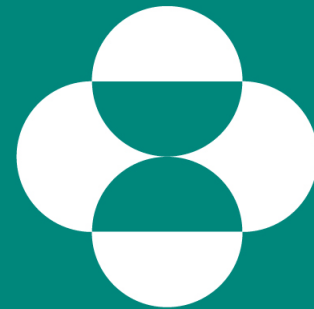


RISK-BASED PROGRAM VALIDATION FOR CLINICAL TRIAL ANALYSIS AND REPORTING



MERCK

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Paper SP06

Objective

- Propose methodology for clinical programmers to align validation of clinical programs with regulations
 - Implement “improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and data integrity.”
- Suggest a way to adopt a risk-based approach to validation allowing us to
 - Vary degree of testing rigor
 - Focus validation activities on the most critical analyses
 - Work efficiently while still ensuring high quality, accurate analysis of data.
 - Accurately analyze the safety and efficacy of medications
 - Ensure human subject protection.

Regulations

- Guidances to identify, assess, control, communicate, review and report risks as they relate to program validation for clinical trial analyses.
- ICH E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)
- ICH Quality Risk Management (Q9)

What is Risk

In clinical trials, risk can be defined as “the combination of the probability of occurrence of harm and the severity of that harm.”

Principles of Quality Risk Management

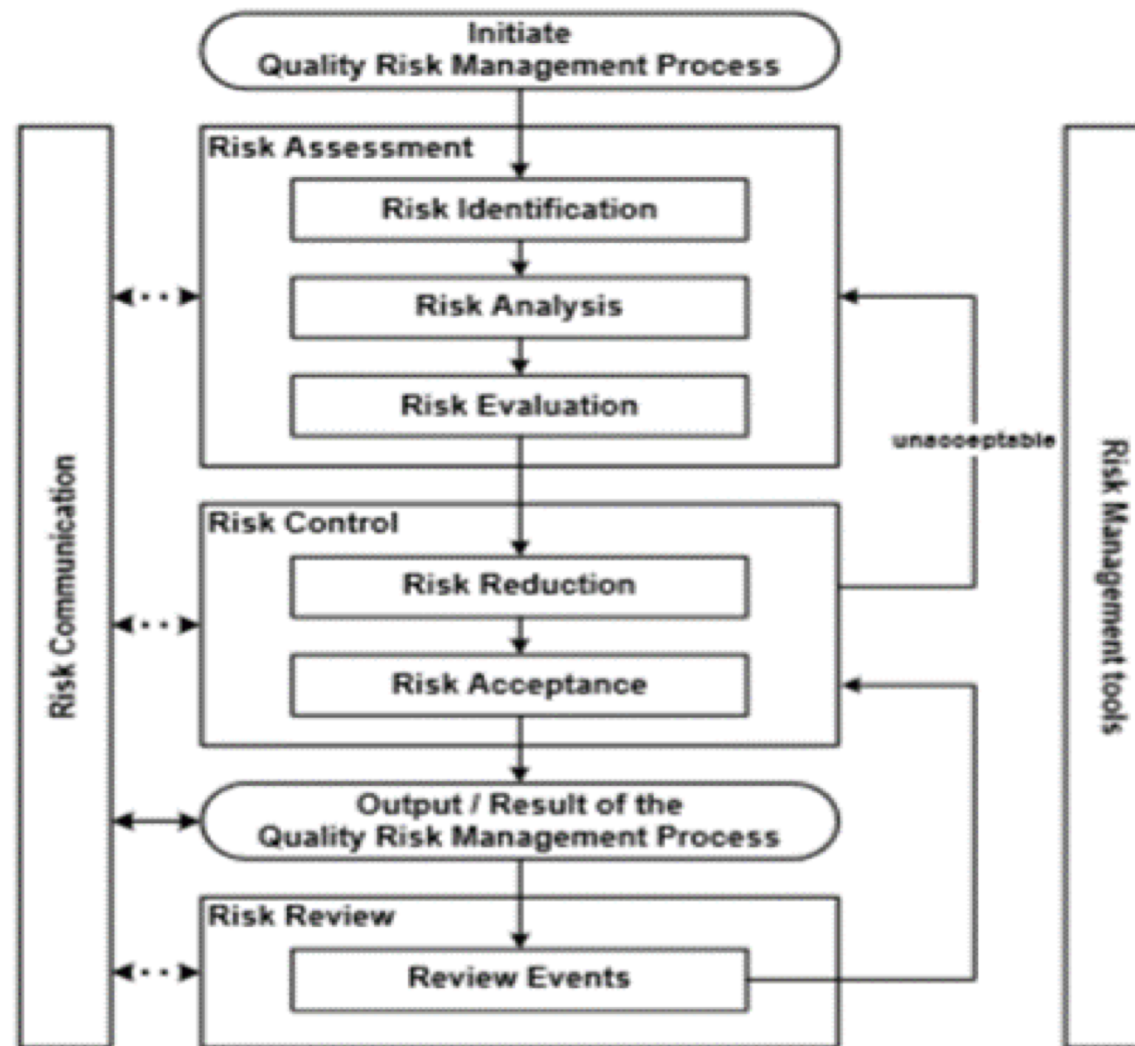
- Level of risk to quality and accuracy of our results
- Protection of the patient linked to that accuracy
- Level of effort that aligns with the risk.

ICH – Q9 Quality Management Plan

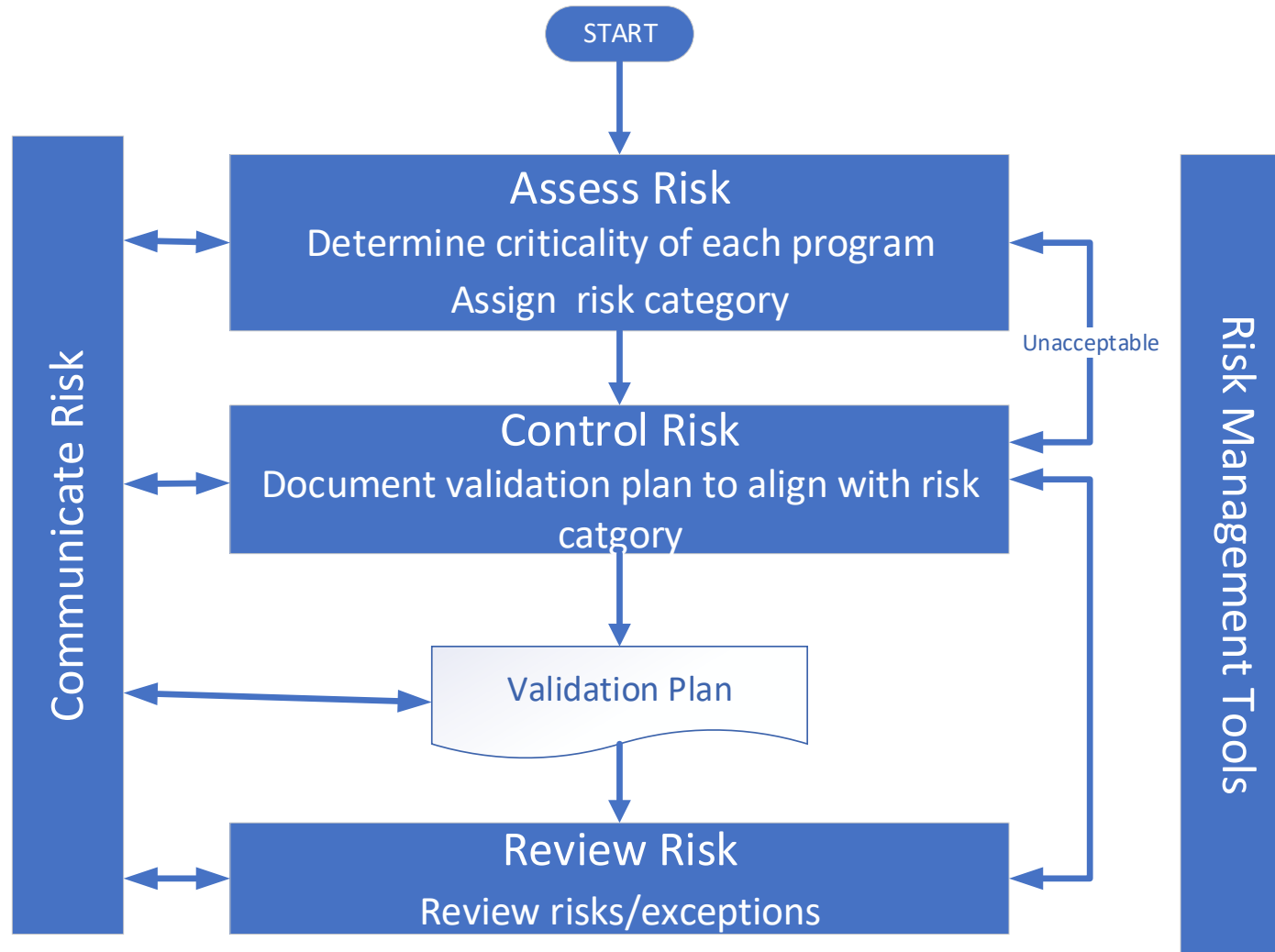
Quality Management Plan in Q9 can be adapted to fit program validation:

- Determine timing, outputs/deliverables and decision-making responsibilities
- Statistician, clinician and clinical programmer partner to follow the risk management process and evaluate risks
- When beginning a quality risk management process for clinical programming, the team must work to identify potential risks associated with each program including the potential harm or human health impact of the associated analyses. A leader and resources to support the process must be identified.

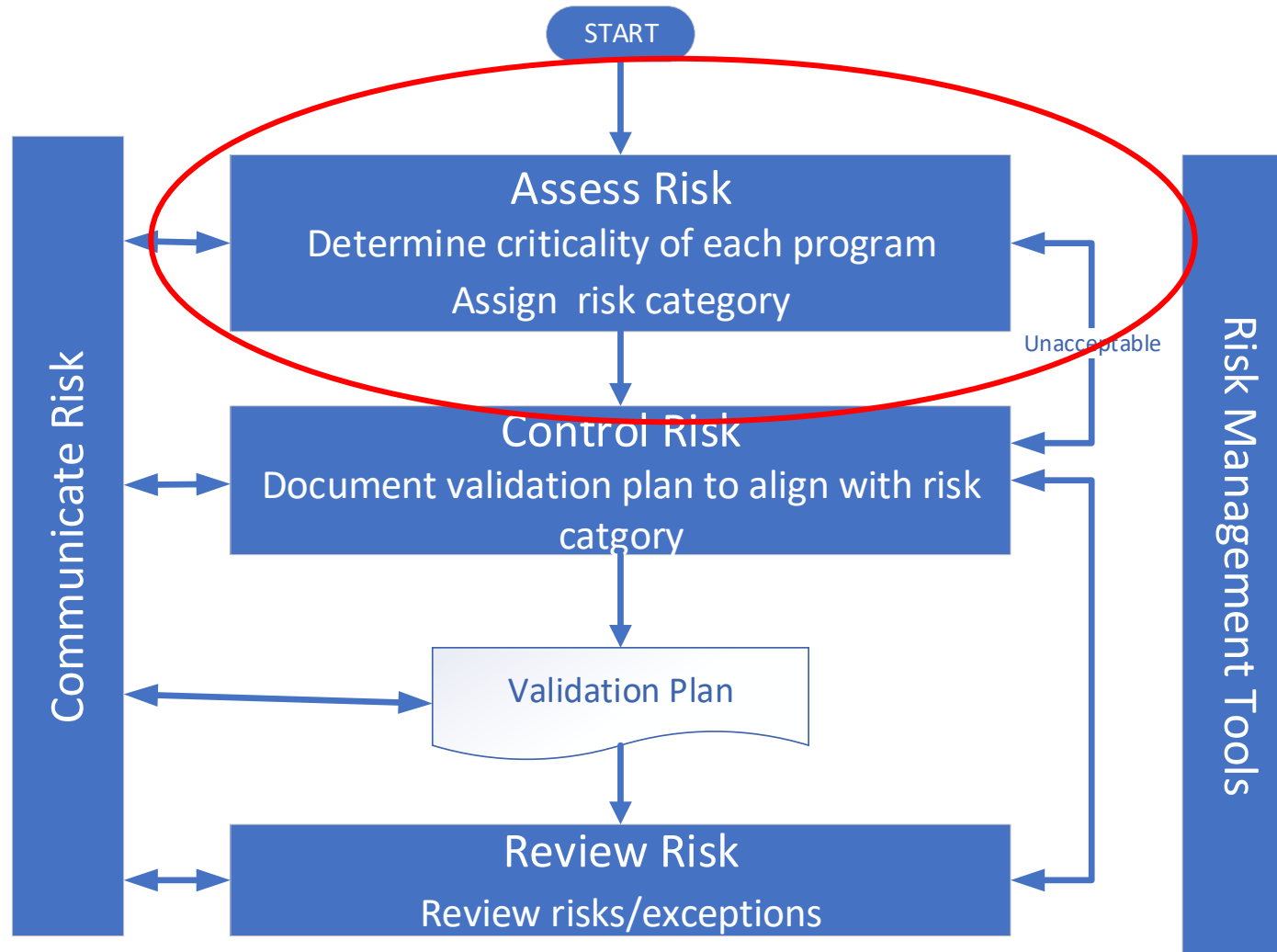
ICH Q9 – Figure 1 – Example of a typical quality risk management process



Suggested quality risk management process for program validation



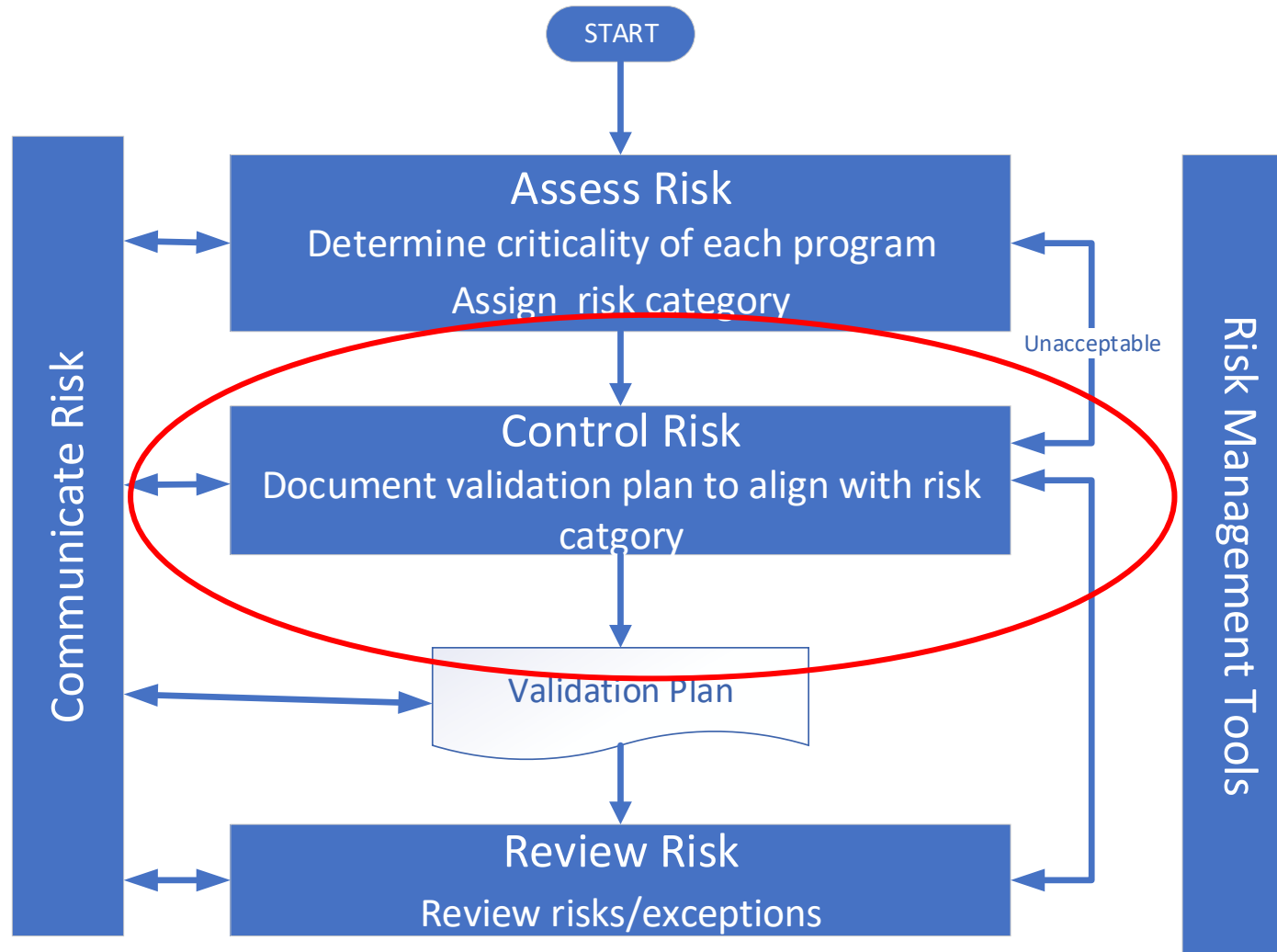
Assess Risk



Risk Category – Probability and Severity (High, Medium or Low)

Risk Severity	Risk Probability		
	High: New logic, Complex algorithm, Use across areas, Major changes to critical derivations	Medium: TLFs with simple counts (n and %), Non-critical variable dataset changes, Minor changes to critical derivations (i.e. change 2 to 4 in algorithm) TLF changes	Low: Calling programs, Utility macros, Re-use of validated program, Minor updates to validated programs
High: Critical analysis, primary hypotheses for efficacy or safety, CSR/CTD analyses, cross projects	High	High	Medium
Medium: Appendices, 2ndary/Exploratory analyses, Publications	High	Medium	Medium
Low: Non-submitted analyses, Cosmetic changes (labels, variable names, footnotes)	Medium	Low	Low

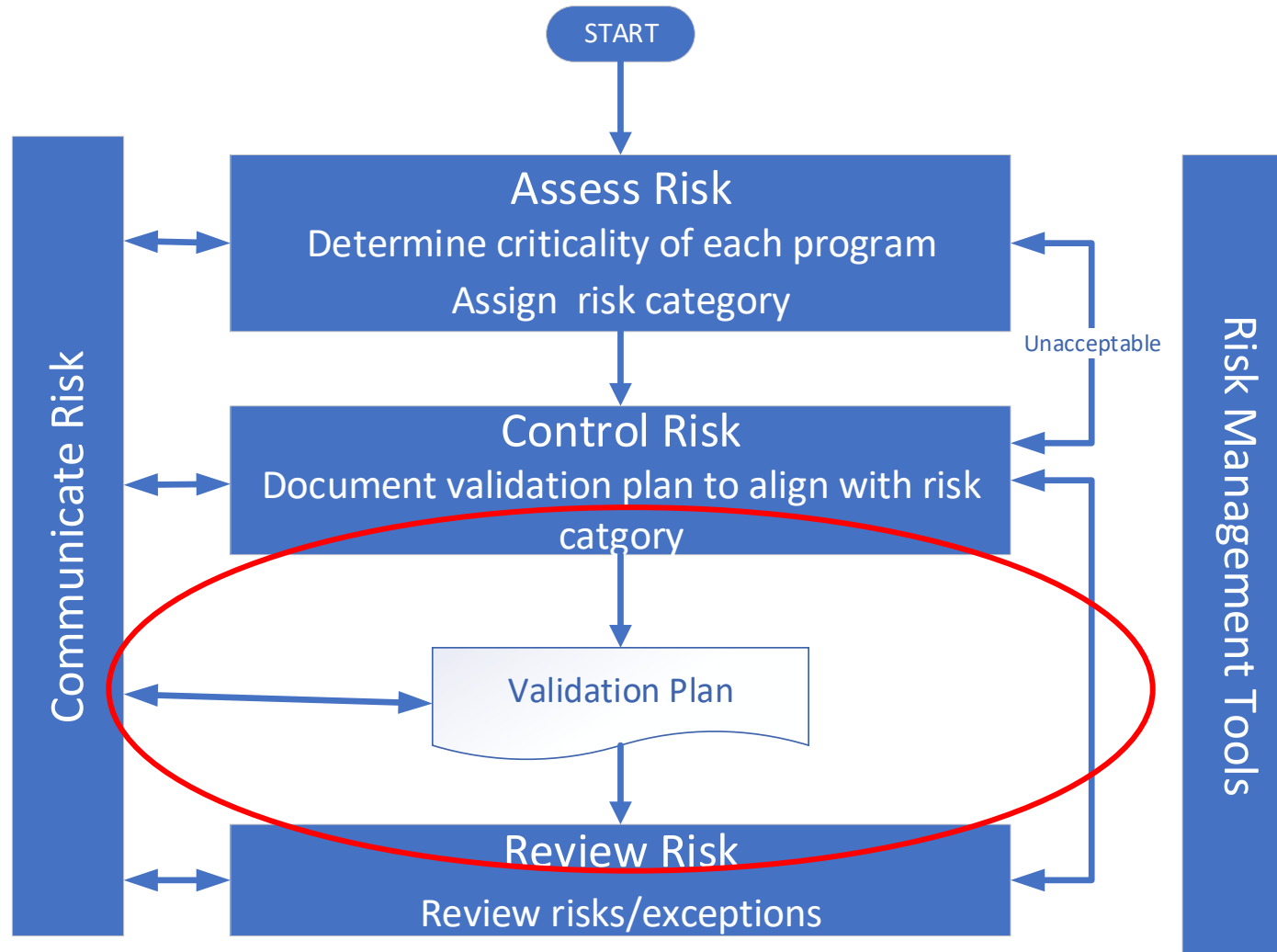
Control Risk



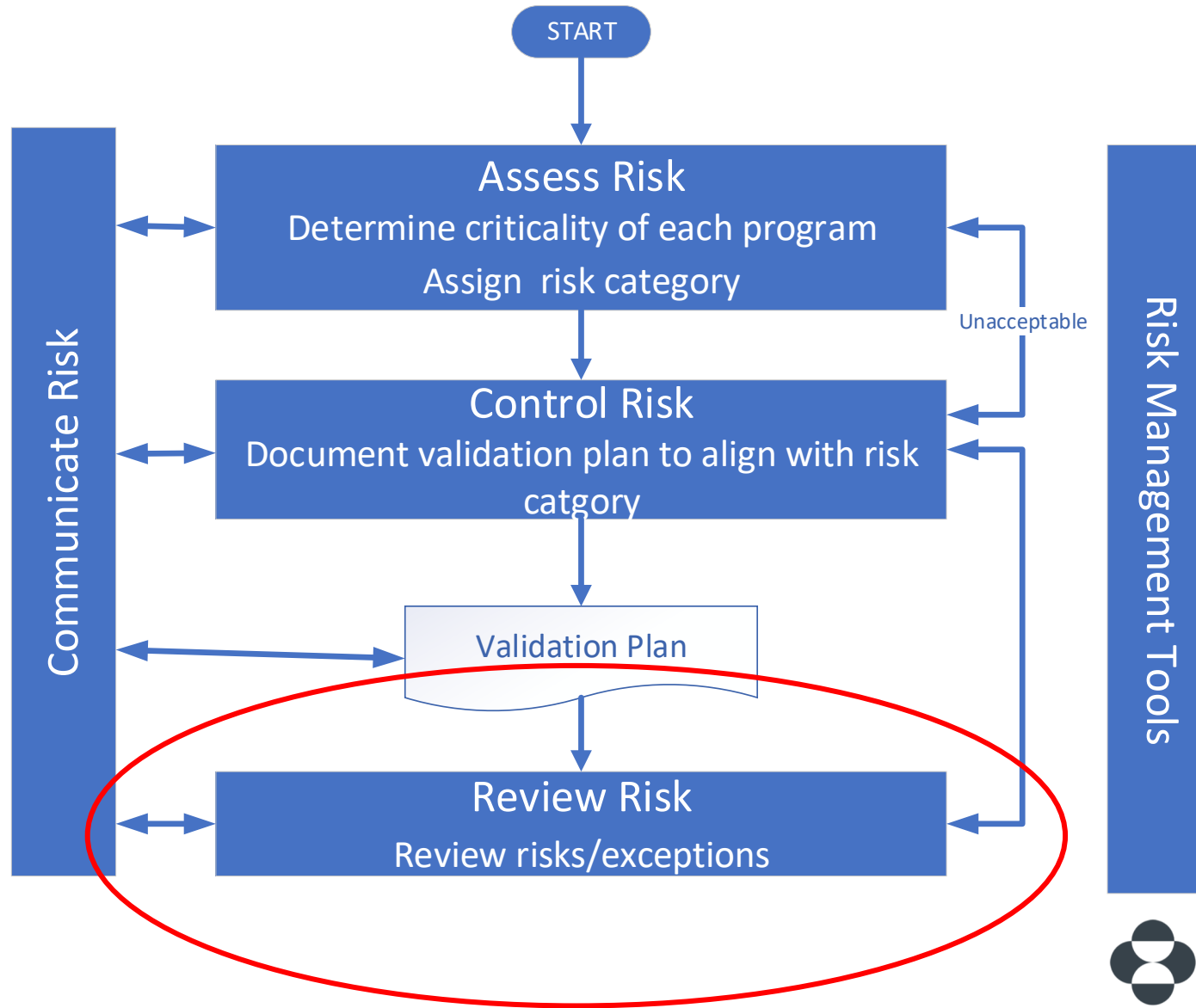
Validation Activities – based on Risk Category

Category	Required Validation/QC
High	• Developer testing activities • Statistical review of output with focus on complex derivations • Double independent coding of critical dataset/variables (list variables in plan) • User acceptance testing across multiple trials as appropriate • Clinical review of dry run TLFs • Independent code review
Medium	• Developer testing activities • Statistical review of output • Clinical review of dry run TLFs • Independent code review
Low	• QC of logs and output • Customer review of dry run TLFs • Cross table count checks • Compare to prior output for changes

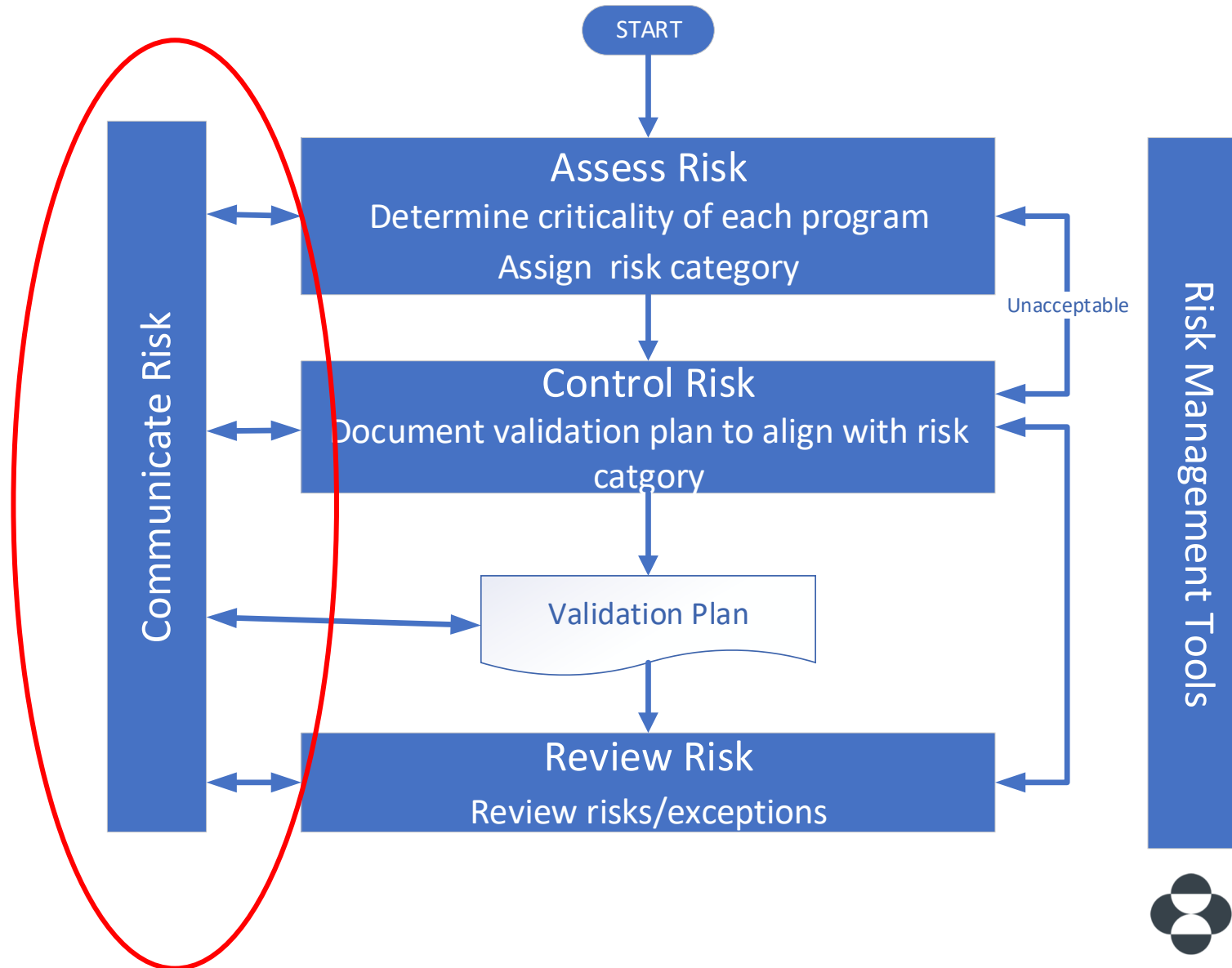
Validation Plan



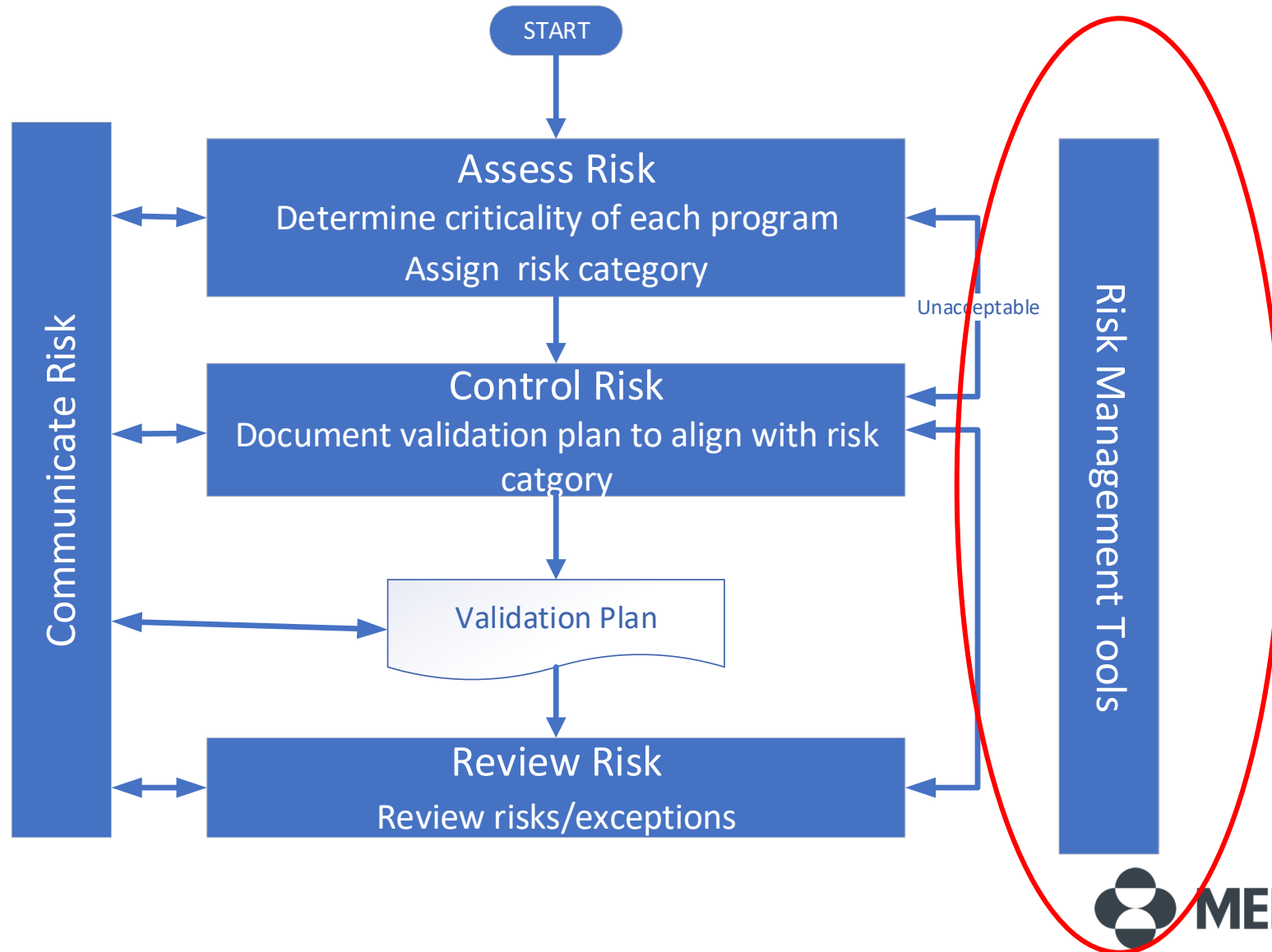
Review Risk



Communicate Risk



Risk Management Tools



Conclusion

- Consider having a quality risk management plan for validation of programs
- Create standard risk-based program categories and define expected validation activities aligned with each
 - Testing activities align with the risk associated with results analysis

THANKS

Your comments and questions are valued and encouraged.

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