Technology Licensing & Commercialization Considerations for Clinical Scientists

By

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Introduction

Excellent scientific and medical skills are alone not sufficient for clinical scientists to see the results of their medical research effectively move from "bench to bedside" and then eventually on to "standard of care." For clinical research discoveries to have a true and lasting impact on patient care, they typically need to be transitioned to industry for further development and commercialization. This process from the research institution's perspective is known as "technology transfer" and will involve a number of patent, business and legal components in addition to the underlying medical science to be successful. Clinical scientists need to appreciate and fully integrate the tools of technology transfer within their research programs to achieve their medical and public health goals.

Clinical Research Collaborations with Industry

Research collaborations with industry can take several forms as researchers and clinicians can work with industry under different collaborative modalities. For example, research institutions may need to access technologies developed by industry—an imaging tool, a sequencing platform, or a drug discovered and in development by a company. The technology transfer office then works with companies and clinical partners to memorialize the understanding between the scientists and/or clinicians to allow the collaborations to happen.

Of course, as with all arrangements, each party desires to obtain terms that they feel are the most equitable for the party they represent. The key components of a collaboration agreement that are often the subject of most negotiations are terms related to inventions, rights to inventions, confidentiality versus publication, managing conflicts of interest, and finally, indemnification. Indemnification (having one party to bear the monetary costs, either directly or by reimbursement, for losses incurred by a second party) is very important to research institutions when working with new clinical technologies that will be used in patient care.

Collaboration Agreements with Industry

There are several types of research or collaboration-related agreements that clinical scientists will commonly encounter in working with pharmaceutical and biotechnology companies. These are shown in Figure 1 and discussed in more detail below.

FIGURE 1- Technology Transfer Agreements

■ Confidential Disclosure/Nondisclosure Agreements (CDA/NDA)

Prior to engaging in any collaboration, each party may need to disclose to the other party some proprietary information that if passed on to third parties might be detrimental to the interest of the disclosing party. Such a discussion is a necessary first step to determine the interest in, and the breadth and scope of any potential collaboration. The parties will negotiate a CDA/NDA that ensures the information disclosed is held confidential, is only used for establishing the collaboration, stipulates a term of how long the information needs to be held confidential, and describes the consequences of nonadherence to the terms of the agreement.

■ Material Transfer Agreement (MTA), Sponsored Research Agreement (SRA), and Cooperative Research and Development Agreement (CRADA)

Companies, both small and large, expect to invest a lot of research and development funds toward developing drugs or other biotech products. Research institutions on the other hand, have several programs that are geared towards understanding the fundamental biology and clinical applications underlying a wide variety of commercial products. When these two entities desire to collaborate, they have very different things at stake. For the company, they are hoping to learn more about their product concept, get mechanistic insights they can exploit to position their product better in the marketplace and have discoveries come out of this collaboration related to their product which may extend the patent life of their eventual product or open new clinical applications. In the case of collaborations with clinical research centers, companies would like access to patient samples in addition to the valuable clinical insights they hope would guide them through the process of clinical validation of their product whether it be a drug, medical device, or diagnostic. For the clinical investigator, they would like to test various drugs from various companies to build a scientific story or medical knowledge that they can publish. Even more importantly, their activities can be supported through monetary support from the company. MTAs and SRAs are agreements that dictate the terms of the transfer of material and/or money from the company to the clinical institution. Similarly, at federal labs research projects for basic research or clinical studies utilize Cooperative Research and Development Agreements (CRADAs) which can also provide funding to the research agency from the company partner.

Key Elements of Clinical Collaboration Agreements

Provided below are key elements that are at the heart of the negotiation of these clinical collaboration agreements:

■ Inventions

The definition of "invention" is crucial. Research centers will typically require that any inventions be both conceived and reduced to practice during the term of the collaborative research using the company material and/or money. Companies want it to be conceived "or" reduced to practice. The problem for the technology transfer offices with agreeing to "or" is simply that clinical researchers collaborate with lots of companies, often at the same time on similar broad programs but with different individualized projects. If institutions agree to the "or" language, it creates several issues: (a) it is nearly impossible for the technology transfer office to police when conception of the invention happened and when it was reduced to practice and (b) the institution may end up with conflicting arrangements with companies. Federal laboratories (by statute) use the language of "conceived or actually reduced to practice" in their agreements. Practically speaking, technology transfer offices may only hear of inventions when the researchers decide to disclose them as investigators at clinical research institutions are not under as tight control as their counterparts in industry.

■ Ownership Of Inventions

Companies may want clinical researchers to assign their inventions to the companies. This is a hard one for research institutions to accept since, in the instance of an MTA, there will likely be funding from the federal government, and under the terms of the grant such assignments are prohibited without specific permission from the funding agency. Even under the terms of a sponsored research arrangement where the company is providing money in addition to providing the material, given the large amount of federal dollars that most clinical research institutions receive with the lab resources and several personnel being funded by the government, research institutions are unable to agree to the assignment of inventions to companies as it would again be in violation of the terms of the grant from the federal agency. Instead, typically the company will be granted the desired license options by the research institution to new discoveries during the collaborative or sponsored research program.

Rights To Inventions—Freedom to operate (FTO) rights are very important to pharmaceutical and biotechnology companies. They have invested a lot of money into their drug discovery or device-development programs. These firms do not want the clinical research collaborator to make important inventions that are somehow related to their drug or device in development and then not have the needed rights to the very inventions that they helped with their material and money to discover. There is often no right or wrong answer to this question, and it can be subject to negotiation depending on what items each party feels are equitable for the specific collaboration. Potential outcomes can vary from a royalty-bearing to a non-exclusive royalty-free (NERF) license or option to a license.

■ Confidentiality and Publication

An important aspect of the clinical research mission and spirit is to publish and disseminate the results of research widely to the public. This is sometimes at odds with the company's best interest which may need to keep things under cover until they are very sure and ready to disclose especially to their competitors. A typical compromise is for the publication/public disclosure to be provided to the company ahead of

time and for the company to remove its confidential information while still providing for a meaningful publication in the scientific journal of choice by the clinical investigators. For example, if the scientific journal required publication of the structure of the compound to make it meaningful, and if that were not already in the public domain through publication (journal or patent) of the company, then that constraint should be discussed at the time of the negotiation of the contract.

Licensing of Clinical Research Inventions

Inventions made by the clinical research center's investigators are the currency that drives the licensing operations of their technology transfer office (TTO). As shown earlier in Figure 1, the technology transfer office personnel have the huge responsibility of reaching out to their research community to educate them about the process, evaluate and access patentability of inventions, devise simple to complex IP strategies for the inventions, and finally to work with attorneys to protect these inventions – all of which hopefully results in a license agreement to commercialize a given discovery made at the research institution.

In looking for companies to work with a clinical investigator and their technology transfer office, there is both push (when the technology transfer office reaches out to companies to license/partner the technologies) and pull (when companies contact the investigator and/or the technology transfer office) marketing. Companies contact technology transfer offices typically following a public presentation—a publication that is either in a scientific paper from an inventor or a published patent. For companies seeking a license from a research institution, the following outlines a typical approach that they follow: (1) identify the institution technology that is of interest; (2) provide a plan for diligent development of technology, if licensed, along with an estimated timeline; and (3) indicate if the technology will add to, replace an existing product, or be a new line of products for the company. Having this basic information available will accelerate the time to a term-sheet for negotiation purposes and eventually a completed license.

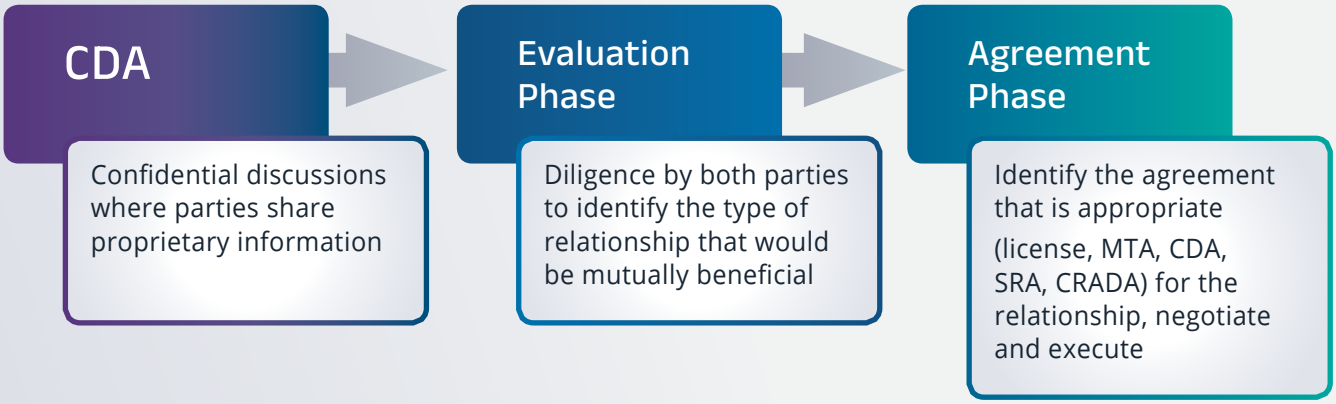
Once the clinical research institution and company feel there is a path forward to bring the technology into the company then it proceeds to a license. Oftentimes the company is not sure and needs to bring the technology in under an evaluation license to ensure that the technology or treatment works well before they can commit to a full license. This is accomplished via an option agreement that would (a) obligate the research institution to hold the rights to the technology for a certain period within which it will execute a license to the company and (b) grant the company rights to test/evaluate the technology. These agreements are accompanied by nominal fee arrangements, oftentimes to cover patent costs previously incurred and/or that would be incurred during the option period. Once the parties are engaged in negotiations, it is typical to start with a term sheet. It is good to get all the major areas of concern addressed in the term sheet and get verbal understanding of the key terms before committing to paper. For clinical research institutions, a typical concern is companies not committing to diligent development of technologies they license. This would be an issue that is best addressed early in the negotiation. A combination of an exchange of a written draft agreement and periodic verbal communication will ensure that things will proceed in a reasonable manner.

Time periods to complete these transactions can vary widely and clinical scientists should be aware of this. Option agreements typically take a few days to a month. Agreements for nonexclusive license to technologies take on average about two to six months to finalize. For exclusive license agreements, the period varies quite widely. If there are two committed parties that want to get a deal done it can be as quick as three to four months. An average deal would probably take six to nine months to complete. In all instances of licenses, clinical scientists should be aware that technology transfer offices always prefer to start from their template. Given that most companies' license agreements are designed for company-to-company transactions, it is very cumbersome and time-consuming for the institution licensing professional to adapt the company template to fit the research institution's needs. If the institution has previously licensed the technology either nonexclusively or exclusively in another field, there would be a constraint to using terms they have agreed to with the other parties on the same technology. Also, if that company and the research institution have a prior license agreement, the quickest way to a deal would be to start with that as a template for at least the nontechnology-specific terms.

Basic Licensing Principles for Clinical Research Institutions

Compared to biomedical licensing from corporations, clinical research institutions bring a different focus and perspective to the table when negotiating their technology transfer license agreements. Because these agreements are used to further overall institutional missions, clinical scientists should be aware that such nonprofit institutions consider the public consequences of such licenses as their special priority, not the financial terms that may be involved. For example, nonprofit clinical research institutions, compared with their peers in industry, have the mandate to make new technology

FIGURE 2 - Fundamental Steps Leading To Agreements By Clinical Research Institutions



as broadly available as possible. This means that there is a strong preference to limit the scope of a license to only what is needed to develop specific products. Exclusive licenses are still quite typical for biomedical products such as vaccines, therapeutics, and others where the underlying technologies require substantial private risk and investment (and a prior public notice and comment period in the case of federal laboratories). In their agreements, clinical research institutions would also typically expect to retain the right to permit further research use of the technology whether to be conducted either in the private or public sector. Because the commercial rights granted represent institutional (and often public) assets, these agreements have enforceable performance benchmarks to ensure that the public will eventually receive the benefit (through commercialized products) of the research it funded. With many clinical research discoveries based upon U.S. federal financial support, regulations governing the license negotiation of federally-funded technologies and their mandated requirements are described in more detail at 37 Code of Federal Regulations (CFR), Part 401, while those for federally owned technologies can be found at 37 CFR, Part 404.

Figure 2 illustrates the fundamental steps that lead up to a license or other types of agreements by clinical research institutions.

In a license agreement the research institution essentially grants rights to a company to make, use, and sell products that, were it not for the license, would infringe on the patent rights that the research center owns and/or controls. In some instances, the research center also grants the company rights to use technological information/know-how or materials that goes together with the information in the patent application and that is valuable to the company as it hopes to commercialize the technology into products. As mentioned earlier, licensing is at the heart of operations of a tech transfer office and is the core of its set-up. This is a critical element of technology transfer from clinical research organizations since, as nonprofits, they do not and cannot have a product commercialization arm and so cannot themselves convert research inventions into commercial products and processes. They must partner with industry to do that. Hence these out-licensing activities are the key to fulfilling the core mandates of commercializing inventions that arise from federal funding as well as the societal goals of the institution.

Characteristics of License Agreements from Clinical Research Institutions

Generally, it is considered good business practice in licensing from a research institution that the organization would standardize license terms to the extent possible. Standardizing nonfinancial license terms levels the playing field for licensees (an important concept for public institutions) and creates a common understanding of the balance of risks acceptable to a research institution (which may differ markedly from the for-profit sector).

FIGURE 3 - Factors Influencing Royalty Rate Negotiations by Clinical Research Institutions

- **Stage of Development**
- **Type of Product Market Readiness & Value of Product**
- **Uniqueness of Biological Materials**
- **Scope of Patent Coverage**
- **Research Institution "Content"**
- **Public Health Significance**

Clinical research scientists should appreciate that royalty rate negotiations with companies are influenced by factors (Figure 3) commonly encountered in other negotiations of early-stage biomedical technologies. Unique to research

institution negotiations are factors relating to the public health interest in the technology being licensed and the products to be developed from it (so-called "white knight clauses"). Examples of this may include supply back of materials for clinical use, indigent patient access programs in the U.S., commercial benefit sharing for natural product source countries or incentives for developing country access to the licensed products.

The royalty payments themselves (Figure 4) consist of license payments received for execution royalties, minimum annual royalties (received regardless of the amount of product sales), earned royalties (a percentage of product sales), benchmark royalties and payments for patent costs. Some research institutions do not seek equity payments in licenses or directly participate in company start-ups due to conflict-of-interest concerns. Instead, in lieu of equity, these can consider equity-like benchmark royalties that track successful commercial events at the company. However, many research institutions do take equity payments in their license agreements to assist a new start-up company even though there is considerable risk in accepting equity in lieu of cash payments since such equity is illiquid and has no present value at the time the license is executed.

FIGURE 4 - Types of Royalty Payments in License Agreements with Clinical Research Institutions

- **Execution Fees**
- **Minimum Annual Royalty** (regardless of the amount of Net Sales)
- **Earned Royalties** (fixed % of Net Sales)
- **Benchmark Royalties**
- **Patent Costs**
- **Sublicense Fees** (% of income)
- **Equity** (varies by institution)

Research institutions will often opt to take an equity or equity-like position when available from their licensees for several reasons. For example, equity would provide for additional revenue in addition to the licensing royalties, especially if the licensed product failed in development but the company itself later become successful. Equity also can be seen as a risk premium for the research institution that provides additional inducement to grant the license to a new start-up company versus a more-established firm. Perhaps most importantly, equity allows a licensee who is cash poor but equity rich to substitute an ownership position for a cash payment (in full or in part) for an up-front licensing fee and/or a reduced royalty rate. Finally, research institutions accept this risk to support their mission to assist in commercialization of early-stage technologies, which may not be turned into marketable products otherwise, and to encourage small business development. However, research institutions do recognize that holding ownership rights in a start-up company creates potential conflicts of interest and adopt various internal policies that mitigate and/or manage such conflicts.

Unlike their corporate counterparts, clinical scientists at nonprofit clinical research institutions do receive a share of the royalties generated from the licensing of their inventions. However, each institution might have a slightly different revenue-sharing policy with respect to the percent of licensing revenues that are shared with inventors. These payments are made to the inventor by the institution rather than the licensee and do not constitute any direct conflicts of interest, but inventors still do not conduct clinical studies involving their own inventions for ethical reasons.

Results of Technology Transfer from Clinical Research Institutions

With the rising costs of traditional drug discovery and mounting pressures on healthcare costs, companies are increasing their work with clinical research scientists and clinical research institutions. Scientists from research institutions are embracing this model as well given the pressures of funding their research as well as their drive to see their work not only published in leading journals but also having new discoveries from their research turn into clinical products that can benefit the public at large. Exemplary of this activity, for example, is the intramural research program at NIH, now with a tally of 53 FDA-approved drugs and vaccines based upon discoveries licensed from its technology transfer offices.

Although product launches based upon research discoveries have been a model in showing the value of technology transfer from nonprofit clinical research institutions, it is of course not the entire story. The final tally must include the economic impact of such commercial activity but also more importantly the full societal value of new lifesaving or life enhancing therapeutics, vaccines, diagnostics, and other biomedical products that have origins from this research. This is thus believed to be the truest measure of the value and importance of technology transfer for clinical scientists and their work at our research institutions. ■