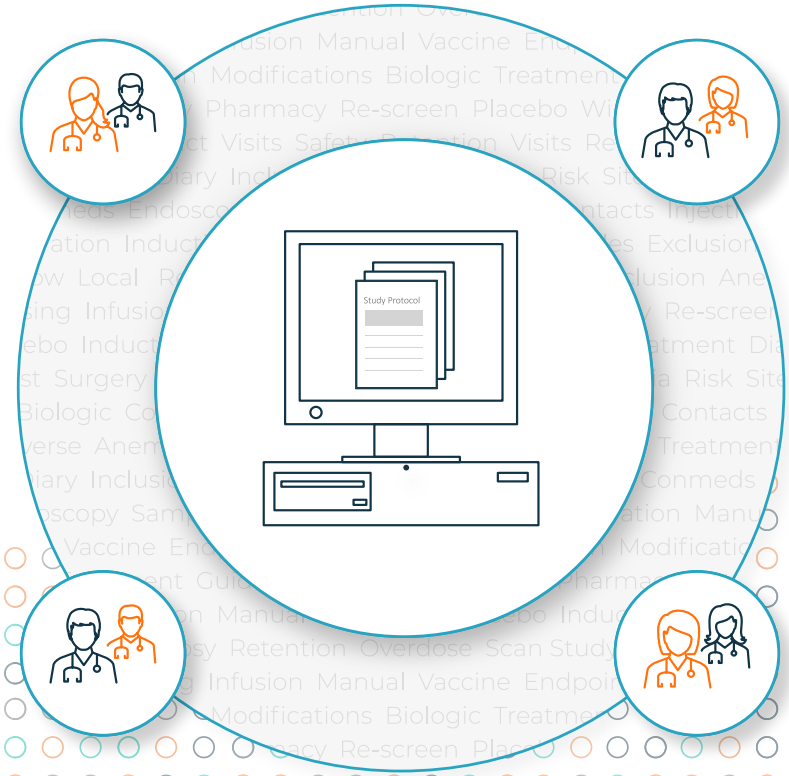
The Digital Paradox:

Research Sites and Clinical Trial Protocols



Analysis of Industry Research: Tufts CSDD - Teckro 2020 Study on Investigative Site Protocol Administration Referencing Practices

July 21, 2020

Foreword

It all started with a question.

We asked, "What research has been done to quantify how investigators and research staff interact with the protocol?"

In looking at published research, we couldn't find much. We then asked the Tufts Center for the Study of Drug Development (CSDD) whether they had any. It turns out, the question hasn't really been researched before.

What started with a question turned into a collaborative research project between Teckro and Tufts CSDD. I am proud of Teckro's involvement in this industry research. The results point to ways we need to make it easier for research staff to conduct clinical trials.

When we started thinking about this project at the end of 2019, COVID-19 wasn't in the public spotlight. Now, making clinical trials simpler, more accessible and transparent is a discussion not just within the pharma industry, but it is a global topic as the world watches for progress with a COVID-19 treatment. Nearly every day, mainstream media is now reporting on clinical trials, which casts a spotlight on an industry that hasn't necessarily been optimized for efficiency or speed.

They say out of crisis comes opportunity. What better time for us to capture feedback from research staff on how they are interacting with the protocol, so we can use the momentum for change started with COVID-19 to impact the future.

I can't help but wonder for all of the millions – possibly billions – of people who are reading the news about COVID-19 clinical research, what would they think if they knew how much of the clinical trial process is actually based on paper? For an average person who keeps a shopping list by telling Alexa or who pays bills from a banking app on a smartphone – what would these people think about someone sitting at a desktop computer scrolling through a table of contents to find a clinical trial answer?

Depending on the generation, some people might be surprised that modern medicine is governed by seemingly antiquated methods to find answers. The younger, "digitally native" generations will likely be baffled both by what a desktop computer is and by the concept of scrolling in a document to find an answer. In today's digital world, we ask a question and we get an answer immediately.

Why isn't it the same with clinical trials?

We hope that this research will advance the conversation on how we can make it easier for research staff to conduct clinical trials so that the industry can safely bring more treatments to market to ease the suffering and improve quality of life.

Brendan Buckley MD DPhil,
Chief Medical Officer, Teckro

Chapter 1

Executive Summary

Teckro teamed up with the Tufts Center for the Study of Drug Development (CSDD) to capture feedback from research site staff on how they interact with the clinical trial protocol. More than 220 staff participated, and the results are published in "Tufts CSDD - Teckro 2020 Study on Investigative Site Protocol Administration Referencing Practices." The official report is available here.

This paper provides an analysis of some of the topline results. We of course invite you to read the report yourself for your own conclusions.

53%
of respondents "very often" refer to the protocol on a desktop computer

80%
"very" or "somewhat often" direct protocol questions to study monitors

58%
say it takes >20 minutes to get an answer from monitors

7%
store the paper protocol in the clinic area where patients are seen

42%
"rarely" or "never" refer to the toxicity management section of the protocol

What the Research Tells Us

Research staff reference the protocol online via a desktop computer, through hard copies, and by asking study monitors. The process by which site staff find information from the protocol is electronic, but it lacks the accessibility, convenience and immediacy typically associated with digital.

There are a few contradictions. For example, while the protocol may be electronic, it is most often referenced via a desktop computer in a fixed location. Questions are commonly answered by scrolling through the index to find a page number or by asking someone else. And while the most commonly accessed sections of the protocol are eligibility criteria and schedule of visits, the protocol doesn't tend to be stored where patients are seen.

We organized our analysis of the research into three main areas:

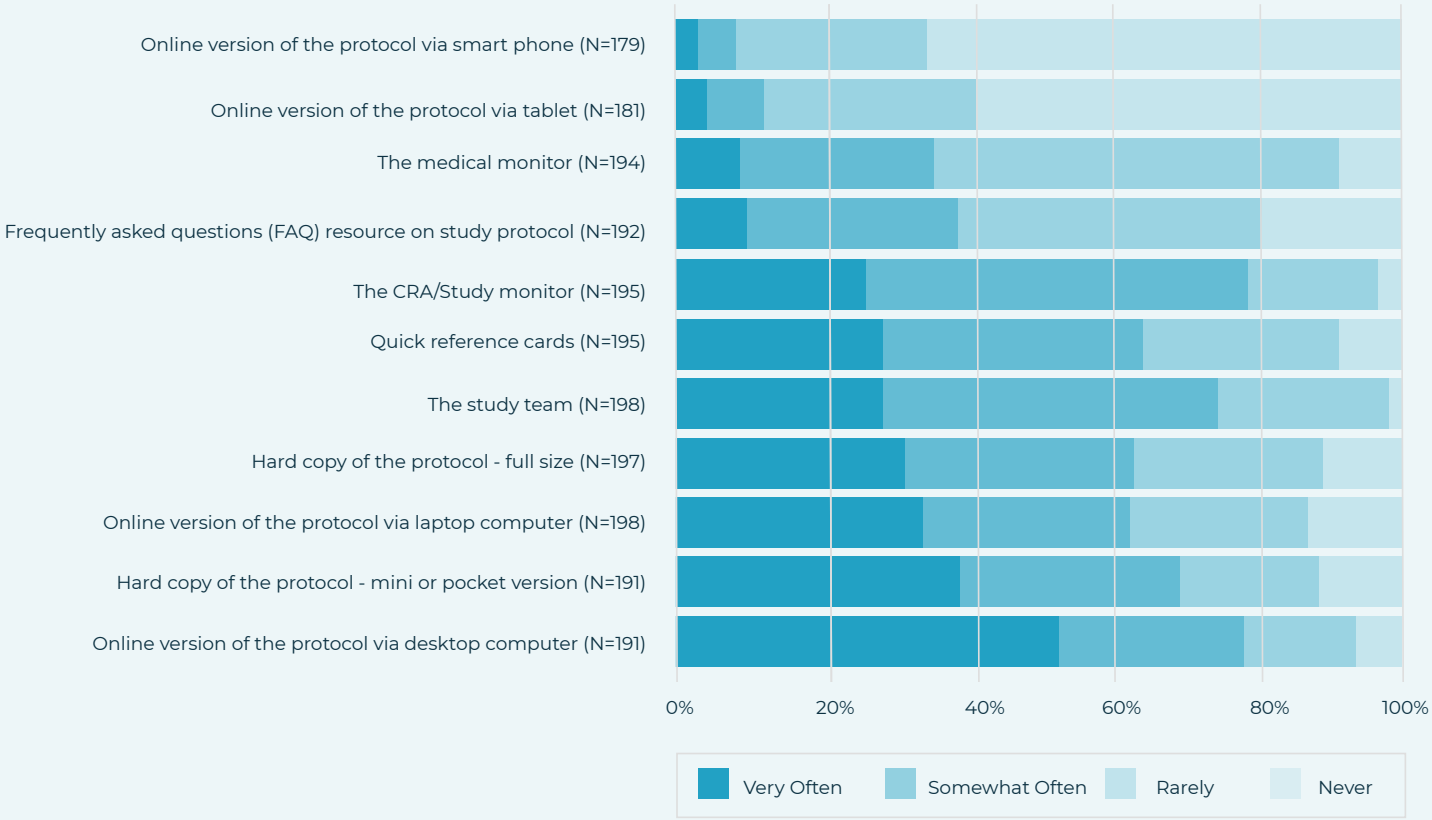
1. The conduct of clinical trials is guided by "electronic paper"
2. There is a degree of separation between the protocol and the patient
3. Study design complexity presents challenges for staff to find answers in the protocol

Chapter 2

The conduct of clinical trials is guided by “electronic paper”

The most common information source that respondents “very often” refer to is the protocol online via a desktop computer (53%), followed by 40% referring to hard copies of the mini-protocol (Chart 1). However, if we also look at the combination of “very” and “somewhat often,” we see that respondents refer the most to CRAs (80%) and desktops (79%).

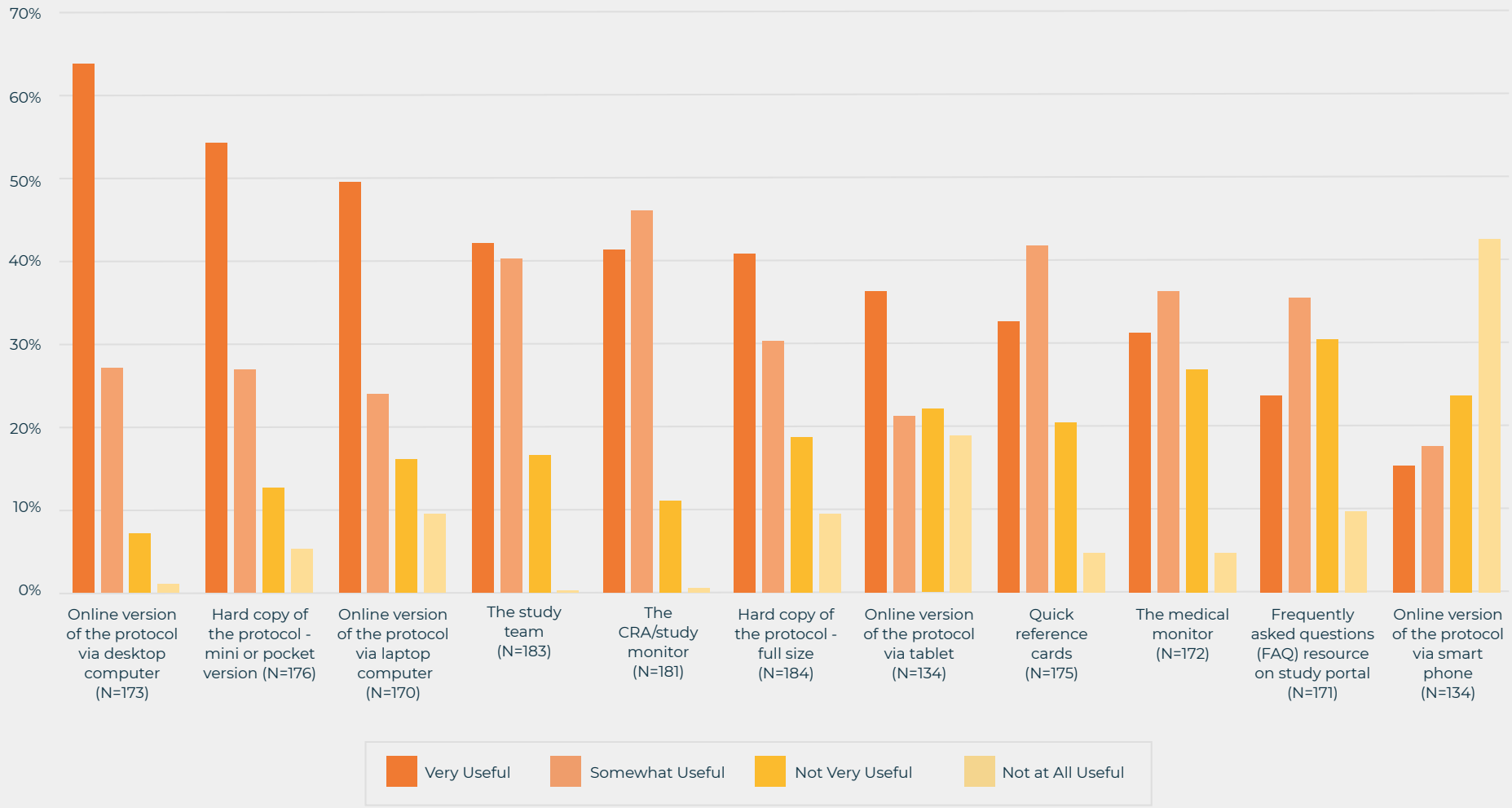
Chart 1: Frequency of Protocol Information Sources



Q15: In terms of accessing resources to help with the administration of the protocol and/or to gain quick access to the information you are seeking, please rate how often you access each of the following.

The picture is similar in terms of usefulness, where respondents cite online desktops as the highest “very useful” source (64%), followed by 54% citing hard copies of the mini-protocol as very useful (Chart 2). Similarly, if we look at the combination of “very” and “somewhat useful,” we see that desktops (91%) and CRAs (87%) are the top responses.

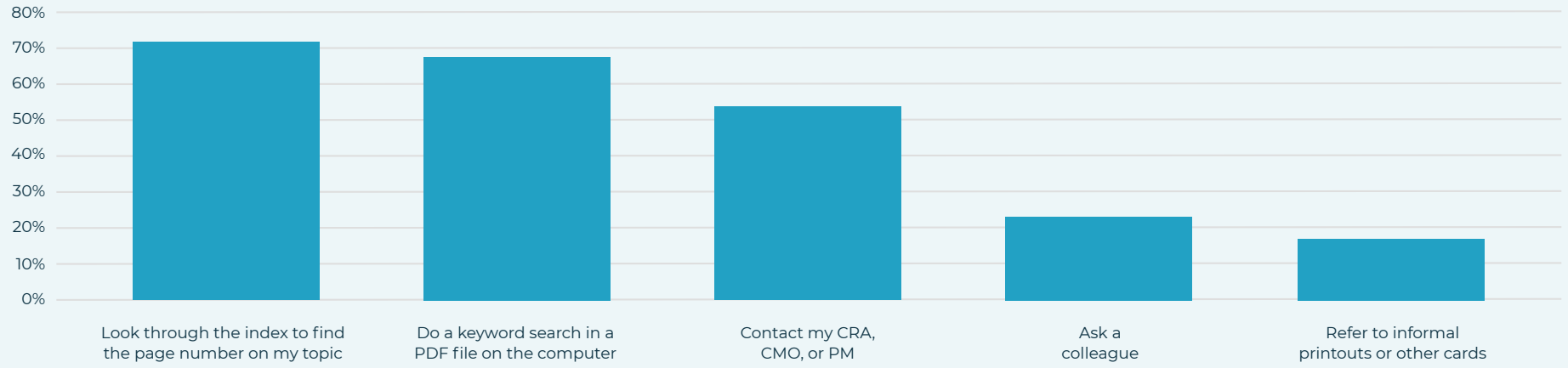
Chart 2: Usefulness of Protocol Information Sources



Q16: In terms of accessing resources to help with the administration of the protocol and/or to gain quick access to the information you are seeking, please rate the usefulness of each of the following

When asked how they are searching for information, the majority (73%) look through the index to find the page number corresponding to their topic, while 68% perform a keyword search (Chart 3). Still, 78% of respondents would either contact their CRA or ask a colleague. Only 18% of respondents would find answers from informal printouts or quick reference cards.

Chart 3: Searching for Protocol Information



Q21: How do you typically find answers in the protocol for issues that may arise while the study is underway?

What the Research Tells Us

Research staff are interacting with the protocol more as "electronic paper" than as a digital resource. This is illustrated first by the fact that the protocol is most often referred to on a desktop computer. Very rarely are respondents using mobile devices, such as tablets or smartphones. Considering that most are scrolling through an index to find a page number, it is not surprising that they aren't accessing the protocol via devices with smaller screens. Even the modes of search are manual – looking up a page number, scrolling through perhaps dozens of instances of a keyword search, or asking someone else.

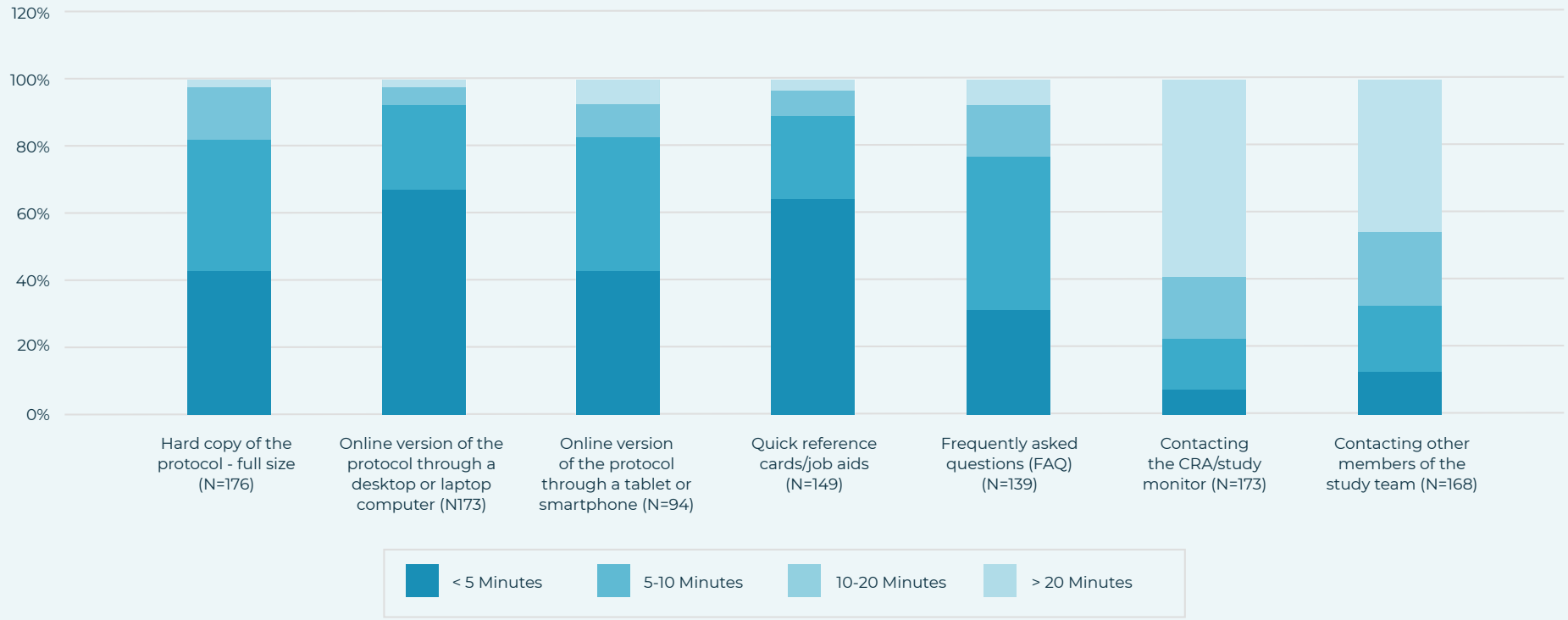
In some ways, a desktop computer is perhaps even less convenient than paper in that it is in a fixed location. While staff may think they are "digital" because they are referring to an online version of the protocol, truly digital would be untethered access with instant, contextually aware answers to precise questions rather than broad brush category references. It's the difference between finding the page number for the schedule of assessments section and getting answers on what specific procedures must be performed during Visit 3.

Chapter 3

There is a degree of separation between the protocol and the patient

More than three-quarters (77%) of respondents reported that it takes longer than 10 minutes to get an answer from the CRA, and more than half (58%) responded that it takes more than 20 minutes (Chart 4). One-quarter of respondents (25%) reported that it takes 5-10 minutes to find answers from a desktop or laptop, with 67% responding that it takes less than 5 minutes.

Chart 4: Time Spent on Protocol-Related Answers

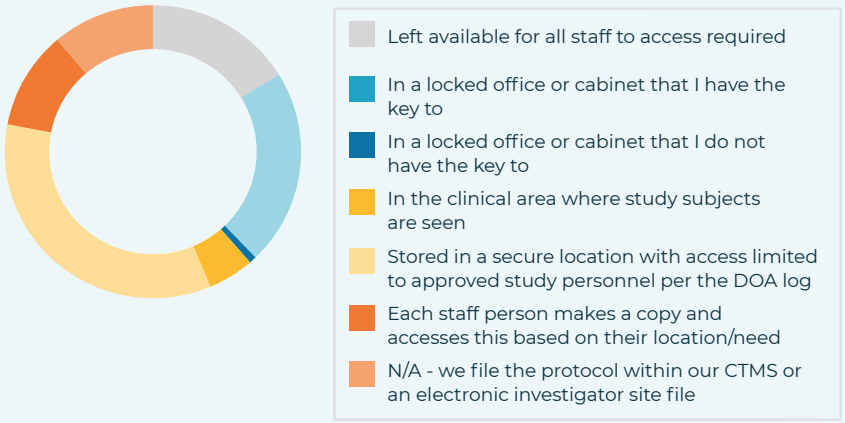


Q23: Recognizing that the amount of time will vary depending on what you are looking for, as a general rule, how long does it typically take for you to locate an answer to your question per resource for most protocol related questions?

Paper-forms of the protocol are still prevalent at research sites. When we looked at where the paper binders are stored, only 7% of respondents said it is stored in the clinic where patients are seen (Chart 5). And 15% said staff make their own copies, which raises questions about version control.

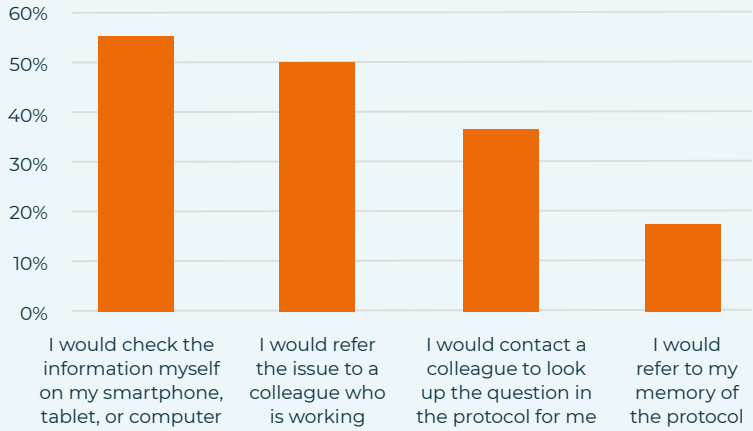
With the protocol not always immediately accessible, we wanted to know what staff would do if they were contacted in off hours by a patient. Half of the respondents (50%) said they would refer the patient to someone else on duty, while more than one-third (37%) said they would ask a colleague to look up an answer in the protocol (Chart 6). And 18% of respondents would refer to memory.

Chart 5: Physical Binder Storage



Q18: If the typical means to access the protocol is a physical binder, how is it stored?

Chart 6: Off Hours Protocol Access



Q22: What do you do if you need to find an answer in the protocol and you are not on duty?

What the Research Tells Us

The protocol is treated more like a static reference, rather than a real-time resource to guide the conduct of clinical trials. Patients' lives have adapted to include the investigational products of clinical trials, they're living with – and possibly because of – these treatments. AEs don't know office hours, they can impact patients at any time, which therefore necessitates that research staff have immediate access to quickly and correctly make decisions.

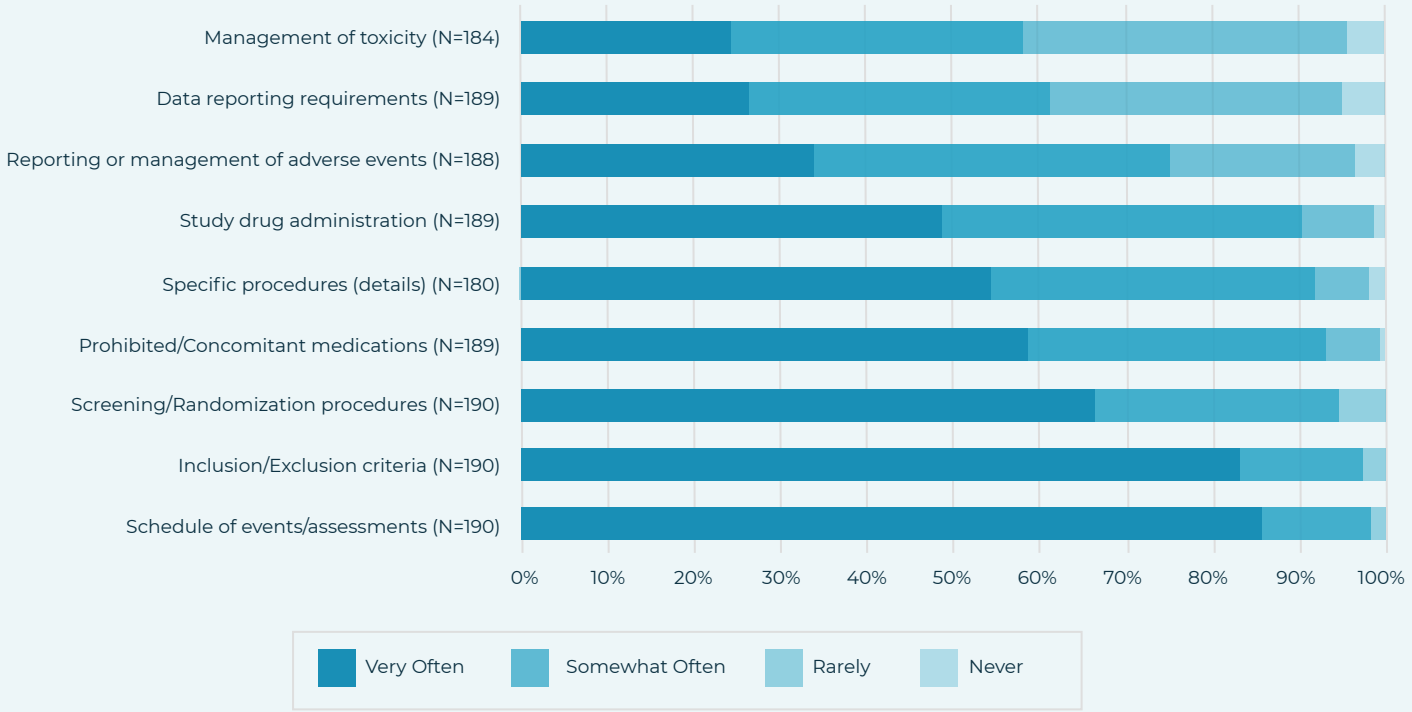
There are inefficiencies and time lost in providing answers for research staff when they are engaged with a patient. Typically, physicians won't have more than a few minutes with a patient to determine if he or she is eligible, and for which clinical trial. If information is not readily accessible, this can lead to challenges with enrollment, which we already know is a problem for many sites.

Chapter 4

Study design complexity presents challenges for staff to find answers in the protocol

The sections most often referred to in the protocol are the schedule of assessments (86%) and eligibility criteria (83%), followed by 66% of respondents very frequently referring to screening/randomization procedures (Chart 7). In contrast, the least accessed is management of toxicity as 42% of respondents rarely or never refer to this section, followed by data reporting requirements (40%) and reporting or managing adverse events (25%).

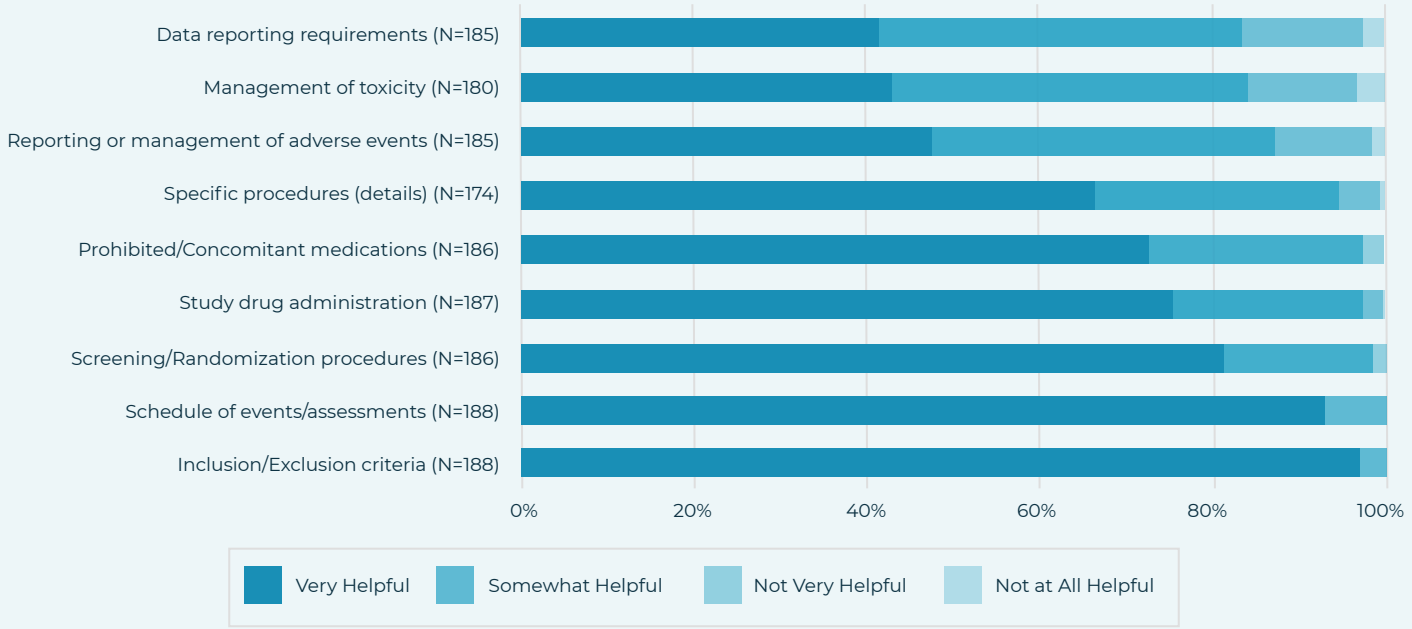
Chart 7: Frequency of Referring to Protocol Sections



Q19: Recognizing that studies vary by complexity, as a general rule, please rate how often you access the actual section of the protocol

Nearly all respondents find inclusion/exclusion (97%) and schedule of assessments (93%) very useful (Chart 8). Unsurprisingly, data reporting requirements and managing toxicity were the sections that respondents found to be the least useful.

Chart 8: Usefulness of Protocol Sections



Q20: Recognizing that studies vary by complexity, as a general rule, please rate the helpfulness of each actual section of the protocol

What the Research Tells Us

The way research staff find answers in the protocol is time consuming and manual. Managing toxicity and adverse events are typically guided not only by sponsor SOPs but also other regulatory and safety reporting guidelines. As a result, these sections of the protocol could have potentially confusing or contradictory instructions when considered against these other sources.

As we saw in the previous section, medical monitors are not frequently a direct source of information for sites (Chart 1). With the CRA often as the intermediary between sites and medical monitors, this delays answers and also limits the visibility of medical monitors into the trial performance.

Chapter 5

Redefining the Digital Protocol for Research Staff

Electronic and digital aren't the same thing. So, what does it mean when the protocol is digital? We believe that answers are available in seconds, contextually aware, and present with the patient.

Answers in Seconds

In the digital world, you ask a question and you get an answer. Under the covers, the search engine is analyzing all of the available information to generate the most relevant results – in seconds.

In clinical trials, there are multiple questions. And answers may come from a variety of documents beyond the protocol, including investigator brochures, lab manuals, CTCAE, etc.

What if any research staff could type a question into a search bar from any digital device and the results are returned in seconds after analyzing all available documents? The focus then shifts to the best answer instead of what section of a document. It reduces the burden on the user because the best answer is found among all of the documents. And it also eliminates any worries about document version because answers are only returned from the approved, current protocol for that site.

Contextually-Aware Answers

Let's take the example of "hypertension." It may be part of the eligibility and so it may appear in either the inclusion or exclusion criteria of the protocol. But if during the trial a patient develops hypertension, the word could also appear in the toxicity management section of the protocol.

A simple scroll through the index of a PDF directs the user to a list of topics but doesn't necessarily answer the specific question. Similarly, doing a keyword search in a PDF would return multiple hits to the keyword, which then puts the onus on the user to look at the context of each instance of the word.

What if a physician could just type in eligibility 140/90 – and get an answer whether the person is eligible for a clinical trial? Or dose 160/95 to understand whether to modify dosage based on the current blood pressure levels? Physicians and nurses can spend less time and be more precise to find answers in the context of their questions.

Present with the Patient

Time with patients is limited. Decisions need to be made quickly and in compliance with the protocol. Whether the patient is eligible for a given clinical trial, what conmeds are permitted, and which procedures should be performed for a given visit, investigators and research staff need to make decisions from the latest study information.

From any smartphone or digital device, answers from the protocol are always where the patient is. This means physicians and nurses can focus on patient care.

For example, protocols may be amended to update enrollment criteria. Therefore, it is critical investigators and research staff have the latest study information when they are with patients to enroll the right study participants and reduce errors.

Gone is the need to walk to another room to log into a computer or flip through paper.

Chapter 6

Digital Protocols – What's in It for Sponsors and Monitors

If sponsors and monitors aren't asking how research sites are interacting with the protocol, they should. Why?

First, it is a measure of how engaged sites are with the trial. Actively looking at eligibility criteria, for example, is a good indication of whether sites are trying to recruit for the study. It also speeds enrollment of the right patients because research staff are confirming the criteria on the spot. Second, conducting trials strictly by the protocol reduces errors, minimizes deviations and protects patient safety.

Sponsors and monitors have a role to play in helping to alleviate the burdens on research staff in conducting trials. And they both have something to gain with better visibility and earlier insights into trial performance.

Better Visibility

It may sound obvious, but paper protocols don't give sponsors or monitors any idea who is looking at the protocol or what answers they are trying to find. Similarly, "electronic paper" documents don't offer much more insight.

Usage trends of portals are nice to have stats – if you can get them in the first place. And unless you are regularly running a report, they offer a picture that is after the fact. And usage still doesn't answer the question of what the person was really looking to answer.

When the protocol is truly digital, sponsors and monitors can see in real time who is looking at the protocol, how often and what they are trying to find. In fact, remote monitoring necessitates this digital insight.

CRAs can target precise support for sites who aren't meeting their enrollment targets. Site queries can also be handled faster. And central monitors can compare usage trends across sites to evaluate key indicators, such as enrollment or protocol deviations.

Early Insights

With real-time insights, sponsors and monitors can proactively address risk factors. High profile search terms may indicate safety issues, while high frequency search terms could highlight where further clarification is needed.

Let's take the example of toxicity management. If there are known symptoms that could be an early indicator of a known side effect, alerts when sites are searching for this would allow sponsors to react more quickly to guide the investigator on specific actions.

Similarly, if there are consistent questions in the same area, such as permitted conmeds or certain eligibility criteria, sponsors could provide clarifications to monitors and site staff so that everyone has consistent, real-time guidance.

By connecting sponsors with the staff conducting the trial, they have a better understanding of performance and can proactively offer guidance or additional support for items blocking sites and trial success.

Chapter 7

Where Do We Go from Here?

At the end of the day, it's about making it simpler for research staff to safely conduct clinical trials so that life altering treatments can safely come to market faster.

We see that research sites are stuck in a bit of a time warp. Physical paper is still a dominant source of information. Even when the protocol is referenced "electronically," it is used more like paper on a desktop than a digital resource. There is still a reliance on CRAs as an information source, which delays responses to questions.

If you think about the patterns in your own life, how much of it is digital and mobile? Physicians, nurses and CRAs aren't any different. And as we have more "digital native" staff, it is unlikely that they will be satisfied with antiquated practices.

With COVID-19, paper itself poses risks of contamination. And with more remote monitoring, clinical trials must move to be more digital.

Speed and quality of answers are critical to any clinical trial. In a digital world, answers for research staff are just a couple of clicks away – anytime, anywhere. Every answer provided itself tells a bigger story for sponsors and monitors to evaluate trial performance and proactively address issues.

Appendix: About the Research

The Tufts CSDD - Teckro 2020 Study on Investigative Site Protocol Administration Referencing Practices was conducted by Tufts CSDD, in collaboration with Teckro. The research was conducted between April 28 and June 5, with 228 responses. The study highlights were published by Tufts on July 21

Respondents represented a mix of institutions (Chart 9) and job functions (Chart 10). The majority of respondents conduct Phase II and Phase III clinical trials across a range of therapeutic areas (Chart 11).

Chart 9: Respondent Demographics - Type of Institution

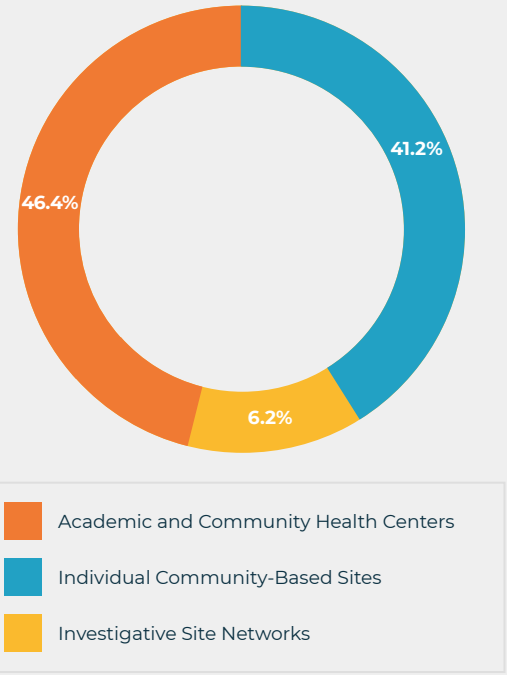


Chart 10: Respondent Demographics - Job Function

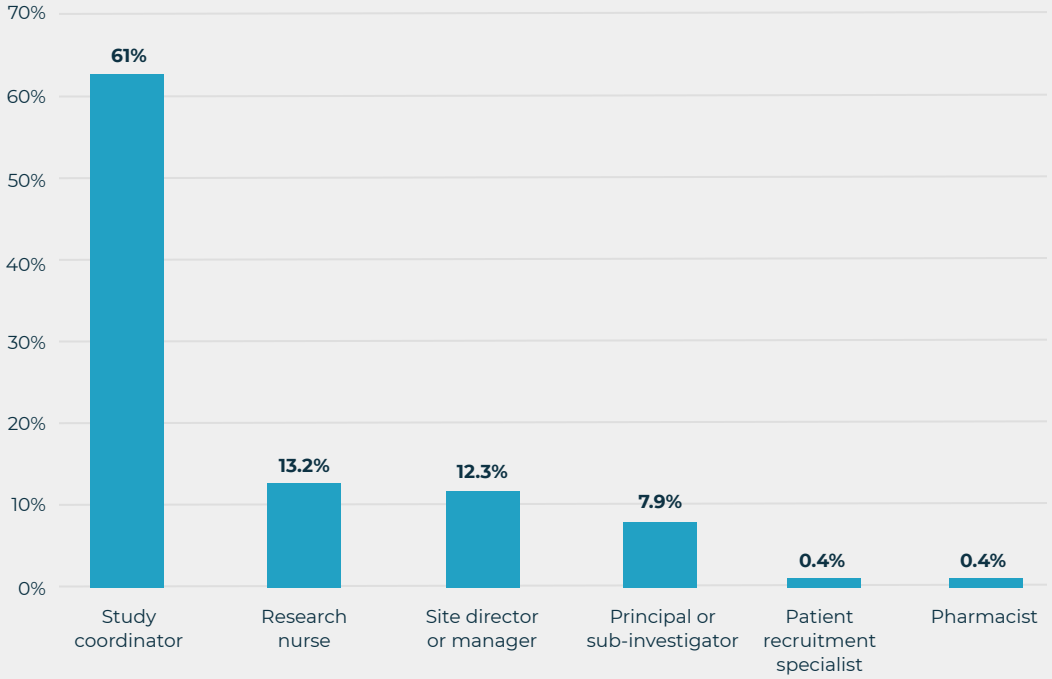
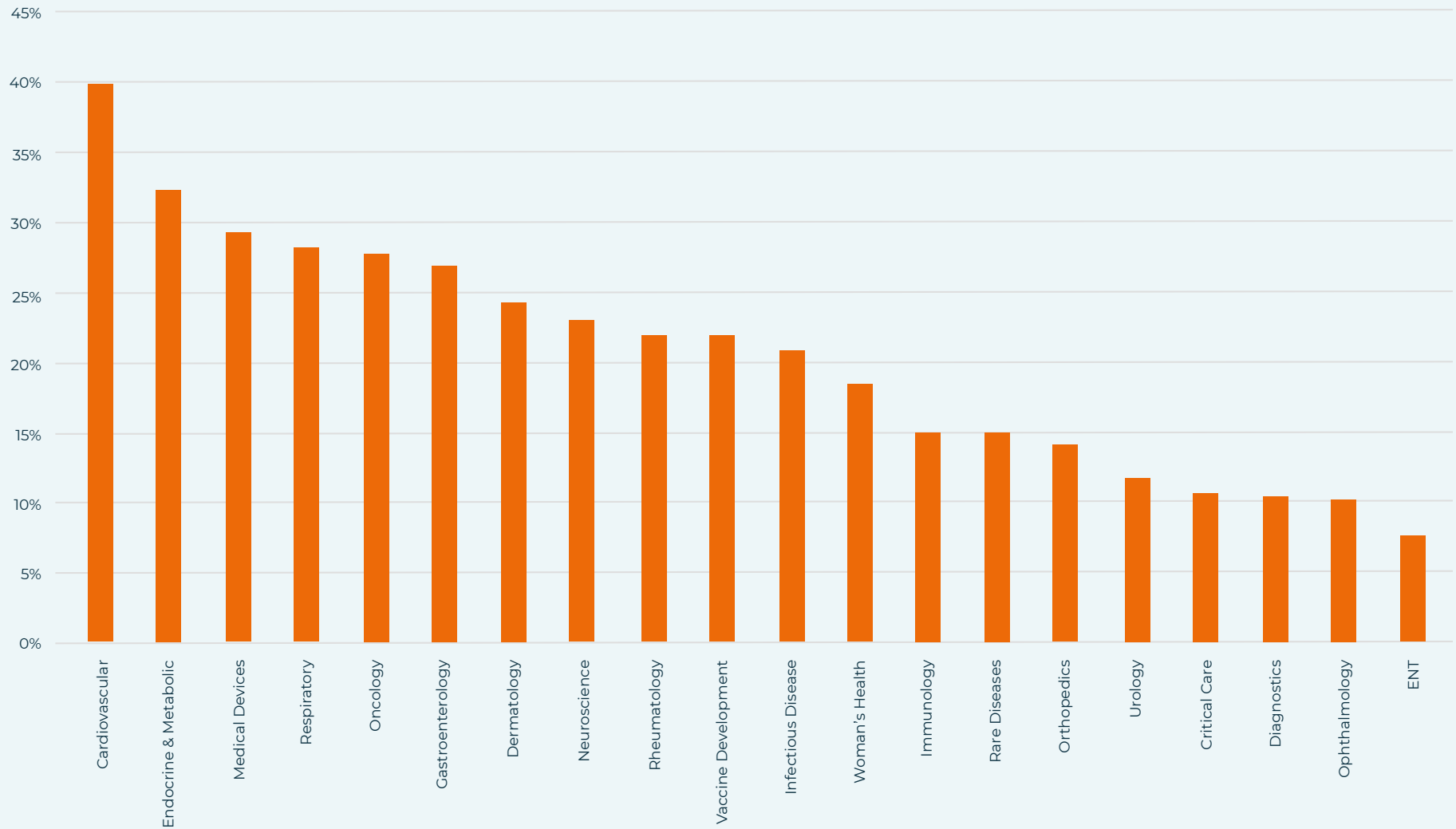


Chart 11: Respondent Demographics - Therapeutic Areas



Have a Study Question?

teckro the Answer

For more information about the research or to find out more about Teckro, please visit teckro.com or email us at connect@teckro.com.