions for many cell types in pre-clinical settings and in early controlled clinical trials is still needed.

Many of the cell types being investigated are readily accessible. Furthermore, there are fewer limitations related to intellectual property rights or cell-based technology methods than those customarily present during the development of small- and macro-molecule drugs. While these freedoms promote robust, legitimate research and development, it has also led to the parallel development of clinics worldwide that offer cellular therapies with questionable safety or efficacy data or unclear scientific rationale for the treatment of a variety of diseases. This has led to vulnerable patients subjecting themselves to unproven cellular therapies in an environment with inadequate regulatory oversight or reliable information about potential risks or benefits.\(^6\),\(^7\)

HOW TO DEFINE (AND RECOGNIZE) UNPROVEN CELL THERAPIES

The definition of unproven cell therapies is broad and could also be related to legitimate in-process research activities aimed to improve and verify certain cell-based approach hypotheses. While new investigational medicinal products are tested under duly authorized clinical trials, many remain unproven or insufficiently proven. Unfortunately, many unproven or insufficiently proven cell therapies have been proposed to patients as “treatments or therapies” for a specific financial cost and without recognized biological and medical proofs of safety and efficacy (ie, without a positive benefit-risk assessment in place). Most of these therapies are offered outside of properly authorized channels and fall outside the realm of conventional clinical trial models, supervised and monitored by regulatory agencies (with the appropriate exceptions being compassionate use, or hospital exemptions). Although the legal definition of authorized cell therapy resides in the governing hands of each country’s regulatory authority for drugs and therapeutic products, narrowing the scope to a handful of characterizations may assist the cell-therapy community to initiate the process of reaching a universal definition. The following series presents a starting point for clarification of defining an unproven cell therapy (Table 1.1).
Table 1.1 Unproven cell therapies are characterized by:

<table>
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<tr>
<th>Unproven cell therapies</th>
<th>Characterized by:</th>
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<tr>
<td>✓</td>
<td>unclear scientific rationale to suggest potential efficacy</td>
</tr>
<tr>
<td>✓</td>
<td>lack of understanding on the mechanism of action and/or the biological function to support clinical use</td>
</tr>
<tr>
<td>✓</td>
<td>insufficient data from in vitro assays, animal models, and clinical studies regarding the safety profile to support the use in patients</td>
</tr>
<tr>
<td>✓</td>
<td>lack of a standardized approach to confirm product quality and ensure consistency in cell manufacturing</td>
</tr>
<tr>
<td>✓</td>
<td>inadequate information disclosed to patients to enable proper informed consent</td>
</tr>
<tr>
<td>✓</td>
<td>use within non-standardized or non-validated administration methods</td>
</tr>
<tr>
<td>✓</td>
<td>uncontrolled experimental procedures in humans</td>
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The lack of (reliable) information for patients on unproven cell therapies may be inversely proportional to the price for these treatments that are generally associated with a considerable economical and psychological impact for patients and their families. They generally take place in countries where such therapies are not regulated, and for this reason those practices have been dubbed “stem cell medical tourism.” Recently, these practices have been occurring with greater frequency in countries where regulation is stricter but loopholes exist in the regulatory policies.

Most of these unproven cell therapy scenarios provide very little local follow-up for treated patients. Since the clinicians involved are not required to provide data on their patients, few authentic reports of the success or failure of these therapies exist for appropriate peer review and regulatory oversight. Apart from being potentially unethical and possibly causing harm, unproven cell therapies may negatively impact the legitimate development of cell-based therapies.

RAISING THE INTEREST ON UNPROVEN CELL THERAPIES

Therefore, it is in the interest of the International Society for Cellular Therapy (ISCT; www.celltherapysociety.org) and other stakeholders within this field to raise awareness of unproven cell therapies. As a professional scientific organization, ISCT maintains the power and authority to define how the world will develop cell therapy principles and processes. There is a particular need to determine what methods will be considered scientifically sound and ethically acceptable in this area of development.

The current environment is complicated to say the least. Varied circumstances exist throughout different parts of the world, thus creating diverse logistical, regulatory, social, economic, and ethical challenges to developing this area of medicine. Further, stem cells hold a near magical role in the eyes of patients. This leads clinicians to have an unusual amount of responsibility to properly communicate and moderate treatment expectations. In order to provide proper informed consent, patients must possess a realistic understanding of cell therapy. How health care is even approached can differ by country. Adding to the complexity and intricacy of the situation includes an honest acknowledgment of the varying motivations among stakeholders within the field, from the idealistic scientist to the financially motivated capitalist, opinions color the landscape in shades of grey. Unfortunately, there are also individuals using this opportunity to prey on vulnerable patients. As such, there is need to find common ground between all involved stakeholders in order to promote greater cooperation and a balanced approach that facilitates the development of safe and effective therapies and the patients’ access to them without causing undue risks to patients or exploiting their vulnerability.
This text is an open, updatable document intended to be actively shared with other professionals (ie, bioethicists, scientific organizations, and patient associations) as we work together to define and constructively discuss these issues and forge a path forward. With hastened immediacy, we also hope to promote a strategy for communication with patients considering unproven cell therapy as a treatment option. It is imperative these people have the intellectual liberty to make an informed decision.

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Part 2
Making the “Unproven” “Proven”

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THE RATIONAL PATH TOWARDS THE USE OF LIVING ENTITIES: FROM CELLS TO CELL THERAPIES

The use of living, disaggregated cells in medicine involves a number of aspects that make this approach distinct from traditional pharmaceutical products. Cells are not metabolized by the liver or kidney, unlike most small-molecule drugs, but are potentially capable of distribution throughout the entire body. Cells are also highly complex and change dynamically in response to their environment and over time, making it difficult to standardize them in the same way that molecules can be engineered and mass-produced. Some type of cells may also secrete multiple bioactive molecules, such as cytokines and growth factors, as well as microvesicles, which may be released in different amounts or combinations, depending upon the cells' immediate environment or the pathophysiological state of the body into which they are introduced.

These properties of heterogeneity, complexity, and malleability can make it challenging to test cell-based products using paradigms developed for highly standardized and stable molecular products. This does not, however, mean that it is impossible to determine the safety and clinical usefulness of such products, nor does it remove the responsibility to provide rigorous, independently verifiable evidence from those who seek to develop cell-based interventions for commercialization or use in standard of care.\(^1\)

Therefore, the clinical translation of cell-based research towards development of specific therapies for a variety of diseases faces several challenges, not dissimilar to what took place in the 1990s during the early manufacturing of monoclonal antibodies for therapeutic uses.\(^2\) After proper and rigorous assessments, these therapies are now clinically utilized for several diseases with good success for large numbers of patients.

Next to (1) challenges related to the choice of a characterized cell type; (2) understanding of its potential mechanisms of action for a specific disease; (3) the technical aspects of its isolation, characterization, and possible expansion under appropriate current good manufacturing practice (cGMP) conditions; (4) dose, dosing, and mode of administration for any given clinical indication; and (5) the pre-clinical disease models in which to confirm proof of principle, it is crucial to define what evidence is needed to conclude that a particular therapy is safe and efficacious and can be considered as “standard of care,” or at least a legitimate and viable option for that particular condition. While the scientific aspects of this process can be reasonably defined, and should indeed be uniform worldwide, medical, regulatory, social, and ethical aspects vary with respect to actual implementation of these approaches. These issues need to be addressed to help the development of these therapies.\(^3\)

The scientific principles and the path required to move towards the goal of finding safe and effective cell therapies are reasonably well defined.\(^1\) Initially, this involves developing proof-of-concept with both in vitro work and appropriate pre-clinical animal models using clearly defined cells. Subsequent steps then include moving on to well designed and monitored clinical studies with cells substantially or non-substantially manipulated using reproducible methods under classified conditions. Clear documentation of defined and measurable outcomes that can establish unequivocal safety and efficacy must be included. Importantly, there should also be proper follow-up to provide proof of long-term safety. We also advocate that mechanistic studies be built into clinical investigations to provide further information to uncover and validate potential mechanisms of action of the cells introduced in a given disease.\(^3\)

One increasingly common approach is to offer autologous therapies in which cells are harvested from a patient’s own bone marrow, adipose, or other tissues, and then reinfused into the patient. While this is perhaps less problematic in terms of safety issues, efficacy of such therapies need to be evaluated by well-defined and measurable parameters. It is also important that long-term studies be performed for each potential clinical use. There is often little or no justification for claims of efficacy used to lure patients into
undergoing these therapies. Furthermore, these approaches are most often done outside of legitimate clinical trials, without defined measurements of outcomes or adequate follow-up, and patients often pay large and unreasonable sums of money to undergo them.6

“IN CASE OF EMERGENCY”: COMPASSIONATE USE OF CELL THERAPIES

At the same time, it is also recognized that in medical emergencies or other difficult medical situations that have exhausted other treatment options, the use of cell-based therapies may be implemented on a compassionate use basis. While regulations surrounding this vary in different countries, they have to be applied in each situation with appropriate rigor. Furthermore, if a compassionate use approach is found to be safe and consistently effective in any given disease, these instances should lead to the development of clinical trial protocols appropriate for that condition. Data from such trials will then be subjected to appropriate sharing and peer review.

The concept of “medical innovation” has been an important approach in the history of medicine for developing innovative therapies, but it still has to work within certain safeguards. A system needs to exist within institutions that consider such approaches. This should rely on a physician presenting the need for such a therapy for a patient who has run out of options. An appropriate oversight committee shall be then in place in order to assess this scientific rationale and the potential clinical benefit. This also must include a process to ensure that the patient or legal representatives have understood the unproven nature of such a therapy and to provide appropriate voluntary informed consent. It must also be ensured that the concerned physician or institutions have no conflicts of interest in promoting such therapies. Very importantly, no more than a few patients (usually < 5) may be treated this way after which a clinical trial protocol must be established, if that particular approach needs to be continued.

If these principles can be followed universally, many of the current problems with unauthorized and illegitimate use of cell-based therapies may be avoided. However, the easy access to certain types of cells, frequently autologous MSC or immune cells, the unmet medical needs of desperate patients and their families seeking care and potential for cure, as well as the business potential and financial gain from these interventions have all led to a large and increasing number of centers around the world that offer cell therapies that are yet to be established as safe and effective to patients.

THE NEEDS AND THE CHALLENGES OF GENERATING DATA ON UNPROVEN CELL THERAPIES

The next important issue to address is the amount of data on clinical efficacy that is needed before a therapy may be considered to be of proven value for that condition. As with any other new potential therapeutic agent, this would require an initial well designed and well regulated phase (Phase 1) study assessing initial safety and feasibility studies that include attempts at defining appropriate doses to be utilized. These would then be followed by studies on efficacy and further safety studies (Phases 2 and 3), preferably in comparison to the best existing therapies, if any. Depending on the condition being treated, the selected endpoints, the sample size, and the trial design will vary and the result would determine the status of that therapy.

In ideal circumstances, any new treatment would be considered to be not only effective but also the standard of care, if it has been compared and found to be superior to the current best option in an adequately powered randomized trial. A parallel outcome would be that the new treatment is found to be not inferior to the current standard of care and thus be available as a legitimate alternative therapeutic approach. As mandated by the regulatory agencies in each country, there is no reason why these standards should not be uniformly applied worldwide for development of cell therapies.
We also acknowledge that in some ultra-rare, still-lethal conditions large, sufficiently powered, Phase 3 randomized cell-based clinical trials, using reliable and valid primary endpoints are not always feasible. For these situations the scientific community, the health care providers, and the regulatory agencies should allow early access to new therapies, including cell-based therapies. In such cases, a risk-based assessment should be taken into account that combines patient prognosis and safety aspects on manufacturing and delivery, with sufficient peer reviewed scientific evidences of efficacy. A good example is the first gene therapy product that has been given market authorization by the European Medical Agency (EMA), an adeno-associated virus-vector-based product for lipoprotein lipase deficiency.\(^8\)

Additional issues may arise from the way the cells are harvested and handled \textit{ex vivo}, such as the case of the so-called, non-substantially manipulated autologous cells.\(^9\) The debate on the topic continues as to whether these should be considered as medicinal products when utilized for non-autologous uses.\(^10,11\) Regardless of autologous vs allogeneic use, or use of non-manipulated or manipulated cell products, it is imperative to generate rigorous peer-reviewed scientific evidence on their safety and efficacy and subsequent review by proper regulatory authorities before they can be used as medical treatment. Nevertheless, a regulatory agency (EMA) claims, “The Committee of Advanced Therapy classification is based on existing scientific knowledge of cell biology. Classification may vary according to the evolution of science.”\(^9\) This suggests a framework for logical progression in which clinical development will follow and inform peer-reviewed science, and vice versa, in a mutually constructive relationship for the patient’s benefit.

Challenges arise within these models at different levels and in different countries. If there is no system to support such a graded development process or if there is no access to the current standard of care in certain parts of the world, it will be difficult to apply the principles described above. Social and ethical issues with regard to access to some or any care may then come into the decision-making process for the approach to the development of these therapies in those countries. While making adjustments for those circumstances, it is critical to have independent review mechanisms of the process to ensure that the driving force is the concern for the patient and not any conflict of interest on the part of the physician or the institution. Going forward, the data acquired from such innovations need to be peer reviewed, and a clear regulatory path should be devised for the further development and approval of these therapies.\(^12\) Data should be reviewed by peers to decide when such a therapy may be considered to be adequately safe and effective as an option of treatment outside of clinical trials or indeed become the standard of care or a viable parallel approach. Depending on the disease and the type of cell therapy treatment, this could be done at the local or international level. As such, there is significant potential for cell-based therapeutic opportunities for a range of diseases, but only if investigated and validated in the most rigorous manner.
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Part 3
Understanding the Manufacturing of Unproven Cellular Therapy Products

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SHINING THE LIGHT ON THE BLACK BOX

As stated in the other parts of this guide, the delivery of cells to patients requires transparent, rigorous manufacturing steps that are clearly defined and well understood. What raises a concern is the manufacturing of cellular-therapy products that seem to originate in an engineering “black box.” Tissues go in to the black box, and cells emerge ready for use despite the fact that there is little clarity about what has occurred. Production for clinical use encompasses a wide array of possible manufacturing approaches ranging from essentially no processing or manipulation to extensive procedures including ex vivo culture and gene modification. Similar to the concerns of how to evaluate the appropriate use and clinical indication of cellular therapy products, it is of utmost importance to consider cell manufacturing in order to properly assess the risk factors in certain treatments. In recent years, there have been instances of safety concerns about cell therapy products and their manufacturing steps particularly within unproven cellular therapy approaches. Although these concerns can be independent of the broader question of the product efficacy, they contribute to the controversy of unproven cellular therapy products.

The providers of these approaches should be able to share what they know and, more importantly, what they do not know, about the cell product and its mechanism of action. Regardless of whether the manipulation and processing of the cell product is simple or highly complex, the manufacturing of cellular therapy products includes many other critical facets such as donor evaluation, cell procurement, manufacturing process control, and quality control testing for the evaluation of potency, purity, identity and traceability, safety, and product stability. The competency of manufacturing and supervisory personnel and the appropriateness of the production environment are also critical for safe manufacturing. In the cases of unproven cellular therapies, there were frequently no guarantees that these technical aspects were taken into account, irrespective of whether the tissue source was autologous or allogeneic.

Several layers of complexity exist in the assessment of cellular therapy product manufacturing, thus the evaluation of an unproven cellular therapy product can be challenging. Even in situations where production is properly performed, the lack of experimental data to support cell delivery in a specific disease can render a cell therapy approach “unproven.” For this reason, manufacturing related factors should be considered when evaluating the risk of an unproven cellular therapy application with the expectation that the quality level of the manufacturing process should be equivalent to the level for proven cellular therapies, such as those for in vitro fertilization or bone marrow transplantation. In addition to the use of a novel product with no previously recognized basis for clinical indication, a previously “accepted” product for a demonstrated purpose might be used in an unproven manner. For this reason, scientific evidence of efficacy as well as other planned outcome measures should connect with the manufacturing steps. One example of this fusion between the manufacturing process and clinical outcome is ensuring the safety and consistency of the cell product via potency assays prior to final release. In this situation, the release criterion process step validates the safety and consistency of the product being infused into the patient.

REGULATORY STATUS AND ACCREDITATION OF MANUFACTURING FACILITIES

Assurance of high quality manufacturing operations, and accompanying reduction in risk, is most commonly obtained through independent assessments by regulatory agencies or voluntary accrediting organizations. Across the globe there is a wide variation in the degree of regulatory stringency for cellular therapy product production (see also Part 4). When evaluating the degree of risk associated with a particular product, it is important to understand the regulatory framework of the geographic location of the manufacturing facility and to confirm compliance to local regulations. Complexity exists because in many countries regulations about manufacturing are related to the degree...
of manipulation of the product, independent of the clinical use of the product. For example, if a product requires less complex manufacturing (or “minimal manipulation”), as long as the correct manufacturing regulations are followed, clinical use in any disease indication is permitted. This is similar to the “off-label” use of licensed drugs prescribed for different indications. Moreover, some competent authorities have not established any specific regulations for cellular product production. Manufacturing facilities in these locations require a very high level of scrutiny in evaluating the degree of risk. In some cases, product manufacturing occurs in a location that is covered by one set of regulatory oversight and yet is independent of the regulatory controls in place at the location of clinical treatment. This situation may require more detailed evaluation. The relative complexity of different product manufacturing processes is just one confounding issue in establishing harmonized regulatory guidelines.

Independent of regulatory oversight, an important tool in evaluating risk is to determine whether a broadly recognized, non-governmental authority has accredited the manufacturing operations of an unproven cellular therapy product. Independent assessment of manufacturing operations by a third party can provide a critical perspective without conflicts of interest. Organizations such as the Foundation for the Accreditation of Cellular Therapy (FACT), Joint Accreditation Committee-ISCT (Europe) & EBMT (JACIE), or the AABB offer voluntary accreditation services. These groups have established standards that represent the highest level of best practices. Accreditation standards can be applied to situations where cellular therapy is being performed as “clinical practice” and not necessarily subject to typical manufacturing regulations.

When assessing a manufacturing operation, it is important to independently review the actual documentation of a given facility’s current accreditation or regulatory status and not rely on statements contained in marketing materials often offered on the website. This can be done by checking the websites of the local government authority and accrediting bodies, most of which maintain public listings of registered or accredited facilities. Alternatively, calling such organizations directly may provide even more information about the level of external oversight to which the manufacturing facility is truly subject. It is also worth considering the validity of any accrediting groups listed by an unproven cellular therapy provider, as organizations have been created in order to falsely legitimize activities. High quality accrediting organizations will have a diverse client base that includes facilities in multiple geographic locations, under different parent companies, and in mainstream healthcare organizations. Some clinical practitioners reject the concept that any “manufacturing” is occurring and view the handling of the cellular product as “practice of medicine,” either in the simpler manufacturing processes or by virtue of the cell source being autologous. This viewpoint is generally not supported by many regulatory authorities. It also should not negate the applicability of external accreditation for assurance of high quality operations for the handling of cell therapy products.

GOOD PRACTICES AND QUALITY CONSIDERATIONS

In practice, patients and medical professionals will encounter situations in which they are self-evaluating unproven cellular therapies that lack the above described accreditation or regulatory clearances. To the inexperienced, this can be daunting. Manufacturing of cellular therapy products can involve an extremely wide range of possible operations. This can vary from minimal to complex with long duration steps. Regardless of the degree of complexity, there are several core practices that should be followed by facilities striving to operate at the highest level of quality and safety. The standard operating procedures of all practices should be outlined in writing and reviewed and approved by knowledgeable individuals prior to implementation. Some of these core practices are listed in Table 3.1.
Table 3.1 Basic core practices for cell therapy production:

| ✔️ quality assurance functions such as audits, investigation of errors and deviations |
| ✔️ control of facility operations such as cleaning and sanitization |
| ✔️ control of manufacturing environment such as air quality, temperature, and humidity |
| ✔️ control of equipment such as calibration and preventive maintenance schedules |
| ✔️ control of supplies and reagents such as using before expiration dates, qualified vendors, and grades of materials |
| ✔️ processing and process controls such as established criteria at critical points, final release specifications |
| ✔️ labeling controls to ensure product traceability and identity |
| ✔️ control of storage such as inventory control, product stability |
| ✔️ receipt, release, and distribution procedures |
| ✔️ donor eligibility determinations, donor screening, and donor testing |
| ✔️ cell and tissue collection procedures |
| ✔️ staff qualification and training procedures |
| ✔️ adequate record keeping for each manufacturing run and all core practices listed above |

This list should be considered as an example of minimal key factors to examine when considering the quality of a manufacturing facility and the relative risks associated with cellular therapy products produced at a specific facility. The core concepts outlined here should provide a starting place from which to begin when it is necessary to assess the overall quality of cellular therapy products that are being used outside of established and accepted practices. Consistent manufacturing of a high quality product is an essential part of a successful clinical application for any treatment. In conclusion, a close review of the manufacturing facility and operations is important when evaluating the general safety and risk factors of a cellular-therapy product. Considering the evaluation may require a significant degree of relevant expertise, certification provided by a rigorous governmental agency or internationally recognized accreditation body is the most reliable mechanism for evaluation. It is important to understand that all regulatory environments and all accrediting groups may not provide equal degrees of assurance. It is also important to review credentials and potential conflicts of interests for these entities. Absent of external assurance, basic criteria that should be considered in a risk evaluation are presented here and should be provided by the unproven cellular therapy provider upon request.
REFERENCES


Part 4
Interaction Between Unproven Cellular Therapies and Global Medicinal Product Approval Regulatory Frameworks

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⁵ Moffitt Cancer Center and Research Institute, Tampa, FL, USA. Chair, ISCT NA LRA Committee 2014-16. Co-Editor of the Telegraft.
CELLULAR-BASED PRODUCTS: PROVIDING REGULATORY FRAMEWORKS

Medicinal product (drugs, devices, biologics) regulatory requirements are primarily based on preventing public harm and promoting public health. Harm or injury can occur when a patient is exposed to a medical treatment or device for which the consequences of using that product are not well understood. Therefore, regulations are mostly focused on minimizing potential risks of harm when using unknown, untested, or new medical treatments. Cellular therapies are medical treatments. As explained in previous parts, the diseases and conditions treated are numerous and fall under the aegis of either direct effect (for example, cell or tissue replacement with the same systemic effect) or indirect effect (such as cell-to-cell interaction or immunomodulation). Use of cellular therapies is complicated by the fact that a positive result could be the outcome of one or more different mechanisms of action from the same treatment. There is no way to be completely certain that a cellular therapy is free from harm. Therefore, regulations provide the framework whereby treatments can be provided using a reasonable risk/benefit paradigm. Regulations should not be more burdensome than is required to appropriately reduce risk, while allowing access to treatments by needy patients.

Cellular- and tissue-based products are subject to complex regulations that vary widely according to country and product type. Consequently, it is often difficult to determine how different products will be categorized and regulated, especially in advance of using them in clinical practice. Such confusion is compounded when existing regulatory frameworks for conventional pharmaceuticals are used to regulate cellular and gene therapies.

With so many countries grappling with how to balance patient safety with patient and economic demand for unproven cellular therapies, it is meaningful to analyze maturity levels of different national and regional regulatory structures, and identify the gaps and limitations in their design and enforcement. Interagency and international collaborations and third-party accrediting organizations should also be considered with regard to improving, enforcing, and supplementing regulations. This is done with appropriate regard for variations in socio-economic development, cultural norms, regulatory capacity, and medical infrastructure.

COUNTRY LIST BY POPULATION

There are 56 countries with populations greater than 20 million people. They are located in all developmental regions, with no guarantee that a highly populated country is also indicative of a highly developed country. It would be convenient to argue that the rigor of regulatory framework for any healthcare product can be correlated roughly to economic developmental maturity—developed, in transition, or developing economies—however, this is not always the case. Economic development and regulatory maturity are on separate sliding scales though not mutually exclusive. Economically developed regions are characterized by several features: the transition from an agriculture-based economy to an industry-based economy, an ability to adopt and utilize technologies, a high standard of living and access to healthcare, and a highly educated and trained workforce. Rapid economic growth can outpace the creation and implementation of health product regulations, leaving uncertainty and a structural vacuum until the government is able to catch up. Opinions vary as to whether certain regions have reached a mature state of economic development or are in the process of achieving such. There are several organizations that have attempted to define countries and regions in this way; however, it is not the purpose of this part to endorse or analyze these definitions.
REGULATORY STRUCTURES BY DEVELOPMENT STATUS AND GEOGRAPHY

Economically developed countries typically have a regulatory infrastructure that has come as a result of early failures in public protection. Decades of legislation created an intricate set of regulations designed to protect public safety and assure that any products sold for detection, treatment, or cure of disease, are required to demonstrate safety, purity, and efficacy. For the most part, this process works. However, the introduction of new therapies, such as cell or gene therapies, is often implemented through a long period of regulatory approval, which consequently delays patient access to these programs. For patients most in need of new therapies, this lag between introduction and access can literally be too long, since, while waiting, their disease may have progressed beyond the point for any interventional therapy to be effective. The extended approval time reflects the regulatory uncertainty as authorities work to find a path forward using existing frameworks.

For patients and clinicians in particular, it is important to understand that a given country’s degree of economic development is not necessarily indicative of its regulatory capacity for overseeing the quality and efficacy of any unproven cellular therapy. A growing economy in a developing country may have a “products and services vacuum” that can attract all manner of goods and activities that might exploit this gap. Intent on building a thriving economy, national leadership may be so eager to attract industry and entrepreneurs that it does not adequately understand and weigh the potential risks of those therapies or evaluate the training and skills of their manufacturers and providers. Lack of education, lack of regulation, ease of access to potential patients, and low barriers to entry may all contribute to the continuing risk to patients using unproven cellular therapies.

Table 4.1 provides an overview of regulatory authority for medicinal products by country or region. Often, but certainly not always, more “regulatory-developed” countries offer more regulatory options or pathways, especially for products that target diseases with few effective treatments. These options have come about primarily because patient communities have advocated strongly for access to new medicines in time to make a difference for their constituents. Several examples of products that have been accelerated or “fast-tracked” through a nation’s regulatory approval process include HIV drugs, treatments for certain orphan diseases, and forms of cancer. In permitting access to a product before it has completed a country’s formal process for pre-market approval, regulators may rely on a partial data set and defer, but not waive, the requirement for the complete safety and efficacy data package that is normally required. In order to convert to a full approval, the product manufacturer remains accountable for studies that are required to fulfill all pre-approval requirements.
### Table 4.1 Regions/Countries and Regulatory Frameworks

<table>
<thead>
<tr>
<th>Region</th>
<th>Name</th>
<th>Regulatory Agency(ies)</th>
<th>Practice of Medicine</th>
<th>Medical Products not Requiring Regulatory Pre-approval Prior to Sale</th>
<th>Medical Products Requiring Premarket Approval</th>
<th>Regulatory Accelerators</th>
<th>Special Access Programs</th>
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</thead>
<tbody>
<tr>
<td>North America</td>
<td>United States</td>
<td>FDA (Food and Drug Administration)</td>
<td>Yes</td>
<td>PHS 361 Tissues and Cells</td>
<td>Biologics, Drugs, Combination (drugs and/or biologics and/or devices) Class I Medical Devices</td>
<td>Orphan Product Designation (drugs, biologics, devices). “Expedited Programs for Serious Conditions [with Unmet Needs]—Drugs and Devices” including Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval, Priority Review Designation</td>
<td>Compassionate Use11, Treatment IND12,13</td>
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<td>Canada</td>
<td>Health Canada</td>
<td>Yes</td>
<td>Cells/Tissue/Organ Transplantation Class I Medical Devices</td>
<td>Biologics, Drugs, Combination (drugs and/or biologics and/or devices) Class II and III Devices</td>
<td>Orphan Product Designation (proposed framework due 2015)14 Priority Review (fast track)15</td>
<td>Special Access Programme16</td>
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<tr>
<td></td>
<td>Mexico</td>
<td>Federal Commission for the Protection Against Sanitary Risk17</td>
<td>Yes</td>
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<td>South America</td>
<td>Argentina</td>
<td>National Administration of Drugs, Foods and Medical Devices18</td>
<td>Yes</td>
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<td></td>
<td>Brazil</td>
<td>Brazilian Health Surveillance Agency19</td>
<td>Yes</td>
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<tr>
<td>Region</td>
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<td>Practice of Medicine</td>
<td>Medical Products not Requiring Pre-approval Prior to Sale</td>
<td>Medical Products Requiring Pre-Market Approval</td>
<td>Regulatory Accelerators</td>
<td>Special Access Programs</td>
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<tr>
<td>Europe</td>
<td>European Union 20</td>
<td>EMA (European Medicines Agency)</td>
<td>Yes</td>
<td>Centralized authorization procedure for ATMPs among other human and veterinary medicines (including biologics)</td>
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<tr>
<td></td>
<td></td>
<td>National Competent Authorities (different for transplants, medicinal products and medical devices)</td>
<td>Yes (Clinical trials are authorized by national medicine agencies)</td>
<td></td>
<td>Human medicines not subject to centralised authorisation procedure and Medical Devices</td>
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<td></td>
<td>Compassionate Use</td>
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<tr>
<td>Norway</td>
<td>Norwegian Medicines Agency31</td>
<td></td>
<td></td>
<td></td>
<td>Orphan Product Designation (drugs and biologics)</td>
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<tr>
<td>Switzerland</td>
<td>Swiss Agency for Therapeutic Products42</td>
<td></td>
<td></td>
<td></td>
<td>Exceptional Circumstances</td>
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<tr>
<td>Iceland</td>
<td>Icelandic Medicines Agency43</td>
<td></td>
<td></td>
<td></td>
<td>Conditional Marketing Authorization</td>
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<tr>
<td>Russian Federat.</td>
<td>Russian MOH – Federal Medical-Biological Agency / Federal Service for Supervision of Health44</td>
<td>Yes</td>
<td>Drugs, Biologics, Medical Devices</td>
<td></td>
<td>General Law re: Rare Diseases (no acceleration)</td>
<td></td>
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<td>Commonwealth of Independent States</td>
<td>Various45 (Azerbaijan, Armenia, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russia (see above), Tajikistan, Turkmenistan46, Uzbekistan, Ukraine47)</td>
<td>Each Country has its own National Health Authority</td>
<td>Yes</td>
<td></td>
<td>Ukraine – Ministry of Health Regulation Orphan Policy</td>
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<tr>
<td>Region</td>
<td>Name</td>
<td>Regulatory Agency(ies)</td>
<td>Practice of Medicine</td>
<td>Medical Products not Requiring Regulatory Pre-approval Prior to Sale</td>
<td>Medical Products Requiring Pre-Market Approval</td>
<td>Regulatory Accelerators</td>
<td>Special Access Programs</td>
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<tr>
<td>Asia</td>
<td>China</td>
<td>China Food and Drug Administration&lt;sup&gt;15, 43&lt;/sup&gt;</td>
<td>Yes</td>
<td></td>
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<td></td>
<td>Hong Kong</td>
<td>Hong Kong Health Authority</td>
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<td></td>
<td>India</td>
<td>Central Drugs Std Ctrl Organization&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Yes</td>
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<td></td>
<td>Singapore</td>
<td>Health Sciences Authority</td>
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<td></td>
<td>South Korea</td>
<td>MFDS Ministry of Food and Drug Safety&lt;sup&gt;46&lt;/sup&gt;</td>
<td>RFDA – regional surveillance and compliance</td>
<td>Yes</td>
<td>Biopharmaceuticals, Drugs, Medical Devices&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Designation of Orphan Drugs, Conditional marketing approval before concluding clinical trials for certain cell therapy products&lt;sup&gt;48&lt;/sup&gt;</td>
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<td></td>
<td>Taiwan</td>
<td>Ministry of Health and Welfare, TFDA&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Yes</td>
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<td></td>
<td>Japan</td>
<td>Pharmaceutical and Medical Devices Agency / MHLW</td>
<td>Yes</td>
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<td>Rapid Authorization of Unapproved Drug&lt;sup&gt;51, 52&lt;/sup&gt;</td>
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<td></td>
<td>Oceania</td>
<td>Australia&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Therapeutic Goods Administration&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Yes</td>
<td>Class 2 Biologicals&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Class 3, 4 Biologicals, Drugs, Devices (all classes)</td>
<td>Orphan Product Designation (drugs, vaccines, IVD agent – none for biologics)</td>
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<td>New Zealand</td>
<td>NZ Medicines and Medical Devices Safety Authority</td>
<td>Yes</td>
<td>Schedule 1 Medicines and Devices&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Drugs, Biologics, Schedule 2 Devices&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Unapproved Medicines Access Program&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Provisional Consent</td>
</tr>
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</table>

<sup>References: </sup><sup>15, 43, 45, 47, 49, 51, 52, 53, 56, 57, 59</sup>
INTER-AGENCY COLLABORATIONS

Many countries have engaged in cross-border efforts to exchange information about medicinal products and health care in general, and harmonize regulations. These efforts primarily have occurred between developed regions. Some examples include:

- **The US FDA’s “Global Initiative”** is dedicated to increasing collaboration with other countries on many issues, including medical products. Its goal is “to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal agreements.” To date, the agency has established permanent offices on all continents except for the Polar Regions. It has also executed Confidentiality Commitments on sharing information regarding biologics, medical drugs, and devices with at least 12 countries in addition to the EU and the World Health Organization. Bilateral and multilateral Memoranda of Understanding (MOU) have been reached on medical product safety in general, inspecting and auditing, good manufacturing, and good laboratory practices, regulating orphan drugs and sharing information about therapeutic products. Canada, Australia, Brazil, and China are among the more frequent partners to these agreements.

- **EU Mutual Recognition Agreements** exist between the European Medicines Agency and various countries.
and international organizations such as Australia, Canada, New Zealand, Switzerland, the US, and the World Health Organization. The areas of cooperation mainly include GMP inspections of manufacturers.

- **Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S)** develop, implement, and maintain harmonized Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products. There are 46 participating authorities on a worldwide basis.

- **Asia-Pacific Economic Cooperation (APEC)** is a consortium of 21 countries whose primary goal is to support sustainable economic growth and prosperity in the Asia-Pacific region and which aspires to foster regulatory convergence. In August 2008, the APEC Harmonization Center (AHC) was established under the authority of the APEC Life Sciences Innovation Forum (LSIF). Korea led and funded this proposal, which resulted in the approval of the AHC, at the sixth LSIF in August 2008. The AHC regularly convenes specialist workshops for industry and regulators including some specifically targeting cell-based therapies.

- **European Commission-Japan Mutual Recognition Agreement** covers GMPs for medicinal products and their import and export.

- Japan’s Confidentiality Agreements with various partner countries provide for information sharing on such items as procedures, post-market vigilance data, risk management plans, regulation of manufacturers, laboratory testing of therapeutic products, and counterfeit therapeutic products.

**Filling the Gaps**

Computerization of all aspects of regulatory activities has accelerated the ability for any country to gather information about products and therapies, regardless of formal agreement. Despite the ready availability of such information, countries vary widely in their ability to act on that information to protect individual patients and overall public health. For this and other reasons, third party accreditation agencies can play an important role in reducing the risks of unproven cell therapies, particularly in countries where medical entrepreneurship outpaces regulatory capacity. Third party groups can usually work more quickly and effectively than government bodies. At a minimum, they can provide structure to all steps of the cell therapy preparation process and product output. Despite these advantages, they are disadvantaged by their lack of enforcement authority. This can be overcome by legislative action that links third party licensing and accrediting decisions to legal enforcement mechanisms.

Currently, third party accreditation organizations include the following:

- The Foundation for the Accreditation of Cellular Therapy (FACT) is a non-profit accreditation organization that evaluates the quality of cellular therapy processes based on established standards. The standards are peer-generated and reviewed. This is an end-to-end evaluation process (from collection to administration), used on a world-wide basis.

- JACIE is a mostly EU-based non-profit accreditation organization that evaluates the quality of cellular therapy processes based on established standards, similar to FACT standards.

- AABB (formerly American Association of Blood Banks) is a non-profit accreditation organization originally chartered to advance the practices and standards for blood banking and transfusion medicine. Subsequently, this organization devised standards for multiple hospital services as well as cellular therapies. AABB accredits transfusion and cellular therapy programs against independent peer-reviewed standards, on a world-wide basis.
• American Association of Tissue Banks\textsuperscript{78} is a non-profit accreditation organization that establishes standards for tissue banking. AATB accredits tissue banks, primarily donor tissues and allograft distributed products, against peer-generated and reviewed standards. AATB is primarily a US-based organization.

• International Organization of Standardization (ISO)\textsuperscript{79} is a non-governmental organization that provides specifications and systems for a wide range of products and services. In healthcare, they are primarily focused on medical devices and equipment.\textsuperscript{80} ISO standards have been reconciled with regional and national regulations (eg, ISO 13485 for medical devices with compliance required for CE marking). There are no standards specifically for pharmaceuticals, biological medicinal products, or cellular and gene therapies. ISO accreditation is performed by third party accreditors, which are recognized as notified bodies by regulatory agencies. ISO is recognized on a world-wide basis.

• International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a consortium whose mission is to bring about greater harmonization of scientific and technical aspects of drug registration in order “to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.”\textsuperscript{81} The steering committee is comprised of regulatory authorities and industry groups.

PATIENT SAFETY AND RECOUSe IF HARMED

Most, if not all, regulatory frameworks are risk-based, meaning that they are designed to weigh a product’s benefits against its risks of doing harm and, to a lesser extent, of being ineffective. In theory, products with more risk will face more rigorous oversight and more demanding approval processes before they can be marketed or used in clinical practice. A particular challenge with cellular therapy products is that most regulatory structures were built to evaluate conventional drugs and devices. Therefore, well-known product characteristics for drugs do not necessarily have analogs in cell therapies, further complicating how to assess a cellular therapy product’s risk profile. Compounding this situation is that standard clinical trials have their own limitations in determining a product’s safety risks. Because no study design is perfect, no study can deliver perfect information about potential risks. Further, while clinical trials in countries with developed regulatory systems have adverse-event-reporting requirements for all patients treated, these too are limited. Because clinical trials inevitably involve limitations of design, size, and time, adverse-event reports cannot provide a complete safety profile of every medicinal product seeking market approval.

Developed regulatory systems also have post-market surveillance processes to report, track, and trend post-treatment medical events of approved products.\textsuperscript{82-86} Through post-marketing vigilance the regulator can track a product’s long-term safety performance across a large population of users. Manufacturers rely on this information for the same purpose, as well as to drive product improvements. While valuable, the resulting data are vulnerable to irregular or incomplete reporting. Organized and objective monitoring of patient safety following initial market approval can become sporadic or incomplete.

Beyond regulation, more developed countries typically offer additional mechanisms to promote patient safety. Informed consent, the operation of independent review boards and ethics committees, constraints on physicians’ practice of medicine, quality control of product preparation, and personal injury litigation can work together and individually to reduce the chance of a patient suffering direct or collateral damage from an unproven cell therapy.

Civil litigation is a common tool for redressing product-related harms, especially in developed countries where strong economies correlate with advanced legal
protections. Patients who suffer adverse events from medical treatment in these countries can take legal action against multiple entities, including, where relevant, the manufacturer, retailer, and providing clinician. The outcome of a successful lawsuit is often financial remuneration to the patient.

Patients who travel to a foreign country, particularly with a less developed regulatory infrastructure, and suffer adverse events as the result of treatment, have little to no legal recourse for the lack of efficacy or worse, harm, they have suffered from an unapproved or untested cellular therapy, making their effort a true case of caveat emptor.

PATIENTS’ RIGHT TO CHOOSE

There is a fundamental human precept that all patients have the right to choose their own treatment. This right is recognized worldwide.87 That said, patients do not have an unqualified right to access because the medicinal product approval process often requires that manufacturers closely manage and test for the safety and efficacy of almost any medical treatment before it is used commercially on humans.88, 89 Therefore, a patient has no practical ability to access a therapy commercially that is required to have, but has not obtained, regulatory approval. The right to choose one’s medical treatment is dependent on being fully informed of the treatment, procedures, risks, and known benefits. Absent a life-threatening emergency, treatment should not be given unless and until the patient or patient’s representative gives consent.

Patients must be proactive in becoming as informed as possible about treatment options. This may involve seeking input from relevant government agencies, reputable medical professionals, and medical associations. Patient advocacy organizations have a significant role to play in educating their constituents and protecting them from inadequately trained providers and charlatans, while legitimately advancing the medical science, regardless of regulatory constraints, where it makes sense to do so. Sustained and effective patient advocacy has prompted many countries to develop new regulatory pathways for allowing the sickest and neediest patients to receive untested therapies in controlled clinical settings.

Such measures reach beyond the traditional “one size fits all” investigational drug clinical testing and development process and have found new ways of delivering experimental treatments in controlled and closely monitored environments, while preserving product quality controls. When making a choice, a patient must consider the regulatory structure that governs the treating establishment, and proactively ask questions about the product’s risks and benefits as well as the applicability and satisfaction of regulatory approval processes for that product or treatment. The right to decide for one’s self must respect the need to protect one’s self. This can only be accomplished by understanding the trade-offs of making a particular choice within a particular country’s regulatory framework.

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Part 5
Unproven Cell Therapies & the Commercialization of Cell-Based Products

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THE BUSINESS OF UNPROVEN CELLULAR THERAPIES

The market of “medical tourism” that broadly includes patients that travel for cheaper treatments because of the high cost of care in their own countries is approximately $20 to 60 billion and growing at constant rate. We can estimate that the market for unproven cellular therapies can vary between $300 million and $2.4 billion based on recent analyses reporting more than 60,000 patients treated every year for unproven cellular therapies, with an estimated charge for those procedures between $5,000 and $40,000 each. Although these are significant numbers, in all likelihood most unproven cellular therapies will generate no predictable benefit for patients, despite the fact that in some countries the business of unproven cellular therapies is partly supported by governmental development strategies.

As previously described, there is a long and “inglorious” tradition of bogus medical treatment offerings for needy patients, predating the field of cellular therapy. Unfortunately, presumed medical innovations, often prematurely described in the lay press as “treatments,” quickly become the anticipated standard of care in the public eye, and for patients that are often desperately looking for novel interventions. There are many factors limiting the diffusion and successful commercialization of cellular therapies; however, the ultimate success of the field is dependent on the level of regulation, both in pre-marketing and in post-marketing phases of product development and translation. Without sufficient regulatory controls in place, unscrupulous commercial entities might be able to upset the commercial balance with unsubstantiated claims and unethical marketing practices. In addition, if patients are physically or economically harmed, there will be a detrimental effect further inhibiting the commercialization of cellular therapies.

In fact, if efficacy is never established and side effects are documented, then commercial entities will be hindered in their ability to generate a solid business case that could benefit industry, the biomedical field, society worldwide, and, most importantly, the patients. Furthermore, the market for unproven cellular therapies is volatile, particularly since these therapies are often associated with countries with developing economies. A series of factors, including economic and political instability, policy changes, restrictions on travel, and advertising practices, contribute to such uncertainty.

Investors understand the difference between unproven cellular therapies and therapies that have been evaluated in a thorough development and regulatory process. They do not want to be associated with approaches that may be perceived as unethical, with uncertain risks and benefits, and that may be promoted in a misleading manner. Therefore, unproven cellular therapies, which are marketed as safe and effective, can have a destabilizing influence on financial sector confidence that emerging cell therapeutics are well founded and ready for development. These approaches, which lack an evidence-based development process, erode confidence that core therapeutic hypotheses have been validated. This further exacerbates concerns that scientific platforms are adequately durable to support clinical proof of concept, and therefore further restricts investment decisions in the cell therapy space. It is important for investors to understand the regulatory pathway for development of cellular therapies. For a typical investor, predictability and milestone achievements are critical to management of ongoing investments. The unethical commercialization of cellular therapies complicates the development pathway for an ethical developer and introduces an unpredictable factor into an investor’s decision to invest in a cell therapy company.

For these reasons, it is very difficult to identify big multinational players in the unproven cellular therapies field; more often, small to medium enterprises are involved with manufacturing sites located very close to or in the same clinic where the patients are treated. Thus, cell manipulation and administration can take place within the same structure or institution, creating a sense of security about a product generated in house (“homemade”) and, therefore, apparently more controlled. This goes back to the “black box of unproven cellular therapies manufacturing” and to the challenges for both established and
under-development regulatory frameworks, as already discussed in Parts 3 and 4.

This “homemade” manufacturing model favors the grey area where unproven cellular therapies can proliferate with several advantages for the companies involved. A localized manufacturing process is less visible and less subject to regulatory and scientific scrutiny, a situation that typically characterizes these approaches. In addition, the entire process executed within a single clinic can provide the impression of a “compassionate use” that, without identifiable scientific bases and proper information, may be useless and even harmful. Finally, this model of unproven cellular therapies features a business model where cell manipulation takes place at relatively low production costs due to the limited controls introduced during the manufacturing process, and without investment into complex logistics or storage apparatus and procedures.

Advancing cell therapeutics to commercialization and standard of care requires very significant capital investment from pharma and healthcare, and to date, while investments in the field are progressively increasing, they have been somewhat cautious. Investors are looking for predictability in a validated business model, an attribute that is currently growing in the field of cellular therapy but that is put in danger when discussing unproven cellular interventions. Industry players realize the importance of validation of key market segments, such as the ones for mesenchymal stromal cells (MSC) or chimeric antigen receptor (CAR) T cells. These are healthy signs reflecting a maturation that cannot be hindered by unethical, unproven, only-for-profit–based cell therapeutic procedures.

UNPROVEN CELLULAR THERAPIES, MEDICAL INNOVATION, AND COMMERCIALIZATION

One of the most frequent claims supporting unproven cellular therapies delivery is that those strategies carry the unique opportunity to rapidly transfer promising cell-based therapeutic approaches for still unmet clinical needs. This not only represents a marketing strategy “to sell” these products, it is also aimed to convince society and patients of the innovative nature of the unproven cell therapy, and to support the false concept that medical innovation is slowed, or even stopped, by consolidated regulatory frameworks. However, we contend that many unproven cell therapies are actually anti-innovative. We are naturally supportive of scientific and medical innovations in cellular therapies; however, we do not consider unproven cellular therapies as a solution for still unanswered medical questions. In the last ISCT paper on the topic, it has been stated: “Medical innovation in cellular therapy may be viewed as ethical and legitimate use of non-approved cell therapy by qualified healthcare professionals in their practice of medicine. Patients not eligible for controlled clinical trials should be able to choose unproven but scientifically validated cell therapy medical innovations, if the researchers are competent and those seeking treatment are truthfully and ethically informed. There is a place for both paradigms in the cell therapy global community”.

Traditionally, innovation in biomedicine has mostly been linked with academia and translated to industry. In that process, by pre-clinical experimental approaches, scientists and industry used intuition, observation, and accurate data collection to draw results that were then further challenged into a relatively small number of patients. Those human subjects should be considered extremely precious for both ethical and business reasons; therefore, they should be carefully followed during and after the experimental treatments.

On the contrary, unproven cellular therapy strategies are generally introduced for a larger number of individuals with the stated intent of rapidly transferring the laboratory promise to patients without unacceptable waiting time. In this context, the loose scientific background together with the lack of basic scientific method cannot be considered as a spark for innovation. In fact, after unproven cellular treatments, patients are generally discharged from the clinic with no or limited follow-up on either possible benefits or side effects. In this way, even if there might be some
positive impact of the procedures, there is an absolute lack of interest in rigorously observing these outcomes to generate larger, controlled studies that are essential in validating hypotheses generated within clinical trials.

This abrogation of a scientific approach is generally unclear to patients that often read informed consents that can be misleading and result in the final decision to undertake risky procedures. Further details on this issue can be also found in Part 6 dealing with communication.

COUNTERACTING DISTRUST DUE TO UNPROVEN CELLULAR THERAPIES

One of the most critical aspects of unproven cellular therapies—commercial practices—can be related to the negative impact generated by distrust of cell therapy approaches. This lack of trust is the consequence of lack of efficacy and from adverse events. The negative impact of aversion to innovation will be and has been felt by regulators, payers, prescribers, and, most importantly, in the court of public opinion. The unethical promoting of unproven cellular therapies is also of particular concern since it is based on unfounded claims, unfounded promises, and targets vulnerable patients and families.

Regional economic development strategies are beginning to include accelerated regulatory approval options as an enticement for investment. This may represent tightening of standards for unproven cellular therapies in emerging markets, but also reinforces a competitive regional landscape, bringing therapeutic sponsors closer to nontraditional regulatory strategies. There are, of course, provisions for accelerated or conditional regulatory approval for traditional pharmaceutical products. Heterogeneity in global regulatory approaches based on accelerated or conditional approval or, if different tiers of regulation are adopted in different regions, will inhibit true harmonized development of cell therapy products and ultimately retard development of the field.

ISCT and related societies are positioned to work with regulators to implement harmonization of regulatory structures and to address commercialization roadblocks, and can have significant impact on controlling public and private sector perspectives on the cell therapeutic space. Unfortunately, there has been little progress in this area to date, and for this reason we are proposing a series of actions (Table 5.1) to ensure that patient welfare is kept first and foremost in the agenda to increase trust regarding cells as therapeutic agents.

Table 5.1 Proposed action steps:

| a) Establish a multilateral task force comprised of patient organizations, professional societies, and regulatory agencies to outline necessary actions to ensure patients are protected. |
| b) Implement a longterm program to promote global regulatory harmonization, including 1) early access programs for unmet needs that permit cost recovery and reimbursement, and 2) regulation that recognizes different tiers of risks and benefit and provides appropriate levels of regulation. |
| c) Establish a global, publically accessible, cell therapy patient safety registry. |
| d) Promote rationale scientific development of the field |
| e) Enable ethical and compassionate early access to promising cellular therapies |
| f) Cooperate with patient, scientific, and professional organizations to leverage and share existing processes and resources with potential patients |
| g) Provide tools to patients that can be used as guidance in evaluating a potential treatment |
| h) Establish a reimbursement clearing house to assist early stage companies that are developing ethical cellular therapies, an inexpensive source of reimbursement strategy and know how |

The goal is to extend ethical therapeutic sponsor and regulatory networks globally, such that incentives for
operating outside of the mainstream are reduced, and incentives for rational product development are in place. This can be achieved without diminishing economic development drivers or restricting cultural interests in clinical practice. If we work together to balance the rights of needy patients to receive unproven therapies with the protection of patients, and we achieve a relatively harmonized global regulatory structure, this will benefit not only patients, but also commercial organizations in the field.

THE ECONOMICS OF UNPROVEN CELLULAR THERAPIES

One important aspect of this issue is the practicing physician’s views and behavior. The prescriber has a responsibility to educate and inform the patient. The physician or other primary health care provider should guide the choices of the patient when there are no available alternatives for the treatment of the patient’s condition. The physician is there not to decide but to facilitate and inform decision-making and should not shy from expressing an opinion on the validity of some approaches when questioned by the patient.

If the physician or primary care provider prescribes unproven cellular therapies, this could generate support for those strategies and the perception that the approach could be acceptable or validated, despite the lack of what we normally would consider as adequate evidence. This could also create issues in terms of reimbursement. In fact, a very significant driver for unproven cellular therapies is the failure of patients to find promised new medicines reaching reimbursement expectations in traditional healthcare markets, driving individual patients to look for economic treatment solutions not accessible under traditional healthcare plans.

Patients are turning to unproven cellular therapies as an alternative when faced with a gap in approved therapies in standard of care and reimbursement policy. With approval in traditional markets in place, an economic driver in seeking non-traditional treatment remains. It is not unreasonable to anticipate medical treatments moving to regions providing reduced cost treatment—not unlike outsourcing manufacturing.

Patients certainly have the right to decide where to obtain treatment, provided they make informed decisions about the evidence supporting those treatments. There is also no issue when patients elect to travel to take part in bona fide and ethical clinical studies. The issue for patients is the manner in which unproven cellular therapies are sometimes marketed and promoted, with a minimum of efficacy or even safety data.

Thus, “medical tourism” is driven by an unmet market need, and while regions are moving to regulate activity, they are also acting to preserve market segment. Capital incentives to commercialize cell therapeutics have become an important driver for regional economic development. Regulatory policy is becoming a tool to stimulate this regional economic development, with incentives for accelerating regulatory approval or providing access under unproven cellular therapies at the forefront. A key issue is when and whether private insurers are going to reimburse unproven procedures. The health technology assessments supporting reimbursement must rely on adequately generated and assessed medical evidence, even if sometimes limited, in order to limit the use of unproven cellular therapies and further support provision of quality medical treatments.

A CALL FOR A NEW GLOBAL MULTILATERAL COLLABORATIVE FRAMEWORK

Few professional societies have taken action on unproven cellular therapies. The International Society for Stem Cell Research (ISSCR) has published patient guidelines for stem cell therapies and ISCT has published a paper on the subject, as well as conducted several public workshops. In addition, the US NIH has published a web-based tool on stem cell therapies. Unfortunately, the impact of these efforts has probably been minimal as most
patients do not read the scientific journals or visit the society or government web sites. In addition, there may be a perception that professional societies are excessively pro-industry and that their pleas for more regulation are based on anticompetitive interests, rather than altruism and true patient concern.

Although bone marrow transplantation, as a paradigm for cell delivery in humans, has been utilized for almost 60 years now, the field of cellular therapy is still relatively young. Even so, a surprisingly large number of translational organizations have developed in the field, most of which have unique missions, but also many overlapping interests. Unfortunately, there has been little cooperation among the cellular therapy organizations to date. What is needed is a broad alliance of the various players in the field. To enhance credibility and ensure that a patient’s interests and rights are preserved, it is essential to include patients and patient organizations in this alliance. The alliance would need to balance the rights of patients to obtain treatment with the rights of patients to participate in an ethical informed consent process, where all relevant risks and potential benefits are disclosed. Without patient leadership, the alliance may be accused of bias toward large commercial players in the industry. It is our hope that, working together with a coalition of stakeholders, we can fulfill this vision of a broad, pro-patient alliance in the near future.

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Part 6
The Role of Communication in Better Understanding Unproven Cellular Therapies

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MEDICAL CLAIMS AND UNPROVEN CELLULAR THERAPIES

There are many unsupported claims on the Internet regarding the commercial use of so-called ‘cell therapies’ for an extraordinarily wide range of medical conditions.1-3 Such putative cell-based therapies include so-called ‘immunotherapies’ for advanced-stage cancer and treatments using stem cells from various sources that are marketed in ways suggesting that they are effective against many different diseases affecting the brain, heart, lungs, kidneys, metabolism, muscle, cartilage, and bone. Additional unsubstantiated claims include the use of purported stem cells in cosmetic surgery or cosmetic products, the use of nutritional supplements to ‘enhance’ or ‘improve’ cell function, applications of stem cells in veterinary medicine, and the use of animal- or plant-derived cells for medical or ‘anti-aging’ purposes.

The majority of such claims have not been subjected to the rigorous scientific testing for safety and effectiveness that approved (or licensed) medicinal products must undergo before they can be sold, and for this reason have not been validated as standard of care by the greater community of medical professionals. The plausibility of claims made regarding such unproven cell-based interventions varies widely, from promising to implausible. Therefore, consumers should be aware that it is the responsibility of businesses and individuals making therapeutic claims—especially when they have a financial interest in the product or procedure—to provide evidence that their products are both safe and effective. Patients should not assume that putative stem cell interventions are safe and effective simply because particular products and procedures are available on the market. Rather, appropriate evidence that is accepted by the broader expert medical community and independent regulatory authorities is required to demonstrate an acceptable level of safety and efficacy and provide credible basis for marketing particular interventions as plausible therapies.

THE IMPORTANCE OF RIGOROUS TESTING BEFORE CLINICAL USES

Many cell-based interventions are advertised in a direct-to-consumer fashion without first being tested to determine levels of safety and efficacy. Such premature commercialization represents a significant risk to both individual patients and to healthcare systems (Table 6.1). For patients, such risks include the clear risk of physical harm caused by poorly characterized products of unknown safety and efficacy. Patients and their families are also exposed to financial risks and the possibility of psychological harm.

Table 6.1 Risks related to direct-to-consumer marketing of cell-based therapies

| • Patient physical harm |
| • Patient psychological impact |
| • Family psychological impact |
| • Financial loss with no benefit |
| • Damage to the integrity of healthcare |
| • Generating unrealistic expectations |

Unproven cell therapy marketed on a direct-to-consumer basis frequently cost thousands to tens of thousands of dollars. Patients are thus also exposed to the risk of paying substantial fees with little or no prospect of meaningful clinical benefit. There can also be psychological harm to patients and their loved ones when interventions marketed as effective therapies have no clinical benefits, raising and then dashing hopes of a cure.

The risks of unproven cell-based interventions extend to healthcare systems as well, as extensively discussed in Part 5. For example, direct-to-consumer marketing of unproven cell-based interventions can contribute to the undermining of regulatory frameworks intended to protect patients from physical harm and financial exploitation. Regulatory frameworks are also designed to protect the integrity of healthcare markets and provide a level playing
field based on requirements for rigorous, independently validated evidence prior to gaining market access or to incorporating into clinical practice as standard of care. Premature commercialization of unproven cell-based interventions damages the integrity of such markets and results in an uneven playing field in which companies that ignore regulations reap financial returns while businesses and individuals that comply with regulations are punished for respecting legal norms. For these reasons, it is important that cell-based interventions be carefully tested and reviewed before they are provided to patients.

Many cell-based interventions of unknown safety and efficacy are marketed directly to patients via online marketing. The promotional claims made by such companies suggest that the safety and effectiveness of such products is well established. However, such claims rely mainly on anecdotal evidence, patient testimonials, and poorly designed, small scale open label studies, which are not considered to be sufficient to provide reliable evidence of the safety or clinical benefit of medical interventions.

Properly designed clinical studies that have become the gold standard in evidence-based medicine are the accepted scientific tools for generating evidence that maximizes reliability and minimizes risks of bias, statistical error, misinterpretation, and potentially misleading anomalous findings. In such clinical studies, the investigational agent is tested, typically in a small group of research subjects, to determine whether it is sufficiently safe to continue testing in larger groups. If preliminary safety is determined, the clinical research may proceed to testing in larger groups, first to determine early signs of efficacy and to identify the optimal dose, and then to determine on a statistically meaningful scale whether the product or procedure is likely to be efficacious in the general population of patients with the same medical indication. Additional studies also help establish whether there are any rare adverse reactions to the intervention that were not detected during testing in smaller groups. Most such clinical research focuses only on a single indication for a particular disease or other medical condition. Results from testing in a group of research subjects with a given indication are not necessarily representative of the intervention’s safety or efficacy in individuals with other medical conditions. For these reasons, communications relating to experimental-stage interventions must be clear, accurate, and specific in order to appropriately reflect the state of scientific understanding and to prevent exploitation of patient hope for financial gain.

Some companies that market unproven cellular therapies have begun to advertise patient funded clinical trials, in which patients must pay substantial fees, if they wish to participate as research subjects: a practice that is highly problematic for both scientific and ethical reasons. In such studies, the fact that patients pay to serve as research subjects makes it difficult to randomize or blind the subjects, because patients are typically paying for access to a particular intervention. Charging patients to participate in such studies may also have serious adverse influences on important features of the study design, such as standardization, statistical power, and inclusion and exclusion criteria. Additionally, as sicker patients may have exhausted their personal savings and be unable to afford the cost of participating in patient-funded trials, the results from such pay-to-participate studies may not be representative of the larger population of people affected by the indication. Another possibility is that only comparatively well-off individuals can afford to participate in such studies, resulting in selection bias that includes some individuals and excludes others on basis of personal wealth, which may skew the study results.

MARKETING CLAIMS AND TOKENS OF SCIENTIFIC CREDIBILITY

Many strategies are used to convince patients that they stand a good chance of benefiting from purchasing unproven cellular therapies (Table 6.2). Companies marketing cell-based interventions often use testimonials to promote their purported “therapies” as both safe and effective. Such testimonials can be found on companies’ websites, Facebook pages established by clinics and
Table 6.2 Tokens of scientific credibility and the marketing of unproven cellular therapies:

- Patient testimonials on websites of sellers
- Patient testimonials on social networks
- Linking the advertised cell-based intervention to data published in scientific journals by researchers unrelated to the sellers
- Linking the delivered cell-based intervention to data published by in-house researchers in "predatory journals" that lack meaningful publication standards
- Identifying an IRB willing to approve patient-funded clinical studies that involve administration of unproven cell-based interventions
- Packaging putative cell-based “therapies” as clinical studies, and registering such studies with clinicaltrials.gov or other trial registries

Patient testimonials are among the many marketing devices used to persuade patients to purchase unproven cell-based therapies. Many clinics attempt to legitimize cell-based interventions lacking evidence of safety and efficacy by providing links to articles published in scientific journals. However, these articles are often about pre-clinical studies conducted using animal models and thus provide no insights into whether cell-based interventions are safe and effective in treatment of humans. Beyond linking to their work, clinics typically have no relationship to the researchers publishing such articles.

In other cases, individuals employed by companies and clinics marketing unproven cellular therapy interventions succeed in publishing case reports or other studies often involving paying human subjects, which by design are incapable of yielding generalizable knowledge of clinical risk and benefit. As the number of “predatory” journals proliferates, it is becoming easier to place poor-quality articles in journals that lack robust scientific peer review. These articles, even when based upon research of little or no scientific value, can influence decision-making by prospective patients by helping persuade them that they are gaining access to legitimate, evidence-based treatments. Reference to patents can also help legitimate cell-based interventions even though both patents and patent applications provide no insight into whether particular cell-based procedures are safe and effective.

Another recent trend involves clinics marketing access to clinical studies and then finding an institutional review board (IRB), also known as research ethics boards or research ethics committees, willing to provide approval even when patients are charged to participate, inclusion and exclusion criteria make little sense, pre-clinical research has not been conducted, and national regulatory bodies have not reviewed the studies and allowed research to proceed. Clinics then register such studies in clinicaltrials.gov and databases used by patients searching for clinical trials related to their illness or injury. This approach to marketing can help convince patients that legitimate clinical research is underway, even though no adequate vetting takes place before studies are registered.

In short, there are many marketing strategies that clinics advertising unproven cellular therapies use to convince patients that they are accessing evidence-based treatments.

It can be very difficult for patients (and even sometimes for physicians) to distinguish well designed and properly conducted clinical studies from cell-based interventions that do not have a credible basis in scientific research. Clinicians and stem cell researchers can play an important role in helping patients assess marketing claims and whether clinics marketing cell-based interventions are making scientifically credible statements.
“SAFETY-ONLY” REGULATORY ENVIRONMENTS

Globally, unproven cellular therapies require approval by regulatory agencies at different levels. In many countries, before applying for a biologics license, pre-clinical research and then clinical trials are undertaken. In such regulatory environments, cell-based interventions must have been demonstrated to work for a particular intended use in treatment of illnesses or injuries before entering the market. However, in some countries there is pressure to shift away from regulatory frameworks that require evidence of both safety and efficacy toward a regulatory model in which safety only has to be demonstrated before cell-based interventions can be marketed. The assumption is that market forces will, over time, ensure that only the most efficacious interventions are commercially successful.

Acknowledging the serious consequences that flow from abandoning requirements for credible evidence of efficacy, it is also important to emphasize that safety is a complex concept encompassing many factors. Safety of cell-based interventions is not only related to the type of cell, but also to such factors as the method of administering cells, where cells are administered, cell dose, and the number of deliveries that are used for a specific clinical indication. The multifactorial nature of safety is often unrecognized. Even when evidence of an adequate safety profile exists for treating a particular clinical indication, it is important not to assume that the same level of safety exists when the same cell-based approach is used in the treatment of other medical conditions. Therefore, in countries where evidence of efficacy is not required before cell based interventions are granted market access, patients need to understand that they risk their health and personal savings for procedures that may have no credible evidence of effectiveness.

Some advocates argue that as long as there is evidence that cell-based interventions are safe, it should be permissible to sell and buy them, even if the intervention does not prove to be effective. However, patients generally pay for cell-based interventions because they are ultimately persuaded that what they are receiving is or will be effective, whereas in such regulatory environments sellers inevitably benefit financially, irrespective of whether their products actually work as described.

WAIVERS OF LIABILITY AND CONFIDENTIALITY AGREEMENTS

Companies marketing unproven cellular therapies often ask patients to sign waivers of liability. These documents typically state that patients who sign them agree that companies are not liable in the event that cell-based interventions are ineffective, cause harm, or otherwise result in unintended and undesired outcomes. Some waivers have confidentiality agreements attached, in which patients agree not to disclose even the fact that they have waived liability, as well as details about the cell-based intervention and whatever other contracts they have been asked to sign.

Before entering into such disadvantageous agreements, patients need to understand that they have legal rights, and they should exercise great caution whenever they are presented with documents that can be used to restrict their rights. Likewise, they should be wary of signing any document that imposes a gag order on them and prohibits them from discussing the details of their treatment and agreements with the provider. Credible companies with legitimate treatments have few, if any, reasons to impose such restrictions on patients. Patients should be advised to obtain legal counsel, review all such documents with their lawyers, and determine whether they are wrongly being asked to surrender their legal rights. Before signing such documents, patients need to read and understand what they are signing and consider how these agreements might subsequently be used to limit their options for legal recourse.
INFORMED CHOICE

Patients, often in discussion with loved ones, need to ensure they make informed choices. When deciding whether to have a cell-based intervention or any other procedure, there are many details patients need to know before they can make informed choices. At the most basic level, they need to know whether they are receiving an established, evidence-based medical intervention that falls within the current standard of professional care or an experimental intervention for which evidence of safety and efficacy is currently lacking. If the latter, patients need to be informed of the need to decide autonomously whether they wish to participate in clinical research. All clinical studies must clearly indicate that the purpose of the study is research—not routine, established treatment—and that participation entails both risk and no guarantee of benefit.

If patients are considering participating in clinical research, they first need to be given detailed information concerning the purpose of research, all procedures and tests (see also Parts 2 and 3), both routine and experimental, that will be performed during the study, the anticipated length of the study, all foreseeable risks and discomforts, all foreseeable benefits to the research subject or others, alternative procedures or courses of treatment, the extent to which confidentiality will be maintained, who will have access to their medical records, and whom patients can contact if they have any questions, concerns, or complaints about the research. Patients should also be told what compensation they will receive and what medical interventions will be provided without cost to them, if they are injured or otherwise harmed as a result of participating in research. In order to objectively establish safety and efficacy, patients should expect detailed follow-up requiring subsequent visits and testing.

Patients considering participating in clinical research must always be informed that their participation is voluntary. They must be told that they are free to refuse to participate and that this decision will not in any way be held against them. If they decide to participate in a study and then decide that they wish to withdraw, they are free to do so at any time without penalty. Research subjects who choose to withdraw from clinical studies should promptly be referred for appropriate treatment. Patients and prospective research subjects must also be told about the circumstances under which the study may be terminated by the investigator or study sponsor, whether they must bear any costs as a result of participating in research, the anticipated number of subjects to be involved in the study, and whether they will be reimbursed for any expenses (such as taxi rides or parking fees) that they incur during the study. Potential financial conflicts-of-interest of the investigators—both personal and institutional—must be disclosed to prospective research subjects.

POINTS FOR EMPHASIS

Three points must always be kept in mind whenever approaching patients and discussing clinical studies with them. First, informed consent and informed choices involve processes of communication and deliberation. “Informed consent” is never just a signature on a form or a rote exercise in “getting consent.” Rather, it is important to provide information to prospective research subjects, give them opportunities to ask questions, make sure they understand the information they have received, and provide occasions for additional conversations following the initial “informed consent” process.

Second, research subjects often overestimate benefits from participating in research and confuse participation in clinical studies with obtaining access to established treatments. It is imperative that benefits are not exaggerated, risks are discussed in an honest manner, and research is clearly distinguished from treatment. Pains must be taken to ensure that research subjects do not interpret experimental interventions as established therapies.

Third, scientific knowledge is dynamic. During the course of research, evidence of new risks and benefits can emerge, either within a study, in related studies, or in determinations by regulatory bodies, expert panels, and
other qualified independent bodies. When new evidence concerning risks or benefits emerges, this information needs to be promptly conveyed to researchers, IRBs, national regulatory bodies, and research subjects. Informed consent forms need to be revised and research subjects need to be approached and asked whether they still wish to participate in research. In some cases, new evidence of benefits or risks can be so significant that studies must be halted; either to ensure that all research subjects have access to a newly identified treatment or to ensure that research subjects are no longer exposed to larger than anticipated risks. Data Safety and Monitoring Boards play an important role in weighing evidence as it emerges during the course of clinical studies.

COMMUNICATION BETWEEN SCIENTIFIC SOCIETIES, PATIENTS AND THE PUBLIC

ISCT members and other professionals in the cell therapy industry and academia should expect to receive inquiries from patients and others considering unproven cell-based interventions. Preliminary evidence suggests that information from clinicians and other professionals can influence patients’ decisions. ISCT members should be prepared to address these inquiries in a responsible, evidence-based manner to help patients, and sometimes their families or physicians, make informed decisions. These discussions should be informed by an understanding of the current state of knowledge of various cell-based interventions as demonstrated in the peer-reviewed literature and through clinical trials. In addition, these patients are often highly networked with others in their specific disease community. Such communities and patient advocacy groups need to be better included in the development of education and communication programs; such as the one here proposed with this web-based resource. Clinicians, scientists, and other industry professionals are well positioned to provide valuable guidance as patients make decisions that can have significant consequences. Clinicians, in particular, should be aware that patient interviews suggest that vague or ambiguous responses to patient queries about specific unproven cell-based interventions may be interpreted as a sign of tacit materials. In many cases, patients considering unproven cell-based interventions are doing so because they have a chronic or degenerative condition for which they have been told there are no effective treatment options beyond palliative care. Such patients often report that obtaining access to unproven cell-based interventions provides them with a much-needed sense of hope, even if they realize there is little likelihood of a cure (or even significant improvement). Indeed many patients realize they are considering an unproven treatment but want to take action in hope of improving their health or slowing a decline in health.

As might be expected, patients considering unproven cellular therapy interventions are often interested in learning as much as possible about the benefits and risks associated with the intervention before making a decision to proceed. Interviews with patients suggest that assessments of efficacy rely heavily on anecdotal data, including testimonials posted on clinic websites, media reports, and conversations with fellow patients. Assessments of risk often rely on anecdotal data as well, including assurances from clinicians providing unproven cell-based interventions that side effects are rare and risks are minimal.

Cell therapy organizations and professionals consulted by patients considering UCT interventions should understand that they are typically only a single voice among many sources consulted by such individuals; indeed, these patients are often highly networked with others in their specific disease community. Such communities and patient advocacy groups need to be better included in the development of education and communication programs; such as the one here proposed with this web-based resource. Clinicians, scientists, and other industry professionals are well positioned to provide valuable guidance as patients make decisions that can have significant consequences. Clinicians, in particular, should be aware that patient interviews suggest that vague or ambiguous responses to patient queries about specific unproven cell-based interventions may be interpreted as a sign of tacit
Great care must be taken when responding to questions in an informed and evidence-based manner that encourages patients to ask questions and have a meaningful conversation.

Physicians, scientists, patient advocacy groups, and professional societies can all play important roles in promoting informed decision-making by patients and helping patients understand the risks and benefits of participating in research. While there is a long history of advances in biomedical research, there is an equally lengthy history of research abuses and of profiting from the sale of unproven, overhyped, and sometimes dangerous medical interventions. It is important to ensure that all research subjects make informed choices, are exposed to a favorable risk/benefit ratio, and are treated with dignity, honesty, compassion, and respect. ISCT communication aims to help researchers, research participants, patients, and their associations in assessing unproven cell-based interventions in an informed manner and promoting informed, critical understanding of key ethical, legal, and scientific elements of human subject research.

REFERENCES


ON UNPROVEN CELLULAR THERAPIES 2015

Talking About Unproven Cell-Based Interventions
A Project by the ISCT Presidential Task Force on the Use of
Unproven Cellular Therapies

First Edition

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