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CRO, TLF, SOP? OMG!: A Beginner's Guide to the Clinical Research Organization

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ABSTRACT

Navigating the operational activities of a Clinical Research Organization (CRO) can perhaps be daunting to newly hired entry level employees; in addition to being a complex web of interrelated entities and divisions of labor, the industry is replete with acronyms, protocols, and esoteric jargon. To hopefully help alleviate this confusion, we present this paper as an introduction to the general workings of the CRO industry and its place in the larger clinical trial process. We will focus on the involvement of the sponsor, the CRO, and the Food and Drug Administration (FDA) in the development, analysis, and approval processes.

INTRODUCTION

So you have recently been hired at a Clinical Research Organization (CRO). Wonderful! What exactly does that mean though? Do you really have any idea what to tell your parents or friends if they ask what your company does? If you are anything like us, the answer is "sort of." You probably have at least a basic understanding of what a CRO does by virtue of the fact that you applied to one in the first place, not to mention that depending on how long you have been working there you have probably learned a little more simply by way of immersion.

At least for now though, CROs are not like hospitals, courtrooms, and classrooms; it is common for people to know what a doctor, lawyer, or teacher does because it is not unusual to personally know individuals who have these professions. What is more, CROs do not receive the same level of media attention that fields such as law enforcement and criminal investigation enjoy -- it is no secret that the interest in forensic careers grew dramatically with the advent of criminal investigation television shows [Paton 2009]). Unless you have a friend or relative who has some experience with one, we would guess you did not really know much about them until not too long before you began applying to them. At least, this was certainly the case for us.

What was also true of our experience was that we found that despite how good our mentors and trainers were at introducing us to our department and teaching us specific job-related skills, there were several "big picture" dimensions of CRO work that we just did not quite grasp. Everyone was very willing to help and offer their time, but it was not uncommon for them to assume we knew something we did not. Of course, many times we were also too embarrassed to admit it, so we continued on until we gradually absorbed more and more information through a combination of experience, self-directed research, and the occasional epiphanic tip.

Our goal here is to relieve those new to the industry of the same kind of confusion and potential embarrassment that we experienced through a gentle introduction to the general services that CROs may provide and the various departments that offer those services, along with the phases of clinical research and how these services tie into them. We assume that those reading this paper will have less than one year's experience in the industry.

Much of the information contained in this paper has come mostly from our own experience, first-hand or vicarious, and as such, is subject to at least one noteworthy irregularity. We should point out that we are Statistical Programmers, and much of our knowledge is driven by that fact. Our backgrounds will likely be much different than those of Medical Writers or Clinical Research Associates (CRAs) with similar levels of experience.

We hope that the organization of the paper will also prove helpful; the information presented here will essentially fall into one of two categories: one of which will be dedicated to describing some of the typical departments and services characteristic of a CRO, while the other will provide a general description of the larger clinical trials process. These are so intertwined that separating them into two distinct sections is quite difficult. Instead, we take a more interleaved approach, where we will treat the discussion as an overview of the clinical trial process, during which we will take the opportunities to point out where and how CROs might be involved.

In the interest of providing some context (and hopefully some comic relief), we will also describe these functions and phases in relation to a fictional condition characterized by the inability to sing on key, despite being able to recognize what key a song *should* be sung in. Taking the pun opportunity, we will claim that this condition is caused by a build-up of "key-tones" deep in the mouth and upper throat. Once singing on key becomes a chronic problem, we will say that it can be formally diagnosed as *Discordia*.

We should also mention that for the duration of the paper, we will be referring to the clinical development and approval process of chemical medications, as opposed to biomedical devices. Both drugs and medical devices have

to go through a federally regulated approval process, but the processes slightly differ (Chittester n.d.). Our experience is primarily with pharmaceuticals, and we will therefore focus on them. We feel it is important, though, to point out to those new to the industry that chemical compounds are not the only thing that CROs help bring to market.

In the following sections, we will provide examples of how different departments and positions contribute to different stages of the clinical trial process. There is much overlap between the various phases, with the same position often providing similar functions during different stages. Because of this, we wish to acknowledge that the following is a sampling of the different services provided by a CRO during a clinical trial, rather than an example study in full detail. We take effort to avoid redundancy.

We will also point out that this overview is quite a general one; if any one aspect of CRO functionality or clinical trials is particularly interesting, we encourage a self-directed inquiry into that topic. We hope to provide a gentle introduction, but many of the areas and concepts discussed below can be elaborated upon into entire papers or presentations all their own. Each of these topics contains a rich and deep wellspring of information, but further elaboration is beyond the scope of this paper.

With these disclaimers in place, we will begin our narrative on the various phases of the clinical trial process. We will go in chronological order, beginning with some of the details surrounding the development of a pharmaceutical compound in a laboratory setting, continuing on through Phases I, II, III, and IV, ending with the drug in the marketplace.

CLINICAL TRIALS

The very first event that must take place on the long journey to get a drug to market is to discover a chemical compound that could be used to treat a condition. Before any testing or data analysis can take place, there must first *be* a drug to be tested. How this discovery takes place can happen in several ways. As it relates to our own contrived condition of Discordia, it may happen at a university where a chemistry professor has discovered a helpful compound with assistance of graduate students after doing in-depth secondary research on the condition itself. It could even be the case that someone serendipitously discovered that his singing voice in the shower was much better than out of the shower. Through informal experimentation, the connection is made that the singing is only actually better in the presence of a mixture of one brand of shampoo with another brand of hair conditioner, where the active ingredients in each mix to form a vapor that dissolves malignant key-tone deposits.

In reality though, drug development is often the result of high levels of interaction and interdependence of separate bodies like pharmaceutical companies, private or public investors, universities, and small research organizations (Warren 2011). The organization that is primarily responsible for the funding of the research is commonly known as the *sponsor*. For our purposes here, we will assume that the sponsor is a pharmaceutical company who has proprietary ownership over a compound called *arpeggizine*, and wishes to bring it through the clinical trial process and finally to market.

This then puts the pharmaceutical company in a position where a decision must be made; should the company take on the rigors of clinical trials to get *arpeggizine* into the hands of physicians and patients in the general public, or should it instead opt to hire a CRO to perform some or all of the activities necessary to do this? The answer depends on a multitude of factors. Does the company have ready access to research sites where experimental patients can take the drug under close supervision? If not, does it know where to *find* such a site? Does it have the in-house staff trained in experimental design, good clinical practice (GCP), medical communication, etc.?

The answer to any or all of these questions could be "yes," in which case perhaps it would not be worth it to hire a CRO, or at least not for the *entire* process. For our demonstrative purposes here however, we will assume that the pharmaceutical company in question will relinquish all relevant tasks to a CRO.

In any case, once the decision has been made to hire a CRO, the *proposals department* of several CROs will be contacted by the pharmaceutical company with a Request For Proposal (RFP), letting the CROs know that they are in the market for a capable CRO with experience in this particular *therapeutic area* (which here might be vocal tonality issues, but in a more realistic example could take the form of gastrointestinal conditions, emotional conditions, etc.). It is the responsibility of the CRO's proposals department to write a compelling argument for why their particular organization should be chosen over others to take *arpeggizine* from the laboratory to the market. The pharmaceutical company will receive several proposals in a bid-making process, until it finally decides on one and hires that CRO to take on the process (Wright 2012).

Again, while a pharmaceutical company may only hire a CRO to take on the duties of *part* of clinical trials process, we will assume here that the CRO has been commissioned to take on the process in its entirety. Given this assumption, once this pharmaceutical company has decided which CRO is a good match for *arpeggizine*, it has now come time to think about actually testing this compound. With that in mind, the CRO can already begin to make itself useful to the sponsor in the *preclinical* phase, to which we now turn our attention.

PRE-CLINICAL: ANIMAL TESTING

With *arpeggizine* successfully discovered and replicable, it is time to consider testing it for its effects – desired or otherwise. Before testing can take place on humans however, it must take place on animals (Stages of Drug Development and Review 2014). While it is true that some "animal testing" is actually experimenting with drug effects on living animals as the term would suggest (often referred to as *in vivo* testing), it is also common to test the drug on a much smaller scale. This occurs on the cellular level in devices such as test tubes or petri dishes, at which point it is referred to as *in vitro* testing. While there is some discussion over which method is more beneficial (Polli 2008) animals that are as closely related to humans as possible with regard to key-tone build up will be used. Ideally, two separate species will be used to increase the generalizability of the results (US Department of Health and Human Services 1997).

How should the drugs be administered though? How many individual animals must be sampled to ensure that the information collected is representative of other animals within the same species, or of other animals of different species? How should the data be collected to ensure that the information is not confounded and that there is little room for error?

These are all questions that can be asked of a CRO's *biostatistics department*, which will have experienced statisticians on staff who will be able to provide insightful answers. Before the preclinical testing even begins, these statisticians can design the most optimal study structure for the particular drug being developed, and later on can also help analyze the findings from these studies.

With the study designed, the actual testing can begin, during which time reactions are carefully monitored to determine if the drug may be safe enough to test on humans. Also, appropriate *dosages* are discovered during this phase, ensuring amount of *arpeggizine* can be used during the human testing that is to follow.

Once the animal testing is complete, all the information that has been recorded must be compiled and submitted to the Food and Drug Administration (FDA) in an effort to make a convincing argument that *arpeggizine* is indeed safe enough to begin testing on human subjects (Stages of Drug Development and Review 2014). As part of this process, an Investigational New Drug (IND) application is filled out and submitted to the FDA along with the bundle of other relevant information that came from the preclinical trials.

Fortunately for the sponsor, this is a task that can be done by the CRO's Medical Writers, individuals typically trained in the natural sciences who use their knowledge to communicate the findings from the animal trials into a coherent package that should be easily read by their target audience ("About Medical Communications" 2013). If the FDA approves the IND application, *arpeggizine* can move on to the next step, Phase I.

PHASE I: SAFETY

Phase I has one main purpose: to establish the safety of the experimental drug (Stages of Drug Development and Review 2014). The entire point is to make sure that whether or not *arpeggizine* actually *helps* Discordia, it does not *hurt* the situation by making anything any worse. To do this, a small sample (about 20 – 80 people) is selected to take *arpeggizine* in the dosages deemed safe by the animal studies done in the preclinical phase.

It is important to point out that during this phase, the volunteers chosen are ones that do *not* actually have the target condition. For our example, these would be 20 – 80 people who *can* sing on key just fine. Someone still has to select these volunteers though, not to mention notify people that volunteers are needed in the first place. Also, a site needs to be selected where administration of *arpeggizine* can take place at all, and this site must meet a very specific set of criteria to comply with strict regulatory obligations. Choosing a site is deceptively complicated, and careful measures must be taken in choosing a site that will not cause delays or other problems (Fischer 2011). Even once an appropriate site is selected, it must continue to be monitored to make sure the day-to-day activities of the trial are consistent with Good Clinical Practice. These are things that Clinical Research Associates (CRAs) do, whose responsibilities include making sure the facilities are up to standard for clinical research and checking the Case Report Form (CRF) on which the actual data from the clinical trials are being recorded.

The CRF data is also not necessarily in a format that is instantly helpful for data analysis, and it has to be transformed in such a way that it can be easily taken apart, spliced together, and transformed as needed to increase focus on different aspects of the study (e.g., inspecting how the drug affected only the males in the study, or organizing the findings by date of *arpeggizine* administration). Clinical Programmers from the *data management department* will therefore take the information from the CRF – the most pristine form of the data – and use their knowledge of data base structures and architecture to organize the data in such a way that is much more malleable.

From this point, Statistical Programmers from the *biostatistics department* can then manipulate the data sets created by the data management department to create Tables, Listings, and Figures (TLFs) that summarize the data in an easily readable format, after which statisticians from the same department can then review the results with the sponsor, and a decision can be made regarding the demonstrated safety of *arpeggizine*. If there are few enough strong *adverse events* (negative side-effects), the drug can then move on to Phase II.

PHASE II: EFFECTIVENESS

While the primary goal of Phase I was to test the *safety* of the investigational drug, the main purpose of Phase II is to test its *effectiveness*. Phase I selected up to 80 people *without* Discordia to receive dosages of *arpeggizine*, but in Phase II up to 300 people *with* the target condition will be recruited (Stages of Drug Development and Review 2014). *Arpeggizine* will be given to experimental groups subdivided from the pool of volunteers and the reactions compared to control groups receiving a placebo or a drug similar to *arpeggizine* that has already passed a different set of clinical trials and is currently being prescribed to the public.

While the goal of Phase II is different, many of the same functions the CRO performed in Phase I will be "recycled" in Phases II and III. As was the case in Phase I, staff at the CRO will be responsible for patient recruitment. They can screen volunteers confirm that they actually do have a built-up level of key-tones to be officially diagnosed with Discordia, as well as that they are healthy enough in other regards to receive the experimental treatment.

The CRO will also still be responsible for selecting an appropriate site to perform the trials, as well as continuing to monitor the site to make sure it is in compliance with good clinical practice. Data will once again go from the CRF to a database to tables, listings, and figures where it will be interpreted and communicated to the sponsor.

Once the drug has been seen to be acceptably effective in comparison to placebos and/or other similar medications, it can then progress to Phase III.

PHASE III: GENERALIZABILITY

Phase I was primarily to evaluate the *safety* of the drug, Phase II was primarily to evaluate the *effectiveness* of the drug, and Phase III is primarily to test the *generalizability* of the results from the first two phases. While Phase I may have up to 80 subjects and Phase II may have up to 300, Phase III may have up to 3,000 participating (Stages of Drug Development and Review 2014) at multiple centers at multiple times (for example, Fizazi et al 2015). By doing this, there can be a much higher level of certainty that the drug will be both safe and effective once it is released on the market.

As far as the CRO is concerned, many of the same responsibilities from the first two phases will remain. Sites still need to be selected and monitored; data still needs to be collected, organized, analyzed, and interpreted; and the results still need to be communicated to the sponsor. Once all this is done however, there is yet another application that must be submitted to the FDA. Phase III is the last phase that occurs before *arpeggizine* is released to the market, and because of this, all the relevant information must be collected and submitted to the FDA in a similar fashion as was done for the IND application after the preclinical trials.

For the New Drug Application (NDA) that must be filled out and accepted before *arpeggizine* can be marketed to the public, all information recorded from all the testing done up to this point must be submitted to the FDA. This application process is quite extensive; beyond looking at the safety and effectiveness of *arpeggizine*, the FDA will inspect the facilities where the drug will be mass-produced, how the drug will be marketed, and the labeling that goes on the drug's container (Stages of Drug Development and Review 2014). If the FDA approves of all these things, *arpeggizine* can now move on to Phase IV, during which point it will officially be on the market under the brand name Harmonex!

PHASE IV: SURVEILLANCE

The fourth and final phase of the clinical trials is all about monitoring the drug while it is actually being prescribed to and used by real patients, not just volunteers. Should there be any issues with the drug, its use may be restricted by either removing it from the market altogether or by restricting the populations that can receive it (Stages of Drug Development and Review 2014).

While the time to complete clinical trials varies, by this point 18 years could have passed since *arpeggizine* was discovered, and it may have cost upward of 1 billion USD to take it through the clinical trials (Adams and Brantner 2006). It was well worth it though -- think of the millions people who will now be able to sing on key to their favorite songs!

CONCLUDING REMARKS

So congratulations! You now hopefully have a better understanding of the clinical trial process, as well as what a CRO might do during that process to help a company bring their medication from the lab to the pharmacy. We hope that this discussion has been helpful in providing a sort of "overhead" picture of how a CRO works, which will also hopefully provide some context to the particular position in which one might find oneself.

As novices to the industry ourselves, we will take this opportunity to provide some last-minute advice and share some of the tips we wish we were told from the very beginning.

Don't Be Overwhelmed

There is a great deal of information that will come flooding in simultaneously, and this is especially true at

the very beginning of your time in the industry. Take comfort in knowing that you are not the first person to feel that you will never be able to retain all the information found in the piles of Standard Operating Procedures (SOPs) you will likely be reading in the first few months of your time in the industry. Also know that after some time, you will eventually have a much better grasp of how your own position fits in to the larger operations of your department and your company.

Try to Understand the "Big Picture"

While our goal here was to provide an overarching narrative of how a CRO can help a pharmaceutical company, we realize that it does not necessarily speak to whatever position you may have in particular. We have found that one of the things that is the most helpful in driving our day-to-day activities is an understanding of what the main goal of a certain task is. We recommend becoming as familiar as possible with the broad goals of your position, your department, and your company.

Don't be Afraid to Ask

When we first started, it quickly became clear that there was an assumption that we had a greater amount of knowledge than we did. One of the other things we also noticed was just how willing everyone was to clarify what a particular acronym meant, or what the common practice for a particular task is. In the same way that you will not be the first person to feel overwhelmed by the deluge of information that comes with starting out in the CRO industry, you will also not be the first person who had to be explicitly told how to do something or how something works. Veterans of the industry tend to forget what novices do not know, and a quick question can often remind them. If anything else, remember that you can be of more help to your superiors if you get a question answered in five minutes than if you spend three days in a fog of ignorance. So if you have a question, do yourself and those around you a favor and just ask!

Enjoy Yourself!

Realize that you are in a position where you can be surrounded by people that likely have interests very similar to yours. Whether you are interested in data and numbers, written communication of medical terminology, or dealing directly with patients, you are contributing to a large and complex process that can help millions of people through the use of medical science. Take pride in the fact that the world can be a better place because of something to which *you* contributed.

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APPENDIX: COLLECTION OF ACRONYMS USED IN THIS PAPER

Acronym	Meaning
CRO	Clinical Research Organization.
CRA	Clinical Research Associate. CRA's are often responsible for choosing a site in compliance with good clinical practice, as well as continued maintenance of this site.
RFP	Request for Proposal. A sponsor will do this when it is ready to begin choosing from a group of CROs to take on some or all parts of the clinical trials process.
GCP	Good Clinical Practice.

Acronym	Meaning
FDA	Food and Drug Administration. The key regulatory body in the United States that pharmaceutical and biotechnology companies form whom approval must be received before drugs or medical devices can enter the market.
IND	Investigational New Drug. This refers to the chemical compound that will hopefully pass the clinical trials. The application that must be filled out after completing the pre-clinical phase but before Phase I can begin is the Investigational New Drug Application.
CRF	Case Report Form. This is the document on which information is recorded directly from the sites where the clinical trials are taking place. It is often put into a more usable for by the Data Management department .
TLF	Tables, Listings, Figures. These are the typical outputs where information is presented in a succinct format.
NDA	New Drug Application. This is the formal request from the sponsor of the FDA to review all the relevant materials collected after Phase III in hopes of bring a medication to the public.
SOP	Standard Operating Procedure. This is a document that describes standardized practices in various areas of CRO services and/or clinical research.