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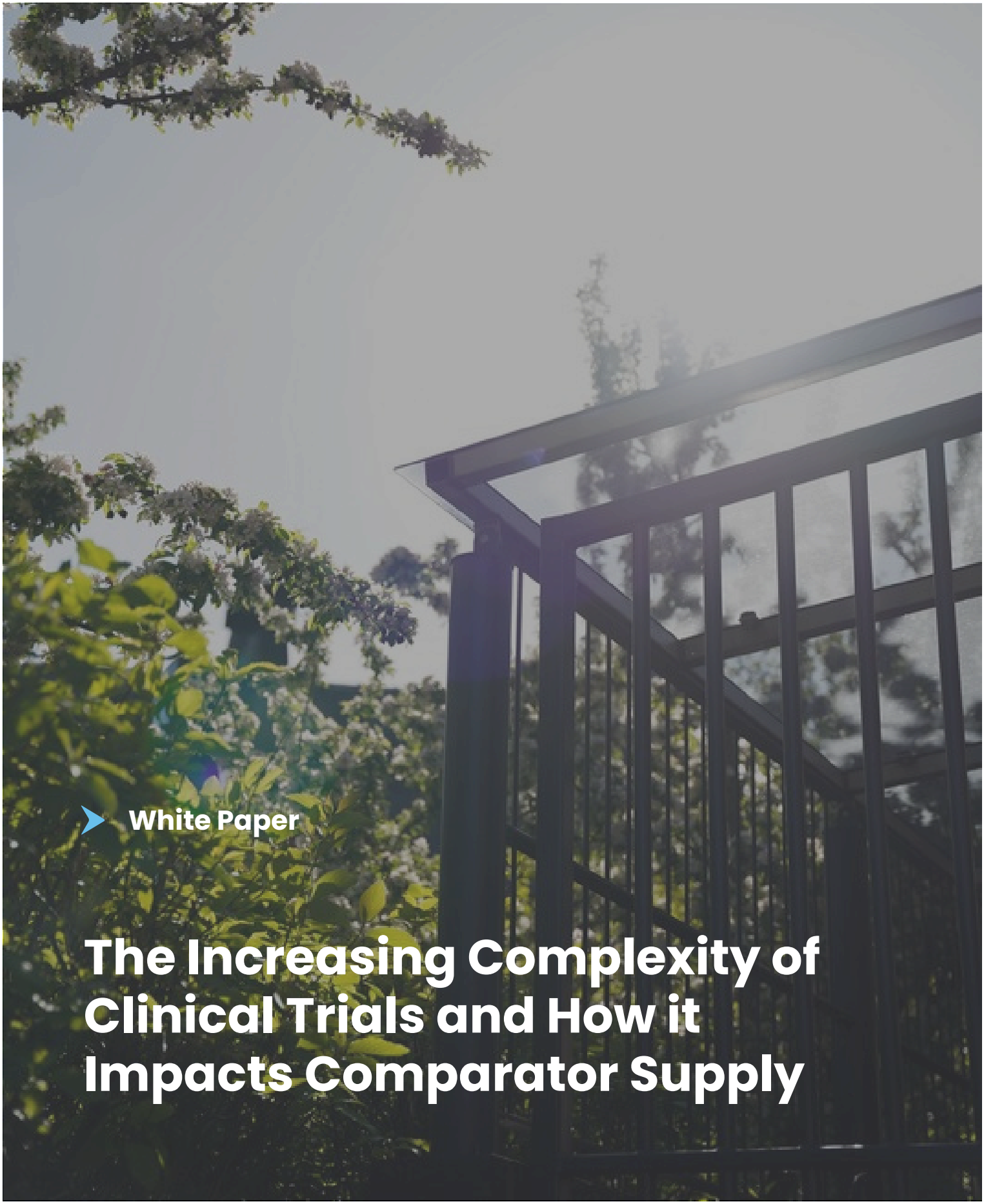

White Paper

The Increasing Complexity of Clinical Trials and How it Impacts Comparator Supply

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The trend of increasing complexity in clinical trial designs has been gathering pace for several years, with several factors playing a part in its seeming acceleration. The necessity for complexity will always be debated, but what is not negotiable is that those of us involved in supporting global clinical supply chains must understand the evolution of our industry so that we can adapt.

This White Paper looks at why complexity has now become the norm, what it means for the traditional sourcing strategies that we've become so accustomed to over the years, and how we can give ourselves the best chance of building strategies that can be as flexible and adaptive as the studies they are supporting.

Why Are Trial Designs Increasing in Complexity?

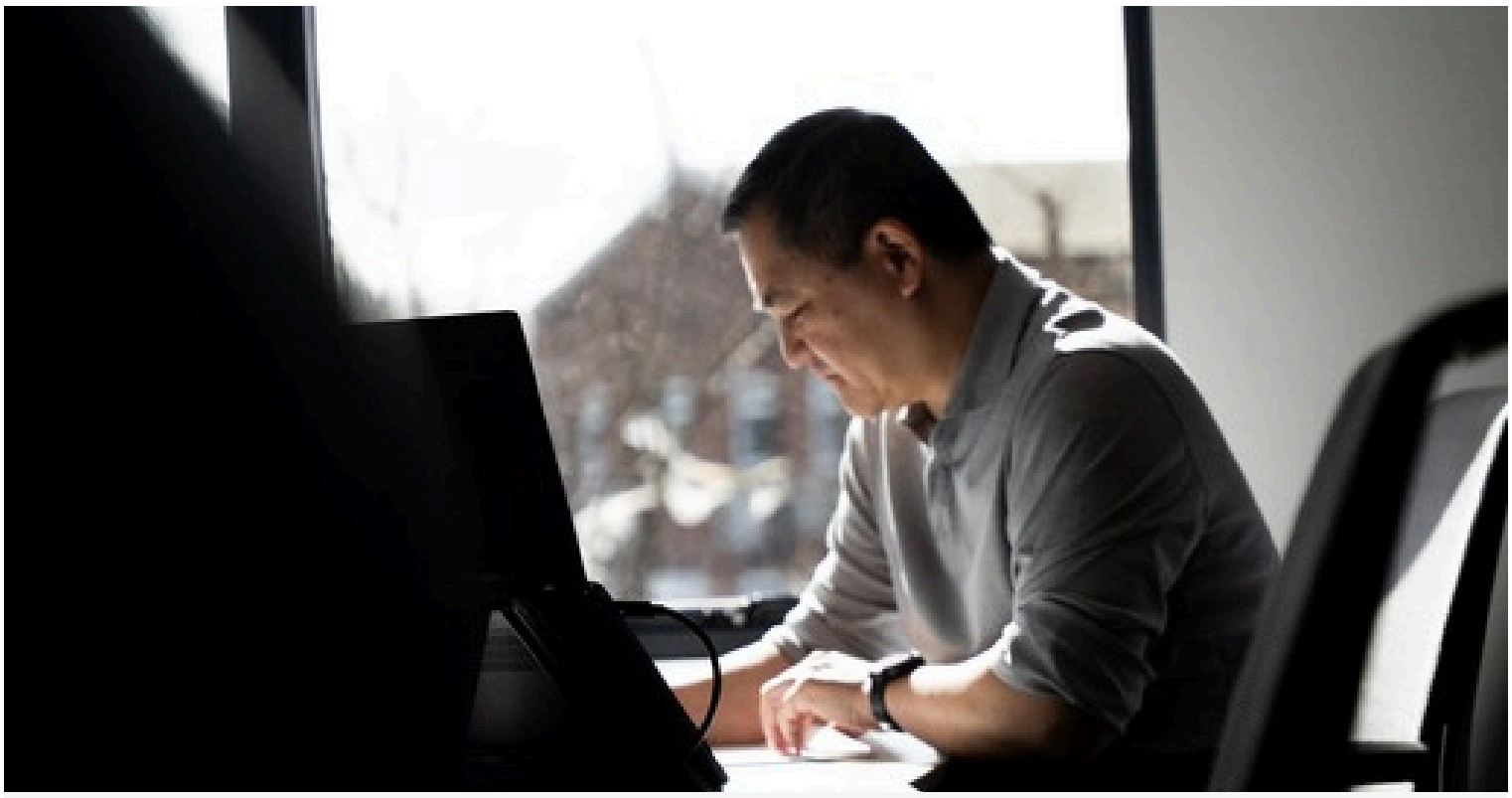
Complexity is now closer to being the rule than the exception. On a personal level, I can say that the trial protocols I read are longer, the country lists are more exotic, and the average number of comparators per study is higher than when I started my clinical supplies journey back in 2009. But why?

There are many factors, perhaps too many to list within these short paragraphs, but let's look at some of the main ones.

Drug development has become more targeted with the emergence of precision medicine, cell and gene therapies, and rare diseases, and in recent years we have seen Regulators becoming more encouraging of innovative trial designs. What may have been a 'one drug vs. control' model several years ago with very little by way of moving parts, is more likely to be an adaptive trial design, which allows for elements of an ongoing study to shift based on incoming data.

Whilst many of us operate in a clinical space day-to-day, it is commercial pressure that so often drives our industry, impacting study designs in everything from start dates to endpoints. Sponsors are naturally motivated to reduce time to market which means development times are squeezed, more cohorts are run in parallel, multiple diseases are targeted within the same study, and with a glimpse of possible success on the horizon, expansion studies can be greenlit.

Each of these key drivers is (seen in a positive light) exciting, innovative and challenging; they push the barriers of what we think is possible and they help to advance outcomes. They also, undeniably, add operational demands to our clinical supply chains, which is what we all need to position ourselves to manage.



How is Design Complexity Impacting Traditional Comparator Supply Strategies?

Comparator strategies have long been simplified into two categories; Local Sourcing (sourcing a drug from within a given territory, for use within that same territory) and Central Sourcing (sourcing a drug from one territory, to be used across many territories).

These two approaches do capture the entire spectrum, but that is exactly where supply strategies sit: on a spectrum. The reality is that your comparator strategy is incredibly unlikely to be wholly in one camp or the other.

For example, a Central Source (let's say European drug, non-CoA) is working just fine until the country list expands into LATAM, and the CoA that you are missing suddenly becomes essential. Central Source doesn't cut it anymore, and an additional approach is needed.

Conversely, you have your heart set on Local Sourcing for all comparators, but then you hear that 'Cohort 5' is going ahead, and it involves a comparator that isn't yet licensed in some of the trial countries. Again, a different strategy needs to be implemented.

Enter the ‘Hybrid Strategy’.

A Hybrid Strategy is exactly what you would expect it to be; it has elements of both Local and Central Sourcing in order to tackle some of the complexities that are presented by long country lists and multiple comparators.

It acknowledges the need for more than one approach to ensure all trial sites can benefit from a robust supply chain.

But Hybrid Sourcing can hardly claim to be the new kid on the block; if you’ve run a global Phase III trial using comparators, then it’s very likely that you’ve experienced a hybrid supply strategy already, even if it wasn’t by design.

It is also likely that your approach will shift during the trial, and that it doesn’t stay in the same place throughout the entire trial, and that the flexible and adaptive clinical trials being run will need a flexible and adaptive comparator strategy to match.

What Does a ‘Modern’ Supply Strategy Look Like?

The goal of any good comparator strategy is efficiency: achieving a robust, compliant and sustainable supply chain, whilst keeping costs and waste under control. By combining a modern trial design with a traditional supply strategy, we are unlikely to achieve efficiency.

A modern supply strategy nearly always means Hybrid, but we are perhaps in an era when the term ‘Hybrid’ is itself an oversimplification. Comparator solutions now need to be as modern and adaptable as the trials that they are supporting. By acknowledging that we may encounter complexities that mean our initial strategy may not get us all the way from FPI to LPO, we can start looking at how flexible we really need to be from the outset. A Hybrid Strategy doesn’t just sit on the spectrum, it moves about on that spectrum throughout the study.

Cross functional governance is required more than ever before, largely due to increasing complexity. As comparator solutions become more creative, the need for QA and Regulatory input is essential, and planning discussions need to expand beyond Clinical Ops, Supply and Vendor.

A working example:

The most popular region for a Central Source is often the EU with their mature regulatory framework, comparatively low prices, and often good access to drug. But when the EU is not viable for whatever reason (i.e. a product that has a restricted distribution model in the US and Europe may be more accessible in certain APAC regions) a Central Source may still be needed. Utilizing other territories, such as APAC, is becoming more common, but as that path is not so well trodden, engaging with Regulatory early in discussions is imperative and the availability of documentation becomes ever more important.

Scenario based forecasting now needs to be included in comparator discussions. Simply knowing that the proposed supply route is only able to cope with the initial study estimates is no longer sufficient where adaptive designs are being used. Comparator A may drop off mid-study, but Comparator B's demand may double, and that needs to have been stress tested before the eventuality arises.

What Can I Do To Be Prepared?

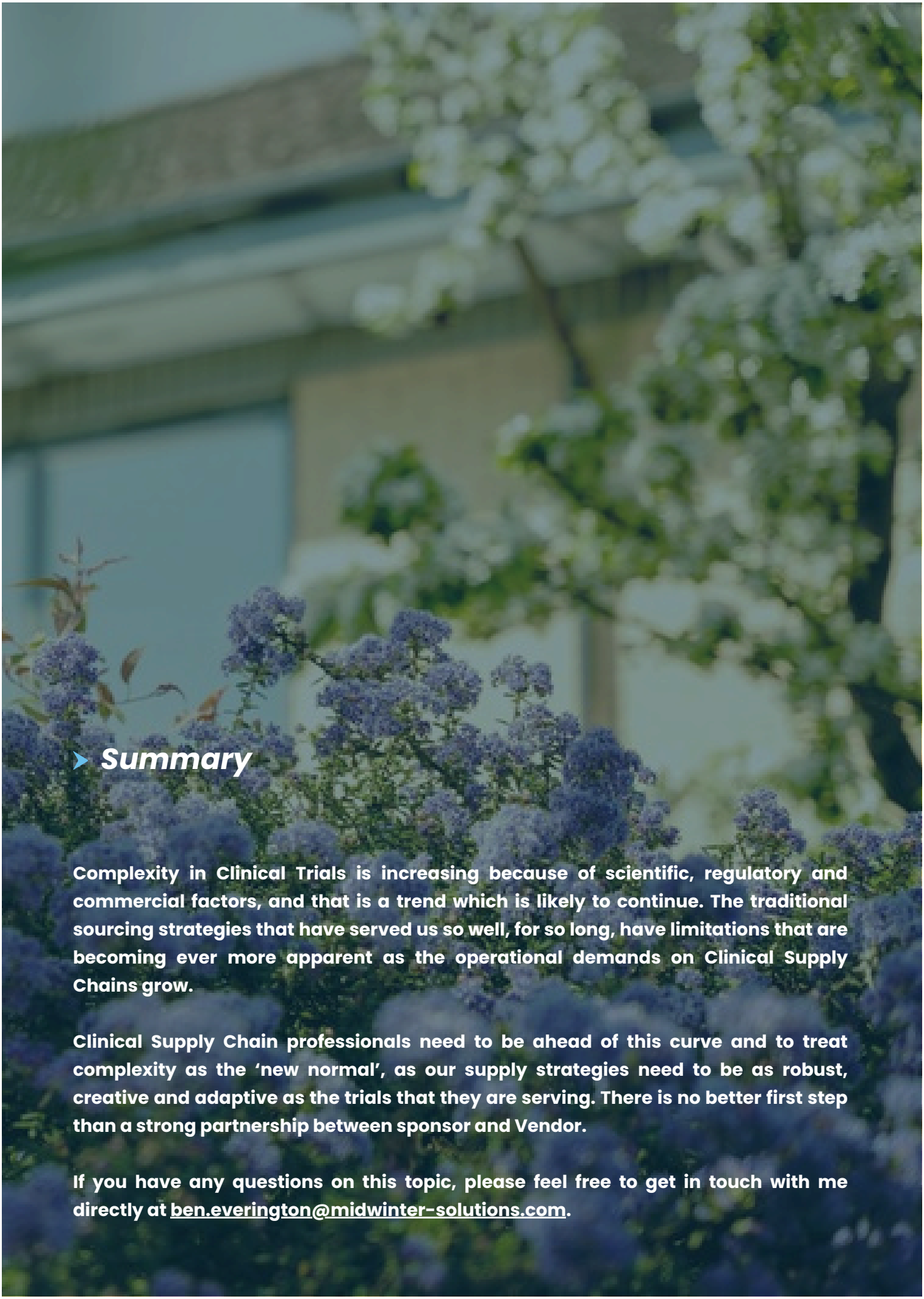
Having a trusted and proactive Vendor is essential and building that Sponsor: Vendor partnership over time is always going to pay dividends, but in the meantime, here are a few tips that may help:

Country Lists: As a Sponsor, discuss your country list with your Vendor, as a long country list is a strong indicator of complexity. Resist the temptation to only discuss the countries that initiate first. By sharing the entire country list (even the proposed countries that may get crossed off later) you can understand what those countries might do to the comparator strategy if they are utilized.

Scenario Planning: It's important to be honest with your Vendor about the likely scale of the study, but there is no harm in asking them to stress test certain eventualities. "If our demand doubles, what does this do to the proposed supply route?"

Share the Protocol: An experienced Vendor can glean important information from the Protocol, and those may be the bits that are otherwise overlooked. This is particularly true if you have inherited a study part way through and may not be entirely aware of the comparator opportunities/limitations yourself.

Proactivity: Treat Comparator Strategy as part of the trial design, and not just a by-product of it. Identifying the right strategy in the age of trial complexity is a time consuming and often ongoing process, and it cannot start early enough.



Summary

Complexity in Clinical Trials is increasing because of scientific, regulatory and commercial factors, and that is a trend which is likely to continue. The traditional sourcing strategies that have served us so well, for so long, have limitations that are becoming ever more apparent as the operational demands on Clinical Supply Chains grow.

Clinical Supply Chain professionals need to be ahead of this curve and to treat complexity as the 'new normal', as our supply strategies need to be as robust, creative and adaptive as the trials that they are serving. There is no better first step than a strong partnership between sponsor and Vendor.

If you have any questions on this topic, please feel free to get in touch with me directly at ben.everington@midwinter-solutions.com.

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