

Making sense of Quality by Design and Risk Proportionality.

Danish Society for Good Clinical Practice, 11. September 2025

Introduction

A central theme in the updated ICH GCP (R3) is **risk proportionality and quality by design**.

At its core, this approach is about **embedding quality into clinical trials**, not by adding layers of checks everywhere, but focusing on what truly matters for patient safety and the reliability of trial data.

The growing emphasis on this topic raises three immediate questions:

- **What is “Quality by Design”?**
- **What does “Proportionate” really mean in practice?**
- **and are we looking at a fundamental shift in how clinical trials should be designed?**

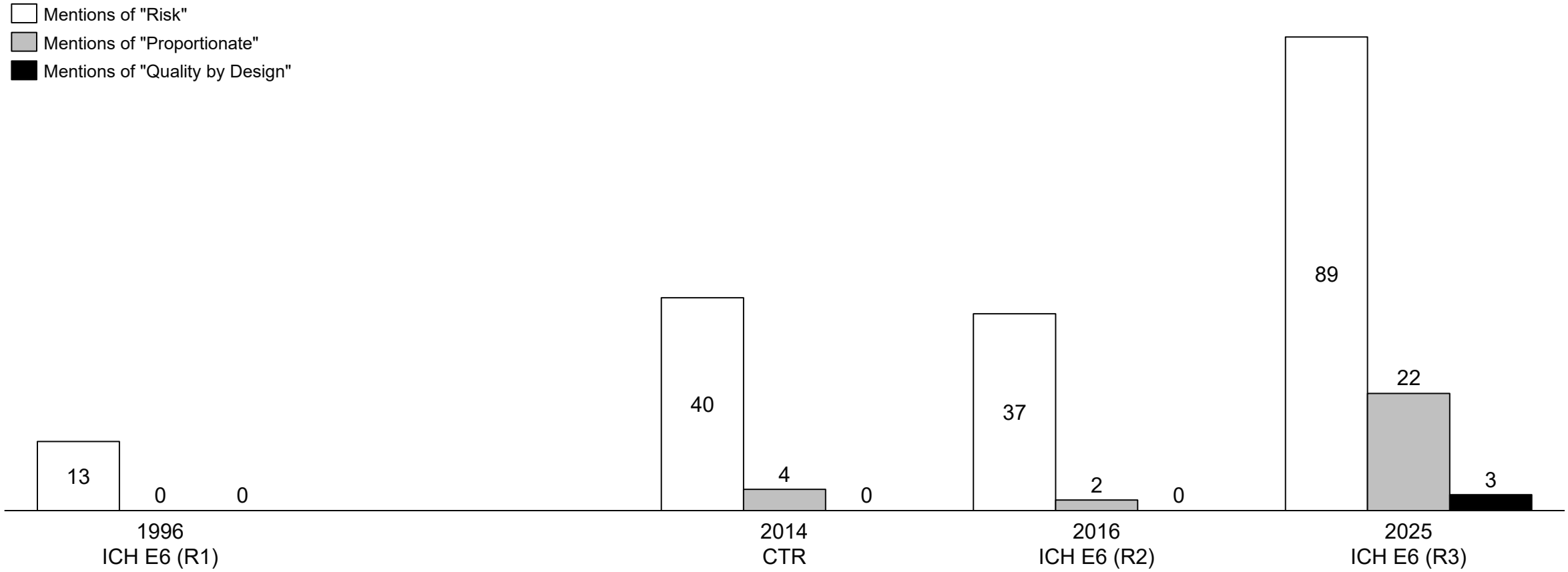
Agenda

1. **Why is this a topic now?**
2. **Quality by Design**
3. **Risk proportionate**
4. **What can we learn from other areas?**
5. **Applying Quality by Design and Proportionality to clinical trials**

GCP requirements increasingly emphasizes risk, with new terms added...

The concept of risk in clinical development has always been in focus. In recent years, new terms have been added, but the emphasis on risk has always been central.

In 2025, ‘Risk’ is mentioned more than twice as often in ICH guidance, and for the first time ‘Proportionate’ and ‘Quality by Design’ appear in ICH guidance



...However, GMP has already led the way 20 years ago.

GMP introduced “Proportionate” and “Quality by Design” already in 2006, which makes sense as the volume of harm in GMP is larger, demanding stronger safeguards upfront.

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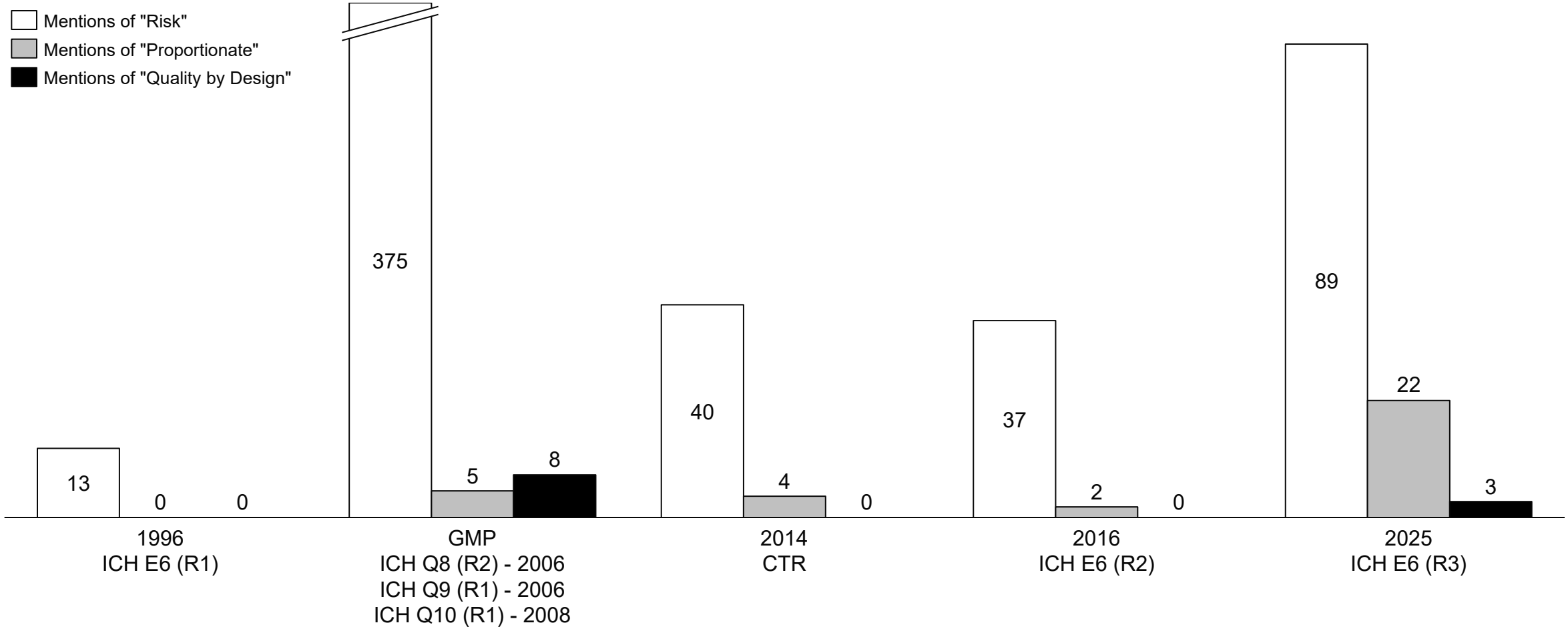

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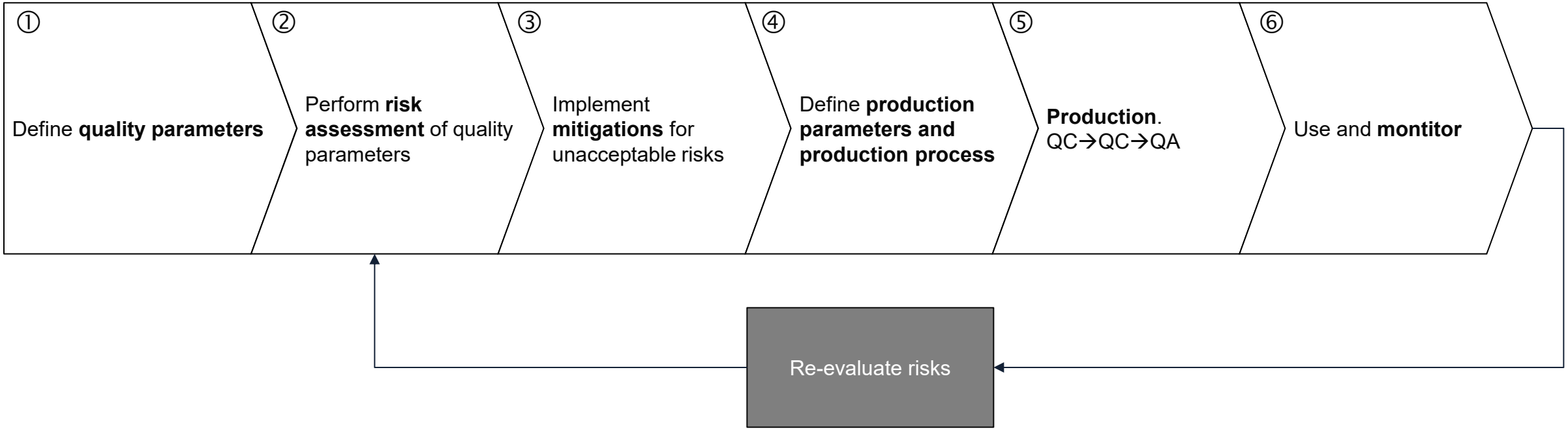
Quality by Design follows a sequence of structured steps.

Quality by Design embeds quality from the very first definition of parameters through risk assessment, process design, and production, ensuring that quality is a built-in, self-sustaining outcome.

Embedding quality through a structured, risk-based process.

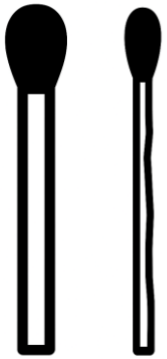


Step 1: Make a clear definition of quality parameters.

Quality can only be secured if we carefully define the relevant criteria; function, looks, price, materials, and more. Without this, specifications risk missing what really matters.

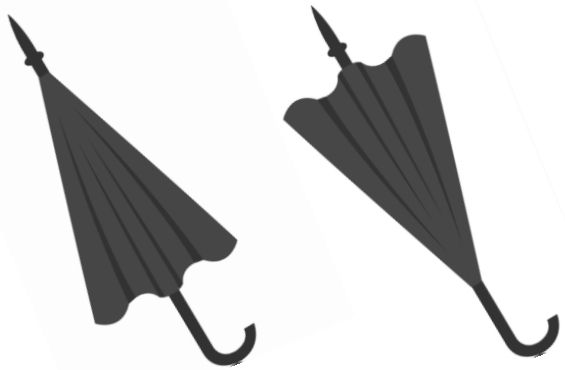
Example: Quality specifications for a match

- Made of wood
- One end covered in sulfur
- ...



Example: Quality specifications for an umbrella

- Water repellent and resistant material
- Mechanism for opening and closing the umbrella
- Includes a handle
- ...

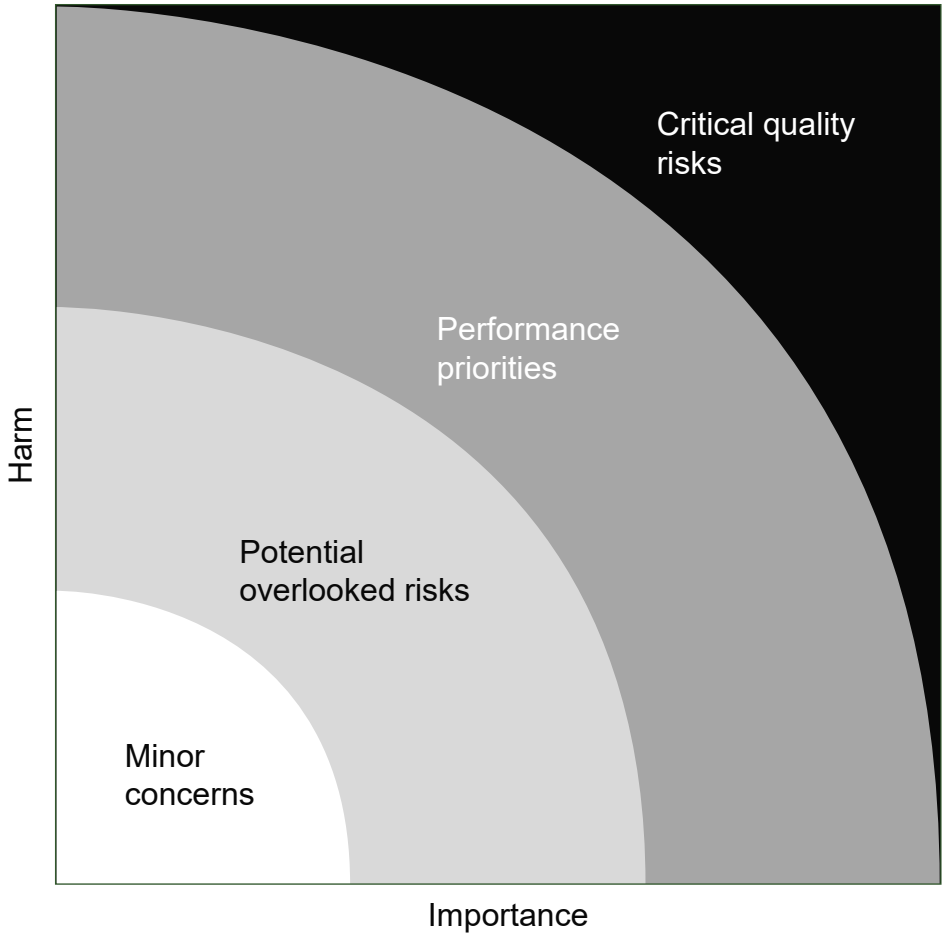


- If strength is not specified, the **match may be too thin and break.**
- If orientation is not specified, the **umbrella may open in an unexpected way**.
- **Quality requires defining the relevant parameters** clearly and precisely every time.

Step 2: Assess risks to identify and mitigate unacceptable risks.

Not all risks are equal. By weighing importance against potential harm, we can see which quality parameters are most critical and where our attention must be focused, so that resources are directed where they protect quality most effectively.

Map risks by importance and harm



Two questions that define your priorities

1. **How important is this parameter?**
   How important is this parameter to product quality (e.g. core to safety, function, or reliability vs. minor or supportive role)?

2. **What is the harm if it fails?**
   What would be the impact on safety or function if this parameter does not perform as required?

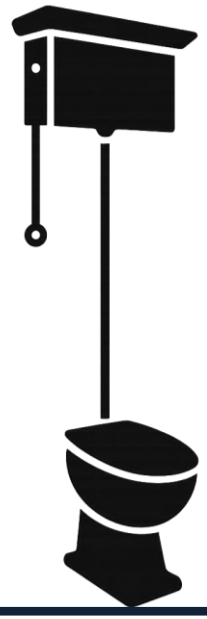
Risk assessment directs focus to the parameters where failure would matter most.

Step 3: Implement mitigating actions for unacceptable risks.

Mitigating actions are essential because they ensure that unacceptable risks not only stay identified on paper, but are actively reduced. By targeting the most critical harms, smart design and controls, we secure reliable quality in practice.

Child-proof design

By placing the pull chain high above the toilet, children cannot reach it, mitigating the risk of unintended use.



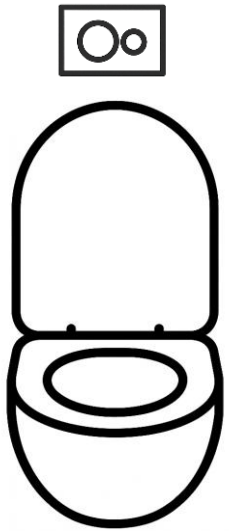
Camouflaged dirt

A fully black toilet hides stains and dirt more easily than a white one, mitigating the risk of the toilet appearing visibly dirty.



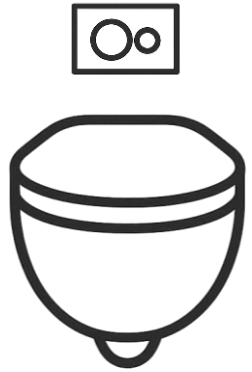
Easy to clean floor

A wall-mounted toilet leaves space underneath, making it easier to clean the floor, mitigating hygiene risks from difficult-to-reach dirt.



Seat down enforcement

Flush buttons placed behind the seat force users to close it first, mitigating the risk that the toilet is left open.



Step 4: Define production parameters and production process.

Previous steps identified what matters for quality and where risks lie. These insights are now translated into production parameters and a structured process. By linking user needs to CQA, CPP, and controls, quality is consistently delivered by design rather than by chance.

User needs

Identify what patients and users truly require;
- **Safety**
- **efficacy**
- **usability**
- **price.**

This is the anchor for all downstream decisions.

CQA - Critical Quality Attributes

Translate user needs into **measurable product characteristics**.

Define which attributes must consistently stay within limits to protect safety and performance.

CPP - Critical Process Parameters

Define the process **factors that directly impact the critical quality attributes**.

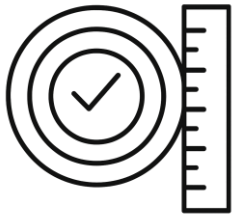
Controlling these parameters ensures the process consistently produces the right quality.

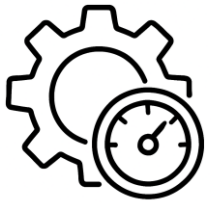
Control strategy

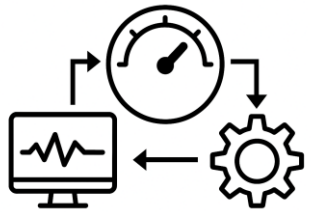
Integrate;
- **monitoring**
- **testing**
- **process controls.**

This secures robustness of production and prevents deviations from harming patients or undermining data integrity.









Step 5: Execute production with quality built in.

Now the process moves from planning to execution: production is carried out under defined parameters, with quality checks integrated at relevant stages. By embedding QC and QA throughout, we ensure that the product consistently meets requirements, not only by design, but also in practice.

Production starts

- Execute the defined process parameters and **production setup**.
- Ensure operators and systems follow the planned **control strategy**.

In-line Quality Control (QC)

- Monitor **critical process steps** continuously.
- Detect **deviations** before they impact the final product.

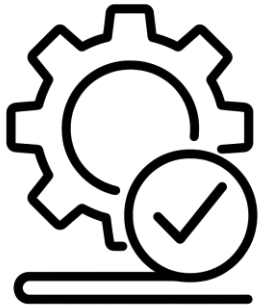
End-product Quality Control (QC)

- **Test and verify** that finished products meet the defined critical quality attributes.
- Secure product release only if requirements are met.

Quality Assurance (QA)

- Independent oversight verifying that processes, controls, and documentation are followed.
- **Ensures compliance** and confidence in outcomes.









Step 6: Use and monitor

Quality is not a one-time achievement at release. Continuous monitoring ensures that risks remain controlled, and contingency plans provide additional security if problems arise.

Continuous monitoring detects emerging risks directly or via validated proxies.



- **Direct monitoring**: Observe the product itself whenever technically feasible to capture the most reliable signals.
- **Use validated proxies**: If direct monitoring is not possible, use credible indicators (e.g., Pentagon Pizza Index) that reflect product performance.
- **Maintain ongoing monitoring** to detect weak signals of emerging risks before they affect safety, efficacy, or compliance.

Deploy contingency plan when risks emerges to contain impact and ensure compliance.



- **Immediate action**: When an unacceptable risk is triggered or confirmed, activate the predefined contingency plan without delay
- **Risk containment**: Deploy measures that prevent escalation, protecting patients, data integrity, and regulatory compliance.

DEFCON 5 - FADE OUT
LOWEST STATE OF READINESS

5
DEFCON LEVEL

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ting to
ump
iles a…
VIEW

U.S. President Donald J. Trump is weighing a number of options for carrying out military strikes against narco-terrorist cartels operating in Venezuela, including…
LIVE
VIEW

Overnight, several aircraft wit
Bolivarian Military Aviation of
overflew the USS Jason Dunham (
the Southern Caribbean Sea for
LIVE

TIMELINE VIEW: SUN MON TUE WED THU FRI SAT LIVE

DOMINO'S PIZZA

QUIET

1.4 mi

POPULAR TIMES ANALYSIS

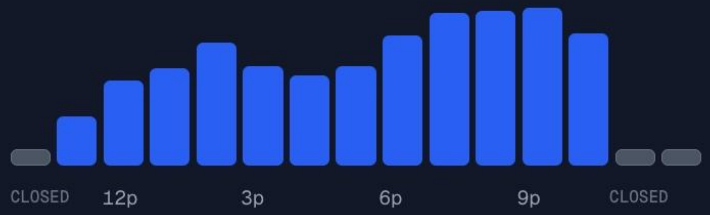


EXTREME PIZZA

NOMINAL

0.5 mi

POPULAR TIMES ANALYSIS



Pentagon Pizza Index is a classic example of using a **proxy** when direct monitoring is not feasible.

Analysts observed that spikes in **late-night pizza deliveries to the Pentagon** reliably signaled heightened internal activity, serving as an **early warning** of significant events.

WE, THE PIZZA

NOMINAL

1.0 mi

POPULAR TIMES ANALYSIS



PIZZATO PIZZA

NOMINAL

2.2 mi

POPULAR TIMES ANALYSIS



PAPA JOHNS PIZZA

QUIET

2.3 mi

POPULAR TIMES ANALYSIS





Designing a clinical trial with **Quality by Design** is like building **rice terraces**.

- You don’t wait for the rain to come and then react.
- You plan the flow of water, reinforce the vulnerable points, and define acceptable ranges.

This way, the system is resilient.

Quality by design

Quality by Design **builds quality into the product from the start**.
It is inherent, not added later.

Controls are embedded in the production process, making it impossible to produce without the intended quality.

But the **real test lies in our standards**:

- set them high and the process delivers value
- set them too low and we risk delivering a product that meets the specifications, but fails the purpose.



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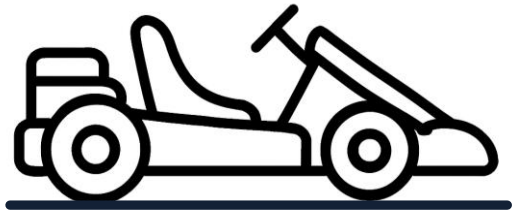
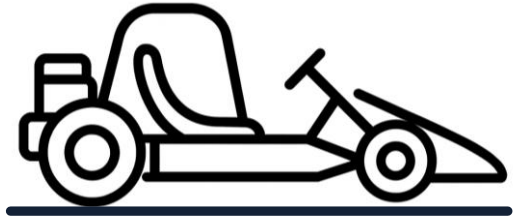
Risk proportionate protection grows with the level of harm...

Risk proportionate reflects that safeguards must scale with risk. What begins with bumpers in go carts evolves into roll bars in pro racing and culminates with the Halo in Formula 1, where extreme forces demand extreme protection to keep drivers alive when accidents occur.

Key characteristics	**Go-Cart**: Low speed where helmet and bumper are sufficient.	**Pro cart**: Higher speed where roll bars add protection.	**Formula 1:** Extreme speed and G-forces requiring Halo.
Top speed:	40-60 km/h	120-140 km/h	350+ km/h
Typical G-forces at cornering and braking:	<1.5 g.	2-3 g.	4-6 g sustained.
Survivable crash g-forces:	10–15 g Low-speed impacts, helmet protects.	30–40 g Serious crashes, survival possible with roll-bar & gear.	> 50–70 g survivable Documented cases up to ~75 g, thanks to Halo & cockpit cell.
Safety measures:	**Bumper frame, helmet**.	**Roll-bar, harness, advanced helmet.**	**Halo, survival cell, Head-And-Neck-Support, multi-point belts.**







The Halo is the latest Formula-1 safety innovation.



The Halo was introduced in Formula-1 in **2018** and has significantly improved driver survival rates by **preventing fatal head injuries** from debris, collisions, and impacts with barriers. It is a titanium bar that surrounds the driver's head. It has been credited with saving several drivers' lives, including Romain Grosjean in 2020 and Lewis Hamilton in 2021.

Zhou Guanyu in Alfa Romeo in 2022.

… and risk proportionate safeguards must scale with likelihood of harm …

Safeguards should scale with risk: simple measures suffice when exposure is low, but stronger protections are essential where the stakes are higher in traffic and in trials alike.

Signs only



- On a **quiet country road**, simple signs are enough to warn the occasional driver.
- Likewise, in **low-risk trials** with well-understood treatments, limited oversight may be sufficient.

Signs with lights and sound



- At **busier crossings**, added lights and alarms reduce the chance of accidents.
- Similarly, in **moderate-risk trials**, extra monitoring and data checks help ensure safety and reliability.

Signs with lights, sound, and barrier



- On **heavily trafficked lines**, only a full barrier system can prevent catastrophic collisions.
- In the same way, **situations with greater potential for harm or complexity** demand comprehensive safeguards, with intensive monitoring and strict controls to ensure protection and reliability.

Safeguards must scale with risk. Too little leaves gaps, too much wastes resources, but the right level sustains both safety and efficiency. And this is never a static state.

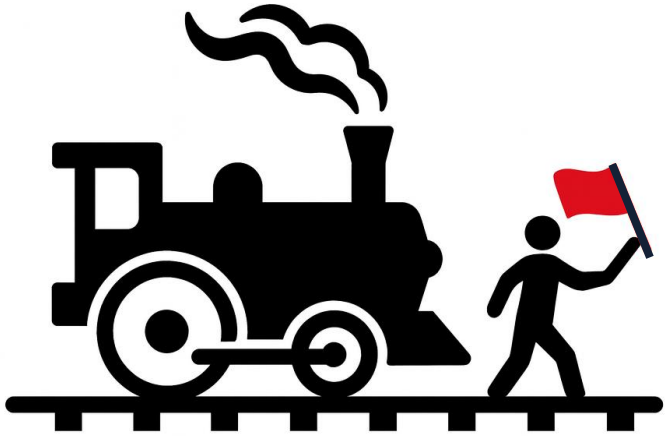
... but we must remove safeguards when they are no longer needed.

The Red Flag Act of 1861 required locomotives to be preceded by a man carrying a red flag. What once made sense is now obsolete, showing that risk proportionate safety must be continuously reassessed and adapted as knowledge and technology evolve.

Risk proportionate must evolve with knowledge and context

In the mid-1800s, the UK introduced the so-called *Red Flag Acts* to regulate the safety of early road locomotives:

- In 1861, speed was limited to 10 mph in rural areas and just 5 mph in inhabited areas.
- A man had to walk at least 60 yards ahead of the vehicle carrying a red flag to warn others. He was also required to assist with the passage of horses and carriages .
- The Acts were repealed in 1896, once vehicle technology and infrastructure had advanced.



Risk proportionate measures must evolve with knowledge and technology, otherwise precautions that once seemed essential can quickly become unnecessary or even counterproductive.

Authorities also take risk-proportionate action when harms materialise.

Authorities introduce safeguards not just based on theoretical risk, but when the volume and severity of harm demand action. This risk-proportionate evolution ensures that regulation focus resources where failures have proven most consequential.

When risks emerge, regulation follows. Authorities strengthen safeguards risk proporationately over time.

	Event / Product	Problem	Regulatory Response (What is regulated)	Legal / Guideline Framework
1960s	Thalidomide.	Severe birth defects due to insufficient safety testing.	**Requirement for regulatory approval before human testing.**	National drug laws.
1990s	Terfenadine.	QT prolongation and risk of fatal arrhythmias.	**Requirements for QT studies in drug development.**	ICH E14 (QT/QTc evaluation).
2000s	Selective reporting of trial data.	Companies published only positive results, withheld negative findings.	**Obligation to register trials and publish results.**	ICMJE requirements for trial registration
2000s	Opioid crisis.	Deceptive marketing, downplaying addiction risks.	**Tighter rules on drug marketing and promotion.**	FDA/EMA advertising rules, national legislation.
2010s	Valsartan data falsification.	Fabricated clinical trial data undermining integrity.	**New law to ensure research integrity and independent oversight.**	Japan Clinical Trials Act (2018).



Rice farmers also apply **risk proportionality** in practice.
They don’t reinforce every single part of the field equally.
Rather the most vulnerable terraces get extra care, e.g. steep edges and water inlets.

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GMP principles of Quality by Design turn clear objectives into consistency.

The GMP principles for Quality by Design closely mirror the structured approach we have already explored earlier today.

GMP QbD-objective	Purpose		Outcome
1. Define **quality target product profile.**	Clarify what the product must achieve in terms of **safety**, **efficacy**, and **usability**, such as route of administration, dosage form, and bioavailability.	»	A clear **target** that guides all subsequent development decisions.
2. Identify potential **critical quality attributes.**	Determine which product **characteristics** are essential to quality and must remain within defined limits.	»	Focused attention on **attributes** most relevant for product quality.
3. Assess **risks** and influencing factors.	Evaluate which material **attributes** and **process parameters** can impact these critical attributes.	»	Insight into **vulnerabilities** and priorities for control.
4. Select an appropriate **manufacturing process.**	Choose the **process design** that best supports consistent delivery of the target profile.	»	A **robust process** capable of delivering reproducible quality.
5. Define a **control strategy.**	Integrate **monitoring, testing**, and **process controls** to maintain robustness and prevent deviations.	»	Long-term **assurance** that quality is consistently achieved.

GMP principles for Quality by Design connect clear **objectives**, their underlying **rationale**, and tangible **outcomes**, ensuring that product quality is built systematically and maintained consistently.

GMP use “Design Space” to drive risk-proportionate Quality by Design

By aligning risk, control, and Design Space, GMP transforms variability into predictable quality - ensuring safe products, efficient use of resources, and regulatory flexibility.

Risk Assessment
Understand the consequences

- Evaluates the **consequences of operating outside** the Design Space.
- Severe outcomes require **stricter controls**; minor risks may justify lighter controls (e.g., reprocessing or discarding a batch).
- **Ensures resources are focused** where deviations truly matter, balancing efficiency and protection.

Control strategy
Apply the right process levers

- Defines the **set of process adjustments** that transform variable inputs into consistent outputs.
- **Intervention level depends on input quality**: low-purity requires more processing, high-quality inputs need minimal adjustment.
- In GMP, serves as **the operational lever** linking material attributes and process parameters to the target profile.

Design space
Operate within validated boundaries

- Represents the **validated range of acceptable outputs**, linking process inputs to critical quality attributes.
- Not binary but a **spectrum** (e.g., “yellow” as a range of shades rather than a single tone).
- Operating within the Design Space provides **flexibility without reapproval** (ICH Q8), while ensuring reproducible quality and enabling continuous process improvement.

The goal in Quality by Design is consistent quality, not identical copies

By linking product, process, and inputs to a defined Design Space, GMP accepts controlled variation while still ensuring safe, effective, and reliable outcomes; the key challenge is deciding how much variation is acceptable.

With Design Space

In GMP, Quality by Design accepts variation like siblings, not identical, but consistently meeting the same standards of quality and performance.



GMP**: Millions of batches** using the same target profile and manufacturing process.

Without Design Space

Traditional clinical research emphasizes exact replication, like identical twins, where every copy must match perfectly.



GCP: **One batch** using the same quality target product profile and manufacturing process (**SOP**).

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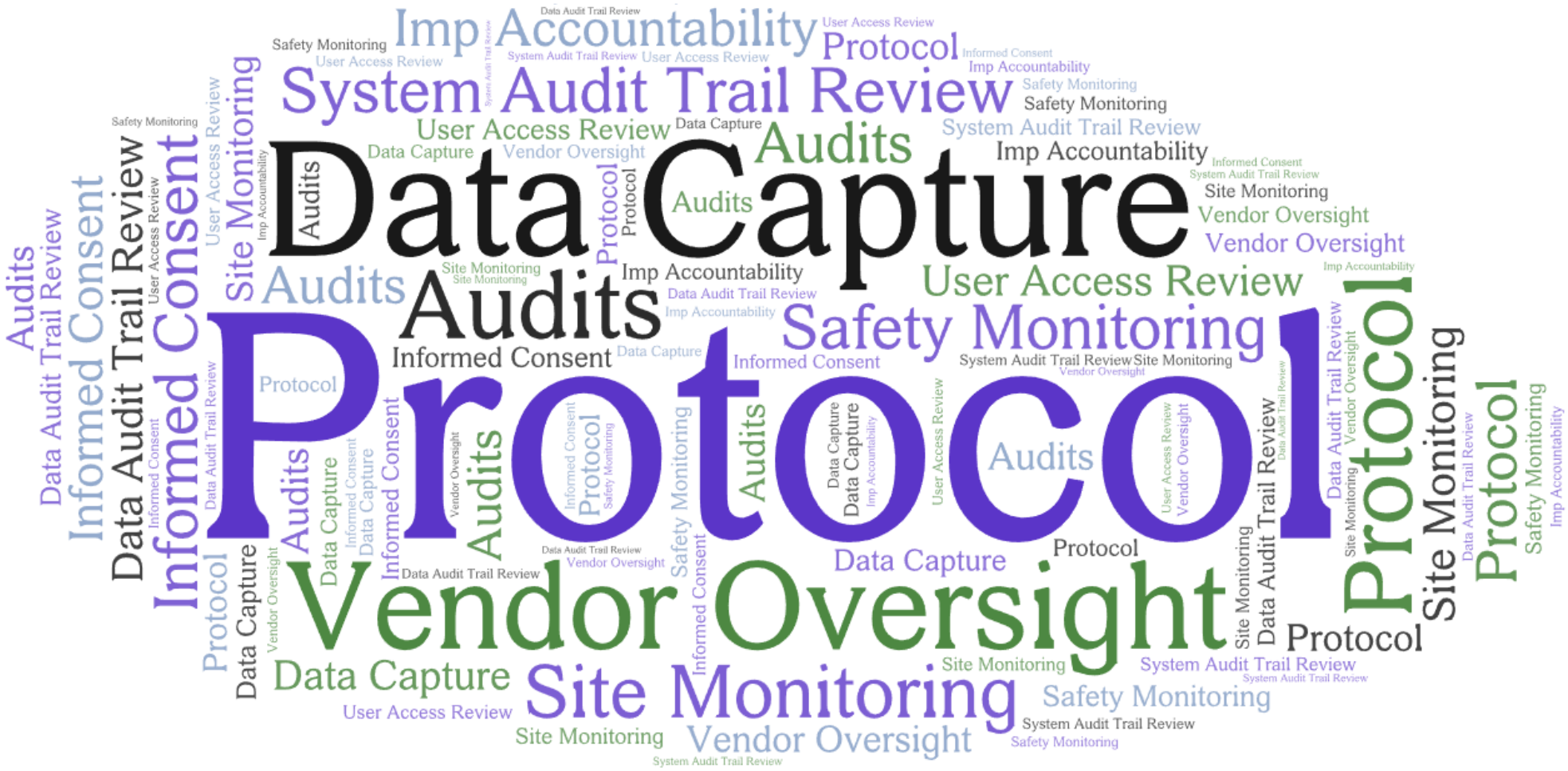
Quality by Design and Risk Proportionate apply to all trial deliverables.

It is not about one single quality system or design, but about embedding Quality by Design into every deliverable; from protocol to data capture and vendor oversight. This ensures that safeguards are proportionate, resources are used efficiently, and patient safety and data integrity remain central.



Definition of Quality by Design in ICH E6 R3

ICH E6 (R3) makes clear: Quality by Design ensures reliable trials by focusing on what matters, scaling safeguards with risk, and avoiding unnecessary complexity.

"**Quality by design** should be implemented to **identify the factors** (i.e. data and processes) **that are critical to ensuring trial quality and the risks** that threaten the integrity of those factors and ultimately the reliability of the trial results.

Clinical trial **processes and risk mitigation strategies** implemented to support the conduct of the trial **should be proportionate to the importance of the data being collected and the risks to trial participant safety** and the reliability of trial results.

Trial designs should be operationally feasible and avoid unnecessary complexity."

ICH E6(R3) Guideline - II Principles of ICH GCP

Applying QbD, Design space and Risk Proportionality to data capture

The more complex data capture, the bigger the need for clearly defined Design Spaces and risk assessments.

Critical to Quality (CtQ) parameters	Design space	Risk analysis	Risk proportionality	Design control
Accuracy of entered data. Timeliness of data entry. Completeness. Traceability.	Who enters data? How is data entered? How is data transferred? When is data entered? What controls are in place?	Manual transcription errors. Missing data. Data not available when needed. Audit trail does not support chain of events.	Not all data points are equally important. - Primary endpoints. - Safety data.	Edit checks for critical fields. Differentiated "timelines" for data entry and use of "time ranges“.

Integrating QbD, Risk Proportionality and Design Space into protocols.

By tailoring endpoints, eligibility and visit schedules through a risk-proportionate lens, protocols become more feasible, safer, and focused on what truly matters. This ensures reliable results without unnecessary complexity.

	CTQ	Design space	Risk	Risk proportionality	Design control
Endpoint selection	Clinically meaningful, measurable, and feasible?	Range of acceptable endpoints (e.g., HbA1c vs. fasting glucose in diabetes)	Infeasible endpoints.	A mistake in primary endpoint definition can be catastrophic. A mistake in exploratory biomarker is inconvenient but not critical.	Spend most effort and controls on high-risk areas. Use lighter, proportional oversight on lower-risk aspects.
Eligibility	Ensure patient safety but not over-restrict recruitment?	Too strict leads to slow recruitment and unrepresentative population. Too loose leads to safety risk and confounding.	Unethical to enroll participants in trial that will never complete enrollment. Inability to conclude on the trial.	Focus on fast enrollers.	Close monitoring of screening faillures in the beginning of the trial. When “criterias” are validated, monitoring may be reduced.
Visit schedule	Is it proportional to the risk/needs of the study?	Too frequent increase patient burden and dropout. Too infrequent may miss safety signals.	Patient burden. Safety risk.	Focus reinforcement activities towards infrequent visits (too long intervals).	Only check for out of visit windows above limit, unless there is a different medical rational.

In conclusion: Not a revolution, but a more structured way forward.



Nothing has changed.

We use more explicit terms, but the principles and goals remain; **Patient Safety and Data Integrity.**
We are not looking at a fundamental shift in how clinical trials should be designed.

Quality by design is <u>not</u> difficult:

- It is time consuming.
- Requires multidisciplinary teams
- Is an ongoing process.

Risk proportionality is:

- realising that no matter the effort, it will never be perfect or risk free.
- all about spending resources where it matters most.

Puente de Alcánta, Toledo, Spain
Built 106 AD by Roman Emperors.
The bridge is still in use today.

Get in touch!

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