Clinical Study Issues in Early Phase Trials of Cell and Gene Therapies

SLIDE 1
This presentation will discuss early clinical study issues in cell and gene therapy.

SLIDE 2
The FDA has regulations describing clinical trial types and designs, and those regulations are listed on this slide. The definitions in the regulations largely follow those in the ICH E8 document on general considerations for clinical trials. This talk will address largely issues for Phase I and some Phase II studies.

SLIDE 3
This presentation will review the clinical risks associated with cell and gene therapy products; some caveats for clinical protocol design, implementation and analysis particular to these products; and, finally, issues regarding donors for certain cell therapies.

SLIDE 4
The foremost concern in reviewing any clinical trial is safety, but there are additional risks with cell and gene therapies that need to be considered. For gene therapies, these risks include direct effects on the recipient genome, including transformation to a cancer or a modification of germline DNA that can be passed down to the next generation; direct effects of the transgene expressed by the gene medicine; or toxic responses to the vector itself, such as exaggerated cutaneous reactions or coagulopathies.

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Cell therapies are even more complex as a result of the nature of the product. The mode of action is not always clear, and potency assays are imprecise, so it may not be possible to completely predict the risks. As far as manufacturing goes, small changes in manufacturing could have an impact on clinical outcome. The clinical reviewer of INDs looks at the CMC information in an application because changes in the manufacturing process may affect the toxicity of the final product. And like many of the gene therapies, the cell therapies may have an extended life span in the recipient. In fact, some cell therapies are expected to last a life time. The stability of the cell function and its activity can only be assessed by long-term observation.

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For cell therapies, the clinical adverse effects may result from differentiation in vivo into undesired cell types or formation of tissues ectopically, including transformation to tumors; trafficking to sites distant from the desired location; induction of an immune response to the transplanted cells; or if the cell therapy has a lymphoid component, it may induce graft-versus-host disease.

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And for gene modified cell therapies, all of the risk factors mentioned in the previous three slides apply.

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Mitigating these risks for first-in-man clinical trials depends heavily on the data generated by preclinical animal studies. The adverse event rate in the animals is used to find the best starting dose. The organ toxicity profile is used to try to devise the safety monitoring plan and any additional monitoring that would be required for the clinical study. The biodistribution in the animals is looked at to try to figure out the best way to do pharmacokinetic sampling or biodistribution in humans, and to assess whether there is any dose-schedule dependency in animals, which might give ideas of the best regimen to select for the clinical protocol. Now, this sounds a lot like what you would see with a basic small molecule, but there may be some confounding issues for cell and gene therapies.

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Some cell and gene therapy products are relatively nontoxic, making it difficult to identify a safe starting dose. Some products may be very human specific, so results from testing in an animal model may not accurately predict toxicity in humans. And, finally, when products are to be administered via a specific device, such as stem cells injected into the heart or brain using a catheter, it is expected that the preclinical testing will include testing the same route of delivery. This would demonstrate safety of the procedure, which may be complicated if a device small enough for delivery in the animal is not available.

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Let's move on now to protocol design.

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For the early clinical phase trials, especially first-in-man studies, the major objective is usually to identify a safe dose, such as the MTD, or maximal tolerated dose, and establish the safety profile. Many investigators will simply indicate the objective is safety. But establishing that a drug is safe will take thousands of patients, so for these early-phase clinical trials, far more specific objectives in the protocol are expected.

And since the product may in fact have little or no toxicity, it may not be worthwhile to use toxicity as an endpoint. Biologic outcomes, such as

engraftment, transgene expression, optimal biological dose or immune response to a vaccine are alternatives for primary endpoints.

Finally, it is also expected that even in early phase trials, secondary objectives for efficacy measures, either short-term response or longer-term outcomes, should be included. This data will be very helpful is designing later phase trials.

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In fact, if the eligibility criteria are highly selective, such as, for example, a limited volume of tumor when testing a cancer drug, it may be recommended that the design include a control group, that is, a randomized Phase I, since outcomes for such subgroups may not be readily available in the literature.

FDA looks at the risk-benefit for the population described, since cell and gene therapy products may have long-term risks. Good risk patients are almost never included in first-in-man trials for these products. However, one does not want to be too restrictive in the patient population, nor do you want a population that is so ill that the toxicity cannot be assessed. A balance between the science and the risk-benefit must be met.

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Manufacturing a personalized medicine poses additional challenges in the study design, since one needs to take into account the time frame for manufacturing when establishing eligibility criteria. For example, the eligibility criteria when the tissue is first collected may differ from the eligibility criteria at the time of administration. The later criteria may need to reflect the expected clinical status of the recipient who waited four months for their therapy. In fact, the protocol should be specific about when consent is obtained for treatment, at the time the tissue is collected or when the first dose of therapy is administered. Similarly, the protocol should specify when patients are taken off study, and when they are replaced. For example, if there was a manufacturing failure, is that considered an endpoint in the study for feasibility, or does that subject get replaced for accrual purposes?

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Let's move on now to the treatment plan. First, how is the starting dose determined? If there are animal or in vitro data to support a starting dose, the pharm/tox reviewer can generally determine whether the proposed starting dose is safe. If there are no animal or in vitro data, but there is substantial literature on the product class, that information might be used to justify the starting dose. For example, if someone comes up with a new method to select CD34 cells from marrow, the manufacturer would probably not be required to do a lot of preclinical studies, or even a Phase I study, since it is already known how many CD34 cells are needed for hematopoietic stem cell transplantation. However, if there are no animal data and no experience with the product class, it may be difficult to justify

the starting dose. Discussion with other reviewers may be useful in identifying the safest way to approach such circumstances.

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Secondly, what units should be used for dosing? The products can be very heterogeneous with regard to active, inactive, and toxic fractions. For example, some viral particles may be empty and therefore have no therapeutic activity, but if the vector itself is toxic, then the total particle number needs to be incorporated into the dosing scheme.

Cell therapies are equally complex. For example, for an allogeneic stem cell product, dosing might need to be based on the active component, the CD34 cell. But, to prevent graft-versus-host disease, there would need to be a limit on the toxic cell type, the CD3 T cell.

However, frequently the active cell subset has not even been identified clearly, so the dose is based on the total number of nucleated cells. In this situation FDA frequently asks the sponsor to collect data on various subsets in the final cell therapy product, and plan a comparison to the clinical outcomes, in an effort to identify the important cell subset.

For gene-modified cells, in the past, the efficiency of transducing cells has been extremely low, 10-20 percent. With the new viral vectors, such as late generation retroviral vectors and lentiviral vectors, transfection rates are up to the 70 - 90 percent range, although they still vary from lot to lot. This variation may lead to substantial differences in active cell dose between patients. If the transduced cells can be identified easily, using the transduced cell number would ensure consistent dosing between patients.

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For the treatment plan, FDA generally asks for single-dose regimens for first-in-man trials. Repeat dosing is generally not allowed until there is a good understanding of the toxicity of the product. Also, it is expected that multiple patients do not start treatment at the same time. There should be a minimum follow-up after the first patient is treated to ensure safety before the next patient can start.

If there is a control group, several ethical issues need to be considered if the study is blinded. For example, for a cell therapy delivered surgically into the brain, the control group might need to have a burr hole placed in order to preserve the blind. Or the control patients may need to receive an injection of a painful inflammatory substance if the experimental product is known to produce local irritation. Whether such controls are allowed, or even needed, is very specific to the product and the intended population, although in general they are best avoided.

Add-on regimens are allowed, but FDA needs to be aware of certain potential problems with such a design. For example, when given concurrently, will the chemotherapy inhibit the development of an immune response to a vaccine? Or will a relatively nontoxic biologic interact with chemotherapy or radiation and increase their toxicity? This latter case is especially problematic when defining dose-limiting toxicities.

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For first-in-man studies, all potential toxicities are considered even if the therapy is an add-on on top of chemotherapy, radiation, or another drug. It is important to know everything that is going on for the first 30 days after that drug or combination regimen is given. For products with well-developed toxicity profiles, target safety monitoring may be sufficient, but that is clearly not the case for any first-in-man study.

The choice of dose-limiting toxicity may vary from study to study based on the natural history of the disease and the level of toxicity expected from standard therapy. For example, one might accept a greater degree of toxicity for a patient with end-stage cancer who has no other options, but less toxicity for a healthy individual getting a preventive medicine.

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Let's look at some examples. Listed on this slide are the dose-limiting toxicities that have been established for patients with active cancer being treated in the outpatient setting. Unacceptable toxicities include a low neutrophil count for at least seven days or, with sepsis, a low platelet count for at least seven days, a very low platelet count, or any grade 3 or 4 organ toxicities. And it has been established now for decades that it is unacceptable when more than 30 percent of the outpatients develop any of these toxicities. This limit varies around the world, between 17 and 30 percent, so check with your colleagues in your local jurisdiction to determine the appropriate cutoff for DLTs. The percentage serves as the basis for the 3-plus-3 design for identifying the maximum tolerated dose, or MTD, of a drug.

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For some situations, this degree of toxicity might not be acceptable, such as when preclinical studies show no expected toxicities, or when giving a preventive vaccine to a normal healthy population. In these circumstances, even a grade 2 organ toxicity might not be considered acceptable. On the other hand, when adding a new biologic onto a very toxic regimen, such as high-dose chemotherapy and radiation, all patients would be expected to develop a grade 3 toxicity even without the new drug. So, the 3-plus-3 rule could not be used with the usual definition of dose limiting toxicities.

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For these cases, other statistical methods have been developed to establish dosing for phase II trials using the least number of patients possible and using toxicity limits acceptable for the intended population. This table describes some of the newer Bayesian designs that can be used to identify the MTD of a single drug or of a combination of new drugs. In comparison to the standard 3-plus-3 design, they are all much more dependent of the active participation of a statistician, but they are also far more flexible with regard to the actual endpoint specific for the product and the study population.

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Efficacy endpoints for cell and gene therapies are the same for any other product in the indicated population. There is no discount based on the product. Whether the therapy is a small molecule, a gene therapy, or a cell therapy, the end point for a particular disease would be the same.

Definitions of time-to-event endpoints, however, need to take into consideration the manufacturing steps for personalized medicines. For example, survival ends when the patient dies, but does it start at study registration, when the tissue is harvested, or when treatment starts? These questions should be addressed in the protocol up front.

The definition of response generally follows standard accepted criteria, although for immunologic therapies where response may be delayed, or where progression may be confused with an inflammatory response, the protocol should reflect the modification of the definition to accommodate these well-known phenomena.

Finally, if you are conducting a phase 1b study or using an in vitro end point, FDA always asks sponsors to use two assays for an end point, because you can not be sure if a single assay actually reflects the real situation, since most of the in vitro assays used are not validated for a clinical outcome.

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Safety monitoring, of course, is an important element of the protocol. The U.S. has explicit regulations for reporting of serious adverse events and for annual safety reports. These generally follow the ICH guidance for safety reporting. And although expedited reporting is generally limited to suspected unexpected serious adverse reactions, there are several expected adverse events listed here on the slide which may be expected to be reported expeditiously. This is because they may reflect manufacturing issues that need to be addressed before more patients can be treated. The requirement for expedited reporting sometimes may also be broadened, when the product is very human-specific and there are limited preclinical safety data. This allows for catching an unexpectedly unsafe therapy and avoiding toxicity for future patients.

For gene therapies, there are also safety concerns for family members and health care providers when a viral vector is used that can be transmitted to others. In such a case, FDA expects the sponsor to generate data to confirm that there is no transmission of a gene medicine from the study-subject to close contacts or household members.

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FDA has a guidance document for long term safety monitoring for gene therapy. If the vector is integrating or has latency, such as HSV, FDA requires the sponsors to follow the patients for 15 years to make sure that there are no late safety issues. This is especially so if the target is a non-dividing cell, which may not display any problems until many years later.

Similarly, if the transgene is a growth factor or a transcription factor, which may alter cell cycling and predispose patients to cancer, this is also something to be looked at long term, not just 30 days after administration of the product.

For cell therapies, if the transplanted cells can transform or if they can migrate, there is a potential for developing ectopic tissue. Longer-term safety monitoring would be necessary.

FDA tries not to make these monitoring plans burdensome for the sponsor. FDA may ask that, once a year, the sponsor indicates if the patient is alive, or if they developed cancer or any other health issue. The sponsor can do this by sending a letter or making a telephone call to the patient. This is important safety information that does not require a lot of work to collect.

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Finally, let's briefly look at some donor issues.

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Title 21 of the Code of Federal Regulations, section 1271 provides the regulations for screening and testing of allogeneic donors for cell and tissue therapies. This regulation was put in place specifically to prevent the transmission of infectious diseases, such as hepatitis or AIDS, from donor to recipient. If cells are harvested from a directed donor as part of the study, the protocol or a study-related document needs to address how the investigators are to comply with the regulation. The donor treatment plan is also reviewed to ensure that it is not investigational, since that may entail additional consent, IRB oversight, and safety monitoring. If the donor is not a study subject per se, or if the cells are purchased from a vendor for administration to the study subject, then the protocol may need to simply list the details on how the cells are chosen as acceptable for the study. If the cells are to undergo additional manipulation prior to administration to the recipient, the product reviewer will also ensure that the starting material includes the documentation needed to ensure compliance with 21 CFR section 1271.

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So, in conclusion, the cell and gene therapy products have some unique characteristics compared to the small molecule drugs. These products require novel study designs to address their uniqueness. Close attention needs to be paid to the details when defining clinical end points. Special monitoring and reporting should be considered because of the safety issues associated with these products, especially long-term monitoring. And, adequate donor screening is required to prevent the spread of infectious disease.

SLIDE 27
Listed here are guidance documents relevant to Clinical reviewers that can be found on the FDA website.

SLIDE 28
Listed here are references for clinical trial design referred to previously in this presentation.

SLIDE 29
This slide lists the acronyms used in this presentation.

Slide 30
This concludes the presentation, "Clinical Study Issues in Early Phase Trials of Cell and Gene Therapies".

We would like to acknowledge those who contributed to its development. Thank you.