PROCESS CHART

臨床研究の品質向上ツール作成WG

本研究の目的

- ・現時点において品質管理システムあるいは品質管理計画に基づく、Goal志向のデザインアプローチとなるQuality by Design (QbD) において、プロトコルに必須の領域あるいは実臨床に関連する領域での品質管理指標として、何を基準にどのように推奨するかについて、まだ汎用的なツールがないのが現状である。
- 本研究では、被験者保護、データの質確保を目標として、 QbDによる実施計画書の作成に必要なツールを検討及び 作成し臨床研究の品質向上を目指す。

本研究で整備目標としたQbDツール



QbD概念に対する教育コン テンツ

PPT提示



QbDによるプロトコル開発 プロセス チャート

> フローチャート 提示

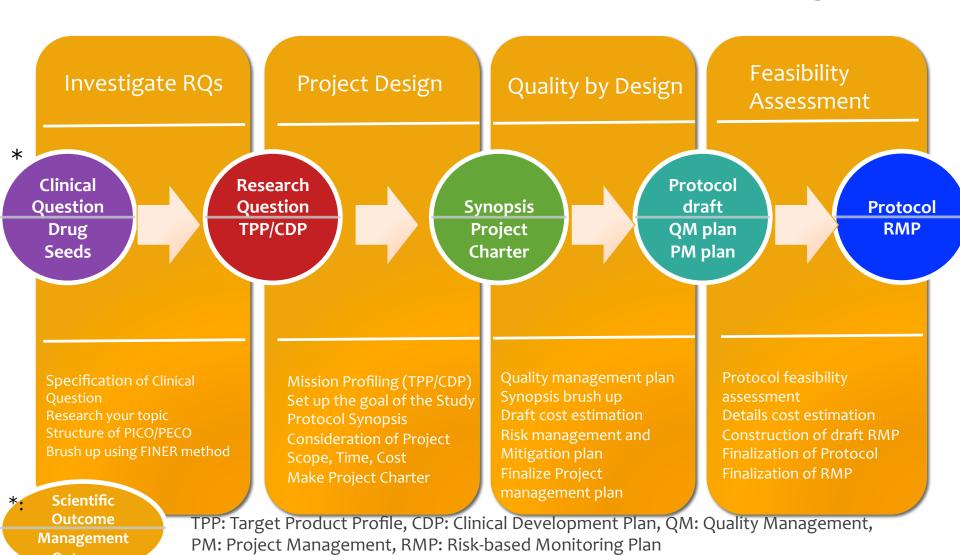


品質管理項目 を組み込んだ 実施計画書

> 次期活動で<mark>検討</mark> (H30年度)

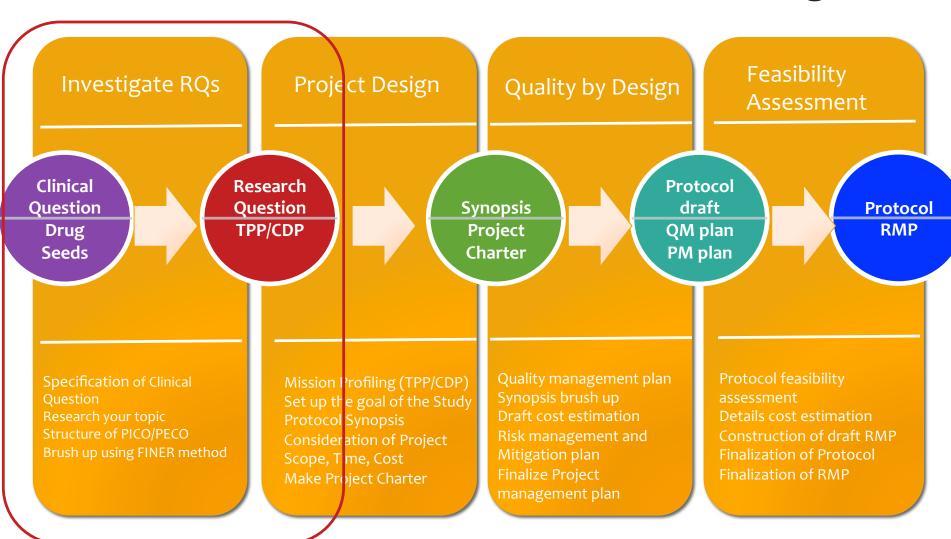
Outcome

Whole Process of QbD protocol planning



INVESTIGATE RQ_S

Whole Process of QbD protocol planning



Investigate Research Questions

input

Specification of Clinical Question

Clinical Question

Research your topic

Structure of PICO/PECO

Research Question

Brush up using FINER method

Output

Specification of Clinical Question

Input

Clinical Question



Process

Wants/Needs specification





Research Topic

clinical question
 from bedside

- •Real unmet needs
- Clinical wants
- •State of the art
- Clinical Guideline
- Case report
- •EHR data
- Reputation survey

- Research hypothesis
- Thesaurus
- Search word

Research your topic

Input

Research Topic



Process

Literature review



Output

Clinical Question (detail)

- Research hypothesis
- Thesaurus
- Search word

- Clinical guideline
- Pubmed
- MEDLINE
- Cochrane Database/
 Systematic Review
- Scopus
- Google Scholar
- Critical appraisal of selected papers

- •Research hypothesis (detail)
- Clinical Question (detail)

Structure of PICO/PECO

Input

Clinical Question (Detail)

Drug Seeds

- Research hypothesis (detail)
- •Clinical Question (detail)
- Compound

Process



Consider Study Design

- •PICO/PECO
 - P(Patient)
 - I (Intervention)
 - /E (Exposure)
 - C (Comparison)
 - O (Objective)
- Study Design (draft)

Output



Research Questions (draft)

- •Research Questions (draft)
- Trial Goal (draft)
- Research benchmark

RQs brush up using FINER method

Input

Research Questions (draft)



Process

Evaluate RQs based on FINER



Output

Research Questions (RQs)

- Research Questions (draft)
- Trial Goal (draft)
- Research benchmark

•FINER evaluation

F: Feasible

I: Interest

N: Novel

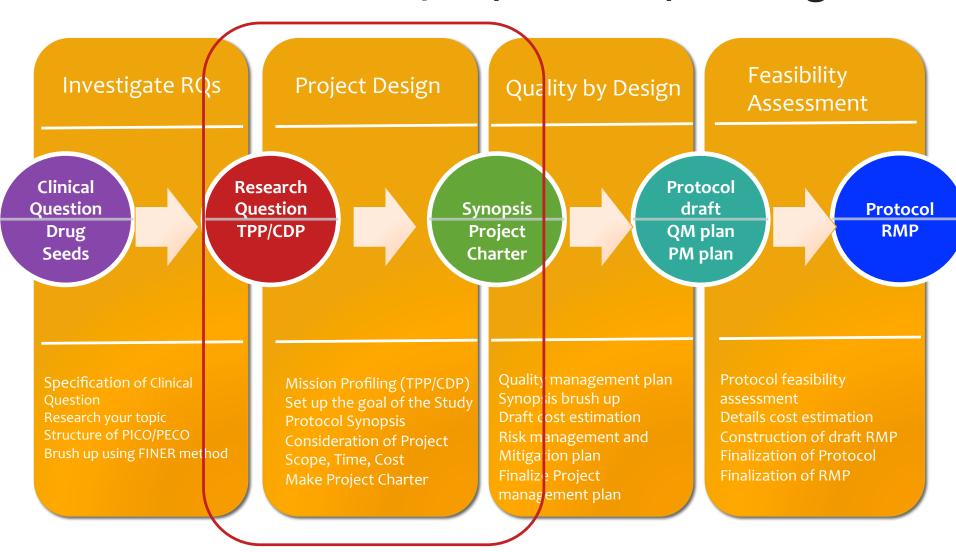
E: Ethical

R: Relevant

- •Research Questions Trial Goal (draft)
- Research benchmark

PROJECT DESIGN

Whole Process of QbD protocol planning



Project Design

Mission Profiling (TPP/CDP)

Research

Question

input

Set up the goal of the Study

Protocol Synopsis

Consideration of Project Scope, Time, Cost

Synopsis Project Chater

Make Project Charter

Output

Mission Profiling

Input

Research Question (RQ)

Drug Seeds Environmental factor

Compound

Patent

Healthcare environment

Hypothesis of the Study

P:Patient

I/E:

Intervention/Exposure

C:Comparison

O:Outcome

Process

Mission Profiling

Identify Target Product Profile

Efficacy/Safety benchmark

Drug Product

Dosing Regimen

Patent

Scientific Interest

Novelty

Social Impact

Medical Real Needs

Positioning in the medical field

Competing product Research

Regulatory Research

Marketing Research

Risk assessment

Output

Clinical Development Plan (Draft)

TPP

Positioning

Competing product

Development Strategy

Regulatory Strategy

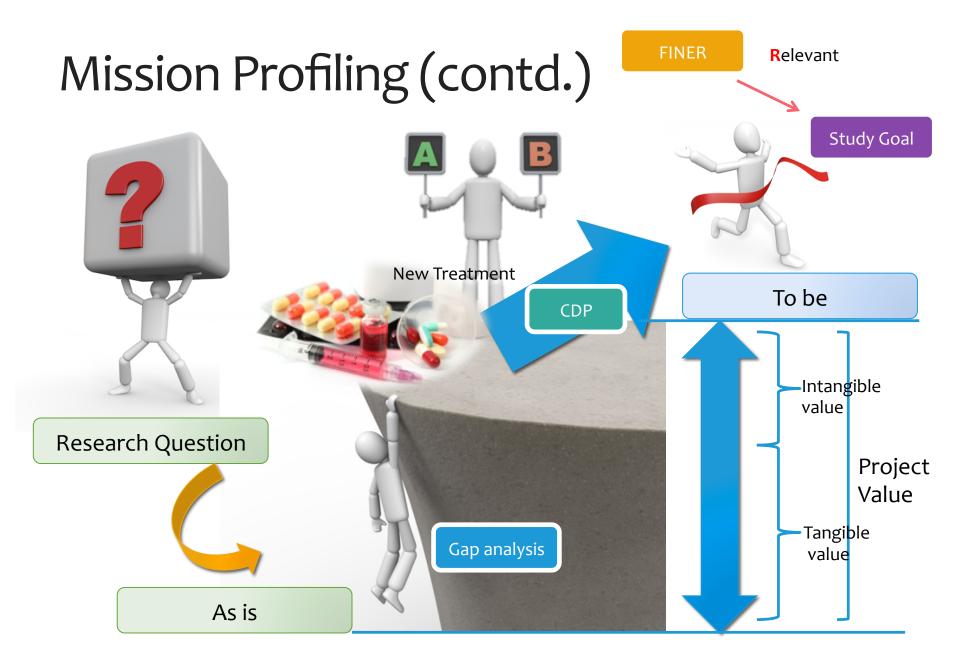
Marketing Strategy

Patent Information

Decision-making approach

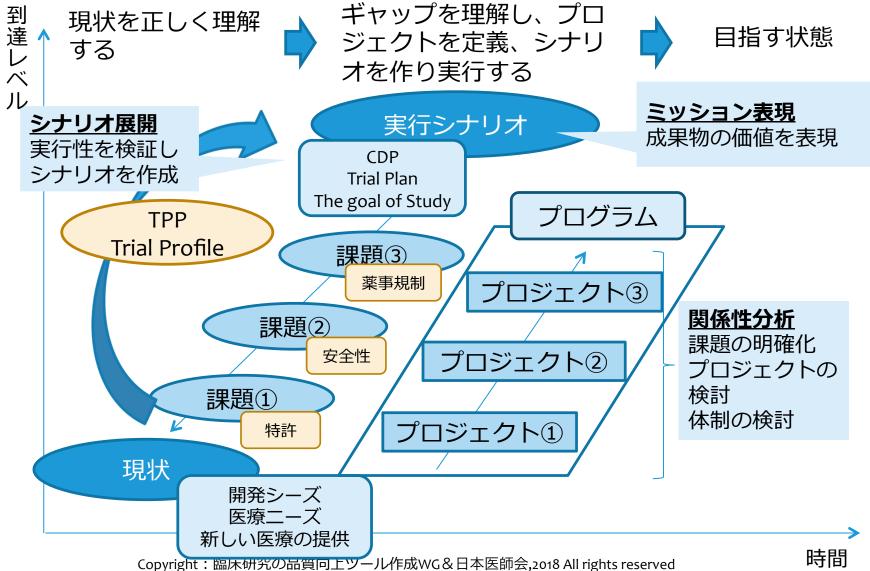
Risk estimation

Define Criteria for Go/No go Copyright:臨床研究の品質向上ツール作成WG&日本医師会,2018 All rights reserved



Copyright: 臨床研究の品質向上ツール作成WG&日本医師会,2018 All rights reserved

Mission Profiling 概念図



Set up the goal of the Study

Input

Clinical Development Plan (Draft)



TPP

Positioning

Competing product

Development Strategy

Regulatory Strategy

Patent Information

Decision-making approach

Risk estimation

Financial requirements

Resource requirements

Development Schedule

Number of Patient

Process

Clarify what to verify

Understand Real Needs

Estimate Cost, Resource, Schedule

Set up the goal of study

Feasibility

Ethicality

Medical Real Needs

Study Goal

Quality Goal

Positioning in the medical field

Estimate cost

Estimate Resource

Estimate schedule

What to verify

Appropriate PICO/PECO

Output

Clinical Development Plan

TPP

Financial plan

Resource plan

Development Schedule

Study plan

The goal of the study

Study Duration

Definite positioning

Quality Policy

Regulatory Strategy

Marketing Strategy

Patent Information

Decision-making approach

Risk and Contingency plan

Target Product Profile (TPP)

TPP:承認申請に必要な開発プログラム全体の意図が記載され、その時点での適切な情報が記載されているもの。 開発のゴールが明記されている。(2007年3月FDAガイダンス)

- TPPに記載すべき項目(例)
 - 製品の概要
 - 疾患セグメント
 - Keyとなる項目
 - 有効性:有効性のベンチマーク、Go/No goの判断基準
 - ・安全性:安全性のベンチマーク、Go/No goの判断基準
 - 製剤:規格・安定性や扱いやすさ(保管条件)
 - 投与計画:経路・用法用量

Clinical Development Plan (CDP)

- · 臨床開発計画(Clinical Development Plan、CDP)
 - どのようなターゲットに対して、どういう試験を実施するかについてまとめたもの
- CDPの項目の例
 - 開発の経緯
 - 薬効・薬理の概略
 - ・臨床的な位置づけ
 - ・ 類薬の開発状況
 - 用量探索・有効性及び安全性評価計画(I相〜III相、長期試験等)
 - ・リスクとその対応策
 - 人員、資金計画
 - タイムスケジュール
 - 意思決定方法

Protocol Synopsis

Input

The goal of the Study

Clinical Development Plan

Study real Objective Study Duration Appropriate PICO/PECO P:Patient I/E: Intervention/Exposure C:Comparison

O:Outcome

What to verify

Quality Policy

Definite positioning

Process

Consider the Study Design

Determine Quality goal

Design the number of subject

Quality goal Target Subject Criteria Number of Subject Comparison **Endpoint**

Analytical method of endpoint

Study Method Investigation Item Output

Protocol **Synopsis**

Objectify RQ Clarify RQ

Determine the

study subject

Study Objective Target Subject Inclusion Criteria **Exclusion Criteria** Study Design Endpoint Comparative **Controlled Therapy** Target number of subjects Statistical Analysis

Consideration of Project Scope, Time, Cost

Input

Protocol Synopsis

Organizational Knowledge

Study Objective
Study Subject
Inclusion Criteria
Exclusion Criteria
Study Design
Endpoint
Comparative Controlled
Therapy
Target number of subjects
Statistical Analysis
Past Cases
Organizational Knowledge

Process

Estimate the project Schedule

Estimate the project cost

Estimate Resource Determine the Deliverable

Definite the

Quality goal

Refer past cases

Study Schedule Requisite Duration to conduct study Requisite Quality goal Requisite cost

Requisite Resource

Regulatory Requirement

Output

Project Charter (Draft)

Project Objective
Quality goal
Project Duration
Project Cost
Deliverable
Study Organization
Study Method

Identify the Stakeholder

Make Project Charter

Input

Project Charter (Draft)

Project Objective
Quality goal
Project Duration
Project Cost
Deliverable
Study Organization
Study Method
Summary of Study

Process



Decide Priority of Project Scope, Time, Cost

Assess the Project Risk

Assess the Study circumstance

Priority (Quality (Scope), Time, Cost)
Project Risk
Regulatory Requirement
Organizational needs
Customer Request
Quality goal
Project member
Project Resource

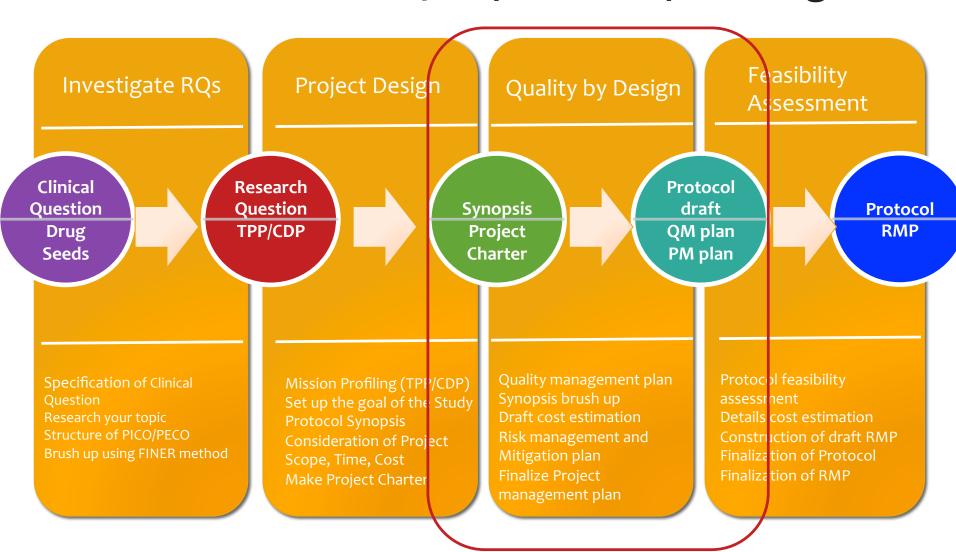
Output



Project Objective
Project Goal
Project Risk
Milestone Schedule
Budgetary Estimate
Stakeholder
Project Exit criteria
Project success criteria
Project Duration
Assumption
Constraint
Project
Requirement (Scope

QUALITY BY DESIGN

Whole Process of QbD protocol planning



Quality by Design

Quality management plan

Synopsis
Project
Chater

input

Synopsis brush up

Draft cost estimation

Risk management and Mitigation plan

Protocol draft QM plan PM plan

Finalize Project management plan

Output

Quality management plan

Input

Project Charter

Protocol Synopsis

Project Objective
Project Goal
Project Risk
Milestone Schedule
Budgetary Estimate
Stakeholder
Project Exit criteria
Project success criteria
Project Duration
Assumption
Constraint

Project Requirement

Process

Identify the Project Risk



Define the quality policies, measurements

Clarify the goal of the clinical trial
Define the quality policy
Define the quality objectives
Risk assessment

Output

Quality Management Plan

- 1. Quality policy of the trial
- 2. Requirements of the trial (customer, laws and regulations, implementation system)
- 3. Scope and authority
- 4. Risk identification and risk management plan
- 5. Quality management plan
- 6. Quality management (monitoring methods, monitoring methods)
- 7. Quality assurance (the presence or absence of audit, system of the audit)
- 8. Change management
- 9. Education and training

Quality Management Plan

- ☐ Clarify the goal of the clinical trial
- Define the quality policy
- Define the quality objectives
- ☐ Risk assessment

Preparation for the quality management plan

Planning the protocol well-behaved from the quality management plan

Preparation for the operating procedure or instructions for trial monitoring and auditing

Quality Management Plan

> Trial Protocol

SOPs, Working Instruction

manuals

- Quality Management System (SOPs, Computerized systems, human resources, outsourcing, infrastructure)
- Clinical trial protocol (investigational new drugs, trial design, data collecting process, monitoring process, documents or records)

Determine the

study outcome

Synopsis brush up

Input

Protocol Synopsis

Study Objective
Target Subject
Inclusion Criteria
Exclusion Criteria
Study Design
Endpoint
Comparative
Controlled Therapy
Target number of
subjects
Statistical Analysis

Process



Consider the QMP

Determine Trial Timeline

Consider the policy of Risk Management

Quality goal
Target Subject
Criteria
Number of Subject
Comparison
Endpoint
Analytical method of endpoint
Study Method
Investigation Item

Output



Protocol draft

Study Objective Target Subject Inclusion Criteria **Exclusion Criteria** Study Design Endpoint Comparative Controlled Therapy Target number of subjects Statistical Analysis Indication **Study Duration** Quality requirement Trial timeline

Determine the

Deliverable

Refer past

cases

Draft cost estimation

Input

Protocol Draft

Project Charter

Project Objective Quality goal **Project Duration Project Cost** Deliverable Study Organization Study Method

Process

Consider Protocol draft

Estimate the project cost

Estimate

Resource

Consider protocol draft, including timeline, outcomes, quality goals, duration, study resource Cost estimation

Output

Project Cost Plan

Project Objective Quality goal **Project Duration Project Cost** Deliverable Study Organization Study Method

Quality requirements

Risk Management and Mitigation plan

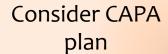
Input

Quality Management Plan

- 1. Quality policy of the trial
- 2. Requirements of the trial (customer, laws and regulations, implementation system)
- 3. Scope and authority
- 4. Risk identification and risk management plan
- 5. Quality management plan
- 6. Quality management (monitoring methods, monitoring methods)
- 7. Quality assurance (the presence or absence of audit, system of the audit)
- 8. Change management
- 9. Education and training

Process

Consider Risk and Assessment



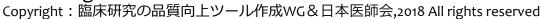
Consider Risk Mitigation Plan

Consider Risk Management plan Identify Risk Risk analysis: Quantitative and Qualitative analysis Consider Risk Mitigation and Risk Control Consider CAPA plan

Output



- 1. Risk Management
- Risk Quantitative Analysis
- Risk Qualitative Analysis
- 4. Risk Mitigation plan
- 5. Risk Control
- 6. CAPA plan



Finalize Project management plan

Input

Process

Risk Management and Mitigation Plan

Project Cost Plan

Quality Management Plan

> Project Objective Quality goal **Project Duration** Project Cost Deliverable Study Organization Study Method

Define Project Activity

Consider Risk Management plan

Consider resource, cost, duration, stakeholders

Consider Quality Management plan Define project activity and scope Define project development and change management method Consider Risk Management plan Consider Protocol Draft

Corrective and Preventive Action

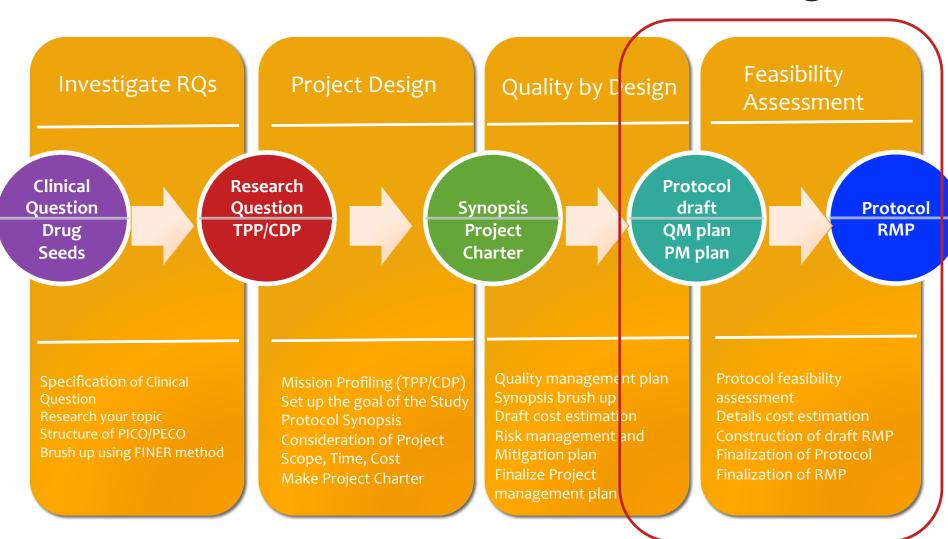
Output

Project Management Plan

- 1.Scope Management
- 2.Project Requirements
- 3. Schedule Management
- 4.Cost Management
- 5.Quality Management
- 6. Resource Management
- 7. Communication Management
- 8. Risk Management
- 9. Procure Management
- 10. Stakeholder Engagement
- 11. Change Management
- 12. Configuration Management
- 13. Scope baseline
- 14. Schedule baseline
- 15. Cost baseline
- 16. Performance baseline
- 17. Project Lifecycle

FEASIBILITY ASSESSMENT

Whole Process of QbD protocol planning



Feasibility Assessment

Protocol feasibility assessment

Protocol draft

QM plan

PM plan

input

Details cost estimation

Construction of draft RMP

Finalization of Protocol

Protocol RMP

Finalization of RMP

Output

Protocol feasibility assessment

Input

Protocol draft

PM plan

QM plan

Design

Patient population

Indication

I/E criteria

Sample size

Endpoints

Duration

Quality requirement

Trial timeline

Process

Review protocol draft

Identify candidate sites

Discuss with PIs, regulatory

Ensure clinical feasibility
Ensure scientific feasibility
Ensure ethical feasibility
Ensure operational feasibility
Ensure regulatory feasibility
Ensure legal feasibility
Discuss with Pls, Regulatory

Output

Protocol final draft

Identify difficulty

Key Role
Introduction

Objective

Study Design, Endpoints

Enrollment

Investigational drug

Study Procedure

Study Schedule

Assessment of Safety

Clinical Monitoring

Statistical Considerations

SDV, Source Data

Ethics

Data Handling

Study administration

COI, Publication

Estimate per

patient cost

Details cost estimation

Input

Protocol final draft

Project Management Plan

PM plan
QM plan
Design
Timeline
Sample size
Trial organization
Regulatory requirement
Protocol requirement
Quality requirement
Critical to Quality (CTQ)
Risk mitigation plan

Process

Share with vendors

Estimate direct cost

Obtain estimate from vendors

Discuss about resource (people, materials, cost)
Share protocol with vendors
Collect all cost estimations
Estimate direct, pass through,
fixes and variable cost

Output

Final cost estimation

Direct cost Pass through cost Fixes cost Variable cost Site cost

Vendor (EDC/CRF,

IXRS, Central lab,

writing, DM/Stat,

Audit) cost

CRO, SMO, Medical

Construction of draft RMP

Input

Protocol final draft

Project Management Plan

PM plan
QM plan
Endpoints
Candidate patients
Budget estimate
Trial cost
Trial organization
Trial complexity
Potential risk
Fixed timeline
Quality requirements

Process

Discuss monitoring plan

Discuss PM plan

Discuss QM plan

Update protocol final draft

Confirm acceptance of procedures
Discuss key risk indicators
Discuss quality requirements
Decide monitoring type (central, on site)
Decide monitoring frequency

Output

Risk-based Monitoring Plan (draft)

Acceptable protocol final draft Monitoring type Monitoring frequency Monitoring team Key risk indicators Risk mitigation plan Draft audit plan

Prepare monitoring plan

Update protocol draft

Finalization of Protocol

Input

Final cost estimation

Draft RMP

Design

Patient population

Indication

I/E criteria

Sample size

Endpoints

Analysis methods

Trial timeline

Trial cost

Trial organization

Trial complexity

Trial difficulty

Potential risk

Monitoring plan

Process

Finalize protocol



Output

Full protocol

Input feasibility result into draft protocol

Re-confirm voice of customer

Re-confirm customer requirements

Discuss output data (Table, Figure,

List etc)

Update draft protocol

Protocol review by team

Protocol review by expert

Fixed full information for protocol Fixed trial cost CRF index

Finalization of RMP

Input

Final Protocol

Draft RMP

Process

Discuss monitoring plan



Output

Risk-based Monitoring Plan (Final)

PM plan
QM plan
Endpoints
Analysis methods
Trial timeline
Trial organization
Trial complexity
Monitoring type
Monitoring frequency
Monitoring team
Key risk indicators
Risk mitigation plan
Draft audit plan

Confirm acceptance of procedures
Discuss key risk indicators
Discuss quality requirements
Decide monitoring type (central, on site)
Decide monitoring frequency
Update protocol draft
Prepare monitoring plan

Acceptable final monitoring plan Monitoring type Monitoring frequency Monitoring team Key risk indicators Risk mitigation plan Audit plan