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How the New Common Rule Will Impact Research in 2018 and Beyond

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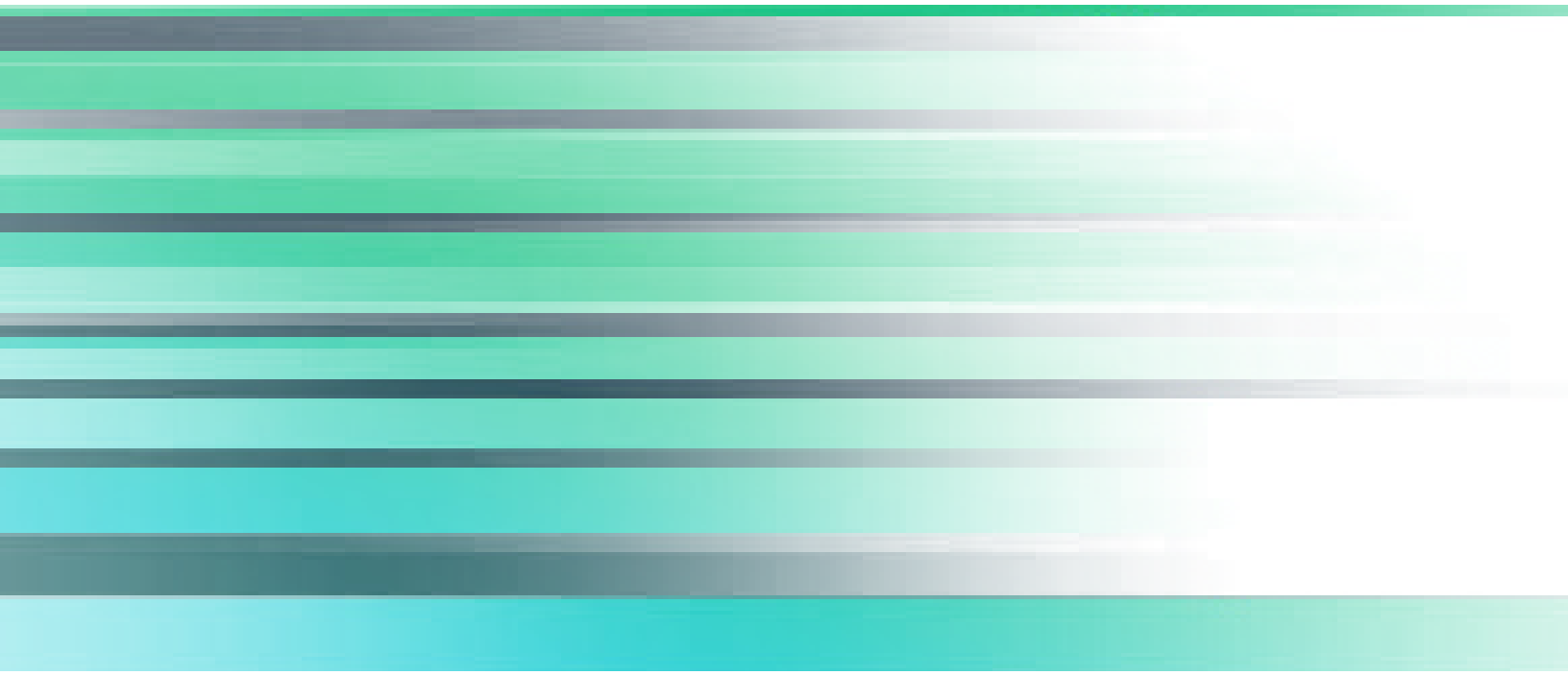

DESCRIPTION

After years of public comment and revisions, the Common Rule has been updated to accommodate new research concerns. In this whitepaper, Kinetiq regulatory consultants review the impact of the final rule in eight key areas, from single IRB (sIRB) review to biospecimen research.

TOPICS

- INFORMED CONSENT
- USE OF BIOSPECIMENS
- ACTIVITIES EXCLUDED FROM IRB REVIEW
- EXEMPT RESEARCH
- WAIVER OF CONSENT
- SINGLE IRB REVIEW
- CONTINUING REVIEW

Evaluating the Impact of the 2018 Common Rule

Following years of debate, speculation, and public comment, sixteen federal agencies published the final changes to the Federal Policy on the Protection of Human Subjects—better known as the Common Rule—in the Federal Register on January 19, 2017. Revisions to the Common Rule will largely go into effect in early 2018.

The landmark changes aim to further enhance human subject protections and facilitate important research while reducing administrative burden, delay, and regulatory ambiguity, bearing significant implications for researchers.[1]

This whitepaper extends the discussion begun in our 2016 whitepaper, *8 Most Significant Changes Proposed to the Common Rule*.[2] That document provides a description of changes proposed in the Notice of Proposed Rulemaking (NPRM) to the Common Rule that the U.S. Department of Health and Human Services (HHS) deemed were the "most significant."[3]

In this continuation, Kinetiq Regulatory Attorneys and Regulatory Consultants revisit the same eight topic areas to describe what changes ultimately made it through to the final rule, and more importantly, to provide an analysis of anticipated key resulting impacts.

Impact of the Final Common Rule on Eight Key Research Areas

1. INFORMED CONSENT

The final rule changes the general requirements for informed consent in several major ways.

First, the U.S. Department of Health and Human Services (HHS) emphasizes autonomy by requiring the informed consent process begin with a "concise and focused presentation of the key information."[4] It does not dictate precisely how the consent document must be organized (ex., the use of appendices for information beyond the core elements is not required);[5] instead, the final rule allows flexibility in researchers' approach to informed consent as long as key information is presented first and the format facilitates comprehension.[6]

While the final rule lacks some of the rigidity of the changes proposed in the NPRM, institutions and IRBs will likely rely on HHS's arguably prescriptive statements, which specify five factors that generally encompass the key information most likely to assist a reasonable person in deciding whether or not to participate in the research.[7]

HHS also aims to bolster the informed consent process through the addition of several new elements—basic and additional—of informed consent.

A new basic element of informed consent requires that, if a study involves the collection of identifiable private information or identifiable biospecimens, participants must be informed whether or not their information or data may be de-identified and used for future research studies without additional informed consent. [8]

> "When developing a protocol and consent form, investigators and sponsors will need to weigh the benefits and burdens of broad consent against study-specific consent."

HHS previously acknowledged that few investigators may elect to limit the potential for future research.[9] Additionally, those investigators who state that de-identified data will not be used without additional consent, or provide participants with an option within the consent form to indicate whether or not to agree to the future use of de-identified data, commit to tracking impermissible uses of the data. The challenge of developing and maintaining such a tracking system may further discourage investigators from obliging themselves to obtain additional informed consent before using de-identified data.[10] However, investigators and IRBs promote autonomy by putting participants on notice that they may not be consulted about this future research. [11]

The final rule includes three new additional elements of consent.[12]

1. If appropriate for a specific study, individuals must be told that their biospecimens may be used for commercial profit.
2. Participants must be told whether the research may include whole genome sequencing.[13]
3. Individuals must be told whether clinically relevant research results, including individual results, will be disclosed, and if so, under what conditions.[14]

To date, the federal human subject protection regulations have not directly addressed the return of individual research results. This new element of consent represents HHS's recognition that autonomy and beneficence may require that a participant be provided clinically significant research results.

One of the more significant changes made to the Common Rule is the addition of new elements of broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.[15] Because the final rule did not extend the definition of human subjects to cover all biospecimens, regardless of identifiability, the informed consent requirements were not extended to secondary research with de-identified biospecimens. Thus, broad consent only applies to secondary research use of identifiable data and is presented as merely an alternative to seeking study-specific consent or asking an IRB to waive the requirement to obtain informed consent.[16]

When developing a protocol and consent form, investigators and sponsors will need to weigh the benefits and burdens of broad consent against study-specific consent or seeking a waiver of informed consent. Because consent for secondary use of research data is already a common feature of most clinical trials, the broad consent elements may provide consistency and transparency across studies and institutions.

In addition to specific broad consent elements, the consent form must contain many of the core elements of informed consent, including informing participants that they may withdraw from the study at any time without penalty or loss of benefits to which they are otherwise entitled.[17] In the final rule preamble, HHS states its intention that this element will be used to inform participants that, if their information has become de-identified, it may not be possible to withdraw consent for future use of the de-identified data.[18] Alternatively, if participants are told that they may withdraw consent for all uses of their information of biospecimens, the investigators commit to maintaining the identifiers indefinitely.[19]

Thus, similar to the new basic elements discussed above, investigators may be incentivized to inform participants that the ability to withdraw consent does not extend to future use of de-identified information. Finally, despite a majority of public comments opposing implementation, the final rule requires that all federally funded clinical trials post an IRB-approved informed consent form to a yet-to-be determined public federal website.[20] The primary purpose of this consent form repository is to improve the quality of consent forms through public scrutiny and transparency.

The posting requirements in the final rule do allow some flexibility. For example, only the consent form used to enroll subjects must be posted, and posting can take place any time after a trial is closed to recruitment, up to 60 days after the last study visit by any subject.[21] Additionally, if the federal department or agency supporting or conducting the clinical trial determines that certain information should not be made public, the department or agency may permit redactions to the information posted.[22] Regarding the website itself, HHS noted that the existing clinical trial registry, ClinicalTrials.gov, may be an appropriate choice to house the consent form repository.[23]

The impact of this new requirement remains to be seen; however, using the existing ClinicalTrials.gov registry may lessen the burden, at least for those clinical trials that already have registration obligations.

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2. USE OF BIOSPECIMENS

The final rule now mandates informed consent can only be waived for research involving access to, or use of, identifiable biospecimens if the research could not practicably be carried out without using the biospecimens in an identifiable format.[24]

Without specific guidance on what is or is not practicable, researchers should be prepared to provide comprehensive rationale on why conducting this research in another manner would not be feasible, including highlighting how a waiver would facilitate carrying out primary study objectives. Given the potential privacy and confidentiality risks to participants when identifiable biospecimens are being collected, researchers should be able to detail safeguards for how access to and use of identifiable biospecimens will meet applicable data access, storage, and use standards for protecting participant information.

Additionally, the final rule prohibits IRBs from waiving informed consent if individuals were asked and declined to provide broad consent to the storage and maintenance for secondary research use of identifiable private information or identifiable biospecimens.[25]

While this language honors autonomy of individuals and furthers the Belmont Report principle of respect for persons, researchers may face a significant and ongoing administrative obligation to develop systematic recordkeeping and reporting of such refusals when seeking downstream waivers for secondary research use. Moreover, for studies where biospecimens are being stored and maintained by third parties or other collaborators during the course of a study, researchers will likely need to develop research plans and communication schemas to ensure that samples from particular participants, who declined consent for secondary research use, are disposed of in a compliant and timely fashion at the end of a study.

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Additionally, it may fall to IRBs to implement verification measures for ensuring that waiver of informed consent determinations are not being provided for research populations that include participants who declined broad consent.

3. ACTIVITIES EXCLUDED FROM IRB REVIEW

The final rule no longer contains the concept of activities excluded from IRB review, resulting in a structure similar to the previous Common Rule. Yet, this removal is inapposite insofar as the majority of the exclusions were redistributed under other previously existing designations.

Four activities excluded under the NPRM, including those regulated under HIPAA, have been incorporated into the revised exempt categories of research.[26] Additionally, three formerly excluded activities—e.g. public health and intelligence surveillance—are now expressly deemed not to be research.[27]

Only three proposed excluded activities have been eliminated, in substance, from the final rule.[28]

The exclusions for certain quality assurance/quality improvement (QA/QI) activities and for program improvement activities have been dropped over concern that they would ultimately create more confusion than clarity for all stakeholders and impose inadvertent—and inappropriate—obstacles to those QA/QI activities that arguably should not fall under the rule.[29]

The third elimination is the category regarding secondary research involving non-identified biospecimens designed only to generate already known information about an individual. This was because the proposed modification of the definition of "human subject" to include all biospecimens regardless of identifiability was not included in the final rule.[30]

While the NPRM identified an $814 million stakeholder benefit over ten years by excluding these activities,[31] the source of that benefit is essentially redistributed, and, though not always a bright line between what activities are and are not research, much QA/QI and program improvement is already understood to be outside the ambit of the Common Rule. Therefore, much of the projected savings should be retained and/or already accounted for.

4. EXEMPT RESEARCH

The final rule modifies existing exempt categories and establishes new categories of exempt research with the objective to allow more low-risk research studies to be eligible for exemption. Indeed, only one exemption category proposed in the NPRM (secondary research use of identifiable private information when notice was given) was not adopted in the final rule. Additionally, a new exempt category for research involving benign behavioral interventions in adult subjects was created.[32]

The final rule consequently opens up a pathway for efficient review of studies that regulators deem to be brief in duration, painless, respectful, and overall harmless—such as subjects playing an online game or solving puzzles under various noise conditions.

Additional new exempt criteria focus on secondary research involving identifiable private information, where some activities may be conducted without consent (provided that they are HIPAA-regulated) or via broad consent.[33]

Theoretically, the goal in expanding exempt research is to allow investigators to proceed without obtaining informed consent for each secondary research study,

and to reduce unnecessary regulatory burden on IRBs. However, any research classified under these new exempt categories is still required to undergo IRB review to ensure there are adequate privacy and confidentiality safeguards in place—the same standards also applied to non-exempt research.

With insightful consideration of public comments, the final rule does recognize that IRBs may not always be equipped with the expertise needed to evaluate risks to privacy and confidentiality (such as with increasingly sophisticated IT security schemas). It requires the Secretary of HHS, in consultation with other federal partners, to issue guidance to assist IRBs in assessing what provisions are adequate to protect privacy of subjects and to maintain the confidentiality of data.

The final rule does not include the use of decision tools for making exemption determinations at this time. Administrators and IRBs will need to continue independently assessing whether studies meet regulatory criteria for exempt research. However, commentary does suggest that the development of a well-designed, validated, and standardized exemption tool remains in sight.

5. WAIVER OF CONSENT

As discussed in section two above (Use of Biospecimens), HHS proposed revisions to the conditions and requirements for waiver or alteration of consent. In the final rule, a waiver of consent for research involving identifiable biospecimens will occur only in very rare circumstances. This new requirement also applies to waiving consent for the use of identifiable private information for research purposes in that researchers will now have to demonstrate the research could not practicably be carried out without using such information in an identifiable format.[34]

Of note, researchers and IRBs are still left without valuable guidance concerning the proper interpretation of "practicably" in the context of waivers, with the final rule instead deferring that the requirements for waiver appropriately balance respect for persons with other ethical principles.

The final rule also updates rules on waivers of consent as it relates to participant recruitment and determining study eligibility.[35] Rather than requiring IRBs to waive the requirement for informed consent to permit researchers to access identifiable private information for screening, an IRB may approve a research proposal in which investigators are able to obtain such information about prospective participants without informed consent for screening and recruitment. This includes access to identifiable information gained through oral or written communication with the potential participants, or through pre-existing records, on the condition that the research proposal includes an assurance that the investigator will implement standards for protecting the information.

With this language, defined as an exception to the waiver of consent requirement, the final rule now parallels the U.S. Food and Drug Administration's (FDA) regulatory approach to similar activities.

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6. SINGLE IRB REVIEW

The final rule embraces the single IRB (sIRB) model for cooperative research. This change, which has been long anticipated, will require institutions and IRBs to draft and revise their policies, procedures, and forms to allow for widespread reliance on external IRBs.[36]

These efforts will require significant time and effort from institutional leadership and staff. The final rule estimates that each institution will spend an average of 150 additional hours drafting and executing reliance agreements in 2019 alone.[37]

This estimate may be optimistic in that it presumably includes consideration of another final rule change that allows for direct oversight of IRBs not operated by a Federalwide Assurance (FWA)-holding institution. This change was intended to ease negotiation of reliance agreements by removing liability as an issue, and to encourage more widespread use of independent IRBs. It is unknown whether this change will actually increase the pace of negotiation.

Perhaps more importantly, reliance agreements only represent one part of the overall reliance process; consequently the amount of time needed to adopt the sIRB model will surely be significantly more than the final rule's estimate.

Not everyone, however, is similarly affected: investigators and research staff are estimated to spend half the time engaging with the review process as they would if they had to support a site-specific protocol review at their institution.

Put succinctly, the final rule's cooperative research standard shifts administrative burden from research staff to institutional staff. The expectation is that this burden will decrease over time once processes and procedures are firmly in place and institutions have executed broad reliance agreements with their usual partners.

An outstanding question is whether the FDA, which is not a signatory to the Common Rule, will mimic this new cooperative research standard. Interestingly, the recent 21st Century Cures Act requires harmonization between the Common Rule and FDA's human subject regulations to the extent practicable.[38]

If the FDA chooses to harmonize with the Common Rule's new approach to cooperative research, the effect will be that the vast majority of research conducted in the U.S. will be overseen according to the sIRB model.

7. CONTINUING REVIEW

With the stated goal of streamlining review for IRBs and institutions,[39] the final rule reduces continuing review requirements, nonetheless allowing the IRB to engage in discretionary review.

The final rule essentially eliminates the need for continuing review for certain types of minimal risk research activities, including any protocol that was initially reviewed using expedited procedures, and any protocol that has progressed to the point

that the only remaining research activity is data analysis or data collection. This change should have a positive net effect (benefit estimated at $107 million over ten years[40]) and focus IRB review on research most in need of attention: initial review and continuing review of ongoing, greater-than-minimal-risk research.

The final rule indicates that of the 75 percent of expedited continuing review left unaffected by other changes, 50 percent will be eliminated.[41]

The global efficiency gain will be tempered by the extent of the research to which it applies. The elimination of continuing review for the listed types of research does not extend to corresponding FDA-regulated clinical trials. Therefore, the efficiency gain will be more modest for IRBs primarily engaged in review of FDA-regulated trials, unless and until the FDA harmonizes continuing review responsibilities under 21 C.F.R. §§ 56.108(a) and 109(f) with the Common Rule. The maintenance of divergent research paradigms may in fact offset gains promised by the 2018 Common Rule.

Even for those circumstances to which expedited review is not required by regulation, the final rule allows an IRB to determine at its discretion whether continuing review may be necessary.

> "The final rule estimated institutions would devote 10 hours to alter existing continuing review notification processes. The actual time will likely be substantially higher."

The final rule indicates that this determination, if made, must be documented over commenter dissent for two reasons:

1. The importance of documenting why an IRB is making a determination that differs from the regulatory baseline, and
2. The promotion of the principle of justice. [42]

Policy development to accommodate these changes presents an initial—though necessary—barrier to implementation. The final rule estimated institutions would devote 10 hours to alter existing continuing review notification processes. The actual time will likely be substantially higher.[43]

In formulating the policy it will be important, as ever, to appreciate that the Sponsor, PI/site, and the IRB must communicate effectively to identify when the criteria for cessation of continuing review are met to ensure compliant implementation of the final rule.

Ultimately, it is unknown whether these discretionary reviews will increase or diminish over time as IRBs become increasingly adept working within the new

framework. Again, safety reporting requirements remain unchanged, and the final rule also makes plain that nothing prevents an institution or IRB from applying standards that exceed those in the regulations.[44]

8. EXTENDED APPLICATION OF THE COMMON RULE

The final rule does not implement the NPRM proposal to extend the Common Rule to any clinical trial conducted at an institution that receives federal support for human subject research, regardless of the funding for the particular study.[45]

In the preamble, HHS acknowledged concerns by commentators that the NPRM proposal would increase administrative burden (such as federal reporting requirements) without a corresponding increase in meaningful protection of human subjects.[46] Additionally, while HHS's intention was to cover certain types of higher risk research not currently subject to the federal policy, the NPRM's definition of "clinical trial" could apply to some low-risk social, behavioral, or educational research as well as to quality improvement or quality assurance activities.[47]

Conclusion

The government has an optimistic view of the final rule's impacts and the time needed to bring all policies and procedures in line.

The practical reality is that **research organizations will need to devote significant resources to updating policies, procedures, forms, training manuals, practices, and agreements**, as well as provide general education to their research community. This is a daunting task that translates to resources that most institutions do not have.

Institutions will have to evaluate **whether this one-time effort is best executed with existing team members or if using expert consultants is more efficient** from a cost and compliance standpoint.

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2. See http://kinetiqideas.com/educate-train/8-most-significant-changes-proposed-to-the-common-rule/

3. See https://www.hhs.gov/ohrp/regulations-and-policy/regulations/nprm-2015-summary/index.html

4. Federal Policy for the Protection of Human Subjects, 82 Fed. Reg. 7149, 7265 (Jan. 19, 2017) (to be codified at §___.116(a)(5)).

5. *Id.* at 7213.

6. *Id.* at 7214.

7. *Id.*

8. *Id.* at 7266 (to be codified at §___.116(b)(9)).

9. Federal Policy for the Protection of Human Subjects, 80 Fed. Reg. 53933, 53971 (proposed Sept. 8, 2015).

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13. *Id.* (to be codified at §___.116(c)(7)).

14. *Id.* (to be codified at §___.116(c)(8)).

15. *Id.* (to be codified at §___.116(d)).

16. *Id.* at 7220.

17. *Id.* at 7266 (to be codified at §___.116(d)(1)).

18. *Id.* at 7221.

19. *Id.*

20. *Id.* at 7267 (to be codified at §___.116(h)).

21. *Id.* at 7267 (to be codified at §___.116(h)(3)).

22. *Id.* (to be codified at §___.116(h)(2)).

23. Id. at 7228.

24. See Federal Policy for the Protection of Human Subjects, supra note iv (to be codified at §_.116(f)(3) (titled Requirements for Waiver and Alteration)).

25. *Id.* (to be codified at §_.116(f)(1) (titled Waiver of Broad Consent by Individuals who Refused to Provide Consent)).

26. *Id.* at 7173 (to be codified at §___.104).

27. *Id.* (to be codified at §___.102).

28. *Id.*

29. *Id.*

30. *Id.*

31. Federal Policy for the Protection of Human Subjects, supra note viii, at 54002.

32. See Federal Policy for the Protection of Human Subjects, supra note iv (to be codified at §_.104(d)(3) (titled Benign Behavioral Interventions Involving Adult Subjects).

33. *Id.* (to be codified at §_.104(d)(4) (titled Secondary Research for Which Consent is not Required), §_.104(d)(7) (titled Storage or Maintenance for Secondary Research for Which Broad Consent is Required), and §_.104(d)(8) (titled Secondary Research for Which Broad Consent is Required)).

34. *Id.* (to be codified at §_.116(f)(3).

35. *Id.* (to be codified at §_.116(g) (titled Screening, Recruiting, or Determining Eligibility)).

36. *Id.* (to be codified at §_.114 (titled Cooperative Research)).

37. Federal Policy for the Protection of Human Subjects, supra note iv, at 7246.

38. 21st Century Cures Act, Pub. L. No. 114-255, § 3023.

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41. *Id.*

42. *Id.* at 7210.

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About Kinetiq

Kinetiq is the consulting and technology division of Quorum Review IRB that delivers innovative solutions to the challenges of human subject protection and compliance in clinical research. Kinetiq works with clinical researchers, research institutions, pharmaceutical, biotechnology and medical device companies as well as others around the world to develop contemporary approaches to a changing landscape.

The new Common Rule represents a landmark pivot in human subject protections on many fronts, from sIRBs to new exemption categories and broad consent.

These changes have the potential to impact organizations on multiple levels. Stand above the crowd and **let our regulatory experts guide you** through challenges and strategic steps required to accommodate the new Common Rule early and thoroughly.

Whether your organization needs a simple human research protection program (HRPP) Health Check or a full suite of training and process development, Kinetiq has the expertise to guide your organization as it navigates the new Common Rule.

> Unlike other consultants who provide you a one-size-fits-all HRPP toolkit, Kinetiq offers custom solutions designed to work for your organization.

Your Processes, Our Expertise

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