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CITELINE

Ebook

Your Keys to Understanding EU Transparency

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Contents

EU Offers 'Timely And Helpful' Advice On Summarizing Trial Results For Laypersons

Vibha Sharma

Oct. 11, 2021

Executive Summary

With around three months left for the EU Clinical Trials Regulation to fully kick in, the European Commission has finalized much-awaited guidance offering practical insights into how companies can comply with new transparency requirements mandated under the legislation.

The European Commission has issued final guidance explaining how sponsors can comply with the upcoming mandatory requirement under the EU Clinical Trials Regulation (CTR) to publish lay summaries of clinical trial results within specified timelines.

The CTR is due to apply from Jan. **31,** 2022, i.e., the date on which the new Clinical Trials Information System (CTIS) goes live. Many companies have already started putting processes in place in preparation for the lay summary-related requirement, which aims to improve the transparency of clinical trial information. (Also see "Pharma Firms Urged To Get Going On EU Lay Summaries" - Pink Sheet, Aug. **18**, 2020.)

The publication of the good lay summary practice (GLSP) guidance is "both timely and very helpful," said Lisa Chamberlain James, of the UK-based medical writing firm, Trilogy Writing and Consulting. "We have certainly seen an increase in companies needing help with Lay Summary production ahead of the imminent deadline," she added.

The CTR requires sponsors to summarize and publish trial results in the CTIS in a form that is understandable to laypersons. The lay summary

must be submitted to the CTIS no later than 12 months from the protocol-defined end of the clinical trial, six months for pediatric studies, and up to 30 months for non-therapeutic Phase I trials.

The GLSP guidance, published on 4 October, offers practical advice on how sponsors can prepare, write, translate and disseminate summaries of clinical trial results in lay language. It recommends that sponsors organize the lay summary process into four steps (planning, development, translation and dissemination) and proactively involve patients in all aspects, where possible.

The importance of early planning for this process, ideally during trial protocol development or even when preparing a research proposal and related budget, is emphasized throughout the guideline.

"Whilst nothing is perfect and no guide can teach how to write, this guide is logical, clearly laid out, and signposts to further information and research if needed," said Chamberlain James, who is a senior partner at Trilogy. "This should be the go-to guide for anyone starting to work on Lay Summaries, or wondering what they are all about."

The guideline recognizes and addresses the need for specific skills and strategies for lay summaries on pediatric trials and highlights the limited experience available so far. Visual icons have been added throughout the guideline to highlight aspects that are mandatory under the CTR and to distinguish these from recommendations on pediatric lay summaries that sponsors are encouraged to consider.

On the readability front, for example, while the CTR only specifies that trial result summaries should be understandable to laypersons, the guideline recommends that a well written summary should normally be accessible by young people from the age of 12 years upwards. The guideline encourages sponsors of pediatric studies "to consider developing a child-focused version" of the lay summary for younger trial participants "in addition to the version for the parents or legal representatives."

The final guideline is the result of a multi-stakeholder initiative and consultation process integrating the experience and recommendations of over 60 international industry, academia, patient and not-for-profit organizations. It was first adopted on 9 July by the EU Clinical Trials Expert Group, a working group of the European Commission representing ethics committees and EU national competent authorities. (Also see "New Guide Offers Practical Insight Into EU Clinical Trial Lay Summaries" - Pink Sheet, July **28**, 2020.)

The guideline incorporates several updates based on stakeholder feedback. On the tricky issue of the ideal length of lay summaries, for example, the previous recommendation of "four to six pages" for trials with intermediate complexity has been dropped altogether. This has been replaced with a generic note that a "readable document can be achieved with a good layout and design for trials with intermediate complexity" while "more complex trials may require more description."

When the draft GLSP guideline was issued for consultation, Chamberlain James said she had "high hopes for a well-researched, pragmatic, and helpful guide." The final guide, she said, met her expectations. "I was not disappointed."

UK Kicks Off Landmark Overhaul Of Clinical Trial Framework

Changes Affect Processes, Requirements & Timelines

Ian Schofield

Jan. 17, 2022

Executive Summary

The UK regulatory agency, the MHRA, is planning to establish a "world-class sovereign regulatory environment" for clinical trials to support the development of new innovative medicines. In the first of two articles, we look at the MHRA's proposals to slim down trial approval processes, lighten the safety reporting burden, and introduce greater transparency of trial registration and results.

The UK Medicines and Healthcare products Regulatory Agency has launched a public consultation to elicit stakeholder input on its plans for a post-Brexit revamp of the clinical trial regulations designed to make the UK "the leading global center for innovative research design and delivery."

Among its plans are new maximum timelines for the combined review of trial applications, more flexibility on requests for information during application review, greater transparency of trial registration and results, and a lighter burden of safety reporting.

Other proposals, to be covered in a second Pink Sheet article, address areas such as patient involvement in trial design and management, adherence to Good Clinical Practice, requirements for investigational medicinal products, and changes to the rules on low intervention trials.
This is the first major overhaul of the UK trial regulations since the provisions of the EU

Clinical Trials Directive were transposed into domestic law in May 2004. The ability to have its own rules in this area has been widely flagged up by the government as one concrete benefit of the UK's decision to leave the EU.

"We aim to reframe the legislation that underpins our regulation of clinical trials to deliver a more streamlined, transparent and flexible regulatory regime" – MHRA chief June Raine

Launching the eight-week consultation on 17 January, MHRA chief executive June Raine described the initiative as a "once-in-a-generation opportunity to review and update the UK legislation for clinical trials in order to make the UK the go-to place to develop new and innovative healthcare products."

"Through the proposals outlined in this consultation we aim to reframe the legislation that underpins our regulation of clinical trials to deliver a more streamlined, transparent and flexible regulatory regime whilst always protecting patients and trial participants," Raine said.

The changes will be implemented by updating the Medicines for Human Use (Clinical Trials) Regulations 2004, which transposed the EU directive into UK law in May that year.

Plans to consult stakeholders on the proposals were first announced at last year's BioIndustry Association-MHRA regulatory innovation conference in December. Raine told drug sponsors at the time to "look forward to that consultation, and get ready to engage." (Also see "UK Plans Major Clinical Trial Legislation Revamp" - Pink Sheet, Dec. **10**, 2021.)

Changes To Regulatory Requirements

As part of moves to streamline the clinical trial approval processes, the MHRA is proposing to give legal shape to its new approach that took effect on 1 January, wherein sponsors have to apply for a combined regulatory and research ethics committee (REC) review of their trial applications.

This follows a pilot on a process that involved a single application route and combined reviews that was carried out last year and that the agency says is now to be embedded in the legislation. (Also see "Combined Trial Reviews To Become The Norm In UK From 2022" - Pink Sheet, Jun**e 10**, 2021.)

Key features of the proposed process include:

- A single UK "front door" in the form of the "Integrated Research Application System" (albeit with the possibility to have separate applications if justified).
- A streamlined appeal process with details to be set out in guidance.
- New maximum standard timeframes for the joint review and decision of 30 days from receipt of the application, after which an approval or a "Request for Information" (RFI) would be issued.
- For multinational trials, in order to minimize or avoid UK-specific changes resulting from "non-concurrent assessment procedures" at regulators in other countries, a "generous" 60-day period would be granted to the sponsor to respond to any RFIs. This would "facilitate the harmonization of international protocols and better align requests for changes from multiple regulators."

The MHRA notes that the current legislation does not explicitly allow a sponsor to withdraw their trial application once the assessment has begun, so it is proposing to allow withdrawal of the combined MHRA/REC application "up until the final assessment decision is issued, with a proportionate fee paid."

Requests For Information

Requests for Information (RFIs) can be issued by the MHRA or REC where information is missing or changes are needed to the trial application, but they can delay the application process because assessment is suspended until the sponsor provides a full response. "Learning from clinical trials during COVID-19 has highlighted the opportunity for greater flexibility in the formal communication between applicants and regulators during the review of a clinical trial application," the MHRA says.

It is therefore proposing that an RFI could be issued relating to just one particular part of a trial, within a maximum timeframe (30 days from receipt of the application). "This approach worked well during COVID-19 on an informal basis, and ensuring there are no blockers to this in legislation would facilitate this option for a broader range of trials when appropriate," according to the agency.

RFIs could also be used to deal with substantial amendments to a clinical trial, it suggests.

Safety Reporting

Some safety reporting requirements in clinical trials "add burden to investigators but do not contribute to patient safety," the MHRA observes. A number of changes are planned here, such as:

- Removing the requirement to report individual suspected unexpected serious adverse reactions (SUSARs) to all investigators. Instead, they would be informed of safety information via the Investigator's Brochure, a comprehensive summary of clinical and non-clinical data compiled throughout the study.
- Abolishing the requirement to report SUSARs and annual safety reports to RECs in order to reduce duplicative reporting requirements. Where justified, SUSARs could be reported in an aggregate manner "provided that the trial protocol mandates continuous monitoring of serious adverse events/reactions."
- Placing a legal requirement on sponsors to have a pharmacovigilance system aimed at periodically reviewing accumulating safety data to detect safety signals and propose risk-mitigating actions.
- Removing the requirement to include listings of serious adverse events and reactions in annual development safety update reports (DSURs). The reports should instead include an appropriate discussion of signals/risks associated with the use of the product.

Transparency

On the transparency front, the MHRA plans a number of moves to make sure trial information is "publicly available for the benefit of all," including legislating for "some of the research transparency provisions policies and processes set out in the Health Research Agency's 'Make it Public' strategy to embed research transparency in the regulation of clinical trials."

There would be a requirement to register a trial in a World Health Organization-compliant public register before it began, and to publish a summary of the results within 12 months of the end of the trial (with deferral possible). Trial findings would have to be shared with participants within 12 months. (Also see "UK To Reveal How Sponsors Are Performing On Trial Transparency Expectations" - Pink Sheet, Dec. **7**, 2021.)

To reduce burden on sponsors with respect to registration, the HRA has started automatically registering all new clinical trials of

investigational medicinal products (CTIMPs) into the ISRCTN, a WHO-recognized global clinical trial registry. (Also see "UK To Up Transparency By 'Auto Registering' Trials" - Pink Sheet, Oct. **20**, 2021.)

Sunset Clause

The legislation also allows a clinical trial approval to remain valid indefinitely, despite the fact that changes in medical practice, for example, could have an impact on whether the decision to approve the trial is still appropriate in future.

For this reason, the MHRA proposes to introduce a sunset provision under which the approval would lapse if no participants were included in the trial within a specified period, for example within two years of the trial approval. If this happened the sponsor would need to apply for an extension.

"As a regulator it is imperative that we are able to take action when absolutely necessary to safeguard patients" – UK MHRA

There are also plans to ensure that the MHRA's regulatory oversight is "both proportionate and strong," so the agency is considering "more risk-proportionate correct measures."

For example, regulators would be able to refuse to approve a new study if there was "ongoing serious non-compliance with the legislation" relating to an earlier trial and where there "could be significant harm to participants."

The agency expects this would be rarely used, but "as a regulator it is imperative that we are able to take action when absolutely necessary to safeguard patients," for example where the non-compliance was "so serious that it would result in regulatory action, such as an Infringement Notice, termination of a trial or possible prosecution."

With regard to the suspension or termination of a trial, and in view of "modern trial design," it is proposed to remove the requirement for the whole trial to be stopped if regulatory action is taken.

"Instead, we want to make clear that regulatory action might apply only to a specific part of the trial eg, recruitment, dosing, a specific arm of the trial or related to a particular trial site," the MHRA says. "This change would help ensure that regulatory actions are proportionate and recognizes the increasing use of innovative trial designs."

Pharma Firms Urged To Get Going On EU Lay Summaries

Encapsulating Clinical Trial Results For Patients Is Not Easy

Vibha Sharma

Aug. 18, 2020

Executive Summary

The upcoming EU requirement for summarizing clinical trial results in plain language is a real opportunity for companies to engage with the public. But if companies don't provide clear and concise information, it may be reduced to a box-ticking exercise.

The setting of a clear implementation date for the EU Clinical Trials Regulation (CTR) has sparked calls for appropriate compliance with a new requirement in the legislation for companies to publish lay summaries of clinical trial results.

There is a concern that without a clear focus on ensuring that the lay summaries are "fit for purpose" — i.e., they provide clear, concise information on clinical trial results in a non-promotional manner — compliance with the obligation may become a pointless, box-ticking exercise.

The CTR is not expected to apply until December 2021, but there is already a wide mix in terms of how the industry is gearing up for the new requirement. (Also see "EU Clinical Trials Regulation To Apply From December 2021" - Pink Sheet, June 16, 2020.)

Some companies are well prepared and have started producing lay summaries on a voluntary basis. This has resulted in some great —and some not-so-great — examples of how complex clinical trial information can be summarized in plain language, said Lisa Chamberlain James of the UK-based medical writing firm, Trilogy Writing and Consulting.

But for some companies "it's just not even on their radar," which Chamberlain James thinks "is a bit scary considering the time it can take for companies to set up the necessary processes." Her advice to such companies is to "get started" and not "leave it until the last minute."

"It almost always takes longer than people expect it to take," said Chamberlain James, who has worked with several drug companies to help them develop templates and prepare their systems to comply with the requirement to publish lay summaries.

"It's not as easy as everyone thinks." – Lisa Chamberlain James, Trilogy Writing and Consulting.

While some companies can move faster than others, she explained that much depends on the company's size and work culture. Larger companies may take longer as they usually have a lot of management levels at which to get approval and buy-in for new processes.

For companies that choose to do this in-house, Chamberlain James recommends they should find somebody, either within or outside the company, with the correct skill set and experience to help. "It's not as easy as everyone thinks," she said.

Describing complex clinical trial results in the right way, with the right level of context and data, can be a "real challenge" because the staff in regulatory departments traditionally do not have to prepare information for these audiences, Chamberlain James told the Pink Sheet. "You really need to start by training your [lay summary] reviewers… and that can take time," she added.

The complexity of the task can be gauged from the fact that a recent multi-stakeholder guideline on preparing concise, plain language summaries of clinical trial results itself runs into 104 pages. The guideline, which is currently out for consultation, includes feedback from over 60 international patient organizations, pharmaceutical companies, academic institutions, not-for-profit organizations and contract research organizations. (Also see "New Guide Offers Practical Insight Into EU Clinical Trial Lay Summaries" - Pink Sheet, July 28, 2020.)

Ridiculously Long

Lay summaries should ideally be as short as possible. Although Chamberlain James has prepared lay summaries that were just one page long, she confesses these are "quite unusual to be fair."

Most of her lay summary documents are three to four pages long. "Any longer than that, and only the most committed patient will wade through the information," she said.

Chamberlain James said she had seen lay summaries running into eight to ten pages and "even longer," which she thinks is "just crazy" as most members of public will not read such long, overwhelming documents. It all then just becomes a "pointless exercise," she said.

The reason a lot of lay summary documents go wrong "is that they provide way too much background" and extraneous information that is not mandated by the regulation, she said. "Their writers should be questioning themselves if all of that information is really necessary… because usually it's not."

Besides brevity, there are other aspects that must be considered for producing fit-for-purpose lay summary documents, such as:

- **Checking readability:** While user testing is strongly recommended at various stages, Chamberlain James said most companies do not go in for full user testing because of the time and budget implications. "There is a big variety of lay summaries out there," she said.

Pharma Firms Urged To Get Going On EU Lay Summaries

- **Non-promotional:** The CTR requires lay summaries to be non-promotional and unbiased, but there is no legal requirement for these to be formally evaluated by the concerned national competent authority. Their public availability will make it possible for the public to scrutinize them and report any issue identified, the European Medicines Agency told the Pink Sheet.
- **Timeliness:** The lay summaries must be submitted no later than 12 months (six months in case of pediatric trials) after the end of a trial, which is defined as the last patient last visit, or at a later point in time as specified in the protocol. The EMA said it was difficult to be specific on when exactly the first set of lay summaries would become available under the CTR as this depended on a combination of factors, such as the transition period and the application of disclosure rules to various categories of trials.

While there are still over 16 months left for the CTR to come into effect, some companies have realized that the lay summary requirement gives them a real opportunity to engage with the general public and to explain their studies.

These companies "have embraced the regulation" and created dedicated areas on their websites for lay summaries "which is fantastic. While some are doing an excellent job, others not so much," said Chamberlain James.

To support compliance, the European Commission is planning to revise its 2018 guideline on lay summaries to provide further details on their preparation and dissemination based on feedback from stakeholders. (Also see "EU Fine-Tunes Guidance For New Clinical Trials System" - Pink Sheet, July **17**, 2020.)

New Guide Offers Practical Insight Into EU Clinical Trial Lay Summaries

Vibha Sharma
July 28, 2020

Executive Summary

Sponsors are being urged to plan early and involve patients in every aspect of preparing the plain language summaries of clinical trial results that will become mandatory when the EU Clinical Trials Regulation starts applying from December 2021.

A draft industry guideline on preparing lay summaries of clinical trial results, which are mandated under the EU Clinical Trials Regulation, recommends early, careful and proactive planning by sponsors to ensure the timely delivery of high-quality and legally compliant plain language summaries.

The guideline on good lay summary practice (GLSP) — which is the result of a multi-stakeholder initiative being jointly led by the European pharmaceutical industry body EFPIA and the Belgium-based think tank, the European Forum for Good Clinical Practices (EFGCP) — recommends that sponsors should commence planning for lay summaries as early as the protocol development phase.

By planning ahead, the guideline explains, sponsors can align lay summaries with aspects such as patient information sheets and informed consent forms to ensure a coordinated approach across these documents and reduce duplication of effort or the discrepant use of plain language terminology.

The draft GLSP guideline, on which comments are being accepted until 14 September, has been developed to accommodate legal requirements under the CTR, which is expected to start applying from December 2021. (Also see "EU Clinical Trials Regulation To Apply From December 2021" - Pink Sheet, June 16, 2020.)

It can also be used by pharmaceutical and academic sponsors to meet their global transparency commitments, for example through voluntary dissemination of lay summaries beyond the EU/European Economic Area. The guideline may also be of use to sponsors of non-interventional and medical device trials, who are not legally required to issue lay summaries of their clinical trial results but may decide to do so in the interest of transparency.

Endpoints, Patient Involvement & Keeping It Short

While the CTR requires lay summaries to include the overall results of a trial, the guideline states that for most trials, a comprehensive discussion of all results would be neither feasible within a concise document nor helpful to a non-scientific audience due to the volume and complexity of the information.

Although results from the primary endpoint should obviously be included in lay summaries, the guideline acknowledges that there may be merit in including results from secondary endpoints that are particularly relevant for patients. The inclusion of selective secondary endpoints, however, "means that the sponsor has to make a selection that could be biased."

As such, the guideline recommends limiting the presentation of trial results to primary endpoints to keep the lay summaries "short and focused." For sponsors who decide to summarize secondary endpoints, it recommends they should have a clear policy for planning non-promotional, prospective selection of patient-relevant information to be consistent across trials. Also within the lay summary, there should be clear separation, in layout and in emphasis, between the primary and the secondary endpoints.

The guideline also offers practical advice on how sponsors should use a patient-centric approach to ensure that lay summaries are suitable, relevant and can be successfully communicated to the intended audience. It identifies tasks that can be performed by patients, depending on their level of expertise, at all four phases of the lay summary process, namely:

- **Planning:** Patients can be consulted to help plan, identify and prioritize patient-relevant outcomes and endpoints. Their contribution may be particularly useful for sponsors who are considering including secondary endpoint information in the plain language summaries.
- **Development:** Patients can help identify content and terminology that are potentially unclear, misleading or unacceptable, and help develop alternative language recognized within the patient community.
- **Translation:** When lay summaries are translated into local languages, sponsors should confirm their readability and understandability by native-language patients or representatives of the public. This can offer valuable insight into any national terminology and cultural expressions that may not otherwise be identified during usability testing.
- **Dissemination:** Patients can offer input on local dissemination, which may be subject to cultural/sub-cultural practices, norms or different acceptability levels across different channels of communication. Consulting patients with local insights can help avoid ineffective and inappropriate dissemination efforts.

While it is generally recognized that lay summaries should be as short as possible, the guideline states that for trials with intermediate complexity "a readable document of four to six pages can be achieved with a good layout and design." It recognizes that summaries of more complex trials may be longer as they may require more description.

New Guide Offers Practical Insight Into EU Clinical Trial Lay Summaries

The Need For Industry Guidance

The draft GLSP guideline has been developed under the EFPIA-EFGCP Roadmap Initiative for Good Lay Summary Practice, which was launched in January 2019. The initiative took shape after it became apparent from discussions held at workshops on this topic in 2015 and 2017 that there was not enough awareness among researchers, sponsors, patients, trial participants and health care professionals about the requirement for lay summaries in the CTR.

The initiative was established to work with representatives from various stakeholder groups to find a systematic, realistic and tangible approach to implement the lay summaries by the date of application of the CTR. The recommendations in the draft guideline include feedback from over 60 international patient organizations, pharmaceutical companies, academic institutions, not-for-profit organizations and contract research organizations.

The GSLP guideline, when finalized, will complement the European Commission's guideline on the content of lay summaries, which was revised in 2018. (Also see "Pharma Requests Pilot To Test Public Value Of EU Guide On Plain Language Summaries" - Pink Sheet, Aug. **16**, 2017.)

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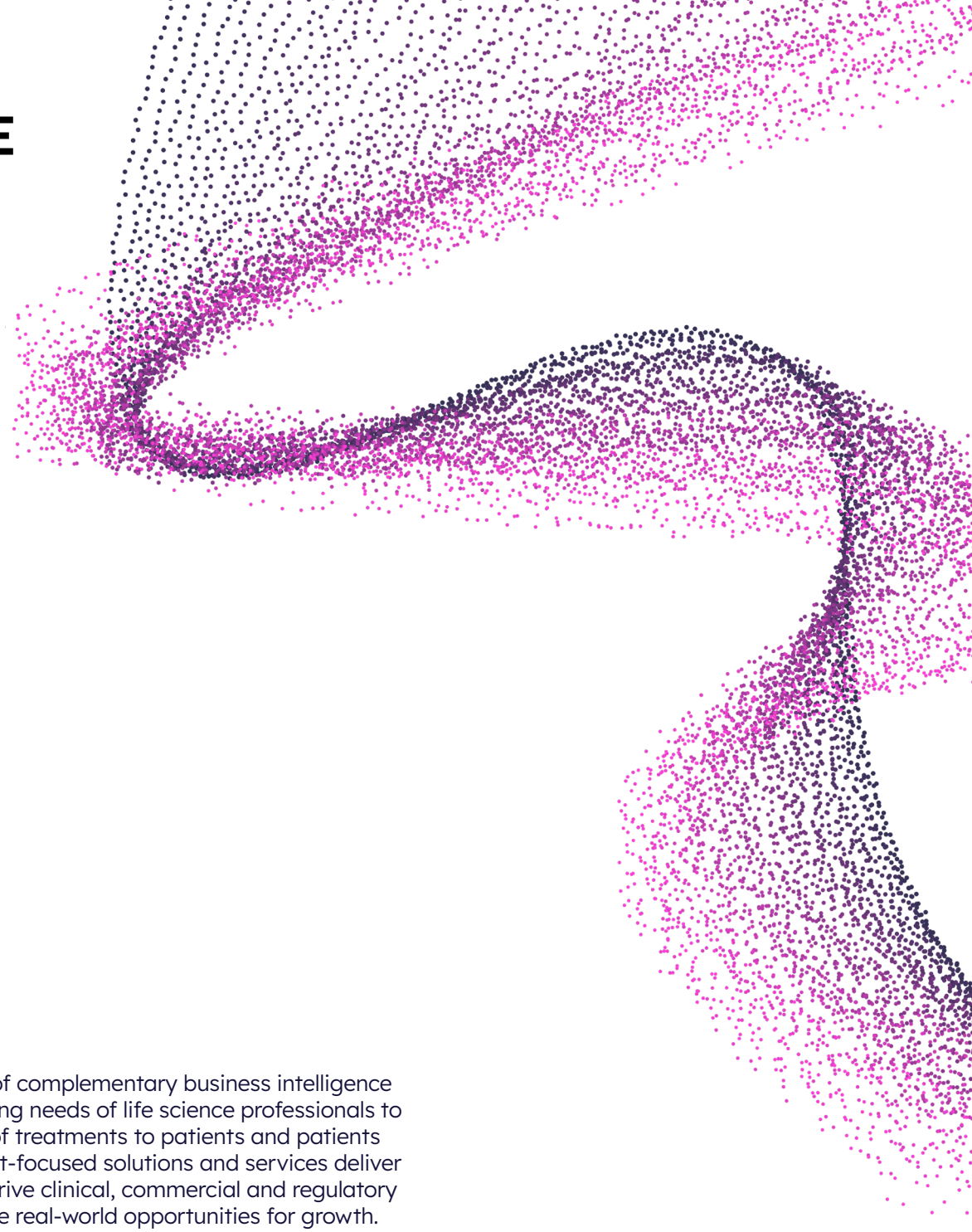

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