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Cellular Therapies Clinical Research Roadmap: Lessons learned on how to move a cellular therapy into a clinical trial

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Abstract

A clinical research roadmap has been developed as a resource for researchers to identify critical areas and potential pitfalls when transitioning a cellular therapy product from the research laboratory, via an Investigational New Drug (IND) application, into early phase clinical trials. The roadmap describes four key areas; basic and preclinical research, resource development, translational research and good manufacturing practice (GMP), and IND assembly and submission.

Basic and preclinical research identifies a new therapeutic concept and demonstrates its potential value using a model of the relevant disease. During resource development the appropriate specialists and the required expertise to bring this product into the clinic are identified (e.g., researchers, regulatory specialists, GMP manufacturing staff, clinicians, and clinical trials staff, etc.). Additionally, the funds required to achieve this goal (or a plan to procure them) are identified. In the next phase the plan to translate the research product into a clinical grade therapeutic is developed. Finally regulatory approval to start the trial must be obtained. In the United States this is done by filing an IND application with the Food and Drug Administration.

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The NHLBI-funded Production Assistance for Cellular Therapies (PACT) program has facilitated the transition of a variety of cellular therapy products from the laboratory into Phase 1/2 trials. The five PACT facilities have assisted investigators by performing translational studies and GMP manufacturing to ensure that cellular products met release specifications and were manufactured safely, reproducibly, and at the appropriate scale. The roadmap resulting from this experience is the focus of this article.

Keywords

cellular therapy; FDA; GMP; IND filing; NHLBI; PACT; preclinical studies; resource development; translational research

Introduction

The National Heart, Lung, and Blood Institute's (NHLBI) Production Assistance for Cellular Therapies (PACT) program was developed to assist investigators to transition promising new cellular therapies into early phase clinical trials. The program provided successful applicants with assistance by developing product manufacturing and testing procedures to support the clinical trial, regulatory assistance for filing the Investigational New Drug (IND) application with the FDA, production of the cellular product for patient administration, and collection of follow-up data for use in IND annual reports.

Experience from this program suggested that many investigators were unfamiliar with the various phases of this process and, as a result, the transition took longer than expected. To address this issue, a clinical research roadmap was developed by the five PACT cell processing facilities, NHLBI, and the Coordinating Center as a resource for researchers new to the cellular therapy field. This was intended to assist them to identify critical areas that must be addressed when transitioning a new cellular therapy into human clinical studies under an -IND- application. (see Figure 1)

Critical Areas of the Clinical Research Roadmap

Basic and Preclinical Research Phase

Basic laboratory research may result in the discovery or identification of a cellular system with therapeutic potential. Many times the researcher is unaware of the steps required to demonstrate this potential in a disease-related model, and of the procedure to transition their discovery into a clinical trial. This can be facilitated by input and advice from other investigators familiar with the design and performance of preclinical studies to demonstrate therapeutic promise. Assistance may take the form of evaluating the cells in animal models of the disease, and/or in vitro experiments to show that the therapeutic candidate can achieve the desired effects in the laboratory.⁽¹⁾ Even at this early stage, a team approach is encouraged, involving individuals with an understanding of experimental models, statistical design, pharmacology/toxicology studies, generation of a preclinical data package, and of potential barriers to manufacturing the therapeutic candidate for therapeutic use. These studies should result in the identification of a cellular product in a form that is ready for (or can easily be adapted to) evaluation in clinical trials.

Resource Development - Study Team

Once a promising therapeutic candidate has been identified, and preclinical studies have confirmed its potential value, a team needs to be assembled to determine the resources required to move the candidate through to a clinical study. The resources are not only financial, but must include individuals with the appropriate expertise. These should include:

- **Principal Investigator (PI):** the individual who has ultimate responsibility for the clinical study and is familiar with the therapeutic potential of the product and the IND process.
- **Project Manager:** the individual who coordinates the efforts of the study team and ensuring milestones and timelines are met within the project budget. The project manager flags issues and works with the team to develop strategies to mitigate risks and serves a key role in facilitating technology transfer and process development through effective management of people and resources.
- **Clinical Research Team:** is composed of physicians, research nurses, clinical research associates (CRAs), and other staff, who conduct subject enrollment, treatment and follow-up care.
- **Technology Transfer, Product Development, and Good Manufacturing Practice (GMP) Manufacturing experts:** work closely together and interface directly with the basic researchers, the PI, study team, quality assurance (QA) and regulatory experts to transition processes from the discovery or translational phases to larger-scale GMP-compliant manufacturing procedures to produce cells for the clinical trials. The manufacturing technologists must be trained in both GMP-compliance and also on the standard operating procedures (SOPs) for making and testing the new product. (See Translational Phase).
- **Biostatisticians:** who assist the PI and Study Team with formulation of aims/hypotheses, study design and identification of appropriate sample sizes. The biostatistician performs interim and final statistical analysis.
- **Regulatory experts:** who provide regulatory oversight of the project from research development through clinical trials. They are involved in preparing and submitting data to the regulatory groups overseeing the clinical trial, such as the US Food and Drug Administration (FDA), Institutional Review Board (IRB) and Data and Safety Monitoring Board (DSMB).
- **Quality Assurance (QA) experts:** who ensure compliance with GMP regulations throughout product development and manufacturing and verify that the clinical product meets predefined lot release criteria. They conduct compliance audits and advise on product manufacturing issues.
- **Quality Control (QC) experts:** who perform release testing on the clinical products under SOPs and provide data to demonstrate ongoing GMP compliance.

Translational Phase

It is not uncommon for a PI to underestimate time, costs, and the regulatory/quality challenges associated with bridging the gap between discovery and clinical trials. In the academic setting, the primary measure of success is a strong publication record, which may be important for product development, but is not predictive for determining product efficacy. Investigators are also motivated, out of necessity, to write grant applications, which, to be competitive, require innovative technologies and ideas that identify underlying mechanisms and continue to build on the core scientific knowledge. Funding for these activities does not traditionally cover development of novel cellular therapies, or the preclinical safety studies required to transition the product into clinical use. Sensitive to these translational challenges, the PACT program aimed to assist investigators to effectively move cellular therapies from the proof-of-concept stage into initial clinical evaluation. A technical liaison, from the PACT cell processing facility designated to manufacture the product was assigned to work with the investigator. A scope of work was developed and usually included an evaluation of the manufacturing process used in preclinical studies, and determination of any changes that would be required (e.g. substitution with clinical grade reagents and material) and their impact. In most cases, the manufacturing procedure needed to be scaled-up to produce sufficient material for the proposed trial. Often this involved adaptation to closed (or functionally-closed) systems for manufacturing, or sometimes substitution of a different method for cell production. Methods for storing and shipping the final cells needed to be developed and product stability during long and short-term storage and shipping had to be studied. These tasks had to be performed on clinically-relevant amounts of human material that had to be sourced. Draft SOPs and worksheets needed to be developed for this part of the study, and once the procedures were nearly finalized, a formal validation plan was established. This described the end points to be achieved by the procedure (usually based on release criteria thought to be acceptable to the FDA), the exact procedure(s) to be followed, the number of experiments to be performed (usually at least three) and the methods for analyzing the data. If the validation studies were successful, the SOPs and worksheets could then be finalized. Staff (usually those who participated in the validation studies) were trained to perform manufacturing.⁽²⁾ Careful documentation during this phase of the roadmap was essential, since the data were required to complete the chemistry, manufacturing and control (CMC) section of the IND application. The required contents this section are comprehensively described in a guidance document from the FDA.⁽³⁾ Any questions about the suitability of reagents and materials, proposed release testing etc. should be raised during a pre-pre or pre-IND meeting with the FDA (see later).

IND Assembly

Regulatory Plan—Developing a regulatory plan early in the development process is vital to the efficient use of resources and for the successful introduction of a new therapy into the clinic. The team approach described earlier is essential at this stage. The PI should become familiar with the cell therapy regulations, including basic principles of GXP (e.g., GMP, good laboratory practice [GLP], and good clinical practice [GCP]). Common regulatory resources include FDA Guidances, International Conference on Harmonisation (ICH)

documents, the FDA website, webcasts and presentations, and formal and informal FDA meetings.⁽⁴⁻⁸⁾

The FDA is divided into Centers (e.g., Center for Biologics Evaluation and Research [CBER], Center for Drug Evaluation and Research [CDER], and Center for Device Evaluation and Radiological Health [CDRH]; each of which is supported by Offices (e.g., Office of Cellular, Tissue and Gene Therapies [OCTGT]; within each Center are Divisions (e.g., Division of Cellular & Gene Therapies). PACT provided regulatory expertise to address all aspects of the translational process, and support for assembling the IND application. Their experience suggests that the following are key for submitting a successful IND application:

- Identification of appropriate FDA contacts
- Identification of Regulatory experts (these may be within the applicant organization and/or through PACT)
- Consideration of a pre-pre IND meeting. This is particularly useful when submitting a new IND, since it provides an opportunity for the FDA to comment informally on the proposed approach and address specific points on which the applicant has questions
- Establishment of a timeframe for IND filing and IRB review, together with review or approval by other regulatory authorities (e.g., Federal Wide Assurance, Office of Human Research Protections [OHRP], and, if appropriate, the Recombinant DNA Advisory Committee [RAC] in accordance with 42 U.S.C. §282(b)(16), section 402(b)(16) of the Public Health Service Act
- Posting clinical trial information to the National Institutes of Health (NIH) clinical trials website (www.clinicaltrials.gov) in accordance with 42 U.S.C. §282(j)(5)(B)

The major components of the IND application are:

Clinical Protocol: this is a detailed description of the trial design, including subject inclusion and exclusion criteria, standard of care, and a summary of preclinical testing and data relevant to the proposed human study.⁽⁹⁾ It provides essential elements of how the study will be conducted with the prospectively defined study plan. It serves as the primary reference document for the clinical research team and for review by regulatory authorities (e.g., IRB, FDA, DSMB). PACT offered statistical and technical support on clinical study design, development, and implementation, in collaboration with the investigator/IND sponsor as appropriate. Key elements of a clinical protocol include:

• Study Summary	• Study Design and Statistics
• Introduction	• Endpoints
• Preclinical Data	• Follow-up Studies
• Effects in Humans, if known	• Summary Data

Chemistry, Manufacturing, and Controls (CMC): the CMC section of the IND contains a detailed summary of the manufacturing process including raw materials, ancillary

components, equipment, testing (i.e., safety, stability, quality), documentation, and quality systems overview.^(3,10-12) The PACT cell processing facilities submitted Type V Facility Master Files (FMF) with the FDA. These contained detailed information about the facility infrastructure, organization, quality program, processes, and materials and supplies management used in the manufacture of investigational cellular products. To facilitate FDA review a letter from the cell processing facility provided permission to the IND applicant to cross-reference the FMF in the IND application. Essential elements in the CMC section are:

• Processing and Manufacturing SOPs	• Product Safety & Quality Testing
• Donor Testing	• Potency Assays
• Raw Materials	• Product Stability
– Cell or Tissue Source (components)	• Other Controls (product container closure, labels, tracking)
– Gene Therapy (vector or genetically modified cell)	• Equipment Specifications
– Reagents and Associated Certificates of Analysis (CoA)	• Environmental assessment or claim for exclusion in accordance with 21 CFR 312.23(a)(7)(iv)(e)
– Cell or Tissue Source (components)	

Pre-IND Meeting: A pre-IND meeting and associated information packet is generally recommended to facilitate effective and open communications with FDA prior to submission of the application. This can be critical in identifying potential safety concerns, clarifying preclinical studies, manufacturing, final product testing, or clinical study design issues. The meeting is formally requested with the FDA and a proposed agenda is submitted. This may be supplemented by additional materials, but the aim should be to provide as concise and focused package.⁽¹³⁾ In response, the FDA will propose dates for the meeting (usually by conference call and lasting no more than an hour).

The PACT cell processing facilities have provided assistance with regulatory content of the IND, with assembly and review of the application, and with arranging and participating in pre-IND meetings with the FDA. The aim has been to obtain concrete decisions on the content of the final IND application. Careful notes should be taken during the pre-IND meeting and a summary of the answers received should be conveyed back to the FDA in writing for confirmation.

Filing the IND Application: The IND application constitutes a formal regulatory submission notifying the FDA of an investigator's intent to evaluate an investigational product in clinical studies. The application must provide evidence that the investigational product is safe for administration to human subjects, with any potential risks being appropriately offset by the severity of the disease to be treated and the potential benefits of product administration. IND content requirements can be found in the Code of Federal Regulations (21 CFR 312 Subpart B- Investigational New Drug Application). Additional information is provided in specific FDA and ICH guidance documents.⁽¹⁴⁾ An IND application typically includes the following elements:

• Cover Sheet (Form FDA 1571)	• Labeling
• Cover Memo	• Environmental Impact
• Statement of Investigator (Form FDA 1572)	• Pharmacology and Toxicology Information

- Table of Contents
- Introductory Statement
- General Investigational Plan
- Investigator Brochure
- Protocol
- Referencing Other Sources
- Introduction
- Drug Substance
- Drug Product
- Placebo
- Responsible Individuals
- GLP Compliance Certificate
- Chemistry, Manufacturing and Controls
- Pharmacology and Drug Distribution
- Toxicology: Integrated Summary
- Toxicology: Full Data Tabulation
- Previous Human Experience
- Additional Information
- Other FDA-Requested Information
- Certification of Compliance (Form FDA 3674)

The FDA has 30 days to respond formally to the submission. If no response is received this means that, theoretically, subject enrollment may begin. It is, however, advisable to confirm this in writing. In many cases, a formal response is received from the FDA describing issues with which there is some concern. These may be sufficiently serious (hold issues) to put the start of the trial on hold until a formal response is received from the PI and accepted by the FDA. In some cases, the issues are less serious (non-hold issues) and the trial may start pending a response from the PI to the FDA within the specified time frame.

Discussion

The NHLBI PACT program provided a variety of resources to assist investigators to transition promising basic research into early phase clinical trials for cellular therapies. These have included performing translational studies to prepare a product for clinical manufacturing, manufacturing cellular products under GMP conditions for use in trials, and providing regulatory assistance with the IND process. In addition PACT has prepared educational materials to assist investigators involved in cellular therapies. Experience from the program has indicated that the process of moving basic research into clinical trials is sometimes poorly understood, especially by new investigators. The clinical research roadmap was an attempt to detail this process and provide advice on some of the common problems that may be encountered. It describes the types of assistance that the program provided to investigators during the various phases of the transitional process and approaches recommended to circumvent potential roadblocks. Although the current PACT program will end in January 2015, these lessons should be valuable to those hoping to move a new cellular therapy into Phase 1 clinical trials.

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Cellular Therapy Clinical Research Roadmap

Figure 1.

The roadmap identifies the critical areas that need to be considered when developing a cellular therapy intended for evaluation in human clinical studies under an IND application.